Novel Self-assembled Hydrogels by Stereocomplex Formation in Aqueous Solution of Enantiomeric Lactic Acid Oligomers Grafted To Dextran

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ABSTRACT: This paper describes a novel hydrogel concept, which is based on self-assembling of enantiomeric lactic acid oligomers (stereocomplex formation) grafted to dextran. The hydrogels are prepared in an all-aqueous environment. For this purpose, L- and D-lactic acid oligomers were coupled to dextran, yielding dex−(L)lactate and dex−(D)lactate, respectively. Upon dissolving each product in water separately and mixing the solutions, we observed that a hydrogel is formed at room temperature as demonstrated by rheological measurements. The storage modulus of the obtained hydrogel strongly decreased upon heating to 80 °C, while it was restored upon cooling to 20 °C, demonstrating the thermoreversibility and the physical nature of the cross-links. Rheological experiments with monodisperse lactic acid oligomers grafted to dextran showed that the degree of polymerization (DP) of the lactic acid oligomers must be at least 11 to obtain a hydrogel. The hydrogel characteristics can be modulated by varying the degree of polymerization (DP, number of lactate units per oligomer) and the degree of substitution (DS, number of lactic acid side chains per 100 glucopyranose units) of the dex−lactate products, as well as the water content of the dex−lactate solutions. Stronger gels were obtained by increasing the DP and DS and by decreasing the water content. FTIR−photoacoustic (PA) analysis demonstrated that in the hydrogels stereocomplexes were formed between the lactic acid oligomers of opposite chirality.

Introduction

Hydrogels are hydrophilic polymeric networks, which can absorb substantial amounts of water.[1] Because of their unique properties, they have attracted much attention in recent years for possible biomedical, biotechnological, and pharmaceutical applications.[2−5]

Cross-linking of hydrophilic water-soluble polymers can be established in different ways. Chemical cross-links can be introduced by reaction of functional groups (e.g., hydroxyl, amines) of a water-soluble polymer with suitable bisfunctional reagents, e.g., diisocyanates,[6] and glutaraldehyde.[7−9] Alternatively, chemically cross-linked hydrogels can be obtained by derivatization of a water-soluble polymer with, e.g., (meth)acryloyl groups followed by radical polymerization of the (meth)acrylate groups after addition of an initiator system.[10−13] In physically cross-linked hydrogels, the use of cross-linking agents is avoided. Physical cross-linking can be established by, e.g., ionic interactions. Alginate gels, in which cross-linking of the anionic copolymer of 1,4-linked-β-D-mannuronic acid and α-L-gluconic acid is established by Ca^{2+} ions, is a well-known example.[14−16] Also, hydrophobic interactions can be exploited to design physically cross-linked gels, such as cholesterol-bearing pullulan.[17,18] In addition, phase-separated systems composed of hydrophilic−hydrophobic block copolymers can be considered as physically cross-linked hydrogels.[19−22] Recently, elegant methods to create hydrogels were published in which protein−protein interactions in coil−coil aggregates[23,24] or antigen−antibody complexes were used.[25]

It has been reported that stereocomplex formation occurs in, e.g., poly(methyl methacrylate) (PMMA)[26,27] and in poly(lactic acid) (PLA).[28,29] However, stereocomplex formation has not been exploited to design hydrogels so far. In a recent paper,[30] we demonstrated that if the degree of polymerization of lactic acid is between 7 and 11, stereocomplex formation occurs in a blend of (L)-lactic acid oligomer and (D)-lactic acid oligomer. However, a minimum DP of 11 is required for crystallization of one of the enantiomers. In this paper, we utilize this finding to design a novel type of hydrogel in which cross-linking is created in water by physical interaction between enantiomeric lactic acid oligomers grafted to a water-soluble polymer (dextran, Figure 1 (**8**)). The gelation kinetics, (thermo)reversiblilty and the effects of different variables (degree of polymerization, degree of substitution, water content) on the rheological properties of the hydrogel were studied. Further, photoacoustic-IR spectroscopy was used to investigate the presence of stereocomplexes in the formed hydrogel.

