

Evaluation of poly(2-hydroxyethyl methacrylate) gels as drug delivery systems at different pH values

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Received 24 May 1999; received in revised form 15 October 1999; accepted 15 October 1999

Abstract

Studies of dynamic and equilibrium swelling, structural characterisation and solute transport in swollen poly(2-hydroxyethyl methacrylate) gels (pHEMA) cross-linked with tripropyleneglycol diacrylate (TPGDA) were done for a wide range of TPGDA concentrations. The influence of the pH on these pHEMA properties was evaluated. In swelling studies it was found that in changing the pH from 6.5 to 12.0, a large increase in swelling occurred, from approximately 48 to 55%, for the lowest concentration of TPGDA (1 mol%), and from 40 to 80% for the highest concentration (10mol%). Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) measurements were made after the equilibrium swelling of the gels at different pH values, to explain these results. The advantage of using these gels as controlled drug delivery systems is illustrated using salicylic acid (SA) as a model drug. The loading and the release of the SA were made at different pH values and the results obtained showed that it is possible to modulate the hydrogel performance by controlling an external factor, the pH at which the drug loading and release were performed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Hydroxyethyl methacrylate; Hydrogels; Swelling; Salicylic acid; Controlled release; Structural characterisation

1. Introduction

pHEMA gels are very resistant to high temperatures, to acid and alkaline hydrolysis, and they have a low reactivity with amines (Ratner and Hoffman, 1976). Such chemical and thermal stability make pHEMA gels suitable materials for the development of controlled drug delivery systems (Huglin and Sloan, 1983; Denizli et al., 1988;

Blanco et al., 1994; Garcia et al., 1994; Teijon et al., 1997), and for other biomedical and pharmaceutical applications (Montheard et al., 1992; Peluso et al., 1997).

The release of a drug through a network gel based on pHEMA polymer is strongly affected by the water swelling capacity of the gel. Therefore, swelling ratio changes induced by external conditions (pH, temperature, ionic strength) are of special importance for controlled release systems, since they offer the possibility of a direct control of drug release at a convenient place and predetermined time. Since the gels of pHEMA are consid-

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ered non-ionic gels, most of the studies reporting pH-sensitive swelling behaviour involve modified pHEMA, either copolymerised with acrylic or methacrylic acids (Bettini et al., 1995; Khare and Peppas, 1995), or pHEMA gels partially hydrolysed with alkali at high temperatures (Svecik et al., 1995). To date, as far we know no work has been reported on the literature showing a pH-sensitive swelling behaviour of unmodified pHEMA gels. Further, no studies have been reported using pHEMA gels as drug delivery systems at different pH values.

In this work, we have prepared pHEMA gels crosslinked with tripropyleneglycol diacrylate (TPGDA). Water swelling behaviour, DSC and FTIR spectroscopy studies were made of the samples treated at different pH values, over a wide range of crosslinking agent concentrations. These gels, particularly those prepared with the highest concentrations of crosslinking agent, showed an exceptional pH-sensitivity. The advantage of using these gels to design controlled drug delivery systems is illustrated by using salicylic acid (SA) as a model drug whose loading is possible either for high or low values of pH. The capacity of SA loading and apparent diffusion coefficient through these gels were compared under different conditions.

2. Materials and methods

2.1. Materials

Hydroxyethyl methacrylate (HEMA) was purchased from ACROS organics (New Jersey, USA) and was vacuum distilled at 65°C/5 mmHg (Khare and Peppas, 1995); ammonium persulphate and sodium methabisulphite were supplied by May & Baker (Dagenham, England); tripropyleneglycol diacrylate (TPGDA) was kindly offered by UCB Chemicals; salicylic acid (SA) was purchased from Sigma Chemical Company (England).

2.2. Methods

2.2.1. Gel preparation

The pHEMA gels were prepared in 10 ml glass beakers (diameter 3 cm) by polymerizing the mono-

functional monomer, HEMA (200 µl) with multi-functional monomer TPGDA (1–10 mol% relative to the monomer) in the presence of a radical initiator, consisting of an ammonium persulphate/sodium methabisulphite mixture (3 mg, 1:2 w/w), in 1 ml of the ethylene glycol/water 70:30 (v/v) mixture. After homogenisation, solutions were bubbled with N₂ gas (5 min), stoppered and the temperature increased to 55°C. The polymerization reaction proceeded for 4 h. The above procedure followed a modification of the protocol suggested by Refojo and Yasuda (1965).

The resulting gels were kept overnight at room temperature and were subsequently separated from the glass beakers after adding some distilled water. To remove unreacted monomers, gel samples were immersed in distilled water for 5 days, changing the water every day. The gels were then dried at room temperature, under vacuum, in the presence of phosphorous pentoxide, and weighed to determine the dried weight, W_d . The pHEMA gels were denoted by: pHEMA1, pHEMA2, pHEMA3, pHEMA4 and pHEMA5 with 1, 2, 3, 5, 10 mol% (relative to HEMA monomer) of TPGDA, respectively.

2.2.2. Gel characterisation

2.2.2.1. *Dynamic and equilibrium swelling experiments.* The degree of swelling (W_t) in distilled water and in aqueous solutions with different pH was determined by immersing the gels either in distilled water or in NaOH/HCl aqueous solutions of desired pH, in sealed containers, at 25°C. At regular period of time, they were removed from the aqueous solution, blotted with filter paper to remove surface water, weighed and returned to the same container until weight stabilisation was observed. The W_t was determined using Eq. (1) (Corkhill et al., 1987):

$$W_t = (W_s - W_d) / W_s \times 100 \quad (1)$$

where W_s is the weight of swollen gel and W_d is the weight of dry gel.

