



In situ synthesis of magnetic CaraPVA IPN nanocomposite hydrogels and controlled drug release

Gholam Reza Mahdavinia^{*}, Hossein Etemadi

Department of Chemistry, Faculty of Science, University of Maragheh, 55181-83111, Maragheh, Iran



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ABSTRACT

In this work, the magnetic nanocomposite hydrogels that focused on targeted drug delivery were synthesized by incorporation of polyvinyl alcohol (PVA), *kappa*-carrageenan (Cara), and magnetite Fe₃O₄ nanoparticles. The magnetic nanoparticles were obtained *in situ* in the presence of a mixture of polyvinyl alcohol/*kappa*-carrageenan (CaraPVA). The produced magnetite-polymers were cross-linked with freezing–thawing technique and subsequent with K⁺ solution. The synthesized hydrogels were thoroughly characterized by transmittance electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD), thermal gravimetric analysis (TGA), Fourier transform infrared spectroscopy (FT-IR), and vibrating sample magnetometer (VSM) techniques. The dynamic swelling kinetic models of hydrogels were analyzed according to the first- and second-order kinetic models and were found that the experimental kinetics data followed the second-order model well. Drug loading and release efficiency were evaluated by diclofenac sodium (DS) as the model drug. The *in vitro* drug release studies from hydrogels exhibited significant behaviors on the subject of physiological simulated pHs and external magnetic fields. Investigation on the antibacterial activity revealed the ability of drug-loaded hydrogels to inactivate the Gram-positive *Staphylococcus aureus* (*S. aureus*) bacteria. The mucoadhesive properties of the hydrogels were studied and the hydrogels containing *kappa*-carrageenan showed good mucoadhesiveness in both simulated gastric and intestinal conditions.

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1. Introduction

Hydrogels are cross-linked hydrophilic polymers which can expand their volume because of highly swelling ability in aqueous solutions [1]. Owing to their significant behaviors, the application of hydrogels has widely evaluated in many fields such as biomedical [2], horticulture [3], controlled release of drug [4], and wastewater treatment [5]. In recent years, considering the importance of targeted drug delivery, there has been growing interest in hydrogels composed of biodegradable, biocompatible and non-toxic biopolymers. In this case polysaccharides such as chitin, chitosan, alginate, and *kappa*-carrageenan are highly recommended for colon-specific drug delivery [6–8]. The necessity of this concept is based on this fact that, various substrates could be recognized by anaerobic bacteria and degraded by enzymes in the colon, so it is worthwhile to fabricate new materials based on polysaccharides which are stable in the gastric environment and subsequent colon targeted delivery [9]. In addition to biopolymers, non-ionic and water soluble polyvinyl alcohol (PVA) have attracted the attention of researchers. Because of non-toxicity, biocompatibility, and gelation ability, the PVA has been widely used in biomedical and pharmaceutical

fields [10]. However, the applications of this kind of hydrogel have been limited in many fields due to low degree of swelling and lack of responding to external stimulants [11].

The PVA-based hydrogels can be produced by chemical and physical methods. Among the physical methods, freezing–thawing is of extreme importance because of ease of operation and deleting of toxic cross-linker [12]. The swelling degree as well as the responding of PVA hydrogels can be improved by imparting of ionic polymers. Sodium alginate with carboxylate groups ($-\text{CO}_2^-$) [13], *kappa*-carrageenan with sulfate pendants ($\text{O}-\text{SO}_3^-$) [14], chitosan with primary amine ($-\text{NH}_2$) [15], and poly (N-isopropyl acrylamide) with hydrophobic isopropyl pendants ($\text{CH}_3-\text{CH}-\text{CH}_3$) [16] are ionic or non-ionic polymers with active functional groups and responsiveness properties that have been utilized to fabricate new functionalized PVA hydrogels.