Experimental Section

Materials. L-Lactide ((3*S-cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) and D-lactide ((3*R-cis)*-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) were obtained from Purac Biochem BV (Gorinchem, The Netherlands) and used without further treatment. Stannous octoate (tin(II) bis(2-ethylhexanoate),

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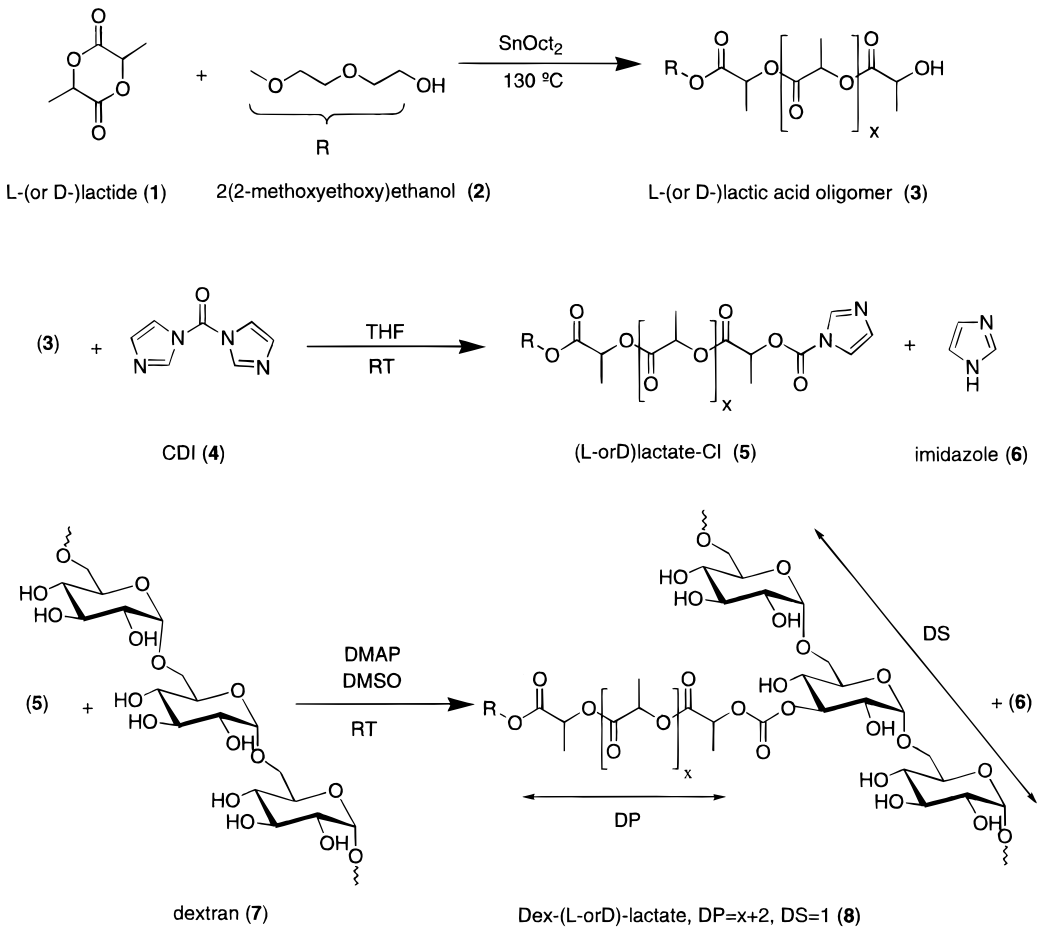

Figure 1. Reaction scheme for the synthesis of dex−lactate (**8**), in which DP is the degree of polymerization and DS is the degree of substitution (number of lactic acid oligomers per 100 glucopyranose units of dextran).

