



Electrophoretic deposition of vancomycin loaded halloysite nanotubes-chitosan nanocomposite coatings

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ABSTRACT

The vancomycin loaded halloysite nanotubes (HNTs)/chitosan nanocomposite coating with drug delivery and antibacterial activity was fabricated by electrophoretic deposition (EPD) on titanium substrate. Suspensions of HNTs were prepared in different alcohols containing water, chitosan and acetic acid (AA). The amount of chitosan adsorbed on HNTs decreased with increasing the AA concentration. In contrast to isopropanolic suspensions, the zeta potential of HNTs decreased with increasing the AA content in methanolic and ethanolic ones. Current density increased or remained nearly constant during EPD for all suspensions due to the increased electrolysis of water. Despite of the lowest zeta potential, the coating deposited from isopropanolic suspension with 0.1 vol% of AA had the finest microstructure and the lowest roughness. Coatings were characterized by microstructural (SEM and AFM), thermal (TG/DTA) and mechanical (pull-off adhesion test) analyses. Ethanolic suspension with 1 vol% of AA was selected as the optimum suspension and drug (vancomycin) loaded coating was prepared using it. The coating exhibited desired drug release profile: initial burst release and then long term slow release. The loading of coating with vancomycin increased (about 27%) its antibacterial performance against Gram-positive *Staphylococcus aureus* bacteria.

1. Introduction

Electrophoretic deposition (EPD) is a coating method which has been extensively used to deposit ceramic coatings on metallic substrates. EPD is a two-step process: in the first step charged particles dispersed in an appropriate solvent move toward the oppositely charged electrode under the influence of an applied electric field. In the second step, the charged particles reaching the substrate deposit on it and form a relatively dense particulate layer there [1–4]. EPD has several advantages such as simplicity, need of low cost equipment, depositing coatings with even thickness on substrates with complex geometries, fast processing rate and possibility of controlling the thickness and microstructure of coatings by simple adjustment of EPD parameters like voltage and time [1]. The main drawback of EPD process is the necessity of post sintering step to consolidate the particulate ceramic layer to enhance its mechanical strength and adhesion to the metallic substrate. A high temperature sintering step increases the processing costs and can lead to the cracking of the coatings due to the thermal expansion coefficient mismatch, chemical reaction between coating and substrate, oxidation of metallic substrate as well as its

annealing and consequent reduction in its mechanical strength [5, 6]. The need to sinter is eliminated by the EPD of ceramic-polymer composite coatings [6]. Chitosan is a biopolymer that can be prepared by the alkaline *N*-deacetylation of chitin. Chitosan is a biocompatible, non-toxic, biodegradable, and antibacterial polymer resulting in its extensive applications in biomedical field [7–10]. Variety of chitosan matrix composite coatings containing bioceramic particles like hydroxyapatite, calcium phosphate, bioactive glass and HNTs have been processed by EPD method [11–23]. Halloysite nanotubes (HNTs) are naturally occurring nanoclay with a tubular nanostructure and a chemical formula of $Al_2Si_2O_5(OH)_4 \cdot nH_2O$ ($n = 0$ and 2 for dehydrated and hydrated states respectively) [24–26]. Halloysite nanotubes (HNTs) are biocompatible and most drugs can be loaded into their hollow tubular nanostructure [27–30]. HNTs have also high mechanical strength and modulus so that they can be effectively used as the second phase reinforcement in polymer matrix composites [31, 32]. So bioactive and biocompatible composites with drug delivery capability can be processed by dispersing drug loaded HNTs in biopolymer matrixes like chitosan.

The growth of bacterial biofilms on the surface of orthopedic

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implants is a critical problem that can result in implant failure [33]. A promising method to prevent implants from bacterial infection is its coating with bioactive coating with drug releasing capability [34, 35].

Radda's et al. [35] developed the tetracycline hydrochloride loaded HNTs/bioactive glass/chitosan nanocomposite coatings via EPD in a water/ethanol suspension. They found that the coatings exhibit suitable drug release profile: initial burst release and then slow and sustained prolonged release.

In this work, HNTs-chitosan nanocomposite coatings were electro-phoretically deposited from different alcoholic suspensions at various pHs (varied content of acetic acid). The first novelty of the work is studying the effect of suspensions composition (medium and pH) on the EPD process as well as the characteristics of coatings. The optimum composition of suspension was determined by characterization of coatings via microstructural (SEM and AFM), thermal (TG/DTA) and mechanical (adhesion strength) analysis. Drug (vancomycin) loaded HNTs-chitosan nanocomposite coatings were deposited using the suspension with optimum composition. To the best of our knowledge, this is the first work reporting the fabrication of vancomycin loaded HNTs/chitosan nanocomposite coatings. The drug (vancomycin) release capability of composite coating was investigated in PBS at 37 °C. The antibacterial activity of composite coatings without and with vancomycin loading was also investigated against Gram-positive *Staphylococcus aureus* bacteria.

