Carbohydrate Polymers 77 (2009) 634–638

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

pH-sensitive starch hydrogels via free radical graft copolymerization, synthesis and properties

Mohammad Reza Saboktakin *, Abel Maharramov, Mohammad Ali Ramazanov

Nanostructured Materials Synthesis Laboratory, Department of Nanotechnology, Baku State University, Baku, Azerbaijan

ARTICLE INFO

Article history:
Received 5 November 2008
Accepted 4 February 2009
Available online 11 February 2009

Keywords:
Starch
pH-sensitive hydrogel
Free radical graft copolymerization
Drug release

ABSTRACT

Natural polymers are considered high value polymeric materials because of their potential as biocompatible materials with medical applications. The chemical modification of natural polymers by grafting has received considerable attention in recent years because of the wide variety of monomers available. As the first part of a continued research on conversion of carboxymethyl starch (CMS) to useful biopolymer-based materials, large numbers of carboxylic functional groups were introduced onto CMS by grafting with polymethacrylic acid (PMAA). Free radical graft copolymerization was carried out at 70 °C, bis-acrylamide as a crosslinking agent and persulfate as an initiator. Equilibrium swelling studies were carried out in enzyme-free simulated gastric and intestinal fluids (SGF and SIF, respectively). Also, the sodium dicofenac as a model drug was entrapped in these nano-gels and the in vitro release profiles were established separately in both enzyme-free SGF and SIF. The drug release was found to be faster in SIF. The drug-release profiles indicate that amount drug release depends on their degree of swelling, and crosslinking. This hydrogel converted to nano by freeze-drying method and characterized by scanning electron microscopy, differential scanning calorimetry and FT-IR spectrometry.

1. Introduction

Natural polymers have potential pharmaceutical applications because of their low toxicity, biocompatibility, and excellent biodegradability. Starch is the most abundant, renewable biopolymer, which is very promising raw material, available at low cost for preparing of various functional polymers. Carboxymethyl starch (CMS) widely used in pharmaceuticals; however, it may need to be further modified for some special applications (BrØndsted & Kopeček, 1990; Chiu, Hsiue, Lee, & Huang, 1999; Fanta & Doane, 1986; Giammona, Pitarresi, Cavallora, & Spadaro, 1999; Jabbari & Nozari, 2000; Krogars et al., 2000). Among diverse approaches that are possible for modifying polysaccharides, grafting of synthetic polymer is a convenient method for adding new properties to a polysaccharide with minimum loss of its initial properties (Athawale & Rathi, 1997; Peppas, 1987; Saboktakin, Maharramov, & Ramazanov, 2007). Graft copolymerization of vinyl monomers onto polysaccharides using free radical initiation, has attracted the interest of many scientists. Up to now, considerable works have been devoted to the grafting of vinyl monomers onto the substrates, especially Starch and cellulose (Xu, Li, 2005; Jabbari & Nozari, 2000). Existence of polar functionally groups as carboxylic acid need not only for bioadhesive properties but also for pH-sensitive properties of polymer (Ratner, 1989; Thierry, Winnik, Mehri, & Tabrizian, 2003). Because the increase of MAA content in the hydrogels provides more hydrogen bonds at low pH and more electrostatic repulsion at high pH. It is as a part of our research program on CMS modification to prepare materials with pH-sensitive properties for uses as drug delivery (Bloembergen & Pershan, 1967; Mahfouz, Hamm, & Taupitz, 1997; Schmitz et al., 2000). The free radical graft copolymerization poly methacrylic acid onto CMS was carried out at 70 °C, bis-acrylamide as a crosslinking agent and persulfate as an initiator. Polymer bonded drug usually contain one solid drug bonded together in a matrix of a solid polymeric binder. They can be produced by polymerizing a monomer such as methacrylic acid (MAA), mixed with a particulate drug, by means of a chemical polymerization catalyst, such as AIBN or by means of high-energy radiation, such as X-ray or γ-ray (Jabbari & Nozari, 2000). The mixture modified hydrogel and dicofenac as a model drug was converted to nano by freeze-drying method. The equilibrium swelling studies and in vitro release profiles were carried out in enzyme-free simulated gastric and intestinal fluids [SGF (pH 1) and SIF (pH 7.4), respectively)] (Bloembergen, 1999). The influences of different factors, such as content of MAA in the feed monomer and swelling were studied (Saboktakin, Maharramov, & Ramazanov, 2008; Xu & Li, 2005).

