Research Article

Electrical Signal Guided Ibuprofen Release from Electrodeposited Chitosan Hydrogel

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Electrical signal guided drug release from conductive surface provides a simple and straightforward way for advanced drug delivery. In this study, we investigated the ibuprofen release from electrodeposited chitosan hydrogel by applying electrical signals. Specifically, chitosan hydrogel was electrodeposited on titanium plate and used as a matrix for ibuprofen load and release. The release of ibuprofen from the chitosan hydrogel on titanium plate was pH sensitive. By applying a positive or negative electrical potential, the release rate of ibuprofen from the electrodeposited chitosan can be facilely controlled. Thus, coupling chitosan electrodeposition and electrical signal control spurs new possibilities for biopolymeric coating and drug elution on conductive implants.

1. Introduction

External stimuli triggered drug release alters the traditional way of drug delivery and causes substantial attention and interests [1]. Generally, on demand release happens when external stimuli such as light [2], magnetic field [3, 4], heat [5], or pH [6] were applied to the release matrix. Electrical signal is simple to use and has the advantage of easy combination to remote control, and, thus, it has been used in embedded drug delivery chips [7, 8]. Recently, using electrical signal to control the drug release from biopolymers prompts even more opportunities for biomedicine and advanced therapy.

Chitosan is an aminopolysaccharide derived from chitin, which can be found in the shells of crabs and shrimps [9]. Due to its intriguing biocompatibility, biodegradability, and nontoxicity, chitosan has been studied extensively as drug carrier in the field of pharmaceutics and biomedicine [10–16]. Previously, we showed that chitosan could be electrodeposited on electrodes as a hydrogel by enlisting its pH responsive and film forming properties [17, 18]. The electrodeposition process includes the neutralization of chitosan chains by locally generated pH gradient and the sol-gel transition of chitosan *in situ* [19, 20]. Strong noncovalent bonds such as hydrogen bonds and hydrophobic interactions

are responsible for the generation of chitosan hydrogel. Various biocomponents such as proteins [21–23], cells [24, 25], antibiotics [26], and nanocomponents [27] can be entrapped in the porous network of the deposited chitosan hydrogel. The above work demonstrates the capability of electrodeposited chitosan as drug reservoir and the potential for controlled drug release.