The equilibrium degree of swelling (W_{∞}), W_t for gels in equilibrium, was attained after 1–7 days depending on the degree of cross-linking and the pH of the aqueous solution.

The volume equilibrium swelling ratio of the different gels, Q , was determined as the ratio of the volumes of the swollen and the dry specimens (Bettini et al., 1995). The gels were allowed to swell until equilibrium in aqueous solution of different pH both in the absence or in the presence of SA (drug concentration of 0.1 g/100 ml).

2.2.2.2. Salicylic acid (SA) release measurements

Loading of SA at pH 2.5. After equilibrium in distilled water at pH 6.5 or NaOH aqueous solution at pH 12.0 (see later), swollen gels were immersed for 8 days in 10 ml of a SA aqueous solution (0.10%, w/v), pH 2.5 at 25°C. After blotting, the gels were immersed in 100 ml of distilled water at 37°C with magnetic stirring (150 rpm). The released SA was monitored by its UV absorption band at 300 nm (Garner and Sugden, 1973) until no further changes of absorbance values were observed. These absorbance measurements were converted to SA concentrations using an SA calibration curve, and the total amount of SA released was calculated.

Loading of SA at pH 12.0. After equilibrium in distilled water at pH 6.5, swollen gels were immersed for 8 days in 10 ml of aqueous NaOH solution containing SA (0.10%, w/v), pH 12.0 at 25°C. At this pH, the SA was present as its corresponding salt, sodium salicylate (SS) (Shane and Routh, 1967). After blotting, the gels were immersed in 100 ml of distilled water, or HCl aqueous solution at pH 2.0 (see later), with magnetic stirring (150 rpm), at 37°C. The released SS was monitored at 300 nm, on an UV spectrophotometer, until no further changes of absorbance values were observed. To determine the residual SS concentration, these gels were pulverised, dried at room temperature under vacuum over phosphorous pentoxide, and then washed with 10 ml of a base solution, pH 12.0. The absorbance of this alkaline solution was determined at 300 nm. Finally, SS loading was calculated by adding the SS residual concentration to the concentration of the SS released.

2.2.2.3. Differential scanning calorimetry (DSC). DSC thermograms were carried out using a Polymer Laboratories DSC apparatus. The gels were dried until constant weight under vacuum in the presence of P_2O_5 , at 25°C. Samples with weights between 2 and 5 mg were then sealed into an aluminium pan. An empty aluminium sealed pan was used as reference material. The temperature was raised from 10 to 400°C at a heating rate of 10°C/min under nitrogen atmosphere (flow 10 ml/min).

2.2.2.4. Fourier transform infrared spectroscopy (FTIR). FTIR spectra were recorded on a Nicolet-750 spectrometer. The dry samples were powdered, mixed with KBr and pressed into pellets under reduced pressure. The FTIR spectra were obtained by recording 128 scans between 4000 and 450 cm^{-1} with a resolution of 2 cm^{-1} .

3. Results and discussion

3.1. Structural characterisation, equilibrium and dynamic swelling studies

3.1.1. In distilled water (pH 6.5)

The water absorbed by a gel network is quantitatively represented by the equilibrium degree of swelling, W_{∞} , expressed by Eq. (1). The W_{∞} is the most important single property of a gel, influencing as it does the permeability, mechanical, surface and other properties of the gel (Corkhill et al., 1987).

The Curve C in Fig. 1 shows the variation of W_{∞} for pHEMA gels as a function of the cross-linking agent concentration, for gels equilibrated in distilled water at pH 6.5. The effect of the cross-link density on the W_{∞} of pHEMA gels follows the expected trend of a decrease in W_{∞} with increasing cross-link density (Robert et al., 1985; Allen et al., 1992). Table 1 shows the results of the thermal analysis study for these gels (at pH 6.5). As it can be seen, melting temperatures and enthalpy changes decrease with increasing cross-

linking agent concentration, showing that less crystalline gels are getting formed. This means that the few amorphous zones present in the gels prepared with less cross-linking agent are free and elastic enough to swell and hold large amounts of water.

According to the literature, there are three different diffusion mechanisms for the transport of water through cross-linked pHEMA gels, which depend on the crosslinker content: a pore flow mechanism for low cross-linking content (approximately 0–2.5 mol%), a water-matrix interaction mechanism for higher cross-linking content (above 4 mol%) and an intermediate mechanism at intermediate cross-linker concentration (Wisniewski et al., 1976). In our study the pHEMA gels prepared fulfill all the above situations.

To study the uptake of water by pHEMA gels, gel discs with 4.8 ± 0.4 mm thickness and 13.1 ± 0.5 mm diameter were employed. As it can be seen in Fig. 2, W_∞ was attained at ≈ 40 h, for all cases.

