Synthesis and Unusual Swelling Behavior of Combined Cationic/Non-Ionic Hydrogels Based on Chitosan

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Introduction

Hydrogels are water-swollen networks based on hydrophilic homopolymers or copolymers. Synthetic hydrogel applications began to grow rapidly from the mid 1980s.[1] The most common synthetic route is the free radical polymerization of vinyl monomers in the presence of a difunctional crosslinking agent and a swelling agent. However, considerable efforts have also been made to synthesize hydrogels based on the chemical modification of natural polymers.[2–7] Currently they are being used widely in a variety of applications such as thickening agents in food, moisture releaser to plants, fluid uptake and retention in the sanitary area, hydrophilic coatings for textile applications, separation and diffusion gel in chromatography and electrophoresis, contact lenses, and in pharmaceutical applications, principally as drug-delivery matrixes.[8–15]

On the other hand, it is well-known that hydrogels based on cationic polyelectrolytes have higher swelling capacity under acidic pH while those of an anionic nature have this maximum capacity at basic pH.[1] In the case of polymers with non-ionic functionalities, such as those with amido

groups, the swelling capacity depends, fundamentally, on controlled diffusion phenomena driven by concentration gradients.[1] When in a polymer macromolecular domains with functional groups of a different nature are combined, one can expect that the swelling process should be controlled by different mechanisms. In this case, the final result depends on a balance among the capacity of the response of different functional groups under a determined condition.[7,16] A synthetic way for obtaining hydrogels of a mixed nature is by grafting a second polymer with different characteristics on a polymer used as scaffold. In this work we present the synthesis and characterization of hydrogel-forming copolymers starting from chitosan (CHI), a cationic polyelectrolyte, grafted with different degrees of polyacrylamide (PAAM), a characteristic non-ionic polymer. Moreover, the drug release behavior of a copolymer sample was tested by using theophylline as a water-soluble drug.

Experimental Part

Chitosan (high molecular weight, purchased from Aldrich, Milwaukee, U.S.A.) was purified by extraction with acetone in a Soxhlet apparatus for 24 h and dried under vacuum at room temperature. The degree of deacetylation and molecular weight were determined according to the procedures described by Rinaudo and Domard.[17] The degree of deacetylation was 83 weight percent (wt.-%) and the average molecular weight was estimated as 3.55×10^5 by combined viscosity/light scattering measurements. Acrylamide 97% p.a. was purchased from Aldrich Milwaukee, U.S.A. and was used without further purification. Potassium persulfate was from BDH Chemicals (U.K.) and *N*,*N*-methylenebisacrylamide was purchased from Fluka and were used as received. Theophylline, Avicell type PH101, and magnesium stearate were a gift from Laboratorio Saval (Chile) and were used as received. All solvents were of analytical grade.

Characterization

The existence of grafting was confirmed by FT-IR spectroscopy.[18] The spectra of grafted chitosan samples were taken by using a Bruker IFS-28 instrument. The samples were prepared as KBr pellets.

Grafting Reactions

The grafting reactions of PAAM on CHI have been carried out in a homogeneous phase at 50–70 °C using potassium persulfate as redox initiator in the presence of *N*,*N*-methylenebisacrylamide as crosslinking agent. The technique used has been described previously.[18–20] Different grafting percentages (%G) of PAAM on CHI were obtained by varying reaction parameters such as temperature, solvent volume, and relative concentrations of monomer, crosslinking agent, and initiator.[18] The grafting extent was estimated by considering the increase in weight of the original CHI and the weight of CHI after grafting and purification by extraction. Grafted CHI was extracted with water in order to remove any PAAM homopolymer that could form during the grafting process. The grafting percentage was then calculated by using the expression $\%G = (W_2 - W_1)/W_1 \times 100$, where W_2 and W_1 represent the weights of grafted chitosan and initial chitosan, respectively.

Swelling Determinations

The swelling behavior of grafted chitosan samples in the form of coarse powder was studied at 37 °C as a function of time in buffer solutions at different pH values. The well-known tea-bag method was used. An exact amount of pre-dried sample was placed into a tea bag made of 200 mesh nylon screen. This was then immersed either in distilled water, sodium chloride, or buffer solution at 37 °C. After a certain time, the tea bag containing the swollen sample was taken out and hung up for 5 min in order to eliminate excess unabsorbed liquid and then weighed. The degree of swelling at time t was calculated using the relation $(W_s - W_0)/W_0$, where W_s and W_0 are the weights of swollen and dry polymer respectively.

