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Research Paper

Latex nanoparticles surface modified via the layer-by-layer technique for two drugs loading

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ABSTRACT

The emerging field of bionanotechnology aims at advancing colloidal through the development of multi-functional nanoparticle-based containers for drug delivery systems. The primary focus is to enhance the loading/release of therapeutic agents. Herein, nanocarriers with a synthetic polymer core and multilayers of polysaccharides were elaborated by combining two techniques to load all at once two different drugs. The present strategy is advantageous in comparison with other synthetic routes because at all steps, only water is used as a solvent and not organic one. Poly(vinyl acetate) (PVac) latex particles, loaded with tocopherol acetate (vitamin E) through hydrophobic interaction, were prepared via miniemulsion polymerization of vinyl acetate in the presence of sodium dodecyl sulfate (SDS) as an emulsifier. This latter leads to a negatively charged surface of latex nanoparticles and was advantageously used as a core to be coated with natural polyelectrolytes (alginate and chitosan) via the layer-by-layer deposition. Entrapment of amoxicillin (an antibiotic) into the multilayer shell was then induced through a simple diffusion process/electrostatic interaction. The loaded nanocarriers covered by $(chitosan/alginate)_n$- chitosan layers showed high zeta-potential value (about +35 mV provided by zeta potential measurement). Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM) highlighted a spherical shape and a size lower than 200 nm. Finally, we evidence the pH-triggered drugs release (tocopherol acetate and amoxicillin) and the impact of the parameter constituting the multilayer, i.e. (i) number and (ii) crosslinking. Our results demonstrate that the elaborated latex-core polysaccharide-coated nanoparticles are promising as multifunctional nanocarrier.

1. Introduction

Recent years have seen an increase of interest in the development of nanoparticles towards the delivery/loading of drugs [1,2]. In this respect, emergence of advanced synthetic techniques leads to the development of polymeric particles as a popular class of vectors [3,4]. These latter can easily be engineered to facilitate targeting, release, cellular uptake or non-viral nucleic acid delivery [5–7]. Towards this aim, drug and targeting moieties can be covalently grafted to a biodegradable polymer backbone via a biodegradable bond [8]. Polymers drug carriers can even be involved in micellar/aggregated structures [9] or as polymer nanoparticles [10]. Several parameters are well-known to strongly impact on the resulting physico-chemical property as the size, the shape, the surface chemistry and the surface properties of the nanoparticles [11–16].

Nowadays, the nanomedicine research focuses on the enhancement of new efficient nanocarriers, a colloidal character being a key prerequisite for this purpose. In this regard, core/shell nanoparticles prepared via layer-by-layer (LbL) deposition could be considered. This technique is classically based on the gentle assembly between positively and negatively charged polymers on colloids [17] allowing nanometer-scale control [18] and is then very promising in the biomedical area [19,20]. For instance, this method could be employed for modification of nanoparticles such as silica [21,22], gold nanoparticles/quantum dots [23,24], and even latex particles [25].

Latex particles are generally directly obtained from preformed commercially available polymers by using solvent extraction/evaporation, nanoprecipitation or emulsification − diffusion processes [26,27]. Among all heterogeneous polymerization processes, the miniemulsion polymerization is a versatile one-step technique to encapsulate hydrophobic compounds in vinyl polymer nanoparticles [28]. The miniemulsion polymerization is a multi-skill tool to obtain in one-step latex nanoparticles [29]. This process lies in the elaboration of a submicronic emulsion of vinyl monomer droplets in which the radical polymerization is initiated with a hydrosoluble or organosoluble initiator [30–32]. Each droplet acts as an isolated micro-reactor. To prevent the Ostwald

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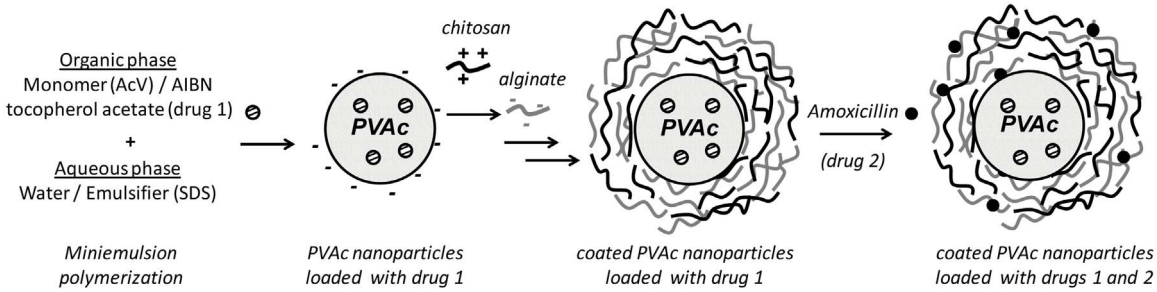

Fig. 1. Schematic illustration of the elaboration pathway for the preparation of latex nanoparticles involving the assembly of chitosan/alginate multilayers.

ripening mechanism, the presence of an additional compound, called "the hydrophobe" [33–36], is required in the organic phase. We can take advantage from this latter to load a hydrophobic compound of interest (i.e. a drug), opening a new route for biomedical or cosmetic applications. For instance, this challenge was successfully achieved by using Miglyol (a biocompatible hydrophobic oil, useful in cosmetic domain) instead of hexadecane [28]. Furthermore, vinyl polymers are an interesting class of polymers if taking into account both the varying chemical nature of the monomers and the possibility to get statistical copolymers and then various physico − chemical properties.