From these results, the fractional swelling, F_w , due to water uptake for a controlled diffusion process was calculated using the equation (Garcia et al., 1994):

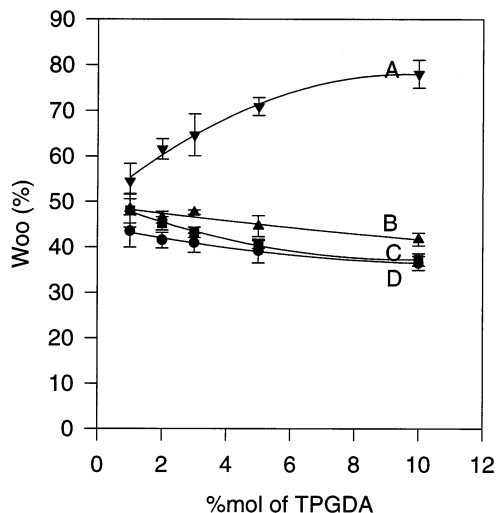


Fig. 1. Equilibrium degree of swelling (W_∞) of pHEMA gels with different concentrations of cross-linker agent (TPGDA), at 25°C, in different pH solutions: pH 12.0 (A); pH 10.0 (B); pH 6.5 (C); and pH 2.0 (D). Values of W_∞ are given as average and standard deviation over three experiments.

Table 1

Thermal analysis data obtained for pHEMA gels after equilibrium at different pH solutions

pH	Gel	T_g (°C)	T_m (°C)	ΔH_f (mCal/mg)
6.5	pHEMA1	88.1	365.0	113.2
	pHEMA2	— ^a	— ^a	— ^a
	pHEMA3	79.2	366.4	90.3
	pHEMA4	77.5	375.5	80.5
	pHEMA5	68.7	369.8	78.3
12.0 ^c	pHEMA1	— ^b	317.6	9.6
	pHEMA2	— ^b	321.5	8.1
	pHEMA3	— ^b	327.2	5.7
	pHEMA4	— ^a	— ^a	— ^a
	pHEMA5	— ^b	339.8	1.9
2.0 ^d	pHEMA1	100.0	353.0	93.0
	pHEMA2	95.5	357.9	87.1
	pHEMA3	92.6	360.9	91.3
	pHEMA4	88.8	363.4	80.8
	pHEMA5	84.1	367.0	69.7

^a Not determined.

^b Difficulty in the determination.

^c The gels were transferred from a solution at pH 6.5 to an aqueous NaOH solution pH 12.0 and they were allowed to reach the equilibrium. After, they were dried and DSC studies were made.

^d The gels were transferred from a solution at pH 12.0 to an aqueous HCl solution pH 2.0 and they were allowed to reach the equilibrium. After, they were dried and DSC studies were made.

$$F_w = W_t/W_\infty = 4 (D_w t / l_o^2 \pi)^{1/2} \quad (2)$$

Here, D_w is the apparent diffusion coefficient for the transport of water into the gel, t is the time and l_o is the thickness of the dried gel. Linearity between F_w and $t^{1/2}$ was found for values of F_w less than 0.6 at constant temperature T and fixed l_o , so D_w can be obtained from the slope (Crank, 1975). The D_w values obtained for each gel are presented in Table 2. It is clear from the results that high degrees of cross-linking lead to reduced D_w , showing that swelling is less favourable when the TPGDA concentration is higher.

Moreover, the D_w values presented in Table 2 show differences from the values reported in the literature (Khaw et al., 1976). For example, pHEMA hydrogels with 26% water and 1% (v,v) ethyleneglycol dimethacrylate in the feed mixture yield a D_w of $2.4 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$. The differences

can be related to factors such as the initiator nature, cross-linking agent and its concentration and water content (Trigo et al., 1994).

3.1.2. Aqueous solutions at different pH values

Fig. 1 also shows the effect of pH on the equilibrium swelling of pHEMA gels at 25°C. For pH 2.0 (curve D) a slight decrease in W_∞ is observed. This can be explained by the reduction of the solvent power of water by the chloride counterion which makes solvent/polymer interactions weaker and favours hydrophobic interactions between polymeric chains (Refojo, 1967; Warren and Prins, 1972). As a consequence, a

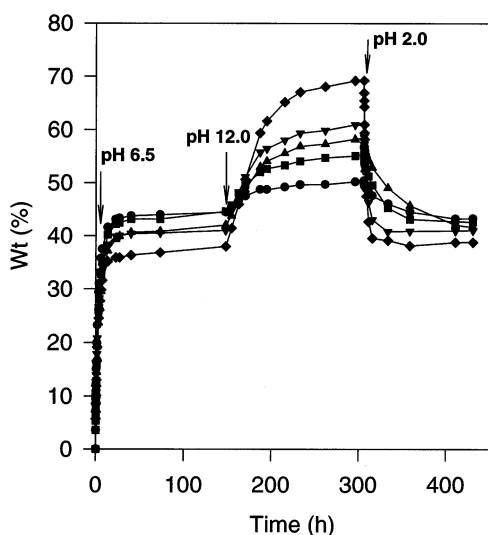


Fig. 2. Dynamic swelling behaviour of pHEMA gels with different concentrations of cross-linker agent (TPGDA), in different pH solutions, at 25°C. Data are for pHEMA gels with 1 mol% (●), 2 mol% (■), 3 mol% (▲), 5 mol% (▼) and 10 mol% (◆).

Table 2

Values of the apparent diffusion coefficient for water uptake (D_w) into pHEMA gels cross-linked with different concentrations of TPGDA

Gel	D_w ($\text{m}^2 \text{s}^{-1}$)
pHEMA1	6.1×10^{-11}
pHEMA2	5.0×10^{-11}
pHEMA4	3.8×10^{-11}
pHEMA5	3.2×10^{-11}

tighter polymeric network is formed, showing lower swelling levels.