The swelling degree of grafted chitosan samples was determined in samples with %G = 102, 150, 290, and 573 at 37 °C, as function of time, in buffer solution at pH 1.2 and 8.0, as well as in a dilute solution of sodium chloride, and in distilled water (pH 5.8). The swelling degree at any time was determined using the relationship (PH – PS)/PS where PH and PS are the humid and dry weights of the sample, respectively.

Drug Release Study

Chitosan and grafted chitosan tablets (400 mg) containing theophylline, Avicel® PH 101, and magnesium stearate were obtained by direct compression and were used as a polymeric matrix for prolonged drug release. Three formulations were prepared; theophylline 20 wt.-%, Avicel® PH 101 (28 wt.-%), chitosan (Formulation F1) or grafted chitosan (Formulation F2, %G = 300 and F3, %G = 570) 50 wt.-%, and magnesium stearate 2 wt.-%. The drug release process was studied by following the degree of swelling and erosion of the tablet. The fraction of the drug released was estimated by UV spectroscopy at 272 nm. The erosion study was carried out in dissolution equipment at 50 rpm and at 37 °C using the paddle method (USP Type 2).[21] The tablet was placed over a container made of stainless steel No. 18 mesh size and then submerged into 900 mL of 0.2 N HCl and 0.2 N KCl solution (pH 1.2) for 2 h. The tablets were then transferred to an alkaline solution (0.2 N boric acid + 0.2 N KCl solution, pH 8) and were left in this medium for a period of 6 h until completion of a total of 8 h. At different times, the tablets were removed and then dried in a vacuum oven at 60 °C to constant weight. Each assay was done in triplicate. The degree of total erosion of the tablet (DEτ) was estimated from $DE\tau = [(W_0 - W_t)/W_0] \times 100$ where W_0 is the initial weight of the tablet and W_t is the weight of the tablet at time t.

The fraction of drug released was estimated by a dissolution test, which was performed under the same conditions as the

erosion test described above. In this case, aliquots of 10 mL were taken at different times and the content of theophylline was determined by UV spectroscopy at 272 nm. Each assay was done in triplicate. The drug fraction released was analyzed by applying the simple power law expression $M/M_\infty = k \cdot t^n$, where M represent the amount of drug released at time t, M_∞ is the total amount of drug, k is a kinetic constant, and the exponent n is indicative of the release order.

Results and Discussion

Swelling Studies

Figure 1 to 4 represent the swelling kinetics for four different and growing degrees of grafting. Figure 1 for %G = 102 shows a very fast swelling at acidic pH, reaching its maximum in few minutes, which, however, decreases with longer contact time. The quick response of the hydrogel can be attributed to a fast protonation of the amine groups of the CHI. The interaction of the NH_3^+ groups with amido-groups belonging to the PAAM grafted chains could lead to a closed structure that would allow the hosting of a great amount of acid solution, which at longer contact times could diffuse to the exterior until reaching the equilibrium. It should be considered that chitosan has a high ionization degree in acid media since its pK_a is 6.3,[22] thus almost all $-NH_2$ groups are in its protonated ($-NH_3^+$) form. In the other studied aqueous media, a gradual swelling, controlled by diffusion, takes place. The process is controlled by PAAM macromolecules, essentially by diffusion. However, it can be noted that the hydrogel network swells quickly and strongly at basic pH and in sodium chloride solutions as in distilled water. A convincing explanation of this unusual behavior could not be given at this stage however it should consider the predominant effect of the non-ionic part (PAAM) of these copolymers and the sodium ion hydration on the swelling process.[2] This behavior is less notorious for products with higher PAAM content (Figure 2–4), probably because of an increased curl up of the grafted chains leading to more compact structures and therefore hindering the diffusion of the solution inside the hydrogel. Furthermore, a decrease in swelling at pH 1.2 at longer times could be caused by partial dissolution of samples with lower degree of grafting (Figure 1 and 2).

Indeed, in the case of the sample with a very high degree of grafted PAAM (Figure 4) the swelling behavior is only marginally affected by media with more or less ionic character and acidity because the ionizable properties of the amino groups of chitosan are screened by the wrapping caused by PAAM grafted chains where neutral amido groups are present.

