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# Biofunctional Composites of Polysaccharides Containing Inorganic Nanoparticles

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## 1. Introduction

In the last years, a variety of biopolymers have been investigated as soft matrices to accommodate inorganic nanoparticles (Darder et al., 2007; Dias et al., 2011). Innovation in Nanomedicine has been a major driving force to create new bionanocomposites because these materials bring together the intrinsic functionalities of inorganic nanoparticles and the biointerfaces offered by polymers of natural origin. On one hand, this type of hybrid materials can be designed to perform a specific function, depending on the characteristics of the loaded inorganic nanoparticles and, on the other hand, the composite can be easily adapted to biosystems due to the potential biocompatibility and low-toxicity of the biopolymer matrix.

In view of the large number of available polymers to produce such bionanocomposites this chapter has focus on the use of polysaccharides derived from natural sources, i.e. polymeric carbohydrate structures, that have been intensely investigated in the context of bio-applications. As such, cellulose, that together with lignin forms the ubiquitous composite wood, will be only briefly mentioned in specific contexts. Since synthesis conditions play a determinant role in the performance of the final materials, the chemical strategies for the production of bulk and nanodispersed bionanocomposites will be reviewed. Depending on the type of envisaged bioapplication, aspects related to the performance of the polysaccharide will be highlighted. These include relevant biochemical interactions with the surroundings and, the biofunctionality of the nanocomposite that results from the conjugated action of both the biopolymer and the inorganic nanofillers.

Recent years have witnessed the implementation of new therapeutics, clinical diagnostic techniques and disease preventive strategies that directly emerge from Nanotechnology (Sakamoto et al., 2010; Seigneuric et al., 2010). Therefore this chapter concludes with illustrative examples of bionanocomposites whose properties are of great interest in bio-applications such as magnetic nanocarriers for drug delivery and antimicrobial composites based on nanometals. As a final note, the challenging field comprising the development of multifunctional bionanocomposites will be put in perspective.

## 2. Relevant properties of polysaccharides for bio-applications

The polysaccharides most commonly used for preparing bionanocomposites are summarized in Table 1 and Fig. 1. They can be classified according to their ionic character

(neutral, anionic, cationic) and they bring different properties and chemical functionalities to the nanocomposites. The polysaccharides indicated in Table 1 derive from natural sources, hence presenting advantages in terms of biodegradability, low-toxicity and low cost. An exhaustive description of the properties of the polysaccharides is out of the scope of this chapter and can be found in the references included in Table 1.

Ionic character	Polysaccharide	Source	Functional Groups	Reference
Neutral	Agarose	Marine red algae	OH	(Nijenhuis, 1997)
	Dextran	Produced by lactic acid bacteria	OH	(Heinze et al., 2006)
	Pullulan	Produced by yeast-like fungus	OH	(Singh et al., 2008)
	Starch	Green plants	OH	(Le Corre et al., 2010)
Anionic	Alginate	Brown algae	OH, COO <sup>-</sup>	(Augst et al., 2006)
	Carrageenans	Red seaweeds	OH, OSO <sub>3</sub> <sup>-</sup>	(Campo et al., 2009)
	Gum Arabic	Acacia trees	OH, COO <sup>-</sup>	(Ali et al., 2009)
	Heparin	Animal tissues	OH, OSO <sub>3</sub> <sup>-</sup>	(Rabenstein, 2002)
	Hyaluronan	Animal tissues	OH, COO <sup>-</sup>	(Gaffney et al., 2010)
Cationic	Chitosan	Shellfish and fungi cell wall	OH, NH <sub>3</sub> <sup>+</sup>	(Rinaudo, 2006)

Table 1. Polysaccharides commonly used in the preparation of bionanocomposites.

Polysaccharides have been used as composite matrices due to several characteristics of relevance for biological and medical applications, namely:

*i. Biocompatibility*

Polysaccharides are very often incorporated into nanocomposites aiming to improve their biocompatibility, namely because they are hydrophilic, and administered in approved conditions, are non-toxic. For example, the intravenous administration of less biocompatible nanoparticles may elicit a response from the immune system that results in their uptake by macrophages, rendering them useless. Heparin, a polysaccharide with anticoagulant properties, has shown to be effective as a coating agent to increase the biocompatibility of several materials (Kemp & Linhardt, 2010) including carbon nanotubes (Murugesan et al., 2006) and metal nanoparticles (Kemp et al., 2010). Also dextran and carboxydextran coated magnetite nanoparticles have been commercialized as contrast agents for magnetic resonance imaging of liver tumors. Other nanocomposite systems are currently under clinical investigations (Corot et al., 2006).

*ii. Biofunctionalization*

Polysaccharides have specific functional chemical groups in their structure (Table 1) and as such they can serve as a springboard for the creation of multimodal and multifunctional systems through the addition of reactive and bioactive groups at the composites surface,

