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Influence of free chains on the swelling pressure of PEG-HEMA and dex-HEMA hydrogels

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Abstract

Insight in the osmotic behavior of degrading hydrogels is of great importance in the design of biodegradable hydrogels for biomedical applications. This study compares the degradation behavior of PEG-HEMA (hydroxyethylmethacrylated polyethylene glycol) and dex-HEMA (hydroxyethylmethacrylated dextran) hydrogels. The degradation of PEG-HEMA gels takes several months to over a year, while that of dex-HEMA gels takes only days or weeks. The faster degradation kinetics of dex-HEMA networks can be attributed to stabilization of the keto–enol form by hydroxyl groups. Upon degradation of PEG-HEMA and dex-HEMA hydrogels, respectively, free PEG and free dextran chains are produced. We investigated the effect of unattached PEG and dextran chains on the swelling pressure of the degrading gels. It is found that low molecular weight free chains significantly increase the swelling pressure. However, the contribution of higher molecular weight free chains ($M_w > 10$ kDa) is similar to that of the network chains.

Keywords: Drug delivery; Biodegradable hydrogels; Swelling pressure; Osmotic pressure

1. Introduction

Recently biodegradable hydrogels have gained much attention because of their useful properties in various applications, such as drug release (Jeyanthi and Rao, 1990; Lee and Chien, 1996; Peppas et al., 1999; Ruel-Gariepy et al., 2000; Cerchiara et al., 2002; Vinogradov et al., 2002; Hennink et al., 2004; Van Tomme et al., 2006) and tissue engineering (Hill-West et al., 1994; Kaufmann et al., 1997; Anseth et al., 2002; Yang et al., 2002; Kast et al., 2003). Previously we reported results on the synthesis and characterization of "self-rupturing microcapsules" (van Dijk-Wolthuis et al., 1997a,b; De Geest et al., 2005a,b) (Fig. 1) consisting of a biodegradable dextran gel core surrounded by a (lipid or polymeric) membrane, which is permeable for small molecules (e.g., water and ions) but impermeable for the degradation products of the hydrogel (free polymer chains). In the course of the degradation process the swelling pressure of the hydrogel (π_{sw}) gradually increases (Stubbe et al., 2003). Provided that the increase in swelling pressure is sufficient to overcome the tensile strength of the surrounding membrane, the latter ruptures (Fig. 1D). The *time* of rupturing is primarily determined by the degradation kinetics of the gel core that governs the increase of π_{sw}.

To design self-rupturing dextran-based microcapsules we recently investigated the swelling pressure of degrading hydroxyethylmethacrylated dextran (dex-HEMA, Fig. 2A) hydrogels (Stubbe et al., 2002, 2003). The polymer network in these hydrogels is formed by radical polymerization of a dex-HEMA solution. The HEMA based crosslinks, which connect the dextran chains, contain hydrolysable carbonate esters that make the dex-HEMA hydrogels (bio)degradable (Fig. 2B). The completely degraded dex-HEMA hydrogel forms a solution consisting of dextran and poly(HEMA) chains (van Dijk-Wolthuis et al., 1997a,b, 2003).

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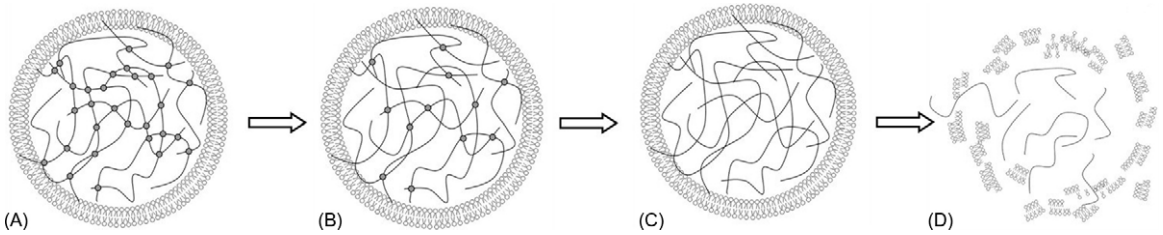

Fig. 1. Schematic representation (Stubbe et al., 2003) of a "self-rupturing" microcapsule (De Geest et al., 2005a,b) based on a degradable microgel surrounded by a semipermeable membrane: (A) Before degradation the polymer chains are connected into a three-dimensional network by chemical crosslinks. (B) The gels described in this paper degrade by hydrolysis of the crosslinks connecting the polymer chains. As degradation proceeds, the crosslink density decreases and free polymer chains are produced. (C) At the end of the degradation process the hydrogel becomes a polymer solution. (D) When the swelling pressure is sufficiently high the membrane will rupture.

