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Temperature Sensitive Hydrogels Based on Hydroxypropylcellulose by High Energy Irradiation

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Summary: Stimuli sensitive hydrogels change their properties in dependence on a liquid environment. The temperature sensitive hydroxypropylcellulose (HPC) gel shows a volume phase transition in water at about 48 °C. For different applications a crosslinking of a preformed layer of the dry polymer on a support is necessary. It is known, that HPC dissolved in water is crosslinkable by high energy irradiation (electron beam). Now, we could show, that HPC can be crosslinked in the dry state by high energy irradiation. This allows the preparation of thin crosslinked layers of HPC on silicone substrates.

Keywords: high energy irradiation; hydrogel layers; hydroxypropylcellulose; silicon substrate

Introduction

Stimuli sensitive hydrogels are three-dimensional networks of crosslinked sensitive, hydrophilic polymers swollen in water. They undergo a discontinuous volume phase transition. Hydrogels, based on a polymer showing a lower critical solution temperature (LCST) are in a highly swollen state at temperatures below this temperature (for gels: volume phase transition temperature (PTT)). At temperatures above PTT they are in a shrunken state.[1] A well established route to crosslink hydrophilic polymers is high energy irradiation (e.g. electron beam, γ-rays) of their aqueous solutions.[2,3] The irradiation provokes a radiolysis of water. Reactive H- and especially OH- radicals are formed. These radicals are able to attack the polymer chain, abstract hydrogen and transfer the radical center to the chain. Combining of two polymer radicals forms a crosslink. These so called ''clean'' method leads to an additive free crosslinking process (no need of crosslinker, initiator, stabilizer). The structure of polymer chains in aqueous solution can be fixed. The crosslinking mechanism of some temperature sensitive polymers in aqueous solution is studied in the literature.[4,5] Polymer networks are formed above the gelation dose D_g. The influence of synthesis parameters (applied dose, dose rate, atmosphere during irradiation) on the properties of the formed hydrogels (e.g. gel fraction, crosslinking density, equilibrium degree of swelling, PTT) is investigated for different polymers.[6–8] A temperature sensitive polymer that can form a liquid crystalline phase (lyotropic polymer) is hydroxypropylcellulose (HPC). Figure 1 shows the phase diagram in water.

HPC is soluble in cold water (isotropic solution). When the aqueous solution of HPC is warmed up to about 40 °C, a phase separation occurs connected with a strong increase in turbidity (white suspension). Higher concentrated solution of HPC in cold water (40–90 wt%) forms a cholesteric liquid crystalline phase (anisotropic solution). Warming up this solution to about 45 °C results in formation of a white gel (physical gelation). Dry films of HPC are clear. HPC is crosslinkable by the chemical

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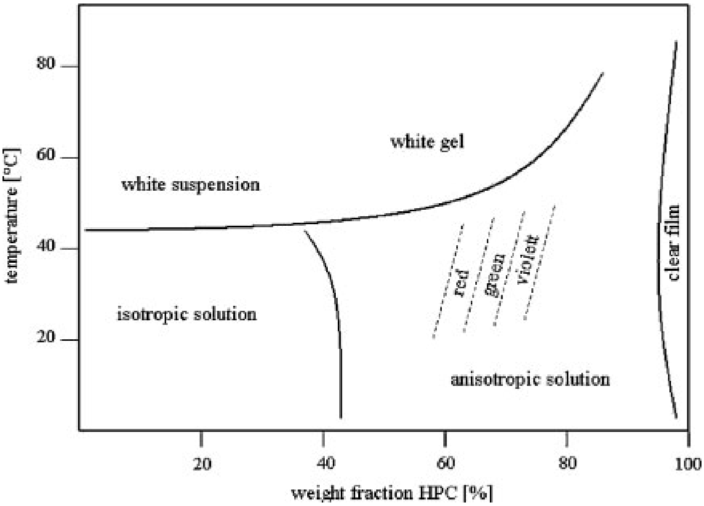

