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Release of small hydrophilic molecules from polyelectrolyte capsules: Effect of the wall thickness

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ABSTRACT

Polymer nanocapsules assembled on cationic liposomes have been built through the layer-by-layer (LbL) technique. Chitosan and alginate, two biocompatible polyelectrolytes, were used to cover the template, where the Rhodamine B was previously loaded. The multishell formed with the alternate deposition of the polyelectrolytes, according to the principles of the LbL assembly, was supposed to change the permeability of the capsule wall. The thickness of the multishell was seen increasing with the number of layers deposited through the observations with the Transmission Electron Microscope. The permeability of the capsules was studied through Rhodamine B release assays. Nanocapsules with seven layers of polyelectrolytes released the dye slowly compared to the capsules with three or five layers. The Ritger–Peppas model was applied to investigate the release mechanisms and a non-Fickian transport behavior was detected regardless of the number of layers. Values of diffusion coefficients of Rhodamine B through the capsule wall were also calculated.

1. Introduction

In the last few years, the development of multi-compartmental tools is providing delivery devices especially relevant in the fields of medicine and biology [1–7]. A great number of them is designed by taking advantage of the self-assembly properties of the constituents [8–14]. Among the emerging materials the polymer capsules are drawing great attention. They are considered as challenging devices because of their unique structural properties. Polymer capsules are structures having mainly spherical shape and are produced by coating templates made of different materials using different strategies [15–17]. One of the approaches generally recognized as effective in the assembly of polymer capsules is the layer-by-layer technique (LbL) [18,19]. This technique is based on the alternate deposition of oppositely charged polyelectrolytes onto templates of different size and composition [20–23]. The main driving force for LbL assembly is the electrostatic interaction among templates and polyelectrolytes. The electrostatic attraction, in fact, rules the polyelectrolyte association and, the repulsion between assemblies with the same surface charge is essential to the stability of the assembled micro- or nano-sized containers. The alternate deposition of polyelectrolytes generates a polymer wall surrounding the template, which can be removed thus leaving a spherical volume, generally filled with water, which remains separated from the external environment thanks to the presence of the polymer multishell. According to the type of polyelectrolytes assembled and to the assembly method, new materials are formed having different properties from those offered by the individual polymers. The matrix formed by the polymer assembly is a network that controls the permeability of the capsule wall. Permeability can be modified varying the number of assembled layers or the number of interactions between the polymers, for instance, by changing the pH or the ionic strength [24–28].

Kinetics studies on molecular release from these devices represent a relevant aspect to evaluate the utility of such systems as drug delivery devices in biological and biomedical applications. Drug encapsulation is, therefore, another key point. Polymeric capsules can be filled with drugs before the layer deposition or after the core removal. In some cases the LbL procedure is applied to micro- or nano-dispersions of drugs [24,29].

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The interest in the use of compartmentalized systems as drug delivery devices is due to the opportunity they offer of enhancing the therapeutic efficacy and of reducing the dose of drug administered and, consequently, the side effects of a drug therapy [22,30–32].

The production of containers loaded with drugs is mainly directed towards the realization of drug delivery systems having dimensions in the nanometer range because nano-sized systems should remain in the circulation for longer times compared to the micro-sized particles, which are subject to clearance via the lymphatic system [33]. Therefore, the biological activity of nano-systems would be of a higher extent [34].

Very recently, Łukasiewicz and Szczepanowicz [35] demonstrated that nanocapsules assembled on a liquid oil core stabilized by AOT (dioctyl sodium sulfosuccinate) and covered with polyelectrolyte shells of PLL (poly-L-lysine) and PGA (poly-L-glutamate) are quite safe for use as delivery vehicles. Parekh et al. [36] produced nanocapsules made of heparin and a block-copolymer of poly-l-lysine and polyethylene glycol, containing camptothecin in the core. In order to prevent the clearance of nanocapsules in the circulation, the outer surface of the nanocapsules was modified with polyethylene glycol of 5 kDa or 20 kDa molecular weight. These authors demonstrated that these LbL-coated capsules are effective in the preservation of the lactone form of camptothecin, which is the active form of the drug. Thomas et al. [37] investigated the release of doxorubicin encapsulated in hollow biocompatible nanocapsules made of chitosan/heparin assembled onto SiO_2 nanoparticles. The doxorubicin encapsulated was successfully internalized in MCF-7 cell lines and in vivo experiments on BALB/c mice it was revealed that the drug circulation time was increased compared with free doxorubicin. Yan et al. [38] demonstrated the loading and sustained release of 5-fluorouracil, a hydrophobic molecule, in microcapsules made of poly (L-glutamate)/chitosan assembled onto melamine formaldehyde (MF) templates. The drug was encapsulated into the capsule core after template dissolution.

