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Synthesis and characterization of hyperbranched polyglycerol hydrogels

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Abstract

Hyperbranched polyglycerol (HyPG; M_n 2000 g/mol) was derivatized with glycidyl methacrylate (GMA) in dimethyl sulfoxide using 4-(*N,N*-dimethylamino)pyridine as a catalyst to obtain methacrylated HyPG (HyPG-MA). The degree of substitution (DS, the percentage of derivatized hydroxyl groups), established by NMR and RP-HPLC, was fully controlled in the range of 0.7–70 by varying the molar ratio of GMA to HyPG in the reaction mixture. This indicates that for e.g. a DS of 28, 9 out of the 32 hydroxyl groups of a HyPG molecule were esterified with methacryloyl groups. Under the selected conditions, the reaction reached an equilibrium within 4 h. Furthermore, it was demonstrated that under the applied conditions the reaction was reversible. Hydrogels were obtained by crosslinking HyPG-MA in aqueous solutions using potassium peroxodisulfate (KPS) and *N,N,N′,N′*-tetramethylethylenediamine (TEMED) as initiator and catalyst, respectively. Within 10 min, 99% of the methacryloyl groups were polymerized. Rheological analysis showed that the storage modulus of these gels could be tailored by varying the concentration of HyPG-MA in the aqueous solution as well as by the DS. Moreover, the obtained hydrogels have a limited swelling capacity indicating that rather dimensionally stable networks were obtained. As an alternative for radical polymerization with KPS and TEMED, the HyPG-MA could also be crosslinked by photopolymerization using Irgacure 2959 as photoinitiator. A methacrylate conversion of 99% was obtained within 3 min of illumination. As for the gels prepared with KPS and TEMED, networks formed by photopolymerization also had a high shear storage modulus and showed limited swelling. Hydrogels based on HyPG have great potential as drug delivery matrices and for tissue engineering purposes.

Keywords: Hyperbranched polyglycerol; Hydrogels; Methacrylation; Polymerization; Viscoelasticity

1. Introduction

In recent years, there has been an increasing interest in dendrimers. Unmodified as well as end-group modified dendrimers are under investigation in a variety of applications such as unimolecular nanocarriers for entrapment of catalysts, drugs and other guest molecules, functional crosslinkers and rheology modifiers [1–5]. However, the major drawback of this type of polymers is their multistep synthesis and, therefore, as an alternative for dendrimers, hyperbranched polymers have been introduced. These tree-like structures were until recently regarded as poorly defined compared to the perfectly structured dendrimers due to their broad molecular weight distribution and random branching. However, recently novel synthetic methods were developed in which substantially better-defined hyperbranched polymers with low molecular weight distributions were obtained [1,3,6–8]. As an example, the anionic ring-opening multibranching polymerization (ROMBP) [1,2,6,9] of glycidol resulted in hyperbranched polyglycerol (HyPG). HyPG's were synthesized with molecular weights ranging from 1000 to 30,000 g/mol and with narrow polydispersities ($M_w/M_n < 1.5$) [2,8,10]. HyPG consists of an inert polyether-backbone with functional hydroxyl-groups at every branch-end. This structural feature resembles the well-known poly(ethylene glycol) (PEG) that is accepted for

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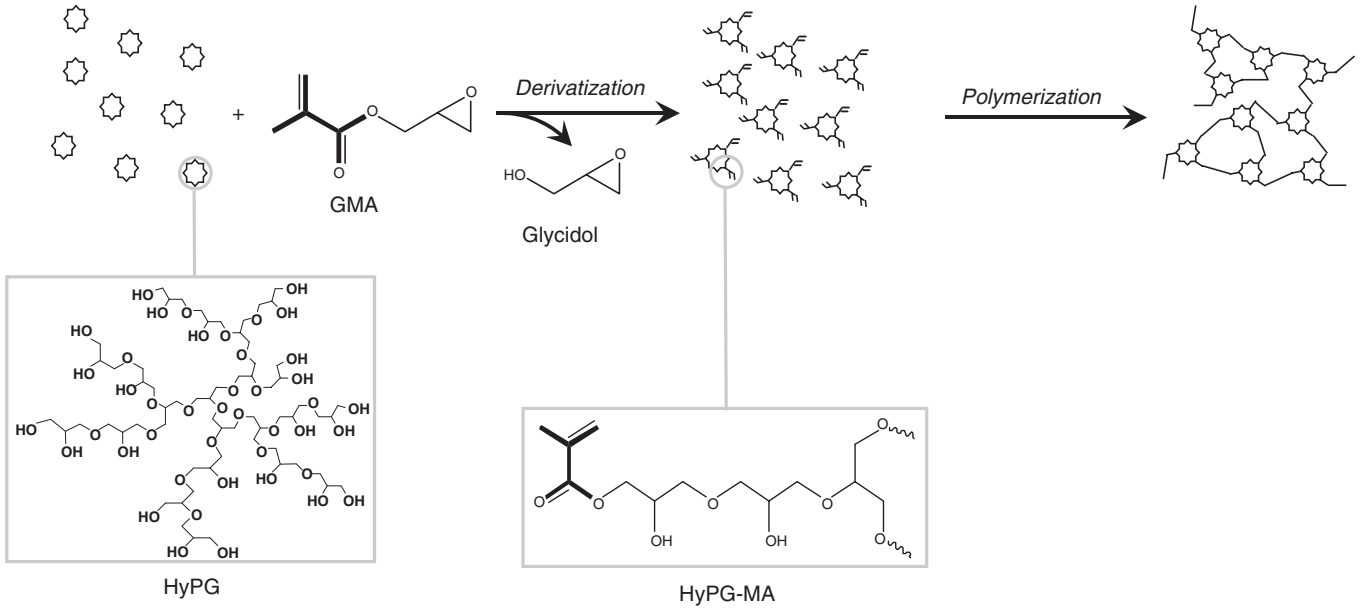