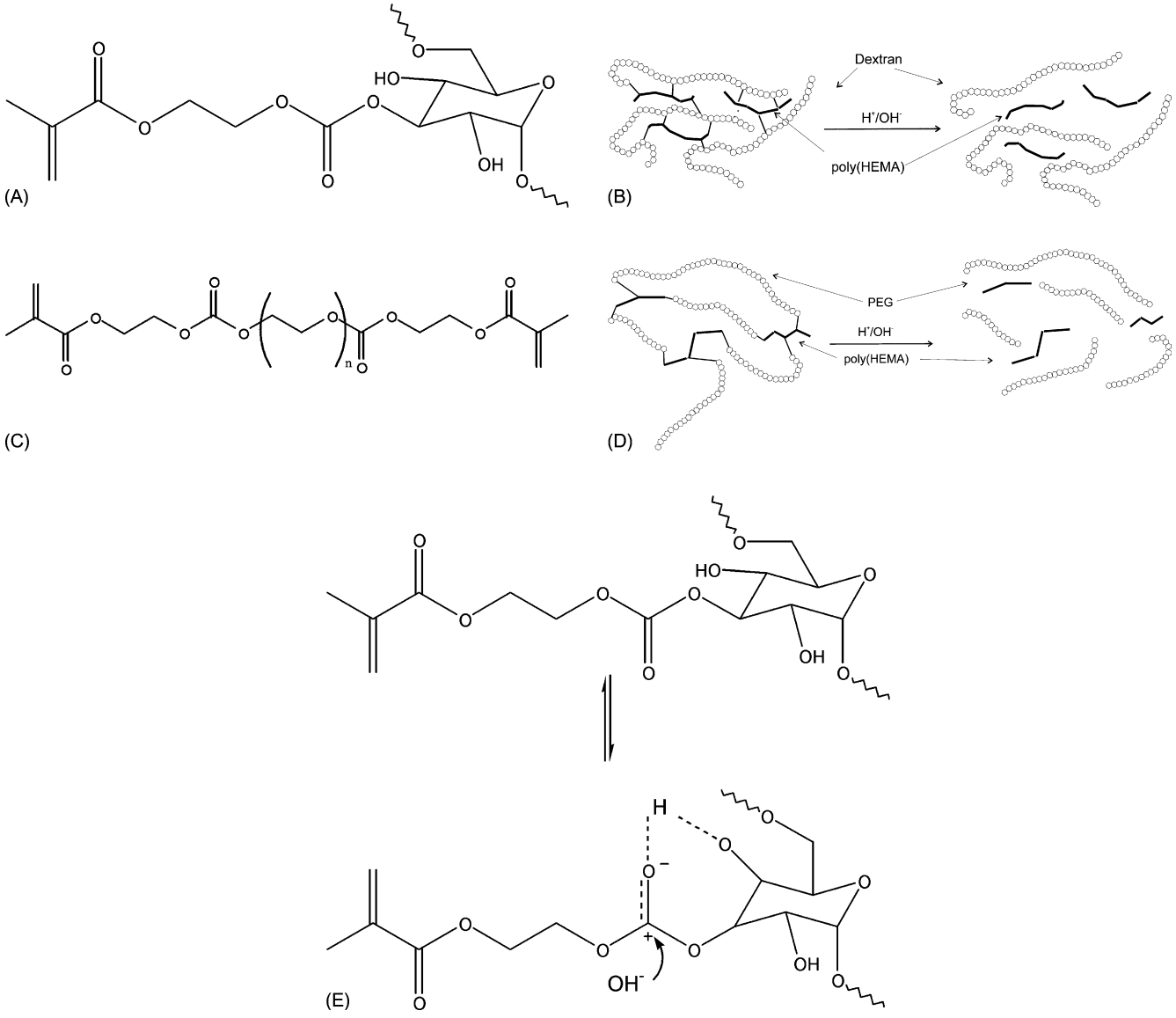

Fig. 2. (A) Chemical structure of the monomer in dex-HEMA, i.e., glucopyranose substituted with HEMA and (B) schematic representation of a dex-HEMA network before and after degradation. (C) Chemical structure of PEG-HEMA and (D) schematic representation of a PEG-HEMA network before and after degradation. The HEMA crosslinks degrade through hydrolysis of the carbonate esters, resulting in dextran chains/PEG chains and poly(HEMA). (E) Keto–enol tautomerism in dex-HEMA: adjacent hydroxyl groups on the glucose unit facilitate keto–enol tautomerism.

The swelling pressure of a neutral polymer gel is determined by two opposing effects (Flory, 1953): the osmotic pressure (π_{osm}) that expands the network and the elastic pressure (π_{el}) that contracts the network:

$$\pi_{sw} = \pi_{osm} + \pi_{el} \quad (1)$$

where $\pi_{el} = -G'$, G' being the elastic (shear) modulus of the hydrogel. Eq. (1) predicts that π_{sw} of a completely degraded hydrogel (i.e., $G' = 0$) is equal to the osmotic pressure of the solution of the degradation products. We found previously that Eq. (1) satisfactorily describes the osmotic pressure of dex-HEMA hydrogels in the course of degradation (Stubbe et al., 2003).

To break the membrane surrounding the microgel particles π_{osm} should exceed the tensile strength of the membrane. To satisfy this requirement polymers that exhibit high osmotic pressure in solution are ideal candidates.

In this study we report swelling pressure measurements for degrading hydroxyethylmethacrylated poly(ethylene glycol) (PEG-HEMA) gels. At identical crosslink density PEG-HEMA gels are expected to display higher π_{sw} than dex-HEMA gels since the osmotic pressure of the PEG solution exceeds that of the dextran solution at the same polymer concentration (Nichol et al., 1967). PEG is biocompatible and PEG based gels are widely used in drug delivery (Anseth et al., 2002; Li et al., 2003; Choi et al., 2004; Jabbari, 2004; Quick and Anseth, 2004; van de Wetering et al., 2005) and tissue engineering applications (Anseth et al., 2002). Rathi et al. studied thermoreversible hydrogels made of the triblock copolymer PLGA-PEG-PLGA (PLGA being poly(DL-lactide-co-glycolide). Dissolving PLGA-PEG-PLGA in water results in a solution at room temperature that becomes a hydrogel at body temperature. Due to hydrolysis of the PLGA blocks, PLGA-PEG-PLGA hydrogels degrade slowly over a period of 4–6 weeks (Cha and Choi, 1997; Rathi and Zentner, 1999; Rathi et al., 2000). Other biodegradable PEG hydrogels have been made from PEG-fumarate and *N*,*N*′-methylene-bisacrylamide (Suggs et al., 1998) or by conjugate addition of PEG multiacrylates (with a multi-armed structure) and dithiotreitol (van de Wetering et al., 2005).