Among the most used models for quantitative studies of drug release profiles from particles there are the Higuchi model, the Ritger–Peppas model, the Weibull function, and the Hixson–Crowell model. All of them take into consideration the relation between the structure and the function of the device, the release environment, and the possible interactions between the wall of the device and the drug molecules [39,40]. These models describe the transport behavior as strictly related to the Fick's law of diffusion and suggest that the description of solute transport from polymeric matrices can be divided into two categories: Fickian and non-Fickian behavior.

Recently, we proposed a way for producing hollow nanocapsules by covering a liposome core with biocompatible polyelectrolytes, namely chitosan and alginate, via the LbL self-assembly method [25,26] and, moreover, we have demonstrated that these structures can be used as drug reservoirs of hydrophilic molecules with high molecular weight on the basis of release assays from liposome based polymer nanocapsules [41].

In the present study, the investigation is extended to the encapsulation and release from liposome based polymer nanocapsules of a small hydrophilic molecule as a function of the multishell thickness.

2. Materials and methods

2.1. Materials

L-α-phosphatidylcholine (egg yolk lecithin) was purchased from Avanti Polar. Lipids, didodecyldimethylammonium bromide (DDAB), sodium chloride, low molecular weight sodium alginate, low molecular weight chitosan and Triton X-100, Rhodamine B and dialysis tubing cellulose membranes, with a molecular weight cut off at 3.5–5 kDa and at 100 kDa, were purchased from Sigma–Aldrich.

2.2. Preparation of liposome-templated chitosan/alginate nanocapsules

Unilamellar liposomes (80 nm) were prepared by reversed phase evaporation according to the method described by Szoka and Papahadjopoulos [42] with a 6.5:3.5 M mixture of phosphatidylcholine and DDAB. Lipid and surfactant were dispersed in 3 mL of diethyl ether and to this 1 mL of PBS buffer (pH 7.2) containing 0.5 mg/mL of Rhodamine B was added, forming a two-phase system, which was mixed by means of a sonicator tip to form a dispersion of inverted micelles. A rotary evaporator removed the organic solvent, thus, the inverted micelles became an aqueous suspension of liposomes. Finally, additional two milliliters of buffer were added and the suspension was left for further 45 min at the rotary evaporator to remove any trace of solvent. The final lipid concentration was 16 mg mL^{-1} (i.e., 20 mM). The liposomes were then sequentially extruded through 0.1 and 0.05 μm polycarbonate membranes before use. The excess of fluorescent dye was removed through a dialysis membrane (12 h) with a cut-off of 100 kDa against 500 mL of buffer solution (PBS pH 7.2). The procedures of chitosan/alginate deposition onto the surfaces of colloidal particles, as well as lipid core removal, were reported elsewhere [26].

2.3. Transmission Electron Microscopy

TEM high resolution characterization of the samples was carried out placing appropriately diluted drops of each suspension on formvar coated 100 mesh size grids for 5 min. Excess of suspension was adsorbed touching the edge of the grids with filter paper. Finally, the grids were air dried, observed and photographed with a JEOL 100S Transmission Electron Microscope.

2.4. Rhodamine B encapsulation efficiency

The encapsulation efficiency (*EE*%) of Rhodamine B into liposomes and into core–shell capsules was calculated as follows:

$$EE\%\ (\text{liposomes}) = \frac{\text{amount of Rhodamine B entrapped in liposomes}}{\text{amount of Rhodamine B loaded}} \times 100$$

$$EE\%\ (\text{core}-\text{shell}) = \frac{\text{actual amount of Rhodamine B entrapped in core}-\text{shell capsules}}{\text{theoretical amount of Rhodamine B in core}-\text{shell capsules}} \times 100$$

The theoretical concentration of Rhodamine B in core–shell capsules was calculated as the expected concentration of the dye after the dilution of dye entrapped into liposomes after the polyelectrolyte deposition.

2.5. Rhodamine B release

The samples were dialyzed through a membrane with a cut off of 100 kDa to follow the release of Rhodamine B. The bulk dialysis was prepared according to the ionic strength of the sample and with PBS mM at pH 7.2. The samples were left in the bulk to equilibrate for half an hour and in this time window we did not observe any change in Rhodamine B concentration. Subsequently a volume of 100 μl of 11 mM Triton X-100 solution was added to the sample