$SnOct_2$, 95%) (Sigma Chemical Co., St. Louis, MO), dichloromethane, potassium peroxydisulfate (KPS) (Merck, Darmstadt, Germany), and 2(2-methoxyethoxy)ethanol (Aldrich-Chemie, Steinheim, Germany) were used as received. Tetrahydrofuran (THF) and acetonitrile (HPLC-S, gradient grade) were purchased from Biosolve LTD (Valkenswaard, The Netherlands). THF was distilled from $LiAlH_4$ immediately before use. Dextran (from *Leuconostoc mesenteroides*, M_n = 15 000 Da, and M_w = 32 500 Da, as determined by GPC analysis), dimethyl sulfoxide (DMSO, <0.01% water), glycidyl methacrylate (GMA, (±)-2,3-epoxypropyl methylpropenoate, 95% by GPC), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), and silicon oil (DC 200, 110 mPa·s), were obtained from Fluka Chemie AG (Buchs, Switzerland). 4-(*N*,*N*-Dimethylamino)-pyridine (DMAP, 99%) and *N*,*N*′-carbonyldiimidazole (CDI, 98%) were from Acros Chimica (Geel, Belgium). Dialysis tubes (cellulose, molecular weight cutoff 12 000−14 000 (based on proteins)) were purchased from Medicell International Ltd. (London, U.K.). Methacrylated dextran (dex−MA) with a degree of substitution (DS, the number of methacryl residues per 100 glucopyranose units of dextran) of 4 was synthesized according to the procedure by Van Dijk-Wolthuis et al.[10,31]

Synthesis of Polydisperse Lactic Acid Oligomers. Lactic acid oligomers with varying DP values were synthesized by a ring-opening polymerization reaction of lactide with 2(2-methoxyethoxy)ethanol (MEE) and stannous octoate as initiator and catalyst, respectively, according to De Jong et al.[30] The average degree of polymerization (DP_{av}) of the formed MEE−lactate was controlled by the MEE/lactide ratio.

Preparation of Monodisperse Lactic Acid Oligomers. Monodisperse lactic acid oligomers were prepared by fractionation of polydisperse MEE−lactate with preparative HPLC (column: Econosphere C8, 10 μm, 250 × 22 mm; Alltech) with an ÄKTA purifier (Pharmacia Biotech AB). Polydisperse oligomer (1 g) was dissolved in 1 mL water/acetonitrile (50 w/w%), and 500 μL of this solution was injected onto the column. A gradient was run from 100% A (water/acetonitrile 95:5) to 100% B (acetonitrile/water 95:5) in 50 min. The flow rate was 5.0 mL/min; detection by UV (λ = 195 nm). The chromatograms were analyzed with Unicorn Analysis module (version 2.30) software. The individual oligomers were collected and fractions with corresponding DP were pooled. The solvent was removed under reduced pressure. The oligomers were characterized by HPLC, NMR, and MS.[30]

Synthesis of Activated Lactic Acid Oligomer. To couple the oligomers to dextran, the hydroxyl group of the oligomer was activated using *N*,*N*′-carbonyldiimidazole (CDI). Essentially the same procedure was used as for the synthesis of hydroxyethyl methacrylate (HEMA)−lactate−CI.[32] In brief, CDI (3.6 g, 22 mmol, 2 equiv) was dissolved in dried tetrahydrofuran (THF, 100 mL) in a nitrogen atmosphere. MEE−lactate (e.g., DP_{av} 9; 8.46 g, 11 mmol, 1 equiv) was dissolved in THF (10 mL) and added to the CDI solution. The reaction mixture was stirred for 4 h at room temperature in a nitrogen atmosphere. Thereafter, dichloromethane (DCM, 200 mL) was added, and the reaction mixture was washed with water (100 mL), to decompose the excess CDI and to remove the imidazole. Next, the water layer was extracted with DCM (50 mL) two times. The organic layers were combined and dried over magnesium sulfate. After filtration, the organic solvent was removed under reduced pressure to yield the MEE−lactate−CI DP_{av} 9.