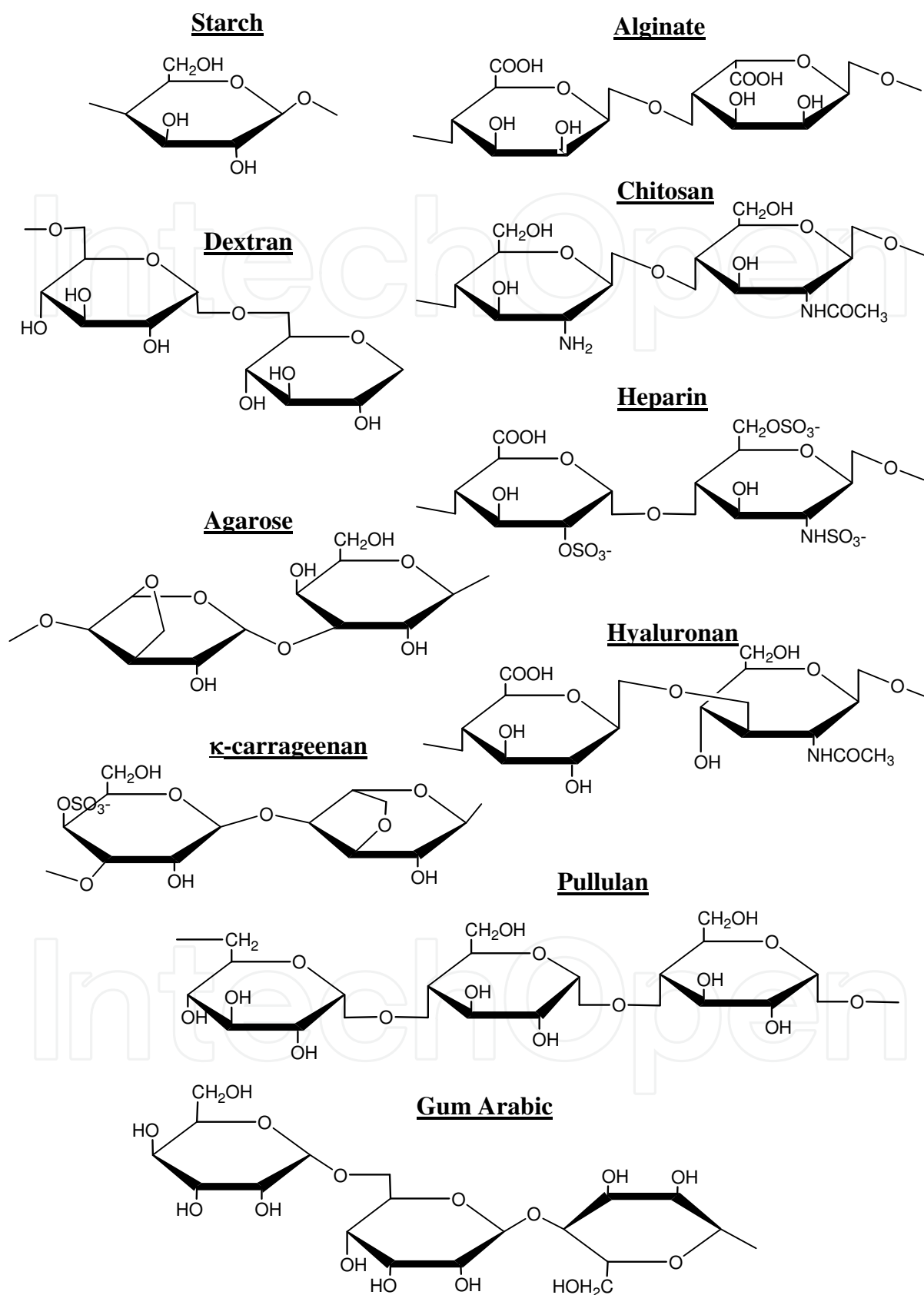


Fig. 1. Chemical structures of polysaccharides commonly employed in the preparation of nanocomposites for biomedical applications.

which further augments the range of applications. For example, hydrogels of  $\kappa$ -carrageenan containing magnetic nanoparticles were chemically modified by carboxymethylation of the polymer chains and further coupled to an antibody envisaging applications as targeted local nanodelivery system (Daniel-da-Silva et al., 2009).

### iii. Sensitivity to external stimuli

Overall polysaccharides form gels that respond to physiological changes in temperature and pH or even to mechanical stress. This property has been explored in the preparation of composite systems for remotely triggered applications including bioadhesives and drug delivery, amongst others. Chitosan for instance, due to its excellent biocompatibility and mechanical properties (it forms films with high mechanical strength and elasticity) is a very attractive polysaccharide for applications such as wound dressing and tissue repair. Very recently it was found out that nanocomposite films of chitosan with gold nanorods can bound to biological tissues by activation of the embedded nanoparticles with a near-infrared (NIR) laser device (Matteini et al., 2010). This outcome represents an opportunity for the development of remotely activated bioadhesives useful for applications where suturing may be hardly feasible such as for poorly accessible or delicate body regions. Alginate (Brulé et al., 2011) and chitosan (Hu et al., 2007) were used in the preparation of magnetic composite hydrogels for magnetically triggered drug release. The application of a high-frequency magnetic field caused a local increase of the temperature of the embedded magnetic nanoparticles that induced structural changes in the polysaccharide matrix, thus leading to a controlled and enhanced release of an encapsulated drug.

## 3. Inorganic nanoparticles

This section summarizes relevant properties of inorganic nanoparticles (magnetic, metal and luminescent nanoparticles) employed as dispersed phases in the preparation of functional bionanocomposites.

### 3.1 Magnetic nanoparticles

Iron oxide nanoparticles are by far the most extensively investigated magnetic nanoparticles for biomedical (*in vivo* and *in vitro*) applications due to their particular magnetic properties and low toxicity. Most commonly are magnetite ( $\text{Fe}_3\text{O}_4$ ) and maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ), the latter results from the topotactic oxidation of magnetite, and both phases exhibit the inverse spinel crystal structure. Other magnetic nanoparticles include metal alloy nanoparticles (e.g. FePt, FeCo, and CoPt<sub>3</sub>) (Behrens et al., 2006; Gu et al., 2003; Martins et al., 2007) and metallic nanoparticles (e.g. Co and Ni) (D. Guo et al., 2008; Zeisberger et al 2007). However at the present stage these nanoparticles are limited to *in vitro* applications due to toxicological concerns.

Unlike bulk magnetite (a ferrimagnetic material composed by multiple magnetic domains and that exhibits a permanent magnetization in the absence of a magnetic field)  $\text{Fe}_3\text{O}_4$  nanoparticles smaller than *ca.* 30 nm contain a single magnetic domain and exhibit superparamagnetic behavior (Fig. 2a). The magnetization curve of superparamagnetic nanoparticles does not exhibit hysteresis loop (Fig. 2b) which means that in the absence of an external magnetic field these particles have zero magnetization and less tendency to agglomerate. This is a key feature for some bio-applications as the magnetic properties and the particles bio-distribution depends strongly on the aggregation of the nanoparticles. Another important feature of superparamagnetic nanoparticles for Nanomedicine is their

ability to dissipate heat when exposed to an external ac field (magnetic hyperthermia) a property that is currently being explored for the treatment of cancer. More detailed description of the physical phenomena subjacent to bio-applications of iron oxide nanoparticles can be found elsewhere (Daniel-da-Silva et al., 2011; Laurent et al., 2008).

The biomedical and biotechnological applications of magnetic nanoparticles and their composites include magnetic separation, medical imaging, drug delivery and cancer hyperthermia (Dias et al., 2011; Laurent et al., 2008; Tartaj, 2011) and will be described in section 5 of this chapter. The properties required for the magnetic nanoparticles differ according to the application envisaged and are strongly dependent on the particle size and shape. Thus, a number of synthetic strategies have been developed for the synthesis of magnetic nanoparticles with uniform morphology, narrow size distribution and tailored properties, as extensively reviewed elsewhere (Dave & Gao, 2009; Jeong et al., 2007; Laurent et al., 2008; Lu et al., 2007).