In the same figure, curve A shows a large increase in the swelling when the pHEMA gels are immersed in an aqueous NaOH solution, pH 12.0. Relatively to the swelling behaviour in distilled water, a pH 12.0 solution induces equilibrium swelling transitions from approximately 48 to 55%, for the lowest concentration of TPGDA (1 mol%), and from 40 to 80% for the highest concentration (10 mol%). At the same time, from Fig. 2 we can observe that the W_∞ at pH 12.0 is attained between 75 and 145 h depending on the degree of cross-linking of the gel.

As far we know, such a marked dependence of the pHEMA gel equilibrium swelling ratio on pH has never previously been reported in the literature. For the pHEMA gels crosslinked with ethyleneglycol dimethacrylate (0.5% mol) Brannon-Peppas and Peppas (1991) described only a slight increase in equilibrium swelling values, at pH between 6.0 and 8.0, which was constant for pH up to 12.0. The slight dependence on pH was explained by a delocalization of the electron density on the single bond oxygen to the electron-attracting carbonyl group. As presented in Fig. 1, this agrees with the slight increase of W_∞ in pHEMA gels, at pH 10.0 (curve B).

However, a distinct behaviour was found in the present work for the pHEMA gels crosslinked with TPGDA (using a wide range of crosslinking agent concentration from 1 to 10 mol%) at pH 12.0 (curve A). The gels prepared with high crosslinking content (5–10 mol%), present a high W_∞ , nearly twice the value obtained for the same gels when immersed in distilled water. To understand these results the pHEMA gels were structurally characterised by FTIR and DSC measurements, after equilibrium at different pH values. The FTIR spectra of pHEMA gels with different cross-link densities after equilibrium at pH 6.5 (A1, A2) and at pH 12.0 (B1, B2) are shown in Fig. 3. Taking into account the overlap in the contribution of the different bands from TPGDA and HEMA, the most important bands from pHEMA are at: 3400 [$\nu(\text{OH})$], 2990 [$\nu(\text{CH}_3)\text{as}$, $\nu(\text{CH}_2)\text{as}$], 2959 [$\nu(\text{CH}_2)\text{s}$, $\nu(\text{CH}_3)\text{s}$], 2882 [$\delta(\text{CH}_3)$], 1726 [$\nu(\text{C}=\text{O})$], 1484 [$\delta(\text{CH}_2)$],

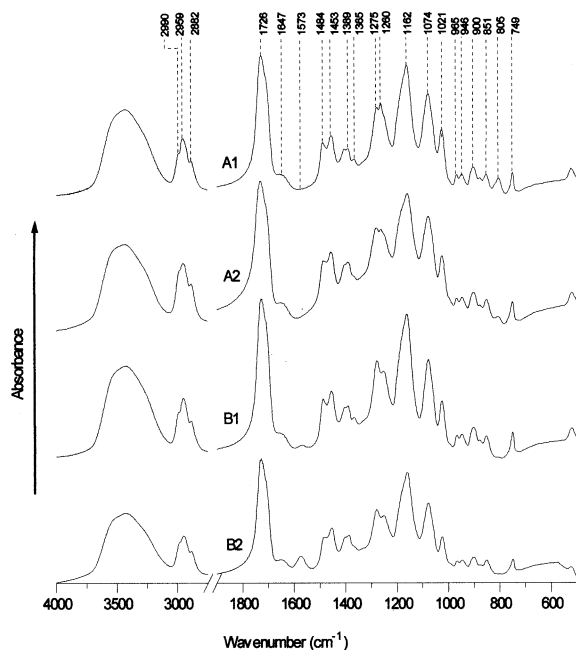


Fig. 3. FTIR spectra of pHEMA gels with 1 mol% (A1, B1) and 10 mol% (A2, B2) of TPGDA after equilibrium at pH 6.5 (A1, A2) and pH 12.0 (B1, B2).

1453 [$\delta(\text{CH}_2)$, $\delta(\text{CH}_3)$ as], 1389 [$\delta(\text{CH}_3)$ s], 1365 [$\omega(\text{CH}_2)$], 1275 [$\omega(\text{CH}_2)$, $\delta(\text{CH})$], 1260 [$\nu(\text{C}-\text{O})$], 1162 [$\gamma(\text{CH}_3)$, $\tau(\text{OH})$], 1074 [$\nu(\text{O}-\text{C})$, alcohol], 1021 [$\nu(\text{C}-\text{O})$, ester], 965–805 [$\nu(\text{C}-\text{C})$, $\gamma(\text{CH}_3)$, $\gamma(\text{CH}_2)$] and 749 [$\delta(\text{O}=\text{C}-\text{O})$] cm^{-1} (Faria et al., 1991; Kulbida et al., 1995). Here, ν is the bond stretching; δ , the bending; ω , the wagging; γ , the rocking and τ , the torsion.

In a general view, the spectra of pHEMA gels after the equilibrium at pH 6.5 and 12.0 are similar, with the exception of a peak at 1573 cm^{-1} in spectra B1 and B2, which can be assigned to the stretching of the COO^- group (Zalipsky et al., 1983). As it can be seen, the intensity of this peak increases as a function of crosslinking density (this linear behaviour was maintained for the other gels). Probably, the increase of the intensity is related to the slight hydrolysis of the pHEMA network, at pH 12.0, which is favoured by the increase of cross-linker concentration. FTIR studies of pHEMA gels after equilibrium in an NaOH aqueous solution at pH 10.0 (results not shown) show the absence of the band at 1573

cm^{-1} , which suggests that are not hydrolysed.