In the present study we describe the syntheses of PEG-HEMA hydrogels and investigate their degradation behavior. To the authors' knowledge the osmotic properties of PEG-HEMA hydrogels have not been studied before. Our further aim is to determine the swelling pressure of degrading PEG-HEMA hydrogels at different stages of degradation. Particularly, we intend to quantify the effect of unattached PEG chains on the swelling pressure of degrading gels. To this end we made osmotic swelling pressure measurements on PEG-HEMA hydrogels containing controlled amounts of PEG chains of known molecular weights. We also compare the swelling and degradation behaviors of PEG-HEMA and dex-HEMA hydrogels.

2. Materials and methods

2.1. Materials

Dextran (from *Leuconostoc Mesenteroïdes*, $M_n = 19$ kDa), HEMA, dimethyl sulfoxide (DMSO < 0.01% water), $MgSO_4$, *N*,*N*,*N*′,*N*′-tetramethylenediamine (TEMED), PEG (M_n = 200 Da; 600 Da and 1.5 kDa) and hydroquinone monomethyl ether (HQM) were purchased from Fluka Chemie AG (Switzerland). 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) and 1,1′-carbonyldiimidazole (CDI) were from Acros Chimica (Belgium). PEG ($M_n = 4$ kDa; 10 kDa and 20 kDa), potassium persulfate (KPS) and dichloromethane (DCM) were purchased from Merck (Germany). Dextran ($M_n = 600$ Da and 800 Da) was obtained from Dextran Products (Canada). Dextran ($M_n = 5$ kDa and 77 kDa) were purchased from Sigma–Aldrich (Belgium). Dialysis tubes with different molecular weight cut offs (MWCO, regenerated cellulose) were obtained from Spectrum Labs (The Netherlands).

2.2. Synthesis of PEG-HEMA and dex-HEMA

The synthesis of PEG-HEMA comprised of two steps: the first step being the activation of HEMA with CDI (resulting in HEMA-CI), the second step being the coupling of HEMA-CI to the terminal hydroxyl groups of PEG.

The synthesis of HEMA-CI was performed as described by van Dijk-Wolthuis et al. (1997a,b). Briefly, 29 g (179 mmol) CDI was dissolved in 300 ml dichloromethane. 11.6 g (89 mmol) HEMA was added and the mixture was stirred for 1 h under N_2 at room temperature. Then the solution was washed by water to remove imidazole, unreacted HEMA and CDI. The HEMA-CI solution in dichloromethane was dried over $MgSO_4$. Subsequently HQM was added to avoid the formation of poly(HEMA) and the solvent was evaporated resulting in a light yellow oil: HEMA-CI.

PEG-HEMA was synthesized as follows: 50 g (12.5 mmol) PEG ($M_n = 4$ kDa), dried in a vacuum oven for 24 h at room temperature, and 5 mg HQM were dissolved in 500 ml DMSO in a 1 l three-neck round bottomed flask under N_2 stream. After dissolving 10 g DMAP in the PEG/DMSO solution 14 g HEMA-CI (62.5 mmol, 5 equiv.) was added dropwise while stirring vigorously. This mixture was allowed to react for 5 days under N_2. The reaction was terminated by decreasing the pH to 4.0 with HCl solution. DMSO was removed by dialysis against deionized water for 1 week (MWCO of the dialysis tubes was 2 kDa), the water was refreshed twice a day. Subsequently the solution was freeze dried and the fluffy white powder was stored at −20 °C under N_2. Purity was determined by proton nuclear magnetic resonance spectroscopy (^{1}H NMR) in D_2O with a Gemini 300 spectrometer (Varian). The degree of methacrylation was determined by ^{1}H NMR and found to be 96%, i.e., 96% of the terminal hydroxyl groups of PEG were substituted with HEMA.

Importantly, in the storage of PEG and in the synthesis of PEG-HEMA the formation of PEG peroxides should be avoided (Wade, 1999). Such peroxides spontaneously initiate the polymerization of PEG-HEMA solutions. To prevent peroxide formation we added HQM to the PEG-HEMA and stored the polymer at −20 °C under N_2.

Dex-HEMA was prepared and characterized as described elsewhere (van Dijk-Wolthuis et al., 1997a,b). Dextran ($M_n = 19$ kDa) was used in the synthesis of the dex-HEMA. The

degree of substitution (DS), defined as the number of HEMA groups per 100 glucose units, was determined by ^{1}H NMR. The DS of the two dex-HEMA samples used in this study were 2.5 and 5.4, respectively.

2.3. Gelification procedure and swelling pressure measurements

The swelling pressure of dex-HEMA and PEG-HEMA hydrogels was measured using a home-made apparatus described elsewhere (Stubbe et al., 2003). The device consists of two stainless steel chambers: a "sample chamber", containing the hydrogel and the calibrated pressure transducer, and a "buffer chamber". The chambers are separated by a semipermeable membrane supported by a porous Bekipor frame, and further supported by a perforated Teflon cylinder. The nominal MWCO of the membrane was respectively, 100 Da (for π_{sw} measurements on PEG-HEMA gels and on dex-HEMA gels containing 600 Da and 800 Da dextran chains) and 2 kDa (for π_{sw} measurements on dex-HEMA gels containing 5 kDa, 10 kDa, 19 kDa and 77 kDa dextran chains).

The *buffer chamber* was filled with phosphate buffer (PB, 10 mM, pH = 7.5). The *sample chamber* was filled with dex-HEMA (or PEG-HEMA) hydrogels. To generate a hydrogel out of the polymer (dex-HEMA, PEG-HEMA) solutions KPS and TEMED were used as initiator and catalyst respectively, following the method as described by van Dijk-Wolthuis et al. (1995).