In this work, we demonstrate the controlled drug release from electrodeposited chitosan by applying electrical signals. The manipulation of electrical signals causes the on-site generation of chitosan hydrogel and sequentially controlled drug release from the hydrogel. It couples the advantage of chitosan hydrogel as preferable drug carrier and the straightforwardness of electrical signals. The procedure was illustrated in Scheme 1. Firstly, chitosan was electrodeposited on titanium plate by biasing a negative potential to generate a hydrogel. Then the titanium plate with electrodeposited chitosan hydrogel was immersed in ibuprofen solution (pH 10) for drug load. The profile of ibuprofen release from the chitosan hydrogel was adjusted by applying electrical potentials. Electrochemical reactions on the titanium plate caused by the negative or positive potential changed the local pH of the chitosan hydrogel, thus varying the ibuprofen release rate. We believe that this easy and benign drug load
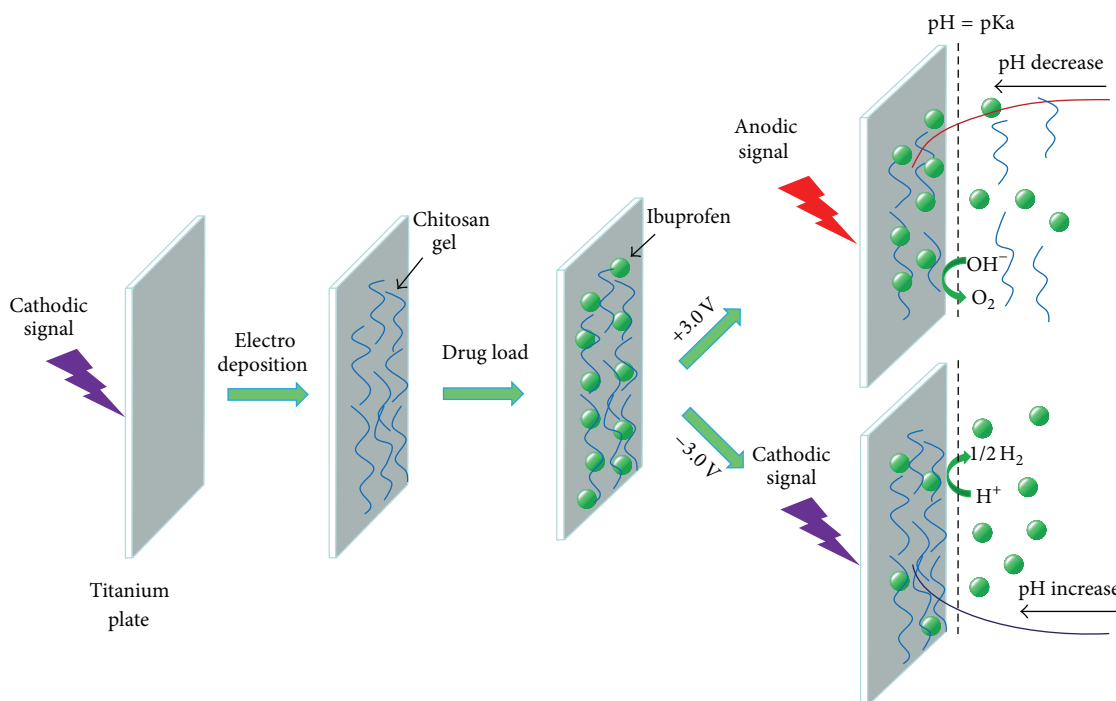
SCHEME 1: Illustration of electrical signals guided ibuprofen release from electrodeposited chitosan hydrogel.

and release procedure should have potential applications in smart drug release from conductive implant or lab on a chip.

2. Experimental

2.1. Materials. Chitosan with medium molecular weight and a degree of deacetylation (DD) of 85% was purchased from Sigma. Ibuprofen was purchased from Shanghai Yuan-Ji Chemical Reagent Co., Ltd. Titanium plates with a thickness of 100 μm were purchased from Baoji Titanium Company, Shanxi. Other chemicals were of analytical grade and were purchased from Sinopharm Chemical Reagent Co. without further purification.

2.2. Electrodeposition of Chitosan Hydrogel on Titanium Plates. Electrodeposition of chitosan hydrogel on titanium plates was carried out by using a conventional two-electrode system as described previously [26]. The working electrode was a titanium plate with a size of $1.5 \times 3.5 \, \text{cm}^2$ and the reference electrode was a platinum wire. All the electrodes were sonicated consecutively before use in the bath of acetone, ethanol, and water for 5 min each. Chitosan solution (1%, wt) was prepared by mixing chitosan flakes with distilled water followed by adjusting the pH to 3 by adding HCl solution. Undissolved part was removed by a 0.45 μm syringe filter unit. The pH of chitosan solution was adjusted to ~5 by using 1 M NaOH. Before deposition, H_2O_2 and NaCl were added to the chitosan solution to a final concentration of 20 mM for H_2O_2 and 43 mM for NaCl [28]. The electrodes were partially dipped into the chitosan solution and the distance between the electrodes and the immersion depth were both kept at

2 cm. Then the electrodes were connected to a power supply (CHI 624D electrochemistry workstation, Shanghai, China) and applied a constant voltage of −3.0 V for 30 min. After that, the titanium plate with electrodeposited chitosan hydrogel was removed from the system and rinsed briefly with distilled water for further usage.

