Tailoring the Swelling Pressure of Degrading Dextran Hydroxyethyl Methacrylate Hydrogels

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Swelling pressure measurements were performed on degrading dextran hydroxyethyl methacrylate (dex-HEMA) hydrogels. In these networks, the cross-links are hydrolyzable carbonate ester bonds formed between methacrylate groups and dextran molecules. It is demonstrated that dex-HEMA gels made in the presence of a known amount of free dextran chains exhibit osmotic properties similar to those of partially degraded dex-HEMA gels. The swelling pressure, Π_{sw}, of degrading dex-HEMA gels is controlled primarily by the cross-linked dex-HEMA polymer and the free dextran molecules, while the contribution of short poly-HEMA fragments (produced in the degradation process) is negligible. It is found that Π_{sw} only slightly changes during the first 15 days of degradation. Close to the end of the degradation process, however, a much faster increase in Π_{sw} is observed. The swelling pressure profile of these gels strongly depends on the concentration of the cross-linked dex-HEMA and its chemical composition (amount of HEMA groups per 100 glucose units).

Introduction

In the field of drug delivery, there is a growing interest in biodegradable hydrogels.[1−5] To achieve *pulsed* drug delivery, we propose a new concept based on the controlled variation of the swelling pressure of degrading hydrogels. We envision a delivery device that consists of a micron-sized degradable gel particle surrounded by a water-permeable membrane (Figure 1). As the gel gradually dissolves, the swelling pressure (Π_{sw}) increases. When Π_{sw} exceeds the tensile strength of the surrounding membrane, the membrane ruptures and the drug is promptly released. In this "degradation-controlled exploding system", the release of the drug is governed by the degradation kinetics of the hydrogel particle. In this respect, it is similar to the bursting capsules outlined in the patent of Baker[6] and modeled by Kuethe et al.[7] The difference is that these devices rely on the degradation of a hydrogel whereas the system of Baker relies on small molecular weight compounds.

The swelling behavior of polymer gels has been investigated intensively.[8−11] Although many gel characteristics have been thoroughly studied, the variation of the swelling pressure during the degradation process has attracted only little attention. Recently, we have reported swelling pressure measurements performed on degrading dextran hydroxyethyl methacrylate (dex-HEMA, Figure 2) hydrogels.[12] The cross-links in this system are hydrolyzable carbonate ester bonds formed between the methacrylate groups and the dextran molecules. As the gel degrades, free dextran chains, as well as short poly-HEMA fragments, are produced. We found that Π_{sw} after a weak initial growth exhibited a steep increase close to the end of the degradation process.

This knowledge of the variation of Π_{sw} during gel degradation is important to design pulsed delivery systems with tailored swelling pressure profile. Here, we investigate the effect of different factors that influence the kinetics of degradation and Π_{sw}. The degree of substitution (DS, which is the amount of HEMA groups per 100 glucose units) and the initial concentration of dex-HEMA are varied. Furthermore, a comparison is made between Π_{sw} of degrading dex-HEMA gels and dex-HEMA/dextran gels. The latter system, containing controlled amounts of free (unattached) dextran chains, mimics partially degraded dex-HEMA gels because dextran is liberated as degradation proceeds. These investigations are expected to provide insight into the swelling properties of degradable dex-HEMA gels that may help to design "membrane-coated" gel systems for drug delivery after a certain lag time.

Materials and Methods

Dex-HEMA Preparation and Characterization. The synthesis and characterization of hydroxyethyl methacrylated

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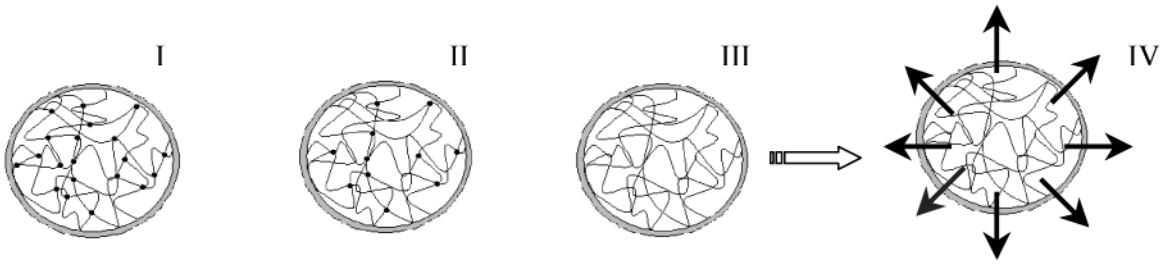

