I.A.U
Karaj branch

Journal of
A p p l ied
C hemical
R esearch
jacr.kiau.ac.ir

Journal of Applied Chemical Research, 18, 3, 43-55 (2024)

Construction and Characterization of polyvinyl alcohol-sodium alginate magnetic hydrogel for use in release of famotidine

Mahdiyeh Poorgholam[1], Masoud Mokhtary[1*], Mohammad Alikarami[2]

[1]*Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran*

[2]*Department of Chemistry, Ilam Branch, Islamic Azad University, Ilam, Iran*

(Received 07 Mar. 2024; Final revised received 04 Jun. 2024)

Abstract

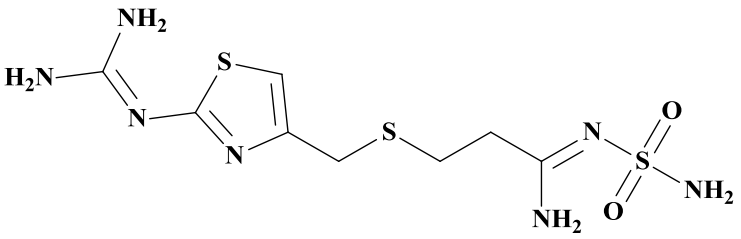
Polyvinyl alcohol-sodium alginate magnetic hydrogel was prepared using $K_2S_2O_8$ in aqueous media in the presence of *N*,*N*′-methylenebisacrylamide and Fe_3O_4 nanoparticles. The magnetic polyvinyl alcohol-sodium alginate (nano-Fe_3O_4/PVA-SA) hydrogel was characterized by FT-IR, SEM, and EDX methods. Also, magnetic characterization of the synthesized nano-Fe_3O_4/PVA-SA hydrogel was identified by vibrating sample magnetometer (VSM) method. Then, loading and release of famotidine drug was studied by nano-Fe_3O_4/PVA-SA hydrogel. The FT-IR results confirmed the formation of nano-Fe_3O_4/PVA-SA hydrogel. The effects of temperature and pH on the loading and release of famotidine drug in gelatin-polyvinylalcohol magnetic hydrogel were studied. The polyvinyl alcohol-sodium alginate magnetic hydrogel is sensitive to pH and temperature and provides the controlled release of famotidine. The results showed that the highest drug loading was achieved at 37 °C after 6 hours. Farther more, the highest drug release rate was obtained after 6 hours at 37 °C at pH = 2 with 57.95 ppm.

Keywords: Sodium alginate, Polyvinylalcohol, Magnetic hydrogel, Famotidine, Drug release.

[*]***Corresponding author:*** *Masoud Mokhtary, Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran. E-mail: mmokhtary@iaurasht.ac.ir*

Introduction

Hydrogels are a particular class of macromolecular gels obtained by the chemical crosslinking of hydrophilic polymers in a three-dimensional network. They are able to absorb and retain large volumes of water from any aqueous solution or biological fluid and release it in response to specific environmental stimuli [1,2]. The use of PVA based hydrogels as biomaterials has recently gained great importance in view of the non-carcinogenic, high biocompatibility and low toxicity [3]. Sodium alginate is an anionic linear polysaccharide from algae with β-(1-4)-linked d-mannuronic acid units and α-(1-4)-linked l-guluronic acid units, low toxicity, low cost and non-immunogenic. It is good biocompatibility with living tissue [4]. Hydrogels containing magnetic nanoparticles (MNPs) have been demonstrated to be more convenient for controlling drug delivery and biomedical applications due to their super-paramagnetic properties, fast response, and non-contact action [5–8]. Alginate magnetic hydrogels have been applied to control drug and cell release both in-vitro and in-vivo by causing large deformation and volume changes of over 70% using an external MF [9]. Also, hydrogels with super-paramagnetic iron oxide nanoparticles have been used to increase the temperature of various drug-target systems by magnetic coupling between the magnetic moment of the nanoparticles and the alternating MF, which may be utilized for cancer hyperthermia treatments [10–13]. When specific drugs are loaded with magnetic hydrogels, they can be used for controlled drug release. Thus, the development of magnetic hydrogels holds high potential applications in tissue engineering and cell/drug delivery. Famotidine[3-(((2-((diaminomethylene)amino)thiazol-4-yl)methyl)thio)-*N'*-sulfamoylpropanimid amide] (Scheme 1) used for treatment of gastroesophageal reflux disease (GERD), duodenal ulcers and esophagitis [14]. The drug in the form of regular pills may cause side effects such as short and severe periods of diuresis, which causes severe discomfort to patients [15]. In order to overcome the limitations of the conventional release system, it is suggested to develop a new method for existing drugs in order to modify the release mechanism. These changes can increase drug therapeutic efficacy, reduce toxicity/ side effects, and improve patient compliance, which is attractive to the pharmaceutical industry because the development of new alternatives to expensive drugs requires a great deal of research and time [16, 17].



