Automated Solvent-Free Polymerization of Hyperbranched Polyglycerol with Tailored Molecular Weight by Online Torque Detection

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Polymerization processes with high reproducibility, traceability, and nontoxic compounds are required for biomedical applications. Here an automated solvent-free polymerization of hyperbranched polyglycerol has been established on a multiple-hundred gram scale. Performed is an anionic ring-opening multibranching (ROMB) polymerization with slow addition of glycidol. The solvent-free approach avoids commonly used organic solvents during the polymerization and work-up. Due to the automation of the polymerization process high reproducibility and traceability is accomplished. The used reactor is equipped with an anchor stirrer and stirrer control, which measures the applied torque. A linear correlation of the increasing torque and the degree of polymerization is observed, which can be used to monitor the molecular weight in situ during the polymerization.

1. Introduction

Several studies on polyglycerol (PG) have been reported within the last two decades with the aim to establish the biocompatible, nontoxic, and water-soluble polymers as an alternative to polymers being approved for therapeutics and diagnostics, such as polyethylene glycol (PEG) and poly(vinyl alcohol) (PVA).[1] Various synthetic processes for PG have been established in the last couple of years, which have an influence on the polymeric scaffold, its architecture, size, and functionality. All of them, however, require partially organic solvents, such as N,N-dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP) during polymerization or work-up. Residues of organic solvents in the final polymer could lead to a reduced biocompatibility due to their toxicity.

The production and functionalization of hyperbranched polyglycerols (hPGs) have been well established. Anionic ring-opening multibranching (ROMB) polymerization of glycidol is the most frequent method for the preparation of hPG. The deprotonated initiator 1,1,1-trimethylpropane (TMP) enables in combination with a slow monomer addition and a rapid cation exchange equilibrium a good control over the molecular weight, polydispersity index (PDI) as well as the multibranched structure of the hPG.[2,3]

Recently, Kizhakkedathu and coworkers developed a two-step polymerization of glycidol to extend the maximum of the molecular weight of hPG up to 9 MDa. Here, a macroinitiator approach in combination with solvent-based ROMB polymerization is used to achieve mega hyperbranched polyglycerols (mega hPGs).[4] The type of the used solvent during the polymerization has a major impact on the resulting polymer properties.[5] Most approaches are performed in batch processes; however, the hPG synthesis was also studied in a continuous flow microreactor.[6]

Furthermore, linear polyglycerol (lPG) can be produced using an acetal-protected glycidol derivative as monomer. Ethoxylated glycidyl ether (EEGE) was polymerized and the protective groups were removed by acidic hydrolysis after polymerization resulting in linear polyglycerols. The linear conjugates are as useful for many biomedical applications.[7,8]

Besides variations in architecture and size, the production of biodegradable PGs is of interest. A cationic polymerization of glycidol by citric acid at ambient and solvent-free conditions was established to produce degradable polyglycerol units with a molecular weight of 1–2 kDa in a green chemistry approach.[9] Furthermore, one-pot synthesis strategies for biodegradable copolymers based on polyglycerol and polycaprolactone, polysuccinic acid, or poly(lactide) were developed and tested for biological applications.[10–14] These modifications and variations offer a toolbox of various PG versions for the development of more complex...
architectures, which has been relevant for the transportation and release of active compounds in biomedical applications. Here, stimuli-sensitive groups or cleaving points could be incorporated to degrade the polymer backbone or more complex architectures like PG based: micelles, hydrogels, nano capsules, or core–shell structures, in a controlled way, and transport and release the encapsulated therapeutic cargo at the target site.\textsuperscript{[15–19]} Furthermore, PG was used as multifunctional scaffold for applications like virus-binding inhibition\textsuperscript{[20,21]} and anti-inflammatory therapy.\textsuperscript{[22]} In the cosmetic industry PG was also applied as ingredient or used as precursor for surfactants and emulsifiers.\textsuperscript{[23]}

