Swelling Pressure of Hydrogels That Degrade through Different Mechanisms

B. G. Stubbe,[†] W. E. Hennink,[‡] S. C. De Smedt,*[,†] and J. Demeester[†]

Laboratory of General Biochemistry and Physical Pharmacy, Department of Pharmaceutics, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium, and Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, University Utrecht, 3508TB Utrecht, The Netherlands

Received June 7, 2004; Revised Manuscript Received September 8, 2004

ABSTRACT: This study compares the behavior of dextran-based hydrogels that degrade through different mechanisms. The major aim is to investigate how the degradation mechanism influences their swelling pressure. The release of degradation products, the mechanical and swelling properties, and swelling pressure of the degrading gels are measured. Two types of dextran-based hydrogels are investigated: dextran methacrylate (dex-MA) hydrogels with entrapped dextranase which degrade by hydrolysis of the polymer backbone and dextran hydroxyethyl methacrylate (dex-HEMA) hydrogels which degrade at their cross-links. The release of degradation products, but especially the swelling pressure profile, seems to be strongly dependent on the mechanism underlying the degradation of the gels. In the case where the dextran gels are degraded at their backbone the swelling pressure increases rather continuously; in the case where they are degraded at the cross-links it increases more discontinuously as a sudden increase occurs when the gels are (nearly) completely degraded. This study reveals that the increase in swelling pressure in degrading dex-MA/dextranse gels is (nearly) completely attributed to an increase in osmotic pressure. However, in degrading dex-HEMA gels the increasing swelling pressure seems to be mostly attributed to the decrease in elastic pressure (i.e., elasticity) of the gels. Indeed, during a substantial period the osmotic pressure of degrading dex-HEMA gels does not change. At complete degradation the maximum swelling pressure is obtained and equals the osmotic pressure of the solution of degradation products. A much higher maximal swelling pressure is obtained when the gels are degraded at their backbone than when degraded at their cross-links.

Introduction

There is a general interest in biodegradable polymer networks for use in controlled drug delivery devices.[1] In addition, there is also a major interest in pulsed drug delivery devices which release the drug at preprogrammed times. Several concepts show potential to release drugs in a pulsed way.[2] However, many of the proposed systems have several drawbacks like initial drug release (the so-called "burst release"), sustained like release instead of pulsed release, etc. Our research group aims to develop "exploding microcapsules" for pulsed drug delivery.[3,4] We envision a delivery device that consists of a micron-sized degradable gel particle surrounded by a water permeable membrane. As the microgel degrades, the internal pressure rises, resulting in a burst of the membrane followed by a fast drug release. The microgels in our study are degradable dextran-based hydrogels. As membrane components we investigate lipids and polyelectrolytes. The exploding microcapsules which we try to design should show a behavior comparable with the osmotic bursting of red blood cells when immersed in a hypotonic solution. The difference being that the bursting in the microcapsules relies on the increase in swelling pressure of the degrading hydrogel core which, on its turn, depends on the degradation kinetics of that microgel.

With this purpose in mind it is extremely important to be able to evaluate the degradation of the (dextran) microgel core and, especially, to understand which parameters govern its swelling pressure increase. In the literature, mechanical properties, degree of swelling, and release of degradation products are typically reported in studies on degradable hydrogels.[5−9] In a previous paper of our group we also measured the swelling pressure of degrading hydrogels. We developed therefore a swelling pressure meter similar to the device described by Han et al.[10] Furthermore, we modified the osmotic deswelling technique as reported by Horkay et al.[11] to measure the swelling pressure of the dextran-based hydrogels during degradation.

Degradation of polymer networks can occur by different mechanisms: (i) by hydrolysis of side chains or pendant groups, (ii) by cleavage of the polymeric backbone, and (iii) by cleavage of labile groups in the cross-links. As shown in Figure 1, two types of dextran-based hydrogels, which degrade by different mechanisms, are investigated in this study: dextran methacrylate (dex-MA) hydrogels that degrade by cleaving the dextran backbone by the endoenzyme dextranase (entrapped within the hydrogel during polymerization) and dextran hydroxyethyl methacrylate (dex-HEMA) hydrogels that degrade by hydrolysis of the cross-links that contain hydrolyzable carbonate esters (between the methacrylate group and the dextran).[12,13]

The aim of this study was threefold. First of all, we aimed to evaluate how the degradation mechanism of the hydrogels influences the release of the degradation products and the mechanical and swelling properties of the gels. Second, we aimed to reveal how the swelling pressure of the gels changes during degradation and how this depends on the mechanism behind the degradation. Third, on the basis of the release of the degradation products and the elasticity of the degrading gels,

[†] Ghent University.
[‡] University Utrecht.
* Corresponding author: tel 0032-(0)9 264 80 76; fax 0032-(0)9 264 81 89; e-mail Stefaan.Desmedt@Ugent.be.