Scheme 1. The molecular structure of famotidine.

Experimental

General

Polyvinylalcohol (PVA) with molecular weight of 60000 and sodium alginate were purchased from Merck Germany. sodium alginate was purchased from Merck. Buffers; pH= 2 (Citric acid/hydrochloric acid/sodium chloride), pH=7 (potassium dihydrogen phosphate/disodium hydrogen phosphate), and pH = 8 (sodium tetraborate/hydrochloric acid) were purchased from Merck, redistilled water was used as a solvent. Potassium peroxodisulphate (KPS) extra pure and *N*,*N*′-methylenebisacrylamide (MBA) was purchased from Merck. Nano Fe_3O_4 particles (20-30 nm) were purchased from Aldrich.

Preparation of Fe_3O_4@PVA-SA hydrogel

In a three-necked round bottom flask equipped with a condenser and argon gas inlet, a solution of PVA (4.5g), sodium alginate (1.5g), nano-Fe_3O_4 (0.2g), and *N*,*N*′-methylene bisacrylamide (0.03g) was prepared by using redistilled water (100 mL). The solution was kept under nitrogen atmosphere at room temperature for 1h to remove air. Then potassium peroxodisulphate (0.09g) was added carefully and cross-linking reaction was carried out at 80°C under vigorously mechanical stirring. After 3h the reaction mixture was poured in to a Teflon mold and dried overnight at 80°C in a vacuum oven.

Drug loading

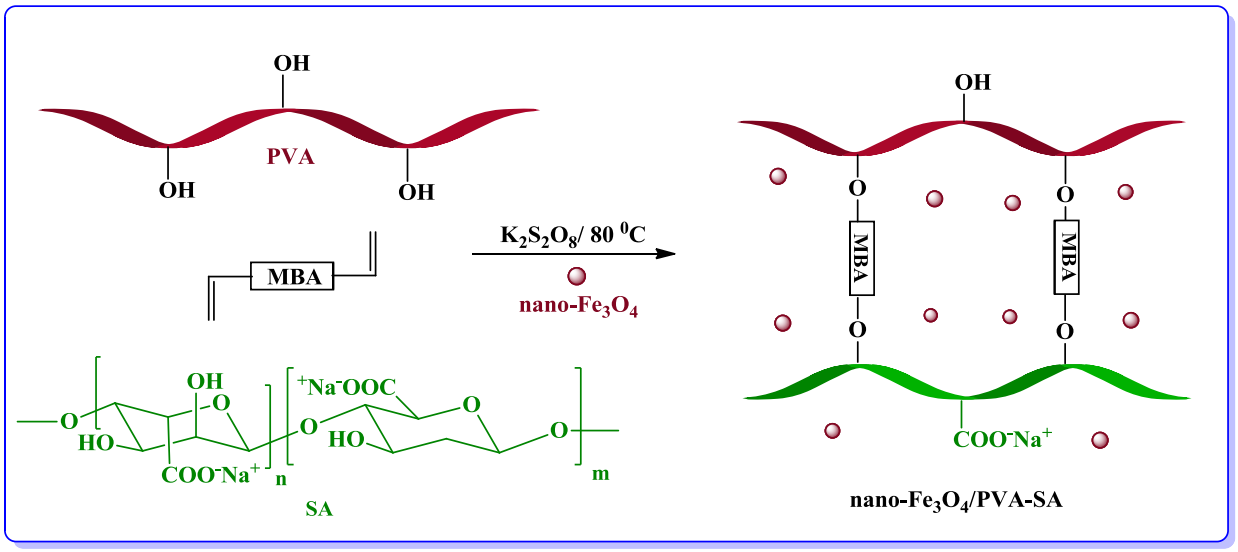
Fe_3O_4@PVA-SA (0.2 g) was added to 10 ml of drug solution (100 ppm) and put in a dark place for 6h to be completely trapped. In order to measure drug trapping, the amount of trapped drug at desired times was determined using UV spectroscopy and with the help of a calibration curve depicted of a set of drug solutions with known concentrations.

Drug releasing

Drug release of loaded famotidine in the Fe_3O_4@PVA-SA hydrogel in pH 2, pH 7 and pH 8 solutions buffered were performed at 25°C, 37°C and 40°C under static conditions. Hydrogel containing a specific amount of famotidine drug was added to release environment (20 ml). In a specific period of time, 5 ml of filtered samples were trapped and investigated as a function of time to determine the amount of released drug. The amount of released drug was determined using UV-Vis spectrophotometer at λ_{max}= 285 nm and with the help of a calibration curve depicted of a set of drug solutions with known concentrations. Also, cumulative percentage drug release was calculated using an equation obtained from a standard curve [18].

