

SYNTHESIS AND CHARACTERIZATION OF AMPHIPHILIC POLY(PROPYLENE SULFIDE)-BASED BLOCK COPOLYMERS. MACROAMPHIPHILES FOR SURFACE FUNCTIONALIZATION AND DRUG DELIVERY SYSTEMS.

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INTRODUCTION: In the present communication we report the synthesis and characterization of functional amphiphilic block copolymers able to assemble in water into lamellar and micellar mesophases (also termed *lyotropic*, induced by the solvent).

When designing such macromolecules, a major effort was devoted in having a simple and reliable chemistry and in introducing novel degradation properties. The result has been a macroamphiphile containing as the hydrophobe a linear atactic poly(propylene sulfide) chain (PPS) and as the hydrophile poly(ethylene glycol) (PEG).

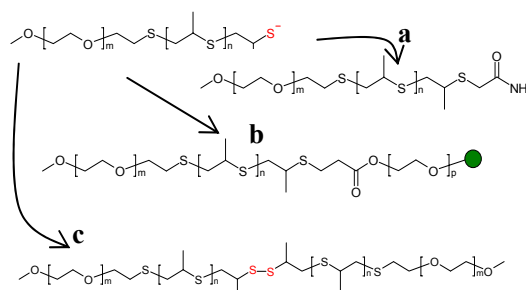
PPS is a “newcomer” in the biomedical field possessing interesting properties like: a low T_g , its conversion into a hydrophile upon exposure to oxidative conditions and the ability to strongly bind to gold (as thiols in SAMs do). Last but not least it is based on thiol chemistry making its functionalization with peptides easy.

METHODS: The synthetic path¹ is based on the anionic ring-opening polymerization of episulfides, initiated by a thiolate group. The initiator is generated in situ from a PEG chain containing a protected thiol (a thio- or dithioester), avoiding the use of free thiols and thus the problems arising from disulfide formation.

The living anionic process produces a polysulfide chain (e.g. poly(propylene sulfide) PPS) with a reactive thiolate end, which was used to couple the polymer with an acrylate-terminated PEG through Michael-type addition or upon exposure to air to form symmetric triblocks bearing a disulfide bridge. The mild character of the end-capping reaction allows the insertion of sensitive biological groups, e.g. peptides and quantitative end-capping with low molecular weight molecules.

The polymerization and the end-capping reaction has been investigated by H^1 -NMR and Gel Permeation Chromatography (GPC).

RESULTS & DISCUSSION: We explored the lyotropic behavior and oxidative stability of the lyotropic mesophases in water of PEG-PPS-PEG, using the $EG_{16}PS_{50}EG_{16}$ symmetric triblock macroamphiphile as an example. We have previously described that this liquid polymer forms lamellar phases in water².



Scheme 1: End-capping for PEG-PPS living polymerization may lead to: a) diblock copolymer using a low molecular weight agent; b) asymmetric triblock using a PEG acrylate; c) by simply exposing the reaction mixture to air, symmetric triblocks are obtained via disulfide bridge formation.

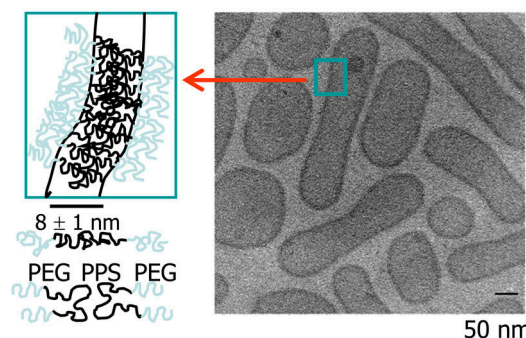


Fig. 1: Vesicles formed by $EG_{16}PS_{50}EG_{16}$ block copolymer imaged by Cryo-TEM (bar represents 50 nm). In the box a scheme of the polymeric membrane with the PPS in black and the PEG chains in cyan.

These copolymers are structurally similar to the well-known poloxamer macroamphiphile (copolymers of PEG and poly(propylene glycol), PPG), but the substitution of S atoms for the O atoms in the PPG block renders the hydrophobe much more hydrophobic and the otherwise relatively unstable poloxamer vesicles into structures that are stable in aqueous environments for months (herein).

REFERENCES: ¹A. Napoli, N. Tirelli, G. Kilcher, J.A. Hubbell (2001) *Macromolecules* **34**:8913. ²A. Napoli, N. Tirelli, E. Wehrli, J.A. Hubbell (2002) *Langmuir* **18**:8324.