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Regular Article

Role of poly-beta-amino-esters hydrolysis and electrostatic attraction in gentamicin release from layer-by-layer coatings

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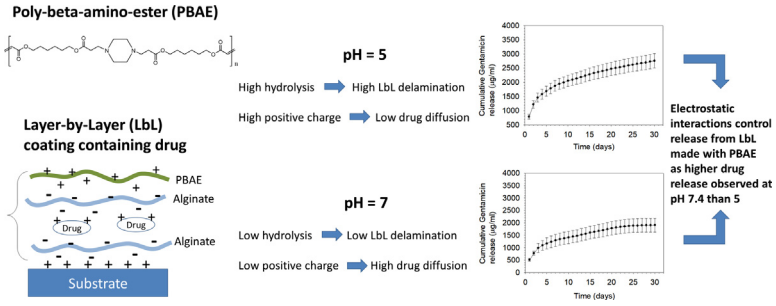
GRAPHICAL ABSTRACT



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ABSTRACT

Layer-by-layer (LbL) deposition is a versatile technique that has been employed in numerous industrial applications i.e. biomaterials, drug delivery and electronics to confer peculiar properties to the system. When LbL is employed for drug delivery, the active molecule is sandwiched between layers of polyelectrolytes and the release is controlled by the diffusion of the drug through the layers and the possible hydrolysis of the coating (delamination).

Poly-beta-amino-esters (PBAEs) are a class of hydrolysable polyelectrolytes that have been widely used in DNA delivery and for LbL on medical devices. Their use allowed the controlled release of antibiotics and other bioactive compounds from the surface of medical devices without cytotoxic effects. The general accepted consensus is that drug released from LbL coating assembled using PBAEs is the results of the polymer hydrolysis; however, no attention has been paid to the role of the electrostatic attraction between PBAE and the other polyelectrolyte utilised in the LbL assembly.

In this work, we prepared LbL coatings on the surface of silica nanoparticles entrapping gentamicin as model drug and demonstrated that the drug release from PBAEs containing LbL coatings is predominantly controlled by the electrostatic attraction between opposite charged electrolytes. The positive charge of PBAE decreased from pH = 5 to pH = 7.4 while alginate negative charges remained unchanged in this pH range while PBAE hydrolysis kinetics was faster, as determined with Gel Permeation Chromatography (GPC), in acidic conditions. When PBAE were employed in the LbL construct higher levels of drug were released at pH = 7.4 than at pH = 5; additionally, replacing PBAE with chitosan (the charge of chitosan is not influenced in this pH range) resulted in comparable gentamicin release kinetics at pH = 5.

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1. Introduction

Layer-by-layer assembly (LbL) is based on the deposition of alternative oppositely charged polyelectrolytes on different substrates; allowing control of the thickness and composition of the coating at nanoscale level in a reproducible manner [3,36],. Moreover, the coating process is simple, low-cost, scalable and does not comprise harsh organic conditions, as it involves mild aqueous solutions. Because of these advantages, LbL has numerous applications in drug delivery [7,11,45,33]. Nanoparticles have been extensively explored and successfully applied as drug carriers for antibiotics and others drugs [6,37],. Among all nano-carriers, silica nanoparticles are commonly preferred as a drug carrier, because of their unique physicochemical properties, biocompatibility and low cost [47,19]. Silica nanoparticles have also large ratio of surface area to mass, small size and ease of structural or functional modification because of silanol-containing surface [10,34],.

Gentamicin is an antibiotic broadly used to prevent infection in implants coatings [17] and orthopaedic bone cement [35]. Gentamicin is a small molecule with five ionisable amino groups that can attach on negatively charged surfaces after protonation in aqueous media enabling the deposition of this molecule in LbL constructs [6,37],. Antibiotic releasing biomaterials are the standard approach for the prevention and treatment of biomedical devices associated infections [34,22,39,1]. However, the development of controlled release drug delivery systems is vital for effective therapeutic treatments [17] as high drug loading and prolonged release kinetics can be achieved through delivery systems [4,12],. This would overcome the current limitations, for example, antibiotic laden bone cement is effective only for about 1 week whereas infections can develop even months after surgery [2].