Figure 1. Schematic representation of a gel particle surrounded by a semipermeable membrane: (I) before degradation the polymer chains are connected into a three-dimensional network by chemical cross-links (●); (II) the gels described in this paper degrade as a result of hydrolysis of the cross-links, and as degradation proceeds, the cross-link density decreases and free polymer chains are produced; (III) at the end of the degradation process, a polymer solution is present; (IV) when Π_{sw} exceeds the tensile strength of the membrane, the membrane ruptures and drug molecules are released.

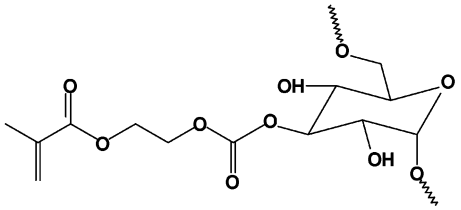

Figure 2. Chemical structure of the monomer in dex-HEMA, that is, glucopyranose substituted with HEMA. As dex-HEMA gels are degraded by hydrolysis of the HEMA cross-links, free dextran chains are produced.

dextran was performed as described by Van Dijk-Wolthuis et al.[13] The number-average molecular weight (M_n) of dextran (from *Leuconostoc mesenteroides*, Merck) and poly-HEMA were 19 000 and 1300 g/mol, respectively (for the dextran, $M_w/M_n = 2.1$ was found). The degree of substitution (DS), defined as the number of HEMA groups per 100 glucose units, was determined by proton nuclear magnetic resonance spectroscopy in D_2O with a Gemini 300 spectrometer (Varian). Three batches of dex-HEMA having degrees of substitution of 2.9, 5.0, and 7.5 were prepared.

Preparation of dex-HEMA Hydrogels and dex-HEMA/Dextran Hydrogels. Dex-HEMA hydrogels were prepared by radical polymerization of aqueous dex-HEMA solutions. The solution was prepared by dissolving dex-HEMA in phosphate buffer (PB, 10 mM Na_2HPO_4 adjusted with 1 N HCl to pH of 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 process was initiated by 50 μL of TEMED solution and 90 μL of KPS solution (per gram of hydrogel). Gelation required approximately 1.5 h. The extractable sol fraction of the dex-HEMA gels was less than 3%.

Dex-HEMA/dextran hydrogels were made using the same procedure in the presence of a known amount of dextran. The solutions were prepared by dissolving dex-HEMA and dextran in phosphate buffer. The dextran was the same as that used in the dex-HEMA synthesis.

Hydrogel slabs used for the rheological measurements were made separately in cylindrical molds (diameter 2.3 cm, height 2 mm).

Swelling Pressure Measurements. Osmotic deswelling measurements were performed on degrading dex-HEMA gels using a method described by Horkay and Zrinyi.[9] Deswelling was achieved by enclosing the gels in a semipermeble membrane (Medicell dialysis bags, M_w cutoff between 12 000 and 14 000 g/mol). surrounded by aqueous poly(ethylene glycol) (PEG) solutions of known osmotic pressure. At equilibrium, the swelling pressure of the gel in the dialysis bag is equal to the osmotic pressure exerted by the PEG solution outside. After different degradation times, dex-HEMA gel samples were equilibrated with PEG solutions at 4 °C. PEG (Merck, M_n of 20 000 g/mol) was dissolved in citrate buffer (9.44 g/L of Na_2HPO_4, 10.3 g/L of citric acid, and 0.2 g/L of NaN_3, pH of 4.4). It was verified that further degradation of the dex-HEMA gels did not occur during the measurements. Equilibrium swelling was attained within 7 days. The reversibility of the swelling process was checked.