Like PVA, the non-toxicity, biodegradability, and biocompatibility of anionic *kappa*-carrageenan make considerable attention to provide new carrageenan-based materials [17]. The gelling of *kappa*-carrageenan can be achieved physically (in the presence of K⁺ cations) and chemically (non-toxic genipin) [18,14]. Over two decades the use of *kappa*-carrageenan in oral drug delivery has greatly increased [19,20]. On one hand the sweet flavor of galactose that unites within the *kappa*-carrageenan chains can be useful for covering the bitter taste of some drugs; and on the other hand the formation of ionic bonds between the negatively charged on sulfate pendants ($\text{O}-\text{SO}_3^-$) on *kappa*-

^{*} Corresponding author.

E-mail addresses: grmnia@maragheh.ac.ir, gholamreza.mahdavinia@gmail.com (G.R. Mahdavinia).

carrageenan and positively charged on mucin in the saliva helps the adhesion properties of the final formulation [21]. Recently, magnetic hydrogels have developed a promising candidate and investigated in controlled drug release [22]. By introducing magnetic iron oxide nanoparticles into pH sensitive delivery systems, there is a possibility to obtain dual sensitive hydrogels which can respond to external magnetic field and the change of pH at the same time [23]. The magnetite type of iron oxide (Fe_3O_4) with great saturation magnetization and biocompatible properties has been used to prepare magnetic hydrogels [22]. Recently, the modification of magnetic nanoparticles has been performed to enhance their biocompatibility. The coating of magnetic nanoparticles by inorganic and organic materials is an efficient route with high performance [24]. The presence of an external magnetic field can influence the release of bioactive agents from hydrogels containing magnetite. In fact, the magnetic carriers lead to decreased circulation time, decreased the required dosage of drug and thereby reducing side effects [25].

Magnetic PVA [22,26] and κ -carrageenan [27] hydrogels have been synthesized by incorporation of magnetic Fe_3O_4 nanoparticles and evaluated in the pharmaceutical and biomedical applications. Although the hydrogels based on PVA and κ -carrageenan show excellent properties, the low swelling of PVA hydrogels [11] and low apparent strength of κ -carrageenan hydrogels (cross-linked with K^+ cations) [18] restrict them in some applications. In this work, we attempt to evaluate the synthesis of magnetic hydrogels by incorporation of a mixture of PVA and κ -carrageenan.

The main objective of the present study was to examine the capability of drug release from hydrogels under variation of pH of media and applying external magnetic field for oral administration of drug to the colon site. Especially, this paper focuses on the influence of different amounts of magnetic iron oxide nanoparticles and κ -carrageenan biopolymer on the swelling and drug release behavior of magnetic hydrogels. To nutshell we characterized the morphology and the formation of magnetic iron oxide nanoparticles in the structure of hydrogels by SEM, XRD, VSM, TGA and FT-IR spectroscopy. Diclofenac sodium was used as a non-steroidal and anti-inflammatory drug for drug release studies. It is widely metabolized in the liver and absorbed in the gastrointestinal tract [28] and because of a very quick metabolism, it has a short biological half-life. So frequent injection is required which can cause some problems in the gastrointestinal tract [29]. So, presentation of a therapeutic approach to achieve maximum therapeutic effects with minimum side effects is in demand.

2. Experimental

2.1. Materials

κ -Carrageenan (MW = 100,000) was obtained from Condinson Co., Denmark. Polyvinyl alcohol (MW 89,000–98,000; degree of hydrolysis 99%) was purchased from Aldrich Chemicals, United States. Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* (*E. coli*) bacteria were received from NIGEB Bacterial Bank (Tehran, Iran). Agar powder, mucin (type II) from porcine, basic fuchsin (pararosaniline), sodium metabisulfite and diclofenac sodium were provided by Aldrich Co., United States. All other chemicals were analytical grade and used without any purification.