Figure 1.
Schematically phase diagram of HPC in water, according to.[9].

way[10,11] as well as by photo polymerization.[12,13] Crosslinking of cellulose derivates in aqueous solution by high energy irradiation was investigated by Wach et al.[14–16] Irradiation of HPC in aqueous solution at moderate concentrations results in the formation of hydrogels. It was found,[16] that apart the concentration, irradiation dose and dose rate could affect the results of irradiation. Electron beam irradiation gives higher gel fraction, up to 90%, than gamma irradiation (maximum gel fraction of 65%). The degree of swelling of the crosslinked hydrogels, which is related to the density of crosslinks, was the highest at low irradiation doses. Crosslinked HPC shows a reversible volume phase transition (PTT about 48 °C).

For different applications, e.g. adhesion/detachment devices, micro reactors, sensors, a crosslinking of dry polymer films is necessary. By spin coating it is possible to form dry polymer films on different supports with defined thickness. Crosslinking of the spincoated films would give hydrogel layers with good quality and reproducible thickness. In the past, experiments were done with poly(vinyl methyl ether) and poly(vinyl pyrrolidone).

In this work we intend to broaden the palette of sensitive polymers, which are crosslinkable in the dry state by high energy irradiation. Up to now, a crosslinking of HPC in the dry state is not reported. In a first step, we prepared and irradiated (electron beam) isotropic aqueous solutions of HPC. The effects of synthesis parameters on the properties of irradiation products (D_g, swelling behavior) were discussed. In a second step, we prepared and irradiated (electron beam) dry HPC films. Sol-gel analysis as well as swelling measurements was reported. In the third step, we show a route to synthesize thin HPC hydrogel layers (thickness of about 200 nm) on silicon substrates.

Experimental Part

Materials

HPC was obtained from ALDRICH Co. and used as received. The molecular weight, as determined by static light scattering (in ethanol), was $M_w = 200{,}000$ g/mol (from SEC in THF we get $M_w = 180{,}000$ g/mol).

Synthesis

Isotropic aqueous solutions of different concentrations (5, 10, 20, 30 wt%) of the pure HPC were prepared by dissolving the polymer in distilled water. Dry films were prepared by filling of the polymer solution in Petri dishes and by evaporating of the solvent at room temperature. Thin polymer layers on silicon substrates were prepared by spin coating of a 3 wt% solution of HPC in ethanol. To crosslink polymers accelerated electrons with 1.0 MeV (thin polymer films and layers on silicon substrate) and 1.5 MeV (isotropic solution) and a beam current of 4 mA (ELV-2, Budker, Novosibirsk) were used. A control of the temperature during the irradiation process was not possible.

Characterization

After irradiation of the isotropic solution samples were dried in vacuum for several days. All samples were extracted with cold water and subsequently dried in vacuum to a constant weight. The gel fraction g, respectively the sol fraction s $(s = 1 - g)$ was calculated. The sol-gel analysis was done by using the Charlesby-Rosiak equation:[17]

$$s + \sqrt{s} = \frac{p_0}{q_0} + \left(2 - \frac{p_0}{q_0}\right) \cdot \left(\frac{D_v + D_g}{D_v + D}\right) \qquad (1)$$

s sol fraction, p_0/q_0 ratio of probability of degradation reaction to probability of crosslinking reaction, D irradiation dose, D_v virtual dose, and D_g gelation dose GelSol95 (http://mitr.p.lodz.pl/biomat/gel-sol.html) was used to calculate D_g and p_0/q_0.

The equilibrium degrees of swelling Q_m (mass) were determined for isotropic hydrogels and thin hydrogel films (swelling time 3 days). Volume degrees of swelling were determined in dependence on temperature by a microscope equipped with a CCD camera (JVC). The thicknesses of the hydrogel layers on silicon substrate were measured by laser reflectometry. The temperature dependence of swelling is represented in relation to the swelling at 20 °C (Equation 2), relative degree of swelling Q_V.

$$Q_m = \frac{m_s}{m_0}$$
$$Q_V = \left(\frac{Q_V(T)}{Q_V(20\,^\circ\mathrm{C})}\right) = \left(\frac{d}{d_0}\right)^3 \qquad (2)$$

m_s mass of swollen network, m_0 mass of dry network, d dimension of swollen network at T, d_0 dimension of swollen network at 20 °C.