For polymers that are used in the field of biomedicine it is important to develop a product with defined parameters and to have good control over reaction parameters and kinetics. Earlier works by Frey and co-workers had the goal to study these processes with mechanistic detail.\textsuperscript{[2,3,24]} Laboratory and industrial polymerization processes benefit of online monitoring due to safety aspects for exothermic reactions as well as for providing information on polymer composition and quality.\textsuperscript{[25–27]}

Paulus et al. developed a computational software model of the hPG polymerization to describe and control the experimental parameter dependencies.\textsuperscript{[28]} However, organic solvents for the polymerization process and/or purification of the crude product were used for all above-mentioned production processes of polyglycerol. Besides automatization and digitalization, sustainability aspects play a crucial role in today’s society. The reduction or omission of organic solvents in chemical syntheses contribute to sustainability by saving fossil resources and reducing impacts on health of consumers.\textsuperscript{[29]}

Here, we introduce an automated solvent-free-polymerization of highly biocompatible hPG, which combines and meets the above-mentioned requirements for a modern polymerization via online control over the reaction parameters and a solvent-free approach to produce tailor-made polymers in a reproducible manner.

2. Results and Discussion

Online monitoring of polymerization parameters is of high interest because it enables to run the process in a safe condition, minimizes production cost by controlling the reaction, provides efficient control of constant quality without batch-to-batch variation, and gives information about the reaction progress within the reactor.\textsuperscript{[30]} Important for its useful application is the practicability of the monitoring system. Here a conventional anchor stirrer was used to monitor the torque development during a solvent-free anionic polymerization of hPG. The hypothesis in this study is that monitoring of the torque increased during the polymerization provided information about the actual molecular weight of the polymer in the reactor. To test this hypothesis the polymerization was performed on several torque values. Afterwards, the molecular weight of the resulting polymers was determined. The investigation of the correlation between torque and molecular weight was addressed in this study.

The model system is an anionic ring-opening polymerization of glycidol. TMP is used as a trifunctional starter and is partially deprotonated (≈10% of the OH groups) in a methanolic potassium hydroxide solution. The usage of methanol ensured a homogenous deprotonation of TMP, which is essential to obtain polymers with low dispersity. Afterwards, methanol is evaporated under reduced pressure before the solvent-free polymerization starts with slow monomer addition of glycidol (18 g h\textsuperscript{−1}). The resulting polymer is a hyperbranched polyglycerol (Figure 1).

The polymerization was carried out in an automated reactor system to ensure the same process work flow for each experiment, which was essential for the reproducibility. The temperature was controlled via a water-cooling and -heating thermostat (CC-205C with Pilot ONE controller, Huber, Offenburg, Germany) that was pumping oil through the double wall of the reactor. The pressure was controlled via a vacuum membrane pump (PC 3001 Vario pro, Vacuubrand, Wertheim, Germany). The reactor was additionally equipped with an argon inlet to create an inert atmosphere, which is required for anionic polymerizations to avoid spontaneous termination due to oxygen or water.\textsuperscript{[30]} Monomer addition was realized via a supply flask hanging on a load cell (IL-GRADO1000, HiTec Zang, Herzogenrath, Germany) and the applied force (torque) that was needed to achieve a user-set rotation speed is determined. The anchor stirrer was kept the same for all polymerization to ensure high reproducibility (see Figure S11 in the Supporting Information for detailed stirrer geometry). All mentioned parts are connected to the LabManager (HiTec Zang, Herzogenrath, Germany). Here the commands arrived from a computer and were further translated to actions like open/closing magnetic valves, heating/cooling, adjusting the pressure, or keeping a certain rotation speed. The lab manager also collected parameters such as temperature, stirrer speed, torque, and pressure etc. that were measured during the polymerization. The recorded parameters could be observed in time or afterwards. Our focus was on the torque development during polymerization (blue line, Figure 2a). The torque value increased as expected with the steady addition of glycidol (18 g h\textsuperscript{−1}), while all other parameters were kept constant. 2.5 h after the start of the polymerization process a steeper rise of the torque value occurred, which was flattened to the initial ascending slope after additional 2.5 h. An explanation could have been adhesion of the polymer on the reactor wall. In the beginning just the bottom of the reactor was covered, after a certain time the increasing polymer mass started to climb the reactor wall, which was supported by the movement of the anchor stirrer. The steeper rise of the torque value resulted probably from the higher contact area of the polymer to the reactor wall. At a certain polymer amount, the polymer mass was not able to climb higher and flows to the center of the reactor. In the center the anchor stirrer blades have had a smaller contact area, which led to relative lower required force to stir and the torque increase was mostly due to increasing mass and was raised in a linear fashion.

