Temperature-Sensitive Poly(vinyl methyl ether) Hydrogel Beads

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Summary: Temperature-sensitive hydrogel beads were prepared by radiation crosslinking of poly(vinyl methyl ether) PVME spheres wrapped in Ca-alginate. The obtained gel beads have diameters in the sub-millimeter or millimeter range (depending on the PVME concentration). They were characterized by sol-gel analysis, swelling measurements, and differential scanning calorimetry.
The gel content g increases with increasing radiation dose D. The swelling degree Q_V decreases with increasing PVME concentration c_p and increasing D. In comparison to PVME bulkgels the phase-transition temperature of the synthesized PVME gel beads is a little decreased.

Keywords: alginate technique; electron beam irradiation; poly(vinyl methyl ether); temperature-sensitive hydrogel beads

1. Introductions

'Smart' hydrogels are changing their volume and their mechanical properties as a result of small changes in the properties of the surrounding medium [1-3]. Hydrogels with a lower critical solution temperature LCST are in the swollen state below and in the shrunken state above this temperature. A well-known polymer with LCST behavior in aqueous medium is poly(vinyl methyl ether) PVME with $T_{cr} \approx 34°C$ [4]. High-energy radiation induces in aqueous PVME solutions a radical process and the polymer chains crosslink [5,6].

PVME hydrogels as bulk material were synthesized by electron beam or γ-ray irradiation of its aqueous solution to form temperature-sensitive hydrogels [7-15]. These gels were applied for

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mechanical devices [16,17], for thrombogenicity studies [18], or as fiber material [19].

The synthesis of hydrogels with reduced dimensions by using radiation techniques was reported [20-23]. Pulsed electron beam irradiation of diluted polymer solution leads to intramolecularly crosslinked macromolecules, the so-called nanogels [20]. Microgels can be formed by a radiation induced polymerization and crosslinking of emulsified monomer solutions [21,22], or by the irradiation of phase-separated structures of a temperature-sensitive polymer [23].

Another well-investigated method of the synthesis of micro-sized hydrogels is the alginate technique [24-29]. Calcium-crosslinked alginate spheres are targets for the polymerization and crosslinking of monomers. The dimension of the so-called gel beads is influenced by the droplet size of the alginate beads.

The aim of the work was the synthesis of temperature-sensitive hydrogel beads in the sub-millimeter and millimeter range. We will demonstrate, that micro-hydrogels can be formed by irradiation of Ca-alginate stabilized PVME bead suspensions above the phase-transition temperature of PVME. After crosslinking the alginate layer was removed by washing with EDTA solutions. The possibilities to regulate the diameter of the beads by the polymer concentration was investigated. The gel beads were characterized by sol-gel analysis, swelling measurements, and DSC measurements.

2. Experimental

2.1 Materials

PVME was obtained as an aqueous solution (50 *wt.%*) from BASF (Lutonal M40). Its molecular weight was measured by static light scattering in 2-butanone to M_w = 57,000 *g/mol*. In the experiments PVME solutions were used without further purification. Sodium alginate (Aldrich), ethylene diamine tetraacetate EDTA (Grüssing), calcium chloride $CaCl_2$ (Grüssing), and acetone (Merck) were all used as received.

2.2 Synthesis

The gel beads were prepared according to the method developed by Park and Choi [24]. An interpenetrated network (IPN) was prepared by the gelation of Ca-alginate to form spherical bead shapes. Temperature-sensitive gel beads were obtained by radical polymerization and

crosslinking of poly(*N*-isopropyl acrylamide) PNIPAAm.

The alginate technique should be used for the synthesis of PVME gel beads, too. PVME was incorporated into the alginate beads and subsequently irradiated with electron beam. Sodium alginate (1-2 *wt.%*) and PVME (1-8 *wt.%*) were dissolved in bidestilled water and degassed with nitrogen. The solutions were injected by using a syringe into 300 *ml* aqueous $CaCl_2$ solution (3 *wt.%*) heated to $T = 40°C$. The Ca-ions crosslink the alginate and globular PVME/alginate beads are formed. The scheme of the gel bead preparation is shown in fig. 1.