Fig. 1. A schematic representation of the derivatization of HyPG with glycidyl methacrylate (GMA) to yield glycidol as side product and HyPG-MA followed by the formation of HyPG-MA hydrogels by radical polymerization. The depicted polymer structure shows only a small fragment of the large polymer core (M_n 2000 g/mol).

various biomedical applications [11–15]. The polyether-backbone of HyPG, taking the biocompatibility of aliphatic polyether structures such as PEG into account, makes HyPG an attractive polymer for biomedical and pharmaceutical applications [4–9]. Additionally, the hydrophilicity in combination with its hydroxyl functionalities makes HyPG very suitable for the design of hydrogels. Hydrogels, hydrophilic polymeric networks, are of widespread interest for applications in the pharmaceutical, biomedical and biotechnological fields [11,16–18]. An anticipated advantage of HyPG hydrogels over existing hydrogels is the low viscosity of the hydrogel precursors in water [6,19], which can lead to gels with high solid contents and consequently excellent mechanical properties. A possible route to obtain HyPG hydrogels is depicted in Fig. 1. Here, the hydroxyl groups of HyPG are derivatized with methacrylate groups, which will connect the HyPG molecules with each other by covalent crosslinks. Crosslinking can be achieved by chemical initiation using potassium peroxodisulfate (KPS) and *N,N,N′,N′*-tetramethylethylenediamine (TEMED) or by photopolymerization. The first process has been routinely used for the preparation of macroscopic and microscopic hydrogels [20–22]. Photopolymerization is nowadays commonly applied for the preparation of hydrogels, allowing in situ gel formation of patterned gels in a minimal invasive matter [23–25]. However, it is possible that the network properties of the hydrogels may be affected by the polymerization conditions (type of initiating system and concentration of initiators, wavelength of the emitted light and intensity of the UV-lamp). The aim of this study is the synthesis of methacrylated HyPG (HyPG-MA) and to study the characteristics of hydrogels derived hereof.

2. Materials and methods

2.1. Materials

HyPG (M_n 2000 g/mol, 32 hydroxyl groups per molecule) was purchased from Hyperpolymers GmbH (Freiburg, Germany). Dimethyl sulfoxide (DMSO, $H_2O \leqslant 0.005\%$), glycidyl methacrylate (GMA), (±)-glycidol, TEMED and methacrylic acid were purchased from Fluka (Buchs, Switzerland). 4-(*N,N*-dimethylamino)pyridine (DMAP), acetic acid and 70% perchloric acid were obtained from Acros Chimica (Geel, Belgium). Methyl sulfoxide-d_6 (99.9% atom D) and 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959, purity 98%) were provided by Sigma-Aldrich (Zwijndrecht, The Netherlands). Sodium hydroxide (NaOH) pellets and KPS were obtained from Merck (Darmstadt, Germany). Diethylether and acetonitril (HPLC grade) were purchased from Biosolve Ltd. (Valkenswaard, The Netherlands).

2.2. Kinetics of HyPG-MA formation

The synthesis of HyPG-MA was based on the method described by van Dijk-Wolthuis et al. for the synthesis of methacrylated dextrans [22,26]. In detail, HyPG (1 g) was dissolved in DMSO (9 ml) at room temperature under a nitrogen atmosphere. After dissolution of DMAP (2 g), GMA (251 μl; 2 mmol or 2.51 ml; 20 mmol, corresponding to a molar ratio GMA:OH of 1:1 and 10:1, respectively) was added. Samples of 0.3 ml were taken at regular time intervals, after which HyPG-MA was precipitated in diethylether, washed three times with the same solvent and subsequently dried overnight at room temperature. The degree of substitution (DS, the percentage of derivatized hydroxyl groups) of the HyPG-MA samples was determined by both ^{1}H NMR spectroscopy (Section 2.8.) and reversed-phase (RP) HPLC as described by Stenekes et al. [27].

2.3. Large-scale synthesis of HyPG-MA

Ten grams of HyPG were dissolved in 90 ml DMSO ($H_2O \leqslant 0.005\%$) at room temperature under a nitrogen atmosphere. Next, 2 g of DMAP and a certain amount of GMA (0.15–7.5 ml), depending on the aimed DS, were added. After 5 h stirring at room temperature, the HyPG-MA was