Stereocomplex Mediated Gelation of PEG-$(PLA)_2$ and PEG-$(PLA)_8$ Block Copolymers

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Summary: Stereocomplex mediated hydrogels have been prepared by mixing solutions of polymers of opposite chirality of either PEG-$(PLA)_2$ triblock copolymers or PEG-$(PLA)_8$ star block copolymers. The critical gel concentrations of the mixed enantiomer solutions were considerably lower compared to polymer solutions containing only the single enantiomer. Moreover, gel-sol transition temperatures were increased and gel regions were expanded due to stereocomplexation. Rheology measurements showed that stereocomplexed hydrogels based on PEG-$(PLA)_8$ have higher storage moduli compared to those based on PEG-$(PLA)_2$. Stereocomplexed hydrogels prepared from 13 wt% PEG-$(PLA)_2$ solutions in PBS showed a storage modulus of 0.9 kPa at 37 °C, while at similar conditions stereocomplexed hydrogels of PEG-$(PLA)_8$ showed a storage modulus of 1.9 kPa at 10 wt%.

Keywords: biodegradable; block copolymers; gelation; hydrogels; poly(ethylene glycol)-poly(lactide); stereocomplexation

Introduction

Hydrogels are highly attractive materials for use in biomedical applications, such as tissue engineering and drug delivery, since they possess good biocompatibility due to their high hydrophilicity. Block copolymers of PEG and aliphatic polyesters are of interest in this respect, since PEG is known to have excellent antifouling properties and biocompatibility and is excreted by the kidney at molecular weights up to ca. 30,000.[1] Aliphatic polyesters such as poly(lactide) (PLA) and poly(lactide-*co*-glycolide) (PLGA) are known to be biocompatible and are biodegradable. Block copolymers of PEG and PLA or PLGA form physically crosslinked hydrogels at relatively high concentrations and show a gel to sol transition close to body temperature.[2,3] Recently, several research groups have shown that hydrogels can be prepared from water-soluble PDLA and PLLA based block copolymers, in which the physical crosslinks are provided by stereocomplexation between the enantiomeric PDLA and PLLA blocks. Examples of such physically crosslinked hydrogels include dextran-lactate hydrogels[4] and hydrogels based on PEG-PLA triblock

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copolymers with either a central PEG[5-7] or PLA[8] block. Recently, Li et al.[6] showed that upon mixing 15 wt% polymer solutions containing equimolar amounts of $PDLA_{20}$-PEG8000-$PDLA_{20}$ and $PLLA_{18}$-PEG8000-$PLLA_{18}$, a turbid hydrogel was obtained up to at least 37 °C. This gel has storage moduli of 1.1 kPa and ~0.2 kPa at 20 and 37 °C, respectively. The formation of stereocomplexes within the hydrogels was confirmed by Raman spectroscopy on the hydrogels and X-ray on the lyophilized hydrogels. Fujiwara et al.[7] prepared $PDLA_{15}$-PEG4600-$PDLA_{15}$ and $PLLA_{18}$-PEG4600-$PLLA_{18}$ block copolymers and showed that gelation occurred after mixing 10 wt% polymer solutions containing equimolar amounts of both enantiomers and heating to 37 °C. They ascribed the gelation at 37 °C to weakening of the hydrophobic PLA core at increased temperature, which allows mixing of D- and L-enantiomeric blocks. This gel has a storage modulus of ~1 kPa between 37 and 70 °C. WAXS experiments confirmed the presence of the stereocomplexes within the hydrogel at 37 °C and also at 75 °C. Mukose et al.[8] prepared hydrogels by mixing 35 wt% aqueous solutions containing equimolar amounts of PEG2000-$PDLA_{28}$-PEG2000 and PEG2000-$PLLA_{28}$-PEG2000, and heating the mixed solution to 37 °C. Gelation was thought to be the due to the complementary helix formation of the PEG chains induced by the complementary PDLA and PLLA helices. This gel has a relatively high storage modulus of 31 kPa, which was attributed to the high polymer concentration. The stereocomplexed PEG-PLA hydrogels may be useful materials for biomedical applications, such as drug delivery and tissue engineering. Regarding PEG-PLA block copolymer systems with PLA end blocks, materials with improved mechanical properties are of interest. In this paper we describe the synthesis, characterization and hydrogel formation of PEG-$(PLA)_2$ triblock and PEG-$(PLA)_8$ star block copolymers and the effect of the number of stereocomplex interaction sites on the gelation behavior.