Results and Discussion

In this study magnetic PVA-SA hydrogel is prepared in aqueous solution at 80°C (Scheme 2). Also, the water absorptivity and the effects of temperature and pH on the loading and release of famotidine drug in magnetic PVA-SA hydrogel were studied.



Scheme 2. The preparation of magnetic PVA-SA hydrogel.

Characterization of magnetic PVA/SA hydrogel

The FT-IR spectrum of nano-Fe_3O_4/PVA-SA hydrogel was assigned (Figure 1). The IR spectra of the hydrogel clearly mark the presence of hydroxyl group of PVA and SA at 3278 cm^{-1} (O-H stretching), vibrations of methylene at 1414 cm^{-1} and carbonyl stretching of amide linkage of *N*,*N*′-methylenebisacrylamide at 1644 cm^{-1}. The spectra also contain characteristic bands of C-O-C stretching vibrations due to cross-linking of the chains at 1080 cm^{-1}. These data confirm that nano Fe_3O_4/PVA-SA hydrogel networks are formed.

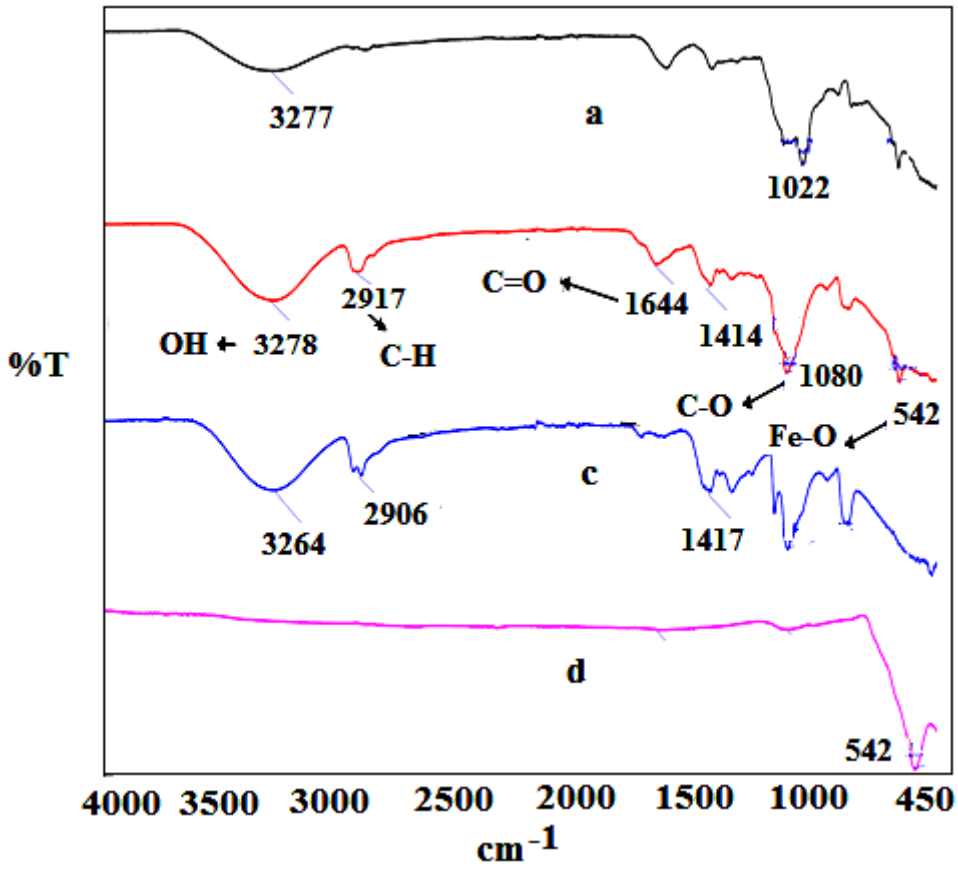


Figure 1. The FT-IR of, a- SA, b- nano-Fe_3O_4/PVA-SA, c- PVA, d- nano-Fe_3O_4.

