ELSEVIER

International Journal of Pharmaceutics 224 (2001) 151–158

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Investigation of active substance release from poly(ethylene oxide) hydrogels

Hülya Savaş *, Olgun Güven

Department of Chemistry, Hacettepe University, 06532 Beytepe, Ankara, Turkey

Received 14 January 2001; received in revised form 1 May 2001; accepted 23 May 2001

Abstract

The uptake and controlled release of model active substances from poly(ethylene oxide), (PEO), hydrogels synthesized by irradiation were investigated. For the characterization of network structure of PEO hydrogels, swelling properties in water and the number average molecular weight between crosslinks were determined. Salicylic acid, phthalic acid and resorcinol were used as model substances for their controlled release from PEO hydrogels. The effects of dose rate, total dose and chemical structure of active substance on the uptake and release have been studied. The active substance uptake capacity of hydrogels was found to be lowest for phthalic acid and highest for resorcinol in the gel system obtained by irradiation both at low and high dose rates. The release was lowest both in rate and in total amounts in hydrogels containing phthalic acid, more in those with salicylic acid and highest in those with resorcinol. The physical and chemical factors affecting the release of model compounds such as the network structure of hydrogels and hydrogen bond formation between the adsorbent and PEO chains were discussed.

Keywords: Controlled release; Poly(ethylene oxide); Hydrogel; Salicylic acid; Phthalic acid; Resorcinol

1. Introduction

Hydrogels are crosslinked hydrophilic polymers capable of imbibing large volumes of water, yet insoluble in water, but swellable when immersed. The water retaining capacity of these materials is due to the presence of hydrophilic functional groups such as –OH, –COOH, $–CONH_2$, –CONH, $–SO_3H$ along the polymer chains (Peppas and Mikos, 1986; Kudela, 1987; Saraydın et al., 1995).

Hydrogels are known as good candidates for controlled release formulations for pharmaceutical applications mostly due to their high biocompatibility. In recent years, these polymeric carriers have been extensively considered in sustained and controlled release devices for the delivery of water-soluble drugs (Korsmeyer and Peppas, 1983; Peppas et al., 1980).

The use of radiation in the preparation of hydrogels has recently been reviewed by Rosiak and Olejnizak, who have investigated the medical ap-

* Corresponding author. Tel.: +90-312-297-7973; fax: +90-312-299-2163.

E-mail address: hulya@hacettepe.edu.tr (H. Savaş).

0378-5173/01/$ - see front matter
PII: S0378-5173(01)00745-1

plications of radiation formed hydrogels (Rosiak and Olejniczak, 1993). Trigo and his coworkers have examined as a function of temperature, initial drug load and thickness of PHEMA disc for drug release kinetics (Trigo et al., 1994). The 5-FU(fluorouracil) release was studied as a function of temperature, disc thickness, disc load and degree of crosslinking of the poly(2-hydroxyethyl methacrylate) gels (Garcia et al., 1994). The controlled release of peptides and proteins from hydrogels obtained by radiation-induced polymerization of 2-hydroxy-ethylmethacrylate at low temperature was studied. The release data as a function of swellability and porosity of polymer matrices were discussed (Carenza et al., 1993).

Saraydın and his coworkers have investigated the swelling kinetics of acrylamide–crotonic acid hydrogels containing active agents such as sodium 2,2 dichloropropionate, ammonium nitrate, potassium nitrate and ammonium sulfate and the release of these active agents from acrylamide–crotonic acid hydrogels (Saraydın et al., 1998).

Pekala and his coworkers have investigated and prepared radiation crosslinked hydrogels as sustained release drug delivery systems (Pekala et al., 1986). The controlled release of proteins and peptides from hydrogels synthesized by gamma ray induced polymerization was studied (Caliceti et al., 1992).

Nontoxic water-soluble PEO polymer is widely used in the chemical, cosmetic and pharmaceutical industries (Powell, 1980). PEO hydrogel is applied as a component of biomedical devices such as wound coverings, drug delivery systems, haemodialysis membrane etc., preferably in the form water-swellable but insoluble hydrogel.