2.3. Drug Load on Titanium Plate. Various concentrations of ibuprofen solution were prepared by dissolving ibuprofen flakes in glycine/sodium hydroxide buffer and the pH was adjusted to 10 by adding 1 M NaOH. The titanium plate with deposited chitosan hydrogel was immersed in ibuprofen solution for 1 h. Then the titanium plate with chitosan hydrogel was removed from the ibuprofen solution and rinsed carefully with distilled water. The amount of ibuprofen loaded in chitosan hydrogel was measured by UV-Vis spectroscopy at 264 nm and determined as the percentage of ibuprofen to the total weight of drug loaded chitosan gel.

2.4. Characterization. The morphology of the chitosan hydrogel with loaded ibuprofen was examined by scanning electron microscopy (SEM). The dried chitosan-ibuprofen coating on the titanium plate was sputtered with gold and the morphology of the film was observed at an acceleration voltage of 5 kV. The infrared spectrum of the chitosan-ibuprofen coating was collected by Fourier transform infrared spectroscopy (FT-IR, Nicolet Corporation 5700) using KBr pellets method. The X-ray diffraction (XRD) patterns were obtained on a SHIMADZU XRD-6000 diffractometer (Cu Kα radiation) with a multipurpose sample holder for nondestructive analysis.
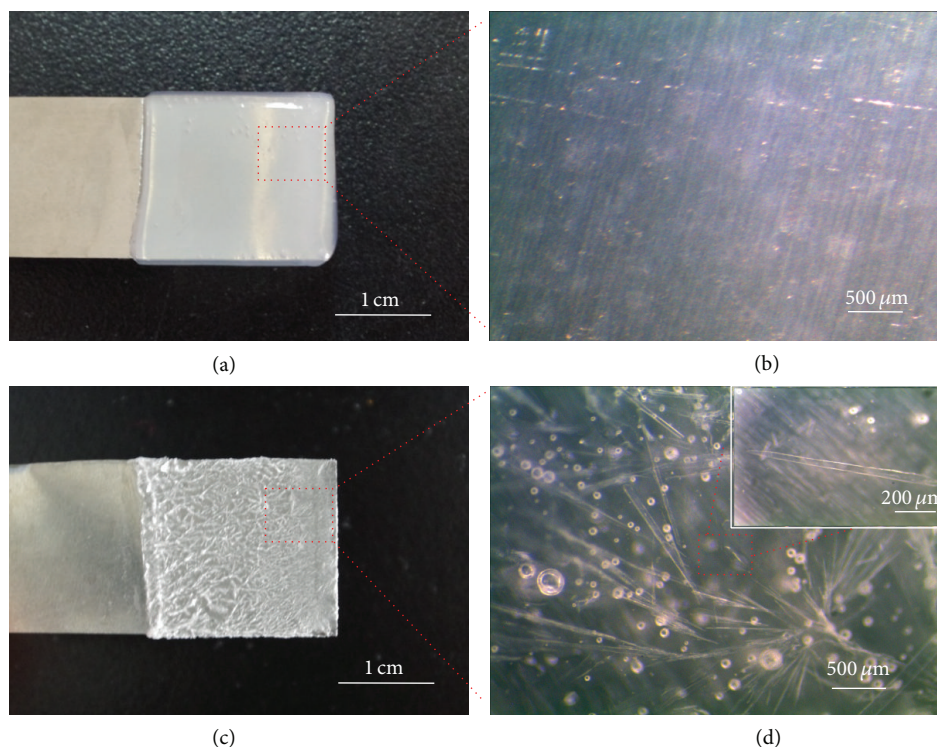
Figure 1: Photographs of the chitosan-ibuprofen composite hydrogel on titanium plate. Wet (a) and dried (c) chitosan-ibuprofen composite hydrogel and its corresponding magnified photographs (b) and (d). The insert of (d) shows the enlarged ibuprofen needle-like crystal.