Experimental Methods

Materials. D-lactide and L-lactide were obtained from Purac and recrystallised from dry toluene. Dihydroxyl PEG ($M_{n,\,NMR}$ = 12500, denoted as PEG12500) and star PEG ($M_{n,\,NMR}$ = 21800, denoted as PEG21800) were supplied by Fluka and Nektar, respectively, and were dried by azeotropic distillation from toluene. Stannous octoate (tin(II) bis(2-ethylhexanoate), $Sn(Oct)_2$, was purchased from Sigma and used as received. The single site Zn-complex catalyst $Zn(Et)[SC_6H_4(CH(Me)NC_5H_{10})\text{-}2]$ was kindly provided by Professor G. van Koten of the University of Utrecht (The Netherlands).

Synthesis. All reactions were performed using Schlenck techniques. PEG-$(PLA)_2$ block copolymers were prepared by the $Sn(Oct)_2$ catalyzed ring opening polymerization of D- or L-lactide initiated by hydroxyl groups of PEG-$(OH)_2$ at 105 °C in toluene for 4 h under an argon atmosphere. In a typical experiment PEG12500 (2.490 g, 0.199 mmol) and lactide (0.510 g, 3.54 mmol) were dissolved in 7.1 mL of toluene at 105 °C (monomer concentration is 0.5 M). To this solution 1 drop of $Sn(Oct)_2$ was added and the polymerization mixture was stirred for 4 h. The polymerization was terminated by the addition of a small amount of glacial acetic acid under stirring. The solution was concentrated under reduced pressure and the polymer was precipitated in a mixture of cold diethyl ether/methanol (20/1 v/v). After filtration, the polymer was dried under reduced pressure for 2 days at room temperature. Conversion: 89%, yield: 75%. ^{1}H NMR ($CDCl_3$): 1.5 (m, 3H, CH_3CH), 1.4 (m, 3H, CH_3CHOH end group PLA), 3.6 (m, 4H, CH_2O), 4.2-4.3 (m, 2H, CH_2CO, linking unit PEG), 4.3-4.4 (q, 1H, *CH*OH end group PLA), (m, 1H, *CH*CO).

PEG-$(PLA)_8$ star block copolymers were prepared similarly at room temperature in dichloromethane for 4 h using the single site Zn-complex catalyst $Zn(Et)[SC_6H_4(CH(Me)NC_5H_{10})$-2]. In a typical experiment PEG21800 (0.730 g, 0.0335 mmol) and lactide (0.270 g, 0.188 mmol) were dissolved in 7.5 mL of dichloromethane at room temperature (monomer concentration is 0.25 M). To this solution, a solution of single site Zn-complex catalyst (0.040 g, 0.134 mmol) in 1 mL of dichloromethane was added and the reaction mixture was stirred for 4 h (molar ratio of hydroxyl groups of PEG21800 to Zn-complex catalyst is 2 : 1). Termination, precipitation and drying methods were similar to those used for the PEG-$(PLA)_2$ block copolymers, as described above. Conversion: 98%, yield: 89%. ^{1}H NMR ($CDCl_3$): 1.5 (m, 3H, CH_3CH), 1.4 (m, 3H, CH_3CHOH end group PLA), 3.6 (m, 4H, CH_2O), 4.2-4.3 (m, 2H, CH_2CO, linking unit PEG), 4.3-4.4 (q, 1H, *CH*OH end group PLA), (m, 1H, *CH*CO).