^{1}H NMR ($CDCl_3$): δ 8.16 (m, 1H, *C*(*O*)−N−C*H*═N), 7.44 (m, 1H, *C*(*O*)−N−C*H*═CH), 7.07 (m, 1H, *C*(*O*)−N−CH═C*H*), 5.35 (q, 1H, C*H*−O−C(O)−N), 5.23−5.12 (overlapping q, C*H*), 4.28 (m, 2H, CH_2−O−C(O)), 3.66 (m, 2H, CH_3−O−CH_2), 3.60 (m, 2H, CH_2−O), 3.51 (m, 2H, CH_2−O), 3.37 (s, 3H, CH_3−O), 1.72 (d, CH_3−CH−O−C(O)N), 1.63−1.50 (overlapping d, CH−CH_3). ^{13}C NMR ($CDCl_3$): δ 169.5 *C*═O, 168.8 *C*(O)−N, 137.1 N−*C*H−N, 121.6 + 117.1 N−*C*═C−N, 71.7 *C*H_2, 71.5

(CH_3)CH−O−C(O)−N, 70.3 CH_2, 69.3−68.7 CH−CH_3 + CH_2−OCH_3, 64.3 CH_2−O−C(O), 58.9 CH_3O, 25.5 CH_3−CH−O−C(O)−N, 16.6/16.5 CH_3.

Synthesis of Dex−Lactate. Dextran−lactate (dex−lactate) was synthesized using the same procedure as for the synthesis of dex−lactate−HEMA.[32] In brief, dextran 40 000 (10 g) and DMAP (2 g, 16.3 mmol, 0.25 equiv to glycopyranose units of dextran) were dissolved in dried DMSO (90 mL). Next, MEE−lactate−CI (e.g., DP_{av} 9, 5.7 g, 6.17 mmol) dissolved in dry DMSO (5 mL) was added. The solution was stirred at room temperature for 4 days in a nitrogen atmosphere, after which the reaction was stopped by addition of concentrated HCl (2 mL, 1 equiv) to neutralize DMAP and imidazole. The reaction mixture was extensively dialyzed against water (reversed osmosis) at 4 °C. The dex−lactate product was collected by lyophilization. To remove traces of uncoupled lactic acid oligomers, the dex−lactate product (10 g) was extracted with dichloromethane (400 mL). The product was dried in a vacuum oven at 40 °C, to yield dex−lactate with DP_{av} 9 and degree of substitution (DS, the number of oligomers per 100 glucopyranose units of dextran) of 3. The DS was calculated by ^{1}H NMR as $(x \times 100)/y$, in which x is the integral of the CH_3 groups of the lactic acid oligomer at 1.41 ppm divided by ($3 \times$ DP), with DP as the degree of polymerization, and y is the integral of the anomeric proton of dextran at 5.14−4.95 ppm.

^{1}H NMR (12.5% ^2H_2O/DMSO-d_6): δ 5.14−4.95 (broad m, residual OH, CH, CH−O−C(O)−N), 4.65 (broad s, anomeric proton dextran), 4.16 (m, 2H, CH_2−O−C(O)), 3.84−3.18 (m, (6H) dextran, (2H) CH_3−O−CH_2, (4H) CH_2−O, (3H) CH_3−O), 1.41 (overlapping d, CH_3−CH−O−C(O)N, CH−CH_3). ^{13}C NMR (12.5% ^2H_2O/DMSO-d_6): δ 170.4 C(O)−O−CH_2, 169.8 C=O, 98.5 $C_{anomeric}$, 73.7 C_3, 72.1 C_2, 71.6 CH_2, 70.7 C_5, 70.3 C_4, 69.9 CH_2, 69.8 (CH_3)CH−O−C(O)−O−dex, 69.3 CH, 68.5 CH_2, 66.2 CH_2(dex), 64.8 CH_2, 58.5 CH, 20.6 CH_3−CH−O−C(O)−O−dex, 16.9 CH_3.

Rheological Experiments. For the rheological experiments two types of polymer solutions were prepared: one contains dex−(L)lactate and the other dex−(D)lactate. The dissolution time was at least 1 day at room temperature. Acetate buffer pH 4 was selected as solvent to prevent hydrolysis of the dex−lactate.[33,34]

Equal amounts of the dex−(L)lactate and the dex−(D)lactate solutions were mixed, homogenized and quickly applied on the rheometer (AR 100 instrument of TA Instruments, Gent, Belgium). For most of the experiments a flat-plate measuring geometry (acrylic, 4 cm diameter; gap 1 mm) was used. A cone−plate measuring geometry (steel, 2 cm diameter with an angle of 1°; gap 31 μm) was used when only a small amount of material was available. Gelation of the dex−lactate solutions took place between the cone and plate of the measuring geometry. A solvent trap was used to prevent evaporation of the solvent. In addition, a thin layer of silicon oil (110 mPa·s) was applied to surround the dex−lactate sample, thereby preventing evaporation.