The gels of PEO produced in water solution can be dehydrated. The material so produced is enormously hydrophilic. These hydrogels are being used as microbiological culture media as well (Bailey and Koleske, 1976).

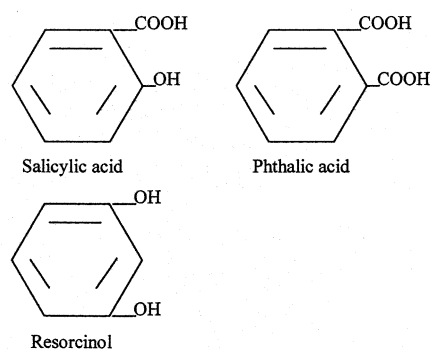
In this study, active substance adsorption capacity and active substance release of PEO hydrogels synthesized by gamma irradiation of respective aqueous solutions has been investigated.

2. Materials and methods

2.1. Materials

PEO used in this study was a commercial product obtained from BDH Chemicals Ltd. The number average molecular weight of the sample, M_n, is calculated by gel-permeation chromatography as 73 000.

The salicylic acid ($C_6H_4(OH)COOH$) used in active substance release was obtained from BDH Chemicals Ltd. Phthalic acid ($C_6H_4(COOH)_2$) was a product of Hopkins and Williams Chemicals Ltd and resorcinol ($C_6H_4(OH)_2$) was obtained from Fisher Chemical Ltd.



2.2. Preparation of hydrogels

Aqueous solutions of 1.50, 1.65, 1.83 and 2.00 g of PEO, have been prepared by dissolution in 100 ml distilled water. They are denoted as G-1, G-2, G-3 and G-4, respectively. The aqueous PEO solutions were placed in sealed glass tubes and irradiated in a Gammacell 220, ^{60}Co γ-irradiator at room temperature at two different dose rates (0.47 and 6.1 kGy/h). Irradiations were carried out up to a total given dose of 50 kGy and % gelation versus dose curves were constructed. About 40 kGy has been determined to be the lowest dose corresponding to maximum gelation (90%) (Savaş and Güven, 2001 in press). After irradiation, hydrogels obtained in long cylindrical shapes were cut into pieces of 3–4 mm thickness.

2.3. Swelling studies

In order to determine the swelling behavior of PEO hydrogels obtained in this study, cylindrically cut, dried PEO hydrogels discs were placed into distilled water at room temperature. Swollen hydrogels were periodically removed and weighed. The water contents of the swollen hydrogels were calculated by using the following relation;

$$\%\text{Swelling} = \frac{(W_s - W_o)}{W_o} 100$$

where W_o and W_s are the weights of gel before and after swelling, respectively. In swelling and active substance loading and release experiments gels prepared from PEO solutions with 1.83 g/dl concentration were used since no significant differences were observed with the gels prepared at other concentrations.

2.4. Loading of active substance

For the investigation of active substance release behavior of PEO hydrogels prepared in this study, salicylic acid, phthalic acid and resorcinol were used as model substances. They were selected as representatives of aromatic structures possessing characteristic carbonyl and hydroxyl functional groups. Dry polymeric gels were loaded with active substance by immersion into aqueous solution of respective active substance at 25 °C for 1 day. Preliminary tests showed that 1 day is the minimum time to ensure complete swelling of gel and maximum loading of active substance.

2.5. Controlled release of active substance from hydrogels

The controlled release of active substance from hydrogels was measured after active substance loading. Active substance release experiments were carried out in a continuously shaked bath. In each experiment, aliquots were drawn from the solutions at selected intervals to follow the active substance release and placed again into the same vessel so that the liquid volume was kept constant. Concentrations of active substances in the release medium were determined by UV spectrophotometry (Philips, PU 8715 model, UV/VIS spectrophotometer) at 232 nm for salicylic acid, at 280 nm for phthalic acid and at 273.6 nm for resorcinol, respectively, from the calibration curves initially prepared at these absorption maxima. The distilled water was used as the blank sample during the measurements. These release experiments were carried out at constant temperature of 25 °C.