Polysaccharides have also gained, in recent years, a considerable attention as one of the most promising polymer for biomedical applications [37]. They are useful materials in designing novel drug delivery devices since they are of natural origin, biodegradable/biocompatible, non-toxic and low production cost [38]. As regard on the polysaccharides gains, materials based on such natural macromolecules can be employed to enhance drugs and macromolecules' lifetime in the body [39]. Among them, alginate and chitosan have received great attention in the pharmaceutical field due to their intrinsic biological properties [40]. Alginate is a hydrophilic macromolecule composed of D-mannuronic (M) and L-glucoronic acid (G) residues linked by 1, 4-glycosidic linkages. Chitosan is randomly composed of β (1–4)-linked D-glucosamine (deacetylated unit) and *N*-acetyl-D- glucosamine (acetylated unit) [41,42]. Combining polysaccharides with synthetic polymers provide advanced materials with adequate biochemical and mechanical properties [43] leading to smart carriers or multi-functional delivery systems [44,45].

Herein, a newly-designed nanocarrier is proposed and allows the loading of two drugs all at one. This system is obtained by combining template-mediated approach and self-assembly processes. The great interest of the present system consists in the loading of drugs through different types of interactions, i.e. hyphobic and electrostatics ones. We focused on tocopherol acetate (vitamin E) and amoxicillin (antibiotic) as payload drugs to illustrate the ability of the elaborated particles to carry and deliver two active agents all at once. Vitamin E corresponds to a generic name for four tocopherols (α-, *β*-, γ- and *δ*-tocopherol) and four tocotrienols (α-, *β*-, γ − and *δ*-tocotrienol). Among these, the α-tocopherol has the highest biological activity [46]. Amoxicillin is a betalactam antibiotic extensively employed to treat infections [47]. Poly(vinyl acetate) (PVac) was selected as the core-forming particles since this inert material is suitable for a diverse range of biological applications, i.e. presents biocompatibility and biodegradability properties [48,49]. The elaboration of SDS-stabilised PVac latex particles was performed through the well-known miniemulsion polymerization process. We have taken advantage of the need of a hydrophobic agent to load the tocopherol acetate (hydrophobic interaction) and from sulfate groups of SDS to access to a negatively charged surface. This latter will enable the sorption of the selected pair of polyelectrolytes, namely chitosan (polycation) and alginate (polyanion) resulting in multilayer formation. The amoxicillin was then loaded via electrostatic interaction/diffusion process in the multilayer.

Morphology of the as-obtained cargo was investigated by Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). The number of layers and the chitosan crosslinking capsule-dependent drug effects were investigated through the determination of drug entrapment efficiency and release.

2. Experimental section

2.1. Materials

The following chemicals were purchased and used as received: chitosan (chi, Sigma-Aldrich), alginate (alg, Sigma-Aldrich), acetic acid (Alfa aesar), sodium acetate (Normapur), glutaraldehyde (25% aq, Alfa aesar), amoxicillin trihydrate (Sigma-Aldrich), vinyl acetate (VAc,Alfa aesar), tocopherol acetate (Sigma-Aldrich), 2,2′-azobis (2-methylpropionitrile (AIBN, Sigma-Aldrich) and sodium dodecyl sulfate (SDS, Alfa aesar). Water was purified with a Milli-Q reagent system (Millipore).

2.2. Poly(vinyl acetate) nanoparticles with a negatively charged surface, loaded with a hydrophobic drug (tocopherol acetate, drug 1) (Fig. 1)

Miniemulsions of the vinyl acetate monomer were prepared according to a classical recipe [28]. The organic (10 wt%) and aqueous phase (90 wt%) components were mixed in separate vessels at room temperature and purged with nitrogen for 10 min. The organic phase is composed by vinyl acetate monomer (0.26 mol), tocopherol acetate (5.3×10^{-3} mol) and AIBN (2.61×10^{-3} mol). The aqueous phase consists in an aqueous solution containing the SDS emulsifier at 4 g L^{-1} (relative to the aqueous volume of the aqueous phase). The dispersion of the organic phase into the aqueous phase is induced through stirring with a magnetic stirrer over 10 min at room temperature. Then, the mixture is poured into an ultrasonic disperser for 180 s in order to obtain submicronic size (apparatus equipped with a 25 mm shaft working at 750W and 75% amplitude). During this step, the system was cooled in an ice-water bath to limit heat-up. Polymerizations were carried out under nitrogen atmosphere in a glass reactor under stirring over 4 h at 70 °C. Excess of reactants (emulsifier, monomer….) were removed by dialysis process. The monomer conversion is determined from solid content, after drying samples in an oven at 120 °C under vacuum.

2.3. Formation of PVac core-polyelectrolyte complexes shell hybrid nanoparticles (Fig. 1)

The surface modification of the negatively charged PVac nanoparticles (NPs) was achieved by a direct LbL saturation method, meaning neither washing nor purification steps. This method is widely described in the literature [50,51]. The possibility to directly incorporate the required amount of polyelectrolyte is suggested to efficiently coat all nanoparticles surface, avoiding/limiting the presence of free polyelectrolyte in the aqueous phase. The saturation concentration has to be empirically defined over zeta potential measurements. The negatively charge poly(vinyl acetate) nanoparticles templates were first covered with a polycation (chitosan). The polyanion (alginate) was then deposited in a similar way. This procedure describes the assembly of