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Facile synthesis of glucose-sensitive chitosan–poly(vinyl alcohol) hydrogel: Drug release optimization and swelling properties

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ABSTRACT

The study describes the development of glucose-sensitive hydrogel and optimization of bovine serum albumin release profile from the hydrogel. To enhance the glucose sensitivity and improve the swelling behaviors of the hydrogel system, boric acid crosslinking, and freeze-thawing cycle techniques were used to prepare chitosan–poly(vinyl alcohol) hydrogel. The structure of the resultant hydrogel was confirmed by scanning electron microscopy and Fourier transform infrared spectroscopy. The experimental results revealed that the swelling of the hydrogel was influenced by the pH of the medium, and the hydrogel displayed explicit glucose-sensitivity under physiological conditions. The values of the diffusion exponent range between 0.34 and 0.44 and the diffusion of water into the gel system are assumed to be pseudo-Fickian in nature. Under optimized conditions, the cumulative Bovine serum albumin (BSA) drug releases ranged between 69.33 ± 1.95% and 86.45 ± 1.16% at 37 °C in the presence of glucose and pH 7.4, respectively.

1. Introduction

"Smart" hydrogels undergo changes in their physicochemical properties in response to various external conditions, due to the presence of certain functional groups along the polymeric chains [1,2]. The swelling behavior of "smart" hydrogel may be dependent on temperature, glucose concentration, pH, and even ionic strength [2]. These hydrogels have been utilized in diverse applications such as immobilization of enzymes, drug delivery system, artificial muscle and gene delivery vectors [3–5].

Intensive research efforts have been committed to developing of glucose-sensitive polymeric systems and insulin delivery technologies, due to rapidly increasing diabetic population [4–6]. Diabetes is a manageable disease, which requires frequent and accurate measurements of a patient's glucose levels to ensure they stay within a permitted range [7]. It has been reported that diabetics still suffer from hyperglycemic and hypoglycemic series as a result of the fluctuation of glucose levels [7]. It is particularly important to develop the biocompatible glucose-responsive system. Until now, three major kinds of glucose-sensitive hydrogels have been reported including hydrogel containing phenyl boronic acid group, lectin-loaded and glucose-oxidase loaded [2,8,9]. However among these, the phenyl boronic acid (PBA) moiety is the ideal candidate for glucose sensor because it can overcome issues such as toxicity, stability and immunogenicity associated with latter types.

Synthetic glucose-sensitive hydrogel systems containing PBA have been identified [8,10]; however, such systems are practically useful at pH values above pK_a (8.7) of PBA. Chitosan (CS) and its derivatives show good biocompatibility and hydrogel properties and have been used in many biomedical applications [11–13]. Poly(vinyl alcohol) (PVA) is a water-soluble polyhydroxy polymer. It has been broadly applied in pharmaceutical and biomedical fields due to its biocompatible, gelation and non-toxic properties [13,14].

Hydrogels containing chitosan and PVA have been synthesized and showed low swelling in basic pH and high swelling in acidic pH [15,16]. This behavior made them unsuited for delivery of the drug. In this study, boric acid cross-linked CS-PVA hydrogels showing high swelling at neutral pH and low swelling at low pH value have been developed. The synthesized hydrogels with a boric acid derivative selectively and reversibly bind with polyol compounds like glucose. This result in a volume changes of the CS-PVA hydrogel system driven by osmotic pressure, and is dependent on glucose concentration [2]. The glucose-responsive behavior occurred at physiological pH, and the release behavior of Bovine serum albumin (BSA) from the hydrogel was optimized using response surface methodology. The developed hydrogel is highly attractive in terms of glucose sensitivity and self-regulated drug delivery. Boric acid is

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well known for its use as a home remedy due to its medicinal properties [10]; however, less information has been reported on boric acid cross-linked chitosan-based hydrogels for glucose sensing.

2. Materials and methods

2.1. Chemicals and materials

All the chemicals used were of reagent grade. Chitosan (medium molecular weight with 85% degree of deacetylation) was supplied by Sigma–Aldrich (Germany). PVA (99% hydrolyzed and MW: 72,000 g/mol), boric acid and acetic acid were obtained from Merck (UK). Aqueous solutions were all prepared with deionized water. The simulated intestinal fluids (phosphate buffer solutions (PBS): pH 7.4) were prepared as described elsewhere [17,18] and ionic strength of the solutions were adjusted to ≈0.1 M using sodium chloride.

