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A pH-sensitive hydrogel based on poly(ethoxy triethylene glycol monomethacrylate)

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Ethoxy triethylene glycol monomethacrylate was synthesized and polymerized at 80°C in dimethylformamide solution with AIBN as initiator. Both monomer and polymer were characterized by ^{13}C n.m.r. spectroscopy. The analysis of the microstructure of the poly(ethoxy triethylene glycol monomethacrylate), PTEG, revealed an isotacticity parameter of 0.24, rather similar to free-radical poly(methyl methacrylate) and other poly(alkyl methacrylate)s. Swelling behaviour of the polymer was studied by the immersion of films in water and in buffered solutions at various pH values from 1 to 10. The hydration process was followed gravimetrically and the diffusion of water was analysed on the basis of the stress relaxation model of polymer chains. The results obtained are in good agreement with a second-order diffusion kinetics. A sharp increase of the equilibrium hydration degree between pH 5.5 and 7.4 is observed. The pH-sensitive transition is reversible, as is shown by the dehydration of swollen gels when they are introduced into acidic solutions (pH 1–5) after swelling in alkaline media at pH 8–10.

(Keywords: pH-sensitive hydrogel; methacrylate; swelling behaviour)

INTRODUCTION

Polymeric hydrogels are of considerable importance because of their potential applications as biomaterials[1]. Biomedical applications of hydrogels include soft contact lenses, artificial corneas, soft tissue substitutes and burn dressings. Furthermore, the application of hydrogels to a variety of substrates leads to the production of thromboresistant coatings, catheters or blood detoxicants. The design of materials that are innocuous in contact with blood has long been one approach to the development of non-thrombogenic materials for use in cardiovascular applications. A polymer that has been at the forefront of this search is poly(ethylene oxide)[2], and interesting reports on hydrogels based on poly(ethylene glycol)[3–5] have been published.

On the other hand, hydrogels have been used widely for the preparation of drug delivery systems with physically or chemically modulated responses, because the water held within the swollen gel matrix acts as an efficient transport agent for low or medium molecular weight species[6]. In addition, the permeability of the body fluids contributes satisfactorily to the biotolerance of this type of biomaterial[7–9]. Much attention has been directed to the study of the behaviour of swollen gels, which exhibit a noticeable change of volume modulated by a physical agent, i.e. temperature, or chemical conditions, i.e. change of pH of the medium[10]. In general, temperature-sensitive hydrogels are based on *N*-substituted acrylamide derivatives which exhibit lower critical solution phase transitions in the vicinity of the body temperature (30–35°C)[11–14]. However, the pH-sensitive hydrogels are based on polymeric and copolymeric systems of ionizable polyelectrolytes, such as acrylic or methacrylic acids or ammonium salts[15–19], but little attention has been directed to the study of hydrophilic non-ionizable polymeric systems. As indicated above, ethylene glycol-based macromolecular systems have been used for the preparation of vascular implants in contact with the blood stream, but to our knowledge they have not been used so far for the preparation of controlled delivery systems.

In the present work we report the preparation, characterization and study of the swelling behaviour of pH-sensitive hydrogels based on a methacrylic system with non-ionizable short ethylene glycol chains as side substituents.

EXPERIMENTAL

Materials

Methacryloyl chloride (Fluka), triethylamine (Merck) and triethylene glycol monoethyl ether (Fluka) were used

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as received for the preparation of triethylene glycol monoethyl ether methacrylate. The solvent (dichloromethane) was reagent grade (Panreac), and used as received. The polymerization initiator was azobisisobutyronitrile, AIBN (Merck), and it was purified by recrystallization from ethanol, m.p. = 104°C.

Synthesis of ethoxy triethylene glycol monomethacrylate

Triethylene glycol monoethyl ether (38.45 mmol), triethylamine (38.45 mmol) and dichloromethane (150 ml) were introduced into a three-necked flask and cooled to 0°C. Methacryloyl chloride (38.45 mmol) was added dropwise with constant stirring and cooling. The reaction mixture was then stirred for 4 h at room temperature[20]. The unreacted reagents were removed by successive extraction with 1 M HCl and saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the methacrylate was distilled off at reduced pressure. The fraction of b.p. 100–105°C (0.5 mmHg) was collected and kept at low temperature.