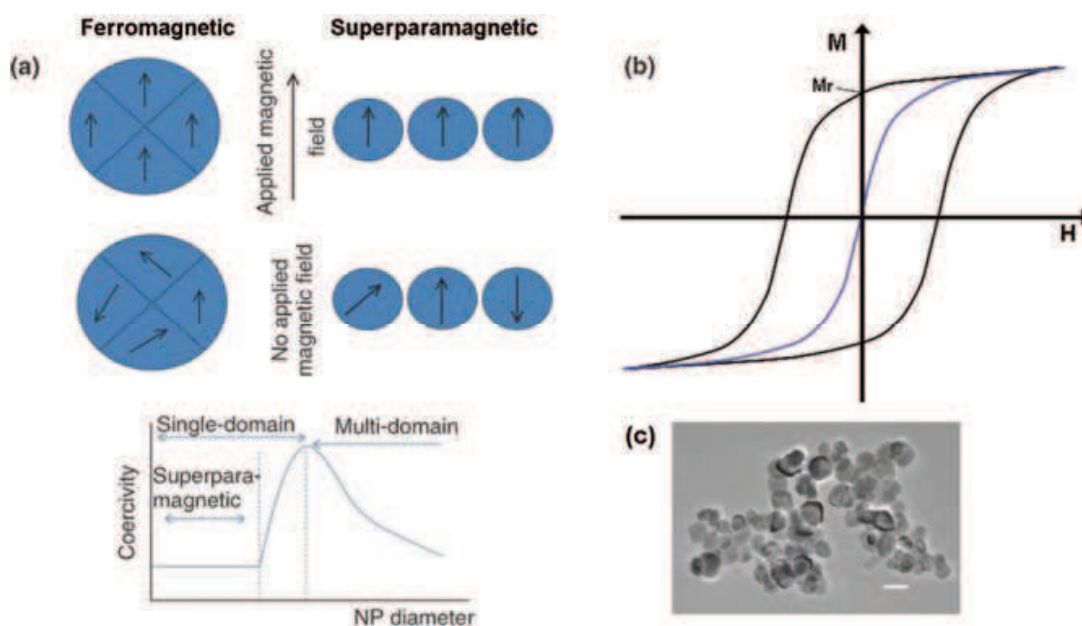


Fig. 2. (a) Under a magnetic field, the magnetic moment of the domains of a ferromagnetic particle and single-domain superparamagnetic particles are aligned. After removal of the magnetic field, ferromagnetic particles maintain a net magnetization (adapted and reproduced from Dave & Gao, 2009, with permission of John Wiley & Sons, Inc., Copyright 2009, John Wiley & Sons, Inc.). (b) Typical magnetization curves of ferromagnetic (black line) and superparamagnetic (blue line) particles. Superparamagnetic nanoparticles show no remanent magnetization ( $M_r$ ). (c) TEM image of magnetic  $\text{Fe}_3\text{O}_4$  nanoparticles prepared by co-precipitation method (scale bar 100nm).

### 3.2 Metal nanoparticles

Silver nanoparticles and composites have been extensively studied for biotechnological and biomedical applications (e.g. wound dressing, water treatment) mostly due to the well-known antimicrobial activity of silver (Pradeep & Anshup, 2009; Rai et al., 2009). In addition, silver nanoparticles exhibit a size and shape-dependent surface plasmon resonance band (Cobley et al., 2009) that is sensitive to the surrounding conditions, a property that is being explored for applications as biosensors (Fan et al., 2010; Le Guével et al., 2009). Silver



nanoparticles also find application in analytical tools such as surface enhanced Raman scattering (SERS) and metal enhanced fluorescence (Nair & Laurencin, 2007; X. S. Shen et al 2009).

Typically Ag nanoparticles are prepared by chemical methods that involve the reduction of silver ions in the presence of sodium borohydride (Nair & Laurencin, 2007) or citric acid, among others. Further chemical treatments can be employed to modify the surface of the nanoparticles in order to promote colloidal stability and/or make the particles compatible with specific environments. Although these methods are simple and effective, the presence of residual amounts of the reducing (or stabilizers) agents may raise toxicological and environmental concerns, limiting the application of these nanoparticles. In this context, some polysaccharides with reducing action are being currently investigated for the development of more friendly strategies of synthesis and surface modification of metal nanoparticles (V. K. Sharma et al., 2009), as detailed in section 4 of this chapter.

Colloidal gold has been used as a therapeutic since remote times, for example it is reported that Paracelsus (15th century) used to prescribe a purple Au colloid, known as *Aurum Potable*, to rejuvenate, as was believed, the human body (Pradeep et al., 2009). The recent interest in Au nanoparticles for biomedical applications relies mostly on their tunable and environment sensitive optical properties. Gold nanospheres exhibit an absorption band (surface plasmon resonance (SPR) band) that is sensitive to the composition, size, shape, inter-particle distance and environment of the nanoparticles (V. Sharma et al., 2009). The sensitivity of the SPR band is in the basis of the application of gold nanoparticles for biological labeling, imaging, sensing and diagnostic (Boisselier & Astruc, 2009; Sperling et al., 2008). When gold nanoparticles absorb light at the wavelength of the SPR band, the dissipation of the energy originates a local increase of the temperature, an effect that is being explored in several applications, including photothermally triggered drug release (Timko et al., 2010) and cancer hyperthermia (Jain et al., 2007). In addition gold nanoparticles have anti-angiogenic properties (i.e. they inhibit the formation and growth of new blood vessels from existing ones) and their application as anti-angiogenic agents in the treatment of cancer is under investigation (Bhattacharya & Mukherjee, 2008).

The most common synthetic method of gold nanoparticles involves the reduction of Au(III) to Au(0), usually starting from  $\text{HAuCl}_4$  complexes and using citrate or borohydride as reducing agent (Daniel & Astruc, 2004). Making use of the strong affinity of sulfur donor ligands to gold, capping agents such as alkanethiols are frequently employed to modify the Au nanoparticles' surfaces. Besides spherical nanoparticles, it is possible to vary the size and shape of gold nanoparticles using appropriate synthetic techniques (Busbee et al., 2003; Grzelczak et al., 2008; V. Sharma et al., 2009). The control of the morphology of gold nanoparticles is an important feature because the surface plasmon resonance (SPR) band is shape dependent. For important therapeutic applications it is convenient to shift the maximum of the SPR band into the biological near-infrared (NIR) window (650-1100 nm) where the absorption and scattering of body tissues is minimal and therefore the penetration into living tissues is much deeper than that of visible light. The shift of the plasmon band to NIR region can be achieved with gold nanoshells or by increasing the morphological anisotropy of NPs as in the case of gold nanorods (Fig. 3).

### 3.3 Luminescent inorganic nanoparticles

A variety of photoluminescent inorganic nanoparticles have been investigated for several bio-applications including as optical biomarkers and biosensors (Burns et al., 2006; Jorge et

al. 2007). In this context, nanoparticles of semiconductors (quantum dots: QDs), nanosized lanthanide compounds and doped amorphous particles, namely of  $\text{SiO}_2$ , are of special relevance. Luminescent nanoparticles appear as an alternative to conventional organic dyes in bioanalysis by photoluminescence (Fig. 4), as the latter have limitations, such as a narrow range of absorption wavelengths, broad emission bands and reduced photostability. However, all these systems have advantages and limitations, relative to each other, depending on the context of application. In fact a number of fluorophores of distinct chemical nature, including a variety of surface functionalized QDs, are already available commercially for biolabeling.

