ELECTRICALLY CONTROLLED RELEASE OF AMOXICILLIN FROM POLYACRYLAMIDE/POLYANILINE HYDROGELS

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Abstract

In a novel approach, submicro/nanofibers of Polyaniline (PANI) were prepared by chemical polymerization in the presence of L-glutamic acid (AG). Subsequently, PANI structures were loaded with therapeutic doses of amoxicillin. Then, the suspension of drug-loaded polymer was incorporated into Polyacrylamide (PAAm) hydrogel during the formation of the semi-interpenetrating network. The composite hydrogel of PAAm/PANI were stimulated electrically to evaluate the release of the antibiotic.

Introduction

Stimuli-responsive materials are of great interest in the field of biotechnology and biomedicine. Drug delivery systems based on controlled release under an electrical stimulus offer the promise of new treatments, as the iontophoretic transdermal patch, for chronic diseases that require daily injections for precise doses of medication. The composites obtained from the dispersion of particles of an electroconductive polymer in a hydrogel matrix are potential electroactive systems because they can retain the electrical properties attained by the electroconductive polymer and the capacity of adsorption/desorption of large volumes of water of the hydrogel feature. This work presents the preparation of semi-interpenetrating network of polyacrylamide (PAAm) and polyaniline (PANI) and the kinetics of release of amoxicillin, a first choice of broad-spectrum antibiotics, from the composite by electrical stimulus.

Experimental

Synthesis of PANI

PANI was synthesized by a chemical-oxidative polymerization of aniline in the presence of the L-glutamic acid (AG) using ammonium persulfate APS as oxidant. The molar ratio of aniline:AG:APS was 1:0.25:1. The solution was cooled at 5°C in an ice bath under nitrogen atmosphere and it was kept under moderate stirring for 24 h. After reaction, the resulting mixture consisting of dark-green suspension of PANI was rinsed thoroughly with deionized water in a Buchner funnel until the filtrate became neutral. The PANI suspension was reserved for TEM and loading/releasing studies of amoxicillin.

Characterization

The morphology of synthesized PANI was studied by TEM using a JEOL2010F microscope. PANI suspensions were re-dispersed in deionized water through sonication and adequate portion was transferred to copper grids for the analysis.

Loading of amoxicillin

For the loading of amoxicillin, 25 mL of PANI suspension (0.0148 g mL^{-1}) were mixed with 5 mL of an aqueous solution of the drug (0.2 g mL^{-1}). After stirring for 24 h, the resultant mixture was carefully transferred to dialysis tubing (acetate of cellulose, purification capacity M.W. > 12,000). The dialysis tubing was then put into 500 mL of deionized water at room temperature for removing the drug that was not adsorbed on PANI structures. The dialysis solution was periodically replaced with fresh deionized water until the amoxicillin release was below0.1%.

Incorporation of amoxicillin-loaded PANI particles into polyacrylamide hydrogel

An aliquot of suspension of amoxicillin-loaded PANI was mixed by magnetic stirring with 10 mL of an aqueous solution of (AAm)/bisacrylamide (MBAAm) (58:2), subsequently adding an initiator agent (APS) and a reaction catalyst (TEMED). The mixture was placed in a cylindrical mold. Before the gelation point was reached, a thin copper electrode was introduced in the center of the composite hydrogel. The system was kept at room temperature to complete the process of polymerization and gelation. The preparation of the composite hydrogel [PAAm/(PANI-amoxicillin)] is illustrated in Figure 1.