SEM Analysis

Surface morphological study of magnetic PVA/SA hydrogel explored by scanning electron microscope is presented in Figure 2. The result of SEM analysis revealed that the surface of the magnetic PVA-SA hydrogel is porous that facilitates absorption of the drug after swelling. The average diameter of the fine non agglomerated particles was obtained to be nearly 82 nm for magnetic PVA-SA hydrogel. Moreover, dispersion of nano-Fe_3O_4 in the cross-section of magnetic PVA-SA hydrogel was examined through the EDX mapping image. The EDX image of magnetic PVA-SA hydrogel indicated homogenous distribution of of nano-Fe_3O_4 in the PVA-SA hydrogel matrix (Figure 3).

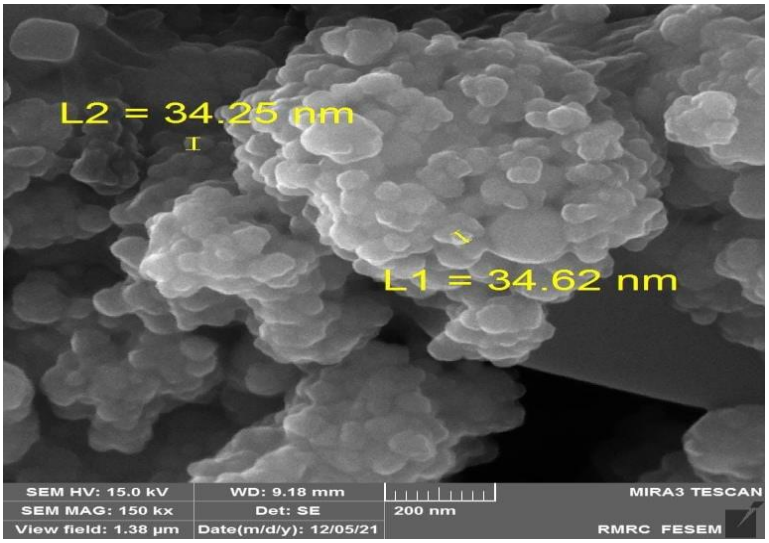


Figure 2. SEM image nano-Fe_3O_4/PVA-SA hydrogel.

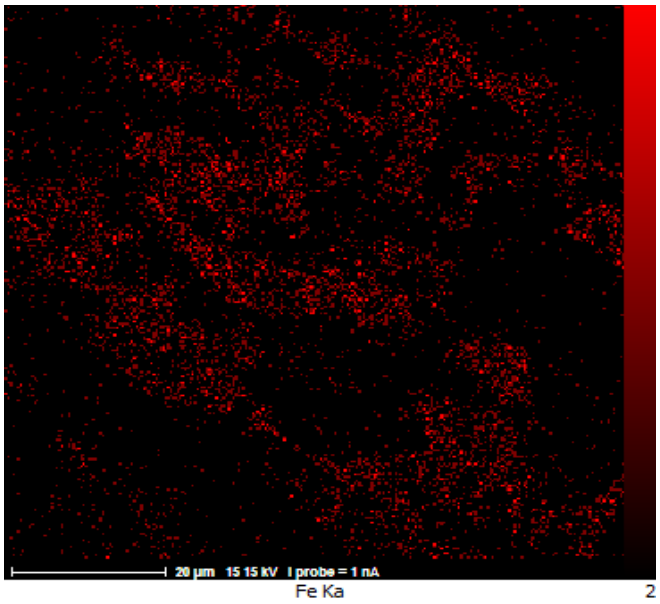


Figure 3. EDX distributions of nano-Fe_3O_4/PVA-SA hydrogel.

Also, The EDX spectrum of magnetic PVA-SA hydrogel displays the existence of C, N, O, and Fe elements in the nano-Fe_3O_4/PVA-SA hydrogel (Figure 4).