The swelling pressure of gels prepared in the presence of free dextran chains was determined by a home-built "swelling pressure osmometer". This device consists of a calibrated transducer (Honeywell), a sample chamber (volume of 4.2 mL), and a buffer chamber (filled with 15 mL of PB at pH of 7.0). The chambers are separated by a semipermeable membrane (Medicell, M_w cutoff between 12 000 and 14 000 g/mol) supported by a porous Bekipor frame, which is further supported by a Teflon perforated cylinder. The membrane is permeable to small molecules (water and ions) but impermeable to large dextran molecules (the low molecular weight fraction of the dextran was removed by dialysis prior to the swelling pressure measurements). The apparatus measures Π_{sw} up to 7 atm. Π_{sw} measurements were performed on gels made in the sample chamber 12 h after the preparation (i.e., before substantial degradation occurred). Measurements were made at 4 °C preventing hydrolysis of the dex-HEMA/dextran hydrogels. The experimental error of the swelling pressure measurements was found to be less than 5%.

Rheological Characterization of the Hydrogels. Rheological measurements were performed by an AR1000-N controlled stress rheometer from TA-Instruments according to a method described in detail by Meyvis et al.[15] The elastic moduli of the gels were obtained from measurements made in oscillation mode at 1 Hz in the linear viscoelastic region by applying a constant strain of 0.5%.

Results and Discussion

In Figure 3 is presented the variation of Π_{sw} of a dex-HEMA gel obtained from swelling pressure measurements as a function of the degradation time *t*. The figure also shows

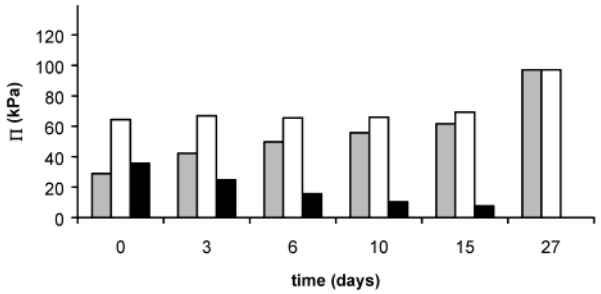

Figure 3. Osmotic pressure (open bars), elastic pressure (black bars), and swelling pressure (grey bars) of dex-HEMA hydrogels (DS = 2.9, 25%) during degradation (designation of the gel sample by degree of substitution and dex-HEMA concentration (w/w %) at cross-linking). The swelling pressure was obtained from osmotic deswelling measurements, while the elastic and osmotic pressures were calculated from the measured swelling pressure by eq 1.

Table 1. Parameters Obtained from the Fit of Eq 1 to the Swelling Pressure Data for a Dex-HEMA Gel (DS = 2.9, 25%) at Different Stages of Degradation

degradation time (days)	φ_e	A (kPa)	n	R^a
0	0.1128	5562	2.36	0.998
3	0.0919	5563	2.34	0.997
6	0.0745	5554	2.35	0.997
10	0.0598	5487	2.34	0.997
15	0.0493	5337	2.30	0.997
27	< 0.01	7920	2.33	0.993

[a] Correlation coefficient.

the osmotic ($\Pi_{osm,t}$) and elastic ($\Pi_{el,t}$) components of the swelling pressure calculated by the following equation:[9,16,17]

$$\Pi_{sw,t} = \Pi_{osm,t} + \Pi_{el,t} = A\varphi^n - A\varphi_e^{n-(1/3)}\varphi^{1/3} \qquad (1)$$

where φ and φ_e are the polymer volume fractions of the cross-linked dex-HEMA in the nondegraded gel (with φ_e = 0.1128) and of the cross-linked dex-HEMA in the fully swollen gel after degradation time t, respectively, A is a constant, and n is a scaling exponent that depends on the thermodynamic quality of the solvent. In the analysis of the swelling pressure data, A and n were iteratively adjusted to minimize the variation of the Π_{sw} for each set of data points. The resulting values of A and n are displayed in Table 1.