Gelation of the mixture of dex−lactate solutions was monitored by measuring the shear storage modulus (G'), as well as the loss modulus (G'') at 20 °C for 6−18 h. A frequency of 1 Hz and a controlled strain of 1% were applied. The strain used in these experiments was as low as possible to minimize the influence of deformation on the formation of the dex−lactate hydrogels. At the end of gelation, two types of rheological measurements were done. First, creep experiments were carried out to establish the viscoelastic properties of the samples. Therefore, a constant force (equal to the force applied at the end of the gelation measurement to obtain 1% deformation, which is in the linear viscoelastic range) was applied during 60 s while the strain was monitored. Second, the temperature was raised from 20 to 80 °C over 30 min while several rheological parameters were monitored (frequency 1 Hz, 1% strain). At 80 °C, a creep experiment was carried out again. A constant force, equal to the force applied at 80 °C to obtain 1% deformation, was applied. Thereafter, the sample was cooled to 20 °C in 30 min while G' and G'' were monitored (frequency 1 Hz, 1% strain), again followed by a creep experiment.

As a control, the same rheological experiments were performed with a solution of dex−(L)lactate. To compare the rheological behavior of physically cross-linked dex−lactate hydrogels with chemically cross-linked gels, measurements were performed on a hydrogel based on methacrylated-dextran (dex−MA). Dex−MA hydrogels were prepared by radical reaction of aqueous dex−MA solution (DS 4, 10 w/w% dex−MA in 0.01 M phosphate buffer pH 7). Solution A was obtained by adding 50 μL TEMED (500 μL/ml, pH adjusted to 7) to 450 μL of a dex−MA solution, while solution B was a mixture of 410 μL dex−MA solution and 90 μL KPS solution (50 mg/mL in 0.01 M phosphate buffer pH 7). 100 μL of solutions A and B were mixed and directly applied on the measuring geometry of the rheometer.[35] Rheology experiments were carried out in the same way as for the dex−lactate products.

NMR Spectrometry. NMR spectra were recorded with a Gemini 300 MHz spectrometer (Varian Associates Inc. NMR Instruments, Palo Alto, CA). Approximately 30 mg of lactic acid oligomer was dissolved in 0.8 mL deuteriochloroform, and 30 mg of dex−lactate was dissolved in a mixture of 0.8 mL of dimethyl sulfoxide-d_6 and 0.1 mL of ^2H_2O (all solvents were obtained from Cambridge Isotope Laboratories, Andover, MA). For ^{1}H NMR, chloroform (at 7.26 ppm) was used as the reference line, whereas for DMSO-d_6 the central DMSO line was set at 2.50 ppm. A pulse length of 4.5 μs ($PW_{90} \approx 12$ μs) was used with a relaxation delay of 15 s. For ^{13}C NMR spectra, the pulse length was set at 4.5 μs ($PW_{90} \approx 12$ μs), and the relaxation delay at 2 s. The central line in the chloroform triplet at 76.9 ppm was used as the reference line, whereas for DMSO-d_6 (99.9% ^{2}H, Cambridge Isotope Laboratories, Andover, MA) the central DMSO line was set at 39.5 ppm.