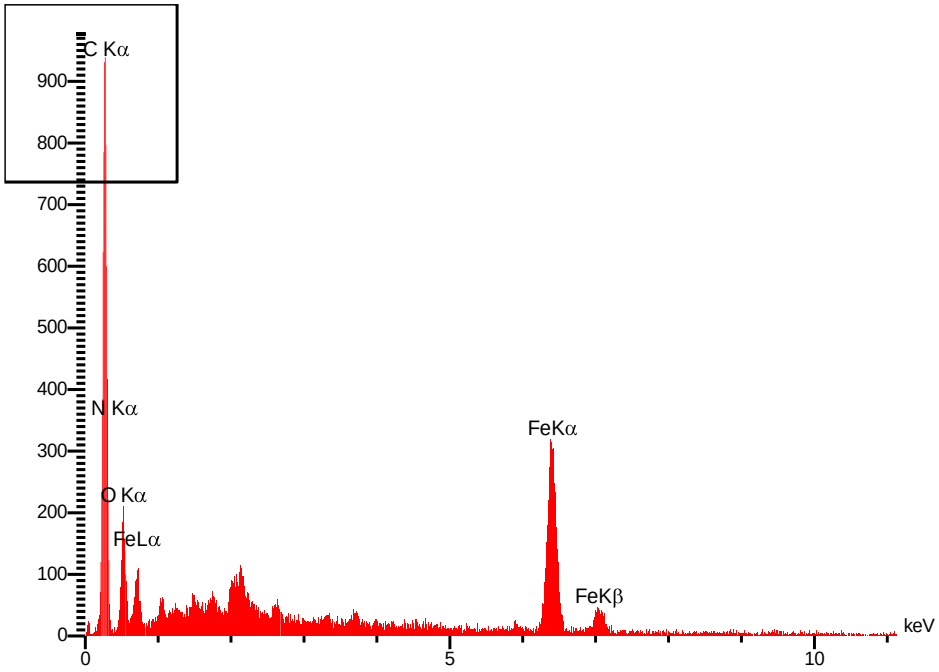


Figure 4. EDX spectra of magnetic PVA-SA hydrogel.

VSM analysis

Magnetic characterization of magnetic PVA-SA hydrogel was determined by vibrating sample magnetometer (VSM). Magnetization increased with increases in the magnetic field. The magnetic hysteresis loops of magnetic PVA-SA hydrogel is provided in Figure 5. The saturation magnetization about of 15 emu/g was determined for magnetic PVA-SA hydrogel. Evidently, the presented result can be attributed to the large amount of diamagnetic PVA and sodium alginate on the of magnetic PVA-SA hydrogel.

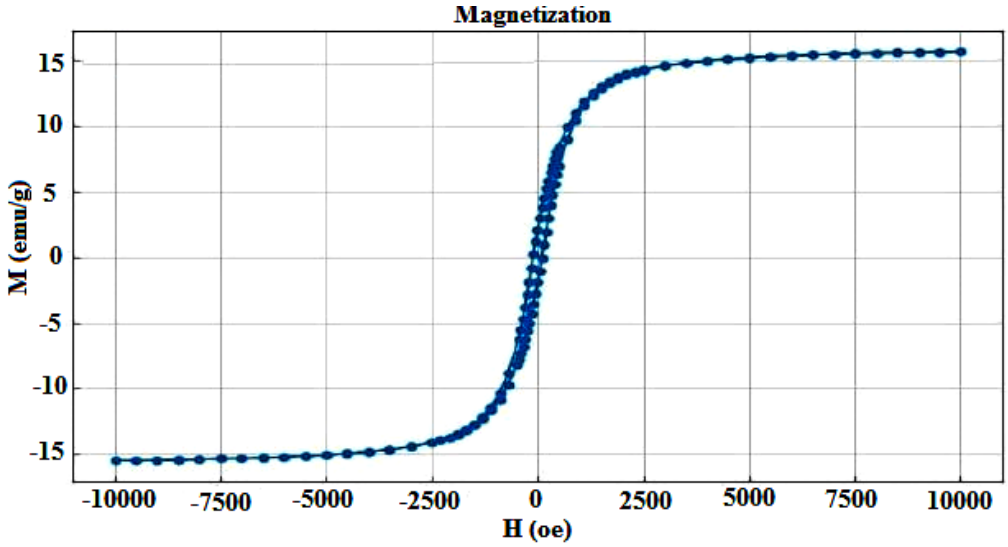


Figure 5. VSM magnetization curve of nano-Fe_3O_4/PVA-SA hydrogel.

Degree of swelling

Degree of swelling could be described as water absorption of the hydrogel (Eq.1). The pre-weighted samples were immersed in redistilled water at 25°C until the gel reached the equilibrium state of swelling. Then, the water on the surface of the swollen gel was removed with tissue paper, and immediately weighted. The degree of swelling was defined as follows:

$$\text{Degree of swelling (\%)} = (W_s - W_d)/W_d \times 100 \quad (1)$$

Where W_s and W_d are the weight of the swollen gel and the weight of dried gel, respectively. As shown in Figure 6 it observed that water absorption of magnetic PVA-SA hydrogel increase with increasing time to 7h and then saturated and reaches to equilibrium.