Figure 3 shows that Π_{el} decreases and Π_{sw} increases as the gel degrades (i.e., the carbonate ester cross-links are hydrolyzed). In the first 15 days of the degradation process, no appreciable change in Π_{osm} can be observed (after 15 days, this dex-HEMA gel became too weak to manipulate and to make swelling pressure measurements). At the end of the degradation, when the dex-HEMA gel turned into a polymer solution, osmotic pressure measurements were performed. This "gel−sol" transition is accompanied by a sudden increase in the osmotic pressure indicating significant differences between the osmotic properties of the cross-linked polymer and the corresponding polymer solution. Similar observations have been reported for other polymer/solvent systems.[18,19]

To estimate the osmotic contribution of the degradation products (low molecular weight poly-HEMA fragments and free dextran chains), we compared the osmotic pressure of a totally degraded dex-HEMA gel and that of a dextran solution (Figure 4). The good agreement between the numerical values indicates that poly-HEMA fragments do not make a significant contribution to the swelling pressure of degrading dex-HEMA gels. This finding is consistent with the expectation that low molecular weight degradation products (from GPC measurements, M_w(poly-HEMA) < 1300 g/mol) diffuse through the semipermeable membrane and leave the gel matrix.

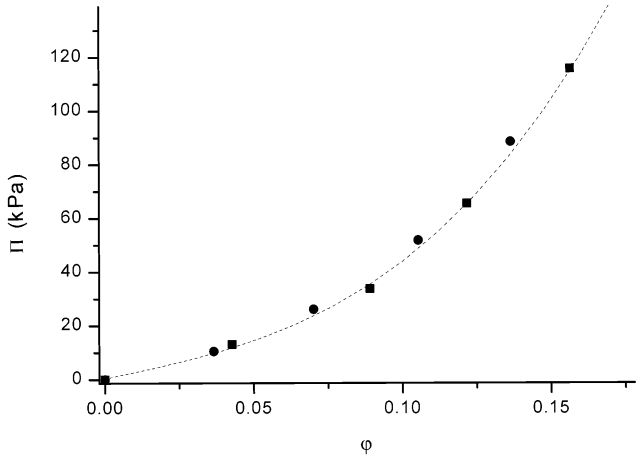

Figure 4. Osmotic pressure of totally degraded dex-HEMA gels (DS = 2.9, ●) and dextran solutions (■) as a function of the concentration.

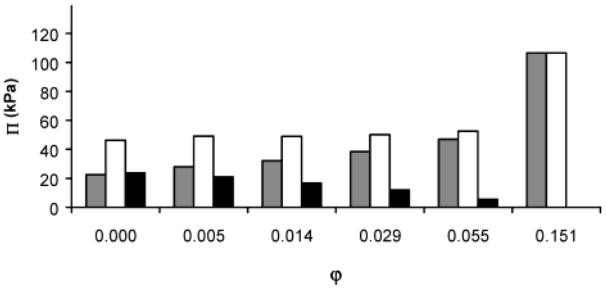

Figure 5. Osmotic pressure (open bars), elastic pressure (black bars), and swelling pressure (grey bars) of dex-HEMA/dextran hydrogels containing increasing amounts of free dextran chains. The DS of the dex-HEMA is 2.9. The total polymer volume fraction (dex-HEMA + free dextran) is 0.151 ± 0.006 for all of the gels. The values on the *x*-axis indicate the volume fractions of *free* dextran in dex-HEMA/dextran gels.