FTIR−Transmission and Photoacoustic Spectroscopy (PAS). IR−transmission spectra of the lactic acid oligomers were recorded with a Biorad FTS-25 interferometer/spectrometer. Thin films of L-lactic acid oligomer, as well as the blend of L and D form, were cast from dichloromethane solutions onto a KBr tablet. The interferograms were recorded at a spectral resolution of 2 cm^{-1} in the rapid-scan mode (5 kHz) with a deuterated triglycine sulfate (DTGS) detector. A total of 32 scans were averaged to gain a good signal-to-noise ratio. Fourier transformation yields the IR−transmission spectra, which were normalized on background spectra obtained from the pure KBr tablet at an identical parameter setup. IR−Photoacoustic (PA) spectra of dex−lactate were obtained with a Biorad FTS-6000 step-scan interferometer/spectrometer. After the rheology experiment, selected dex−lactate products were dried overnight at room temperature. The IR spectra of these products were measured with the PA detection method. The general benefit of this method is that no further preparation of the sample (i.e., the dex−lactate products) is needed. Therefore, IR spectra of solid materials can be obtained directly and rather quickly. The interferograms were recorded at a spectral resolution of 8 cm^{-1} using a MTEC-200 photoacoustic detector. They were obtained in the step-scan mode of the interferometer, at 800 Hz stepping frequency of the moving mirror. Scanning in the step-scan mode of the interferometer resulted in a far better signal-to-noise ratio. A total of 32 scans were averaged and Fourier transformed to yield the IR−PA spectra of dex−lactate. All IR−PA spectra were normalized using the PA reference sample carbon black.

Results and Discussion

Synthesis of the Lactate-Grafted Dextrans. In the synthesis of dex−lactate (Figure 1) essentially the same strategy was used as for the synthesis of dex−lactate−HEMA.[32] First, the lactide acid oligomer (**3**) was synthesized via a ring-opening polymerization of lactide.[30] After activation of the hydroxyl end group with *N*,*N*′-carbonyldiimidazole (CDI, **4**), the resulting lactate−CI (**5**) was coupled to dextran (**7**) to yield dex−lactate (**8**). The incorporation of the lactic acid oligomers under the standard reaction circumstances, 4 days reaction time at room temperature, was about 30%. Higher

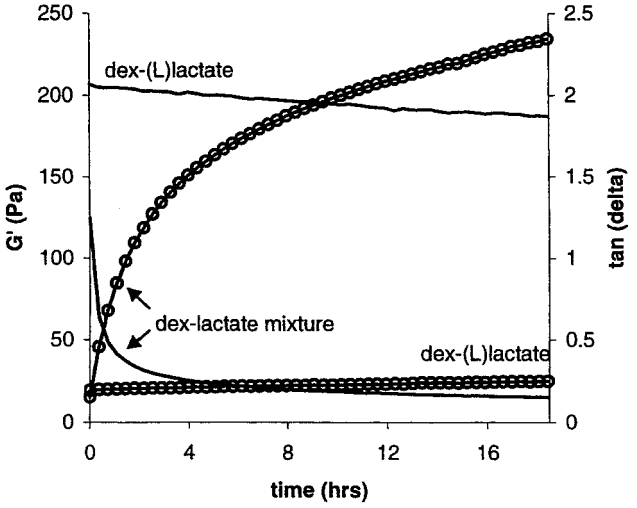

Figure 2. Storage modulus (○) and tan δ (—) at 20 °C as a function of the time of dex−(L)lactate and the mixture of dex−(L)lactate and dex−(D)lactate. The DP_{av} and DS of the dex−(L)lactate and the dex−(D)lactate were 9 and 3, respectively. The water content of the polymer solution was 80%.

degrees of incorporation, up to 60%, could be achieved by longer reaction times (18−24 days) or higher reaction temperatures (80 °C). HPLC analysis demonstrated that under the selected reaction conditions no transesterification occurred.

Gelation of Dex−Lactate Solutions. Figure 2 shows the rheological characteristics as a function of time of dex−(L)lactate solution and a mixture of dex−(L)lactate and dex−(D)lactate solutions. G' and tan δ of dex−(L)lactate did not change in time. In contrast, the dex−(L)lactate and dex−(D)lactate mixture showed an increase in G' (even after 18 h no real plateau value was reached) and a dramatic decrease of tan δ (from 1.2 to 0.1) in time. The network formation can be attributed to association of the enantiomeric lactic acid chains (stereocomplex formation). The fact that no real plateau value of G' was reached is often observed in physically cross-linked networks, such as gelatin.[36]

Figure 3 shows the results of creep experiments on the samples of Figure 2 after about 18 h. The retardation profile shows full viscous behavior for dex−(L)-lactate (Figure 3A), which is in agreement with the high value of tan δ observed (Figure 2). For the dex−lactate mixture, elastic behavior was observed in the creep experiment (Figure 3B), in agreement with the low value of tan δ (Figure 2).