Results and Discussion

Isotropic Hydrogels

In order to quantify the crosslinking of HPC in water by electron beam irradiation the gel fraction is measured in dependence on the applied dose for solutions of different polymer concentrations (Figure 2).

Electron beam irradiation of the HPC solution in water at the chosen conditions leads to the formation of macroscopic hydrogels. The calculated values of p_0/q_0 indicate, that crosslinking is more dominant than degradation. In[16] it is written, that g increases with increasing D for all chosen concentrations. A diversification in the gelation in the investigated region of concentrations is not meaningful. As shown in Figure 2, our results do not completely confirm this statement. For lower concentrations (5–20 wt%) we observe an increase of the g in the range of 40–100 kGy. However, for the 30 wt% solution the gel fraction decreases with increasing D. It seems, that the degradation process for this concentration at higher doses becomes more important. And, in contrast to,[16] our results show a clear dependence of gel fraction on concentration, the lower the initial polymer concentration, the higher g. This effect could have some reasons. As described, high energy irradiation leads to the generation of radicals onto the polymer chain. At lower concentrations, of course, the number of polymer chains is lower than at higher concentrations. The total number of radicals per time unit should be constant. Therefore, we assume, that applying of the equal doses generate more radicals on a polymer chain at lower concentrations. These could enhance the chance for forming of crosslinks (intra-intermolecular) in comparison to higher concentrations. Following, the gel fraction increases with increasing concentration. A further argument for the

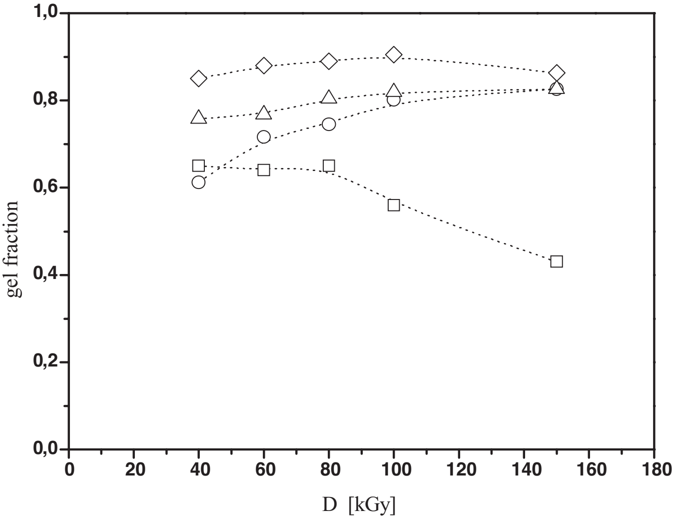

Figure 2.

Gel fraction of isotropic hydrogels in dependence on applied dose *D*; ◇ = 5 wt%, △ = 10 wt%, ○ = 20 wt%, □ = 30 wt% HPC in water (Errors are about 2%). Calculated values of D_g and p_0/q_0: 5 wt%: 21 kGy, 0.4; 10 wt%: 15 kGy, 0.5; 20 wt%: 11 kGy, 0.4; 30 wt%: n/a, n/a.

effect could be the mobility of the polymer chains. The higher the mobility of the chains, the higher should be the possibility for a polymer radical to find another to form a crosslink. Obviously, low concentrations enhance the mobility.