The steeper rise of the torque value was investigated for all polymerizations with fresh distilled glycidol, whereas, at polymerizations with non-distilled glycidol or older distilled glycidol batches, this steeper rise did not appear. Most probably the water residue within the polymer mass decreased its viscosity and hindered it to climb the reactor wall. This hypothesis is supported by the lower measured torque values compared to polymerization
Solvent-free polymerization of glycidol in an automated reactor system (LabKit HiTec Zang, Herzogenrath, Germany). (i) Partial deprotonation (10% OH) of the starter TMP with potassium methoxide for 1 h at 55 °C and subsequent evaporation of methanol by slowly decreasing pressure to 3 mbar. (ii) Polymerization of glycidol at 100 °C with slow monomer addition rate 18 g h⁻¹.

The automatized reactor system, which is controlled by a computer and process data like temperature, pressure, torque, etc., has been recorded. Magnetic valves controlled the addition of monomer or the flow of argon. All controlled parameters are shown live in the software of HiTec Zang. The system is accessible via an App and enables a wireless remote control using a tablet or mobile phone.

After the addition of monomer is stopped, the reaction condition was kept constant for at least 2 h. During this time the torque value stagnated or showed an increase probably due to the reaction of remaining monomer, which acted as a solvent, until all monomer was consumed. The resulting polymer mass in the reactor appeared as highly viscous white mixture. The white color resulted from dispersed gas bubbles within the viscous polymer mass. The polymerization was quenched by the addition of water and led to a drastic decrease of the torque value. The torque value after quenching is comparable with the torque value before the polymerization. After the addition of water, the polymer was dissolved and due to the lower viscosity, the trapped gas bubbles were able to escape, which led to a slightly golden transparent polymer solution.

Seven individual polymerizations were performed to predefined terminal torques. The absolute targeted torque values were between 15 and 27 Ncm. This range was chosen because the empty system itself needed already ≈10 Ncm for stirring and the engine of the stirrer was limited to 28 Ncm. The used stirrer seal out of PTFE closed tight to ensure a good vacuum but caused high friction and therefore high torque values were needed to stir in empty state. This disadvantage could have been overcome by using a magnetic stirrer seal in the future.

The starting point of the absolute torque values for each polymerization varied. For the seven polymerizations, the mean starting torque value and the standard deviation was 11.4 ± 1.3 Ncm. To overcome this problem, the relative torque increase was compared, which revealed same torque developments for each batch. The same development of the relative torque indicated a reproducible process (Figure 2b). After quenching with approximately 350 mL of water, the polymers were stirred with freshly distilled glycidol. The explanation concluded that the torque trend would have changed with different reactor or stirrer geometry.
with cation exchanger (DOWEX Monosphere 650C; hydrogen form) overnight before the molecular weight and the dispersity (D) were determined by gel permeation chromatography (GPC, Figure 3c). The resulting molecular weight range from \( M_n = 3.9 \text{kDa} \) to \( M_w = 9.7 \text{kDa} \) and the mean dispersity is about 1.75 ± 0.12 for all crude polymers (Table 1).

To prove the reproducibility, the polymerization was performed three times until a relative torque of 10.1 N cm is reached (Table 1; hPG-3a-c). 10.1 N cm was chosen because this terminal torque value was in the middle of the range of torque values tested.

The measured torque values were indicative for the molecular weight of the crude hPG. By plotting terminal relative torque values against the measured molecular weight of the crude polymers (obtained by GPC), a linear correlation between these two parameters was observed (see Figure 3).