Polymerization of ethoxy triethylene glycol monomethacrylate

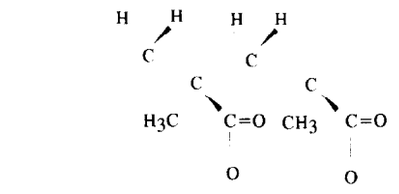
The methacrylate was polymerized at 80°C as a 3 M solution in dimethylformamide using AIBN (0.3 wt% with respect to monomer) as initiator. The reaction ampoule was flushed with oxygen-free nitrogen for 30 min. The tube was tightly closed and kept thermostatically at 80°C. After 3 h the polymer precipitated in the reaction medium. It was analysed by ^1H and ^{13}C n.m.r. spectroscopy at room temperature, using mixtures of deuterated chloroform and deuterated trifluoroacetic acid as solvents, and tetramethylsilane as internal reference.

Swelling behaviour

Transparent films of poly(ethoxy triethylene glycol monomethacrylate) (1 × 1 cm and 0.5 mm thickness) were immersed in buffered solutions of different pH at 37°C, and the hydration degree (H) (weight of water in the gel/total weight of hydrated gel)[21] was determined gravimetrically. The buffered solutions (Titrisol, Merck) ranged from pH 1 to pH 10. The swelling was followed by measuring the weight gain with the time of immersion in 10 ml of the corresponding buffered solution. The gel was weighed every 30 min after drying the surface. Measurements were taken until the equilibrium was reached, which was considered to be when three consecutive determinations gave the same weight.

RESULTS AND DISCUSSION

The behaviour of stimulus-sensitive polymers based on functional hydrogels seems to be very attractive for the preparation of drug delivery systems controlled chemically under specific physiological conditions[17]. These systems may change their structure and physical properties in response to a characteristic stimulus, such as a change of pH, the presence of ions or even specific chemical species. Although pH-sensitive hydrogels are based mainly on ionizable polyacrylic systems, we have found an interesting swelling behaviour for high-molecular-weight polymethacrylic systems with hydrophilic side residues constituted of a short segment of three repeat units of ethylene oxide. The



Scheme 1

molecular structure of repeating diads is represented in *Scheme 1*. For this reason, we were first interested in the synthesis and characterization of the corresponding polymer. It is interesting to note that the free-radical polymerization of triethylene glycol monomethacrylate in DMF solution has a precipitant character and a polymer of high molecular weight ($M_n > 500\,000$ determined by size-exclusion chromatography) precipitates in the medium. The isolated polymer after purification, as indicated in the Experimental section, was analysed by ^1H and ^{13}C n.m.r. spectroscopy. The ^{13}C n.m.r. spectrum of the polymer provides abundant information on the tacticity of the polymer chains. The proton-decoupled spectrum of PTEG together with the expanded resonance signals of quaternary carbon, carbonyl carbon and α-methyl group is shown in *Figure 1*. The enlarged α-CH_3 resonance shows three characteristic peaks at about 16.50, 18.00 and 20.10 ppm which can be assigned to syndiotactic, heterotactic and isotactic triads respectively, following the assignment suggested by Pham *et al.*[22], Bovey[23] and Peat and Reynolds[24] for other poly(methacrylic ester)s. Values of the molar fraction of the stereochemical sequences were obtained by comparison of the areas of each peak determined by planimetry as well as by electronic integration of the corresponding peaks. The average values obtained are collected in the fourth column of *Table 1*, being in good agreement with those calculated according to Bernoullian statistics[25] with an isotacticity parameter of $P_m = 0.24$ (fifth column of *Table 1*). Values of P_m of around 0.24 have been reported for the free-radical polymerization of methacrylates such as hydroxyethyl methacrylate[26], glycidyl methacrylate[27] or t-butyl methacrylate[28].

The expanded resonances of quaternary carbon split into two peaks (see *Figure 1*), which could be assigned to isotactic and heterotactic triads and syndiotactic triads respectively, with increasing magnetic field (*Table 1*). The enlarged carbonyl carbon resonance split into several peaks which could be assigned to sequences of configurational pentads. The peak assignment was done by comparison of the observed peak intensities with those calculated by assuming Bernoullian statistics, as collected in *Table 1*. The good agreement between the observed and calculated values indicates that the free-radical polymerization of ethoxy triethylene glycol monomethacrylate may be described by a single Bernoullian model in spite of the precipitant character of the polymerization reaction under the experimental conditions of the present work. This behaviour demonstrates that there are no specific polar interactions between the neighbouring oxyethylenic chains nor steric repulsion between the relatively voluminous side