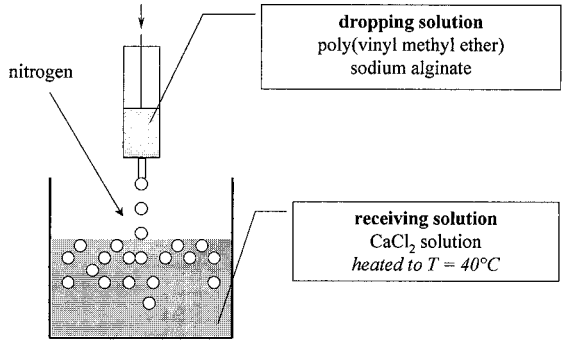

Fig. 1: Scheme of the synthesis principle of temperature-sensitive PVME gel beads. The aqueous PVME/alginate solutions were dropped into the $CaCl_2$ solution ($T = 40°C$) and subsequently irradiated.

The gel beads suspensions were kept at this temperature (at low temperatures parts of PVME diffuse out of the beads) and irradiated with accelerated electrons. The irradiation experiments with an electron beam were carried out with an electron accelerator ELV-2 (Budker Institute of Nuclear Physics Nowosibirsk, Russia). The energy of the electrons was 1.5 *MeV* at a beam power of 20 *kW*. At constant value of beam current the absorbed dose depends on the exposure time (typical < 1 *min*). The radiation dose *D* was varied from 60 *kGy* to 120 *kGy*. The stability of the alginate-shell during high-energy irradiation (possible degradation processes induced by the radiation) was proofed.

2.3 Characterization of gel beads

Sol-gel-analysis

After radiation crosslinking the samples were dried in vacuum for several days and weighted. The uncrosslinked polymer has to be removed. The beads were put into a Soxhlett thimble and the sol was extracted with acetone in a Soxhlett extractor for 5 *d*. The crosslinked alginate was not removed by this method. After the extraction the gel was weighted again. The gel content *g* of PVME is determined as ratio of the mass of the gel after extraction (m_{gel}) to the mass before removing the sol content ($m_{gel} + m_{sol}$).

$$g = \frac{m_{gel}}{m_{gel} + m_{sol}}; \quad s = 1 - g \tag{1}$$

The alginate shell was removed by washing with EDTA solution, and temperature-sensitive PVME gel beads were obtained.

Degree of swelling and differential scanning calorimetry (DSC)

The degrees of swelling (Q_m) in water were measured by weighting the swollen, extracted gel ($m_{swollen}$) and the non-swollen (dry) extracted sample (m_{dry}).

$$Q_m = \frac{m_{swollen}}{m_{dry}} \tag{2}$$

$$Q_V = \frac{V_{swollen}}{V_{dry}} = \left(\frac{d_{swollen}}{d_{dry}} \right)^3 \tag{3}$$

In order to determine the temperature dependence of the degree of swelling in water (Q_V) the change of dimension of the beads was monitored using a digital video system. A JVC (TK C 1380) camera was connected to a PC through a real time video digitalizer card. The diameter *d* of the gel beads, both in the swollen ($d_{swollen}$) and in the dry state (d_{dry}), was followed on the magnified picture by an image analyser program (analysis Doku 2.11.007, Soft Imaging Systems GmbH 1986-97, VGA Driver, Version 1.1a). This method enables us to measure of very small changes in diameter (one pixel on the screen) on the real time video image. The ratio of the dimension of the swollen gel (heating rate appr. 15 *min* / 2 *K*) to the dimension in the dry state is proportional to the volume degree of swelling Q_V (equ. 3). For DSC measurements the 2920 Modulated DSC (TA Instruments) was used. The heating rate was 5 *K/min*.

3. Results and Discussions

3.1 Sol-gel analysis

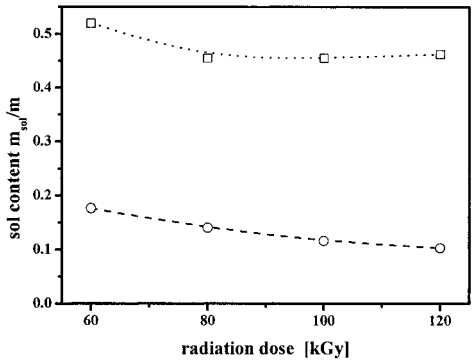

Fig. 2: Sol-gel analysis of the PVME gel beads after extraction with acetone (O) and EDTA (□) solution (c_p = 6 *wt.%*, $c_{alginate}$ = 2 *wt.%*).

The sol contents were analyzed according to their different extraction steps. First, the uncrosslinked PVME was removed by Soxhlett extraction with acetone. Second, the alginate shell was removed by washing with EDTA solution.