A high linear correlation of the weight average (\( M_w \)) with \( R^2 = 0.981 \) and of the number average (\( M_n \)) with \( R^2 = 0.961 \) was discovered. A potential explanation for the slightly lower coefficient of determination of \( M_n \) could have been that small amounts of glycidol did not drop on the bottom of the reactor and became hit by the anchor stirrer blades. In this case, the glycidol could get in contact with the reactor wall, where self-initiation due to the elevated temperature (100 °C) could occur. The resulting polymers or oligomers were smaller than the main polymers, which were initiated by TMP at the bottom of the reactor. Since the smaller polymers had a greater influence on \( M_n \) than \( M_w \) the linear correlation of \( M_n \) may have fluctuated more than the correlation of \( M_w \). However, the difference of the coefficient of determination was small. The mentioned reason for the formation of small polymers is a hypothesis and was not further investigated in this study.

With the knowledge of the correlation of the relative torque value and the molecular weight, it is possible to translate the online measured torque value to the molecular weight of the polymer in the reactor.

Purification of polymer amounts in scales of hundreds of grams was mostly done by precipitation in a nonsolvent, e.g., for hPG acetone. Since our nonsolvent polymerization approach aims at reducing waste and negative human health impacts, an incentive that is in line with the principles of green chemistry, precipitation in organic solvent was refused. Here, tangential flow filtration (TFF) was used instead to purify big amounts of polymer by cycling aqueous polymer solution over an ultrafiltration membrane via size exclusion. Impurities like oligomer, monomer, solvents, salts are removed as permeate and the volume is replaced by fresh water. The setup of the TFF is shown (see Figure S10 in the Supporting Information). Due to the usage of certain ultrafiltration membranes with specific molecular weight cut-off (MWCO), the purification can be controlled. Unfortunately, the lowest available MWCO was 1 kDa. The synthesized polymers showed a molecular weight distribution, where a small fraction reached below 1 kDa (Figure S9, Supporting Information). This fraction was removed during the purification. Hence, a loss of ≈20 wt% of hPG occurs during the TFF purification procedure. The molecular weight fraction below 1 kDa was higher in case of the smaller synthesized polymers, which

| Table 1. Overview properties of crude hPG. |
|------------------------------------------|
| Rel. torque | Glycidol | \([\text{M}/\text{I}]_{\text{Theo}}\) | Theory | GPC |
| [N cm] | [g] | [mol] | [-] | \( M_n \) | \( M_w \) | \( D \) |
| hPG-1 | 4.3 | 58.6 | 0.79 | 32.7 | 2.6 | 2.2 | 3.9 | 1.75 |
| hPG-2 | 7.5 | 80.2 | 1.08 | 44.7 | 3.4 | 2.7 | 4.9 | 1.85 |
| hPG-3a | 10.1 | 132.8 | 1.79 | 74.1 | 5.6 | 3.8 | 6.5 | 1.72 |
| hPG-3b | 10.1 | 132.6 | 1.79 | 74.0 | 5.6 | 3.6 | 6.5 | 1.80 |
| hPG-3c | 10.1 | 131.5 | 1.78 | 73.4 | 5.6 | 3.2 | 6.1 | 1.90 |
| hPG-4 | 13.7 | 173.3 | 2.34 | 93.6 | 7.3 | 4.9 | 8.5 | 1.72 |
| hPG-5 | 17.6 | 253.7 | 3.42 | 128.2 | 10.6 | 6.2 | 9.7 | 1.52 |
Table 2. Polymer properties after purification by TFF (MWCO: 1 kDa).

|          | Theory | GPC | Overall yield | $^{13}$C NMR |
|----------|--------|-----|---------------|-------------|
|          | M      | $M_n$ | $M_w$ | D | [wt%] | DB [%] |
| hPG-1$^a$ | 2.6 3.5 5.0 | 1.41 | 85.2 | 57.8 |
| hPG-2$^b$ | 3.4 4.2 6.0 | 1.43 | 33.7 | 59.1 |
| hPG-3a | 5.6 5.7 7.5 | 1.33 | 74.4 | 61.5 |
| hPG-3b | 5.6 5.2 7.1 | 1.37 | 84.5 | 53.9 |
| hPG-3c | 5.6 4.7 6.7 | 1.41 | 79.3 | 60.3 |
| 4-hPG | 7.3 6.2 9.0 | 1.45 | 90.1 | 60.5 |
| 5-hPG | 10.6 8.9 11.0 | 1.24 | 85.7 | 60.8 |