10.1021/ma040103s CCC: $27.50
Published on Web 10/21/2004

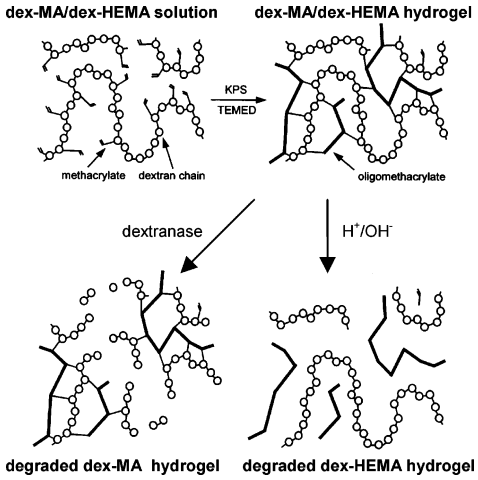

Figure 1. Schematic representation of the polymer network in dex-MA and dex-HEMA hydrogels. (○) represents glucose units in the dextran chains, and (/⁼) represents the reactive methacrylate or hydroxyethyl methacrylate groups in dex-MA and dex-HEMA, respectively. The enzymatic hydrolysis by dextranase of the dextran chains in dex-MA gels and the hydrolysis of the cross-links in dex-HEMA gels is also illustrated.

we aimed to calculate the swelling pressure of the degrading gels. The calculated swelling pressure values were then compared with the experimentally measured values.

Materials and Methods

Preparation of the Hydrogels. Dex-MA and dex-HEMA were synthesized and characterized as described in detail elsewhere.[14−16] Dex-MA and dex-HEMA were synthesized from dextran (from *Leuconostoc ssp*, Merck) with an average molecular weight of 19 000 g/mol. The degree of substitution (DS) of the dex-MA and dex-HEMA, which is the number of (HE)-MA groups per 100 glucose units, equaled 3.1 and 2.9 for dex-MA and dex-HEMA gels, respectively.

Dex-MA and dex-HEMA hydrogels were prepared by radical polymerization of aqueous dex-MA and dex-HEMA solutions, respectively. The solutions were prepared by dissolving the polymer in phosphate buffer (PB: 10 mM Na_2HPO_4, 0.02% sodium azide, adjusted with 1 N hydrochloric acid to pH 7.0). The polymerization reagents were *N,N,N′,N′*-tetramethylene-ethylenediamine (TEMED; 20% v/v in deoxygenated PB, pH adjusted to 8.5 with HCl) and potassium persulfate (KPS; 50 mg/mL in deoxygenated PB). The gelation of dex-MA and dex-HEMA solutions was initiated by adding 50 μL of TEMED solution and 90 μL of KPS solution (per gram of hydrogel). Gelation occurred at 4 °C.

When "dex-MA/dextranase" gels were prepared, prior to addition of the gelation reagents, a dextranase solution (D-1508 Sigma; diluted to 10 U/mL in 10 mM PB pH of 7.0; one unit will deliver 1 μmol of isomaltose per min at pH 6 at 37 °C) was added to the dex-MA solution (cooled to 4 °C). Throughout this work the dextranase concentration in the dex-MA gels was always 0.2 U/g gel.

"Dex-HEMA/dextran" hydrogels were made by radical polymerization (as described above) of solutions containing both dex-HEMA and dextran (19 000 g/mol, Merck).

Rheological Characterization of the Hydrogels. Rheological measurements on the hydrogels were performed by an AR1000-N controlled stress rheometer from TA-Instruments according to a method described in detail by Meyvis et al.[6]

Characterization of the Degradation Products of the Hydrogels. Individual hydrogel slabs were submerged in 10 mL phosphate buffer (pH 7.2) and stored at 37 °C. Samples (2.5 mL) were taken at regular time intervals and replaced by fresh buffer. Twice a day the containers were slightly shaken.

The concentration of reducing oligosaccharides released from the degrading dex-MA hydrogels was determined spectrophotometrically with Sumner reagent as described by Franssen et al.[17] In brief, 1.5 mL of Sumner reagent (0.2 g/mL sodium potassium tartrate, 10 mg/mL dinitrosalicylic acid, 10 mg/mL sodium hydroxide, and 2 mg/mL phenol) and 100 μL of freshly prepared sodium sulfite solution (30 mg/mL) were added to 1 mL of the sample. This mixture was incubated for 15 min at 95 °C. After cooling to room temperature, the absorbance was measured at 620 nm (Biochrom 4060 spectrophotometer). The concentration of reducing oligosaccharides was calculated from a calibration curve using glucose solutions as a reference.

