PREPARATION OF HYDROGELS BY PHOTO-CROSSLINKING OF FUMARIC ACID MONOETHYL ESTER (FAME) FUNCTIONALIZED OLIGOMERS

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Summary
Linear and star-shaped, hydroxy-terminated polyethylene glycol (PEG) and 1,3-trimethylene carbonate (TMC)-based oligomers were functionalized by esterification with fumaric acid monoethyl ester (FAME) in the presence of \( N,N \)-dicyclohexyl carbodiimide (DCC) and 4-dimethylamino pyridine (DMAP) at room temperature. Networks, designed to release only nontoxic degradation products, were obtained by UV irradiation of the macromers using 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photo-initiator. The swelling properties of the hydrogels in water largely depend on the composition and architecture of the macromers, as well as on the temperature.

Introduction
Due to their excellent biocompatibility, good control of solute transport characteristics and tunable physical properties, hydrogels are widely being employed as drug delivery vehicles, cell carriers and tissue engineering matrices [1,2]. Especially hydrogels prepared from (meth)acrylated PEG and poly(lactide) macromers have been much studied [3]. However, degradation products and (meth)acrylate residues might be toxic. For this reason, the use of macromers based on fumaric acid derivatives is expected to be advantageous [4].

In block copolymers based on hydrophilic PEG and hydrophobic poly(TMC), the poly(TMC) segment degrades in vivo to nonacidic degradation products. This makes these systems interesting for the controlled release of sensitive biologically active molecules such as peptides and proteins. Furthermore these block copolymers display thermo-sensitive behaviour.

This paper describes the synthesis and properties of hydrogels by UV photo-crosslinking of FAME functionalised oligomers based on PEG and TMC.

Materials and methods

Hydroxy-terminated oligomeric precursors
Linear PEG (molecular weights 2000 and 4000) were obtained from Fluka, 3-arm star-shaped PEG (molecular weight 10000) was obtained from Shearwater. Hydroxy-terminated block copolymeric precursors were prepared by ring opening polymerisation of TMC (Boehringer Ingelheim) in the presence of linear or star-shaped PEG and stannous octoate (Sigma). The TMC content was 50 mol%.

Functionalization with FAME
Macromers were prepared by reacting the hydroxy-terminated oligomeric precursors with FAME (Aldrich) in dichloromethane at room temperature, using DCC (Fluka) as a coupling agent and DMAP (Aldrich) as a catalyst [5]. The macromers were purified by filtration and precipitation in petroleum ether of chloroform solutions.

Photo-crosslinking of the macromers
Macromer and DMPA photo-initiator (Aldrich) (1 wt.% of macromer) were mixed in chloroform and cast on glass. Transparent films 0.2 to 0.5 mm thick were exposed to UV light (15 W, 360 nm, Philips) for 3 h, the distance between the UV source and the sample was 10 cm. After photo-crosslinking, the gel content of the resultant networks was determined.

Characterizations
The synthesized oligomers and macromers were characterized by nuclear magnetic resonance (NMR) spectroscopy. Thermal properties of the oligomers and the polymer networks were determined after quenching by differential scanning calorimetry (DSC) at a heating rate of 10 °C per min. Network gel content determinations using chloroform and water uptake experiments were performed at 25 °C. Mechanical properties were determined at room temperature at 50 mm/min according to ASTM 882-91.

Results and discussion
After the purification step, FAME-functionalled oligomers (macromers) were obtained in yields of approximately 80%. NMR analysis of the purified products shows that the esterification reaction between FAME and the hydroxy-terminated oligomers under the applied mild reaction conditions is successful.
Resonances in the NMR spectrum at 6.80–6.84 ppm (A, 2H), 4.20–4.24 ppm (B, 2H) and 1.25–1.29 ppm (C, 3H) can be assigned to the FAME component. By calculations based on the initial molecular weight of the hydroxy-terminated precursors (GPC data not shown) and the macromer composition determined by NMR, the degree of functionalization with FAME is estimated to be 90%.