$hPG-1$ was dialyzed in a dialysis tube (MWCO: 0.5 kDa); $^b$ Loss occurred due to the TFF membrane cutoff (MWCO: 1 kDa).

led to a higher loss for smaller polymers like hPG-2 (overall yield: 33.7 wt%; Table 2). To prevent a high loss of hPG-1, the polymer was dialyzed in a dialysis tube with a molecular weight cut-off of 500 Da against water (overall yield: 85.2 wt%). All other polymers were purified with TFF using 1 MWCO. The mean dispersities decreased from 1.75 to 1.37, which showed that oligomers or small polymers were formed during the polymerization that could have been removed using the TFF purification procedure (Figure 4c). The here-obtained dispersity values were comparable with the ones of other studies. For example, Paulus et al. used NMP and THF during the polymerization and obtained hPGs on a kilogram scale with dispersities of $D = 1.9$ (target $M_n = 2.5$ kDa), $D = 1.4$ (target $M_n = 5$ kDa), and $D = 2.27$ (target $M_n = 20$ kDa).$^{[28]}$ Kainthan et al. achieved hPG without solvent in 27 g scale with $D = 1.2$ (target $M_n = 3$ kDa) and $D = 1.6$ (target $M_n = 20$ kDa).$^{[33]}$

This shows that the here-developed solvent-free polymerization method is in case of the dispersity able to produce similar qualities of hPG.

The purified polymers were further characterized by $^1$H NMR to verify the structure of the polymer (Figure 4a). Additionally, the methyl- and methylene group of the starter TMP could be identified, which indicated that the polymerization started from the deprotonated TMP and not by thermal self-initiation of glycidol. As discussed before self-initiated polymers were smaller and might have been removed by the TFF before the NMR measurement.

The different structural units within the polymer like 1,3 linear ($L_{13}$) or 1,4 linear ($L_{14}$), dendritic ($D$), and terminal units ($T$) were investigated from $^{13}$C NMR measurements (Figure 4b; Figures S2–S7, Supporting Information). On the basis of the structural units the degree of branching (DB) could be calculated according to Frey and co-workers.$^{[2]}

$$DB = \frac{2D}{2D + L_{13} + L_{14}}$$ (1)

Additionally, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry was used to characterize the hPGs. Due to the hyperbranched nature of hPG the transfer of the ionized polymer into the gas phase was difficult, especially the higher molecular weights above 5 kDa with broad dispersity.$^{[28]}$ Therefore, the detected molecules might represent only a certain molecular weight fraction of

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Figure 4. Characterization of hPG-3a after TFF purification. a) $^1$H NMR (300 MHz, D$_2$O). b) Inverse-gated $^{13}$C NMR (700 MHz, D$_2$O). c) Gel permeation chromatography (GPC), crude polymer (dashed line), and after purification with TFF (solid line, 1 kDa MWCO). d) Matrix-assisted-laser-desorption-ionization time of flight (MALDI-TOF), peak difference determined the molar mass of the repeat unit, the two-peak pattern resulted from ionized molecules with different counter ions ([Na$^+$] and [K$^+$] adducts).
the real molecular weight distribution. Hence, the distribution of the molecular weight based on MALDI is not included in this study. In the MALDI spectra two distributions were visible, which could have been assigned to polymers ionized by [Na\(^+\)] and/or [K\(^+\)] adducts (Figure 4d). The source of potassium ions was most probably from residual deprotonated hydroxyl groups, which possessed potassium as counter ions. Sodium ions may have come from solvents, used reactants, or glassware contaminations.[14] However, the difference of the mass peaks revealed the molecular weight of the repeat unit. The determined difference is 74 g mol\(^{-1}\) and matched with the expected molecular weight of the monomer glycidol (74.08 g mol\(^{-1}\)). Therefore, it could be verified that hyperbranched polyglycerol was obtained with the solvent-free polymerization method.