To a deoxygenated dex-HEMA (or PEG-HEMA) solution in PB were added KPS solution (90 μl KPS solution/g gel; 0.05 g KPS/ml PB) and TEMED solution (50 μl TEMED solution/g gel; 20% (v/v) TEMED in deoxygenated PB, pH was adjusted to 8.5 with HCl). After homogenization one part of the solution was transferred into the sample chamber. The other part of the solution was poured into a cylindrical stainless steal mould (diameter 2.3 cm, height 2 mm); the gel slabs thus made in the mould were used to measure G'. The polymer volume fraction of the hydrogels was calculated using the relationship

$$\varphi = \frac{w_{pol}}{w_{pol}v_1 + w_{buffer}/\rho} v_1 \quad (2)$$

where w_{pol} and w_{buffer} are, respectively, the weight of the polymer and the buffer, ρ is the density of the buffer (1.07 g/ml) and v_1 is the specific volume of the polymer (being 0.84 ml/g for PEG and 0.72 ml/g for dextran) (Nichol et al., 1967).

As described above the PEG-HEMA solutions also contained KPS and TEMED. As KPS and TEMED cannot diffuse through the MWCO 100 Da membrane, we added the same amount of TEMED and KPS to the PB in the buffer chamber.

2.4. Rheological measurements

Rheological measurements on hydrogel slabs, prepared in the mould as described above, were made using an AR1000-N controlled stress rheometer (TA-instruments) according to a method described in detail by Meyvis et al. (1999). The elastic moduli of the gels were obtained from oscillation measurements at 1 Hz applying a constant strain of 0.5%. For G' measurements on degrading hydrogels, the hydrogel slabs were submerged in PB at 37 °C. At regular time intervals, G' of the hydrogel slabs was measured.

Table 1
Molecular weights of the dextran samples measured by GPC

Supplier info (kDa)	M_n (kDa)	M_w (kDa)	Pd
0.60	0.86	1.24	1.44
0.80	1.82	3.40	1.87
10.00	10.80	18.47	1.71
19.00	17.28	28.26	1.63
77.00	28.69	45.30	1.58

2.5. Gel permeation chromatography

The molecular weights of the dextran samples used in this study were determined by gel permeation chromatography (Table 1). An aliquot (20 μl) of the samples (1% solution) was injected into a Waters GPC system (Waters 600 HPLC pump, Waters 2410 Refractive Index detector). A Plgel 5 μm Mixed-C column (Polymer Laboratories) was used. The mobile phase was DMSO and the flow rate was 0.5 ml/min at 70 °C. Pullulans with varying molecular weight (Polymer Laboratories) were used as molecular weight standards.

2.6. Determination of the critical overlap concentration

The critical overlap concentration (c^*) of the PEG and dextran solutions was estimated from viscometric measurements by using Eq. (3) (Rubinstein and Colby, 2005):

$$c^* = \frac{1}{[\eta]} \quad (3)$$

where $[\eta]$ is the intrinsic viscosity

$$[\eta] = \lim_{c\to 0} \frac{\eta_{sp}}{c} = \lim_{c\to 0} \frac{\ln \eta_{rel}}{c} \quad (4)$$

In Eq. (4) η_{sp} is the specific viscosity, η_{rel} is the relative viscosity and c is the polymer concentration in g/100 ml. The kinematic viscosities were measured by a Micro-Ubbelohde viscometer with Lauda S5 detector, which was connected to Lauda PVS1 Processor Viscosity System with a PVS 2.46 analysis program. The measurements were performed at 4.0 ± 0.1 °C. The flow time of the PEG and dextran solutions was at most 10–20% over the solvent flow time.

3. Results and discussion

3.1. Comparison between the osmotic pressure of PEG and dextran solutions

As outlined in the Section 1, totally degraded PEG-HEMA hydrogels are expected to exhibit a higher osmotic pressure than degraded dex-HEMA hydrogels. Fig. 2B and D shows that degradation of dex-HEMA and PEG-HEMA hydrogels

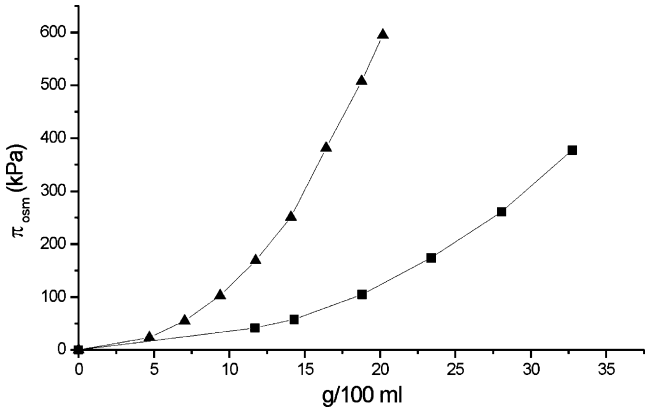

Fig. 3. Osmotic pressure of dextran (M_n = 19 kDa, ■) and PEG (M_n = 20 kDa, ▲) solutions in water as measured in the swelling pressure device.

produces dextran and PEG molecules, respectively. We made osmotic pressure measurements on solutions prepared from dextran and PEG samples of comparable molecular weights (approximately 20 kDa). Fig. 3 shows that the osmotic pressure of the PEG solution is significantly higher than that of the dextran solution at identical polymer concentration. This result indicates that water is a thermodynamically better solvent for PEG than for dextran. Note that in the degradation process a small amount of poly(HEMA) chains is also produced (see Fig. 2B and D). However, its contribution to the osmotic pressure is negligible (Stubbe et al., 2003).

3.2. Degradation of PEG-HEMA hydrogels versus dex-HEMA hydrogels

Addition of KPS and TEMED to the PEG-HEMA (or dex-HEMA) solution results in gelation. In Fig. 2B and D are compared the structure of networks made from PEG-HEMA and dex-HEMA solutions: in PEG-HEMA the polymer molecules are end-linked, while in dex-HEMA the dextran side chains are crosslinked.