* Corresponding author.
E-mail address: saboktakin123@yahoo.com (M.R. Saboktakin).

0144-8617/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2009.02.004

2. Materials and methods

2.1. Measurements

The Fourier transfer infrared (FT-IR) spectra of the copolymer were recorded on Perkin 810 spectrometer in KBr disks at room temperature, in the region 4000–450 cm^{-1}. The powder morphology CMS/MAA copolymer in the form of pellets (to measure grain size) was investigated using Philips XL-30 E SEM scanning electron microscope (SEM) at 30 kV (max.). The samples were prepared by physical vapor disposition method. The gold layer thickness at these samples was 100 Å. There was carried out in chemistry department of Tarbiat Modares university. The DSC curves were obtained on a TGA/SDTA 851 calorimeter at heating and cooling rates of 10 °C/min under N_2. The amount of released drug was determined on a Philips PU 8620 UV spectrophotometer at the absorption maximum of the free drug in aqueous alkali) λ_{max} = 275 nm) using a 1 cm quartz cell. Enzyme-free SGF (pH 1) or SIF (pH 7.4) were prepared according to the method described in the US Pharmacopeia.

2.2. Synthesis of carboxymethyl starch

Starch (M_w = 9500 g mol^{-1}, 1 g) and NaOH (1.2 g) were suspended in isopropanol/H_2O (85/15, 22 ml) and heated to 60 °C. Monochloroacetic acid (1.5 g) was added slowly and the mixture was stirred for 2 h at 60 °C. After cooling to room temperature, the organic solvent was removed under reduced pressure and the aqueous phase was neutralized with acetic acid. Cold MeOH (30 ml) was added and the solution was kept at 4 °C overnight. After drying of the precipitate at high vacuum carboxymethyl starch (1) (1.5 g) was obtained. Titration of starch–methylcarboxylate (1) (57 mg) with 0.1 M HCl (2.6 ml, 0.26 mmol) and bromophenol blue in acetone/H_2O (1:1, 10 ml) resulted in 3.3 mmol COO^- g^{-1}. Therefore, on average, degree of substitution of carboxymethyl starch (1) is 0.49 (DS = 0.49) (Xu & Li, 2005).

2.3. The free radical graft copolymerization of carboxymethyl starch

CMS with different molar ratios of methacrylic acid were polymerized at 60–70 °C in a thermostatic water bath, bis-acrylamide as a crosslinking agent (CA), using persulfate as an initiator ([I] = 0.02 M) and water as the solvent (50 ml). The polymeric system was stirred by mechanical stirrer to sticky hydrogel was formed and it was separated from medium without solvent addition. All experiments were carried out in Pyrex glass ampoules. After the specific time (48 h), the precipitated network polymer was collected and dried in vacuum.

2.4. Preparation of nanoparticle

Copolymer (50 mg) and sodium dicofenac (10 mg) was dispersed with stirring in 25 ml deionised water. After approximately 180 min, the sample was sprayed into a liquid nitrogen bath cooled down to 77 K, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze–dryer. In the freeze-drying process, the products are dried by a sublimation of the water component in an iced solution.

3. Results and discussion

The composition of the polymer defines its nature as a neutral or ionic network and furthermore, its hydrophilic/hydrophobic characteristics. Ionic hydrogels, which could be cationic, containing basic functional groups or anionic, containing acidic functional groups, have been reported to be very sensitive to changes in the environmental pH. The swelling properties of the ionic hydrogels are unique due to the ionization of their pendent functional groups. The equilibrium swelling behaviour of ionic hydrogels containing acidic and/or basic functional groups is illustrated in Fig. 2. Hydrogels containing basic functional groups is found increased swelling activity in acidic conditions and reduced in basic conditions but on the other hand pH-sensitive anionic hydrogels shows low swelling activity in acidic medium but very high activity in basic medium. As shown in Fig. 1, an increase in the content of MAA in the feed monomer mixtures resulted in less swelling in simulated gastric fluid but greater swelling in and simulated intestinal fluids. This is because the increase of MAA content in the hydrogels provides more hydrogen bonds at low pH and more electrostatic repulsion at high pH.

Fig. 3a and b show scanning electron microscope (SEM) of graft starch copolymer with polymethacrylic acid and nano-polymer bonded drug, respectively.

3.1. Compare of swelling ratio nano and micro

It appears that the degree of swelling depends on their particle size. As shows in Fig. 1, a decrease in the molecular size of carriers increased the swelling rate.