2.2. Synthesis of nanocomposite hydrogels

The magnetic Fe_3O_4 nanoparticles were firstly synthesized *via in situ* co-precipitation of iron salts in the presence of a mixture of PVA and κ -carrageenan. The required amounts of materials to synthesize nanocomposite hydrogels are listed in Table 1. In brief, 1 g of PVA was poured in 20 mL of distilled water and the temperature was adjusted at 80 °C and stirred until PVA was completely dissolved. κ -Carrageenan solution was prepared separately by dissolving 1 g

Table 1

Required amount of materials for synthesis of magnetic CaraPVA nanocomposite hydrogels.

	PVA (g)	κ -Carrageenan (g)	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (g)	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (g)
CaraPVA	1	1	0	0
mPVA	2	0	0.28	0.4
mCaraPVA1	1	1	0.28	0.4
mCaraPVA2	1	1	0.56	0.8

of this biopolymer in 25 mL of distilled water at 70 °C. Two solutions were mixed together and the temperature was adjusted at 70 °C. Then, 0.28 g of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and 0.5 g of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ salts were dissolved in 5 mL of water and added into a polymer solution ($n\text{Fe}^{+2}/n\text{Fe}^{+3} = 0.625/1$). The solution was sonicated to obtain a clear solution. In general, magnetic Fe_3O_4 nanoparticles are produced under inert atmosphere when the molar ratio of $n\text{Fe}^{+2}/n\text{Fe}^{+3}$ is 0.5/1 [30]. In this work, we synthesized magnetic hydrogels according to Zhang et al. [31] without using any inert gas. So, due to the oxidation of iron (II) under inert atmosphere, the ratio of $n\text{Fe}^{+2}/n\text{Fe}^{+3}$ was chosen higher [30]. For synthesizing of magnetic nanoparticles in the presence of polymers, the 3 M NH_3 solution was slowly dropped into a solution under condition of ultrasonic and the dark magnetic nanoparticles appeared as the pH was reached to 10. The pH of solution was adjusted at 10 and allowed to stir at 70 °C for 1 h. After formation of magnetite nanoparticles, the cross-linking of magnetic polymer solution was done by the freezing–thawing method and subsequently by immersing in K^+ solution. At first, the obtained solution containing PVA, κ -carrageenan, and magnetic nanoparticles was cooled to ambient temperature and the products were kept frozen overnight. The frozen hydrogels were thawed at 26 °C for 5 h. The process that involved freezing–thawing was repeated 4 times. After freezing–thawing steps, the hydrogels were immersed into 0.5 M of KCl solution for 30 min. The cross-linked magnetic hydrogels were immersed overnight into excess distilled water for purification. Finally, the hydrogels were cut into 0.5×0.5 mm discs with 0.4 mm thickness and dried at 40 °C for constant weight. In Table 1, the samples were coded as CaraPVA (magnetic-free hydrogel composed of κ -carrageenan and polyvinyl alcohol), mPVA (magnetic polyvinyl alcohol), mCaraPVA1 (magnetic hydrogel composed of κ -carrageenan and polyvinyl alcohol with low content of magnetic nanoparticles), and mCaraPVA2 (magnetic hydrogel composed of κ -carrageenan and polyvinyl alcohol with high content of magnetic nanoparticles).

2.3. Swelling measurements

Dried discs were used to determine the water absorbency of hydrogels. The water absorbency (WA) was determined by immersing the hydrogels (~ 0.1 g) in 50 mL of distilled water or 0.15 M of salt solutions and allowed to swell at room temperature for 24 h. Then, they were removed from aqueous solutions and blotted with filter paper to remove surface water, weighed and the WA was calculated using Eq. (1):

$$\text{WA} = \frac{W_s - W_d}{W_d} \quad (1)$$

where W_s and W_d are the weights of the samples swollen in distilled water and in dry state, respectively. For studying the swelling kinetics of the hydrogels, a certain amount of samples (~ 0.20 g) was immersed into 50 mL of distilled water. At consecutive time intervals, the water absorbency of the hydrogels was measured according to the abovementioned method. All swelling data were repeated 3 times and the mean values were shown in graphs (mean $\pm$ S.D.).

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