A possible interpretation for the high swelling of pHEMA gels at pH 12.0 would be due to ionisation of the hydroxyl groups on the main network chains. In the literature, the pK_a values of these hydroxyl groups are reported as being between 11 and 12 (Morrison and Boyd, 1983). The creation of negative charges favours the formation of ionic bonds with counterions as Na^+ , which could contribute for the increase of ionic strength within the gel. Thus, either the repulsion between ionised individual chains and ionised carbonyl groups from cross-linker chains (particularly in the highly crosslinked gels) or the Donnan potential increase could explain the W_∞ increase, displayed by pHEMA gels at pH 12.0 (Ferreira et al., 1999). In addition, as it was shown by FTIR studies, some hydrolysis of HEMA or TPGDA groups, especially for the highly crosslinked gels, can also contribute to the W_∞ increase. Such a relationship between swelling and ionic gradient was checked by transferring pHEMA gels at equilibrium, in aqueous NaOH solution at pH 12.0, to distilled water at pH 6.5. The results obtained for pHEMA2 and pHEMA4 showed an increase in the swelling from 67.7 to 78% for pHEMA2 and from 72.8 to 84.0% for pHEMA4.

Table 1 shows the thermal parameters obtained for the pHEMA gels, after the equilibrium in distilled water and in aqueous NaOH solution at pH 12.0. Comparing the respective values of T_m and ΔH_f , it seems that, after the equilibrium at pH 12.0, there is almost complete destruction of the crystalline zones, suggesting a more open structure. The decrease in ΔH_f with the increase of the crosslinker content can be justified by the high swelling presented by the highly crosslinked pHEMA gels.

When the pHEMA gels were removed from the equilibrium situation in aqueous NaOH solution at pH 12.0 and transferred to an aqueous HCl solution at pH 2.0 they shrunk. In the case of the pHEMA4 and pHEMA5 gels the deswelling rate was considerably faster than the swelling rate at pH 12.0. This agrees with the behaviour observed for poly(2-hydroxyethyl methacrylate-co-methacrylic acid) gels crosslinked with 0.45 mol% of ethyleneglycol dimethacrylate, when the pH

was increased from 4.0 to 7.0 and then decreased from 7.0 to 4.0, where the observed deswelling rate was faster than the swelling rate (Khare and Peppas, 1995).

From Table 1, the crystallinity of pHEMA gels is recovered after transferring all the gels from pH 12.0 aqueous solution to pH 2.0 aqueous solution (the lower T_g values for the gels after equilibrium at pH 6.5 than for the same gels at pH 2.0 could be related to an incomplete dryness). This was also confirmed with FTIR studies, where the disappearance of the 1573 cm^{-1} peak (results not shown) reveals the recovery of the structure presented by the gels at pH 6.5.

The swelling behaviour of the pHEMA gels was also studied in aqueous solutions at different pH's containing SA. In Table 3, the equilibrium volume swelling ratio is presented as a function of the crosslinker concentration. The experiment was performed in aqueous NaOH solution at pH 12.0 containing 0.1% (w,v) of SA, and in an aqueous solution of SA dissolved in distilled water (pH 2.5) with the same concentration of the drug. From these results, practically no effect is observed from the presence of the SA in the different aqueous solutions when compared to the results obtained in the absence of the drug.

3.2. Salicylic acid release studies

The dependence of equilibrium swelling ratio on the pH for the pHEMA gels, in particular

those prepared with high TPGDA concentrations, suggested the possibility to use them as controlled release systems sensitive to an external stimulus.

For the release studies, SA was used as a model drug for various reasons, in particular for its importance in pharmaceutical and food technology application. The SA is employed externally on the skin, where it exerts a slight antiseptic action and a marked keratolytic action. The latter property makes salicylic acid a beneficial agent in the local treatment of warts, corns, fungous infections, and certain forms of eczematoid dermatitis. Salicylic acid is also used as preservative of food products in several countries (Abounassif et al., 1994). Secondly, SA is soluble in water at 0.22% (w/v). In the presence of alkaline solutions the SA can change to its salts: monosodium salicylate (pH 9.0) and disodium salicylate (pH 13.5) (Shane and Routh, 1967). Thirdly, its release into water can be conveniently followed by spectrophotometric measurements at 300 nm.

3.2.1. Swelling in distilled water, loading of SA at pH 2.5, release in distilled water

In Fig. 4 the fractional release of SA, F_{SA} , is plotted versus $(\text{time})^{1/2}$, $(t)^{1/2}$. For a short time period of drug release, $F_{SA} < 0.6$, F_{SA} is linear with $(t)^{1/2}$. Since the drug delivery shows a Fickian diffusion mechanism, the expression used for SA release, through pHEMA gels, can be similar to that used for the fractional swelling due to water uptake (Eq. (2)):

Table 3

Equilibrium volume swelling ratio, Q , in pHEMA gels swollen in aqueous NaOH solution at pH 12.0 with or without SA and in aqueous HCl solution at pH 2.0 with or without SA

Gel	TPGDA (mol%)	Equilibrium volume swelling ratio, Q			
		pH 12.0		pH 2.0	
		With SA	Without SA	With SA	Without SA
pHEMA1	1	2.56	2.18	2.09	1.81
pHEMA2	2	2.79	3.09	— ^a	— ^a
pHEMA3	3	3.39	3.31	1.31	1.51
pHEMA4	5	— ^a	— ^a	1.42	1.72
pHEMA5	10	4.97	4.99	1.44	1.42

^a Not determined.