3. Results and discussion

3.1. Swelling properties

Before studying the active substance loading and release behaviors of PEO hydrogels, first their swelling kinetics and capacities were investigated. Fig. 1 shows the swelling behavior as a function of time for PEO hydrogels prepared at two different dose rates (0.47 and 6.1 kGy/h). As it is seen here, PEO hydrogel discs swell in water rapidly at first and then gradually reach the equilibrium values in approximately 20–24 h. Changing the radiation dose rate produces a pronounced effect on the swelling properties of the carriers. No attempt has been made to remove dissolved O_2 from the polymer solutions prior to irradiation. It is anticipated that this would have lead to an almost identical procedure followed in the commercial production of these type of hydrogels. Since oxygen dissolved in aqueous solutions is a

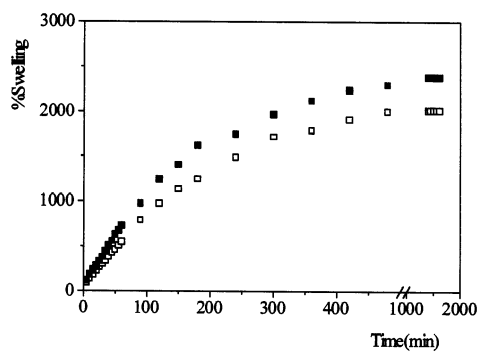


Fig. 1. Swelling curves of PEO hydrogels, prepared by irradiation at two dose rates; (■): 0.47 kGy/h, (□): 6.1 kGy/h, concentration: 1.83 g/dl.

Table 1
Swelling and network properties of radiation crosslinked PEO hydrogels[a]

Gel code	Concentration of PEO (g/dl)	Degree of equilibrium swelling (%S)		Number average molecular weight between crosslinks M_c (g/mol)		Crosslinking density $d_x \times 10^5$ (mol/cm^3)	
		0.47 kGy/h	6.1 kGy/h	0.47 kGy/h	6.1 kGy/h	0.47 kGy/h	6.1 kGy/h
G-1	1.50	2500	2140	12 000	10 200	9.79	11.9
G-2	1.65	2750	2090	12 800	8600	9.24	13.6
G-3	1.83	2700	2420	13 600	12 100	8.96	9.65
G-4	2.00	2760	2220	9800	6100	12.3	18.6

[a] Irradiated to a total dose of 40 kGy.

very effective radical scavenger, initially most of the radiolysis products were used up by reacting with dissolved oxygen. The lower the dose rate, the lower is the rate of generation of the radiolysis products which causes a lower value of the gel fraction reached at the same dose in sample irradiated at low dose rate, as compared with high dose rate irradiation. Consequently, high dose rates enhance crosslinking density for a given dose which leads to low swelling values.

The equilibrium swelling data were used to evaluate the network property of PEO hydrogels. The number average molecular weight between crosslinks, M_c is calculated using the Peppas–Merril relation (Peppas and Merril, 1976);

$$\frac{1}{M_c} = \frac{2/M_n - 1/d_p V_1[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2]}{v_{2,r}[(v_{2,s}/v_{2,r})^{1/3} - 1/2(v_{2,s}/v_{2,r})]}$$

here, χ is the Flory–Huggins coefficient (for the system water–PEO, $\chi = 0.45$) (Brandrup and Immergut, 1967), V_1 is molar volume of water, $v_{2,s}$ is polymer volume fraction in the state of equilibrium swelling; $v_{2,s} = d_w w_a/(d_w w_a + (w_s - w_a)d_p)$ where d_w and d_p are densities of water and polymer, $v_{2,r}$ is polymer volume fraction in the relaxed state(while crosslinked in the presence of water); $v_{2,r} = d_w w_a/(d_w w_a + (w_p - w_a)d_p)$, where w_p, w_a and w_s are the mass of the polymer, gel and swollen gel, respectively.

For the analysis of crosslinked structure of the hydrogels, the crosslinking density, d_x was calculated using the equation;

$$d_x = \frac{1}{vM_c}$$

here, v is the specific volume of the polymer. The results are presented in Table 1. As indicated by the data in Table, the average molecular weight between crosslinks decreased for all four hydrogel systems obtained by irradiation at high dose rate and the network structure became denser, but increased for hydrogels obtained by irradiation at low dose rate. The crosslink density is significantly affected by the dose rate and not so much from polymer concentrations within the interval studied in this work.