2.5. Electrical and pH Controlled Drug Release. The pH responsive ibuprofen release from electrodeposited chitosan hydrogel was monitored by immersing the titanium plate with deposited chitosan in 20 mL buffer solutions with different pH values (pH 4, 7, and 10). At predetermined intervals, the released ibuprofen was measured by UV absorbance at 264 nm. Each assay was performed in triplicate and reported as the average with standard deviation.

The electrical signal controlled drug release was carried out by immersing titanium plates with chitosan-ibuprofen composite hydrogel in NaCl solution (0.9%, w/v). The release of ibuprofen was controlled by applying a voltage to the titanium plate (voltage typically varied between −3 V and +3 V) with a platinum wire working as counter electrode. The elution of ibuprofen responding to applied voltage and time was measured by UV absorbance at 264 nm.

3. Results and Discussion

We first deposited chitosan hydrogel on a titanium plate under a constant current of 0.5 mA for 30 min and then immersed the hydrogel in ibuprofen solution (1%, wt) for 1 h. Figure 1 shows the photographs of the composite chitosan-ibuprofen hydrogel. The hydrogel is transparent and uniform with a smooth surface (Figures 1(a) and 1(b)). The size of the hydrogel is 1.5×2.0 cm, which is corresponding to the area dipped in chitosan solution during electrodeposition process. The thickness is estimated to be 1 mm. When the hydrogel was air-dried, irregular white textures appeared on the titanium

plate (Figure 1(c)). The texture was further observed by a photomicroscope. Crystals of ibuprofen with needle shape are well dispersed in chitosan film (Figure 1(d), the insert of Figure 1(d) shows one crystal with 500 μm length and 30 μm width). The results in Figure 1 preliminarily suggest that ibuprofen can be loaded in the deposited chitosan hydrogel.