The whole sol content (uncrosslinked PVME and alginate) is relatively high (about 50%). However, alginate network is only the target for the crosslinking process. In the literature it is described that alginate as bulk material or in aqueous solution mainly undergo degradation due to the high-energy radiation [30-32]. Parts of the alginate shell can be removed during the irradiation experiment or extraction. Analyzing the sol content of PVME with regard to the PVME gel without alginate the sol content decreases with increasing dose. The values of the sol content are in the same range like for bulkgels [13,14]. These sol contents were analyzed according to CHARLESBY-PINNER [33] (equ. 4).

$$s + \sqrt{s} = \frac{p_0}{q_0} + \frac{1}{q_0 \cdot u_1 \cdot D} \qquad (4)$$

where p_0 is the fracture density per unit dose, q_0 the density of crosslinked units per unit dose, u_1 is the initial number average degree of polymerisation and D the irradiation dose. The gelation

dose D_g is determined for $s = 1$. The plot according equ. 4 is shown in fig. 3.

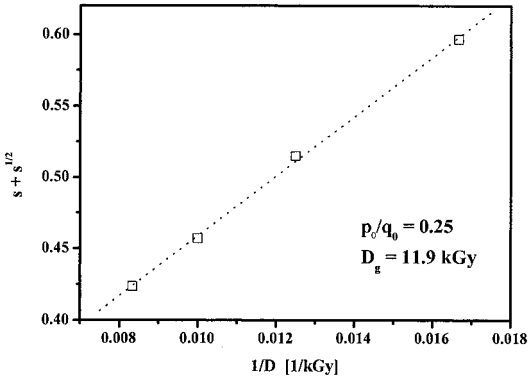

Fig. 3: Results (c_p = 6 *wt.%*, $c_{alginate}$ = 2 *wt.%*) of the analysis according to CHARLESBY-PINNER [33]. The gelation dose D_g is 11.9 *kGy* and the value of p_0/q_0 is 0.25.

Evaluating the data of the sol contents in dependence on the radiation dose leads to a linear behavior. The values of D_g = 11.9 *kGy* and p_0/q_0 = 0.25 were calculated and are typical for PVME (PVME solutions (20 *wt.%*) γ-ray irradiated D_g = 10.9 *kGy* and p_0/q_0 = 0.25 [14]).

3.2 Swelling measurements

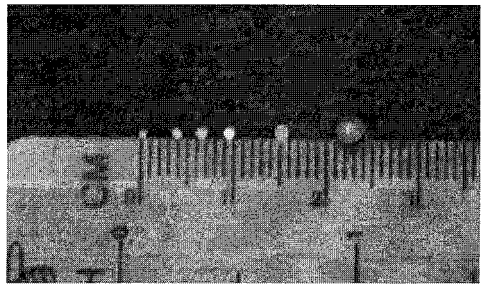

Fig. 4: Photograph of the PVME gel beads in dependence on PVME concentration c_p (from the left to the right side: 1 *wt.%*, 2 *wt.%*, 4 *wt.%*, 6 *wt.%*, 8 *wt.%* in the dry state, and 8 *wt.%* in the swollen state, constant alginate concentration $c_{alginate}$ = 2 *wt.%*).

The degrees of swelling were obtained, both by measuring the mass and the volume of the gel beads, in dependence on the temperature *T*.

Fig. 4 shows a photograph of the gel beads in dependence on the concentration of PVME (constant alginate concentration). The diameters (in the range of *mm*) of the dry gel beads increase with increasing PVME concentration. In the swollen state the dimensions of the beads strongly increase compared to the dry gel beads, but the same tendency was observed.

The degrees of swelling have been analyzed in dependence on the radiation dose, too. Fig. 5 shows the dose dependence of the degree of swelling (both Q_m and Q_V, independently determined). As expected, the degrees of swelling decrease (Q_V from 20 to 9) with increasing radiation dose. At higher doses more radicals are formed and the crosslinking density increases. The volume degree of swelling is almost higher than the mass degree of swelling. The same tendency was obtained as in the case of PVME bulkgels in the same range of dose, but at a higher polymer concentrations (20 *wt.%*).

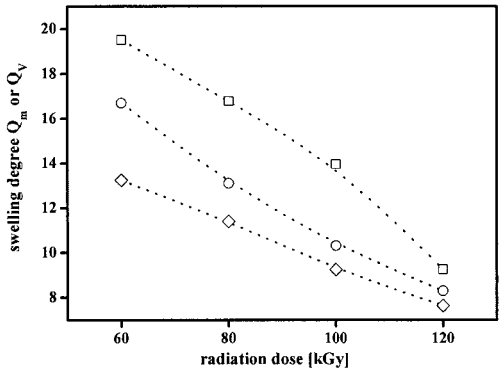

Fig. 5: Swelling degrees Q_V (□) and Q_m (○) of PVME gel beads (c_p = 6 *wt.%*, $c_{alginate}$ = 2 *wt.%*) in dependence on the radiation dose *D* at *T* = 20°C (Q_m of PVME bulkgels (◇) synthesized with 80 *kGy* electron beam were added for comparison).