In case of HPC temperatures of about 50 °C lead to physical gelation (Figure 1). During the irradiation process the temperature raises in dependence on dose to such high temperatures, the mobility decreases. The effect of the concentration

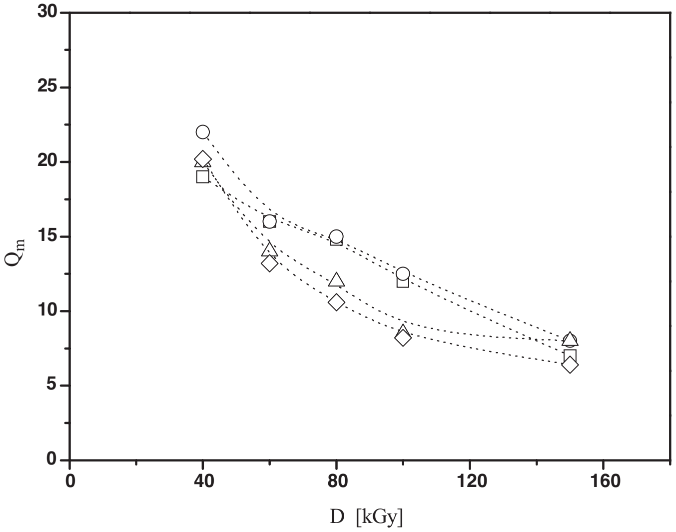

Figure 3.

Equilibrium degree of swelling Q_m at 25 °C in water in dependence on the applied Dose *D*; □ = 5 wt%, ○ = 10 wt%, △ = 20 wt%, ◇ = 30 wt% HPC in water.

dependence on the gel fraction is limited by the overlapping concentration. Irradiation of solutions close above this concentration will cause in decreasing of the gel fraction. Below the overlapping concentration no macroscopic hydrogel could be formed. In conclusion, according to our results, the best conditions for crosslinking of HPC seem to be low doses (40–100 kGy) and low concentrations (higher than overlapping, $c^* \approx 5$ g/l) of polymer in water solution. Q_m depends strongly on D. The higher the dose, the lower the equilibrium degree of swelling (Figure 3). In general, ability to swell decreases with increasing crosslinking density.

Our results indicate, that for HPC in water at the chosen conditions an increase of the irradiation dose results in an increase of the crosslinking density. Furthermore, the results show an influence of the initial polymer concentration. It seems, there is a trend: The lower the initial concentration, the higher the ability to swell (constant D). This seems to be in contrast to the results of the sol-gel analysis. High values of g should mean high crosslinking densities. Our results do not confirm this. Therefore, we assume that at lower concentrations the amount of polymer chains bonded in the network is higher than at higher concentrations. But, the number of polymer chains per volume increases with increasing initial concentration. As a result of both effects, the crosslinking density increases with increasing initial concentration in the shown region.

A feature property of HPC and HPC-gels is the temperature sensitivity. Examples for temperature dependent measurements of swelling are shown in Figure 4. The investigated samples undergo a volume phase transition in a relative broad range of about 45–55 °C (confirms results as reported in[16]). Nevertheless, our synthesized hydrogels are temperature sensitive. At 20 °C the hydrogels have a degree of swelling of about 16. Heating to 68 °C leads to a strong shrinking. The degree of swelling at 68 °C can be estimated to 2.5–3. A significantly influence of the synthesis parameters on the phase transition temperature was not found.

Dry Hydrogel Films

Many applications need defined hydrogel films, e.g. on a support. For this purpose it is necessary to crosslink the polymer film in

