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Preparation and in-vitro characterization of electrospun bioactive glass nanotubes as mesoporous carriers for ibuprofen

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ABSTRACT

$59SiO_2$–$36CaO$–$5P_2O_5$ (mol%) as 58S bioactive glass nanotubes were successfully prepared using a coaxial electrospinning process, loaded with Ibuprofen (IBU), and characterized for in-vitro drug release properties. Polyvinylpyrrolidone (PVP) was exploited to manipulate the precursor solutions viscosity. The influence of PVP concentration on fiber formation and its morphology were investigated. The acceptable formation was achieved eventually by dissolving 8 g PVP in 10 ml ethanol. Bioactive glass nanotubes were characterized by field emission scanning electron microscopy (FE-SEM), X-ray powder diffraction (XRD), simultaneous thermal analysis (STA-TG/DTA), nitrogen sorption porosimetry (BET), Fourier transform infrared spectroscopy (FT-IR), thermogravimetric analysis (TGA), ultraviolet-visible absorption spectroscopy (UV–vis), and energy dispersive spectroscopy analysis (EDS). Accordingly, FT-IR and TG analyses indicated the synthesis of bioactive glass nanotubes has a satisfactory ability to store IBU due to hydrogen bonding between drug and glass. Furthermore, in-vitro drug release tests verified that samples of drug-loaded glass nanotubes were based on Korsmeyer-Peppas model and Fickian diffusion release mechanism. The surface of 58S glass nanotubes was fully crystallized, mostly by hydroxylapatite phase and partially by tetracalcium phosphate layer after immersion in SBF for 14 days.

1. Introduction

Electrostatic forces have been used to fabricate fibers for over 100 years in a process called electrospinning whose principles were firstly established by Rayleigh. This technique is able to provide nanofibers with the characteristics of large surface-volume ratio and high porosity. These specifications make nanofibers proper for many applications in biomedical fields such as controlled drug release, tissue engineering, biosensors, and wound dressing. Some parameters which can greatly influence the fiber formation and structure of the generated fibers need optimization such as polymer concentration, feeding rate, applied voltage, and distance from the needle tip [1–4].

Bioactive glass typically possesses biocompatibility, bioactivity, and osteoconductivity which is mainly composed of silicate, calcium oxide, and phosphorus oxide with different relative compositions. Bioactive glass exists in many forms such as bulks, granules, coatings, and fibers; however, there has been a special focus on nanofibers since 2006, when the first fabrication of bioactive glass nanofibers was reported [1,5]. Coaxial electrospinning technique in fabricating nanotubes might remarkably elevate the bioactivity characteristics. Regarding the apatite layer formed on both outer and inner surfaces of the nanotubes compared to nanofibers, the rate of biomineralization process could be enhanced markedly in nanotubes [1,6]. This layer is responsible for the strong bonding between bioactive glasses and human bone [7]. Considering the bioactivity of silica-based mesoporous materials, a significant development was firstly carried out in 2004. These materials have merits of better bioactive kinetics in comparison to both pure silica mesoporous materials and even sol–gel glasses with similar chemical composition (SiO_2–CaO–P_2O_5). The mesoporous bioactive glass could be a promising research line in the field of bioceramics for bone regeneration. Besides, it might be a substantial factor to take an effective control over the drug release process as a critical issue [8]. The porosity and chemical composition of mesoporous bioactive glasses can heavily influence both loading capacity and kinetics of drug loading [9]. The drug delivery carriers in the context of bone tissue engineering need to fulfill several requirements including biocompatibility, osteoconductivity, and bioresorbability with controllable degradation and resorption rates. Admittedly, bioactive glasses are desirably qualified for these applications [10,11].

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The aim of this study is to examine the mesoporous bioactive glass nanotubes fabrication by coaxial electrospinning method and in-vitro characterization of drug-loaded bioactive glass nanotubes with porous surface structure. In order to this purpose, tetraethyl orthosilicate (TEOS), triethyl phosphate (TEP), and calcium nitrate ($Ca(NO_3)_2.4H_2O$) in the system of $59SiO_2$–$36CaO$–$5P_2O_5$ (mol%) are used to synthesize mesoporous carriers. After IBU-loading process, in-vitro drug release behavior and kinetics of drug-loaded bioactive glass nanotubes with porous surface structure were investigated.

2. Experimental procedure

2.1. Materials

Tetraethyl orthosilicate (TEOS, No. 8.00658), triethyl phosphate (TEP, No. 8.21141), calcium nitrate ($Ca(NO_3)_2.4H_2O$, No. 1.02121), ethanol (No. 1.00983), HCl (1 mol/L, No. 1.00317), poly(vinylpyrrolidone) (PVP, Mw=40,000 g/mol, No. 107443), n-hexane (No. 1.04368), and toluene (No. 1.08323) were supplied by Merck Co. and silicone oil by Acros Organics (No. 163850010). IBU was provided from Jaber Ebne Hayyan pharmaceutical Co. (Tehran, Iran).