Fig. 4A shows that the elastic modulus G' of PEG-HEMA hydrogels decreases in time when stored in buffer at 37 °C. As expected G' also depends on the PEG-HEMA concentration, since with increasing PEG-HEMA concentration the crosslink density (which determines G') increases. The PEG-HEMA hydrogels degrade slowly. In a previous study we found that the degradation of dex-HEMA hydrogels (Stubbe et al., 2002) is roughly 10 times faster than that of PEG-HEMA hydrogels (compare Fig. 4A and B). As illustrated in Fig. 2E, the faster degradation of dex-HEMA networks may be related to stabilization of the keto–enol form by hydroxyl groups (van Dijk-Wolthuis et al., 1997a,b).

3.3. Swelling pressure of PEG-HEMA hydrogels versus dex-HEMA hydrogels

Fig. 4A shows that the complete degradation of PEG-HEMA gels takes several months. It is therefore difficult to measure the swelling pressure of degrading PEG-HEMA gels in *real-time*.

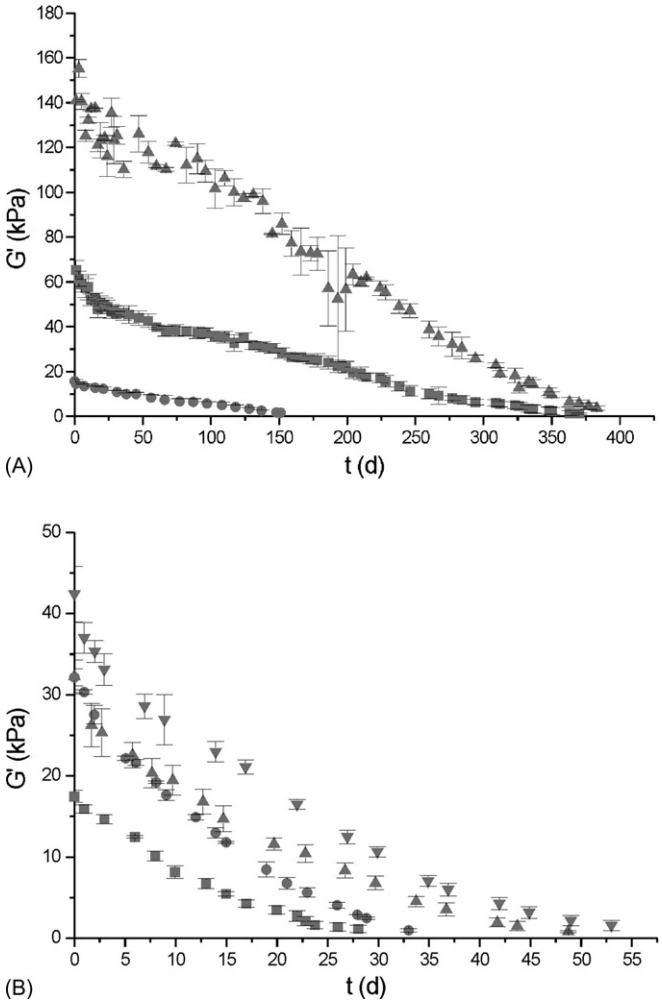

Fig. 4. (A) The elastic modulus of degrading PEG-HEMA. The PEG-HEMA concentration in the gels are 15% (●); 20% (■) and 25% (▲). (B) The elastic modulus of dex-HEMA hydrogels are as follows (Copyright ACS Stubbe et al., 2003): DS 7.5; 20% (▼); DS 5.0; 20% (▲); DS 2.5; 30% (●) and DS 2.5; 25% (■). The data are the average of three independent measurements.

Previously we showed that the swelling pressure of dex-HEMA gels at various degradation times can be "mimicked" by gels containing known amounts of uncrosslinked dextran (dex-HEMA/dextran gels) (Stubbe et al., 2003). In this experiment the dextran chains were introduced into dex-HEMA solutions prior to crosslinking. Assuming that the osmotic behavior of degrading PEG-HEMA hydrogels can be mimicked by "PEG-HEMA/PEG" gels we determined the dependence of π_{sw} and π_{el} ($=-G'$) on the concentration of the uncrosslinked PEG in the gel. PEG-HEMA/PEG hydrogels were made by polymerization of PEG-HEMA solutions in the presence of known amounts of (vacuum dried) PEG. Fig. 5A shows that π_{sw} increases and π_{el} decreases with increasing PEG concentration. Remarkably, π_{osm} ($=\pi_{sw}-\pi_{el}$) only weakly depends on the PEG content at constant overall (crosslinked + uncrosslinked) polymer concentration. However, when the gel turns into a polymer solution π_{osm} exhibits a jump-like increase. These results are consistent with similar observations made on dex-HEMA gels (Horkay and Zrinyi, 1982; Stubbe et al., 2003) (see Fig. 5B).