3.2. Active substance loading

For the investigation of active substance uptake behavior of PEO hydrogels prepared at low and high dose rates, the uptake capacities of PEO hydrogels were determined by measuring the mass of adsorbate per unit mass of adsorbent (q_e) as a function of time. q_e values are calculated from the following equation (Şen et al., 2000):

$$q_e = \left[\frac{C_i - C}{m}\right] V_t$$

where q_e is in g (or mg) adsorbate per g dry adsorbent, C_i and C are the initial and equilibrium concentration of solution of adsorbate, V_t the volume of solution treated, and m is the mass of dry adsorbent in g.

Figs. 2 and 3 show the active substance uptake capacity as a function of time for PEO hydrogels prepared at two different dose rates (0.47 and 6.1 kGy/h). As can be seen from these figures the active substance uptake of PEO hydrogel systems

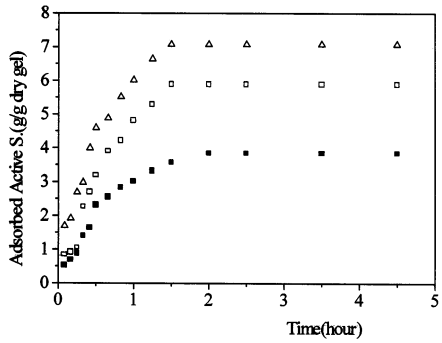


Fig. 2. Active substance uptake of hydrogels (G-3) prepared at 0.47 kGy/h dose rate. Irradiation dose 40 kGy; (■): Phthalic acid, (□): Salicylic acid, (△): Resorcinol.

first increases with time and then reaches a plateau value. It has been found that the active substance uptake capacity was lowest both in rate and in total amounts with phthalic acid, more in those with salicylic acid and highest in those with resorcinol. The relatively lower amounts of phthalic acid uptake is assumed to be mainly due to ionized structure of this compound at the neutral pH conditions held in this work. The coulombic repulsion among the negatively charged phthalic acid molecules adsorbed on the surface and interior of the gels is expected to be the main reason in the reduction of total uptake. When the initial slopes of three active substance uptake capacity curves given in Figs. 2 and 3 are compared, it can be seen that the adsorption capacity rate is the highest for resorcinol and the lowest for phthalic acid.

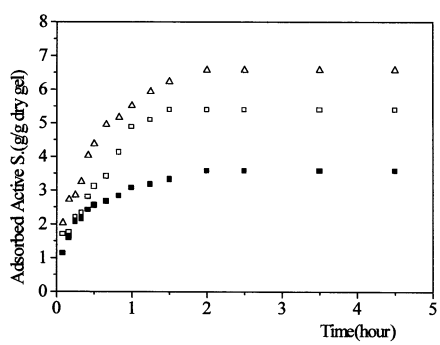


Fig. 3. Active substance uptake of hydrogels (G-3) prepared at 6.1 kGy/h dose rate. Irradiation dose 40 kGy; (■): phthalic acid, (□): salicylic acid, (△): resorcinol.

These figures also depict that the active substance uptake of hydrogels obtained by irradiation at high dose rate were found to be lower than those obtained at low dose rate. This is explained to be due to higher crosslink density of hydrogels prepared at high dose rate conditions Table 1, resulting in smaller pore structures and lower equilibrium swelling ratios. The slight difference observed in the amounts of adsorbed active material by these gels is in fact a reflection of the difference in swelling behaviors of these gels as shown in Fig. 1.

3.3. Release behavior of hydrogels

For examining the release of active ingredients from PEO hydrogels, prepared by irradiation at low and high dose rate, percentage release of the active substances are plotted against time.

The percentage release of active substances into water was calculated from the following equation:

$$\%\text{Release} = \frac{W_t}{W_{total}}$$

where W_t is the weight of released active substance in water at any time and W_{total} is the initial total weight of active substance taken up by the gel system.