The chitosan-ibuprofen composite film was further characterized by SEM. Figure 2 shows the SEM images of the surface of chitosan-ibuprofen composite film. Chitosan film without ibuprofen displays a relatively smooth surface with micropores of ~0.6 μm (Figure 2(a)). When the chitosan hydrogel was immersed in 0.2% of ibuprofen solution for 1 h, the surface of the chitosan film became rough. The fibril structure on the surface was attributed to the crystallization of ibuprofen in chitosan membrane (Figure 2(b)). Figures 3(b) and 4(b) exhibit the surface morphology of chitosan-ibuprofen in 0.6% and 1.0% of ibuprofen solution, respectively. Obvious crystal structure can be observed with the increased concentration of ibuprofen. It is interesting to note that ibuprofen crystal shows well-oriented layer structure, as revealed by inset images in Figures 2(c) and 2(d). It has been reported that the morphology of the recrystallized ibuprofen depends on the crystallization solvents and additives. The crystal forms of ibuprofen were found as {100}, {002}, and {011} [29]. The carboxyl groups of ibuprofen project out from the face (100) and can form hydrogen bonding with hydroxyl groups on chitosan, thus reducing the growth rate on this face. The growth on (011) face leads to large platelet structure as observed in SEM.
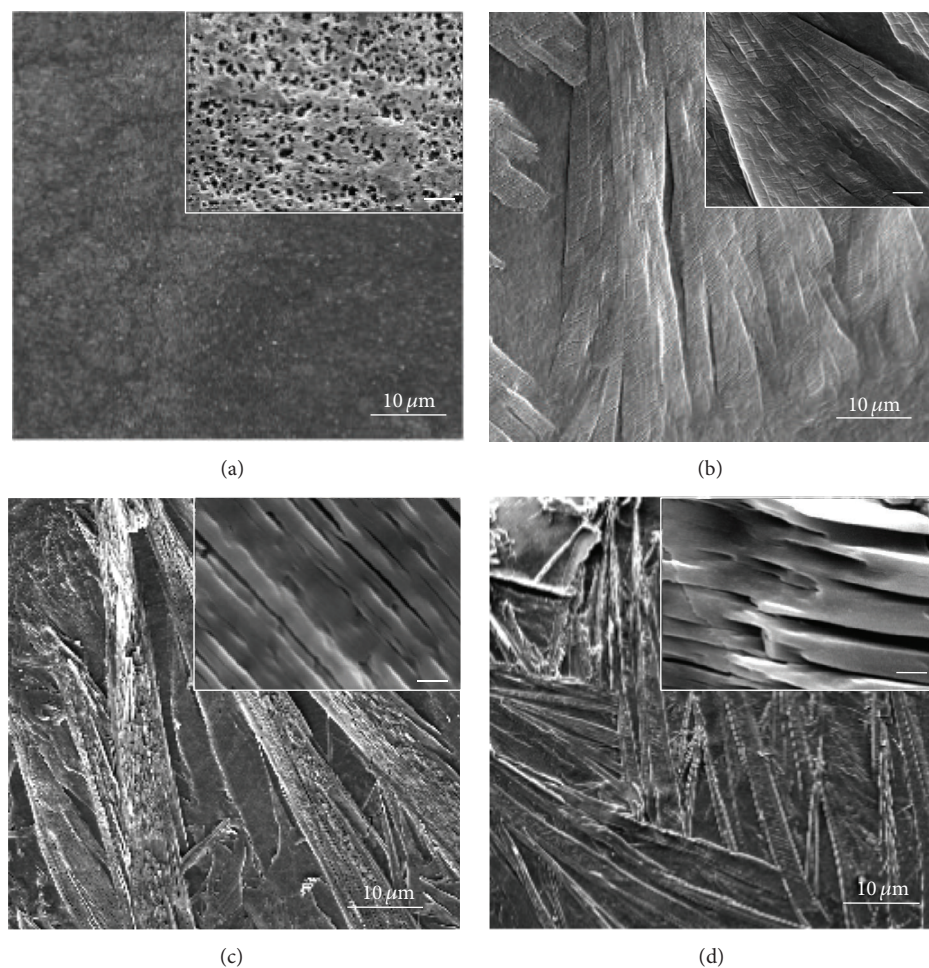
(a)

(b)

(c)

(d)

FIGURE 2: SEM images of the surface of the chitosan-ibuprofen composite hydrogel on titanium plate. Pure chitosan hydrogel (a); chitosan hydrogel with 0.2% ibuprofen (b); chitosan hydrogel with 0.6% ibuprofen (c); and chitosan hydrogel with 1.0% ibuprofen (d). The insert of each SEM image shows high magnified images (the scale bar was 2 μm).

The chitosan-ibuprofen composite film was peeled off from the titanium plate and analyzed by FT-IR (Figure 3). The spectra were compared to that of pure ibuprofen and chitosan. Ibuprofen exhibits characteristic peaks at 2955 cm^{-1} and 1719 cm^{-1}, which can be attributed to O–H stretching and carbonyl stretching, respectively. Due to the presence of benzene ring, the strong peak at 779 cm^{-1} represents the aromatic C–H stretching [30]. The spectrum of chitosan shows absorption bands at 1650 cm^{-1} and 1553 cm^{-1}, corresponding to carbonyl stretching and amide II absorption, respectively. The FT-IR spectra of chitosan-ibuprofen composite films show the peaks at 779 cm^{-1} and 2955 cm^{-1}, providing evidence that ibuprofen exists in the composite film. However, there is no peak showed at 1719 cm^{-1}, suggesting that the carbonyl group might be ionized in the membrane.

The X-ray diffraction patterns of chitosan-ibuprofen composite films are provided in Figure 4. The sharp and intense peaks at 12.1°, 16.6°, 17.7°, and 22.2° suggest that ibuprofen is highly crystallized [31]. The wide crystalline peak at 19.8° in chitosan indicates its partial crystallization feature. In the chitosan-ibuprofen composite films, the crystalline peaks of ibuprofen remain and the intensity is enhanced with the increased amount of loaded ibuprofen, suggesting that the ibuprofen stays in crystalline state in the composite film.