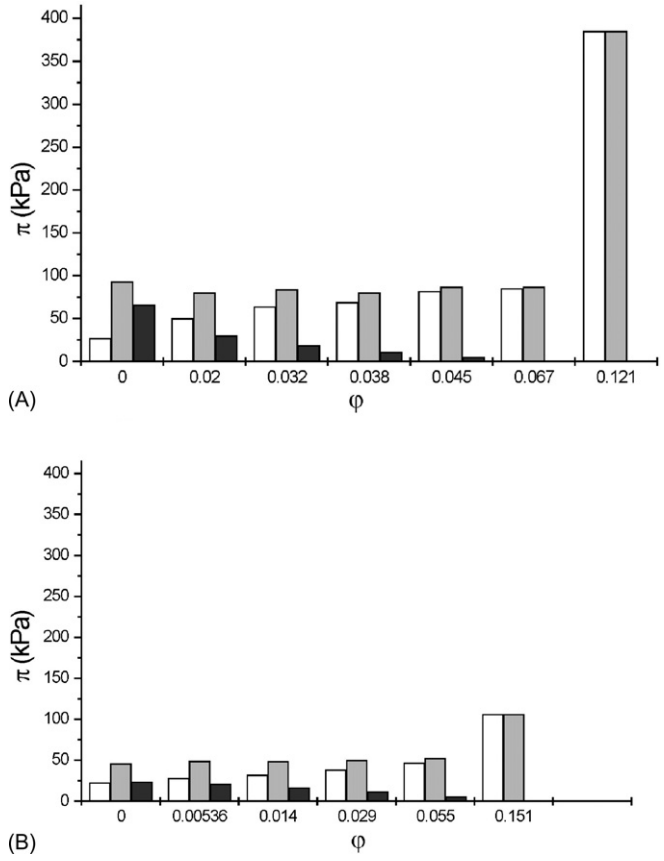

Fig. 5. Swelling pressure (open), osmotic pressure (grey bars) and elastic pressure (black bars) of PEG-HEMA/PEG hydrogels (A) and dex-HEMA/dextran hydrogels (B; Copyright ACS Stubbe et al., 2002) containing increasing amounts of uncrosslinked polymer chains (respectively, dextran 19 kDa and PEG 4 kDa). The values on the *x*-axis indicate the volume fraction of the *uncrosslinked* polymer in the corresponding gel. The total polymer volume fraction in the PEG-HEMA/PEG gels is 0.121. The total polymer volume fraction in the dex-HEMA/dex gels is 0.151.

The effect of uncrosslinked chains on the osmotic properties of polymer gels has been studied on various systems. A recent study on crosslinked DNA gels (Horkay and Basser, 2004) showed that π_{osm} of the gel is significantly lower than π_{osm} of the uncrosslinked DNA solution. The lower π_{osm} of the gels was attributed to permanent elastic constrains generated by the crosslinks. The present results suggest that in PEG-HEMA/PEG and dex-HEMA/dextran hydrogels the "free chains" strongly interact with the crosslinked polymer and behave like "crosslinked chains". When the gel is completely degraded, i.e., the polymer chains are no longer connected, the osmotic pressure increases and approaches that of the corresponding uncrosslinked polymer solution.

3.4. Influence of the molecular weight of free chains in PEG-HEMA and dex-HEMA hydrogels on the osmotic pressure

To gain a better understanding of the contribution of free chains to the osmotic pressure we measured π_{osm} of PEG-HEMA/PEG and dex-HEMA/dextran hydrogels containing known amounts of uncrosslinked polymer of different molecular weights (the molecular weights of the dextran samples determined by GPC are listed in Table 1). Fig. 6A shows π_{sw}, π_{el} and π_{osm} of a dex-HEMA gel containing uncrosslinked dextran chains of various molecular weights.

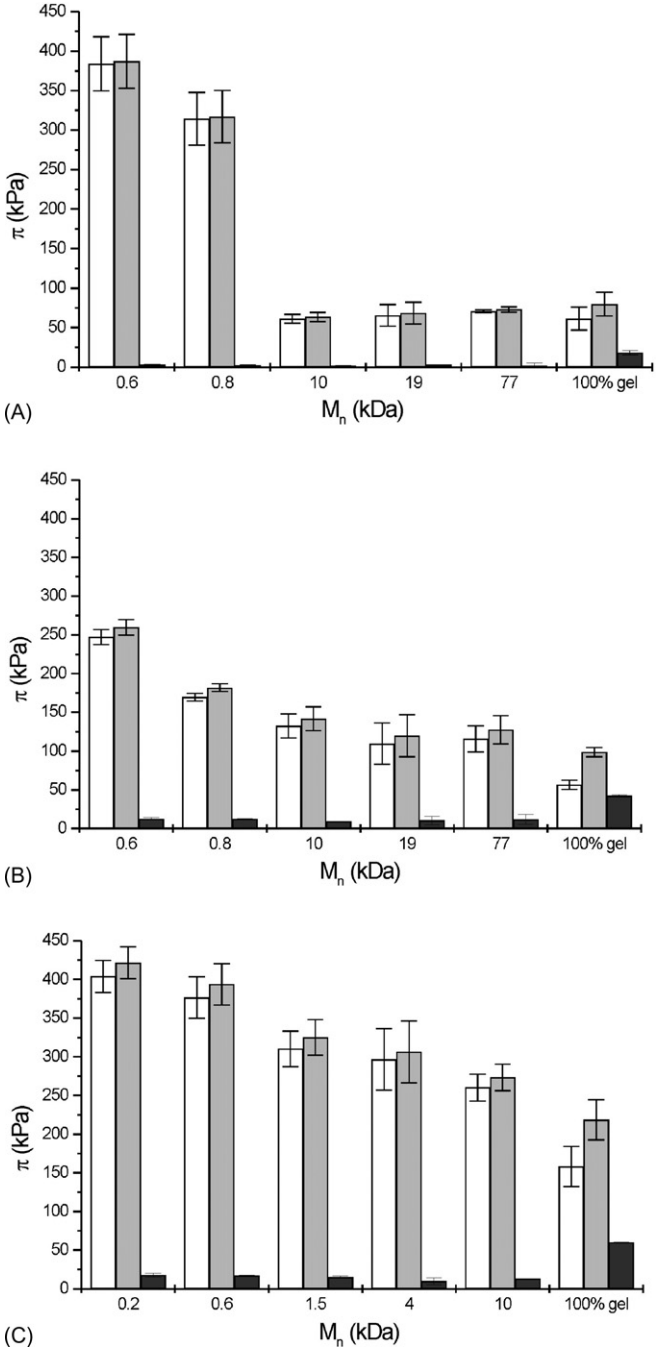

Fig. 6. Swelling pressure (open), osmotic pressure (grey bars) and elastic pressure (black bars) of dex-HEMA/dextran hydrogels and PEG-HEMA/PEG hydrogels (C). The DS of the dex-HEMA used in (A) is 2.5 while it is 5.4 in (B). The *x*-axis indicates the molecular weight of the *uncrosslinked* polymer. In all dex-HEMA/dextran gels (A, B) the total polymer volume fraction is 0.151, while the volume fraction of uncrosslinked dextran is 0.045. In all PEG-HEMA/PEG gels (C) the total polymer volume fraction is 0.121, while the volume fraction of uncrosslinked PEG chains is 0.036.