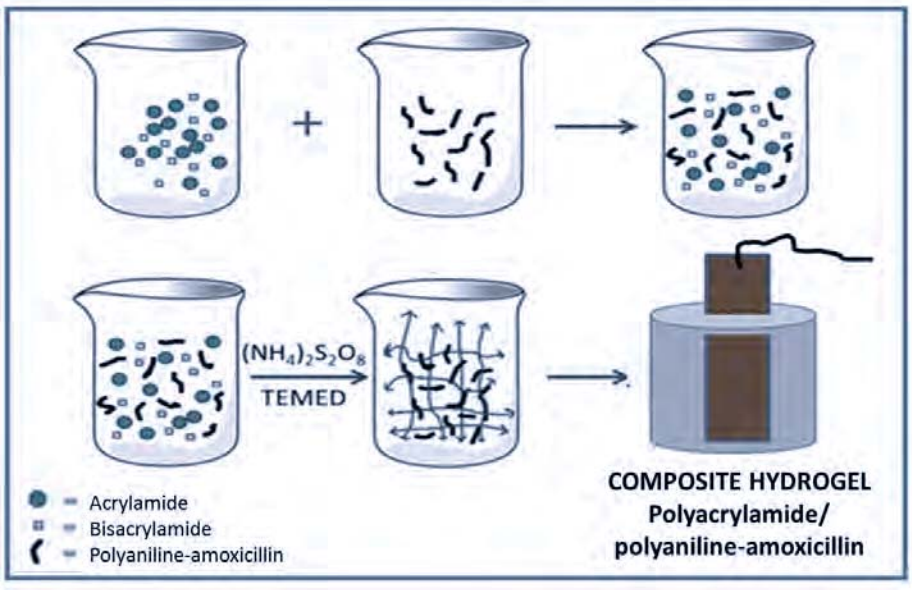

Figure 1. Representation of preparation of semi-interpenetrating network of polyacrylamide (PAAm) and amoxicillin loaded-polyaniline (PANI-amoxicillin).

Controlled release of amoxicillin by electrical stimulus

The study of drug release by electric stimulus was performed at 25 °C, placing the electrode-containing composite hydrogel and uncoated identical electrode in a phosphate-buffered saline solution at pH 7. For the release study, potentials of 5 V (DC power supply Agilent, model E3632A) were applied for 1

minutes between the two electrodes in intervals of 60 minutes. Aliquots of the release medium were taken before and after application of each potential to determine the concentration of delivered drug. The concentration of the amoxicillin was quantified by UV-visible spectroscopy (Perkin-Elmer Lambda 20) at 273 nm, using a calibration curve previously made.

Results and Discussion

Figure 2 showed the TEM images of PANI obtained by the chemical-oxidative polymerization of aniline in the presence of GA. Images revealed fibrous structures with diameters between 100 to 300 nm.

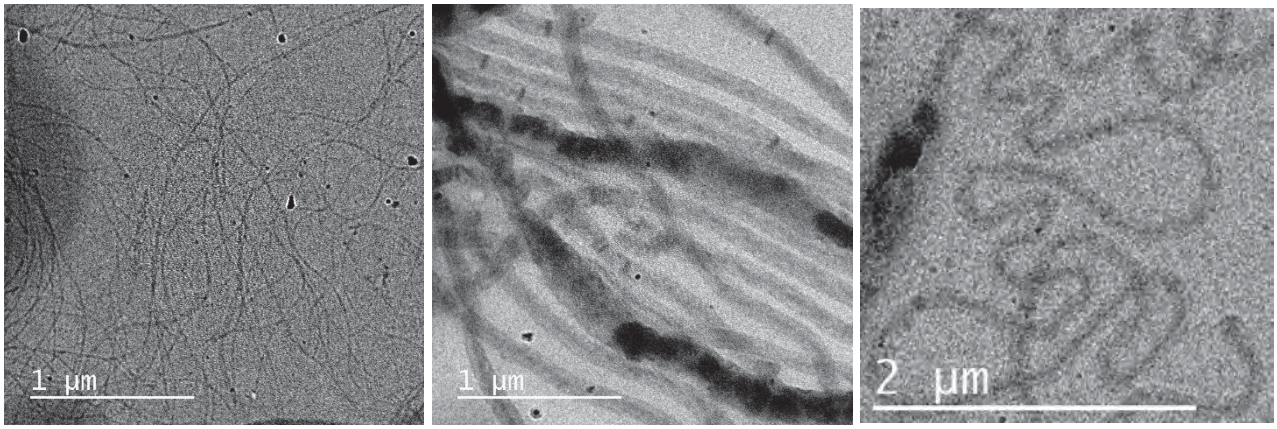

Figure 2. TEM images of nanofibers of PANI synthesized by oxidative polymerization with APS in the presence of GA.

The fiber-like morphology of PANI and its polar nature favors the adsorption of amoxicillin. A therapeutic dose of the drug was added to the suspension of PANI. Un-bonded amoxicillin was removed by dialysis against deionized water and the effective amount of loaded drug was founded to be 80 wt.%, which confirmed the efficiency of the drug adsorption onto PANI particle surface.

The entrapment of amoxicillin-loaded PANI into PAAm network produced composite hydrogels which preserved their geometry once they were removed from molds.