3.3 Temperature-sensitivity

The temperature dependent properties of the PVME gel beads were determined by swelling measurements and by DSC measurements.

Swelling measurements (Q_V) in dependence on the temperature show a decreasing Q_V with increasing T (fig. 6). The same dose dependence is shown like in fig. 5. The phase-transitions are not sharp and can not clearly be determined by swelling measurements.

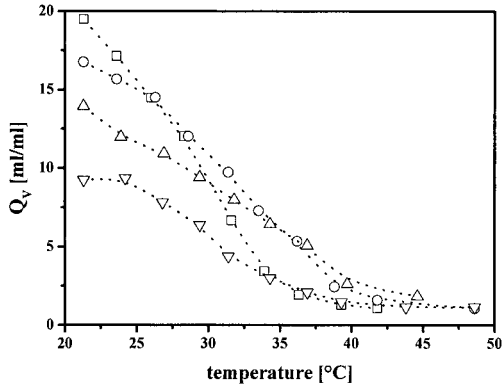

Fig. 6: Swelling degree Q_V of the PVME gel beads (c_p = 6 *wt.%*, $c_{alginate}$ = 2 *wt.%*) in dependence on the temperature T and the radiation dose D (□ - 60 *kGy*, O - 80 *kGy*, △ - 100 *kGy*, ▽ - 120 *kGy*).

For a correct analysis the phase-transition temperature DSC measurements were performed. Fig. 7 shows the results of the DSC measurements of the PVME beads in dependence on the ratio PVME to alginate. PVME bulkgels were used to compare these results.

The DSC graphs show a small decrease of phase-transition temperature of the gel beads in comparison to the bulkgels ($T_{max} \approx 37°C$). This effect can be caused by the crosslinking of small fragments of degradation products of the alginate. The ratio PVME to alginate does not influence the phase-transition temperature.

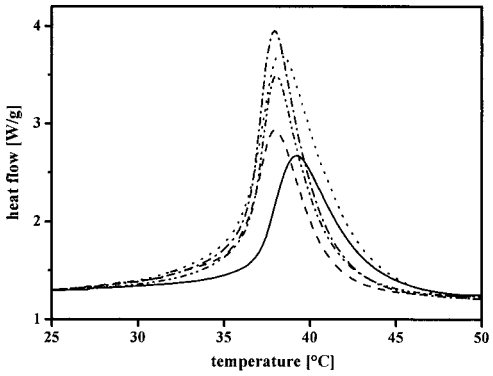

Fig. 7: DSC traces of PVME gel beads in dependence on the ratio PVME to alginate (solid – PVME bulkgel, dash – 1 *wt.%* : 1 *wt.%*, dot 2 *wt.%* : 2 *wt.%*, dash dot – 2 *wt.%* : 4 *wt.%*, dash dot dot – 2 *wt.%* : 6 *wt.%*) .

4. Conclusions

Temperature-sensitive PVME hydrogel beads were synthesized by electron beam irradiation of Ca-alginate PVME networks. The obtained diameters of the beads were varied by the PVME concentration in the range of *mm* (increasing d with increasing c_p). The crosslinking reaction in the beads was not influenced by the alginate shell. The parameters of the CHARLESBY-PINNER equation (by analyzing the PVME content) have nearly the same values like were obtained for PVME bulkgels. The gel beads show a temperature-sensitive behavior.