To determine the amount of ibuprofen incorporated in chitosan-ibuprofen films, the ibuprofen in the film was extracted by immersing the film in ethanol for 1 h and its concentration was determined by UV-Vis spectroscopy at 264 nm. As shown in Figure 5, the amount of loaded ibuprofen in chitosan hydrogel increases proportionally to the concentration of ibuprofen. Due to the limited solubility of ibuprofen in water phase, the highest concentration of ibuprofen tested in this study was 1%. In this case, the load percentage of ibuprofen reaches 39.04%. This relatively large carrying amount of ibuprofen indicates remarkable drug load capacity of the electrodeposited chitosan hydrogel.

Next we investigated the influence of pH in release medium on the release profile of ibuprofen. Figure 6 shows the profiles of ibuprofen release under various pH values. It is obvious that the release rate in neutral buffer (pH = 7) was noticeably higher than that in acidic solution (pH = 4) but lower than that in base condition (pH = 10). As ibuprofen is
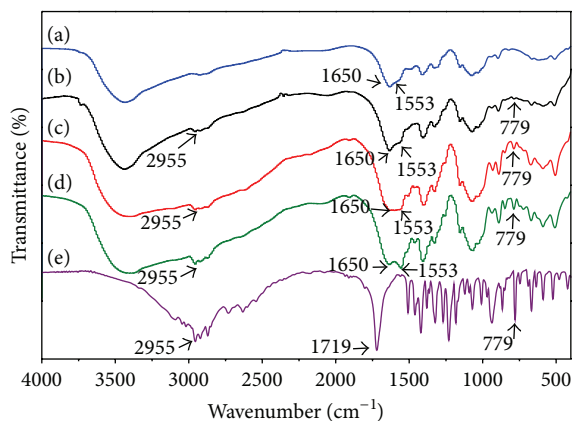
FIGURE 3: FT-IR spectra of the chitosan hydrogels with different concentrations of ibuprofen. Chitosan (a); chitosan with 0.2% ibuprofen (b); chitosan with 0.6% ibuprofen (c); chitosan with 1.0% ibuprofen (e); and ibuprofen (d).
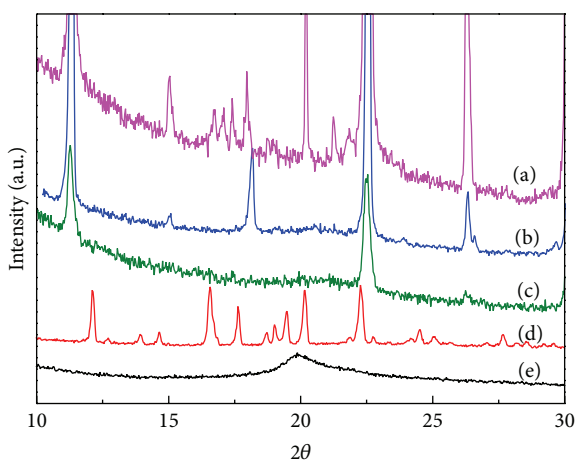

FIGURE 4: XRD pattern of chitosan hydrogel with different concentrations of ibuprofen. Chitosan with 1.0% ibuprofen (a); chitosan with 0.6% ibuprofen (b); chitosan with 0.2% ibuprofen (c); ibuprofen (d); and chitosan (e).
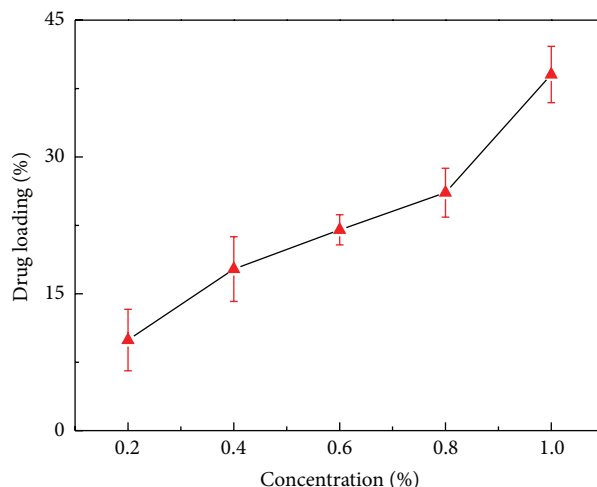