3. Conclusion
In this study, a solvent-free polymerization method for hyperbranched polyglycerol was established. In order to achieve a high reproducibility and ensure traceability an automated reactor system was used. The torque development during the slow monomer addition was the same for all seven polymerizations, when the quality of the reactants was kept constant. Also, the three reproduced polymerizations to the identical relative torque increase of 10.1 N cm resulted in the same amount of added glycidol (132.3 ± 0.7 g). The same torque developments and the repeated polymer batches indicated a good reproducibility of this method. The produced hPG polymers ranged in size from \(M_n = 3.9\) kDa to \(M_w = 9.7\) kDa and have mean dispersity of 1.75 ± 0.12 in crude state and 1.37 ± 0.07 after purification with TFF as well as high overall yield (>75%).

Furthermore, it has been achieved to detect empirically a linear correlation between the relative torque values and the molecular weight of the hPG in the reactor by the generation of a calibration curve. This correlation could be used for future polymer batches to determine online the molecular weight during the polymerization. This approach is an easy, practical, and inexpensive method for online monitoring of the molecular weight. The developed solvent-free polymerization enables to produce multiple-hundreds grams of hPG, which is currently being investigated in several biomedical applications.[13]

4. Experimental Section

**Material:** Glycidol (96.0%) from Sigma Aldrich was purified by vacuum distillation. TMP (97.0%) and Dowex Monosphere 650C (hydrogen form) were obtained from Sigma Aldrich (Steinheim, Germany). Molecular sieves (4 Å, type 514, pearls) were obtained from Roth. Methanol (99.8%, extra dry over molecular sieves) was received from Acros Organics (Geel, Belgium). Potassium hydroxide (KOH, analytical reagent grade) was obtained from Fisher Scientific (Schwerte, Germany). Deuterium oxide (D\(_2\)O, 99.9%) was obtained from Deutero (Kastellaun, Germany). All reagents were used as received without any purification unless otherwise mentioned.

**Distillation of Glycidol:** The distillation apparatus out of 2 Schlenk flasks connected through a distillation bridge was dried three times and flushed with argon. The distillation was done under inert condition. 700–800 mL of glycidol was exposed to reduced pressure and slightly heated to 40 °C. The precarriage of \(\approx 100\) mL was collected in a flask at –78 °C (acetone/ dry ice) until \(10^{-3}\) mbar was reached. Afterwards the desired fraction was collected in a 1 L Schlenk flask filled with activated molecular sieves (pore size 4 Å). After 4 h of distillation at 45 °C and 10 \(\pm\) 1 mbar \(\approx 600\) mL distilled glycidol were collected and stored at 4 °C under argon.

A yellow distillation residue (\(\approx 20\) mL) remained.

**Solvent-Free Polymerization of hPG:** For all performed polymerizations, the preparation and all parameters were kept the same except for the added amount of monomer was varied. The amount of added monomers was stopped when an assigned terminal torque value was reached. The process sequence was controlled by the automated system. See the flow chart of the polymerization (Figure S12, Supporting Information).