Characterization. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Varian Inova Spectrometer (Varian, Palo Alto, USA) operating at 300 MHz. The number of lactyl units per PLA block were calculated rationing the respective areas of the peaks corresponding to the methyl group of lactyl units at $\delta = 1.5$ and the methylene groups of PEG at $\delta = 3.6$.

Differential Scanning Calorimetry (DSC) measurements were performed using a DSC7 (Perkin-Elmer). The polymer was first heated from 30 to 200 °C, kept at 200 °C for 2 min, quenched to 30 °C, kept at 30 °C for 2 min and heated to 200 °C. Heating and cooling rates were always 20 °C /min. The second heating curve was used for thermal analysis.

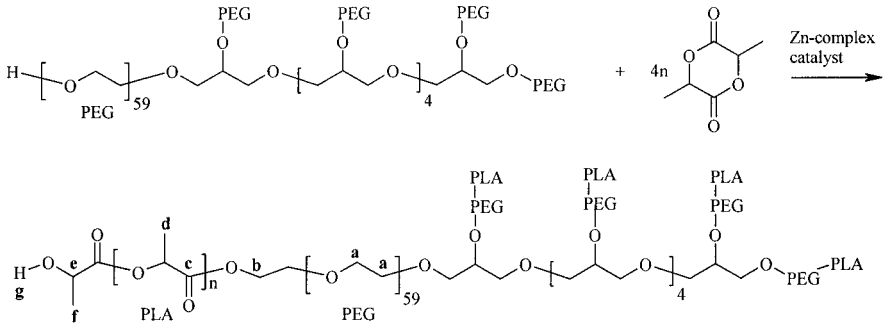
For the determination of gel-sol transitions, aqueous polymer solutions were prepared by dissolving the appropriate amount of polymer in distilled water at room temperature. Solutions containing equimolar amounts of enantiomeric block copolymers were prepared by mixing polymer solutions and vigorously stirring for ~2 min. For both single enantiomer solutions and polymer solutions containing both D- and L-enantiomer, temperature dependent phase behavior was studied using the vial tilting method at temperatures between 5 and 70 °C with intervals of 2 °C. At each temperature, the samples were allowed to equilibrate for at least 10 min. No flow within 20 seconds while inverting the vial was regarded as a gel state.

Rheology experiments were performed on a US 200 Rheometer (Anton Paar). Aqueous polymer solutions of PEG12500-$(PDLA_{15})_2$, PEG12500-$(PLLA_{15})_2$, PEG21800-$(PDLA_{14})_8$ and PEG21800-$(PLLA_{14})_8$ were prepared by dissolving the appropriate amount of polymer in distilled water or PBS at room temperature. Polymer solutions containing equimolar amounts of D- and L-enantiomer of PEG12500-$(PLA_{15})_2$ or PEG21800-$(PLA_{14})_8$ at a concentration of 13 wt% and 10 wt%, respectively, were mixed, homogenized and quickly applied to the rheometer. A flat plate measuring geometry was used (25 mm diameter, gap 0.5 mm). To prevent the evaporation of water, a layer of oil was put around the polymer sample. Gelation of the polymer solutions was monitored by measuring the shear storage modulus G' as well as the loss modulus G" at 20 °C or 37 °C for 48 h. A frequency ω of 1 Hz and a strain γ of 1% were applied to minimize the influence of the deformation on the formation of the hydrogels. This strain is within the linear viscoelastic range. After gelation, amplitude and frequency sweeps were performed at, respectively, γ = 0.01-10% (ω = 1 Hz) and ω = 0.01-10 Hz (γ = 1%). Subsequently, the temperature was increased to 60 °C at 1.4 °C/min or 1 °C/min (ω = 1 Hz, γ = 1%).