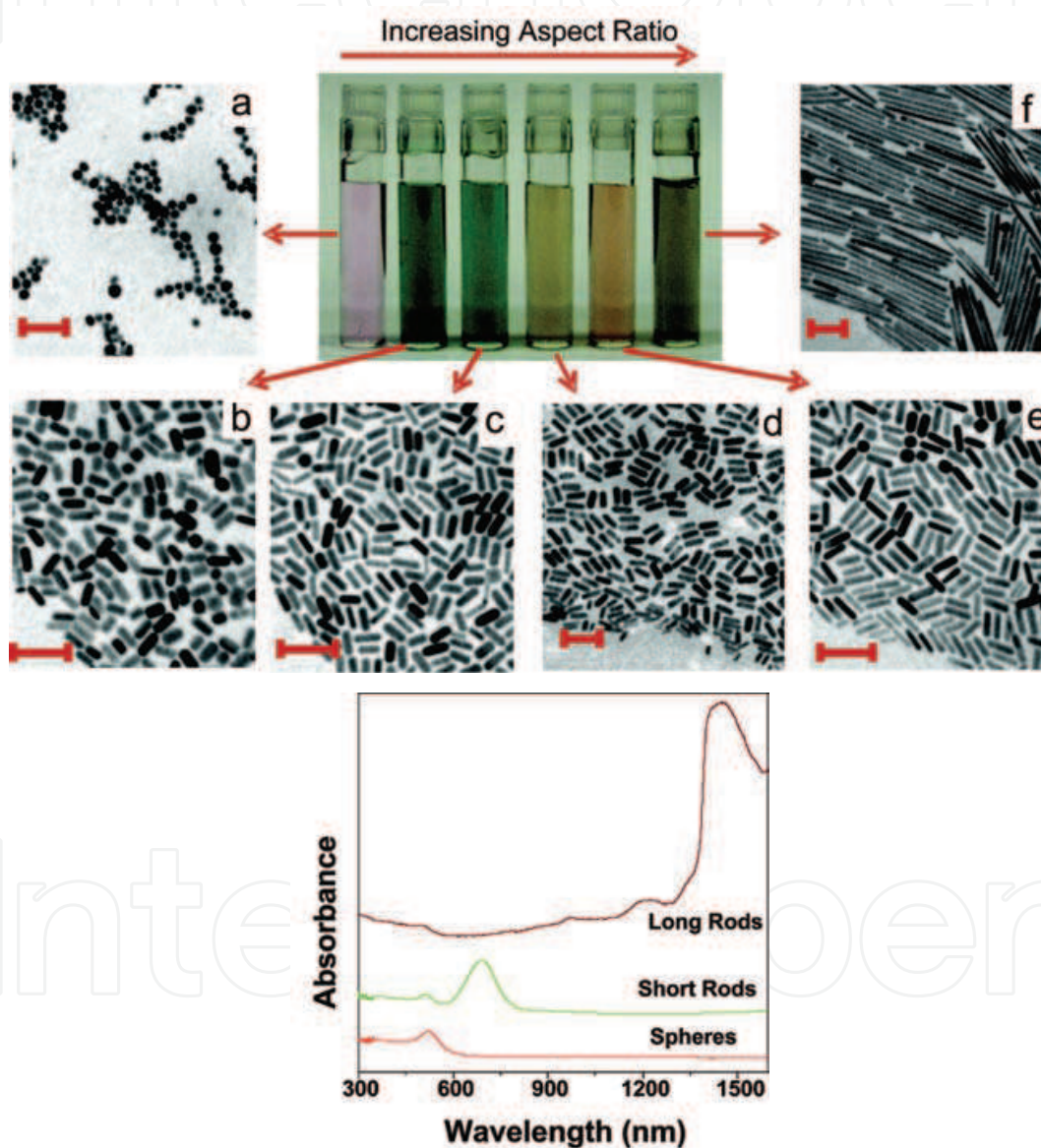


Fig. 3. Top: Photographs of aqueous solutions of gold nanorods with variable aspect ratio and corresponding TEM images (scale bar 100 nm). Aspect ratio varies from 1.3 to 5 for short rods (TEMs a-e) and 20 (TEM f) for long rods. Bottom: Optical spectra of gold spherical nanoparticles (8 nm size), short and long rods (aspect ratio of 3 and 20 respectively). Reprinted adapted with permission from (Murphy et al., 2008). Copyright 2008 American Chemical Society.



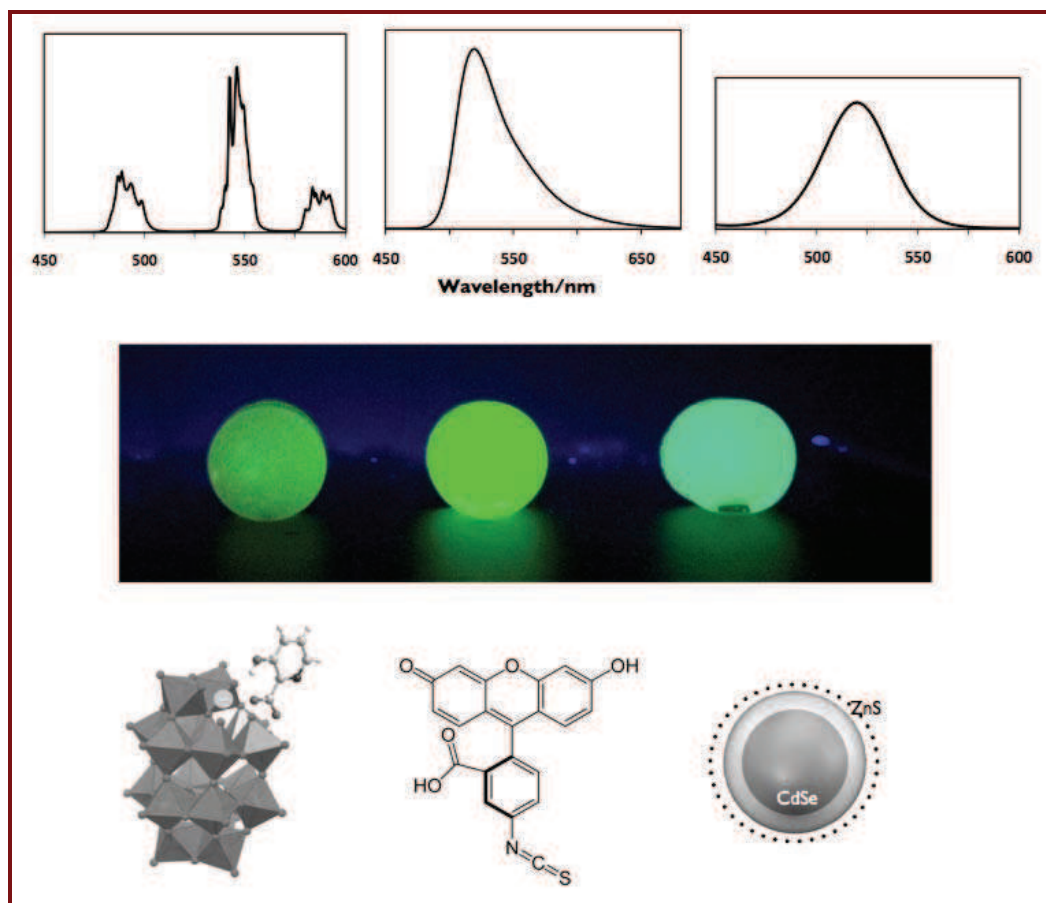


Fig. 4. Upper panel, left to right: Photoluminescence emission spectra (intensity in a.u.) for: i)  $K_{11}[Tb_2(\alpha-P_2W_{17}O_{61})(picOH)_7] \cdot 20H_2O$  polyoxometalate powders (excitation at 320 nm) showing the emission bands due to the intra-f transitions of the lanthanide; ii) fluorescein isothiocyanate (ethanolic solution), an organic fluorophore commonly used in flow cytometry (excitation at 350 nm); iii) Organically capped quantum dots of CdSe overlaid by ZnS ( $d_{core} \sim 2.8$  nm, toluene solution), showing the corresponding excitonic emission band. The middle panel shows photographs of UV light irradiated (325 nm) *k*-carrageenan gels containing the fluorophores that are schematically represented in the bottom panel.