The concentration of dextran chains released from the degrading dex-HEMA gels was measured by differential refractive measurements as described by Stubbe et al.[3]

Swelling Experiments. To characterize the swelling behavior of the degrading dextran hydrogels, they were weighed immediately after preparation (w_0) and at several time points during their degradation (w_t). The swelling ratio (Q) was calculated as follows:

$$Q\,(\%) = \frac{w_t - w_0}{w_0} \times 100 \qquad (1)$$

Swelling Pressure Measurements. The swelling pressure (Π_{sw}) of the dex-MA/dextranase gels was determined by a home-built "swelling pressure meter". This device consists of a calibrated transducer (Honeywell, allows to measures Π_{sw} up to 7 atm), a sample chamber (which contains the gel, volume 4 mL), and a buffer chamber (volume 15 mL). The chambers are separated by a semipermeable membrane (Spectra Por, M_w cutoff 100 g/mol) supported by a porous Bekipor frame which is further supported by a Teflon perforated cylinder. The membrane is permeable to water but impermeable to oligosaccharides being the degradation products of dex-MA/dextranase gels. To measure Π_{sw} of degrading dex-MA/dextranase gels the sample chamber (cooled at 4 °C) was filled with the dex-MA/dextranase solution during gelation. The buffer chamber (also cooled at 4 °C) was filled with PB at pH of 7.0 containing equivalent concentration of KPS and TEMED as present in the dex-MA/dextranase gels. After molding, dex-MA/dextranase hydrogels were allowed to equilibrate at 4 °C (no substantial degradation of the gels occurred) for 12 h. To start degradation, the temperature of the device was increased to 37 °C, and Π_{sw} values were registered as a function of time.

The swelling pressure meter seemed to be less suited to measure Π_{sw} of degrading dex-HEMA gels. We observed that a dex-HEMA gel in the swelling pressure meter degraded slower than the same gel submerged in buffer. The reason is still unclear. Therefore, to measure Π_{sw} of the dex-HEMA gels as a function of degradation time, we worked as follows. The dex-HEMA gels were allowed to degrade during different times in phosphate buffer (pH of 7.0). Then the swelling pressure of the (partially) degraded dex-HEMA gels was measured by "osmotic deswelling" as described in detail by Horkay and Zrinyi.[18] Deswelling was achieved by enclosing the (partially) degraded dex-HEMA gels in dialysis bags (Medicell, M_w cutoff 12−14 000 g/mol) and submerging them into poly(ethylene glycol) (PEG, Merck, M_n of 20 000 g/mol) solutions of known osmotic pressure. Equilibrium swelling was attained within 7 days. At equilibrium, the swelling pressure of the (partially) degraded dex-HEMA gel (in the dialysis bag) equaled the osmotic pressure exerted by the PEG solution outside. As the deswelling in the PEG solutions occurred at 4 °C, the dex-HEMA gels did not further degrade during the osmotic deswelling step (7 days).

Results and Discussion

Dex-MA/dextranase hydrogels degrade through hydrolysis of the polymer backbone. As shown in Figure 1, the endodextranase, entrapped within the dex-MA network during polymerization, hydrolyzes the dextran