Results and Discussion

Synthesis and characterization. A convenient way to prepare PEG-PLA block copolymers is the $Sn(Oct)_2$ catalyzed ring opening polymerization of lactide initiated by hydroxyl end groups of PEG12500 in toluene at 105 °C.[9] The ^1H NMR spectra of the synthesized PEG-$(PLA)_2$ block copolymers revealed that all PEG hydroxyl groups initiated the ring opening polymerization and that the polymers have a well-defined block copolymer structure. The lengths of the obtained PLA blocks, calculated from the ^1H NMR spectra, are close to the theoretical values (Table 1).

PEG-$(PLA)_8$ star block copolymers were analogously prepared by ring opening polymerization of L- or D-lactide in the presence of star PEG21800 and the single site Zn-complex catalyst Zn(Et)[$SC_6H_4(CH(Me)NC_5H_{10})$-2] in dichloromethane at room temperature for 4 h (Scheme I). The advantage of the use of a single site Zn-complex catalyst is the prevention of gelation of the reaction mixture. The ^{1}H NMR spectra of the reaction mixtures revealed high monomer conversions (>97%) (Table 1). A typical ^{1}H NMR spectrum of purified PEG21800-$(PLA_{14})_8$ is shown in Figure 1. Signals at δ = 2.7 and 4.3-4.4 are assigned to hydroxyl end groups and methine end groups of PLA, respectively. The chemical shift of the hydroxyl end groups was confirmed by the addition of trifluoroacetic anhydride, since the signal at δ = 2.7 disappeared completely and the methine protons were shifted to δ = 5.3.



Scheme I. Ring opening polymerization of lactide initiated by PEG21800-$(OH)_8$.

A peak corresponding to methylene end groups of PEG linked to a trifluoroacetyl group was not observed, indicating that all hydroxyl groups of PEG initiated the ring opening polymerization of lactide. Furthermore, the block copolymer structure is confirmed by the presence of a quartet at δ = 4.2-4.3, corresponding to the methylene protons of PEG connected to the PLA blocks. The average block length of the PLA blocks was calculated from the ^{1}H NMR spectra of the block copolymers by rationing the respective areas of the peaks corresponding to the methyl group of lactyl units and the methylene groups of PEG. As shown in Table 1 the obtained PLA block lengths are close to the theoretical values based on the feed composition and conversion. In conclusion, well-defined PEG-$(PLA)_8$

star block copolymers of desired molecular weights could be prepared by the Zn-complex catalyzed ring opening polymerization of lactide.

Differential Scanning Calorimetry thermograms of both triblock and star block copolymers in the solid state showed a single melting endotherm in between 40 and 60 °C due to melting of the PEG crystals. The absence of a melting endotherm at higher temperatures revealed that the PLA blocks are in the amorphous state. This is regarded as beneficial, since crystallization of PLA blocks is expected to decrease the water solubility of the PEG-PLA block copolymer and also may hamper stereocomplex formation.

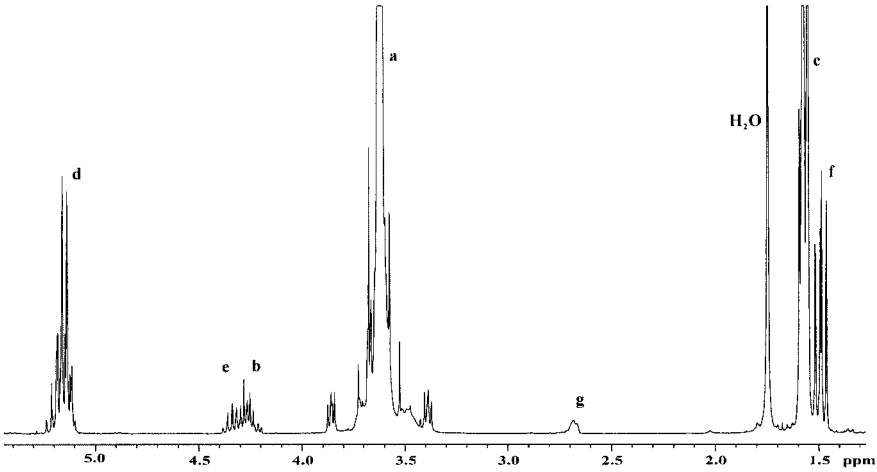


Figure 1. ^{1}H NMR ($CDCl_3$) spectrum of PEG21800-$(PLA_{14})_8$ star block copolymer.