Thermoreversibility. The rheological characteristics of a chemically cross-linked methacrylated-dextran gel were monitored as a function of temperature. Figure 4 shows that G' increased proportionally with temperature, which is in agreement with the rubber elasticity theory of Flory.[37] At 80 °C the dex−MA hydrogel remained fully elastic as observed from a creep experiment (result not shown). During cooling the reverse G' profile was observed, and G' at 20 °C equaled G' before heating.

In contrast, the dex−lactate gels showed a completely different temperature dependency. Upon heating the dex−lactate hydrogels G' dropped (Figure 4). The loss modulus (G'') of the mixture at 80 °C was almost equal to the G'' of a single isomer of dex−lactate (not shown), indicating that no cross-links were left in the mixture. Creep experiments of both systems at this temperature showed viscous behavior as in Figure 3A. Figure 4

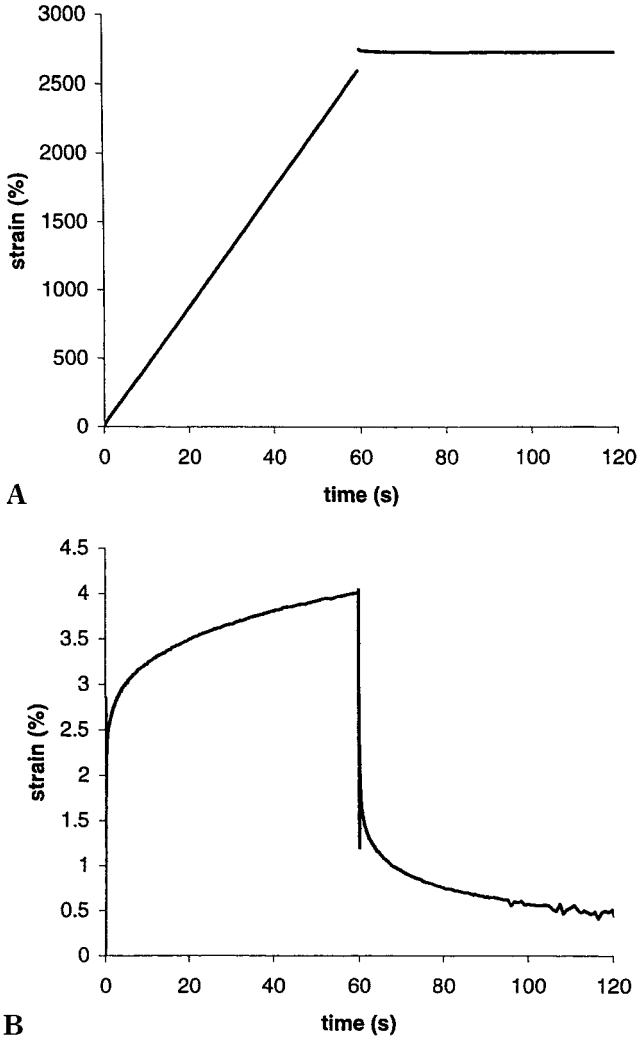

Figure 3. Creep at 20 °C of dex−(L)lactate (A) and a mixture of dex−(L)lactate and dex−(D)lactate (B) (DP_{av} 9, DS 3, and 80% water)

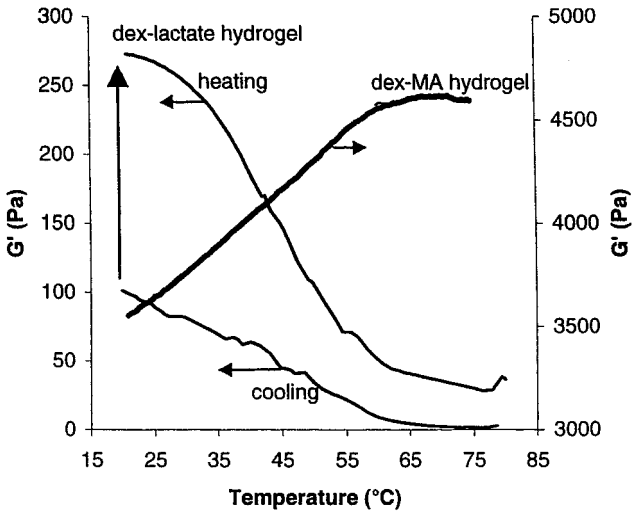

Figure 4. Storage modulus as a function of the temperature of a dex−lactate hydrogel (DP_{av} 9, DS 3, and 80% water) upon heating and cooling, as well as the storage modulus during heating of a dex−MA hydrogel (DS 4, 90% water). The vertical arrow reflects the increase in storage modulus in time at 20 °C to its original value.