As seen from Fig. 4, the amount of active substance that passes into water from hydrogels first increased with time and remained unchanged after a certain time. It has also been found that release was the lowest both in rate and in total amounts in hydrogels containing phthalic acid, higher in those with salicylic acid and highest in those with resorcinol.

The release was the lowest for hydrogels containing phthalic acid obtained by irradiation at both low and high dose rates. Since the molecular sizes of active substances used in this study are almost the same, the reason of the differences in release profiles is mostly due to the strength of association between PEO and the active substances. With decreasing strength of association, the release accelerates. In this context, the slow release of phthalic acid from PEO hydrogel is caused by strong ion–dipole interaction between the dissociated carboxylic group in phthalic acid

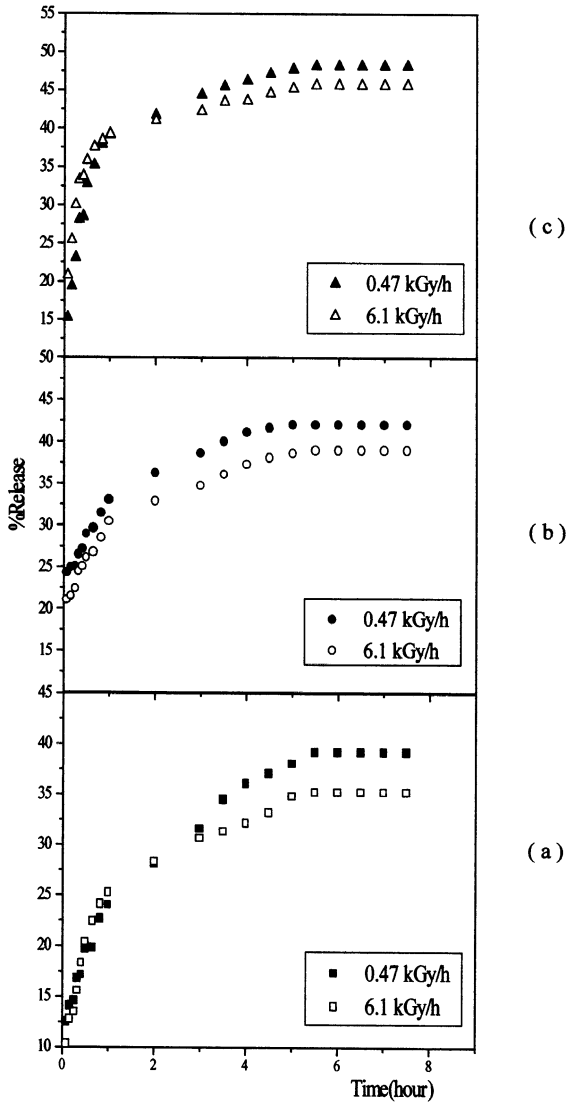


Fig. 4. Release kinetics of active substances from hydrogels (G-3) prepared at 0.47 and 6.1 kGy/h dose rate. Irradiation dose 40 kGy; (a): Phthalic acid, (b): Salicylic acid, (c): Resorcinol.

and the ether oxygens of PEO. There is also the significant effect of hydrogen bonding between the adsorbate and adsorbent in this case. The formation of hydrogen bond is known to be due to the interaction between H-donor and acceptor functional groups. Here, the donor for H-bond is acid groups and the acceptor is PEO. Nishi and Kotaka have studied the complex formation in poly(ethylene oxide): poly(acrylic acid) interpenetrating polymer networks. An evidence from infrared spectroscopy suggested that PEO:PAA complex is formed through hydrogen bonding between the ether oxygens of PEO and the carboxylic acid hydrogens of PAA networks (Nishi and Kotaka, 1985). In the case of salicylic acid availability of sites for the H bond formation is decreased which resulted in the increase of release as compared with phthalic acid. When resorcinol is used as active substance the release is further increased due to its poorer hydrogen bond formation capacity.