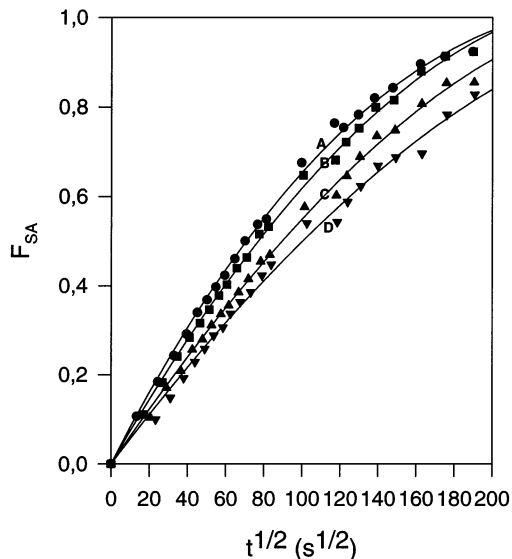


Fig. 4. Fractional release of SA (F_{SA}) versus $(t)^{1/2}$ from preswollen pHEMA gels: pHEMA1, A, (2.4 mm thickness, 15.2 mm diameter); pHEMA3, B, (2.2 mm thickness, 14.4 mm diameter); pHEMA4, C, (1.8 mm thickness, 15.5 mm diameter) and pHEMA5, D, (1.9 mm thickness, 16.0 mm diameter). The loading of SA (0.1%) was made at pH 2.5 and the release in distilled water, at 37°C.

$$F_{SA} = M_t/M_\infty = 4 (D_{SA}t/l_o^2\pi)^{1/2} \quad (3)$$

Here, M_t and M_∞ are the amount of drug released at time t and the maximum amount of SA released, respectively; D_{SA} is the apparent diffusion coefficient for SA release from the hydrogel and l_o is the thickness of the drug-loaded gel. In accordance with Eq. (3) the slope of this plot yields D_{SA} .

The apparent diffusion coefficients D_{SA} obtained for all the gels studied, presented in Table 4, were between $5.3 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ for pHEMA

1 gel and $1.7 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ for pHEMA5 gel. As it can be seen, there is a decrease of D_{SA} values, and consequently a slower SA release, with increasing degree of cross-linking. Also, from the t_{50} values, which refers to the time required to release 50% of the solute, a double increase of the t_{50} was observed from pHEMA1 to pHEMA5 gel.

The diffusion coefficient, D_{SA} , is a function of the polymer chain mobility, the average pore size and the mobility of the solvent in the gel (Teijon et al., 1997). The D_{SA} diminution between pHEMA1 and pHEMA3 can be related essentially to the reduction in polymer chain mobility caused by cross-linking which reduces the average pore size. As it was reported in swelling studies (Section 3.1) for this TPGDA concentration range, the diffusion of SA occurs mainly by a pore flow mechanism.

For pHEMA4 and pHEMA5, as described previously (Wisniewski et al., 1976), the diffusion occurs mainly by a SA aqueous solution/matrix interaction. In this case, the reduction of D_{SA} , compared to the values obtained for pHEMA1 and pHEMA3, is related to the decrease of the non-bounded water and the increase of the percentage of water bounded. SA, as a hydrophilic solute, diffuses mainly through the non-bounded water so the effect of increasing the cross-linker content is to reduce the effective free volume of the polymer matrix. Besides, if diffusion is occurring by an interaction of aqueous solution/matrix, in these gels, the cross-linking density would not be expected to have a significant effect on the apparent diffusion coefficient. Our results for pHEMA4 and pHEMA5 gels, presented in Table 4, show that the apparent diffusion coefficient does not change significantly with crosslinker con-

Table 4

Values of the apparent diffusion coefficient for SA release (D_{SA}), t_{50} values and SA load (A), from pHEMA gels with different cross-linker concentrations^a

Gel	TPGDA (%mol)	t_{50} (min)	D_{SA} ($\text{m}^2 \text{ s}^{-1}$)	A (kg m^{-3})
pHEMA1	1	82.0	5.3×10^{-11}	6.1
pHEMA3	3	99.0	4.0×10^{-11}	7.4
pHEMA4	5	132.0	2.0×10^{-11}	8.8
pHEMA5	10	167.0	1.7×10^{-11}	10.3

^a The loading of SA (0.1%) was made at pH 2.5 and the release in distilled water, at 37°C.