Figure 5 shows the dependence of swelling degree at equilibrium (26 h) on the extent of grafting. It can be observed that the degree of swelling increases with the content of PAAM in the copolymer up to 300% and then it diminishes slightly. By considering that the swelling at equilibrium is similar under either acidic pH or basic pH, it is deduced that both high-molecular structures (CHI

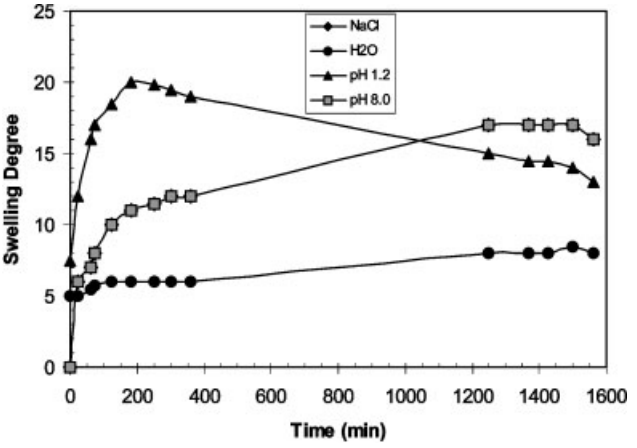

Figure 2. Swelling degree as a function of time for chitosan grafted polyacrylamide (%G = 150).

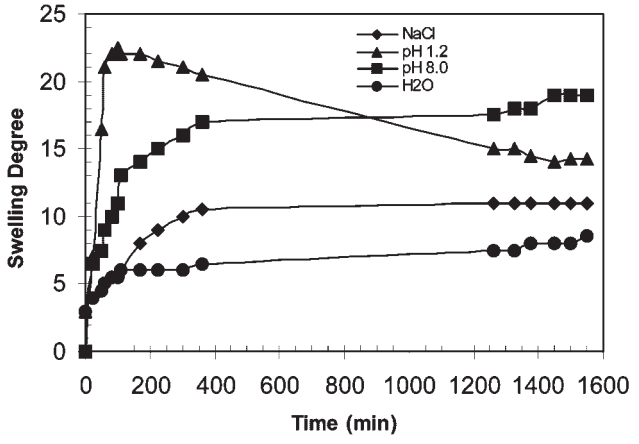

Figure 1. Swelling degree as a function of time for chitosan grafted polyacrylamide (%G = 102).

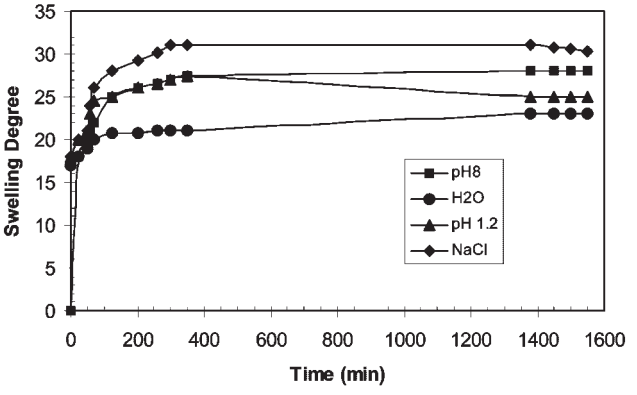

Figure 3. Swelling degree as a function of time for chitosan grafted polyacrylamide (%G = 290).

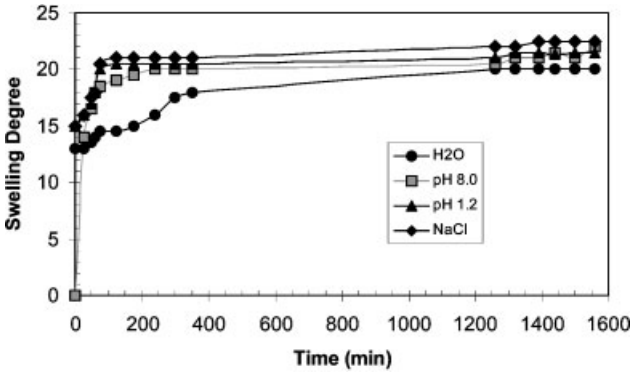

Figure 4. Swelling degree as a function of time for chitosan grafted polyacrylamide (%G = 573).