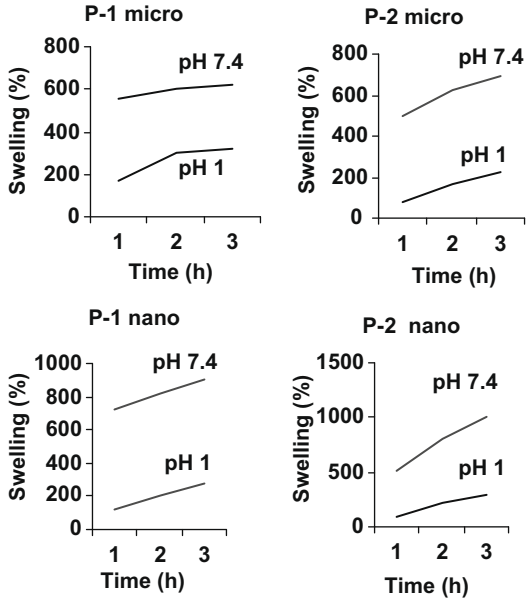

Fig. 1. Time-dependent swelling behavior of micro-and nano-carriers as a function of time at 37 °C.

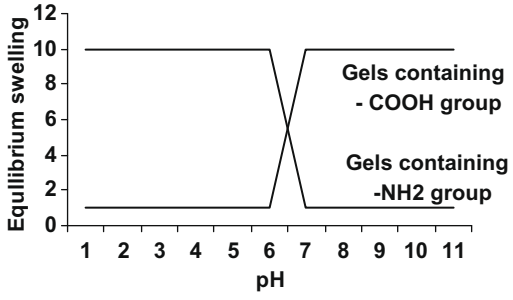

Fig. 2. Equilibrium degree of swelling in response to pH.

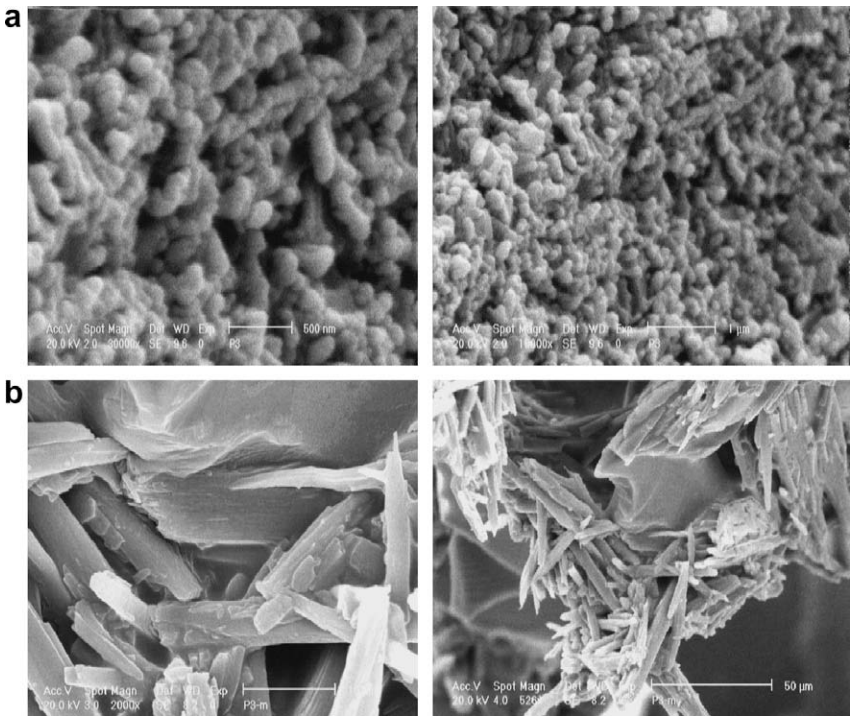

Fig. 3. SEM of (a) grafted starch copolymer (b) nano-polymer bonded drug.

3.2. Thermal behavior

The thermal behavior of a polymer is important in relation to its properties for controlling the release rate in order to have a suitable drug dosage form. The glass transition temperature (T_g) was determined from the DSC thermograms. The values are given in Table 1. The higher T_g values probably related to the introduction of crosslinks, which would decrease the flexibility of the chains and the ability of the chains to undergo segmental motion, which would increase the T_g values (Bloembergen & Pershan, 1967). On the other hand the introduction of a strongly polar carboxylic acid group can increase the T_g value because of the formation of internal hydrogen bonds between the polymer chains.