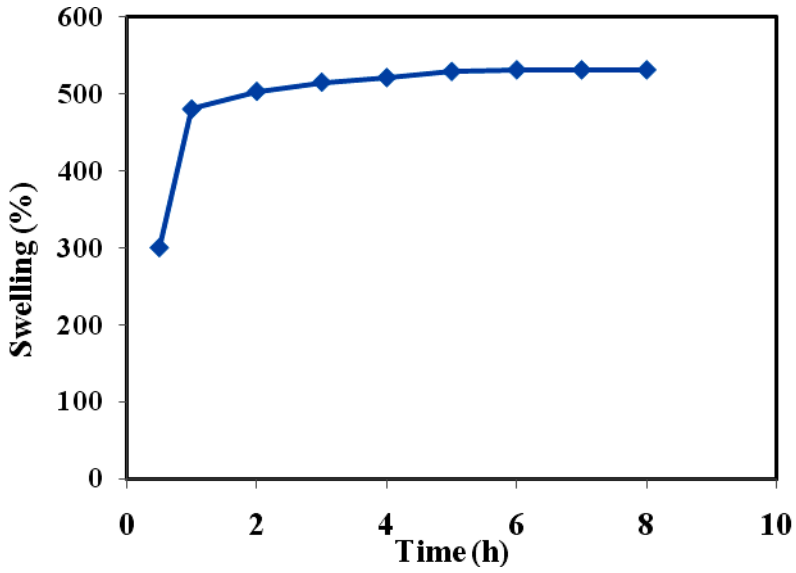


Figure 6. Degree of swelling versus immersion time (h) for nano-Fe_3O_4/PVA-SA hydrogel hydrogel at 25 °C.

The effect of pH on the release of famotidine

The release of the drug from the hydrogel depends on a number of factors, including the composition of the hydrogel, its geometric structure, the method of preparation, the type of drug and the environmental conditions during release, which pH is the most important factor. Selected pHs were 2, 7 and 8, respectively, which corresponded to the pH range in the acidic medium of the stomach, the neutral medium of the plasma and the upper limit of the alkaline environment of the intestine [19]. The amount of release of famotidine in acidic, neutral and alkaline buffers is shown in Figure 7. The highest and lowest releases of the famotidine drug were observed in buffers of pH= 2 and pH=8 respectively. The result showed that the release of furosemide from nano-Fe_3O_4/PVA-SA hydrogel is appropriate in acidic environment after 6 hours at room temperature with a value of 55.98 ppm. This is due to the higher swelling of the magnetic nano-Fe_3O_4/PVA-SA hydrogel in pH= 2 at 25°C.

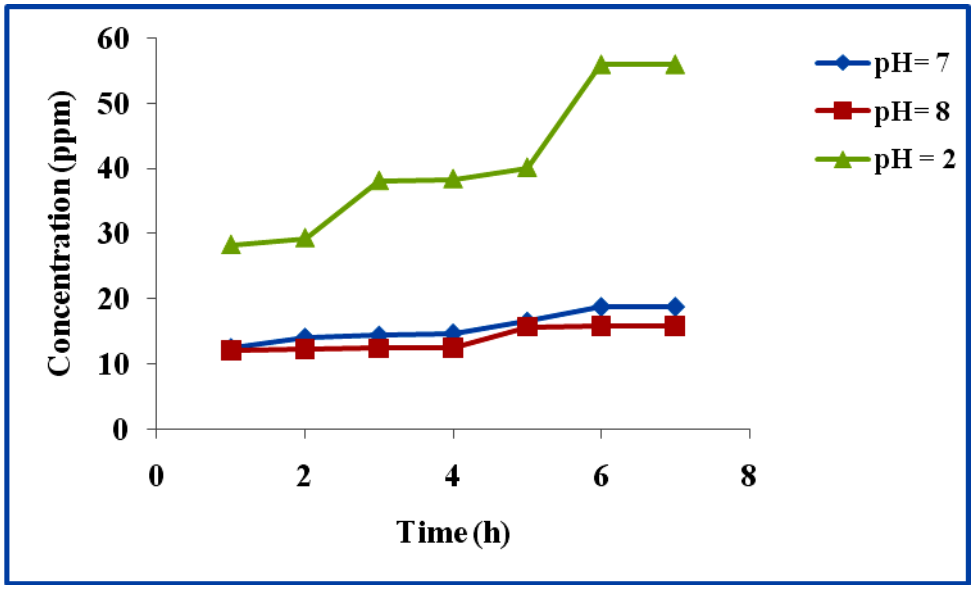


Figure 7. Concentration curve relative to time in different buffers at 25 °C.

