Large-scale Polymerization of Biodegradable Polymers for Surface Modification of Nanomaterials

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Statement of Purpose: The unique properties of magnetic nanoparticles (MNPs) and quantum dots (QDs) have proven to be valuable as biological tags and drug-delivery labels [1]. MNPs have good potential for enhancing the signal in magnetic resonance imaging (MRI). The photoluminescent (PL) properties of QDs illustrate narrow size-dependent emission spectra and multicolor excitation. But, their lack of biocompatibility has obstructed progress in this application.

Hou reported new biocompatible red-light-emitting polylactide-stabilized CdSe quantum dots and showed decreasing surface defects by photochemical oxidation, enhancing PL stability and quantum yield because of the surface modification with new tunable thiol-end functional polylactides [2].

Surface functionalizing nanoparticles require thiol end-functional polylactides with narrow molecular distribution (PDI), typically below 1.2 [2-3]. The sustainable supply of this material will be essential to advance their use in biomedical applications. The first synthetic method was reported by Hou [2]. However, multi-step synthesis was required and the synthetic condition was not optimized for large scale because it took several days to compete the reaction.

The purpose of this research is to reproducibly scale up the synthesis of well-defined thiol end-functionalized polylactides via a one-pot procedure.

Methods: All monomer, solvents, and catalysts were obtained from Sigma-Aldrich (St. Louis, MO). L-lactide was recrystallized with anhydrous ethyl acetate. The other chemicals were used as received. A reactor charged with organic catalyst, recrystallized L-lactide and cleavable initiator was purged with dry N_2 for at least 3 hours. Anhydrous chloroform was transferred to the reactor. Polymerization was carried out at a tightly controlled temperature. The conversion of monomer to polymer was monitored by ^{1}H NMR until 97% conversion. After the reactor was cooled, reduction catalyst was added and the polymer was precipitated from using an appropriate solvent. After filtration, the product was dried in a vacuum oven. The polymer structure, molecular weight, and molecular weight distribution were characterized by ^{1}H NMR and GPC (THF, polystyrene standards). For NMR experiments, O_2 free $CDCl_3$ was used as a solvent to prevent the rapid formation of disulfide (-S-S-). For GPC experiments, addition of small amounts of D,L-Dithiothreitol (DTT) to polymer solution prevented dimerization

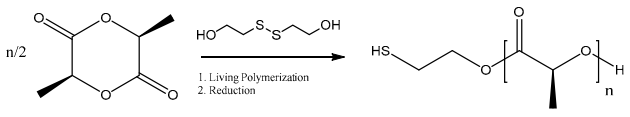

Figure 1. One-pot synthesis of HS-Polylactide-OH

Results: Thiol terminated polylactides were synthesized via a one-pot process as shown in Figure 1. The first step was ring opening living polymerization. The amount of solvent for polymerization was optimized while maintaining a narrow molecular weight distribution (M_w/M_n, PDI < 1.2). Initially, the disulfide polylactide (HO-polylactide-S-S-polylactide-OH) was obtained with a number-average molecular weight (M_n) of 5000 g/mol. Without precipitation, reductive catalyst was added to the polymer solution. Figure 2 illustrates the ^{1}H NMR spectrum of the thiol terminated polylactide. This results show the disulfide groups (adjacent CH_2 group shows up at ~2.9ppm) were fully converted to thiol groups (~2.7ppm). The M_n of the final product determined to be 2400 g/mol based on end group analysis by NMR.

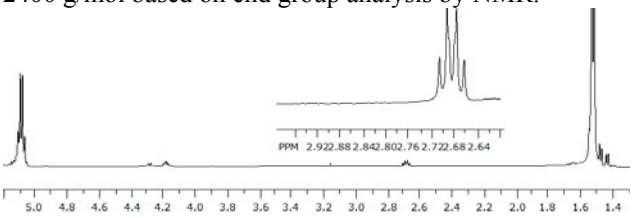

Figure 2. ^{1}H NMR spectrum of HS-PLLA-OH

The GPC curve (Figure 3) showed a single peak and the original data were M_w (5515 g/mol), M_n (4905 g/mol), and PDI (M_w/M_n = 1.12). The corrected M_n was 2800 g/mol (4905 × 0.58[4]), which is in a good agreement with NMR results and a narrow molecular weight distribution was achieved via this method.

Development	Theoretical M_n	M_n by NMR	M_n by GPC	PDI
1	2500	2400	2800	1.12
2	2500	2300	2700	1.15
3	2500	2400	2800	1.13

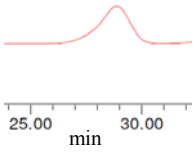

Figure 3. GPC data and curve of HS-PLLA-OH

Conclusions: We succeeded in scaling up the biodegradable polymer in an efficient and economical manner. This polymerization strategy yields reproducible results on a large scale. This process can be adapted to the scale-up of other functional biodegradable polymers and makes them available to broad customer based world-wide.

References:

[1] Oh JK. Soft Matter 2011;7:5096-5108
[2] Hou X. Macromol. Biosci. 2009;9:551-562
[3] Koo D. Poly. Chem. 2012;3:718-726
[4] Kowalski A. Macromolecules 1998;31:2114-2122