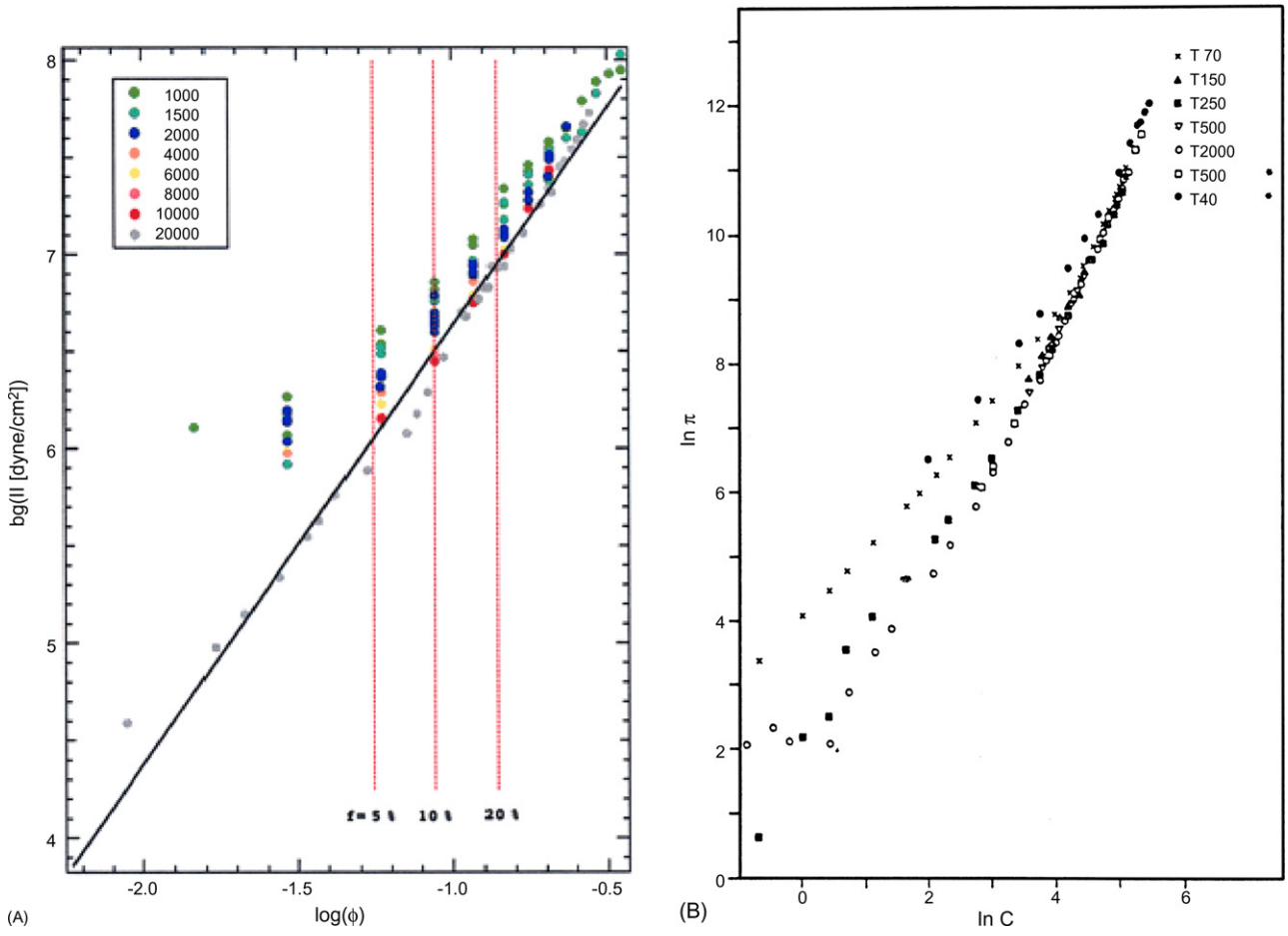

Fig. 7. Dependence of the osmotic pressure on the polymer concentration for aqueous PEG (A) and dextran (B) solutions of different molecular weights. The data are obtained from Hansen et al. (2003) for PEG and from Smit et al. (1992) for dextran.

For all the gels the volume fractions of crosslinked dex-HEMA and dextran were constant, $\varphi_{dextran}/_{dex\text{-}HEMA} = 0.151$ and $\varphi_{dextran} = 0.045$, respectively. Clearly, π_{osm} of dex-HEMA/dextran gels containing 10 kDa, 19 kDa and 77 kDa dextran chains is the same within the experimental error. Furthermore, π_{osm} is close to that of the corresponding dex-HEMA hydrogel in the absence of uncrosslinked dextran (compare Figs. 5B and 6A). However, the osmotic pressure of gels containing low molecular weight dextran oligomers (800 Da and 600 Da) is considerably higher. Similar results are shown in Fig. 6B for a more densely crosslinked dex-HEMA/dextran gel (DS = 5.4 (Fig. 6B) and DS = 2.5 (Fig. 6A)).

Fig. 6C shows π_{sw}, π_{el} and π_{osm} of PEG-HEMA hydrogels containing free PEG chains of various molecular weights between 0.2 kDa and 10 kDa. The results indicate that the osmotic pressure of the gels containing low molecular weight chains (0.2 kDa and 0.6 kDa) is higher than that of the gels containing higher molecular weight (1.5 kDa; 4 kDa and 10 kDa) free chains.