FIGURE 5: Ibuprofen loading in chitosan hydrogel by immersing titanium plates in various concentrations of ibuprofen.

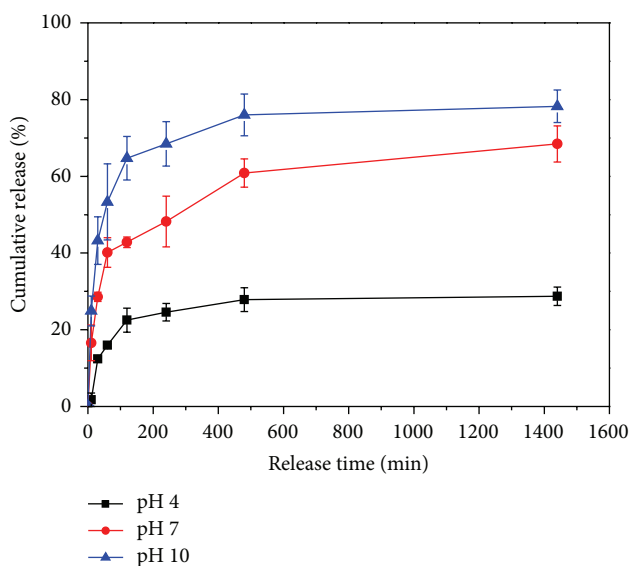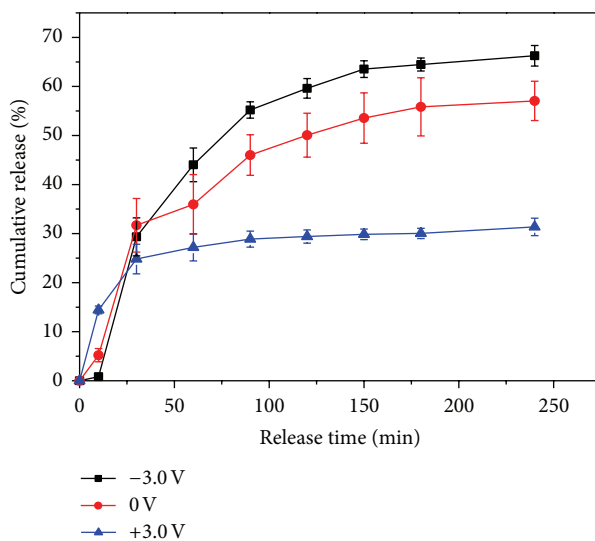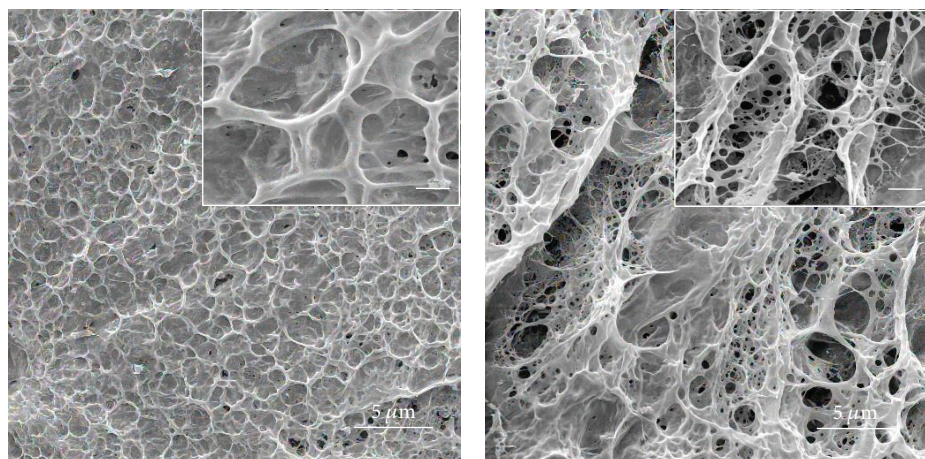FIGURE 6: Cumulative release profiles of ibuprofen from chitosan-ibuprofen hydrogels under different pH conditions.