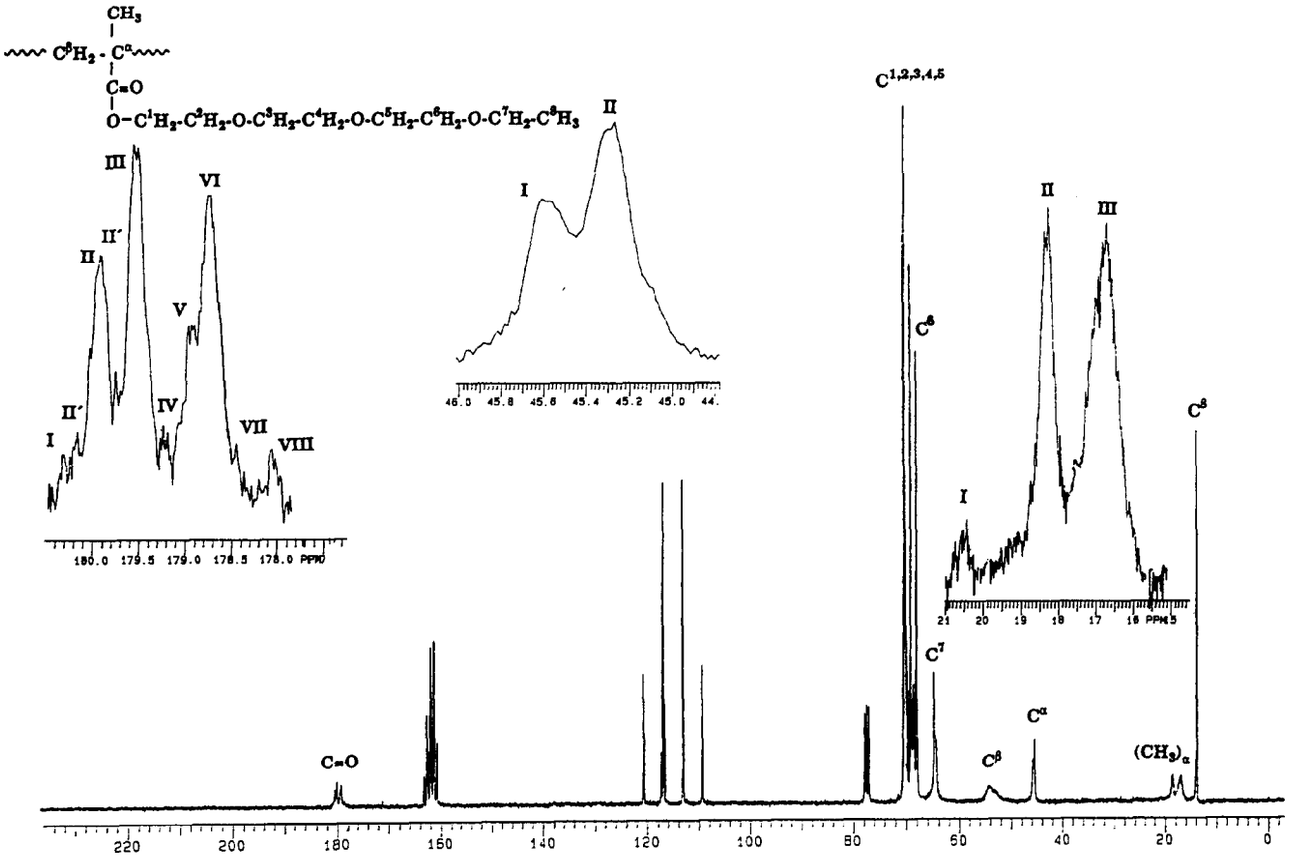


Figure 1 ^{13}C n.m.r. spectrum (75 MHz) of radical poly(ethoxy triethylene glycol monomethacrylate) (PTEG)

substituents of the macromolecular acrylic chains. The fact that the stereochemical arrangement of the substituents on the quaternary pseudoasymmetric carbon is rather similar to that of poly(methyl methacrylate), poly(hydroxyethyl methacrylate) and other poly(alkyl methacrylate)s[22,23] supports the random distribution of stereochemical sequences with little tendency to the formation of syndiotactic segments.

