Tetrahydrofuran (co)polymers as Potential Materials for Vascular Prostheses

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Abstract: Polyethers were studied as potential materials for vascular prostheses. By crosslinking poly(tetramethylene oxide) (PTMO) with poly(ethylene oxide) (PEO), hydrophilic networks were obtained containing PTMO as well as PEO. Attempts were made to reduce the crystallinity and melting point of PTMO because of the required elastomeric behaviour at body temperature. Compared to non-crosslinked PTMO, crosslinking in the melt resulted in a decrease in the melting point from 43.7 to 38.4 °C and a decrease of the crystallinity from 46 to 28%. By copolymerizing tetrahydrofuran with oxetane or dimethyloxetane, melting points below 38 °C were obtained, together with crystallinities lower than 20%.

INTRODUCTION

For the application of polymers for vascular prostheses, hydrophilicity and elastomeric behaviour at body temperature are important parameters. From reports of studies on copolyetherurethanes,¹ Bots *et al.*² derived the hypothesis that polyethers might be promising materials. Poly(ethylene oxide) (PEO) was chosen as the biocompatible, hydrophilic component, and atactic poly(propylene oxide) (PPOx) as the more hydrophobic and mechanically stronger one. Cross-linked blends of PEO and PPOx (ratio : 10/90) appeared hydrophilic and very blood-compatible. *In vitro*, low protein adsorption, platelet adhesion and kallikrein generation was found, as well as a high APTT value. *In vivo*, in the abdominal aorta of rats, no thrombus formation could be detected during the 6 weeks after implantation and furthermore, a thin neointima of smooth muscle cells, lined by an endothelial lining on the surface of the grafts, was found. However, the implantation experiments also showed that the polyether grafts had a limited dimensional stability, which was probably due to thermo-oxidative degradation of PPOx; PPOx contains tertiary hydrogen atoms in the main chain, which are sensitive to oxidation.

This paper reports investigations of homo- and copolymers of tetramethylene oxide as part of our study of the applicability of polyethers for vascular prostheses. Poly(tetramethylene oxide) (PTMO) was studied because this polymer has no tertiary hydrogen atoms in the main chain and will probably be less susceptible to thermo-oxidative attack. From preliminary experiments it could be concluded that UV treatment of mixtures of PTMO and PEO and a crosslinking agent, dicumyl peroxide (DCP), had resulted in the formation of polymer networks, differing in hydrophilicity and containing PTMO as well as PEO.

However, PTMO is semi-crystalline with a melting point higher than 37 °C. Crystallinity not only leads to non-elastomeric behaviour, but semi-crystalline polymers have also been reported to be more reactive than their non-crystalline counterparts with respect to platelet activation.³

In this study, attempts were made to decrease the crystallinity and the melting point by crosslinking of PTMO at various temperatures and by copolymerization of tetrahydrofuran with oxetane (OX) or dimethyloxetane (DMOX).

EXPERIMENTAL

Materials

Monomers and solvents

- Tetrahydrofuran (THF) (Merck) was refluxed over and distilled from sodium wire prior to use.
- Dimethyloxetane (DMOX) was prepared by addition of a 2,2-dimethyl-1,3-propanediol (Merck) solution in H_2SO_4 to a boiling aqueous NaOH solution, according to the method of Shmoyer and Case.⁴
- DMOX and Oxetane (OX) (Fluka) were refluxed over and distilled from KOH prior to use.
- Toluene (Merck) and dichloromethane (Merck) were used as received.
- Dicumyl peroxide (DCP) (Merck), recrystallized twice from methanol, was used as the crosslinking agent.
- SbCl_5 (Aldrich; 1.0 M solution in CH_2Cl_2) was used as received.
- $\text{Al}(i\text{-Bu})_3 \cdot 0.5\text{H}_2\text{O}$ complex was prepared from $\text{Al}(i\text{-Bu})_3$ (Aldrich; 1.0 M solution in toluene) by the addition of water at 0°C .⁵

Polymers

- High molecular weight PEO ($\bar{M}_w = 6 \times 10^5$ and 5×10^6 g/mol) was purchased from BDH Chemicals and Aldrich, respectively.
- High molecular weight PTMO ($T_m = 43.7^\circ\text{C}$, $X_c = 46\%$, $\bar{M}_n = 1.9 \times 10^5$ g/mol; $\bar{M}_w = 4.5 \times 10^5$ g/mol; η_{inh} (inherent viscosity) = 2.8 dl/g (0.25% in toluene)) was synthesized by bulk polymerization of THF with SbCl_5 as catalyst.
- Poly(THF-co-OX) ($\eta_{\text{inh}} = 1.8$ dl/g (0.25% in toluene)) and poly(THF-co-DMOX) ($\eta_{\text{inh}} = 2.2$ dl/g (0.25% in toluene)) were prepared by bulk copolymerization of THF/OX and THF/DMOX mixtures respectively with $\text{Al}(i\text{-Bu})_3 \cdot 0.5\text{H}_2\text{O}$ complex as catalyst.

METHODS

Film preparation

Polymers or mixtures of polymers and DCP (always 2 parts DCP per hundred parts total polymer) were dissolved in CH_2Cl_2 and films were cast from viscous 5% (w/v) solutions, followed by evaporation of the solvent under a hood overnight.

Crosslinking was induced by UV-irradiation (2 h per side) at a distance of 10 cm from a Hanau

Lamp TQ81 (wave length: 254 nm) in a nitrogen atmosphere.