Solubility. The solubility of PEG12500-$(PLA)_2$ block copolymers in distilled water at room temperature was found to decrease rapidly upon increasing the PLA block length. When the number of lactyl units per PLA block was higher than 22, the copolymer was not water-soluble anymore at or above a polymer concentration of 10 wt%. This result agrees well with that found by Vert et al. for similar PEG-$(PLA)_2$ block copolymers.[6]

Gelation behavior. The influence of stereocomplexation on the gelation behavior of aqueous solutions containing equimolar amounts of PEG12500-$(PDLA)_2$ and PEG12500-$(PLLA)_2$ polymers was studied at room temperature. Aqueous solutions of the block copolymers with similar PLA block lengths were mixed and, after at least 1 day of equilibration, the occurrence of a gel phase was tested by the vial tilting method. All triblock copolymers studied showed gelation upon mixing of both enantiomer solutions, while the single enantiomer solutions did not form a gel at similar concentrations. The

Table 1. Composition and molecular weight of PEG12500-$(PLA)_2$ and PEG21800-$(PLA)_8$ block copolymers.

Polymer	Conversion (%)	N_{LA} [a]		M_n	PEG content (wt%)
		Theory [b]	Found [c]		
PEG12500-$(PDLA)_2$	83	10	10	14000	90
	89	16	15	14700	85
	88	20	19	15200	82
PEG12500-$(PLLA)_2$	88	9	10	13900	90
	86	16	15	14700	85
	90	20	19	15300	82
PEG21800-$(PDLA)_8$	98	14	14	29800	74
PEG21800-$(PLLA)_8$	98	14	14	29500	74

a) Number of lactyl units per PLA block.
b) Based on feed composition and conversion.
c) Calculated from ^{1}H NMR integral ratios.

gelation upon mixing solutions of polymers of opposite chirality is illustrated for 10 wt% solutions of PEG12500-$(PLA_{15})_2$ in Figure 2. The critical gel concentration (CGC) at room temperature was found to decrease sharply upon increasing the PLA block length from 10 to 15 lactyl units, while a further increase to 19 lactyl units only caused a minor decrease in CGC (Table 2). It should be noted that enantiomeric triblock copolymers also afford hydrogels at relatively high concentrations at room temperature (Table 2). Considering biomedical applications, like the engineering of soft tissues or drug delivery systems, it is desirable that the cells or molecules to be incorporated may be suspended into these single enantiomer solutions, which upon mixing and stereocomplexation form a hydrogel.

It is well known that upon increasing the hydrophobic block length the CGC is decreased, due to an increase in micelle number and size.[10,11] In addition, BAB type of polymers,

Figure 2. 12500-$(PDLA_{15})_2$ 13 wt% solution (D) and PEG12500-$(PDLA_{15})_2$ + PEG12500-$(PLLA_{15})_2$ 13 wt% hydrogel (D+L) at room temperature.