3.3. Fourier transfer infrared spectra

Fig. 4a shows the FT-IR spectrum of pure carboxymethyl starch (CMS), where the % of transmittance is plotted as a function of wave number (cm^{-1}). The wide peak around 3411 cm^{-1} is attributing to the O–H stretching vibrations of CMS. The peaks at 1597 and 1417 cm^{-1} attribute to the COO^- unsymmetrical and symmetrical stretching vibration, respectively. The peaks from the FTIR spectrum of CMS–polymethacrylic acid graft copolymer at 3250 cm^{-1} showed the presence of terminal primary amino groups (Fig. 4b). In this case, the broad peak at 3200 cm^{-1} is the strong evidence of the presence of NH_3^+.

Table 1
DSC data and composition of copolymer.

Polymers	Molar composition of monomers in the feed				Degree of substitution (DS)[a]	T_g (°C)
	CMS (gr)	MAA (gr)	CA (gr)	IN (gr)		
P-1		1	3	0.05	0.49	130
				0.05	0.49	142
P-2		1	2	0.05		
				0.005		

[a] The method described in the literature (Xu & Li, 2005).

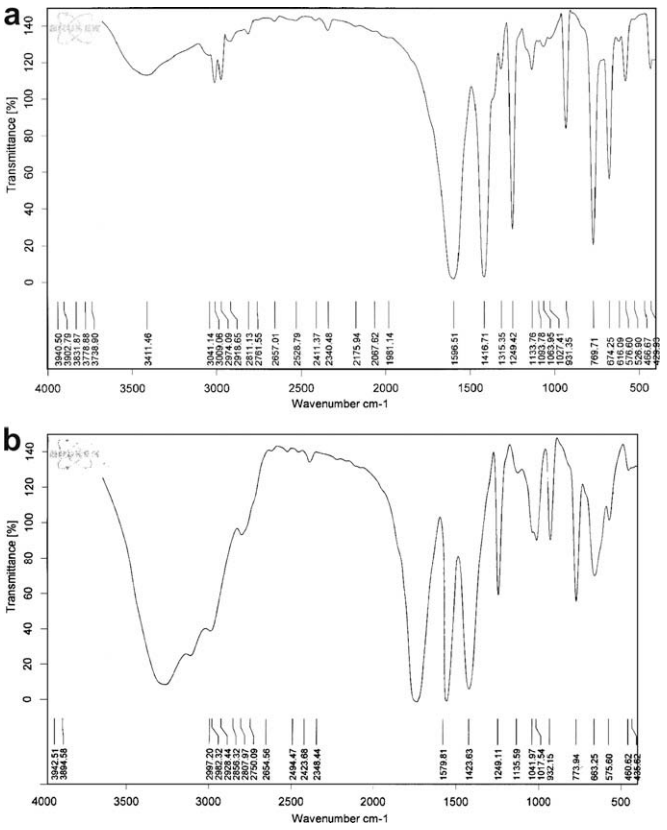

Fig. 4. FT-IR spectrum of (a) pure carboxymethyl starch (CMS) (b) CMS–PMAA grafted copolymer.

3.4. Measurement of swelling ratio

The resulting network polymers swell and become soft in solvents such as H_2O and most organic solvents without dissolving. To measure the swelling, preweighed dry starch hydrogels were immersed in various buffer solutions (pH 7.4 and 1) at 37 °C. After excess water on the surface was removed with the filter paper, the weight of the swollen samples was measured at various time intervals. The procedure was repeated until there was no further weight increase. The degree of swelling was calculated according the relation:

$$SW(\%) = [(W_s - W_d)/W_d] \times 100$$

where W_s and W_d represent the weight of swollen and dry samples, respectively. Time-dependent swelling behavior of crosslinked polymers in pH 1 and 7.4 at 37 °C are plotted in Fig. 1.

3.5. Characterization of hydrolysis compound

Polymer–drug adduct (90 mg) was dispersed in 20 ml of pH 8 buffered solution. The reaction mixture was maintained at 37 °C. After 24 h the hydrolysis solution was sampled and neutralized with 1 M HCl and the solvent was evaporated in vacuo. The resulting crude product was treated with 30 ml of ethyl ether and heated. The suspension was then filtered and the solvent was evaporated under reduced pressure. The residual solid was recrystallized from ethanol and characterized by UV and melting point measurements.