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(1) T. Tanaka, *Phys. Rev. Lett.* **1978**, *40*, 820-823.
(2) Y. Hirokawa, T. Tanaka, *J. Chem. Phys.* **1984**, *81*, 6379-6380.
(3) M. Shibayama, T. Tanaka, *Adv. Polym. Sci.* **1993**, *110*, 1-62.
(4) M. Schäfer-Soenen, R. Moerkerke, R. Koningsveld, H. Berghmans, K. Dušek, K. Šolc, *Macromolecules* **1997**, *30*, 410-416.
(5) I. Janik, P. Ulański, J.M. Rosiak, C. von Sonntag, *J. Chem. Soc., Perkin Trans. 2* **2000**, 2034-2040.
(6) I. Janik, P. Ulański, K. Hildenbrand, J.M. Rosiak, C. von Sonntag, *J. Chem. Soc., Perkin Trans. 2* **2000**, 2041-2048.
(7) B.K. Kabra, M.K. Akhetar, S.H. Gehrke, *Polymer* **1992**, *33*, 990-995.
(8) M. Suzuki, O. Hirasa, *Adv. Polym. Sci.* **1993**, *110*, 241-261.
(9) R. Kishi, H. Ichijo, O. Hirasa, *J. Int. Mat. Syst. Struct.* **1993**, *4*, 533-537.
(10) X. Liu, R.M. Briber, B.J. Bauer, *J. Polym. Sci. B – Polym. Phys.* **1994**, *32*, 811-815.
(11) R. Moerkerke, F. Meussen, R. Koningsveld, H. Berghmans, W. Mondelaers, E. Schacht, K. Dušek, K. Šolc, *Macromolecules* **1998**, *31*, 2223-2229.
(12) R. Kishi, O. Hirasa, H. Ichijo, *Polym. Gels Networks* **1997**, *5*, 145-151.
(13) K.-F. Arndt, T. Schmidt, H. Menge, *Macromol. Symp.* **2001**, *164*, 313-322.
(14) I. Janik, E. Kasprzak, A. Al-Zier, J.M. Rosiak, *Nucl. Instrum. Methods Phys. Res. B* **2003**, *208*, 374-379.
(15) T. Schmidt, C. Querner, K.-F. Arndt, *Nucl. Instrum. Methods Phys. Res. B* **2003**, *208*, 331-335.
(16) R. Kishi, H. Ichijo, O. Hirasa, *J. Int. Mat. Syst. Struct.* **1993**, *4*, 533-537.
(17) H. Ichijo, O. Hirasa, R. Kishi, M. Oowada, K. Sahara, E. Kokufata, S. Kohno, *Rad. Phys. Chem.* **1995**, *46*, 185-190.
(18) C.A. Aziz, M.V. Sefton, J.M. Anderson, N.P. Ziats, *J. Biomed. Mat. Res.* **1996**, *32*, 193-202.
(19) O. Hirasa, Y. Morsishita, R. Onomura, H. Ichijo, A. Yamauchi, *Kobunshi Ronbunshu* **1989**, *46*, 661-665.
(20) S. Kadłubowski, J. Grobelny, W. Olejniczak, M. Cichomski, P. Ulański, *Macromolecules* **2003**, *36*, 2484-2492.
(21) A. Sáfrány, S. Kano, M. Yoshida, H. Omichi, R. Katakai, M. Suzuki, *Rad. Phys. Chem.* **1995**, *46*, 203-206.
(22) M. Graselli, E. Smolko, P. Harigittai, A. Sáfrány, *Nucl. Instrum. Meth. Phys. Res. B* **2001**, *185*, 254-261.
(23) K.-F. Arndt, T. Schmidt, R. Reichelt, *Polymer* **2001**, *42*, 6785-6791.
(24) T.G. Park, H.K. Choi, *Macromol. Rapid. Commun.* **1998**, *19*, 167-172.
(25) M. Kozicki, P. Kujawa, L. Pajewski, M. Kolodziejczik, J. Narebski, J.M. Rosiak, *Eng. Biomat.* **1999**, *2*, 11-17.
(26) S. Sakai, T. Ono, H. Ijima, K. Kawakami, *Biomaterials* **2002**, *23*, 4177-4183.
(27) R. Barbuchi, M. Consumi, A. Magnani, *Macromol. Chem. Phys.* **2002**, *203*, 1192-1300.
(28) T.I. Klokk, J.E. Melvik, *J. Microencapsulation* **2002**, *19*, 415-424.
(29) L.W. Chan, H.Y. Lee, P.W.S. Heng, *Int. J. Pharmaceutics* **2002**, *242*, 259-262.
(30) N. Nagasawa, H. Mitomo, F. Yoshii, T. Kume, *Polym. Degrad. Stab.* **2000**, *69*, 279-285.
(31) N.Q. Hien, N. Nagasawa, L.X. Tham, F. Yoshii, V.H. Dang, H. Mitomo, K. Makuuchi, T. Kume, *Rad. Phys. Chem.* **2000**, *59*, 97-101.
(32) Z.I Purwanto, L.A.M. van der Broek, H.A. Schols, W. Pilnik, A.G.J. Voragen, *Acta Alimentaria* **1998**, *27*, 29-42.
(33) A. Charlesby, S.H. Pinner, *Proc. Royal Soc. A* **1959**, *249*, 367-386.