where B and A are hydrophobic and hydrophilic blocks, respectively, show increased intermolecular and intermicellar association upon increasing hydrophobic block length.[12-14] The gelation upon mixing of aqueous solutions of PEG12500-$(PLA)_2$ polymers of opposite chirality is driven by the stereocomplexation of the PDLA and PLLA blocks, as their precursor single enantiomer solutions stayed fluid-like. Stereocomplexation enhances interactions between the hydrophobic blocks and lowers the CGC, like when increasing PLA block length. The lowering in CGC may be due to similar changes in micelle number, size and association as observed when increasing PLA block length. The decrease in CGC may also be due to an increase in crystallinity or chain packing tendency of the hydrophobic block, as has been proposed by Jeong et al. when comparing PEG-PLLA and PEG-PDLLA diblock copolymers.[15] Eleven lactyl units have been reported to be required for gelation by stereocomplexation.[16] Therefore, the stereocomplexation at 10 lactyl units may not be very efficient. Due to the polydispersity of the PLA blocks, some blocks may be long enough for stereocomplexation, while shorter blocks may only interact weakly.[17] The reduced stereocomplexation at 10 lactyl units may explain the sharp decrease in CGC when going from 10 to 15 lactyl units. The relatively small decrease in CGC when the number of lactyl units is increased from 15 to 19 per PLA block may be the result of a decrease in stereocomplexation efficiency, due to an increased density of the PLA core and a decrease in water solubility as the PLA block length increases, which hampers mixing of D- and L-enantiomer blocks and stereocomplexation.

Table 2. Critical gel concentrations of PEG-PLA block copolymers in distilled water at room temperature.

Polymer	Critical gel concentration (wt%)	
	Single enantiomer	Mixed enantiomers
PEG12500-$(PLA_{10})_2$	80	30
PEG12500-$(PLA_{15})_2$	15	10
PEG12500-$(PLA_{19})_2$	10	7.5
PEG21800-$(PLA_{14})_8$	15	5

The PEG21800-$(PLA_{14})_8$ star block copolymer also showed stereocomplex mediated gelation. The stereocomplexed hydrogel was formed at a relatively low CGC, which is

attributed to the lower PEG content of 74 wt% and increased stereocomplex interaction sites compared to the PEG12500-$(PLA)_2$ polymers (Table 1).

Temperature dependent phase behavior of PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ block copolymer hydrogels was studied by the vial tilting method in a temperature range of 5-70 °C. Figure 3 shows that upon increasing temperature both single enantiomer and stereocomplexed hydrogels of PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ polymers may turn into a mobile phase, which is denoted as the sol-phase. In contrast to PEG12500-$(PLA_{15})_2$ hydrogels, which formed a clear fluid phase, PEG21800-$(PLA_{14})_8$ hydrogels exhibited phase separation, resulting in a clear fluid and a viscous opaque phase, caused by dehydration of the PEG chains. The different phase behavior is probably due to the lower PEG content of the PEG21800-$(PLA_{14})_8$ polymer. The gel-sol transition temperatures of PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ single enantiomer hydrogels are very similar, which indicates that hydrogel gel to sol transition temperature depends predominantly on the PLA block length. Stereocomplexed hydrogels of PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ showed the same trend. PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ hydrogels containing equimolar amounts of D- and L-enantiomers show gel-sol transitions that are shifted to much higher temperatures and the gel regions are expanded compared to the single enantiomer hydrogels at equal concentrations. The increased gel to sol transition temperatures of the stereocomplexed hydrogels is attributed to the stereocomplex formation and may be explained by factors that are also responsible for the lowering of the CGC. The gel-sol transition which occurs upon increasing temperature of amphiphilic PEG block copolymers has been proposed to be due to the disruption of the micelle packing structure, due to a decrease in effective diameter of the micelles as a result of partial PEG dehydration.[10] Li et al.[6] have suggested for stereocomplexed PLA-PEG-PLA hydrogels that the gel-sol transition upon increasing temperature is due to a decrease in the number of stereocomplex crosslinks, caused by a shift in the equilibrium from stereocomplexation to simple D/L interactions in the amorphous state that contribute less to crosslinking. However, Fujiwara et al.[7] have shown by WAXS measurements on stereocomplexed hydrogels that stereocomplexes are present up to at least 75 °C.