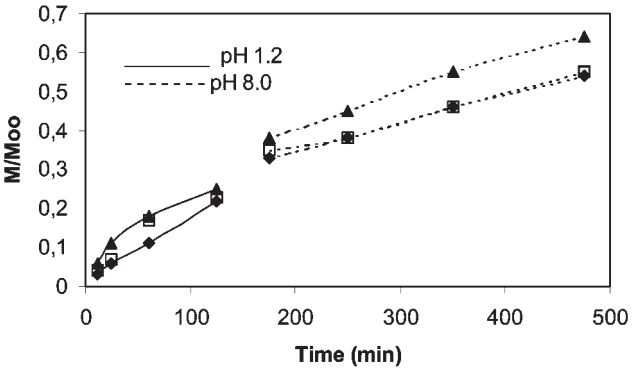

Figure 6. Dissolution profiles for formulations based on chitosan (◆); grafted chitosan with %G = 290 (▲); and grafted chitosan with %G = 573 (□).

and PAAM) contribute to the process. However, higher swelling was observed under basic pH (pH 8.0) for products with %G = 100. On the other hand, for %G = 300 the degree of swelling was somewhat higher at basic pH. This can be explained by considering a higher contribution of the cationic polyelectrolyte (CHI) in comparison with the contribution of PAAM. As explained above, for very high %G, polyacrylamide grafted chains can physically block the trunk polymer part (CHI) and, therefore, similar swelling is observed in all the studied aqueous media. That is because this process should be governed by the balance between the inter- or extragel concentrations at equilibrium. This behavior is typical of non-ionic polymers.

Drug Release

The capacity of grafted chitosan as a matrix for prolonged drug release was compared with a matrix based on unmodified chitosan. Figure 6 shows the fraction of theophylline released as function of time for the three formulations studied. The drug release was controlled by swelling and no marked increase in the degree of swelling was observed with an abrupt pH change from 1.2 to 8.0. The release curves of all formulations point to a prolonged drug release, where 50–70 wt.-% of the drug was released in a period of 8 h.

In acid media, a higher but not significant drug release from the formulation containing modified chitosan with %G = 570 (F3) compared with that of a formulation with %G = 300 (F2) and the formulation with unmodified chitosan (F1) was observed. When the pH changed from 1.2 to 8.0, all formulations showed a diminished theophylline release rate. In basic media, after 240 min, the fraction of drug released from the matrix based on F3 is significantly higher than the drug released from the matrices based on (F2) and chitosan (F1). Since theophylline is soluble in water its release from the hydrogel matrix is controlled mainly by the swelling of the matrix and the dissolution/erosion in the periphery of the matrix. The swelling and erosion behavior of the formulations could explain the dissolution profiles observed.

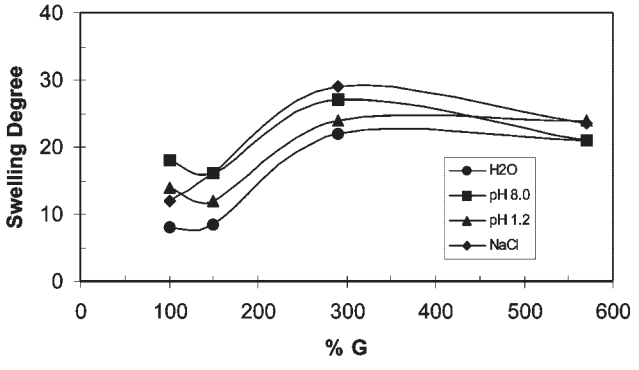

Figure 5. Dependence of swelling degree at equilibrium on the grafting extent.

Conclusions

In conclusion, the copolymers presented in this work are able to form hydrogels of great capacity and effectiveness to retain aqueous solutions of very different natures, contrary to usual hydrogels where this capacity is notably reduced as compared with distilled water. Moreover, our results indicate that the synthesized products are highly efficient as hydrogel-forming materials with swelling at equilibrium going approximately from 300 to 3 000 times the volume of the dry solid polymer in all the investigated media.

Finally, it was found that tablets based on formulations with grafted chitosan show higher erosion and swelling compared with those of the matrix based on unmodified chitosan, leading to a higher fraction of theophylline released. It can be concluded that formulations based on the synthesized copolymers are potentially useful for prolonged drug release by taking into account the specific characteristics of these matrices.

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