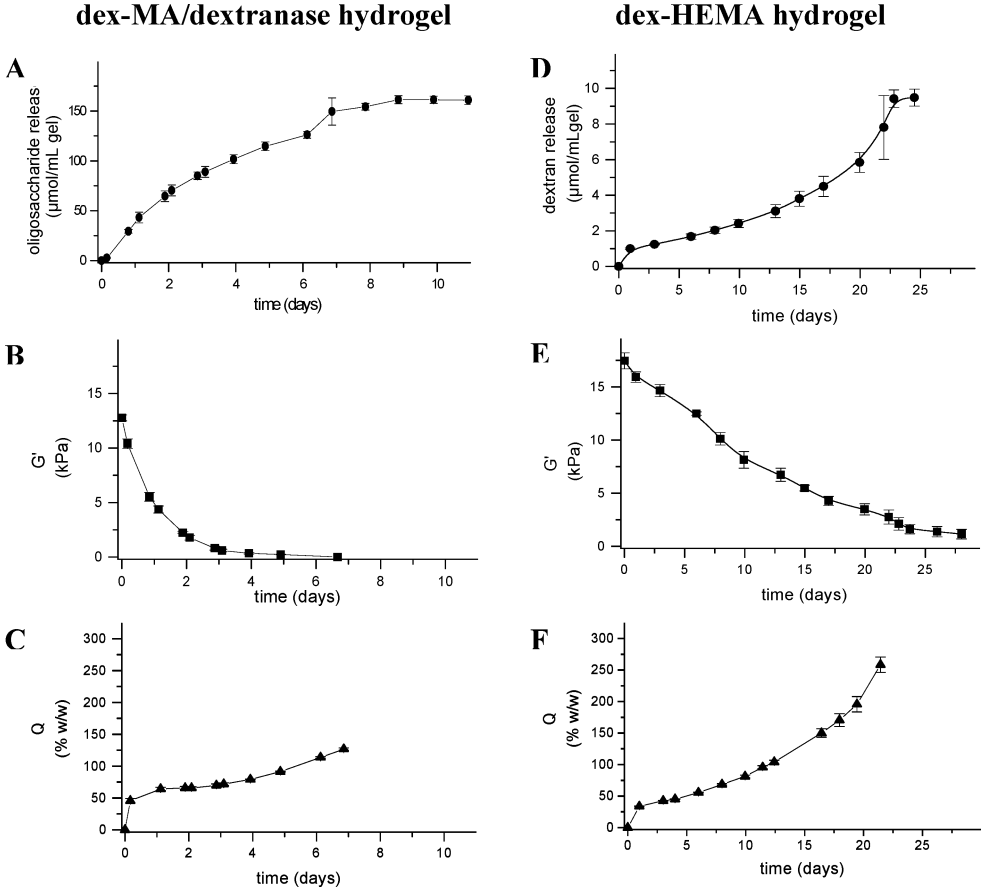

Figure 2. Cumulative release of the degradation products (i.e., oligosaccharides) (A), the elastic modulus (G') (B), and the swelling (Q) (C) of degrading dex-MA/dextranase hydrogels. The dex-MA concentration was 25% (w/w), the DS was 3.1, and the dextranase concentration was 0.2 U/g gel. Cumulative release of the degradation products (i.e., dextran) (D), the elastic modulus (G') (E), and the swelling (Q) (F) of degrading dex-HEMA hydrogels. The dex-HEMA concentration was 25% (w/w), and the DS was 2.9. All data are the average of three independent measurements.

chains of the polymer network. After a first cleavage of a dextran chain, the remaining strands (dangling ends) can be further degraded if they are long enough to fit within the active site of the dextranase.[19] Franssen et al. identified (by electrospray mass spectroscopy) the products obtained by enzymatic degradation of the dex-MA gels. For example, for a dex-MA/dextranase hydrogel of DS 4.0, they showed a variety of degradation products which are mainly oligosaccharides like glucose, isomaltose, etc. and monomethacrylated isomaltotriose.[19] On the contrary, degradation of dex-HEMA gels through hydrolysis of the cross-links results in more well-defined degradation products. As shown in Figure 1, hydrolysis of the carbonate ester cross-links results in the release of dextran chains and low-molecular-weight oligohydroxyethyl methacrylate fragments (from the cross-links).

Figure 2 compares the release of degradation products, the rheological properties, and the swelling behavior of degrading dex-MA/dextranase and degrading dex-HEMA gels. The dex-MA concentration in the (nonswollen) dex-MA/dextranase hydrogel was 25% (w/w) while the DS of dex-MA was 3.1. Similarly, the dex-HEMA concentration in the (nonswollen) dex-HEMA hydrogel was 25% (w/w) while the DS of the dex-HEMA was 2.9.

Figure 2A shows the amount of reducing oligosaccharides released from the degrading dex-MA/dextranase gel. A gradual increase in the amount of degradation products is observed as degradation proceeds: initially large amounts are released per time unit while the release rate slows down as degradation proceeds. This can possibly be explained as follows: the longer the degradation, the more likely that dextranase was released from the (degrading) dex-MA gel either in free form or bound to degradation products. Figure 2B shows the elasticity of the degrading dex-MA/dextranase gel. A major exponential decrease in G' occurs during the initial part of the degradation: already after 2 days the hydrogel lost the majority of its elasticity while after 7 days the gel became a solution. G' only decreases when the dextranase degrades elastic network chains in the dex-MA gels. In opposite, the release rate of reducing oligosaccharides is influenced by the action of the dextranase on both elastic and nonelastic dextran chains present in the hydrogel. The swelling of the degrading dex-MA/dextranase hydrogel is shown in Figure 2C. The first point (at $t = 0$) concerns the hydrogel just after cross-linking, before any degradation occurred (swelling ratio equals zero). The high swelling ratio after 1 day is mainly due to the change of the gel from its relaxed state into its swollen state (upon submerging in phosphate buffer). It was striking to observe that during the first days of degradation the swelling ratio of the dex-MA/dextranase hydrogels hardly changed while the G' of the hydrogels decreased considerably. This is explained as follows and schematically represented in Figure 3A. When an elastic network chain of the dex-MA gel is degraded by dextranase, the concentration of elastic network chains decreases and

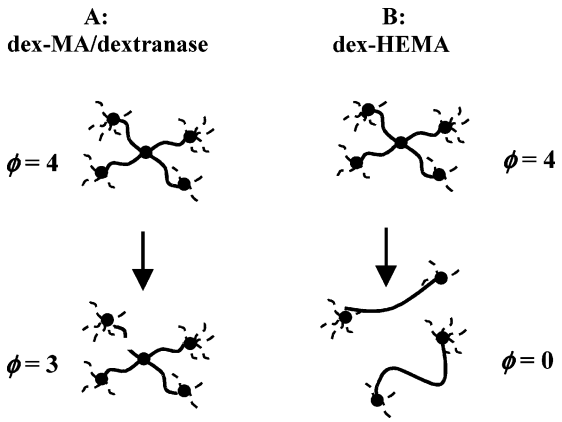

Figure 3. Schematic representation of the degradation of respectively a dex-HEMA network by dextranase (A) and a dex-HEMA network which degrades through hydrolysis of the cross-links (B). (ϕ) refers to the functionality of the cross-links (●).