Figure 3 shows the kinetics of amoxicillin release from composite when the hydrogel-coated electrode was connected to the negative pole of the power supply. It was found an immediate increase of amoxicillin release after the first voltage application. Negligible changes in medium concentration were detected until the application of next stimulus. Similar "ON-OFF" release pattern was observed in the subsequent cycles of application and removal of the electrical potential difference.

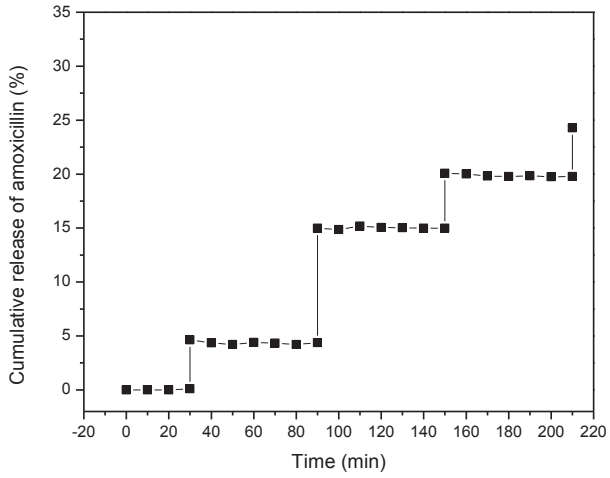

Figure 3. Release of amoxicillin from composite hydrogel of PAAm/PANI under electrical potential application (5V). Composite hydrogel is in cathode.

Figure 4 shows the kinetics of amoxicillin release when the hydrogel-coated electrode was connected to the positive pole of the power supply. After application of the first voltage, the composite hydrogel starts the process of drug release. The amoxicillin concentration increased at a constant rate regardless of subsequent application of electrical stimulus. Furthermore, the cumulative release at the end of the experiment was significant lower than the value obtained when composite hydrogel was placed in the cathode site (Figure 3).

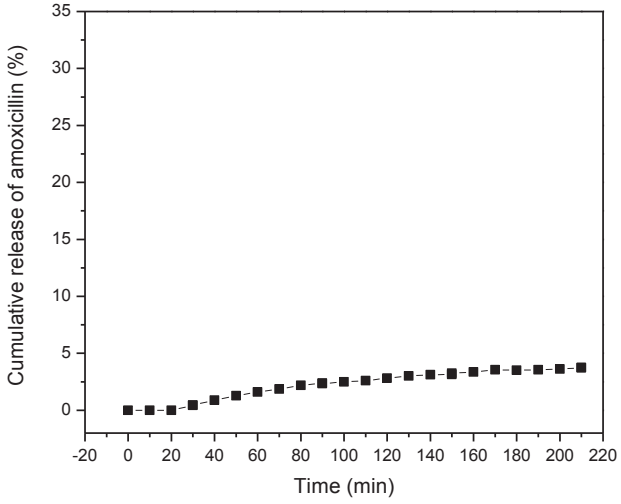

Figure 4. Release of amoxicillin from composite hydrogel of PAAm/PANI under electrical potential application (5V). Composite hydrogel is in anode.

The difference between results of Figures 3 and 4, which were obtained under the same conditions of voltage, time and number of electrical stimulus application can be associated to the change of the overall

net charge within PANI upon reduction or oxidation. The electric-field-driven movement of amoxicillin is discarded because it exists as zero net charge molecule at neutral pH. The electrochemical reduction of PANI caused changes in the charge density of particles, with the synergistically release of noncovalently bonded amoxicillin molecules.

The above results of electrically controlled amoxicillin release, particularly those of Figure 3, showed a cumulative release up to approximately 25% of the drug content, which demonstrated the suitability of the system for drug delivery applications such as iontophoretic systems.

Conclusions

The chemical oxidative synthesis of aniline in the presence of amino acid produced submicro/nanostructures of cylindrical profile. The polyaniline presented fibrillar morphology with diameters in submicro and nanometric scale, which efficiently adsorbed therapeutic doses of amoxicillin. Electroconductive composite hydrogel can be obtained by the entrapment of amoxicillin-loaded polyaniline in polyacrylamide network. The antibiotic molecules can be subsequently released (or sustained) from composite hydrogel in response to application (or removal) of electrical stimulation. This tuning release profile can lead to promising drug delivery applications such as implantable devices and iontophoretic systems.

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