Film characterization

Swelling behaviour

Irradiated films were swollen in water or toluene for 48 h, in which equilibrium swelling was reached, followed by drying the films to constant weight. The swelling is given by the weight ratio of the swollen and the dried films ($W_{\text{wet}}/W_{\text{dry}}$).

DSC analysis

The thermal properties of the films were studied using a Perkin-Elmer DSC 7 Differential Scanning Calorimeter. Crystallinities (X_c) were calculated from the heats of fusion using a value of 167 J/g for the enthalpy of melting for PTMO.⁶

Indium and gallium were used to calibrate the temperature scale and to determine the heat of fusion.

Before heating, the samples were cooled to 0°C and kept there for 5 min.

RESULTS AND DISCUSSION

Characterization of crosslinked PTMO/PEO blends

Blends of PTMO/PEO/DCP were crosslinked by

Fig. 1. Swelling of crosslinked PTMO/PEO/DCP blends as a function of the PEO weight fraction (● = in water; ○ = in toluene).

Fig. 2. Swelling in toluene of PTMO/DCP films (100/2) crosslinked with UV at 20 °C (○) and at 60 °C (●).

Table 1. Melting points T_m and crystallinities X_c (recorded at a heating rate of 2 °C/min). Films were kept at room temperature for 7 weeks after heating to 80 °C

	T_m (°C)	X_c (%)
PTMO/DCP (not crosslinked)	43.7	46
PTMO/DCP (crosslinked at 20 °C)	41.0	37
PTMO/DCP (crosslinked at 60 °C)	38.4	28

Crosslinking of PTMO at various temperatures

Effect on crosslinking density

Crosslinking of PTMO in the melt phase (60 °C) occurred much faster than at 20 °C with the semi-crystalline PTMO (Fig. 2). Furthermore, crosslinking at 60 °C led to a somewhat higher crosslinking density. These results are in agreement with reports from Chen and Rånby⁷ that crosslinking of (semi-crystalline) poly(ethylene) (PE) above T_m leads to a higher crosslinking density than crosslinking in the solid state.

Effect on T_m /crystallinity

PTMO/DCP films, non-crosslinked, crosslinked by UV treatment at 20 °C and 60 °C, respectively, were heated to 80 °C to allow complete melting. They were subsequently kept at 20 °C for 7 weeks because of the possibility of a time-dependent secondary crystallization of PTMO, leading to an increase of T_m and the crystallinity.^{8,9} Table 1 shows the results of the DSC analysis of the films and it is obvious that crosslinking in the solid state (20 °C)

UV treatment and the swelling in water (solvent for PEO, non-solvent for PTMO) and in toluene (solvent for PTMO, non-solvent for PEO) was determined (Fig. 1). Because swelling in water as well as in toluene was observed, it could be concluded that in the networks both PTMO and PEO were incorporated.

Although further characterization of the crosslinked systems was not studied extensively, DSC measurements indicated phase separation of PTMO and PEO.

Fig. 3. DSC curves of PTMO/DCP films (100/2) crosslinked at 20 °C, measured at 20 °C (A) and at 37 °C (B) (heating rate: 2 °C/min).

Table 2. Effect of copolymerizations of THF with OX or DMOX on T_m and X_c

	<i>Poly(THF-co-OX)</i> (mole fractions)	<i>Poly(THF-co-DMOX)</i> (mole fractions)
Monomeric unit		
-CH ₂ -CH ₂ -CH ₂ -CH ₂ -O-	0.908	0.936
-CH ₂ -CH ₂ -CH ₂ -O-	0.092	
-CH ₂ -C(CH ₃) ₂ -CH ₂ -O-		0.064
T_m (°C)	33.7	33.8
X_c (%)	13	17

leads to a decrease of T_m and the crystallinity. Crosslinking at 60 °C resulted in a further decrease of both the T_m and the crystallinity, clearly indicating the effect of a decreased order in the melt phase.

Compared to the results of Chen and Rånby¹⁰ and of Dijkstra *et al.*¹¹ regarding the effect of crosslinking of PE in the melt on T_m and the crystallinity, the decrease of T_m for PTMO is less pronounced. Increasing the amount of DCP will increase the crosslinking density and might lead to larger melting point depressions, but will probably have a negative effect on the mechanical properties of PTMO, such as tear strength and elongation at break.

It should be noted, on the other hand, that Table 1 gives DSC data from measurements at 20 °C. The degree of crystallinity of crosslinked PTMO was found to be significantly lower at 37 °C, as can be seen from Fig. 3 (films crosslinked at 20 °C, but not heated to 80 °C).

Copolymerization

THF was copolymerized to investigate the effect of comonomers on T_m and X_c , because insertion of other monomeric units in the polymeric chains will disturb the regularity. Oxetane (OX) and dimethyloxetane (DMOX) were chosen because polymers will be obtained without tertiary hydrogen atoms in the main chain. In Table 2 the composition of the copolymers is given together with data for T_m and X_c .

The results show that copolymerization is much more effective in decreasing T_m and X_c than crosslinking of PTMO (Table 1).

These copolymers are interesting as materials for vascular prostheses because they show elastomeric behaviour at 37 °C. Therefore, research on the crosslinking of these copolymers with PEO is planned for the future.

CONCLUDING REMARKS

Although a certain decrease of crystallinity and melting point depression of PTMO was achieved by crosslinking in the melt, further research is necessary for a reliable evaluation of PTMO as a potential material for vascular grafts. By copolymerization of tetrahydrofuran with oxetane or dimethyloxetane, the crystallinity and melting point could be reduced significantly, and therefore copolymerizations are being studied in more detail.

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