2.2. Preparation of spinning solutions

The adopted chemical composition of 58S glass is $59SiO_2$–$36CaO$–$5P_2O_5$ (mol%) chosen based on sol–gel calcium silicate bioglass [12]. The glass precursor solution was prepared by sequentially adding TEOS, TEP, and $Ca(NO_3)_2.4H_2O$ into ethanol and HCl in the volume ratio TEOS:ethanol:HCl=1:5:0.05. After stirring for 2 h, 10 ml of this solution was mixed with 10 ml ethanol containing different amounts (4, 5, 6, 7, 8, and 9 g) of PVP that had been stirred for 2 h. Similarly, the mixed solutions required stirring for extra 2 h. In this experiment, the PVP concentration in the solutions was varied from 0.2 to 0.45 g/ml; this factor could have influence on viscosity of the precursor solutions.

2.3. Electrospinning process

The prepared solutions were loaded into a plastic syringe connected to the outer needle (gauge 16). While silicone oil, used as core material, was loaded to another plastic syringe connected to the inner needle (gauge 22). The applied voltage was fixed at 10 kV. A piece of aluminum foil was utilized to collect the ultrafine fibers with a horizontal distance of 8 cm from the needle tip. The feeding rate was adjusted to 0.2 ml/h. All the electrospinning experiments were carried out at room temperature under air ambient using Fanavaran Nano-meghyas Co. electrospinning (Iran). The spun fibers were left at room temperature for 48 h to allow complete TEOS and TEP hydrolysis. In the following step, the aforementioned spun fibers were immersed in toluene for 48 h to remove silicone oil existing in the cores of the fibers; subsequently, dried at room temperature for 24 h. PVP was removed by calcination at 600 °C for 5 h in the air. The heating rate for the calcination was kept at 2 °C/min.

2.4. IBU load and release

IBU was selected as the model drug. 0.5 g glass tubes was added into 50 ml IBU n-hexane solution with concentration of 40 mg/ml at room temperature. Consequently, it was immersed for 24 h with magnetic stirring at rate of 100 rpm in a sealed vial to prevent the evaporation of n-hexane. Afterwards, the IBU-loaded 58S glass tubes were separated from solution by centrifugation. Finally, they were washed with n-hexane twice to remove any loosely attached molecules (the excess IBU resided along the surface region) and dried under vacuum at 60 °C for 24 h. These samples of IBU-loaded 58S glass tubes were named IBU-58S.

The in-vitro IBU release kinetics was studied in the simulated body fluid (SBF, pH=7.45). 5 g IBU-58S was immersed in a polypropylene vial with 5 ml SBF (IBU/SBF=0.1 mg/ml). The vial was incubated in a shaking water bath at the rate of 80 rpm at 37 °C. Different samples (1 ml SBF) were taken from vial to analyse over time intervals, after 0.5, 1, 2, 4, 8, 11.5, 24, and 48 h, then replaced by 1 ml fresh SBF. IBU concentration was determined by ultraviolet–visible absorption spectroscopy (UV–vis). This analysis was carried out to measure the absorbance values at wavelength $\lambda=265$ nm with the immersing time. All experiments were performed in triplicate.

The IBU concentration calibration curve was determined at room temperature by taking absorbance versus IBU SBF solution concentration of 100, 200, 300, 400, and 500 ppm. The UV absorption was measured at wavelength of 265 nm, using a Double Beam OPTIZEN 3220UV UV–vis Spectrophotometer. The calibration curve was in accordance with the Lambert and Beer's law (Eq. 1):

$$A=0.003C+0.008 \quad (1)$$

where A is the absorbance and C is the concentration (ppm).

Typically, the corrected concentration calculation of released IBU could be based on the following equation [13]:

$$C_{tcorr}=C_t+\frac{\upsilon}{V}\sum_{0}^{t-1}C_t \quad (2)$$

where C_{tcorr} is the corrected concentration at time t, C_t is the apparent concentration at time t, ν is the volume of sample taken, and V is the total volume of dissolution medium.

In order to study the IBU release mechanism from bioactive glass tubes, the in-vitro release data was fitted to Korsmeyer-Peppas model [14]. Regarding Korsmeyer-Peppas model, the drug release mechanism often deviates from Fick's law and has an anomalous pattern which can be described by Eq. (3).

$$M_t/M_\infty=kt^n \quad (3)$$

The logarithm form of equation could be written as:

$$ln(M_t/M_\infty) = ln(k) + n\ ln(t) \quad (4)$$

where M_t/M_∞ is the fractional drug release (F) at time t, k is the kinetic constant, and n is the release exponent which indicates the mechanism of drug transport. For n equal or close to 0.5 there is Fickian diffusion mechanism; however, for $n>0.5$ the mechanism is anomalous non-Fickian [13,15].

2.5. Characterization methods

The X-ray powder diffraction patterns were examined on a Philips X'pert with Co K_α radiation in the 2θ range of 10–80° at 40 kV and 40 mA. Besides, the structures and morphologies of the glass nanotubes were observed by field emission scanning electron microscopy coupled with an Oxford energy dispersive spectroscopy analysis system in a Zeiss SEM working at 15 kV. The samples were coated with a thin layer of gold before imaging. In addition, Fourier transform infrared spectroscopy analysis was developed on a PerkinElmer Frontier FT-IR spectrometer in the range of 450–4000 cm^{-1}, prepared by mixing the samples with KBr and compaction. Furthermore, simultaneous thermal analysis was performed on a Seiko model SII 6300 with typical sample weight of 12 mg and heating rate of 2 °C/min in the air atmosphere. The curve was acquired in the temperature range of 30–900 °C. Moreover, thermogravimetric analysis was recorded on an