It has been demonstrated that polyoxyethylene (PEO) chains modify the rheological behaviour of amphiphilic hydrogels and noticeably change the gelation temperature of polymeric compounds such as poloxamer, ABA block copolymers in which A corresponds to a block of oxyethylene chains whereas the B blocks are constituted of oxypropylene chains. This kind of compound shows a reversible gel–sol transition near room temperature, depending on the composition of the corresponding copolymer and the concentration in water solution[29,30]. The PTEG system could present a rather similar trend because of the presence of the oxyethylene short segments, as is shown in *Scheme 1*.

Table 1 Triad and pentad molar fraction of poly(ethoxy triethylene glycol monomethacrylate) (PTEG) prepared by radical initiator in dimethylformamide at 80°C

Carbon	Chemical shift (ppm)	Assignment	Fractions Exp.[a]	Fractions Calc.[b]
α-CH_3	20.10 (I)	mm	0.03	0.058
	18.00 (II)	mr	0.37	0.365
	16.50 (III)	rr	0.59	0.578
C^{α}	45.20 (I)	mr + mm	0.42	0.423
	44.90 (II)	rr	0.58	0.578
>CO	179.95 (I)	mrrm	0.03	0.033
	179.75 (II′)	mmrrrm	0.03	0.012
	179.50 (II + II″)	mmrrrr + rmrrrr	0.19	0.199
	179.15 (III)	rrrr	0.34	0.334
	178.80 (IV)	mmrm	0.02	0.021
	178.50 (V)	rmrm	0.12	0.132
	178.30 (VI)	rmrr	0.23	0.211
	177.75 (VII)	mmmm	0.01	0.003
	177.65 (VIII)	mmmr + rmmr	0.03	0.054

[a] Calculated from the resonance signals in the ^{13}C n.m.r. spectrum
[b] Calculated by assuming Bernoullian statistics ($P_m = 0.24$)

In order to study the behaviour of PTEG films in contact with solution at different pH values, we analysed the dynamic swelling of PTEG samples immersed in buffered solutions at pH values in the range 1–10 at room temperature. As usual, the hydration degree, H, was defined according to the equation:

$$H = \frac{W_w - W_o}{W_w} \quad (1)$$

where W_o is the weight of the dry sample, and W_w is the weight of the wet sample at different treatment times. *Figure 2* shows the dynamic swelling expressed as the variation of the hydration degree H as a function of the time of immersion of PTEG specimens in buffered solutions at different pH values in the range 1–10. It is clearly observed that the dry specimens exhibit a rapid absorption of the solution after immersion. Together with the weight gain of the samples, a noticeable increase of the volume of the specimens was observed, mainly for the experiments carried out at pH >7. It is interesting to note here that the maximum hydration degree changes drastically in the range 0.35–0.82 with the pH of the medium, being very different in alkaline than in acidic

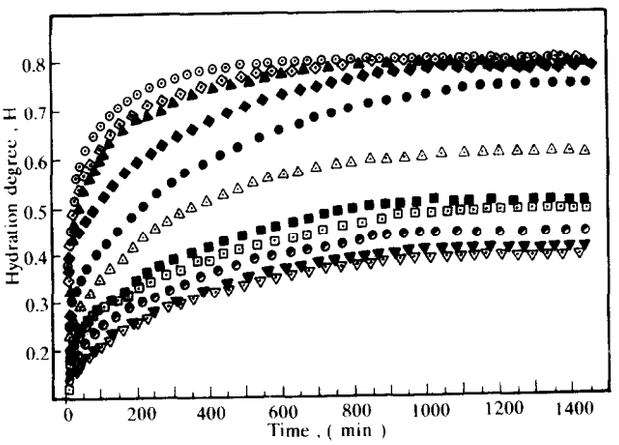


Figure 2 Dynamic swelling kinetics of PTEG from the dry state at various pH values of the buffered solution: (⊙) 10; (▲) 9.0; (◇) 8.0; (◆) 7.4; (●) 7.0; (△) 6.0; (▼) 5.0; (▽) 4.0; (◓) 3.0; (■) 2.0; (□) 1.0

