Synthesis of Polycarbonate Urethanes with Functional Poly(ethylene glycol) Side Chains Intended for Bioconjugation

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Introduction: Synthetic polymers need to be modified with biomolecules in order to increase their affinity with biological system such as cells or tissues. Polyurethane (PU) is a family of highly diverse synthetic polymers that can be further chemically modified in various ways. As a biomaterial with long history, PU is often used in blood-contacting medical devices such as catheters, leads and vascular grafts. However, traditional PUs are not considered "bioactive" and have limited ability to immobilize biomolecules. In this study, we synthesized new PUs with pendant carboxyl groups where PEG chains with distal reactive groups were attached. These novel functional PEG-grafted PUs can potentially form multifunctional biocojugates for various biomedical applications.

Methods: 4,4'-methylene-bisphenyl diisocyanate (MDI) was purchased from Acros Organics (Shanghai, China). Poly(hexamethylene carbonate) diol (PCD, M_n=860 Da), poly(ethylene glycol) diglycidyl ether (PO, M_n=526 Da) and *L*-lysine were all from Sigma-Aldrich (Shanghai, China). Polyoxyethylene bis(amine) (PN, M_n=1000 Da) was bought from Aladdin Chemistry Co (Chengdu, China). The polycarbonate urethanes (PCULs) with pendant carboxyl groups based on PCD as soft segment and MDI/*L*-lysine as hard segment were synthesized through a conventional two-step method. Then PEG side chains were chemically grafted to the PCULs by the reaction between amino or epoxy groups and carboxyl groups. Albumin was used as a model protein to immobilize onto the functional polyurethanes to demonstrate the reactivity.

Results: PUs with pendant carboxyl groups were synthsized and modified with poly(ethylene glycol) side chains. The chemical structure of the PUs was confirmed by FTIR and ^{1}H-NMR. The number average molecular weight (M_n) of the PCULx ranged from 33,000 to 70,000 g/mol. The incorporation of PEG side chains seemingly caused a decrease in M_n for all PEG-grafted samples, which was more obvious in the PCULx-PO (x=1,2,3) group. The glass transition temperature (T_g) of the PUs before and after PEG grafting are compared in Figure 1. For the precursor polymers PCULs, their T_g distributed narrowly from −12 to −10 °C without statistical difference (P>0.05). The glass transition width (ΔT_g) of the PCUL3 seemed narrower than those of the PCUL1 and PCUL2. However, the high standard deviation of these data made them all statistically similar (~20 °C). Within the groups of PCULx-PO, both T_g and ΔT_g increased significantly from sample of x=1 to that of x=3. Compared to each precursor polymer, the PCUL1-PO and PCUL2-PO decreased in T_g value. On the other hand, the PCUL3-PO kept its T_g unchanged (P>0.05), however with an extremely large ΔT_g (50.7 ± 3.4 °C), making the onset temperature the lowermost. Globally, T_g shifted to lower temperature range after PEG-grafting. This trend was also observed in the PCULx-PN group, but to a lesser extent. Except for the PCUL3-PN whose ΔT_g was apparently larger (P<0.05), the PCULx-PN group demonstrated statistically same values of T_g and ΔT_g. The DMF solutions of the PEG-grafted polyurethanes can transform into hydrocolloids when dropped into water, with the hydrophobic backbones surrounding by hydrophilic PEG side chains. The particle size varied among the hydrocolloid samples, ranging from 100 to 190 nm, and the polydispersity index (PDI) scattered between 0.15 and 0.30. Interestingly, zeta potential measurements revealed that the hydrocolloids from PCULx-PO samples were only slightly positively charged (~5 mV) while those from PCULx-PN samples carried much more positive charges (~30 mV). Both blank controls of the PCUL2-PO and PCUL2-PN demonstrated weak self-fluorescence that only large particles could be observed under fluorescence light microscope. On the other hand, the albumin-immobilized samples emitted strong red or green fluorescence, making both large and tiny particles clearly visible.

Conclusions: Functional PCUs have been synthesized. The pedant PEG chains with terminal epoxy or amino groups disordered the hard-segment-dominated phases and plasticized the polyurethanes themselves. The hydrophilic PEG chains were responsible for the formation of colloidal particles. The epoxy groups can react with the amino groups of albumins to immobilize them. The amino groups can help the hydrocolloids capture albumins both chemically and physically. These novel PEG-grafted PUs are intended to form multifunctional conjugates with biomolecules.

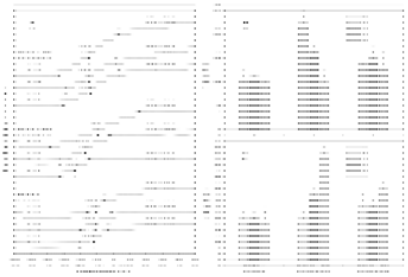

Figure 1. Glass transitions of the polyurethanes. **(A)**: representative glass transition of each polyurethane, where T_g is defined as the middle point of the glass transition indicated by the arrows, and $\Delta T_g = T_g$ (terminal) − T_g (onset), representing the glass transition width between the two triangles. **(B)** and **(C)** show the mean T_g and ΔT_g (n = 3), respectively.