Rheology. To confirm the stereocomplex mediated hydrogel formation and to gain insight into hydrogel properties, oscillatory rheology experiments were performed on polymer solutions containing equimolar amounts of D- and L-enantiomer of PEG12500-$(PLA_{15})_2$ or PEG21800-$(PLA_{14})_8$. Gel formation kinetics were studied by monitoring

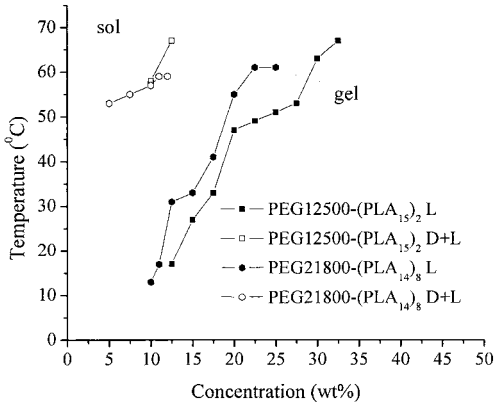


Figure 3. Gel-sol diagram of hydrogels from PEG12500-$(PLA_{15})_2$ or PEG21800-$(PLA_{14})_8$ block copolymers containing either single enantiomer or both D- and L-enantiomer in equimolar amounts.

the storage modulus (G') and loss modulus (G") in time (Figure 4a) for 48 h after mixing polymer solutions of opposite chirality. To study the influence of the gelation temperature and the solvent, PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ stereocomplexed hydrogels containing 13 wt% and 10 wt% of polymer, respectively, were prepared in water at 20 and 37 °C or in PBS at 37 °C. As shown in Figure 4a, the storage moduli of PEG12500-$(PLA_{15})_2$ hydrogels increase rapidly during the first 10 h and finally level off at approximately 48 h, after which gelation is complete.

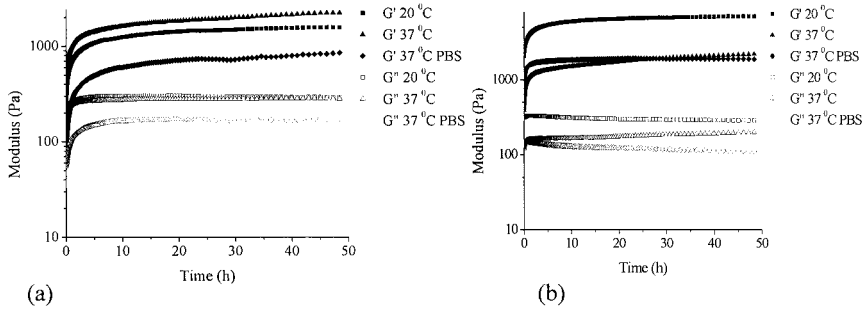


Figure 4. Storage modulus (G') and loss modulus (G") evolutions after mixing enantiomer solutions in water or PBS at 20 °C or 37 °C containing either PEG12500-$(PLA_{15})_2$ 13 wt% (a) or PEG21800-$(PLA_{14})_8$ 10 wt% (b) as a function of time.