Figure 5 shows the dependence of Π_{sw}, Π_{el}, and Π_{osm} on the volume fraction of free dextran chains, $\varphi_{dextran}$, in dex-HEMA gels prepared in the presence of known amounts of dextran (dex-HEMA/dextran gel). Π_{sw} was measured by the swelling pressure osmometer, Π_{el} was estimated from elastic modulus measurements using the relationship $\Pi_{el} = -G'$, where G' is the shear modulus,[20,21] and Π_{osm} was calculated from Π_{sw} and Π_{el} by eq 1. The dextran concentration on the *x*-axis corresponds to $\varphi_{dextran}$ in degrading dex-HEMA gels after degradation times 0, 3, 6, 10, 15, and 27 days. The amount of free dextran was calculated from dextran release data of dex-HEMA gels measured by GPC (see ref 12). Figure 5 shows that Π_{el} decreases, Π_{sw} increases, and Π_{osm} only weakly varies as the volume fraction of free dextran increases. When the system approaches the gel−sol transition, however, Π_{osm} rapidly increases. Clearly, the behavior of these dex-HEMA/dextran gels is similar to that of partially degraded dex-HEMA gels.

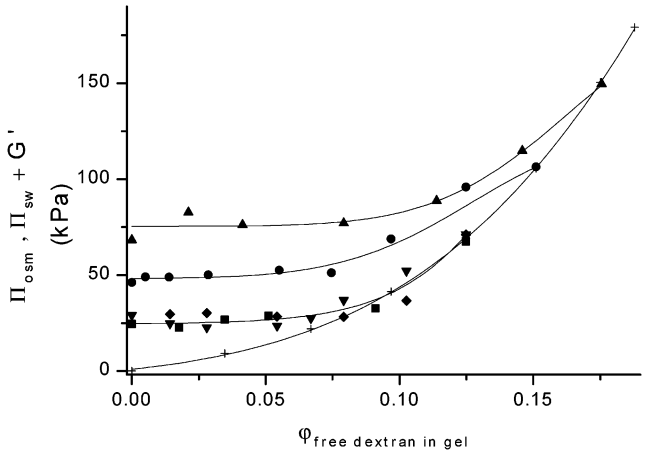

Figure 6. $\Pi_{sw} + G'$ for dex-HEMA/dextran hydrogels containing increasing amounts of free dextran. The DS and the total polymer concentration (dex-HEMA + dextran) of these gels are as follows: (●) DS = 2.9, 25%; (▲) DS = 2.9, 30%; (◆) DS = 3.5, 20%; (▼) DS = 5.0, 20%; (■) DS = 7.5, 20%. The values on the *x*-axis indicate the volume fractions of the free dextran in dex-HEMA/dextran gels. The continuous line shows the osmotic pressure of the un-cross-linked dextran solution (+).

In Figure 6, the quantity $\Pi_{sw} + G'$ is plotted as a function of $\varphi_{dextran}$ for dex-HEMA/dextran gels. These gels differ in the degree of substitution ($2.9 < DS < 7.5$) and the total polymer concentration (cross-linked dex-HEMA + un-cross-linked dextran). In the figure is also shown the concentration dependence of the osmotic pressure of the un-cross-linked dextran solution. At low dextran concentration ($\varphi_{dextran} < 0.1$), $\Pi_{sw} + G'$ is primarily governed by the polymer concentration. As $\varphi_{dextran}$ increases, $\Pi_{sw} + G'$ exhibits an increase and gradually approaches the osmotic pressure of the dextran solution.

To develop a degradation-controlled exploding system as a platform for pulsed drug delivery, it is desirable to design hydrogels that possess different degradation kinetics.[22,23] In Figure 7 are presented swelling pressure versus degradation time plots obtained from swelling pressure measurements of dex-HEMA/dextran gels in conjunction with dextran release data of degrading dex-HEMA gels (ref 12). The composition of these systems corresponds to that of various dex-HEMA hydrogels at different stages of degradation. In Figure 7A,B, the influence of dex-HEMA concentration is depicted. The initial value of the elastic modulus, the height of the "plateau" region of the osmotic pressure plot, and the degradation time increase with increasing dex-HEMA concentration. Figure 7C,D illustrates the effect of DS. Increasing DS increases the amount of possible cross-links. Generally, increasing the cross-link density (due to increasing either DS or dex-HEMA concentration) lengthens the degradation time and, consequently, the time required to attain a certain swelling pressure.