As can be seen from these figure, the active substance release from hydrogels obtained by irradiation at high dose rate is relatively lower than from those prepared by irradiation at low dose rate for a given total dose. This is assumed to be due to a difference in the mesh size of the pores in these two gel systems as shown in Table 1, last two columns. Hydrogels obtained by irradiation at high dose rate were relatively more densely crosslinked and with smaller pore sizes, which causes a decrease in release rate.

The total irradiation dose is another important parameter which affects the network structure and consequently the release of the active substance. In order to determine the effect of irradiation dose on network structure and consequently on active substance release from PEO hydrogels, hydrogels prepared at two different doses (40 and 60 kGy) at low (0.47 kGy/h) and high (6.1 kGy/h)

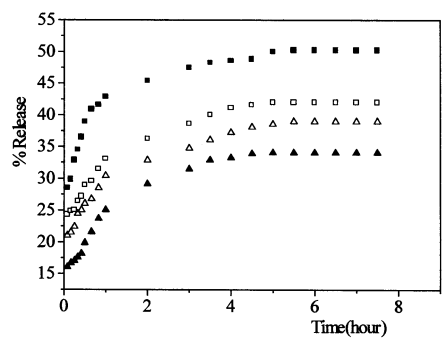


Fig. 5. The release kinetics of salicylic acid from hydrogels obtained by irradiation to 40 and 60 kGy total doses, at 0.47 kGy/h dose rate; (□): 40 kGy, (■): 60 kGy, at 6.1 kGy/h dose rate; (△): 40 kGy, (▲): 60 kGy.

Table 2
Relation between M_c, total radiation dose and irradiation dose rate

Gel code	Concentration of PEO (g/dl)	Number average molecular weight between crosslinks, M_c (g/mol)			
		0.47 kGy/h		6.1 kGy/h	
		40 kGy	60 kGy	40 kGy	60 kGy
G-1	1.50	12 000	13 000	10 200	9000
G-2	1.65	12 800	13 900	8600	7200
G-3	1.83	13 600	14 200	12 100	11 000
G-4	2.00	9800	11 000	6100	5000

dose rates have been studied. Fig. 5 shows the release kinetics of salicylic acid from hydrogels obtained under these conditions. As it can be seen from this figure, the amount of salicylic acid released from hydrogels obtained by 60 kGy irradiation at low dose rate is higher than the amount released from hydrogel obtained by 40 kGy irradiation. The average molecular weight between crosslinks for hydrogels containing salicylic acid and prepared by 40 and 60 kGy irradiation at low dose rate is found to be as 10 500 and 14 000, respectively. This is assumed to be due to low dose rate induced degradation effect at higher irradiation doses. The data indicate that M_c increased with decreasing crosslinking. If network formation is viewed as a competitive processes between crosslinking and degradation reactions, then increased scission will cause higher values of M_c.

On the contrary, the salicylic acid release from hydrogel obtained by 60 kGy irradiation at high dose rate was found to be lower than that obtained by 40 kGy irradiation. The average molecular weight between crosslinks for hydrogels containing salicylic acid and prepared by 40 and 60 kGy irradiation at high dose rate are found as 9600 and 7800, respectively. As can be seen, M_c decreased, i.e. degree of crosslinking increased, as the irradiation dose increased at high dose rate. The equilibrium swelling of the hydrogels decreases when the crosslink density increases. This means lower crosslink densities are achieved at low irradiation dose leading to higher porosities. In addition, macromolecular chain segment flexibility decreased by an increase in crosslink density causing the resistance to the diffusion of active substance to increase, yielding low release rate.

M_c values calculated under different preparation conditions are summarized in Table 2. These results indicate that increasing the total irradiation dose increases the average molecular weight between crosslinks for hydrogels obtained by irradiation at low dose rate. However, increasing the total irradiation dose decreases the M_c for hydrogels obtained by irradiation at high dose rate within the dose rates and total absorbed doses specified in this work.

4. Conclusion

In conclusion, it has been observed that PEO–water is a system that can be easily crosslinked with γ rays at room temperature at various dose rates. By controlling the dose rate, and total dose it is possible to control the network structure of the PEO hydrogels obtained from this system eventually the swelling and release behavior.