The effect of temperature on the release of famotidine

The use of temperature as a biological stimulus is due to the fact that the temperature of human body changes from normal temperature 37°C in the presence of pathogenic and febrile agents. These temperature changes provide the appropriate stimulant for drug release in temperature-responsive systems in febrile illnesses. Figure 8 shows the effect of temperature on the amount of release of furosemide drug from synthesized magnetic PVA-SA hydrogel. As the

temperature increases to 37°C, the flexibility of the magnetic PVA-SA hydrogel increased and the driving force increases to release the drug from the magnetic PVA-SA hydrogel. Consequently, the higher amount of famotidine penetrates into the hydrogel. The highest drug release was obtained after 6 hours at 37°C in pH = 2 with a value of 57.95 ppm. Due to the acidity of the environment at pH = 2, in 37°C, it is suggested that the carboxylate functional groups in the nano-Fe_3O_4/alginate-PVA hydrogel and the amine functional groups of famotidine are protonated, and as a result, the hydrogen bond between the nano-Fe_3O_4/alginate-PVA hydrogel and protonated famotidine is decreases (Figure 9). As a result, more amount of famotidine drug is released from nano-Fe_3O_4/alginate-PVA hydrogel at 37°C.

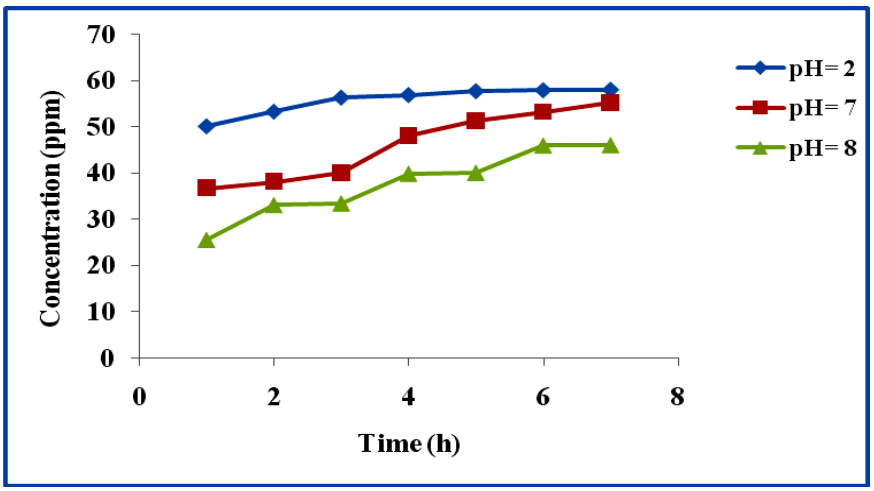


Figure 8. Concentration curve relative to time in different buffers at 37 °C.

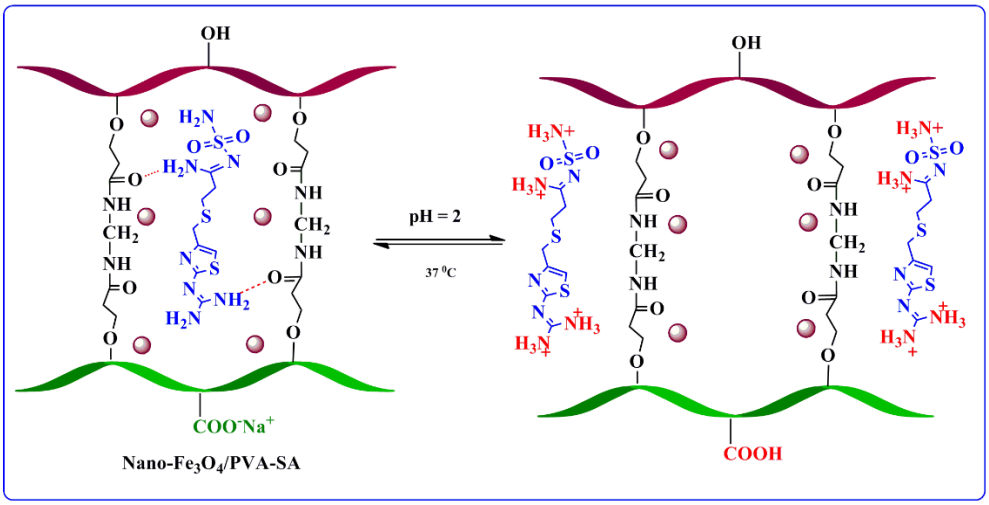


Figure 9. Proposed release mechanism of famotidine from nano-Fe_3O_4/PVA-SA hydrogel at pH=2.

Conclusion

In this work, the nano-Fe_3O_4/PVA-SA hydrogel was prepared from aqueous polyvinylalcohol and sodium alginate by potassium peroxydisulphate in the presence of *N*,*N*′-methylene bisacrylamide and Fe_3O_4 nanoparticles. The prepared magnetic hydrogel showed good swelling capacity in water at room temperature. The magnetic hydrogel was investigated for famotidine release to reveal its potential use in drug delivery system. Nano-Fe_3O_4/PVA-SA hydrogel was shown to have a sustained famotidine release profile at pH 2. These results indicated that Nano-Fe_3O_4/PVA-SA hydrogel is useful as a biodegradable matrix for drug release for pharmaceutical applications. In vivo studies are needed to better evaluate the release of famotidine for use in oral drug delivery systems.