Conclusions

A systematic study was performed to gain insight into the effect of different factors (concentration of free dextran chains, degree of substitution, total polymer concentration) on the swelling pressure of degrading dex-HEMA hydrogels.

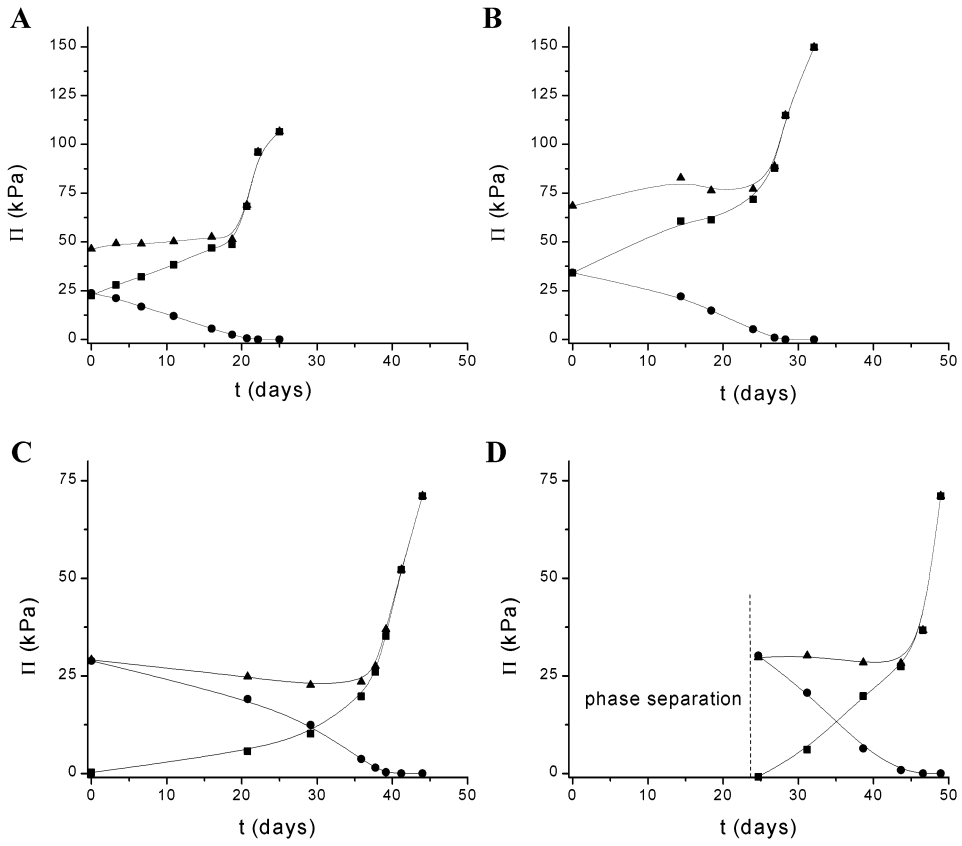

Figure 7. Variation of the elastic (●), osmotic (▲) and swelling pressure (■) of different dex-HEMA hydrogels as a function of the degradation time: (A) DS = 2.9, 25%; (B) DS = 2.9, 30%; (C) DS = 5.0, 20%; (D) DS = 7.5, 20%. Note that at low dextran concentration the dex-HEMA/dextran gel (DS = 7.5, 20%) exhibits phase separation; therefore, in this concentration range, osmotic measurements were not made.

In these networks, the cross-links are hydrolyzable carbonate ester bonds formed between methacrylate groups and dextran molecules. It is demonstrated that dex-HEMA/dextran gels made in the presence of a known amount of free dextran chains exhibit swelling pressures similar to those of partially degraded dex-HEMA gels. It is found that Π_{sw} only slightly increases during the first 15 days of the degradation process. We showed that in this period Π_{osm} of the gels did not change significantly. Close to the gel−sol transition, however, Π_{sw} rapidly increases. The swelling pressure profile of these gels, particularly the variation of the swelling pressure in the final phase of gel degradation, strongly depends on the concentration of the cross-linked dex-HEMA and the chemical composition of the network chains.

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