In general, the osmotic pressure of polymer solutions increases with the number of mobile chains. However, above the overlap concentration many polymer solutions exhibit universal behavior, i.e., the osmotic pressure is independent of the molecular weight of the polymer. This was indeed observed experimentally for PEG (Hansen et al., 2003) and dextran (Smit et al., 1992) solutions (Fig. 7). In samples containing low molecular weight oligomers chemical effects may also be important. Different sites within a chain (chain ends and mid-chain segments) may interact differently with the crosslinked polymer. It is known that many water soluble polymers (e.g., poly(ethylene oxide, poly(acrylic acid)) form clusters due to association of the hydrophobic end groups (Polverari and vandeVen, 1996; Hammouda et al., 2005a,b). The effect of end groups becomes less pronounced as the molecular weight of the polymer increases. We also note that in the present gel systems the concentration of the low molecular weight polymers was below their overlap concentrations (Fig. 8).

Clearly, low molecular weight free chains behave differently from the network chains. The difference between the osmotic contribution of the free chains and the network chains vanishes with increasing polymer molecular weight. Beyond a threshold molecular weight (for the PEG-HEMA/PEG system above 10 kDa) the free chains are practically indistinguishable from the network chains.

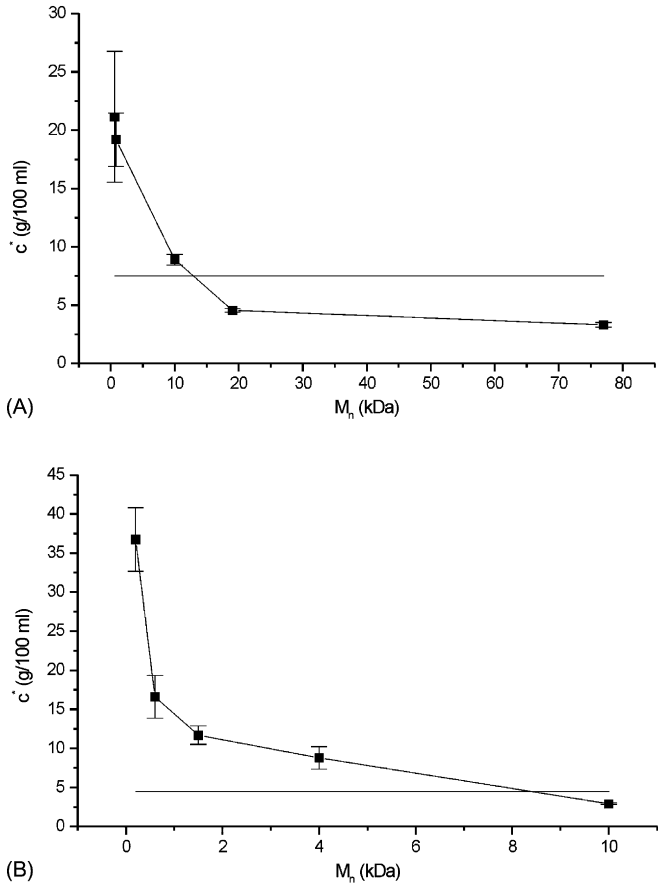

Fig. 8. Overlap concentration c^* as calculated from the intrinsic viscosity for dextran (A) and PEG (B) solutions as a function of the molecular weight. The horizontal line denotes the concentration of the uncrosslinked dextran in the dex-HEMA/dextran hydrogels shown in Fig. 6A and B, and the concentration of the uncrosslinked PEG in the PEG-HEMA/PEG hydrogels shown in Fig. 6C.

4. Summary and conclusions

We demonstrated that degradable PEG-HEMA hydrogels can be made by radical polymerization of aqueous PEG-HEMA solutions using a simple two-step synthesis route by coupling the carbonylimidazole activated HEMA to PEG. Total degradation of PEG-HEMA hydrogels (at pH 7.5) takes several months to over a year, which is significantly longer than the degradation time (days or weeks) of dex-HEMA gels.

Upon degradation of PEG-HEMA and dex-HEMA hydrogels free PEG and dextran chains are produced. It is found that the osmotic pressure of the fully degraded PEG-HEMA gels exceeds that of similar dex-HEMA hydrogels. This observation is consistent with the results of osmotic pressure measurements made on solutions of the corresponding polymers.

To mimic partially degraded hydrogels we used PEG-HEMA gels containing known amounts of uncrosslinked PEG and dextran chains. We studied the influence of the molecular weight of the uncrosslinked polymers on π_{osm}. Different molecular weight dextran and PEG chains were incorporated into PEG-HEMA and dex-HEMA gels. We found that the difference between the contributions of network chains and free chains to the osmotic pressure decreases with increasing molecular weight. Higher molecular weight free chains ($M_w > 10$ kDa) behave like network chains.

The knowledge of the osmotic properties of degradable dex-HEMA and PEG-HEMA gels is of great significance for the design and optimization of self-rupturing microcapsules. The major application of the self-rupturing microcapsules (illustrated in Fig. 1) is pulsed drug delivery. The ultimate goal is to insure that the drug molecules entrapped in the microcapsules are suddenly released when the surrounding membrane is ruptured. Clearly, to realize a sudden release the drug molecules should not leak through the membrane before the membrane becomes disrupted by the swelling pressure of the microgel. An increase in the swelling pressure due to degradation of the crosslinked polymer will exert a force on the membrane making it more permeable and leading to leakage of the drug. It is therefore important to use degradable microgels whose π_{osm} (and thus π_{sw}) remains low during the degradation process and suddenly increases when the gel turns into a polymer solution. Based on the results reported in this paper one may conclude that hydrogels made from high molecular weight polymers are favorable since in these systems the contribution of high molecular weight degradation products to the osmotic pressure is smaller.

Biodegradable hydrogels are also applied in tissue engineering for the encapsulation of cells. The pressure rise during degradation might hamper proper cell growth. A good knowledge of the parameters which govern the swelling pressure of biodegradable hydrogels may allow one to design hydrogels which degrade with low swelling pressure in order to allow optimal cell growth.

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