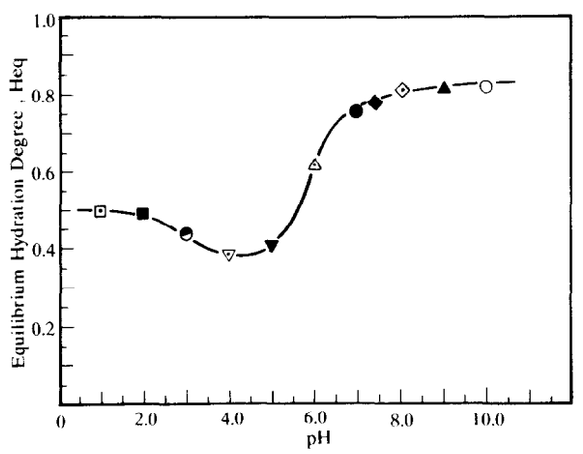


Figure 3 Variation of the hydration equilibrium degree, H_{eq}, with the pH of buffered solution at 37°C

media. In addition, the time necessary to reach the maximum hydration degree seems to be dependent on the pH of the buffered solution.

Figure 3 shows the variation of the hydration equilibrium degree, H_{eq}, as a function of the pH of the solution. H_{eq} was considered to be the maximum hydration degree reached after immersion of three different samples in the buffered solution. There is a sharp change of H_{eq} between pH values of 5.5 to 7.4, which could be very interesting from the point of view of biomedical applications. This behaviour could be ascribed to a sharp transition of extended polymeric chains at pH >7.0 to a compact coiled globular morphology in acidic media. These transitions are characteristic of specimens based on polyelectrolyte gels of poly(acrylic acid) or copolymers bearing carboxylic groups as side substituents[19,31]. When a polyelectrolyte hydrogel bearing weakly carboxylic acid pendent groups is introduced into solutions at several pH values the swelling of the gel increases with the increase of the pH of the solution[31,32]. In general, the pH of the solution has a dramatic effect on the forces that control the swelling process of the gel. In acidic media, the hydrophobic nature of the non-ionized acidic groups affects the conformational arrangement of the random coil and the macromolecular segments tend to collapse, with the resulting exclusion of the buffered solution. In contrast, the mobility of the carboxylic groups after ionization at pH >7 increases the gel osmotic pressure relative to the free solution giving rise to a well defined reversible swelling transition dependent on the pH of the medium[32,34,35]. This is not the case for PTEG because of the non-ionizable character of the oxyethylene side groups. However, the complexation of poly(ethylene oxide) chains with acid or basic compounds as a consequence of intermolecular interactions through hydrogen bonds with the oxyethylene units has been demonstrated[35]. The complexation of oxyethylene chains with non-ionized carboxylic groups (pH <7) results in a compact conformation of the macromolecular random coil with the corresponding contraction of the polymeric segments and the formation of a quasi-globular conformation giving rise to a decrease of the viscosity of the polymer–solvent binary system and logically of the polymer chain mobility[29,34]. In contrast, the ionization of acidic compounds at pH >7.0 gives rise to the reversible uncomplexation with the oxyethylene groups giving rise to an extended conformation of the polymer chains with a corresponding increase of the swelling capacity and an increase of the viscosity of the medium. This mechanism could be operative for PTEG hydrogels.

Moreover, it is clearly observed in *Figure 3* that the minimum equilibrium swelling degree is obtained at pH = 4–5, rather than at 1 or 2, which could be related to the more effective complexation just before the pH-dependent transition of the gel. In this sense, it has been considered that the carboxylic ester groups of acrylic systems do not contribute to the formation of complex structures and therefore it can be expected that the oxyethylene side residues are responsible for this particular behaviour. Also, it is necessary to take into