2.2. Synthesis of boric acid cross-linked CS–PVA hydrogel

CS–PVA hydrogel was prepared via a boric acid cross-linking technique in combination with an alternate freeze–thawed process. CS was dissolved in aqueous acetic acid (2%, v/v). 49 mL of CS solution was mixed with 4.2 mL of PVA aqueous solution (10%) and stirred mechanically at 25 °C for 3 h. After the homogeneous solution was obtained, 2 mL of boric acid aqueous solution (25%) was added slowly in a dropwise fashion into the mixture and continuously stirred for another 4 h to obtain a homogeneous gel. The gel was directly kept frozen at −20 °C for 24 h. Subsequently, the frozen gel was thawed at 25 °C for 6 h. The CS–PVA hydrogel was obtained after three freeze–thawed cycles, immersed in a dilute NaOH solution to neutralize the excess acetic acid, and then washed severally with deionized water. The dehydrated hydrogel was dried in an oven at 70 °C.

2.3. Characterization

IR absorption spectra of CS, PVA, and CS–PVA hydrogel were taken on a Fourier-transform infrared (FTIR) spectrometer (PerkinElmer, 65 FT-IR Spectrometer, USA) over the region from 400 to 4000 cm^{-1}. The surface morphology of the hydrogel was observed using a scanning electron microscope (SEM) (JEOL JSM-6360LV, Japan) at an accelerating voltage of 20 kV for 75 s after coating the sample with a gold film.

2.4. Swelling studies of the hydrogel

The gravimetric method was employed to determine the swelling and equilibrium data of the hydrogels. Briefly, the hydrogels were immersed in given solutions, withdrawn at particular time intervals, gently dried with filter paper and then weighed on an analytical balance to determine the swelling ratio. The equilibrium swelling ratio was determined when the weight of the swollen hydrogel was constant. The swelling studies were conducted in triplicate, average results reported, and the swelling ratio was determined as follows:

$$Q_e(g/g) = \frac{W_{wet} - W_{dry}}{W_{dry}} \quad (1)$$

2.5. Drug loading, controlled drug release experiments and optimization

BSA was selected as a model drug. The loading of BSA into CS–PVA hydrogel network was done using swelling equilibrium method. Briefly, the hydrogels were allowed to swell in 5 mg/mL aqueous solutions of BSA for 72 h at 5 °C and then dried to obtain the BSA-loaded hydrogel.

The drug release experiments were performed by immersing BSA-loaded hydrogel in 50 mL of phosphate buffer, pH 7.4 for 24 h with occasionally shaking at 37 ± 0.2 °C. Aliquots of the solution were removed at pre-determined time intervals, and BSA concentration in the unknown samples was quantified using UV–Vis spectrophotometer (UV-Win 5.0, Beijing, T80+) at 280 nm. All release experiments were performed in triplicate, and the cumulative BSA release was calculated from the averages.

Response surface methodology (RSM) is a proficient approach to the prediction of drug release and optimization of drug delivery devices [2,17–20]. Here, the influences of operating factors (pH and glucose concentration) on responses (cumulative release (*R*%)) were examined by RSM. A total of 20 experimental runs were proposed by SigmaXL software (Ver. 7.0, Discoversim) for two independent variables and the matrix of the design including investigated response, i.e., *R* (%) is presented in Table 1.

3. Results and discussion

3.1. Synthesis and characterization of hydrogels

The chemical structures of CS, PVA and synthesis route of CS–PVA hydrogel are shown in Scheme 1. In the present work, a stable hydrogel with glucose-sensitivity was obtained using boric acid as a crosslinker and alternate freeze-thawed process. The ratio of cross-linking was calculated according to the tri-functionality of boric acid.

The FTIR of the samples is shown in Fig. 1. The pure PVA showed main absorption peaks at 3412 cm^{-1} (—OH stretching), 2862 cm^{-1} (—CH stretching), 1419 cm^{-1} (—CH bending) and 1093 cm^{-1} (—C—O— stretching). In the FTIR spectrum of chitosan, the absorption peaks at 1648 cm^{-1} and 1562 cm^{-1}, are attributed to amide I and II peaks, respectively [1,18]. The broad peak at 892 cm^{-1}, 1092 cm^{-1} indicates saccharine structure; the —C—O— stretching vibration respectively and peak at 2928 cm^{-1} is typical —CH stretching vibrations. The broad peak at 3380 cm^{-1} is attributed —OH and —NH symmetrical vibration.

Table 1
Experimental matrix of 3^2 full factorial design with observed response values (BSA cumulative release %).

Run order	Std. order	Center points	Blocks	A: pH	B: Glucose concentration (g/L)	BSA cumulative release (%)	Predicted cumulative release (%)
1	10	0	1	5.7	3	57.35	57.47
2	9	0	1	5.7	3	59.56	57.47
3	7	1	1	5.7	1	67.88	67.36
4	5	1	1	4	3	38.84	37.56
5	12	0	1	5.7	3	56.49	57.47
6	11	0	1	5.7	3	55.95	57.47
7	2	1	1	7.4	1	86.54	85.05
8	4	1	1	7.4	5	74.57	74.08
9	13	0	1	5.7	3	56.82	57.47
10	3	1	1	4	5	33.25	32.15