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Hydrogel nanocomposite based on starch and Co-doped zinc ferrite nanoparticles that shows magnetic field-responsive drug release changes

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ABSTRACT

This paper describes the synthesis and characterization of a hydrogel nanocomposite based on starch and Co-doped zinc ferrite nanoparticles ($Co_{0.50}Zn_{0.50}Fe_2O_4$) that underwent drug release changes in response to an external magnetic field. The material was prepared using vinylated starch together with *N*′,*N*′-dimethylacrylamide (DMAAm) and $Co_{0.50}Zn_{0.50}Fe_2O_4$ (CZ) via an ultrasound-assisted radical cross-linking/polymerization reaction. CZ was synthesized by an adapted sol–gel method that uses water as solvent, from which nanoparticles with an average crystallite size of 13 nm were obtained. The drug release profile of the hydrogels was obtained by fitting the experimental data to power law equation, using prednisolone as a model drug. In the hydrogel without CZ, the prednisolone release was driven by an anomalous transport, contributions of macromolecular relaxation and the Fickian diffusion. With addition of CZ, the drug release tended towards the Fickian diffusion. In such a case, the macromolecular relaxation is minimized and the Fickian mechanism begins to prevail. When the magnetic field was applied, the anomalous mechanism became more important, which makes the release more favorable. It was shown that, under magnetic field, 90% of initial prednisolone load is released at early times. On the other hand, the more densely cross-linked hydrogels showed irrelevant release changes in response to magnetic field, owing to their tighter polymer structure. Cytotoxicity research showed that both the hydrogels and CZ have great pharmacological potential and an appropriate level of security for use in the biological systems.

1. Introduction

Nanotechnology is an excellent tool in the production of nanostructured materials for drug delivery [1,2]. Such materials have many advantages over conventional systems that require a larger amount of drug for therapy, leading to undesirable side effects [3]. The drug delivery systems show a variety of biomedical applications, being promising for active compounds in water-swellable polymer devices, such as hydrogels [4–6].

The hydrogels are made of three-dimensional (3D) physically and/or chemically cross-linked networks of flexible, hydrophilic polymers [7,8]. Upon contact with water, the 3D polymer network is not dissolved and can absorb and retain up to ca. 1000 g of water per gram of dry hydrogel [7]. The water absorption power of such materials is related to average size of pores and chemical nature of their 3D structure that may carry ionic groups, which are able to provide strong interactions with water. Although the average size of pores throughout hydrogel structure can vary, it is often larger than the hydrodynamic volume of most biomolecules in aqueous solutions.

They show great potential in the production of smart materials. This is a class of advanced materials that show volume changes in response to environmental stimuli such as pH [9], temperature [10], magnetic field [11], and so on. The smart materials have shown encouraging results in the controlled release and targeted delivery of drugs [9,12,13]. The water in the hydrogel may dissolve the drug, allowing it to diffuse into, through and from its polymer network.

There is a great interest from researchers in the area of biotechnology in working with hydrogels for drug delivery [14,15], owing to their similarity close to natural living tissue and inherent biocompatibility, which can be attributed to soft, flexible nature and high water content. Among the various materials used in the production of hydrogels, natural polymers have been widely used as starting compounds [16,17], because they are biodegradable, non-toxic (i.e., very few side effects) and easily eliminated by the human body.

Starch is a natural polymer with important applications in biotechnology. It is obtained from renewable sources and offers important advantages such as low cost, ease of chemical modification, and ability to replace some synthetic polymers [18–20]. The association

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of biomacromolecules, such as starch, with nanoparticles has been used in a variety of applications [21]. Therefore, the combination of starch with magnetic particles for creating a smart hydrogel is an excellent alternative in the production of new materials that may be used in the release of more sophisticated drug.

This work aims at preparing a starch-based hydrogel that undergoes drug release changes in response to an applied magnetic field. For gelation, starch was vinyl-modified with a methacrylate compound and subsequently cross-linked/polymerized with *N*′,*N*′-dimethylacrylamide (DMAAm) under ultrasound. The drug release profile of the hydrogels was studied by the modeling of the release kinetics of prednisolone, which was used as a model drug. The magnetic field-responsive release of prednisolone from the starch hydrogels into a buffer solution of pH 7.4 was achieved using Co-doped zinc ferrite nanoparticles ($Co_{0.50}Zn_{0.50}Fe_2O_4$) (namely, CZ). The nanoparticles were synthesized by an adapted sol–gel method that uses water as solvent.

2. Experimental

2.1. Materials

$Zn(NO_3)_2 \cdot 6H_2O$ (96%) and $Co(NO_3)_2 \cdot 6H_2O$ (98%) were obtained from synth, and ferric nitrate, $Fe(NO_3)_3 \cdot 9H_2O$ (98%) was purchased from Vetec. Starch was purchased from Duryea®. Dimethyl sulfoxide, (DMSO (≥99%) and absolute ethanol (≥99.5%) were purchased from Nuclear. Glycidyl methacrylate, GMA (≥97%), *N*′,*N*′-dimethylacrylamide, DMAAm (≥99%), sodium persulfate (≥98%), acrylic acid, AAc (≥99%) and poly(vinyl alcohol) (PVA) 87–89% hydrolyzed, M_W 146,000–186,000 were obtained from Aldrich. Acetone (≥99.5%) and sodium hydroxide, NaOH (97%) were supplied by Fmaia.