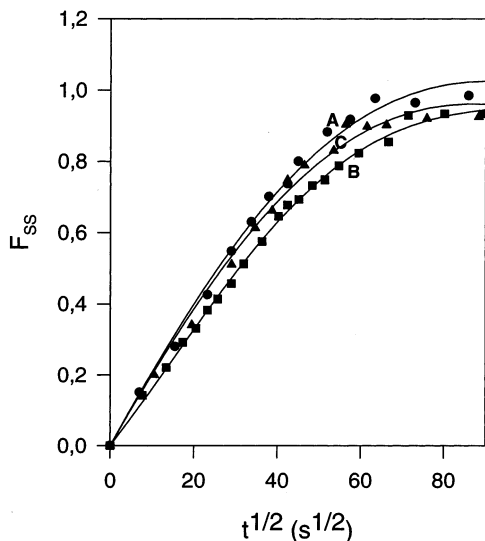


Fig. 5. Fractional release of sodium salicylate (SS) (F_{SS}) versus $(t)^{1/2}$ from preswollen pHEMA gels: pHEMA1, A, (2.3 mm thickness, 17.2 mm diameter); pHEMA2, B, (2.8 mm thickness, 17.9 mm diameter) and pHEMA5, C, (3.3 mm thickness, 21.4 mm diameter). The loading of SS (0.1%) was made at pH 12.0 and the release in distilled water, at 37°C.

centration supporting the idea that the diffusion is not occurring by pore flow in these gels.

The decrease in D_{SA} values with the degree of cross-linking has previously been observed by Wood et al. (1982) for SA delivery from pHEMA gels. The differences in D_{SA} values between our work and that of Wood can be ascribed to the different manner in the pHEMA preparation, different crosslinker agents and the W_{∞} associated to these gels (Garcia et al., 1994).

Taking into account that $M_{\infty} = AV = AS h$ (where V is the disc volume and S its surface area) it was possible to determine the drug load (A) for

all pHEMA gels (Table 4). The results obtained show that there is a slight increase in the drug loading as the cross-linking density increases, revealing an opposite behaviour as it was showed in W_{∞} studies (Fig. 1, curve C). Probably, the differences in drug loading can be related to the interactions between the drug and the polymer matrix. These interactions, which are higher when the crosslinking density increases, prevent drug release thus maintaining a (residual) drug concentration within the gel.

3.2.2. Loading of SS at pH 12.0, release in distilled water

As it was referred previously, the SA, in an aqueous solution of NaOH, is converted to its salt: the sodium salicylate (SS). In Fig. 5 the fractional release of SS, F_{SS} , from pHEMA gels is plotted versus $(\text{time})^{1/2}$, $(t)^{1/2}$. The apparent diffusion coefficients D_{SS} obtained are presented in Table 5. As it can be seen, the D_{SS} values for all gels are larger when compared to the D_{SA} values obtained for pHEMA gels when the loading was made at pH 2.5. Also, the t_{50} values decreases significantly (Table 5). This decrease can be essentially related to the increase of water content (see Fig. 1, curve A). Thus, probably, the increase of diffusion rate can be mainly due to the increase of non-bounded water percentage in the hydrogels water content (Khare and Peppas, 1993).

Also in Table 5, the values of A indicate, unexpectedly, that the drug loading in these conditions is less favourable than when the loading was made at pH 2.5. According to the high W_{∞} values of pHEMA gels at pH 12.0 (Fig. 1, curve A), a larger drug loading should be expected. Also, from the swelling studies in aqueous solutions at

Table 5

Values of the apparent diffusion coefficient for SS release (D_{SS}), t_{50} values and SS load (A) from pHEMA gels with different cross-linker concentrations^a

Gel	TPGDA (%mol)	t_{50} (min)	D_{SS} ($\text{m}^2 \text{s}^{-1}$)	A (kg m^{-3})
pHEMA1	1	11.3	4.0×10^{-10}	1.06
pHEMA2	2	15.5	4.1×10^{-10}	0.80
pHEMA3	3	10.4	6.7×10^{-10}	0.79
pHEMA5	10	12.0	7.1×10^{-10}	0.81

^a The loading of SS (0.1%) was made at pH 12.0 and the release in distilled water, at 37°C.

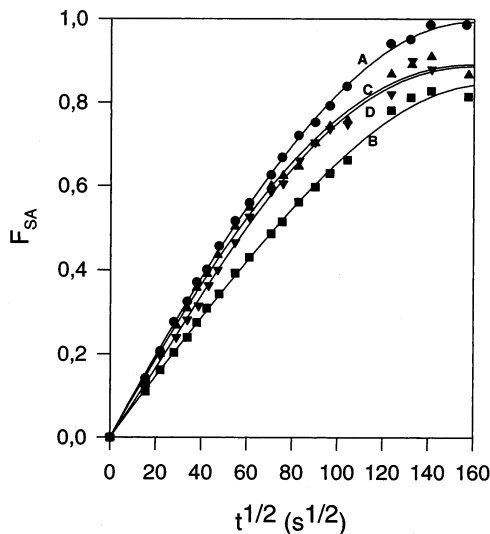


Fig. 6. Fractional release of SA (F_{SA}) versus $(t)^{1/2}$ from preswollen pHEMA gels: pHEMA1, A, (2.0 mm thickness, 15.6 mm diameter); pHEMA3, B, (2.5 mm thickness, 15.9 mm diameter); pHEMA4, C, (2.5 mm thickness, 15.9 mm diameter) and pHEMA5, D, (3.0 mm thickness, 16.0 mm diameter). The swelling was made at pH 12.0, the loading of SA (0.1%) at pH 2.5 and the release in distilled water, at 37°C.

different pH values, either in the presence or absence of SA (Table 3), no effect in swelling was observed for either case. The phenomenon can be explained taking into account the fact that at pH 12.0 the pHEMA gels become ionisable, establishing ionic bonds with sodium ion and thus favouring mainly the sorption of the water. The entrance of the drug, in its salt form, will be allowed until the equilibrium between the drug concentration inside and outside of the gel is reached, thus respecting the Donnan potential.