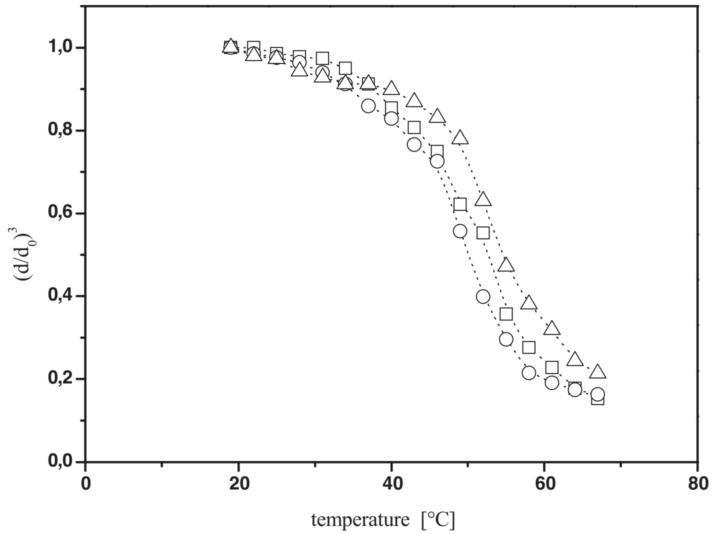

Figure 4.

Relative degree of swelling $(d/d_0)^3$ in dependence on temperature for isotropic hydrogels; □ = 5 wt%, ○ = 10 wt%, △ = 20 wt% HPC in water, $D = 60$ kGy.

the dry state. As far as we know, the crosslinking of a dry HPC film (freestanding or on a support) is not described yet.

Dry HPC films were irradiated under air atmosphere and under oxygen free conditions (N_2 atmosphere). The results of the gel analysis of both series are shown in Figure 5. In both cases HPC is crosslinkable in the dry state by electron beam irradiation. However, in comparison to crosslinking by the irradiation of aqueous solutions the gelation doses D_g are one decade higher. By using Charlesby-Rosiak equation we calculated $D_g = 200$ kGy and $p_0/q_0 = 1$ (irradiation in air atmosphere) and $D_g = 150$ kGy and $p_0/q_0 = 1$ (irradiation in oxygen free atmosphere). $p_0/q_0 = 1$ means that there is no preference between crosslinking or degradation process. The gel fraction increases with increasing dose. At the chosen conditions a gel fraction of about 0.5 is possible. The gel fraction of a sample, irradiated in an oxygen free atmosphere, is higher, because oxygen acts as a radical scavenger.

The crosslinking mechanism for some polymers in aqueous solution is well understood. The mechanism for irradiation of dry polymers must be different. We assume, that high energy irradiation directly generate radicals on the polymer chains. Two polymer radicals close together are able to form a crosslink. However, compared to an irradiated solution, the chance to find a reaction partner is much lower, maybe due to the very low mobility of chains. As a result, higher doses are needed for crosslinking.

For both dose series the equilibrium degrees of swelling Q_m in water at 25 °C were measured (see Figure 6). Q_m decreases with increasing D due to the increasing crosslinking density. Contrary to the gel fraction, an influence of the atmosphere during the irradiation on Q_m was not observed. The results indicate, that higher values of g do not mean a lower degree of swelling (as already discussed for the isotropic hydrogels).

For films crosslinked with $D = 1000$ kGy the temperature dependent swelling was measured (Figure 7). The prepared hydrogel films, synthesized in the dry state, are T-sensitive, too. The film, prepared in air atmosphere, undergoes the volume phase transition in a broad temperature range (45–55 °C), as already found for the isotropic hydrogels (at 20 °C: $Q_m = 16$, at 64 °C:

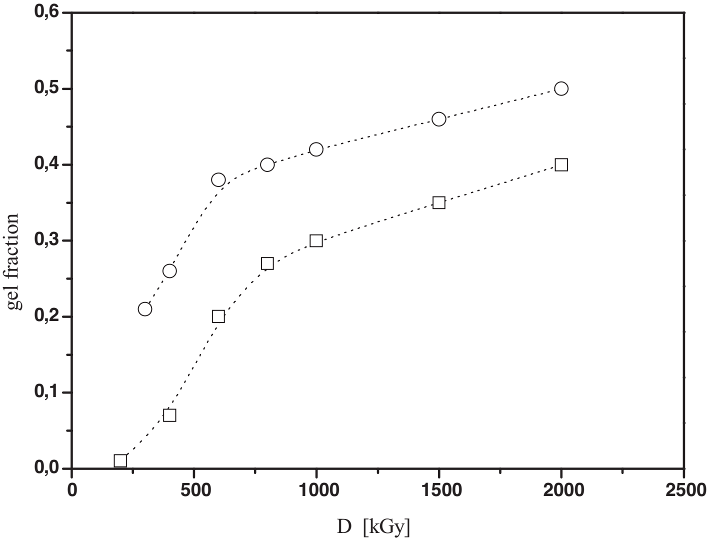

Figure 5.