2.2. Synthesis of $Co_{0.50}Zn_{0.50}Fe_2O_4$ nanoparticles (CZ)

CZ was synthesized by an adapted sol–gel method that uses water as solvent [22,23]. A saturated solution of metal nitrate was added to an aqueous solution of PVA (10% w/v) in a metal:PVA monomeric unit proportion of 1:18. The mixture was stirred for 2 h at room temperature for solubilization. Later, the formed solution was heated to ca. ~250 °C and kept under a vigorous stirring until the water was entirely evaporated from reaction medium. Under this condition, the polymer is partially degraded. The particles were obtained by the calcination of the precursor powders under atmospheric air at a temperature of 400 °C.

2.3. Chemical modification of starch

Starch was modified with GMA at pH 10.5 as previously reported in the literature [24], and briefly described here. Five grams of starch were added to 100 mL of DMSO at 90 °C while stirring. After solubilization, NaOH was added to the solution at 60 °C until a pH 10.5 was achieved. Two milliliters of GMA were added and the solution was left to react for 24 h under stirring. The obtained product was precipitated and washed with ethanol and freeze-dried for 12 h.

2.4. Synthesis of hydrogel nanocomposites containing prednisolone

Prior to the gelation, the prednisolone was introduced to the hydrogel-forming solution to be loaded during the hydrogel synthesis. The prednisolone weight corresponded to 10% (w/w) of the reactants used in the feed solutions.

Known amounts of modified starch, DMAAm, prednisolone and CZ (Table 1) were added to 10 mL of distilled/deionized water while stirring. For gelation, the stirred suspension was sonicated with the use of a probe of ultrasonic oscillation (Cole Parmer® 500, model EW-04711-40) at a frequency of 20 kHz for 3 min. After that, 23 mg of sodium persulfate were introduced. In a few minutes, a translucent, stiff material was formed.

Table 1
Contents of modified starch, DMAAm and CZ used in the hydrogel nanocomposite-forming suspensions.

Samples	Modified starch (g)	DMAAm (g)	CZ (%) (w/w total)
D1	0.50	0.25	0.000
D1CZ	0.50	0.25	0.250
D2	0.50	0.50	0.000
D2CZ	0.50	0.50	0.250

2.5. Release of prednisolone from hydrogel and magnetic hydrogel composites

Prednisolone-loaded dry hydrogels of known weight was immersed into a 500 mL glass reactor containing 200 mL of PBS buffer solution of pH 7.4 at 37 °C, and stirred at 40 rpm using a glass-made stirrer paddle. Aliquots of 5 mL were collected at specified times, and then absorption readings were made at 247 nm, which is the wavelength for the maximum absorption of prednisolone, by means of an UV–vis spectrophotometer (Shimadzu, UV mini 1240). After that, the aliquots were brought back into the reactor to prevent volume loss. The concentrations of prednisolone released from the hydrogels were determined from analytical curves correlating the absorption to the concentration of prednisolone. The measures of release were performed without and with the applying of a constant magnetic field of intensity 48 MGOe.

2.6. Characterizations

2.6.1. Wide-angle X-ray diffraction (WAXD)

WAXD measurements were carried out on a Shimadzu XRD-7000 X-ray diffractometer equipped with a copper tube with Kα radiation of 1.5406 Å, $2\theta = 20–80°$, voltage of 40 kV, current of 30 mA, scan rate of 2° min^{-1}, and slit width of 0.30 mm. Crystallite size was estimated using Scherrer's equation:

$$d = \frac{0.9\lambda}{\beta \cos\theta} \quad (1)$$

where λ is the wavelength, β the full width at half maximum (FWHM) of the peak, and θ the Bragg angle. The (220), (311) and (440) diffraction peaks of ferrite WAXD pattern were used for calculation of the average crystallite size for CZ sample.

2.6.2. Scanning electron microscopy (SEM)

The hydrogel nanocomposites were swollen to equilibrium in water prior to SEM imaging. The swollen hydrogels were withdrawn from water and immediately frozen by immersion in liquid nitrogen before being lyophilized for 48 h. Under these conditions, it is supposed that the morphology of the swollen hydrogels is maintained. The samples were sputter-coated with a thin layer of gold and the SEM images were obtained in a scanning electron microscope (Shimadzu, model SS550 Superscan) by applying acceleration voltage of 15 kV and current intensity of 30 μA.

2.6.3. Transmission electron microscopy (TEM)

Bright field TEM images were obtained in a JEM-1400 microscope (JEOL) by applying acceleration voltage of 120 kV. For observation by TEM, an aliquot of a stirred suspension of powdered samples (hydrogel and CZ) in isopropyl alcohol was added dropwise onto a 200 mesh copper grid covered with a thin layer of carbon.

2.6.4. Measures of ζ-potential

The reading of ζ-potential was made using a zeta potential analyzer from Particulated Systems, with the injection of 0.7 mL into a standard sample flow cell under the desired temperature. Data were processed with the use of a software supplied by own manufacturer. The values were recorded at pH 7.4 in triplicate at room temperature using stirred suspensions of CZ.

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