Preliminary experiments, in which the photo-initiator and the irradiation time were varied, showed that irradiation of macromer films at 360 nm in the presence of 1 wt.% DMPA for 3 h resulted in appropriate network formation. Even though functionalization with FAME is not complete, Table 1 shows that networks with high gel contents up to 96% can indeed be obtained from the different macromers.

The table also shows that upon functionalization and photo-crosslinking of the TMC containing oligomers the thermal properties do not change significantly, and only the melting temperature in PEG networks decreases.

Table 1
Characteristics of PEG-containing hydroxy-terminated oligomers (precursors), FAME-functionalised oligomers (macromers) and the resultant networks after UV photo-crosslinking

<table>
<thead>
<tr>
<th></th>
<th>(T_g, (T_m)) of precursor ((^{\circ})C)</th>
<th>(T_g, (T_m)) of macromer ((^{\circ})C)</th>
<th>(T_g, (T_m)) of network ((^{\circ})C)</th>
<th>Gel content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 2000</td>
<td>n.o., (54.4)</td>
<td>n.o., (43.7)</td>
<td>n.o., (37.3)</td>
<td>88.6</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>n.o., (53.4)</td>
<td>n.o., (53.6)</td>
<td>n.o., (47.6)</td>
<td>96.2</td>
</tr>
<tr>
<td>2000PEG50PTMC50</td>
<td>–44.1, (38.6)</td>
<td>–43.3, (37.9)</td>
<td>–38.8, (40.5)</td>
<td>94.5</td>
</tr>
<tr>
<td>3-arm 10000PEG50PTMC50</td>
<td>–44.7, (44.0)</td>
<td>–43.4, (46.8)</td>
<td>–42.5, (44.9)</td>
<td>90.7</td>
</tr>
</tbody>
</table>

n.o.: Not observed.

Due to the hydrophilic PEG component in the PEG50PTMC50 oligomers, the cross-linked macromers take up significant amounts of water. Table 2 shows the mechanical properties of the networks in the dry state and in the water-swollen state.

Table 2
Mechanical properties of PEG/poly(TMC) networks

<table>
<thead>
<tr>
<th></th>
<th>State</th>
<th>(E)-modulus (MPa)</th>
<th>Tensile strength (MPa)</th>
<th>Elongation at break (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000PEG50PTMC50</td>
<td>Dry</td>
<td>94</td>
<td>3.0</td>
<td>3</td>
</tr>
<tr>
<td>2000PEG50PTMC50</td>
<td>Wet</td>
<td>4</td>
<td>1.0</td>
<td>33</td>
</tr>
<tr>
<td>3-arm 10000PEG50PTMC50</td>
<td>Dry</td>
<td>66</td>
<td>14.0</td>
<td>475</td>
</tr>
<tr>
<td>3-arm 10000PEG50PTMC50</td>
<td>Wet</td>
<td>3</td>
<td>1.5</td>
<td>375</td>
</tr>
</tbody>
</table>

In the wet state, significantly lower values for the \(E\)-modulus and tensile strength are found when compared to networks in the dry state. In both cases, the networks prepared from 3-arm 10000PEG50PTMC50 macromers have significantly higher tensile strengths and elongations at break than networks prepared from linear macromers.

Fig. 1 shows the water-uptake as a function of temperature. It can be seen that the swelling capacity of 2000PEG50PTMC50 networks is much lower than that of networks prepared from 3-arm 10000PEG50PTMC50 macromers, although the weight percentage of the hydrophilic component is comparable.

The higher water uptake of the latter may be due to the different architecture and the higher molecular weight of the PEG segments, which will allow enhanced phase separation in the wet state. In both cases, water-uptake decreases with temperature. Apparently, in these thermo-sensitive hydrogels, hydrophobic interactions dominate upon increasing the temperature.
Conclusions

Functionalization of PEG and PEG/poly(TMC)-based oligomers with FAME (fumaric acid monoethyl ester) allows the preparation of hydrogel networks by photo-cross-linking. In the presence of a photo-initiator, high gel contents can be obtained by irradiation at 360 nm. These networks, designed to release only nontoxic degradation products, display thermo-sensitive behaviour.

References