The storage and loss moduli are listed in Table 3. The crossing of the storage and loss modulus, which is close to the gel point,[18,19] was not observed, showing that the gel is formed almost instantaneously upon mixing of D- and L- enantiomer solutions. Interestingly, PEG12500-$(PLA_{15})_2$ hydrogels showed a somewhat higher storage modulus when the hydrogel was prepared in water at 37 °C (2.2 kPa) compared to the hydrogel prepared in water at 20 °C (1.6 kPa). This may be due to the increased kinetics and/or an increased aggregation tendency at 37 °C, resulting in an increase in stereocomplex interactions between PDLA and PLLA blocks. The PEG12500-$(PLA_{15})_2$ hydrogel could also be formed upon mixing of polymer solutions containing equimolar amounts of D- and L-enantiomer in PBS. For biomedical applications PBS can be used as a solvent, since it has similar osmolarity as most body fluids. The storage modulus of the hydrogel prepared in PBS (0.9 kPa) is lower compared to the hydrogel in water, which is attributed to the reduction in the effective hard sphere volume of the micelles in the salt solution, which is a poorer solvent.[20-22] Storage moduli found for the PEG12500-$(PLA_{15})_2$ hydrogels agree well with previously reported values on similar PEG-$(PLA)_2$ hydrogels.[6,7] As shown in Figure 4b the gelation of the mixed enantiomer solutions of PEG21800-$(PLA_{14})_8$ reveals somewhat faster gelation kinetics as the PEG12500-$(PLA_{15})_2$ hydrogels. Gelation occurred instantaneously upon mixing polymer solutions of opposite chirality and was completed within approximately 48 h. As summarized in Table 3, 10 wt% PEG21800-$(PLA_{14})_8$ hydrogels have higher storage moduli compared to the 13 wt% PEG12500-$(PLA_{15})_2$ hydrogels, which is attributed to the increased stereocomplex interaction sites of the PEG21800-$(PLA_{14})_8$ polymer, causing an increase in crosslinking density. PBS has a negligible effect on the storage modulus of PEG21800-$(PLA_{14})_8$ hydrogels, in contrast to PEG12500-$(PLA_{15})_2$ hydrogels. The storage modulus of the PEG21800-$(PLA_{14})_8$ hydrogels prepared in water at 37 °C (2.2 kPa) is considerably lowered compared to the hydrogels prepared in water at 20 °C (7.0 kPa), in contrast to the PEG12500-$(PLA_{15})_2$ hydrogels. This difference may be due to the lower water solubility of the PEG21800-$(PLA_{14})_8$, which is also seen by the increased turbidity of the PEG21800-$(PLA_{14})_8$ hydrogels with increasing temperature, while the PEG12500-$(PLA_{15})_2$ hydrogels stayed transparent. The lower solubility may cause formation of dense aggregates at 37 °C, which hampers mixing of D- and L-enantiomers and stereocomplexation. Though stereocomplexed PEG21800-$(PLA_{14})_8$ hydrogels show higher storage moduli compared to PEG12500-$(PLA_{15})_2$ hydrogels, the mechanical properties may be improved further to broaden the scope of biomedical applications. Stronger gels may be obtained by, e.g.,

Table 3. Storage modulus (G') and loss modulus (G") of PEG12500-$(PLA_{15})_2$ and PEG21800-$(PLA_{14})_8$ stereocomplexed hydrogels 48 h after mixing.

Polymer	Concentration (wt%)	Preparation temperature (°C)	PBS/water	G' (Pa)	G" (Pa)
PEG12500-$(PLA_{15})_2$	13	20	water	1580	290
	13	37	water	2230	230
	13	37	PBS	850	180
PEG21800-$(PLA_{14})_8$	10	20	water	7040	290
	10	37	water	2200	200
	10	37	PBS	1880	110

increasing block copolymer solubility, since higher concentrations have been shown to give stronger hydrogels.[23]

Conclusions

PEG-$(PLA)_2$ and PEG-$(PLA)_8$ hydrogels have been prepared by mixing aqueous polymer solutions of opposite chirality. The gel formation is driven by stereocomplexation of PLA blocks, since the single enantiomer solutions did not form a gel at similar concentrations. The stereocomplexation has been found to have a pronounced effect on the gelation behavior, as critical gel concentrations decreased and gel-sol transitions increased upon increasing temperature. Rheology measurements confirmed the gel formation upon mixing of polymer solutions of opposite chirality and showed improved mechanical properties for the PEG-$(PLA)_8$ hydrogels compared to the PEG-$(PLA)_2$ hydrogels, which is attributed to the higher number of stereocomplexation sites of the PEG-$(PLA)_8$ star block copolymer. Hydrogels prepared in PBS at 37 °C showed storage moduli of 0.9 and 1.9 kPa for PEG-$(PLA)_2$ and PEG-$(PLA)_8$, respectively. These stereocomplexed hydrogels have potential for biomedical applications, since they can be easily prepared and bioactive moieties (e.g., proteins and cells) can be easily suspended into the single enantiomer solutions before gelation.

Acknowledgements

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