thereby also G'. However, because of the high functionality of the cross-links, the concentration of elastic cross-links will remain the same during a substantial time of the degradation process. As a consequence, the average molecular weight between the remaining cross-links is also unaltered, which does not allow the network to expand.[7]

Figure 2D shows the release of degradation products (i.e., dextran chains) from the dex-HEMA gels. Instead of an immediate release as observed for dex-MA/dextranase gels (Figure 2A), a rather retarded release of degradation products was observed for the dex-HEMA gels (Figure 2D): after the release of the sol fraction (being dex-HEMA chains not attached to the network during cross-linking), a lag phase occurs while toward the end of the degradation the release clearly occurs faster. The lag phase is explained by the fact that all cross-links connecting a single dex-HEMA chain to the network have to be broken before the chain can be released. The amount of dextran released at the end of the degradation equaled the initial amount of dex-HEMA used at cross-linking. A similar release of degradation products was observed by Lee et al. in their study on poly(aldehyde guluronate) hydrogels which also degrade through degradation of the cross-links.[20] Compared with the dex-MA/dextranase gels, G' decreases more continuously during degradation of dex-HEMA hydrogels (Figure 2E). As illustrated in Figure 3B, the hydrolysis of each cross-link in a dex-HEMA gel decreases both the elastic chain and cross-link concentration which is reflected in the G'. However, we should be careful when comparing G' of degrading dex-MA/dextranase and dex-HEMA gels, as the degradation rate of the dex-MA/dextranase gels is strongly dependent upon the enzyme concentration. In Figure 2F the swelling behavior of the degrading dex-HEMA gels was followed. After an initial swelling observed upon submerging the relaxed dex-HEMA gel in buffer, the dex-HEMA gels swelled continuously during degradation. Note that a lag time in swelling was observed for the dex-MA/dextranase gel (Figure 2C). As illustrated in Figure 3B, the hydrolysis of each cross-link on a dex-HEMA chain results in a longer network chain between the remaining cross-links. Consequently, these longer chains can expand which explains the continuous swelling of the hydrogels and which also explains the higher swelling of the dex-HEMA gels compared to the dex-MA/dextranase gels (Figure 3B).[7]

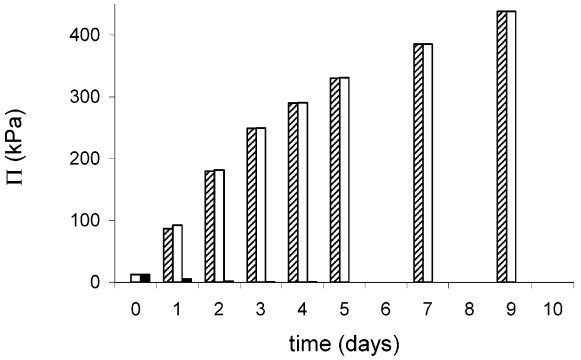

Figure 4. Osmotic pressure (open bars), elastic pressure (black bars), and swelling pressure (striped bars) of degrading dex-MA/dextranase hydrogels (DS3.1; 25% and 0.2 U/g gel dextranase). Note that the swelling pressure of the nondegraded gel (i.e., at $t = 0$) was subtracted from the swelling pressure values of the degrading gels.

Besides being interested in how the degradation mechanism influences the release of degradation products, the rheological properties, and the swelling behavior of the gels, we were especially interested to know how the swelling pressure of the two types of degrading gels builds up during degradation. Figure 4 shows that the swelling pressure of dex-MA/dextranase gels increases gradually during degradation. Besides Π_{sw}, Figure 4 also shows the osmotic pressure (Π_{osm}) and the elastic pressure ($\Pi_{el} = G'$) of the degrading dex-MA/dextranase hydrogels. Π_{osm} was calculated from the experimentally measured Π_{sw} and Π_{el} using the following equation:

$$\Pi_{sw} = \Pi_{osm} - \Pi_{el} \tag{2}$$

Clearly, the increase in Π_{sw} mainly originates from the increase in osmotic pressure and only slightly from the decrease in elastic pressure: the contribution of the elastic pressure to the swelling pressure of degrading dex-MA/dextranase gels seems to be negligible. In other words, the change in osmotic pressure of the dex-MA/dextranase gel nearly equals the change in swelling pressure. One can wonder why the swelling profile in Figure 2C does not follow the swelling pressure profile of the dex-MA/Dextranase gels in Figure 4. Clearly, in the swelling measurements in Figure 2C the degradation products were allowed to diffuse out of the gels and, consequently, did not contribute to the swelling profile. However, in the swelling pressure measurements in Figure 4 the degradation products stayed in the gel (as they could not diffuse through the semipermeable membrane in the swelling pressure device) and contributed to Π_{sw}.