The 0.5 L reactor was heated to 100 °C and the pressure was decreased to 3 mbar. Afterwards, the reactor was filled with argon. This evaporation was repeated after 1.5 and 3 h. To ensure that no water residues were left in the system, the temperature was kept at 100 °C and 3 mbar for 17 h. Afterwards, the reactor was flushed with argon and the temperature was decreased to 60 °C. At that temperature TMP (3.35 g, 24.2 mmol, 1.0 eq.) was added manually under argon counterflow. By increasing the temperature to 65 °C TMP was molten at a stirring speed of 50 rpm (anchor stirrer). Possible water content in the TMP was removed by decreasing the pressure to 3 mbar for 20 min at the molten state. Small gas bubbles indicated the evaporation of the water residues. Then the temperature was decreased to 55 °C and 10 mL methanolic potassium hydroxide (0.52 g, 9.3 mmol, 0.38 eq.) solution added. TMP was dissolved and partially deprotonated (\(\approx 10\%\) of the OH groups) while a stirring speed of 50 rpm. After 1 h the pressure was decreased to remove the methanol. This was done in several steps (see flow chart in Figure S12 in the Supporting Information) to prevent spilling of evaporated methanol. Evaporated methanol was condensed and collected. The final pressure of 3 mbar was kept for 3 h to remove the whole methanol. Then the reactor was flushed with argon, the temperature increased to 100 °C and the stirrer speed was increased to 100 rpm. These parameters were kept during polymerization. With the automated addition (18 g h\(^{-1}\)) of distilled glycidol the polymerization started an assigned torque value was reached. The addition continued until an assigned torque value was reached. The total dosed amount of glycidol was recorded by the system (see Table 1). After the addition of monomer was stopped, the polymerization condition was kept for at least 2 h to ensure no unreacted monomer is left. Finally, the polymerization was quenched with water (\(\approx 350\) mL) and the temperature was decreased to 60 °C. The added water dissolved the polymer and enabled to take out the polymer through a drain valve at the bottom of the reactor.

**Purification of hPG:** The aqueous polymer solution out of the reactor was taken and cation exchange beads (DOWEX Monosphere 650C) were added and stirred for 20 h to remove the potassium ions. By filtration through a filter (size 2), the beads were removed from the polymer solution. Afterwards, tangential flow filtration (TFF) was performed with an ultrafiltration cassette (Millipore Pellicon 2 mini, MWCO 1 kDa) and a mini cassette holder (Pellicon XX42PMINI). Aqueous polymer solution of \(\approx 0.1\) g mL\(^{-1}\) was cycled in the diafiltration system for 72 h. During the filtration small polymers fractions and small molecule impurities were removed via permeation (\(\approx 5\) L) and continuously replaced with fresh deionized water. Afterwards, all polymers were freeze-dried to remove the water and the overall yield was determined. The smallest synthesized polymer (hPG-1) was different purified due to expected high loss during diafiltration with MWCO 1 kDa. It was diazylized in a dialysis tube (300 Da MWCO, cellulose ester, Spectrum Laboratories, Walhamb, US) in water for 72 h.

**GPC:** The molecular weight distributions (\(M_n, M_w\)) and the dispersity were determined by GPC using a refractive index detector (RI) at 40 °C. 100 µL samples were injected with a concentration of 6 mg mL\(^{-1}\). Three columns (Polymer Standards Service GmbH (PSSS), Germany; Suprema 100 Å and two 1000 Å; 10 µm particle size) were used to separate the sample under a flow of 1 mL min\(^{-1}\) sodium nitrate solution as mobile phase (0.1 M) at room temperature. The system was calibrated with pulsedulian standards from PSS.

**NMR:** NMR spectra were recorded with 400 Hz using a JEOL ECX spectrometer (JEOL, Freising, Germany). D\(_2\)O was used as solvent and as reference for all proton (\(1^H\)) and carbon (\(^{13}C\)) NMR measurements. The chemical shifts were determined in ppm. Carbon NMR was measured with inverse-gated decoupling to allow quantification of the spectra.
MALDI-TOF MS: Resulting hPGs were characterized by MALDI-TOF mass spectrometry to derive the repeat unit of the polymer. Ultraflex-II TOF/TOF instrument (Bruker Daltonics, Bremen, Germany) equipped with a 200 Hz solid-state Smartbeam laser was used. α-Cyano-4-hydroxycinnamic acid (CHCA) was taken as matrix. Briefly, 100 µL polymer solution (2 mg mL⁻¹), 100 µL saturated matrix solution (in MeOH), and 20 µL of TA33 solution (33 vol% acetonitrile, 0.1 vol% trifluoroacetic acid in H₂O) were mixed. The samples were prepared via the dried droplet technique by dropping 0.5 µL of this mixture on a stainless-steel target and dried under ambient conditions. All spectra were acquired in positive linear mode and were separated by the m/z range of 500–20 000.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
Research data are not shared.

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