2. Experimental

2.1. Suspensions preparation

Halloysite nanotubes (HNT, Sigma-Aldrich) and chitosan (MW = 300 kDa, Sigma-Aldrich) with a degree of deacetylation of about 85% were used as the starting powders. The morphology of HNTs was observed by a Field-emission scanning electron microscope (FESEM; TESCAN MIRA 3). To prepare the suspensions, Firstly, 0.5 g/l of chitosan were dissolved by magnetic stirring for 24 h in the mixture of alcohol, acetic acid (AA: 0.1, 0.5, 1 and 5 vol%) and deionized water (methanol: 5 vol%, ethanol: 15 vol% and isopropanol: 20 vol%; these contents were determined in our previous work [15]). Then, HNTs powder (5 g/l) was added into the prepared solutions followed by magnetic stirring and then ultrasonic dispersing for 24 h and 10 min, respectively.

The pH and conductivity of suspensions were measured as a function of AA amount. The zeta potential of HNTs was measured using a Malvern instrument. To measure the zeta potential, the suspensions were diluted according to the method described in Ref [36]. FTIR analysis (SHIMADZU) was performed on the as-purchased HNTs powders and those extracted from different suspensions with 0.1 vol% of AA. The amount of chitosan adsorbed on the surface of HNTs in different suspensions was determined by thermal analysis (TG/DTA; STA 504; Bahr). The samples for FTIR and thermal analysis were prepared by extracting some powders from suspensions by centrifugation followed by washing for three times with deionized water and then drying at 120 °C for 24 h.

2.2. Electrophoretic deposition

The titanium (99.7%) plates with the dimensions of 20 mm × 10 mm × 1 mm were used as the substrates. Only 10 mm × 10 mm of substrates was exposed to EPD and remainder of their surface area insulated using polymeric adhesive tape. The counter electrode was a stainless steel plate with the same dimensions as the substrates. A two electrode cell (distance between electrodes: 1 cm) and a D.C power supply were used for electrophoretic deposition (EPD) experiments. EPD was performed at 30 V for different times. The wet deposits were dried at room temperature for 24 h. The kinetics of deposition was investigated by measuring the weights of substrate before

and after EPD using a high accuracy balance (A & D, gr-200: 0.1 mg). The current density was also recorded using computer connected digital multimeter (Fluke, 289) during EPD from different suspensions.

2.3. Characterization of coatings

The microstructure of coatings deposited at 30 V from different suspensions was observed by scanning electron microscope (SEM). The roughness and topography of coatings was also investigated by atomic force microscope (AFM, Nanosurf Co, model: FlexAFM). The amount of chitosan in the coatings was determined using thermal analysis (TG/DTA) on the powders scratched from the substrates.

The adhesion strength of coatings deposited at 30 V for 4 min from ethanolic suspensions with different concentrations of AA was determined by pull-off test according to ASTM D4541.

The corrosion studies were performed on the same sample as for pull-off in simulated body fluid (SBF) environment. SBF was prepared based on the method described by Kokubo and Takadama [37]. The electrochemical polarization method was used to measure the corrosion rate of samples (potentiostat/galvanostat Autolab 302 N) at 37 °C. Bare and coated substrates, platinum wire mesh and saturated calomel electrode were used as the working, counter and reference electrodes in a corrosion cell, respectively. Potentiodynamic polarization curves were recorded in a potential range of ± 250 mV with respect to open circuit potential (OCP) with scan rate of 1 mV/s.

The bioactivity of coating deposited from ethanolic suspension with 1 vol% of AA was investigated by its immersion in SBF at 37 °C. The ratio of coating surface area to SBF volume was 0.05 cm⁻¹. The sample was taken out from SBF after 3 weeks, rinsed with distilled water, dried at room temperature overnight and its microstructure was observed by SEM.

2.4. Drug loaded coatings

2.4.1. Drug loading

The drug used in this work was vancomycin (Jaber Ebne Hayyan Company, Iran). Drug loading into the HNTs was performed according to the method described by Pan et al. [38]. The optimum ratio of vancomycin: HNTs (2:1) obtained in their work [38] was also used in the present study. Firstly, 0.25 g of HNTs was dispersed in 62.5 ml of deionized water (4 mg/ml) and magnetically stirred for 15 min. Then, 0.5 g of vancomycin (8 mg/ml) was added into the suspension followed by its magnetic stirring and ultrasonic dispersion (bandelin, SONOPULSE HD 3200, 20 kHz) for 10 and 30 min, respectively. The prepared suspension was poured into an erlenmeyer flask. The flask was evacuated using a vacuum pump (internal pressure: 0.85 bar). After 10 min the pump was switched off and the suspension shacked for 5 min and then the pump was turned on again. The drug loaded HNTs were extracted using centrifuging at 4000 rpm for 3 min and washed by deionized water. The extracted powder was dried at 60 °C for 16 h in an oven. FTIR analysis was performed on the drug loaded HNTs powder to prove the drug loading into them. Also TG/DTA analysis was used to determine the approximate amount of drug loaded into the HNTs.

2.4.2. EPD of drug loaded coating

Drug loaded coatings were deposited at 30 V for 4 min from ethanolic suspension of vancomycin loaded HNTs with 1 vol% (optimum amount of AA).

2.4.3. Drug release studies

In vitro release of vancomycin from the drug loaded coating was measured using a UV spectrometer (OPTIZEN 3220) at a wavelength of 280 nm. Drug loaded coating was immersed in a falcon tube containing 8 ml of phosphate buffered saline (PBS, pH: 7.4) at 37 °C. PBS was withdrawn after different periods of time (1, 3, 24, 72, 192 and 288 h) from falcon and analyzed by UV spectrometer. After each time, the

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