We further focused on the swelling pressure of degrading dex-MA/dextranase gels by varying the dex-MA concentration of the gels. Figure 5A shows the experimental results obtained with the swelling pressure device. The maximal swelling pressure, which is obtained when the dex-MA/dextranase gels are totally degraded, was higher for more concentrated gels. This was expected as the higher the initial dex-MA concentration at cross-linking the higher the concentration of degradation products which increases Π_{osm} and thus Π_{sw}. Figure 5B shows the osmotic pressure of the degrading dex-MA/dextranase hydrogels in Figure 5A as calculated using the Van't Hoff law:

$$\Pi_{osm} = cRT \tag{3}$$

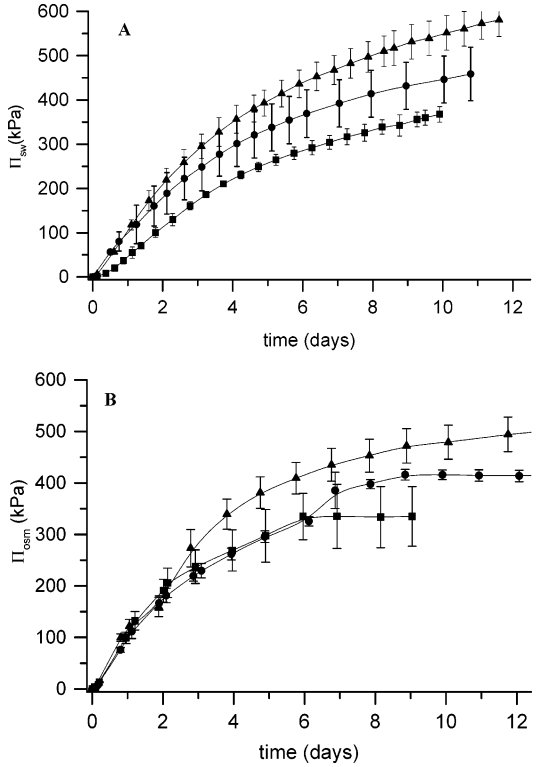

Figure 5. (A) Swelling pressure (as measured by the swelling pressure device) of degrading dex-MA/dextranase hydrogels (DS3.1; 0.2 U/g gel dextranase) with different dex-MA concentrations: 20% (■), 25% (●), and 30% (▲). (B) Osmotic pressure of degrading dex-MA/dextranase gels as calculated from the release of oligosaccharides (see Figure 2A) using eq 3. The data are the average of three independent measurements.

where c is the concentration (in mol/L) of oligosaccharides in the dex-MA/dextranase gels as calculated from the oligosaccharide release experiments in Figure 2A. R is the gas constant and T is the absolute temperature. Comparing parts A and B of Figure 5 reveals that the Π_{osm} profile, as calculated with eq 3, fairly corresponds to the experimentally obtained Π_{sw} profile in Figure 5A. This confirms that the swelling pressure of degrading dex-MA/dextranase gels can be easily predicted from their osmotic pressure as calculated from the amount of oligosaccharides released during degradation.

Figure 6 shows that the Π_{sw} profile of dex-HEMA gels totally differs from the one of dex-MA/dextranase gels. In the first 15 days of the degradation process a gradual increase in swelling pressure was observed. However, the increase in Π_{sw} is completely attributed due to the decrease in elastic pressure as no significant change in Π_{osm} can be observed. Hence, the elastic contribution to Π_{sw} cannot be neglected as is the case for dex-MA/dextranase gels. Second, to the end of the degradation (when the gel becomes a solution), the swelling pressure suddenly increases which seems to originate from a sudden increase in osmotic pressure at the "gel−sol" transition. Similar observations have been reported for other polymer/solvent systems.[21,22]

To explain the osmotic pressure properties of degrading dex-HEMA gels, dex-HEMA gels were made in the presence of free dextran chains. As during degradation of the dex-HEMA gels dextran is released, the dex-HEMA/dextran gels mimic "partially degraded dex-HEMA gels".[4] In Figure 7, the osmotic pressure of a nondegraded dex-HEMA gel (25% dex-HEMA DS 2.9)

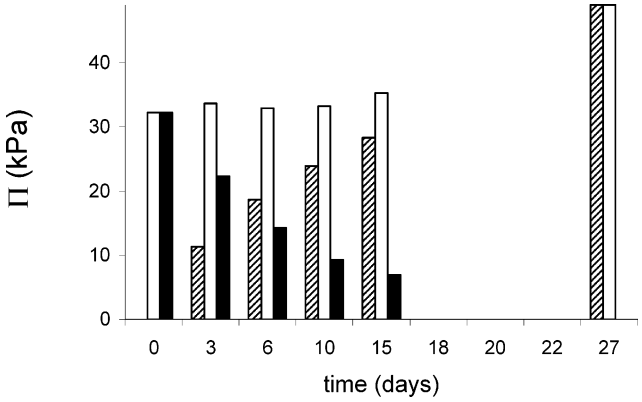

Figure 6. Osmotic pressure (open bars), elastic pressure (black bars), and swelling pressure (striped bars) of degrading dex-HEMA hydrogels (DS2.9; 25%). After 15 days the dex-HEMA gels became to weak to manipulate and to make swelling pressure measurements. After 27 days, when the gel turned into a complete polymer solution, a final measurement could be performed.