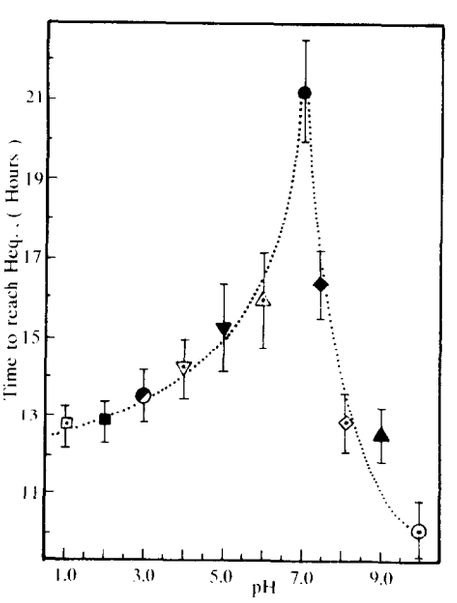


Figure 4 Average time necessary to reach the maximum swelling degree

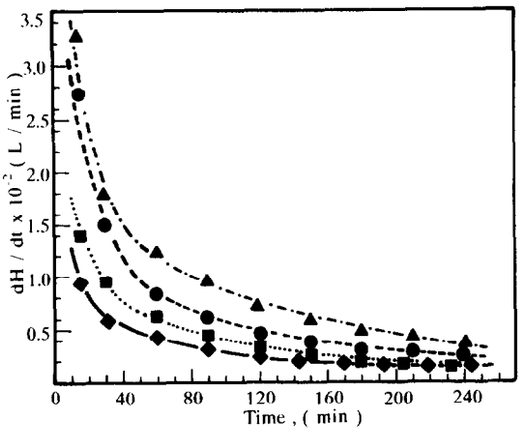


Figure 5 Change of the relative swelling rate dH/dt as a function of the time of treatment at 37°C. pH value of the buffered solution: (▲) 9.0; (●) 7.0; (◆) 5.0; (■) 2.0

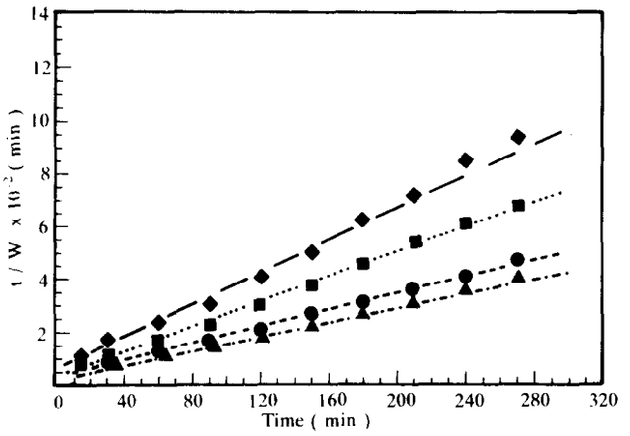


Figure 6 Variation of the reciprocal rate of swelling defined in equation (3) as a function of the swelling time for PTEG at different pHs. pH value of the buffered solution: (▲) 9.0; (●) 7.0; (◆) 5.0; (■) 2.0

consideration that the polymethacrylic backbone has a predominantly hydrophobic character in contrast to the strongly hydrophilic character of the oxyethylene residues, which probably favours the formation of the compact coil arrangement at low pH. This is reflected in *Figure 4*, which presents the time necessary to reach the equilibrium degree at different pH values. Although the estimation of this parameter is rather subjective because of the smooth variation of the swelling degree, as reflected in *Figure 1*, it seems to be clear that the time necessary to reach the maximum hydration degree changes drastically with the pH of the medium, giving rise to a sharp maximum just in the interval of the reversible transition. It is noteworthy that the swelling process is quicker at pH >7.0, just above the transition, than in acidic media.

In general, for polymeric gels the rate-determining factor of the swelling process is the stress relaxation of the polymeric segments responding to the osmotic swelling pressure[37,38]. This results in a progressive softening of the system as the buffered solution permeates into the polymeric mass, giving rise to a continuous change of the rate of swelling with time. In this sense, *Figure 5* shows the variation of the swelling rate expressed by the ratio dH/dt as a function of the time of treatment at different pH values. In all cases the rate reaches a maximum just after the immersion of PTEG samples into the solution and decreases exponentially with time until the equilibrium is reached. The diffusion rate is very sensitive to the pH of the medium and the small variation of the rate at pH <7.0 in comparison with the relatively high initial values at pH >7.0 can be observed clearly in the figure.

Recently Schott[37] has suggested a theoretical model for the diffusion-controlled swelling of rigid polymeric films, considering that first-order kinetics does not apply. Fick's law of diffusion of one-dimensional swelling of films considers that the diffusion coefficient D of the penetrating agent (solvent or solution) and film thickness remain constant during the entire swelling process[35,38,39]. For extensive swelling the film thickness obviously does not remain constant.