3.6. In vitro release studies

Nano- and micro-polymer bonded drug (50 mg) were poured into 3 ml of aqueous buffer solution (SGF: pH 1 or SIF: pH 7.4). The mixture was introduced into a cellophane membrane dialysis bag. The bag was closed and transferred to a flask containing 20 ml of the same solution maintained at 37 °C. The external solution was continuously stirred, and 3 ml samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. Triplicate samples were used. The sample of hydrolyzate was analyzed by UV spectrophotometer, and the quantity of sodium dicofenac was determined using a standard calibration curve obtained under the same conditions. Figs. 6 and 7 show UV spectrum and calibration curve of pure sodium dicofenac at phosphate buffer (pH 8), respectively.

3.7. Drug release studies by hydrolysis of polymer bonded drug

For learn of effect of the nature and size of the drug in drug delivery, we study drug release of the polymers containing nano- and micro-containing sodium dicofenac as a pharmaceutically active compound as a function of time is shown in Fig. 5a and b. The concentration of sodium dicofenac released at selected time intervals was determined by UV spectrophotometry at 275 nm. We have studied the drug release behavior of the polymers under physiological conditions. The concentration of drug released at selected time intervals was determined by UV spectrophotometry. Important parameter for increasing of diffusion coefficient is decreased of particle size. It appears that the degree of drug release polymers depends on their particle size. As shown in Fig. 5, a decrease in the molecular size increased the drug release rate. In the other hand, the chemical structure of the drug too is an important factor in hydrolytic behavior of polymeric prodrugs.

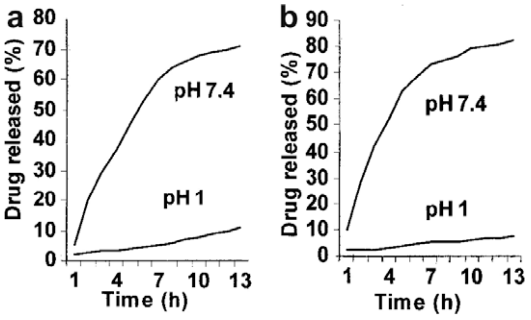

Fig. 5. Release of drug from (a) micro- and (b) nano-polymeric carriers as a function of time at 37 °C.

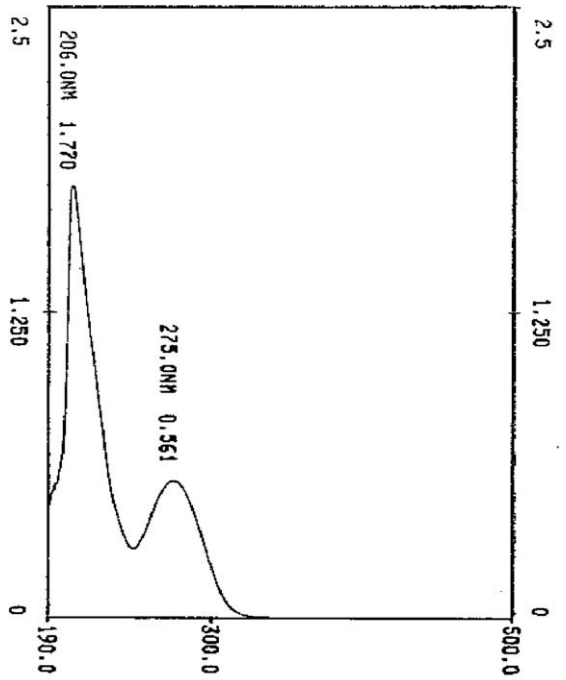

Fig. 6. UV spectrum of sodium dicofenac at phosphate buffer (pH 8).

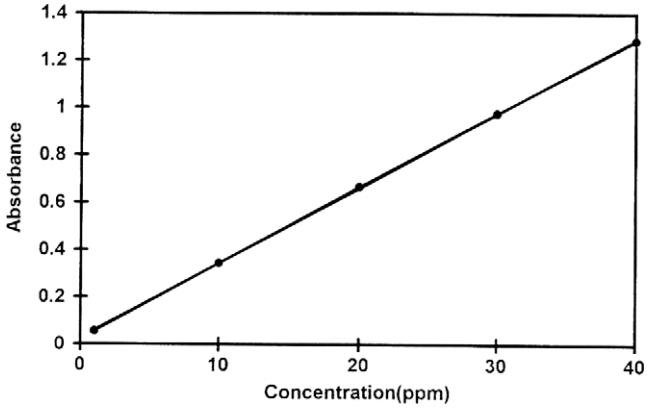

Fig. 7. Calibration curve of sodium dicofenac at phosphate buffer (pH 8).

