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Plurifunctional polyglycidol-based particles prepared by Dispersion Ring-Opening Metathesis Polymerization

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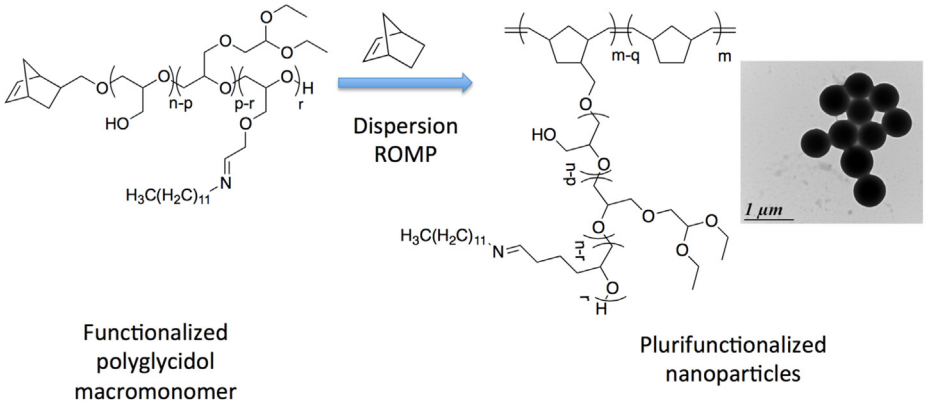
HIGHLIGHTS

- The synthesis of polyglycidol based macromonomers as plurifunctional platforms is described.
- The colloidal properties of polynorbornene-polyglycidol core-shell nanoparticles are studied.
- The synthesis of plurifunctionalized nanoparticles by dispersion ROMP is described.

GRAPHICAL ABSTRACT



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ABSTRACT

Dispersion Ring-Opening Metathesis Polymerization (ROMP) of norbornene (Nb) in the presence of a hydrophilic α-norbornenyl-polyglycidol macromonomer is a powerful method to obtain stabilized polymeric core-shell nanoparticles (NPs). Thanks to their high hydroxyl functionality content, one for every structural unit along the chain, the polyglycidol-based NPs can be viewed as plurifunctional platforms for the attachment of active molecules. The synthesis of polyglycidol macromonomers by anionic polymerization and their copolymerization with norbornene to give the NPs is described in the first part of this paper. In the second part, we take advantage of the presence of the hydroxyl groups to synthesize NPs with a high functionalization capacity. Dodecylamine, a primary amine known for its biocidal properties was selected as a model molecule and conjugated to the polyglycidol chains using a pH-sensitive imine bond.

1. Introduction

The Ring-Opening Metathesis Polymerization (ROMP) of cycloolefins in heterogeneous media, and particularly of norbornene (Nb), is an efficient method to obtain polymeric nanoparticles [1]. Mini- or micro-emulsification in water is a powerful strategy to synthesize such objects [2,3], but these methods

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require large amounts of surfactants that can desorb from the surface of the nanoparticles (NPs) to the water phase, resulting in detrimental effects for most applications. In previous publications, we presented the synthesis of nanoparticles based upon polynorbornene (PNb) by dispersion ROMP. These could have applications in tissue engineering for the biointegration of bone implants [4], as drug carriers for cancer therapy [5–8] or in the treatment of bacterial infections [9,10]. These particles were obtained by copolymerizing Nb with an α-norbornenyl-poly(ethylene oxide) macromonomer serving as stabilizing agent in an organic medium, in the presence of the Grubbs I complex as initiator. In this approach, the PNb particles which precipitate in the medium are stabilized by the poly(ethylene oxide) (PEO) chains to form 250–350 nm nanospheres with a hydrophobic PNb core and a hydrophilic PEO shell. Thanks to the PEO shell these NPs are not cytotoxic [11], and active molecules can be coupled at the ω-end of the PEO macromonomer through either a stable covalent bond [12] or a stimulus-responsive chemical functionality [13]. The main restriction of this approach lies in the limited amount of active molecules that can be linked to the substrate (one molecule per PEO chain).

The present contribution focuses on the preparation of PNb-based NPs with a high concentration of hydroxyl groups at their periphery, to serve as scaffolds for the multivalent linking of an active molecule. The key to this approach is the use of a reactive stabilizer containing a large number of hydroxyl groups per chain, namely a norbornenyl-polyglycidol macromonomer.

Polyglycidol (PGLD) is a water-soluble polymer that attracts increasing interest in the biomedical field due to its biocompatibility and high chemical functionality [14,15]. Glycidol can be polymerized to high molar masses, but its hydroxyl group can lead to hyperbranched macromolecules [16–18]. A linear polymer chain structure can only be achieved if the hydroxyl groups of glycidol monomer are protected, for example with an acetal group. A post-polymerization deprotection step is therefore required [14,19–22]. The preparation of PGLD-based nanoparticles has been described in the literature, by radical copolymerization of either linear or branched PGLD macromonomers functionalized with a styrenic moiety [23–25]. Mendrek et al. also reported the formation of NPs in the 50–550 nm size range by the self-assembly of PGLD-based diblock copolymers incorporating either poly(4-vinylpyridine) or poly(*N*-isopropylacrylamide) as a hydrophobic block [26,27]. To the best of our knowledge, no Nb-PGLD macromonomers have ever been used in dispersed-media polymerization, particularly in combination with ROMP.