Quantum dots are nanosized particles of semiconductors that exhibit quantum size effects due to three dimensional confinement of the charge carriers (Steigerwald & Brus, 1990). As a consequence, the electronic structure of the semiconductor develops from bands of energy into discrete energy levels as the particle size decreases and approaches the molecular dimensions, increasing the band gap of the semiconductor. Noteworthy, the particle size dependent absorption and emission of light observed for a number of materials have been exploited in several applications with great emphasis in nanobiotechnology. Quantum dots of CdSe and InP (typical dimensions 1.5-6 nm) have been of special interest as fluorescent biolabels because their size dependent and bright emission can be precisely tuned across the visible spectrum or, by using narrow band gap materials such as PbS or PbSe, light emission can be extended to NIR. These materials are prepared as colloidal core-shell nanoparticles whose cores (e.g. CdSe, InP) have the surfaces coated with shells of a wide band gap semiconductor, normally ZnS (Dabbousi et al., 1997). An outer layer of organic ligands confers colloidal stability to these particulate systems and also allows surface exchange

reactions for specific purposes such as biofunctionalized tags. In comparison to conventional dyes, QDs are remarkable stable against photobleaching and because they absorb in a wider wavelength region, distinct sized QDs can be excited simultaneously to originate emission bands that depend on the particles size. This interesting feature allows multicolor optical coding using QDs as biotags and in biotracking procedures for several clinical applications. However, toxicity concerns associated to QDs limit their use in a number of applications.

Luminescence of lanthanide ions, in particular for those in the centre of the series, is an iconic feature that has developed intense research in their compounds. The fluorescence observed in these materials, for example when excited in the UV region, arises from  $f \rightarrow f$  transitions that occur in the lanthanide ion, whose chemical environment can vary from coordinating ligands in solution to solid networks (Granadeiro et al., 2009). Efficient emission requires that non-radiate mechanisms in the material are less relevant as compared to the lanthanide emission. The luminescence observed in these compounds, namely of Eu(III) and Tb(III), prompted the development of a number of photoactive devices, which include some appliances of general use such as fluorescent tubes and color monitors. Luminescent nanoparticles of lanthanide compounds can be also useful fluorophores in clinical applications that benefit from long fluorescence lifetimes. Additionally, these systems exhibit sharp emission bands strongly shifted from the excitation line wavelength (large Stokes shifts).

Encapsulation of fluorescent NPs serve multipurposes and can be performed using diverse matrices. Silica encapsulation and polymer encapsulation have been extensively used. Silica encapsulation normally involves the growth of  $\text{SiO}_2$  shells, very often following the hydrolysis of tetraethylortosilicate precursor, in the presence of the above mentioned fluorophores. The literature offers a number of examples of nanoparticles comprising amorphous silica encapsulating fluorophores, these include organic dyes (Ow et al., 2005), lanthanide complexes (Granadeiro et al., 2010; Soares-Santos et al., 2003), gold clusters (Guével et al., 2011) and quantum dots (Darbandi et al., 2005), among other luminescent systems (Burns et al., 2006). Silica coating of fluorophores provides a large surface area for which a number of functionalization procedures that are well known in chemistry can be directly applied. In this way, versatile chemical strategies for silica derivatization can be adapted according to the envisaged bioapplication. Additionally, photobleaching of the fluorophore can be limited by the protective silica shells which is of special relevance for bioanalysis in physiological medium. Earlier reports on the adsorption of organic dyes at silica surfaces point to other possibilities among the immense field of silica nanocomposites (G. Wu et al., 1997).

As it happens with a silica coating, several fluorophores can be encapsulated in a variety of polymers though in these cases, and depending on the type of polymer, biocompatibility issues need to be considered. Synthetic polymers have been investigated aiming to produce fluorescent nanocomposite particles that form the basis to produce multifunctional systems (e.g. fluorescent and magnetic). Hydrophobic colloidal nanoparticles have been frequently used as fillers for *in situ* polymerization in miniemulsions that depending on the synthetic route led to nanocomposites as stable aqueous emulsions (Esteves et al., 2005) or homogeneous spin-coated films (Esteves et al., 2007). A number of polymers have been investigated in this context. For example, polyacrylates and derived co-polymers were used to produce fluorescent nanocomposite particles with great interest for cancer imaging and targeting (X. Gao et al., 2004).

The development of bionanocomposites comprising a natural polymer matrix incorporating inorganic fluorophores has been less exploited. Examples include the synthesis of chitosan beads incorporating CdSe/ZnS QDs that have been previously surface modified with 3-mercaptopropionic acid; the free carboxylic groups of this acid were then cross-linked to the amino groups of chitosan forming a composite with 11.8% quantum yield (Nie et al., 2006). Biodegradable nanocomposites comprising QDs in poly(D,L- lactide-co-glycolide) nanospheres have been investigated as fluorophores with improved efficiency for intracellular delivery, which remains a strong limitation on the use of naked QDs for cell labeling and imaging of cytoplasmic targets (Kim et al., 2008). Multifunctional polysaccharide based microspheres have been prepared using a fluorescent/magnetic poly(styrene-maleic anhydride) composite (0.15-0.7  $\mu\text{m}$ ) that could be conjugated via surface anhydride groups to heparin. The composite contained an Eu(III) phthalate complex as the fluorophore and nanosized magnetite as the magnetic driver (Qiu et al., 2005). The development of multifunctional nanocomposite particles is currently an active research field that calls for a variety of chemical strategies that includes the design of innovative nanocomposites (Corr et al., 2008).

#### 4. Preparative chemical strategies for polysaccharide based nanocomposites

Herein we will draw our attention on the synthetic approaches for the production of bionanocomposites comprising a matrix of a polysaccharide and inorganic nanoparticles as dispersed phases. Overall the strategies for the preparation of polysaccharide based nanocomposites include the encapsulation of the preformed inorganic nanoparticles in the biopolymer (*ex situ*) or the *in situ* synthesis of the nanoparticles in the presence of the biopolymers. The synthesis *in situ* allows a more intimate dispersion of the nanoparticles within the polymer matrix. However the control over size and shape of nanoparticles synthesized in the presence of polymers still remains a challenge. *In situ* synthesized nanoparticles are generally size polydispersed which may limit the application of the composites since most of the properties of the inorganic nanoparticles are size and shape dependent (section 3). To overcome these limitations, the biopolymer encapsulation of preformed nanoparticles is an interesting alternative.

Polysaccharide nanocomposites can be in the form of macroscopic networks ("bulk nanocomposites") or confined to smaller dimensions in the micron and submicron range. Due to their reduced dimensions, nanoparticulate systems may offer unique advantages for biomedical applications such as cellular internalization. In this section, we will briefly describe relevant preparative strategies to obtain polysaccharide composite nanoparticles with controlled size and narrow size distribution.

##### 4.1 Bulk nanocomposites

*Ex situ* strategies for the preparation of functional polysaccharide nanocomposites consist generally in the encapsulation of preformed inorganic nanoparticles by the biopolymer. Due to the hydrophilic nature of polysaccharides, firstly the nanoparticles are dispersed in water and then, the encapsulation can be performed by the homogeneous mixing of the nanoparticles hydrosol with an aqueous solution of the biopolymer. This route has been extensively used for the preparation of functional nanocomposites of chitosan (Liu & Huang, 2010; Matteini et al., 2010), alginate (Brulé et al., 2011; Marsich et al., 2011), dextran

(Hong et al., 2009) and gum arabic (Banerjee & Chen, 2007) amongst other polymers, containing dispersed inorganic phases, such as magnetic (e.g. iron oxides) and optical active (e.g. gold) nanoparticles. The development of bionanocomposites using this strategy relies, as expected, on the ability to produce nanoparticles with the required functionality (optical, magnetic or biological) and with the required chemical moieties at their surfaces. This aspect is not only relevant to enable chemical compatibility between the composite components but can be crucial to guarantee the aimed performance of the material.