The perfect linear chain structure of PEO and identical properties of CH_2 groups on the chain make this polymer ideal for radiation crosslinking purposes. The presence of etheric oxygens on the repeating unit imparts effective hydrogen bonding ability to this polymer. This property brings additional advantages to PEO, providing additional control of release by the formation of association between the guest molecule and PEO chains.

References

Bailey, F.E. Jr, Koleske, J.V., 1976. Poly(ethylene oxide). Academic press, NewYork.

Brandrup, J., Immergut, E.H., 1967. Polymer Handbook Editors. Interscience Publishers, NewYork.

Caliceti, P., Veronese, F.M., Schiavon, O., Lora, S., Carenza, M., 1992. Controlled release of proteins and peptides from hydrogels synthesized by gamma ray-induced polymerization. Farmaco 47, 275–286.

Carenza, M., Lora, S., Caliceti, P., Schiovan, O., Veronese, F.M., 1993. Hydrogels obtained by radiation-induced polymerization as delivery systems for peptide and protein drugs. Radiat. Phys. Chem. 42, 897–901.

Garcia, O., Trigo, R.M., Blanco, M.D., Teijon, J.M., 1994. Inflience of degree of crosslinking on 5-fluorouracil release from poly(2-hydroxyethyl methacrylate) hydrogels. Biomaterials 15, 689–694.

Korsmeyer, R.W., Peppas, N.A., 1983. Swelling-controlled delivery systems for pharmaceutical application. In: Controlled Release Delivery Systems. Marcel Dekker, New York, pp. 77–90.

Kudela, V., 1987. Encylopedia of Polymer Science and Engineering, vol. 7, Second ed. Wiley, New York, pp. 783–789.

Nishi, S., Kotaka, T., 1985. Complex-forming poly(-oxyethylene): Poly8acrylic acid) interpenetrating polymer networks. 1. Preparation, structure and viscoelastic properties. Macromolecules 18, 1519–1524.

Pekala, W., Rosiak, J., Rucinska-Rybus, A., Burczak, K., Galant, S., Czolczynska, T., 1986. Radiation crosslinked hydrogels as sustained release drug delivery systems. Radiat. Phys. Chem. 27, 275–285.

Peppas, N.A., Merril, E.W., 1976. Poly(vinyl alcohol) Hydrogels: reinforcement of radiation-crosslinked networks by crystallization. J. Polym. Sci. Polym. Chem. 14, 441–445.

Peppas, N.A., Mikos, A.G., 1986. In: Peppas, N.A. (Ed.), Hydrogels in Medicine and Pharmacy, vol. 1. CRC, Press, Boca Raton, FL, pp. 1–25.

Peppas, N.A., Gurny, R., Doelker, E., Buri, P., 1980. Modelling of drug diffusion through swellable polymeric systems. J. Membr. Sci. 7, 201–214.

Powell, G.M., 1980. In: Davidson, R.L. (Ed.), Handbook of Water-Soluble Gums and Resins. McGraw-Hill, NewYork.

Rosiak, J.M., Olejniczak, J., 1993. Medical application of radiation formed hydrogels. Radiat. Phys. Chem. 42, 903–906.

Savaş, H. and Güven, O., 2001. Gelation, swelling and water vapor permeability behavior of radiation synthesized poly(ethylene oxide) hydrogels, Radiat. Phys. and Chem., 61, in press.

Saraydın, D., Karadağ, E., Güven, O., 1995. Acrylamide–maleic acid hydrogels. Polym. Adv. Technol. 6, 719–726.

Saraydın, D., Karadağ, E., Güven, O., 1998. The releases of agrochemicals from radiation induced acrylamide/crotonic acid hydrogels. Polym. Bull. 41, 577–584.

Şen, M., Uzun, C., Güven, O., 2000. Controlled release of terbinafine hydrochloride from pH sensitive poly(acrylamide/maleic acid) hydrogels. Int. J. Pharm. 203, 149–157.

Trigo, R.M., Blanco, M.D., Teijon, J.M., Sostre, R., 1994. Anticancer drug, ara-C, release from pHEMA hydrogels. Biomaterials 15, 1181–1188.