However, it has been demonstrated[37] that for second-order swelling kinetics, the reciprocal of the average rate of swelling (t/w) is related to the time of treatment by the linear equation:

$$t/w = A + Bt \tag{2}$$

where w is the swelling or solvent uptake at time t, defined as:

$$w = [W_w - W_o]/W_w = H[W_w/W_o] \tag{3}$$

where W_w and W_o and H have the meanings given in equation (1) and A and B are two coefficients whose physical sense can be interpreted as follows: At a long treatment time, $Bt \gg A$ and according to equation (2), $B = 1/W$, i.e. it is the reciprocal of the equilibrium swelling of the maximum hydration equilibrium degree. On the contrary, at a very short treatment time, $A \gg Bt$ and in the limit, equation (2) becomes:

$$\lim_{t \to 0} (dW/dt) = 1/A \tag{4}$$

Therefore, the intercept A represents the reciprocal of the initial swelling rate.

Figure 6 shows the results obtained by the application of our swelling data to equation (3). In all cases straight lines with an excellent correlation coefficient are obtained, which demonstrates that the swelling process of this system follows a second-order diffusion kinetics, independent of the pH of the medium. This means that the gel transition detected by the change of the pH of the medium is not controlled kinetically and responds to a complexation mechanism rather than to a diffusion process.

In order to test the reversibility of the pH-dependent gel transition, three different experiments were carried out simultaneously. Gels swollen at pH values of 8, 9 and 10 were transferred to buffered solutions at pH 2, 4 and 5 respectively, and the evolution of the weight of the corresponding gels was followed gravimetrically every 15 min in a similar way to the initial swelling process. As shown in *Figure 7*, the hydration degree decreases up to the equilibrium hydration degree determined previously for the corresponding pH. The exclusion process is not controlled by a diffusion mechanism since all three experiments gave similar results within experimental

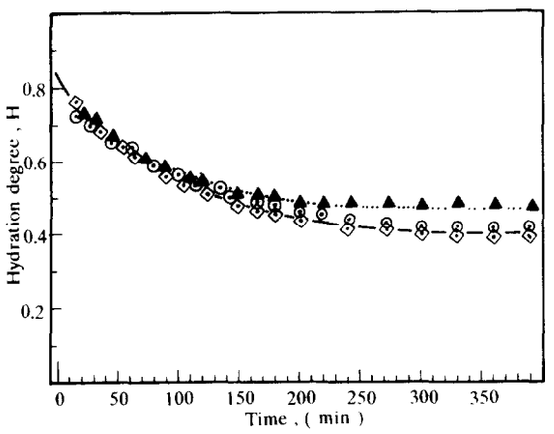


Figure 7 Dynamic deswelling of PTEG hydrogels originally swollen up to equilibrium in alkaline media, and then transferred into acidic media. (⊙) From pH 10 to 2; (▲) from pH 9 to 4; (◇) from pH 8 to 5

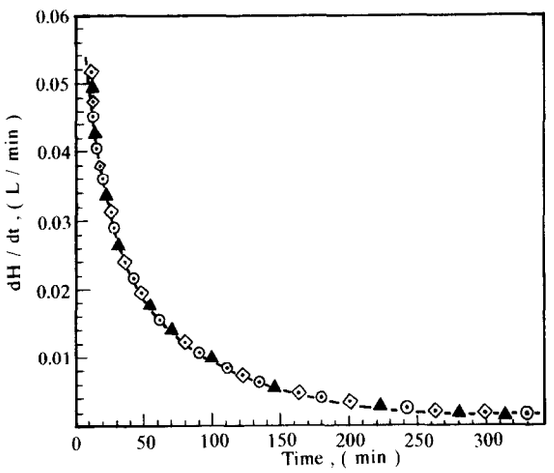


Figure 8 Change of the relative deswelling rate, dH/dt, as a function of the time of treatment at room temperature. For definition of symbols see *Figure 7*

error and the differences are only detected by the values of the equilibrium hydration degrees at pH 2, 4 and 5. This is better seen in *Figure 8*, which shows the variation of the deswelling rate as a function of time. The three experiments fit an exponential decay function up to the equilibrium, independently of the pH interval considered.

CONCLUSIONS

The behaviour of PTEG hydrogels and the pH-dependent transition in a narrow pH interval (5.5–7.5) corresponding to physiological conditions, together with the excellent biocompatibility of the polymeric constituents, offer an excellent system for use as a support for controlled drug delivery formulations. The polymeric system is particularly attractive for intranasal applications because the pH in this area is just that of the transition (5.5–6.5)[40], which provides an excellent vehicle for the administration of proteinic drugs such as insulin, calcitonine, etc.

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