Influence of atmosphere on D-dependence of the gel fraction of hydrogels films; □ = air atmosphere, ○ = N_2 atmosphere (Errors are about 2%).

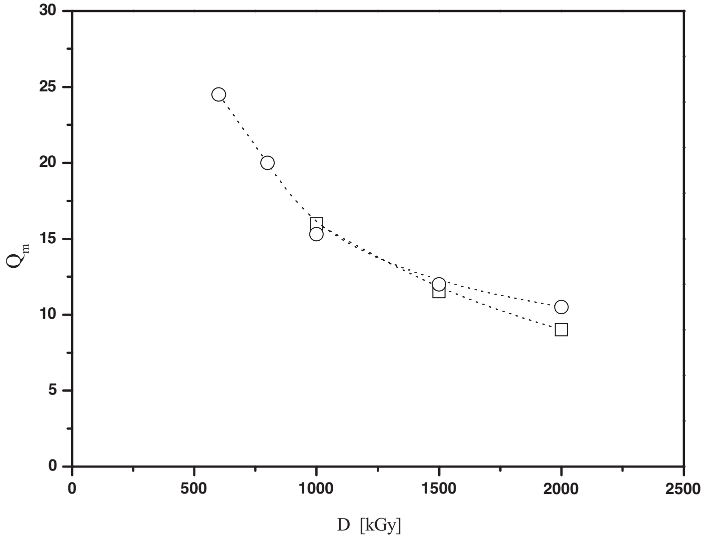

Figure 6.
Dose dependence of Q_m (25 °C, water); □ = air atmosphere, ○ = N_2 atmosphere; thickness of dry film ca. 1 mm.

$Q_m = 2.7$). The sample, prepared in an oxygen free atmosphere, undergoes a volume phase transition in a smaller range (48–52 °C). Q_m in the shrunken state is relatively high (4.7).

A reason for the difference in the phase transition behavior could be a difference in the chemical structure of the hydrogels. It is thinkable, that irradiation of dry polymer films in the air atmosphere leads to formation of e.g. peroxo-groups.

Dry Hydrogel Layer on Silicon Substrate

As shown in the chapter before, HPC can be crosslinked by high energy irradiation, even in the dry state. The prepared

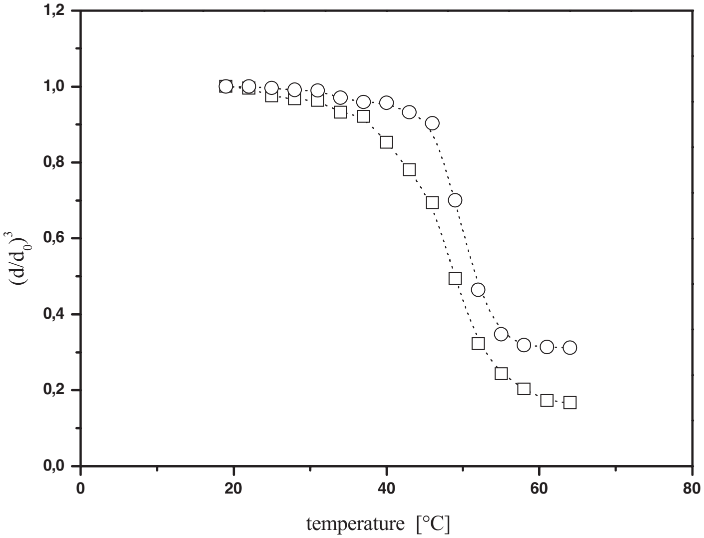

Figure 7.
Relative degree of swelling $(d/d_0)^3$ (see Equation 2) in dependence on temperature for irradiated hydrogel films ($D = 1000$ kGy), □ = air atmosphere, ○ = N_2 atmosphere.

hydrogel films are temperature sensitive. Now, in a next step the irradiation (oxygen free atmosphere) of dry hydrogel layers, spin coated on silicon substrates, is investigated. The thicknesses of dry layers before irradiation (h_0) and after irradiation and extraction (h) were measured. Figure 8 shows the results of the gel analysis (by weight determination) and the ratio of thicknesses in dependence on applied dose.