*In situ* strategies for the preparation of the polysaccharide nanocomposites described here consist on the synthesis of the inorganic nanofillers in the presence of the polysaccharide. In aqueous solutions, most of the polysaccharides, due to their specific functional groups (Table 1), have the ability to interact with positive metal ions via electron rich oxygen atoms. In some of the cases, metal ions act as crosslinkers of the polysaccharide chains and promote the formation of a hydrogel network. For example, carrageenans form gels in the presence of monovalent and divalent cations due to the formation of a double helical configuration and helix aggregation (Stephen, 1995). The guluronic acid units of the polysaccharide alginate can pack forming a network with cavities simulating “egg box” in the presence of divalent cations (Braccini & Perez, 2001). The polymer network can be used as a template for the growth of diverse nanostructures, including magnetic and metal nanoparticles. Each cavity of the network is used for the nucleation of the nanoparticles and acts as a constrained environment that limits the growth of the *in situ* generated particles. The functional groups of the biopolymer will define the affinity towards specific metallic ions and may determine the morphology and the chemical properties of the resulting inorganic phase.

#### 4.1.1 Magnetic nanoparticles

Amongst the several experimental routes developed for the synthesis of magnetic iron oxide nanoparticles (Dave & Gao, 2009; Jeong et al., 2007; Laurent et al., 2008; Lu et al., 2007), some require organic solvents and high temperature, conditions which are incompatible with the hydrophilic nature and thermal properties of most of natural polysaccharides. Thus, the polysaccharide-assisted growth of magnetic iron oxide nanoparticles has been mostly performed using chemical routes that require mild conditions such as the co-precipitation process. This method consists basically in the co-precipitation of a stoichiometric mixture of ferrous and ferric salts in aqueous media under basic conditions and in the absence of oxygen. It is a simple method that yields large amount of nanoparticles, although it does not allow for a fine control over the particle size.

Carrageenan was successfully employed as a colloidal stabilizer in the synthesis of superparamagnetic  $\text{Fe}_3\text{O}_4$  nanoparticles via the co-precipitation method (Daniel-da-Silva et al., 2007; Jones et al., 2000). Besides preventing the spontaneous agglomeration of the nanoparticles, carrageenan induced the formation of smaller particles, when compared to conventional co-precipitation synthesis and allowed to control the chemical stability of the  $\text{Fe}_3\text{O}_4$  towards oxidation, by careful choice of carrageenan type and concentration (Daniel-da-Silva et al., 2007). This is an important outcome since maghemite, the product that results in this case from the oxidation of magnetite, has lower saturation magnetization than magnetite.

Magnetic iron oxide nanoparticles have been also synthesized in the presence of other polysaccharides such as starch (D. K. Kim et al., 2003), alginate (Morales et al., 2008; Naik et al., 2005), dextran (Dou et al., 2008) and chitosan (Hernandez et al., 2009), using the co-precipitation method. The presence of starch molecules limited the size of the  $\text{Fe}_3\text{O}_4$



nanoparticles to 6 nm and the agglomeration of the coated nanoparticles was controlled upon the cleavage of the glycosidic bonds of the polymer, which allowed preparing magnetic composite particles with average size smaller than commercially available dextran-coated magnetic nanoparticles. The starch coated  $\text{Fe}_3\text{O}_4$  nanoparticles were biocompatible and tested for *in vivo* monitoring of the brain of rats using MRI (D. K. Kim et al., 2003). The formation of  $\text{Fe}_3\text{O}_4$  nanoparticles within preformed dextran hydrogel beads (Dou et al., 2008) resulted in superparamagnetic composite particles with magnetization saturation values comparable to those of  $\text{Fe}_3\text{O}_4$  nanoparticles prepared via typical coprecipitation routes, which renders these materials interesting for applications in the biomedical field. The formation of magnetite nanoparticles within chitosan using the coprecipitation route was found to be dependent on the concentration of this polysaccharide (Hernandez et al., 2009). Above a chitosan content of 3 wt%, a non magnetic iron hydroxide was formed instead of magnetite. The slow diffusion of OH-species through the viscous polymer medium was pointed out as a possible explanation for the observed effect.

#### 4.1.2 Metal nanoparticles

Silver and gold nanoparticles are usually synthesized following chemical routes that involve the reduction of metal ions in the presence of a stabilizing agent to prevent the aggregation of the nanoparticles. Polysaccharides, due to their ability to coordinate to metal ions can act as stabilizing agents. The polymer-metal ion complex can then be reduced under mild conditions, resulting in the formation of particles with smaller size and narrower size distribution than those obtained in the absence of polymer. Once the reduction occurred, the polysaccharide chains impair the aggregation of the nanoparticles. Chitosan (Božanić et al., 2010; Travan et al., 2009), starch (Raveendran et al., 2006), gum arabic (Gils et al., 2010) and alginate (Jaouen et al., 2010) are some examples of polysaccharides that were reported as stabilizing agents for the synthesis of metal nanoparticles.

In addition to their ability to complex metal ions, polysaccharides may also exhibit reducing properties and thus can play the role of reducing and stabilizing agent in the synthesis of metal nanoparticles. This dual function of the polysaccharide can be an advantage in the clean synthesis of metal nanoparticles since it avoids the incorporation of interfering and, eventually harmful, chemicals that limit the use of metal composites for bio-applications. Following this strategy, Au and Ag nanoparticles were successfully prepared using chitosan (Huang & Yang, 2004; Laudenslager et al., 2008), heparin (Y. Guo & Yan, 2008; Huang & Yang, 2004; Kemp et al., 2009b) and hyaluronan (Kemp et al., 2009b).

Gold and silver nanoparticles prepared using carboxymethyl chitosan (CMC) exhibited similar particle size distribution than those prepared using chitosan (Laudenslager et al., 2008) despite CMC has a higher reported metal chelation capacity than chitosan. However the ability of the two polymers to stabilize the particles varied and particles prepared using CMC evidenced more aggregation. The reduced cross-linking ability of CMC compared to chitosan was pointed out as a possible explanation for the reported differences.

The use of heparin as reducing/stabilizing agent was found to control the size distribution of gold nanoparticles, and the particle size decreased with increasing heparin concentration (Y. Guo & Yan, 2008). Silver and gold nanoparticles prepared using hyaluronan showed wider particle size distribution than those prepared in heparin (Kemp et al., 2009b). The resulting heparin based metal nanocomposites retained its anticoagulant activity and anti-inflammatory properties as confirmed by *in vitro* and *in vivo* tests (Kemp et al., 2009a). The use of the polysaccharide heparin as simultaneously reducing and stabilizing agent avoided the need of intermediate purification steps to remove any traces of harmful reagents.



## 4.2 Composite nanoparticles

The use of polysaccharide nanoparticles has its roots in drug delivery research as nanocarriers for local targeted drug delivery applications (Liu et al., 2008). The application of polysaccharides nanoparticles was further extended to other biomedical contexts such as medical imaging and hyperthermia. This can be achieved upon the inclusion of inorganic nanoparticles that confer new functionalities to the resulting composite nanoparticles.