a weak acidic drug, the elution of ibuprofen from chitosan is pH dependent. It has a small solubility in acid and can be easily dissolved at high pH. At pH 4, less than 30% of ibuprofen was released in 24 h, while this value increased with the increase of pH in the release medium. At pH 10, ibuprofen was released to 64% in the first 2 h and approximately to 78% in 12 h. The release profiles of ibuprofen indicate the important role of pH in the release of ibuprofen.

Inspired by the pH mediated ibuprofen release, we tested the possibility of ibuprofen release controlled by using electrical signals. In general, the electrochemical reaction induced by applied potential will result in pH gradient near the electrodes. The electrolysis of water induces a local pH increase at the cathode and a local pH decrease at the anode [32, 33]. The titanium plate with ibuprofen loaded chitosan hydrogel was immersed in 0.9% NaCl and external potential was applied (−3 V, 0 V, +3 V). As shown in Figure 7(a), ibuprofen release

from the composite hydrogel depends on the voltage applied for drug release. In the first 10 min, 14% of ibuprofen was released from the titanium plate at +3.0 V, while only 0.8% of ibuprofen was released at −3.0 V. This discrepancy can be explained by the different electrochemically generated local pH values adjacent to titanium plate that modifies the elution behavior of ibuprofen from the chitosan hydrogel. By biasing a negative potential (−3.0 V), the consumption of H^+ will increase the pH near the titanium plate, thus shrinking the chitosan hydrogel on its surface. On the other hand, the increased pH also facilitates the dissolution of ibuprofen. The amount of ibuprofen release reached a plateau of 66% at −3.0 V, while the total cumulative release was merely 31% at +3.0 V. Figure 7(b) and Figure 7(c) show the SEM images of chitosan hydrogels by applying −3.0 V and

(a)

(b)

(c)

FIGURE 7: Cumulative release of ibuprofen from chitosan-ibuprofen hydrogels by applying external potentials (a) and SEM images of the chitosan hydrogel after ibuprofen release by applying −3.0 V (b) and +3.0 V (c). The insert of SEM image shows high magnified images (the scale bar was $1\,\mu$m).

+3.0 V, respectively. No large ibuprofen crystals can be seen, indicating the release of ibuprofen. The hydrogel under +3.0 V reveals a more porous morphology than the hydrogel under −3.0 V, which is in agreement with the different pH environments at different voltages. The results in Figure 7 demonstrate that the flexible ibuprofen release profile can be mediated by applying varying potentials.

4. Conclusions

In this report, we electrodeposited chitosan on titanium plate and ibuprofen was loaded efficiently by a simple immersion method. The elution of ibuprofen is pH dependent. As a proof of concept study, the release profile of ibuprofen can be controlled by biasing negative or positive potentials, which is dramatically different from the situation of no voltage applied. The results provided in this work suggest new possibilities for building functional biopolymeric coat on conductive implant and controlling drug release by external electrical signals.

Conflict of Interests

The authors declare no competing financial interest.

Authors' Contribution

Youyu Liu and Kun Yan contributed equally to this work.

Acknowledgments

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