Beside natural poly-electrolytes such chitosan, alginate and dextran; poly-beta-amino esters (or poly-β-amino esters) (PBAEs), a very well-known class of synthetic polymers obtained from the co-polymerization of diacrylates and amines (Fig. 1) [20], have been extensively used in LbL coating for biomedical applications in virtue of their biocompatibility, positive charge and possible hydrolysis [6]. For example, films made of multiple tetra-layers [PBAE/Poly-anion/Gentamicin/Poly-anion] assembled through LbL have been prepared to sustain gentamicin release for prolonged periods of time [6,48,30]; moreover similar coatings have also been employed to control the release of bone morphogenic protein (BMP) from titanium implants to improve their osseointegration [35,27,29],. Drug release from LbL coatings is the result of two processes: the diffusion of the molecule through the deposited polymeric layers (governed by the nature of the attraction between layers) or the delamination of the coating (dependent on hydrolysis) [30]. In all these studies related to LbL assembled using PBAEs, the drug release was hypothesized to be controlled by the hydrolytic degradation of PBAEs; however the possible role of the electrostatic interactions between the various layers has not been addressed.

In this paper, we aim to elucidate the role of PBAEs hydrolysation and electrostatic attraction between layers in the process of drug release from LbL constructs using gentamicin as a model small molecule drug. LbL coatings containing gentamicin were assembled on silica nanoparticles using chitosan (not hydrolysable) or a model PBAE (hydrolysable). Drug release in buffers of different pH (to modify the electrostatic attraction between polyelectrolytes and kinetics of hydrolysis) was monitored over weeks. Moreover, the kinetic of PBAE hydrolysis in the different buffers was determined using Gel Permeation Chromatography (GPC).

2. Results

2.1. PBAE hydrolysis kinetic (GPC)

At pH = 7, no PBAE hydrolysis was observed for 30 days (Fig. 2); however, at pH = 5 the hydrolysis of PBAE was drastic after 20

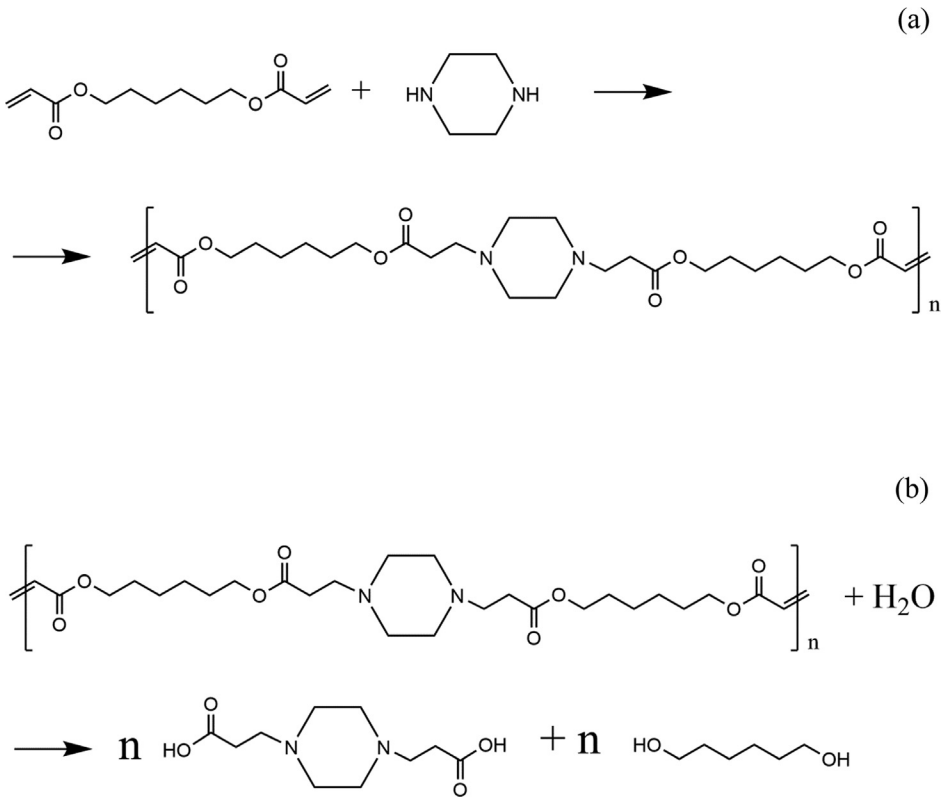

Fig. 1. PBAE synthesis (a) and hydrolysis (b) reaction schemes.