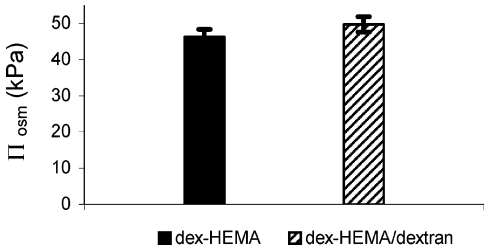

Figure 7. Osmotic pressure of a nondegraded dex-HEMA gel (DS2.9; 25%) and a similar dex-HEMA/dextran gel containing 12.5% dex-HEMA (DS2.9) and 12.5% dextran.

and of a dex-HEMA gel containing free dextran chains (12.5% dex-HEMA DS 2.9 and 12.5% free dextran) is shown. Despite the fact that a high amount of free dextran chains is present in the dex-HEMA/dextran gel, there is no significant difference in osmotic pressure of these gels. Hence, the dextran chains present in the dex-HEMA gel do not behave as free chains but as additional network chains. On the basis of light scattering experiments, Kloster et al.[23−25] reported that the presence of a gel matrix reduces the entropy and hence the osmotic pressure of the free chains present in that gel matrix. This probably explains the constant value of Π_{osm} in degrading dex-HEMA gels (Figure 5): during degradation, the amount of free dextran chains in the dex-HEMA gels increases; however, they do not increase the osmotic pressure as they behave as additional network chains in the remaining dex-HEMA network.

Besides the differences in shape of the swelling pressure curves (Figures 4 and 6), the maximal value Π_{sw} (which is obtained at complete degradation) significantly differs between dex-HEMA and dex-MA/dextranase gels. This is explained as follows. The molecular weight of the dextran chains (being the degradation products in the dex-HEMA gels) is much higher than the molecular weight of the oligosaccharides (being the degradation products of dex-MA/dextranase gels). Consequently, for dex-HEMA gels and dex-MA gels with the same initial (respectively dex-HEMA and dex-MA) concentration at cross-linking, the molar concentration of the degradation products is much higher in the solution obtained by degrading dex-MA gels than in the solution obtained from dex-HEMA gels.

As explained above, for dex-MA/dextranase gels the swelling profile in Figure 2C does not follow the swelling

pressure in Figure 4. Although, for dex-HEMA gels the swelling profile (Figure 2F) does resemble the swelling pressure profile (Figure 6). One could wonder, however, why the sudden increase in swelling pressure is not reflected in a sudden volume expansion of the gel. This is explained by the fact that the increase in swelling pressure occurs at the very end of the degradation process, i.e., when the gel becomes a solution. At this time swelling measurements are no longer feasible.

Conclusions

This study compares the behavior of dextran-based hydrogels that degrade through different mechanisms. On one hand, dex-MA hydrogels that are degraded by entrapped dextranase were used, being a model for hydrogels that degrade by hydrolysis of the polymer backbone. On the other hand, dex-HEMA hydrogels were studied as a model for hydrogels that degrade by hydroysis of the cross-links. Upon degradation of dex-MA/dextranase gels the degradation products, being oligosaccahrides, were gradually released from the gels, and an exponential decrease in G' and a minor increase in swelling were observed. In degrading dex-HEMA gels the release of degradation products, being dextran chains, only began after an initial lag phase, followed by a rather fast release of degradation products. A higher swelling was observed for degrading dex-HEMA gels compared to dex-MA/dextranase with the same dextran concentration.

The main focus of this study was to investigate the swelling pressure profile of the degrading dextran gels and to show how the degradation mechanism influences the change in swelling pressure. Typically, for dex-MA/dextranase gels a gradual increase in swelling pressure profile was observed. For dex-HEMA gels a sudden increase in swelling pressure at the end of the degradation occurred, an interesting feature to use dex-HEMA gels as core in the exploding microcapsules outlined in the Introduction. From the release of the degradation products and the elasticity of the degrading dex-MA/dextranase gels the swelling pressure was also calculated and seemed to be in good agreement with the experimentally measured values. This allowed to conclude that the swelling pressure of degrading dex-MA/dextranase gels can be well predicted from their osmotic pressure, as calculated from the release studies. In other words, the increase in swelling pressure in degrading dex-MA/dextranse gels is (nearly) completely governed by the increase in osmotic pressure. However, in the initial period of the degradation the increase in swelling pressure of the dex-HEMA gels seemed to be completely attributed to the decrease in elasticity as we observed minor changes in osmotic pressure in that period.