Acknowledgements

Financial support by Rasht Branch, Islamic Azad University is gratefully acknowledged.

Declaration of Interests

The authors declare that there is no conflict of interests.

References

1. Campoccia D, Doherty P, Radice M, Brun P, Abatangelo G, Williams DF. Semisynthetic resorbable materials from hyaluronan esterification. Biomaterials.1998;19: 2101-27.

2. Prestwich GD, Marecak DM, Marecak JF, Vercruysse KP, Ziebell MR. Controlled chemical modification of hyaluronic acid: synthesis, applications, and biodegradation of hydrazide derivatives. Journal of Controlled Release. 1998;53:93-103.

3. M.M. Lakouraj, M. Tajbakhsh, M. Mokhtary, Synthesis and swelling characterization of cross-linked PVP/PVA hydrogels. Iranian Polymer Journal. 2005;14:1022-30.

4. Wangkaya R, Chuysinuan P, Pengsuk C, Techasakul S, Lirdprapamongkol K, Srvasti J, Nooeaid P. Electrospinning of alginate/soy protein isolated nanofibers and their release characteristics for biomedical applications. Journal of Science: Advanced Materials and Devices. 2017;2:309–16.

5. Medeiros SF, Santos AM, Fessi H, Elaissari A, Stimuli-responsive magnetic particles for biomedical applications. International Journal of Pharmaceutics. 2011;403: 139-61.

6. Neuberger T, Schöpf B, Hofmann H, Hofmann M, von Rechenberg B. Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system. Journal of Magnetism and Magnetic Materials. 2005;293*:* 483-96.

7. Masoumi B, Mokhtary M, Preparation and characterization of magnetic gelatin-polyvinyl alcohol hydrogel for using in the release of furosemide drug. Journal of Applied Chemical Research. 2023;17: 8-20.

8. Laurent S, Bridot JL, Muller RN. Magnetic iron oxide nanoparticles for biomedical applications. Future Medicinal Chemistry. 2010;2: 427-49.

9. Zhao X, Kim J, Cezar CA, Huebsch N, Lee K, Bouhadir K, Mooney DJ. Active scaffolds for on-demand drug and cell delivery. Proceedings of the National Academy of Sciences of the United States of America. 2011;108: 67-72.

10. Weigel T, Mohr R, Lendlein A. Investigation of parameters to achieve temperatures required to initiate the shape-memory effect of magnetic nanocomposites by inductive heating. Smart Materials and Structures. 2009;18:025011.

11. Hernandez R, Sacristan J, Asin L, Torres TE, Ibarra MR, Goya GF, Mijangos C. Magnetic hydrogels derived from polysaccharides with improved specific power absorption: potential devices for remotely triggered drug delivery. The Journal of Physical Chemistry B. 2010;114: 12002-007.

12. Meyer DE, Shin BC, Kong GA, Dewhirst MW, Chilkoti A. Drug targeting using thermally responsive polymers and local hyperthermia. Journal of Controlled Release. 2002;74: 213-24.

13. Das M, Senapati P. Furosemide-loaded Alginate Microspheres Prepared by Ionic Cross-linking Technique: Morphology and Release Characteristics. Indian Journal of Pharmaceutical Sciences. 2008;70:77-84.

14. Ali S Taha, Caroline McCloskey, Rakesh Prasad, Vladimir Bezlyak, Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. Lancet 2009; 374:119–25.

15. Bhagwat R, Vaidhya I. Novel Drug Delivery Systems: an Overview. International Journal of Pharmaceutical Sciences and Research, 2013;4: 970-82.

16. Bezerra ICS, Moma MSM, Freitas ED, Silva MGC, Vieira MGA. Development of a modified drug delivery system through the incorporation of furosemide into sericin and alginate matrix using the experimental design approach. Journal of Chemical Technology & Biotechnology. 2021;96: 650-661.

17. Meka L, Kesavan B, Kalamata VN, Mohaneaga C, Bandari S, Vobalaboina V, Yamsani MR. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. Journal of Pharmaceutical Sciences.2009;98: 2122-32.

18. Peppas NA, Zach Hilt J, Khademhosseini A, Langer R. Hydrogels in biology and medicine: from molecular principles to bionanotechnology. Advanced Materials. 2006;18:1345-60.

19. Devarakonda B, Otto DP, Judefeind A, Hill RA, de Villiers MM. Effect of pH on the solubility and release of furosemide from polyamidoamine (PAMAM) dendrimer complexes. International Journal of Pharmaceutics. 2007;345:142-53.