Polysaccharide composite nanoparticles from tens to hundreds of nanometers in diameter can be prepared using emulsification techniques. For example, chitosan nanoparticles carrying CdTe quantum dots and magnetite nanoparticles, with an average size of 100 nm, were prepared using water-in-oil (w/o) microemulsions (Li et al., 2007). The composite particles showed superparamagnetic and fluorescent properties favourable for multimodal imaging and were tested for pH controlled drug release for *in vitro* conditions. Thermo-sensitive magnetite/ $\kappa$ -carrageenan nanogels with an average size of 50 nm and narrow size distribution were also prepared using w/o microemulsions (Fig. 5) (Daniel-da-Silva et al., 2009). The magnetic nanogels exhibited superparamagnetic properties at room temperature and have shown thermo-sensitive behavior in the temperature range 37-45°C which is necessary for thermal controlled delivery applications. The nanogels were successfully conjugated to an antibody via a carbodiimide mediated reaction, and after surface carboxymethylation, showing the potential of these nanocomposites for local targeting drug delivery.

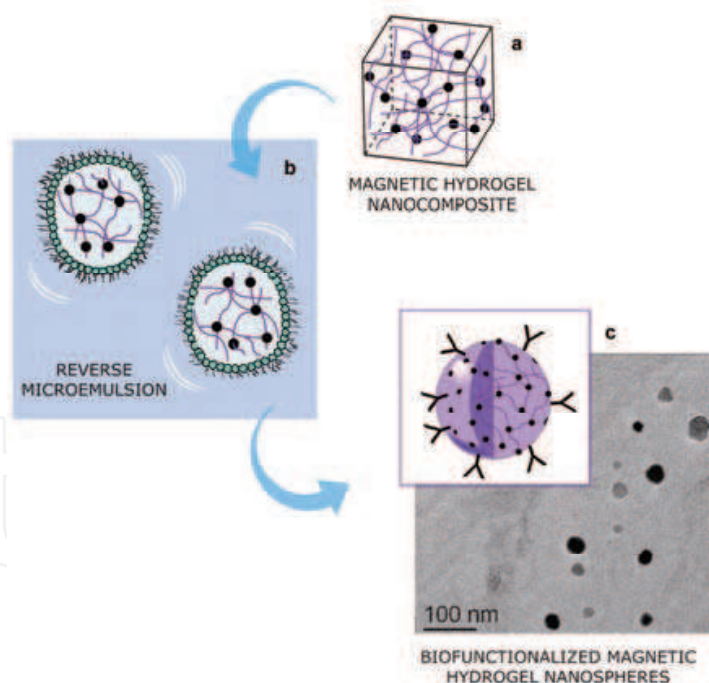


Fig. 5. Scheme of the synthetic steps involved in the preparation and bioconjugation of magnetic  $\kappa$ -carrageenan composite hydrogel nanoparticles. Magnetic bulk nanocomposite is first prepared (a) and then confined to nano-reactors using microemulsions (b). Composite nanoparticles are conjugated to an antibody after surface carboxymethylation (c). TEM image of composite nanoparticles shows an inner darker core that indicates the presence of magnetic nanoparticles (Reprinted adapted with permission from (Daniel-da-Silva et al., 2009). Copyright 2009 IOP Publishing Ltd).

5. Bio-applications of polysaccharide based nanocomposites

The most representative bio-applications of polysaccharide based nanocomposites and some illustrative examples of bionanocomposite systems from literature are listed in table 2.

Applications		Bionanocomposites	References
Biotechnological	Bioseparation	Fe <sub>3</sub> O <sub>4</sub> / dextran Fe <sub>3</sub> O <sub>4</sub> / gum arabic Fe <sub>3</sub> O <sub>4</sub> / chitosan	(Heebøll-Nielsen et al., 2004) (Batalha et al., 2010) (Liu et al., 2009)
	Biolabeling & Biosensing	Au, Ag/ chitosan Au, Ag/ alginate QDs/ chitosan	(Santos Jr. et al., 2004; Wei et al., 2009) (Lim et al., 2010; Saha et al., 2009) (Tan & Zhang, 2005)
	Antimicrobial	Ag/ chitosan Ag/ hyaluronan	(Potara et al., 2011; Travan et al., 2009) (Kemp et al., 2009a)
Biomedical	Clinical Imaging	Fe <sub>3</sub> O <sub>4</sub> / dextran	(Chachuat & Bonnemain, 1995; Corot et al., 2006)
	Drug Delivery	Fe <sub>3</sub> O <sub>4</sub> / alginate Fe <sub>3</sub> O <sub>4</sub> / chitosan Fe <sub>3</sub> O <sub>4</sub> / heparin	(Brulé et al., 2011) (Hu et al., 2007) (Khurshid et al., 2009)
	Cancer Hyperthermia	Fe <sub>3</sub> O <sub>4</sub> / chitosan Fe <sub>3</sub> O <sub>4</sub> / pullulan acetate	(Zhao et al., 2009) (Gao et al., 2010)

Table 2. Examples of bio-applications of polysaccharide based nanocomposites.

5.1 Biotechnological applications

5.1.1 Bioseparation

Several polysaccharides have been explored for the surface coating or encapsulation of magnetic nanoparticles envisaging applications in bioseparation processes (Dias et al., 2011). The polysaccharides protect the inner magnetic core and provide functional moieties for further modification with other specific ligands. For example dextran coated magnetic nanoparticles functionalized with different ligands were tested for the separation of lectins from legume extracts, using high-gradient magnetic separation technique (Heebøll-Nielsen et al., 2004). Gum Arabic coated iron oxide nanoparticles were functionalized with triazine ligands with specificity towards antibodies and successfully used for the antibody immobilization (Batalha et al., 2010).

Due to the intrinsic ability of the polysaccharides to coordinate to metal ions, polysaccharide based magnetic nanocomposites have been explored in magnetically assisted water purification (Ambashta & Sillanpää, 2010; Liu et al., 2009). Polysaccharides offer the advantage of being low-cost biosorbents capable of removing trace levels of heavy metal ions. Their combination with magnetic nanoparticles delivers materials with large surface and that can be conveniently separated from wastewater by magnetic separation.

### 5.1.2 Biolabeling and biosensing

Luminescent inorganic nanoparticles such as quantum dots are promising for the *ex vivo* detection of biomarkers (Jaiswal & Simon, 2003; Wu & Bruchez, 2003). However their use in *in vivo* conditions raises toxicological concerns. The encapsulation of quantum dots in polysaccharides such as alginate, chitosan and dextran sulfate was found to prevent the leakage of the nanocrystals from the microcapsules (Gaponik et al., 2003). More recently it has been confirmed by *in vitro* cell tests that the use of chitosan for the encapsulation of CdSe/ZnS quantum dots improves considerably the biocompatibility of these nanoparticles (Tan & Zhang, 2005), rendering materials with potential application in *in vivo* optical biodetection.