Finally, the maximal swelling pressure which can be obtained by degrading the gels equals the osmotic pressure of the corresponding solution of degradation products. Consequently, as the degradation products are oligosaccharides in dex-MA/dextranase gels while they are dextran chains in dex-HEMA gels, this maximal value of the swelling pressure is higher for dex-MA/dextranase gels than for dex-HEMA gels with the same dextran concentration at cross-linking.

Acknowledgment. Mies van Steenbergen is gratefully acknowledged for the synthesis of dex-HEMA. Ghent University (BOZF) is acknowledged for support through the instrumentation credits (rheometer: TA Instruments AR1000 N). Mr. Velghe from Atlantic Engineering (Nazareth, Belgium) is acknowledged for the support and development of the swelling pressure device.

References and Notes

(1) Davis, K. A.; Anseth, K. S. *Crit Rev. Ther. Drug Carrier Syst.* **2002**, *19*, 385−423.
(2) Stubbe, B. G.; De Smedt, S. C.; Demeester, J. *Pharm. Res.*, in press.
(3) Stubbe, B. G.; Braeckmans, K.; Horkay, F.; Hennink, W. E.; De-Smedt, S. C.; Demeester, J. *Macromolecules* **2002**, *35*, 2501−2505.
(4) Stubbe, B. G.; Horkay, F.; Amsden, B.; Hennink, W. E.; De Smedt, S. C.; Demeester, J. *Biomacromolecules.* **2003**, *4*, 691−695.
(5) Kurisawa, M.; Yui, N. *J. Controlled Release* **1998**, *54*, 191−200.
(6) Meyvis, T. K. L.; De-Smedt, S. C.; Demeester, J.; Hennink, W. E. *J. Rheol.* **1999**, *43*, 933−950.
(7) Meyvis, T. K. L.; De-Smedt, S. C.; Demeester, J.; Hennink, W. E. *Macromolecules* **2000**, *33*, 4717−4725.
(8) Vyavahare, N.; Kohn, J. *J. Polym. Sci.* **1994** *32*, 1271−1281.
(9) Martens, P. J.; Bryant, S. J.; Anseth, K. S. *Biomacromolecules* **2003**, *4*, 283−292.
(10) Han, I. S.; Han, M. H.; Kim, J.; Lew, S.; Lee, Y. J.; Horkay, F.; Magda, J. J. *Biomacromolecules* **2002**, *3*, 1271−1275.
(11) Horkay, F.; Zrinyi, M. *Macromolecules* **1988**, *21*, 3260−3266.
(12) Van Dijk-Wolthuis, W. N.; Hoogeboom, J. A. M.; Van Steenbergen, M. J.; Tsang S. K. Y.; Hennink, W. E. *Macromolecules* **1997**, *30*, 4639−4645.
(13) Van Dijk-Wolthuis, W. N.; van-Steenbergen, M. J.; Underberg, W. J.; Hennink, W. E. *J. Pharm. Sci.* **1997**, *86*, 413−417.
(14) Van Dijk-Wolthuis, W. N. E.; Tsang S. K. Y.; Kettenes-Van Den Bosch, J. J.; Hennink, W. E. *Polymer* **1997**, *38*, 6235−6242.
(15) Van Dijk-Wolthuis, W. N. E.; Franssen, O.; Talsma, H.; Van Steenbergen, M. J.; Kettenes-Van Den Bosch, J. J.; Hennink, W. E. *Macromolecules* **1995**, *28*, 6317−6322.
(16) Van Dijk-Wolthuis, W. N. E.; Kettenes-Van Den Bosch, J. J.; Van der Ker-Van Hoof, A.; Hennink, W. E. *Macromolecules* **1997**, *30*, 3411−3413.
(17) Franssen, O.; Vos, O. P.; Hennink, W. E. *J. Controlled Release* **1997**, *44*, 237−245.
(18) Horkay, F.; Zrinyi, M. *Macromolecules* **1982**, *15*, 1306−1310.
(19) Franssen, O.; Van-Rooijen, R. D.; de-Boer, D.; Maes, R. A. A.; Herron, J. N.; Hennink, W. E. *Macromolecules* **1997**, *30*, 7408−7413.
(20) Lee, K. Y.; Bouhadir K. H.; Mooney D. J. *Macromolecules* **2000**, *33*, 97−101.
(21) Horkay, F.; Hecht, A.-M.; Geissler, E. *J. Chem. Phys.* **1989**, *91*, 2706−2711.
(22) McKenna, G. B.; Horkay, F. *Polymer* **1994**, *35*, 5737−5742.
(23) Mallam, S.; Horkay, F.; Hecht, A.-M.; Geissler, E. *Macromolecules* **1989**, *22*, 3356−3361.
(24) Kloster, C.; Bica, C.; Lartigue, C.; Rochas, C.; Samios, D.; Geissler, E. *Macromolecules* **1998**, *31*, 7712−7716.
(25) Kloster, C.; Bica, C.; Rochas, C.; Samios, D.; Geissler, E. *Macromolecules* **2000**, *33*, 6372−6377.

MA040103S