4. Conclusions

The swelling and hydrolytic behavior of the hydrogels was dependent on the content of MAA groups and caused a decrease in gel swelling in SGF or an increase in gel swelling in SIF. Modified CMS with different contents of MAA and CA by graft copolymeriza-

tion reactions were carried out under microwave-radiation. The swelling of the hydrogels was dependent on the content of MAA groups and caused a decrease in gel swelling in SGF or an increase in gel swelling in SIF. Incorporation of MAA made the hydrogels pH-dependent and the transition between the swollen and the collapsed states occurred at high and low pH. The swelling ratios of the hydrogels increased at pH 7.4, but decreased at pH 1 with increasing incorporation of MAA.

References

Athawale, V. D., & Rathi, S. C. (1997). Role and relevance of polarity and solubility of vinyl monomers in graft polymerization onto starch. *Reactive and Functional Polymers, 34*, 11–17.

Bloembergen, N. (1999). Surface nonlinear optics: a historical overview. *Applied Physics, B Lasers and Optics, 68*(3), 289.

Bloembergen, N., & Pershan, P. S. (1967). Adsorption of 4-picoline and piperidine to the hydrated SiO. *Physical Review, 128*(2), 606.

BrØndsted, H., & Kopeček, J. (1990). Hydrogels for site-specific oral delivery. *Proceedings of the International Symposium on Controlled Release Bioactive Materials, 17*, 128–129.

Chiu, H. C., Hsiue, G. H., Lee, Y. P., & Huang, L. W. (1999). Synthesis and characterization of pH-sensitive dextran hydrogels as a potential colon-specific drug delivery system. *Journal of Biomaterials Science, Polymer Edition, 10*, 591–608.

Fanta, G. F., & Doane, W. M. (1986). Grafted starches. In O. B. Wurzburg (Ed.), *Modified starches: Properties and uses* (pp. 149–178). Boca Raton (Florida): CRC.

Giammona, G., Pitarresi, G., Cavallora, G., & Spadaro, G. (1999). New biodegradable hydrogels based on an acryloylated polyaspartamide crosslinked by gamma irradiation. *Journal of Biomedicals Science, Polymer Edition, 10*, 969–987.

Xu, Honghua, & Li, Tiejing (2005). The analysis of boundary functions of CMS reaction factors. *Journal of Nature and Science, 3*(2).

Jabbari, E., & Nozari, S. (2000). Swelling behavior of acrylic acid hydrogels prepared by γ-radiation crosslinking of polyacrylic acid in aqueous solution. *European Polymer Journal, 36*, 2685–2692.

Krogars, K., Heinamaki, J., Vesalahti, J., Marvola, M., Antikainen, O., Yliruusi, J., et al. (2000). Extrusion–spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery. *International Journal of Pharmaceutics, 199*, 187–194.

Mahfouz, A., Hamm, B., & Taupitz, M. (1997). Characterization of liver lesions with mangafodipir Trisodium enhanced. *European Radiology, 7*, 507.

Peppas, N. A. (1987). *Hydrogels in medicine and pharmacy*. Boca Raton, FL: CRC Press.

Ratner, B. D. (1989). Comprehensive polymer science – The synthesis, characterisation, reactions & applications of polymers. In S.K. Aggarwal (Ed.), Vol. 7. Oxford: Pergamon Press, pp. 201–247.

Saboktakin, M. R., Maharramov, A., & Ramazanov, M. A. (2007). Synthesis and characterization of aromatic polyether dendrimer/mesalamine(5-ASA) nanocomposite as drug carrier system. *Journal of American Science, 3*(4), 45.

Saboktakin, M. R., Maharramov, A., & Ramazanov, M. A. (2008). Poly(amidoamine)(PAMAM)/CMS dendritic nanocomposite for controlled drug delivery. *Journal of American Science, 4*(1), 48.

Schmitz, S. A., Winterhalter, S., Schiffler, S., Gust, R., Wagner, S., Kresse, M., et al. (2000). Superparamagnetic iron oxide-enhanced MRI of atherosclerotic plaques in watanabe hereditable hyperlipidemic rabbits. *Investigative Radiology, 35*, 460–471.

Thierry, B., Winnik, F. M., Mehri, Y., & Tabrizian, M. (2003). *Journal of the American Chemical Society, 125*, 7494.