After extraction the spin coated hydrogel layers remain on the silicon substrate. That means, electron beam irradiation of HPC on the substrate leads to two effects: First, the polymer chains crosslink, and second, the hydrogel layer stick on the silicon substrate. Again, g depends on D. In contrast to HPC films it seems, there is a maximum value of the gel fraction at about 550 kGy. This confirms with the measurements of the layer thickness ratio (maximum at about 500 kGy). D_g was calculated to 50 kGy and $p_0/q_0 = 1$. In comparison to HPC films the D_g is three times lower, maybe because of the lower layer thickness. The most interesting irradiation effect is the sticking of the hydrogel layer on the substrate. We assume, that irradiation generate covalently bonds between hydrogel and silicon, because extraction did not disturb the interactions. The chemical nature of the bonds could be, for example, –Si–O–C– or –Si–O–O–C–.

Conclusions

In a first step we tried to reproduce the results published in.[16] We were able to synthesize temperature sensitive hydrogels by high energy irradiation of aqueous solutions of HPC. In contrast, our results show, that there are influences of the synthesis conditions (e.g. initial polymer concentration) on the properties of produced hydrogels. We get the highest gel fractions at low concentrations (5 wt%). Gelation doses are about 15 kGy. In a second step, we irradiated HPC films in the dry state. We were able to synthesize temperature sensitive hydrogels, too. The gelation doses are ten times higher compared with irradiation of aqueous solutions. Furthermore, we find out, that the atmosphere during the irradiation process has an influence of the crosslinking reaction and

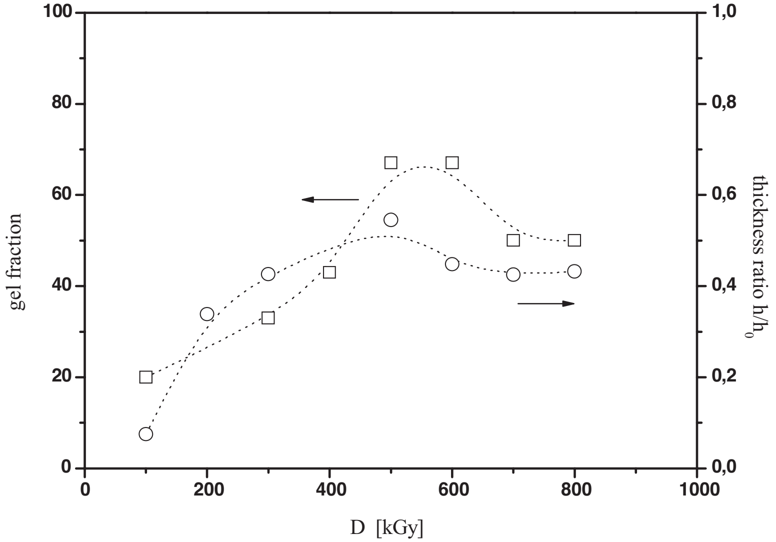

Figure 8.
Gel fraction (□) and thickness ratio h/h_0 (○) of hydrogels layers on silicon substrates in dependence on applied dose (Errors are about 5%).

maybe on the chemical structure of the hydrogels. Oxygen hints this reaction due to its radical scavenger behavior. In the third step we irradiated HPC layers spin coated on silicon substrates. The formed hydrogels stick onto the silicon substrates. The gelation dose is 50 kGy, three times lower than for hydrogel films. We get the highest gel fractions at about 500 kGy.

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