SERS spectroscopy is a well-established analytical technique that permits detection of molecular adsorbates at the surface of silver and gold surfaces. With the development of new instrumental tools and materials platforms, this vibrational spectroscopic method appeared as a powerful method for single molecule detection. It is gaining attention as bioanalytical tool as it can be used to extract information from complex samples such as biological fluids, living tissues and cells (Abalde-Cela et al., 2010). Gold and silver chitosan and alginate nanocomposites were successfully used as substrates in trace analysis using SERS (Saha et al., 2009; Santos Jr. et al., 2004; Wei et al., 2009). Also cellulose of vegetable and bacterial origin were investigated as matrices to fabricate composites containing Ag nanoparticles that allowed the development of handy and sensitive SERS substrates (Marques et al., 2008). The use of the polysaccharides confers flexibility and portability to the substrate which is essential for extending the applications of this technique.

Hydrogel composites containing nanometals have been also reported for the construction of optical biosensors. For example, gold chitosan and alginate nanocomposites have shown good results as glucose sensing platforms (Du et al., 2007; Lim et al., 2010). Alginate hydrogel has shown to provide a protective medium for the bioreceptor glucose oxidase (Lim et al., 2010).

### 5.1.3 Antimicrobials

The use of silver and silver salts in commercial products for antimicrobial purposes is relatively widespread. However studies from the last decade have revealed that silver nanoparticles have improved antibacterial properties than bulk silver and that even nanomolar concentrations of silver nanoparticles can be more effective than micromolar concentrations of silver ions (Kong & Jang, 2008), thus leading to an increased interest on materials comprising nano-silver. In this context, a number of polysaccharide based silver nanocomposites have been reported (Liu & Huang, 2010; Kemp et al., 2009a; Travan et al., 2009; Vimala et al., 2010). These materials exhibit antimicrobial activity and may be considered for applications in wound dressings and for water purification purposes. In this context bacterial cellulose offers several possibilities and the antimicrobial activity of the derived silver nanocomposites has been reported (Pinto et al., 2009). The polysaccharide plays an important role in these materials as stabilizer, preventing the aggregation of the nanoparticles. Moreover, polysaccharide nanocomposites may show a synergistic antibacterial activity and exhibit higher antibacterial activity than their separated components as recently observed for chitosan-silver nanocomposites (Potara et al., 2011). Also, despite the growing use of silver nanomaterials, the potential implications for human health and the environment are not completely clarified (Marambio-Jones & Hoek, 2010).

The immobilization of silver nanoparticles in polysaccharide gels might be a promising strategy to respond to these toxicity concerns, by preventing the cell internalization of silver nanoparticles without affecting the antimicrobial activity (Travan et al., 2009).

## **5.2 Biomedical applications**

### **5.2.1 Clinical imaging**

Magnetic iron oxides are currently used as contrast agents in magnetic resonance imaging (MRI) (Corot et al., 2006). The commercially available compositions include dextran and carboxymethyldextran coated iron oxide nanoparticles (Endorem® and Resovist®, respectively) and other polysaccharide based compositions are under evaluation (Shen et al., 2003). The polysaccharide coating increases the blood circulation time and improves the efficiency of the detection of cancer cells. Moreover, the functional groups of the polysaccharide allow for further bioconjugation for specific cell targeting.

### **5.2.2 Drug delivery**

Magnetic polysaccharide nanocomposites are useful nanocarriers for magnetically driven drug delivery. The polysaccharide matrix stabilizes the encapsulated bioactive molecules, preventing their loss or degradation during the delivery, while the magnetism of the carrier makes possible to target drug to specific sites upon the application of a magnetic field, minimizing any side-effects. Alginate, heparin and gum arabic are some examples of polysaccharides that were investigated in the preparation of magnetic composites for drug delivery (Dias et al., 2011).

Polysaccharides that form networks sensitive to environment changes (e.g. temperature, mechanical stress) when combined with inorganic nanophases with magnetic and/or optical functionalities afford composite materials of interest for remotely triggered drug delivery (Timko et al., 2010). The local increase of the temperature promoted by magnetic nanoparticles, if activated by an alternating magnetic field, or by gold nanoparticles, if activated by adequate optical radiation, originates structural changes in a thermosensitive polysaccharide and the modulated release of an encapsulated drug. This triggering approach has been investigated in alginate (Brulé et al., 2011) and chitosan (Hu et al., 2007) magnetic nanocomposites and in gold nanocomposites comprising thermosensitive synthetic polymers (Shiotani et al., 2007). The advantage of this strategy is that it can provide on demand drug release profiles, according to the needs of each patient.

### **5.2.3 Cancer hyperthermia**

Hyperthermia is a type of cancer treatment in which specific areas of the body undergo a local increase of the temperature to damage and kill cancer cells, or to make cancer cells more sensitive to the effects of other therapies (radiotherapy or chemotherapy). The local increase of the temperature can be achieved exposing magnetic nanoparticles to an alternating magnetic field (magnetic hyperthermia). Alternatively thermal ablation can be obtained exposing gold nanoparticles or nanoshells to near-infrared light. (Cherukuri et al., 2010; Sakamoto et al., 2010).

The challenge of hyperthermia is heating locally, at the tumor site, without affecting the surrounding healthy tissue (Cherukuri et al., 2010). If the nanoparticles possess a specific targeting agent the efficiency of the treatment can be increased. The encapsulation of the nanoparticles using polysaccharides appears as a useful strategy for the biofunctionalization



of the nanoparticles with adequate targeting moieties. Chitosan (Zhao et al., 2009) and pullulan acetate (Gao et al., 2010) coated magnetic nanoparticles were investigated for magnetic hyperthermia.

## 6. Concluding remarks and future trends

In the last decades increasing attention has been devoted to the combination of inorganic nanoparticles with polysaccharides, to benefit from the advantages of both composite components. A number of formulations of such bionanocomposites exhibit magnetic, optical and antimicrobial functionalities of interest for biotechnological and biomedical applications that have been investigated to the present. The performance of those materials strongly relies on earlier steps of the chain production, which emphasises the relevance of preparative strategies that take in consideration the envisaged applications. Although *ex situ* preparations are still of great interest, namely due to their simplicity in terms of composite preparation, other more elaborate strategies that bring together concepts from materials design and chemical synthesis have proved to add great value in new biofunctional composites. In this respect, it will never be over emphasized that the use of polysaccharides in composite synthesis that mimic natural processes is currently a big challenge but that points to unprecedented consequences in terms of high performance materials fabrication. Additionally, it is an approach that in some aspects may help to overcome limitations on the use of nanocomposites due to toxicological concerns. From the recent attempts to find new methods of early-diagnosis of diseases and more effective therapies a new generation of multifunctional nanostructured materials is emerging. Bionanocomposites specifically designed to incorporate multiple functional nanoparticles are attractive materials for the development of integrated platforms merging functions such as targeting, imaging and therapy in one system. It is expectable that medicine platforms based on multifunctional bionanocomposites will enable better detection of the disease across a number of diagnosis techniques and simultaneous treat and monitoring the response to the therapy.

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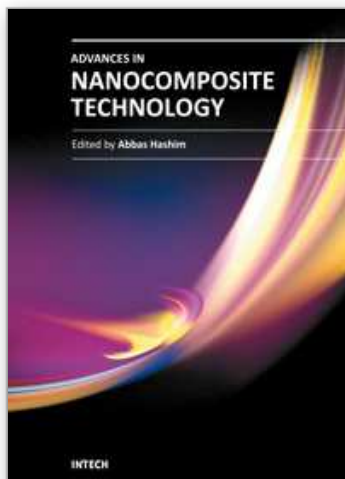


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