Table 6

Values of the apparent diffusion coefficient for SA release (D_{SA}), t_{50} values and SA load (A), from pHEMA gels with different cross-linker concentrations^a

Gel	TPGDA (%mol)	t_{50} (min)	D_{SA} ($m^2 s^{-1}$)	A ($kg m^{-3}$)
pHEMA1	1	47.0	6.5×10^{-11}	5.5
pHEMA3	3	86.0	5.5×10^{-11}	4.5
pHEMA4	5	52.0	9.3×10^{-11}	4.2
pHEMA5	10	60.0	1.3×10^{-11}	4.1

^a The swelling was made at pH 12.0, the loading of SA (0.1%) at pH 2.5 and the release in distilled water, at 37°C.

3.2.3. Swelling at pH 12.0, loading of SA at pH 2.5, release in distilled water

Fig. 6 shows the fractional release of SA, F_{SA} , from pHEMA gels, and in Table 6, the values of the apparent diffusion coefficient for SA release (D_{SA}), t_{50} values and SA load (A) are presented. The D_{SA} values for all gels are larger when compared to the D_{SA} values obtained for gels swelled at pH 6.5 and loaded at pH 2.5, mainly for highly crosslinked gels. Based on the dynamic swelling data showed in Fig. 2, we observe that after 8 days the W_{∞} of pHEMA gels at pH 2.0 is identical or even lower than the swelling exhibited for the same gels at pH 6.5. It would be expected that the SA release behaviour of gels under these conditions would be practically the same, as was observed for the same gels when the swelling was made at pH 6.5 and loading at pH 2.5. Instead, the behaviour of the gels is intermediate between the behaviour exhibited when the swelling was undertaken at pH 6.5 and loading pH 2.5, and when the swelling and loading were made at pH 12.0. A possible interpretation involves an interference of the drug in the water desorption mechanism, changing, consequently, the SA release behaviour from pHEMA gels.

3.2.4. Swelling and loading of SS at pH 12.0, release at pH 2.0

Fig. 7 presents the results of the fractional release of SS, F_{SS} , from pHEMA gels when the swelling and loading of SS is undertaken at pH 12.0 and the release at pH 2.0. Since, the dimensions of pHEMA gels studied change significantly with time, it was not possible to calculate the apparent diffusion coefficient, D_{SS} (Blanco et al., 1994). The t_{50} values obtained for pHEMA1,

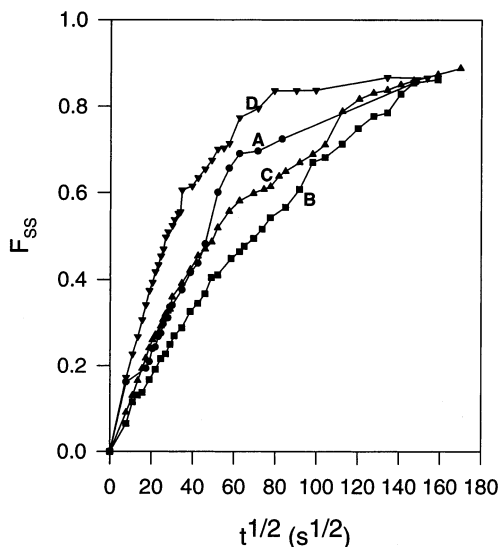


Fig. 7. Fractional release of SS (F_{SS}) versus $(t)^{1/2}$ from preswollen pHEMA gels: pHEMA1, A, (2.0 mm thickness, 17.7 mm diameter); pHEMA2, B, (2.6 mm thickness, 18.6 mm diameter); pHEMA3, C, (2.3 mm thickness, 18.5 mm diameter) and pHEMA5, D, (3.6 mm thickness, 21.0 mm diameter). The loading of SS (0.1%) was made at pH 12.0 and the release in an aqueous solution at pH 2.0, at 37°C.

pHEMA2, pHEMA3 and pHEMA5 gels were 40.0, 79.0, 40.0 and 12.0 min, respectively. These values are larger than the t_{50} values in the release experiments of SS in distilled water. Thus, during the drug release the polymer matrix would close allowing larger release times. In the curve profile it is possible to observe some inflexion points which can be related to the structural rearrangement promoted by the pH variation.

4. Conclusions

In the present study, various pHEMA gels with different crosslinking density were examined. On the basis of equilibrium and dynamic swelling data we have demonstrated that the water uptake of pHEMA gels is governed by the degree of crosslinking and by the external pH. The pHEMA gels, especially those prepared with the highest concentrations of crosslinking agent, showed an exceptional pH-sensitivity. These results can be explained by considering the Donnan potential

increase resulting from the ionic bonds established with sodium ions.

The SA release studies showed that changing the pH in swelling, drug loading or drug release could provide control of the drug release rate and drug loading. When the swelling and drug loading of pHEMA gels is performed at neutral or acidic pH, the release process is slower and the drug load capacity is larger than when these operations are made at basic pH.

Acknowledgements

The authors wish to thank FCT, Portugal, for the grant FMRH//4413 to Lino Ferreira, and Professor Rui Fausto for helping in the FTIR spectra assignment.

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