In the first part of this paper, the synthesis of PNb-PGLD core-shell nanoparticles by ROMP in dispersed medium using strictly linear α-norbornenyl PGLD macromonomers is described. The colloidal properties of these new objects are then investigated. In the second part, the PGLD macromonomers have been modified with primary amino compounds before polymerization by ROMP to give access to highly functionalized NPs.

2. Experimental part

2.1. Material and methods

2.1.1. Materials

Tetrahydrofuran (THF; J.T. Baker) was cryodistilled from sodium benzophenone ketyl before use. *N*,*N*-Dimethylformamide (DMF; 99%; CHROMASOLV PLUS; Aldrich) was dried and stored over molecular sieves. Ethanol (96%; purissimum grade; Xilab) and dichloromethane (purissimum grade, Xilab) were degassed before use. Diphenylmethylpotassium (DPMK; 1 mol L^{-1} in THF) was synthesized and titrated according to established procedures [28]. Sodium hydride (60% dispersion in mineral oil; Aldrich) was washed with anhydrous heptane before use. Grubbs first generation complex $Cl_2(PCy_3)_2Ru$=CHPh (Aldrich) and 5-norbornene-2-methanol (98%; mixture of endo and exo isomers; Aldrich) were used as received and stored in a glove box under argon. Bromoacetaldehyde diethyl acetal (97%; Aldrich), dodecylamine (DDA; 98%; Aldrich) triethylamine (TEA; 99%; Aldrich) and ethanol absolute (VWR) were used without further purification. Macromonomers **(3), (6)** and **(7)** were purified by dialysis to remove residual salts and remaining molecular compounds. In each case, Spectra/Por regenerated cellulose membranes (MWCO = 1 kD) were used. Macromonomer **(4)** was purified by ultrafiltration using a Millipore solvent-resistant stirred cell (model XFUL 047 01) equipped with regenerated cellulose ultrafiltration membranes (NMWL = 1 kD), ensuring that residual molecular compounds and salts were completely eliminated.

2.1.2. Characterization methods

ROMP was performed in a glove box. ^{1}H NMR spectra were obtained on a Bruker 400 MHz spectrometer in $CDCl_3$ or D_2O. Size exclusion chromatography analysis was carried out on a Varian apparatus equipped with TosoHaas TSK gel columns and a differential refractometer detector. THF or DMF served as eluents at a flow rate of 1 mL min^{-1}, and calibration was achieved with low polydispersity polystyrene standards. The conversions of Nb attained in dispersion ROMP were determined by gas chromatography analysis with dodecane as internal standard, using a Varian GC3900 instrument (GC retention times: t^{GC}_{Nb} = 1.77 min; $t^{GC}_{dodecane}$ = 8.55 min), while macromonomer conversion was determined by gravimetry after ultracentrifugation (Eppendorf centrifuge 5804R, 8500 rpm for 30 min at 10 °C) and drying under vacuum. The particle sizes were determined by dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS measurements were performed on a Malvern Zetasizer Nano ZS90 instrument (scattering angle 90°) equipped with a He-Ne laser (4 mW; 633 nm). Before the measurements, the latex samples were diluted about 800-fold to minimize multiple scattering caused by high concentrations. The TEM pictures were obtained with a Hitachi H7650 microscope operating at an accelerating voltage of 80 kV. For the size, distribution and morphology observation, samples diluted about 400 times were deposited on a 200 mesh carbon film-coated copper grid surface (4 μL)

2.2. Synthesis of α-norbornenyl-polyglycidol macromonomer **(4)**

2.2.1. Synthesis of glycidol acetal **(2)**

p-Toluenesulfonic acid (TsOH, 1 g) was added portion-wise to a magnetically stirred solution of 40.0 g (0.54 mol) of 2,3-epoxypropanol (glycidol) (1) in 200 mL (2.09 mol) of ethyl vinyl ether, so as to maintain the temperature below 40 °C when cooling in an ice-water bath. The reaction mixture was stirred for 3 h, and then washed with 100 mL of saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and the excess ethyl vinyl ether was removed under reduced pressure. The product was purified by distillation. Yield: 90% (71.0 g).

^{1}H NMR data in $CDCl_3$ (Fig. S1): δ (ppm) 0.8–1.2 (6H; $-CH_3$); 2.25–2.6 (2H CH_2 acetal); 2.88 (1H; CH glycidol); 3.05–3.7 (4H; CH_2 glycidol); 4.5 (1H; CH acetal).

2.2.2. Synthesis of α-norbornenyl-poly(glycidol acetal) macromonomer **(3)**

For a macromonomer with a number-average degree of polymerization (DP_n) of 25, 1.6 mL (1.37×10^{-2} mol) of 5-norbornene-2-methanol was added to 200 mL of freshly cryodistilled THF, followed by 17.1 mL of DPMK solution (0.8 equivalents, at 0.64 mol L^{-1} in THF). Then 50 g (0.342 mol) of the glycidol acetal **(2)**

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