Reverse thermo-responsive polymers for *in situ* generated implants

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Introduction

The development of injectable materials to be used in non-invasive surgical procedures, has triggered much attention in recent years.

The "reverse thermo-responsive" phenomenon, usually known as Reverse Thermal Gelation (RTG), constitutes one of the most promising strategies available to researchers in this area. The water solutions of these materials display low viscosity at ambient temperature and exhibit a sharp viscosity increase as temperature rises within a narrow interval, producing semi-solid gels at body temperature.

This contribution describes various of the strategies pursued in our laboratory, aiming at tailoring the rheological, mechanical and biological properties of novel reverse thermo-responsive polymers, expanding, therefore, their clinical applicability. Particularly promising are: (i) The generation of RTG-displaying high molecular weight polymers, and (ii) The use of functionalized building blocks that combine thermo-responsiveness and *in situ* crosslinkability**.**

Materials and Methods

(I) Poly(ether-carbonate)s.[1,3] The synthesis of poly(ethylene glycol) and poly(propylene glycol) chains, using phosgene was carried out following two different pathways: two-step reactions in order to obtain alternating A-B copolymers and one-step reactions to synthesize random ones. The PEO/PPO ratio was determined by ^{1}H-NMR, the characterization of the functional groups was carried out by FT-IR and the molecular weight of the different materials was determined by GPC.

(II) Poly(ether-ester)s.[3] The synthetic pathway described in *(I)* was basically repeated but different diacyl chlorides were used as coupling the molecule, instead of phosgene.

(III) Pluronic F-127 dimethacrylate.[4] F-127 was reacted with methacryloyl chloride, using triethylamine as the base. The crosslinking was done using ammonium persulfate as the initiator or by U.V. adding photo-initiator.

The temperature dependent rheological behavior of the water solutions was analyzed in a Brookfield Viscometer DV-II, with temperature control and T-F spindle at 0.05 cycles *per* minute. The water up-take of the different crosslinked gels was evaluated at diverse temperatures.

Results and Discussion

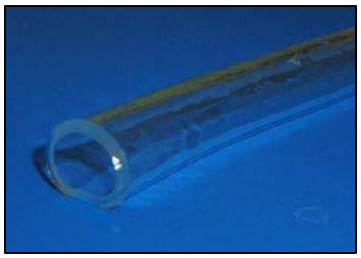
The RTG PEO-PPO-based block copolymers developed in our laboratory have the following basic structures:

$[PEG\text{-}O\text{-}CO\text{-}O\text{-}PPG]_p$ poly(ether-carbonate)

$[PEG\text{-}O\text{-}CO\text{-}X\text{-}CO\text{-}O\text{-}PPG]_p$ poly(ether-ester)

where p is the degree of polymerization. The new gels displayed at 37^{o}C markedly higher viscosities, enhanced stability as well as longer residence times *in vitro*. The figure below exemplifies the viscosity *vs.* temperature profile of these polymers. While the 15% (w/w) F127 solution achieved a modest 5,000 Pa.s maximum viscosity, a [PEG6000-O-CO-O-PPG3000]p random poly(ether-carbonate) solution of the same concentration, attained viscosities above 70,000 Pa.s.

Following a similar working concept, PEO-PPO-PEO triblocks were functionalized with methacryloyl moieties, rendering crosslinkable aqueous solutions. The hydrogels generated presented highly improved mechanical properties.[4] Also, ethoxysilane-capped PEO-PPO-PEO triblocks were synthesized and their mechanical properties gradually increasde over time, as the system crosslinked under pseudo-physiological conditions. For example, a 30%wt gel of this polymer achieved a 2.6 MPa compression modulus after 5 days. The objective of the "*in situ* generated implants" area is not only to deploy materials, but to engineer structures at a precise body site, having specific geometric and mechanical charcteristics. This study presents, therefore, the production of RTG-based constructs (e.g. tubular conduits, as shown in the figure below), capitalizing on the improved mechanical properties of the reverse thermo-responsive polymers developed



Mono-layered structures as well as conduits comprising two and three layers were engineered in vitro and their mechanical response (burst strength, compliance), will be presented.

References

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