shows that upon cooling G' increased and finally reached the original value of G' at 20 °C, indicated by the vertical

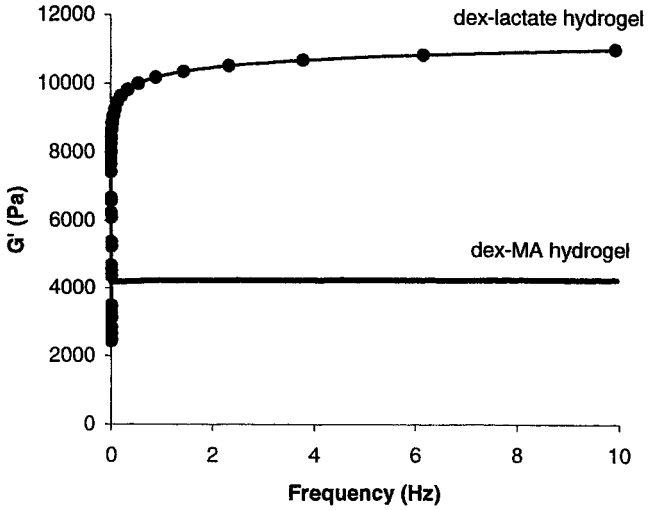

Figure 5. Storage modulus as a function of the oscillation frequency of a dex−lactate hydrogel (DP_{av} 12, DS 5, and 80% water, ●) and a dex−MA hydrogel (DS 4, 90% water, —).

arrow. A creep experiment showed the same pattern as Figure 3B, which proves the full thermoreversible properties of the mixture of both isomers and the physically nature of the cross-links.

Elastic Properties as a Function of the Frequency. Figure 5 compares a G' profile of a dex−lactate hydrogel and a chemically cross-linked methacrylated-dextran hydrogel, respectively, as a function of the frequency. G' of the dex−methacrylate hydrogel was independent of the applied frequency again indicating the existence of a real rubbery network, which is expected in hydrogels with permanent (chemical) cross-links.[35,38] However, G' of the dex−lactate gel decreased considerably with decreasing frequency. This again demonstrates the physical, i.e., reversible (transient) nature of the cross-links[39,40] (Figure 5). At low frequencies the cross-links break and re-form at long time scales (the network relaxation process), whereas at high frequencies the time scale becomes smaller and the cross-links act as if permanent, resulting in increasing G'.

Influence of DP, DS, and Water Content on Gel Formation. The G' profiles shown in Figure 2 were obtained using a dex−lactate sample with DP_{av} 9 and DS 3. When dex−lactates with a higher DP and higher DS were used, the dex−(L)lactate (or dex−(D)lactate) solutions showed viscoelastic behavior. This is probably caused by the association of the longer lactic acid chains with oligomers of the same chirality, which also results in a poorer water solubility. However, in this sample gelation as a function of the time was not observed. In contrast, the dex−lactate mixture clearly gelled as observed from an increase in G' (Figure 6A). The formation of a gel was confirmed by creep experiments: the dex−lactate mixture showed an almost elastic behavior, whereas the dex−(L)lactate system is a typical viscoelastic material (Figure 6B).

Figure 7 shows the influence of the degree of polymerization (A), the water content and the degree of substitution (B) on G', 18 h after mixing the dex−(L)-lactate with the dex−(D)lactate solution. Mixing dex−(L)lactate DP_{av} 5 with dex−(D)lactate DP_{av} 5 solution resulted in a slight increase in G' compared with the G' value of the corresponding dex−(L)lactate system. This indicates that a weak hydrogel was formed. Obviously, the oligomers did not have sufficient length to

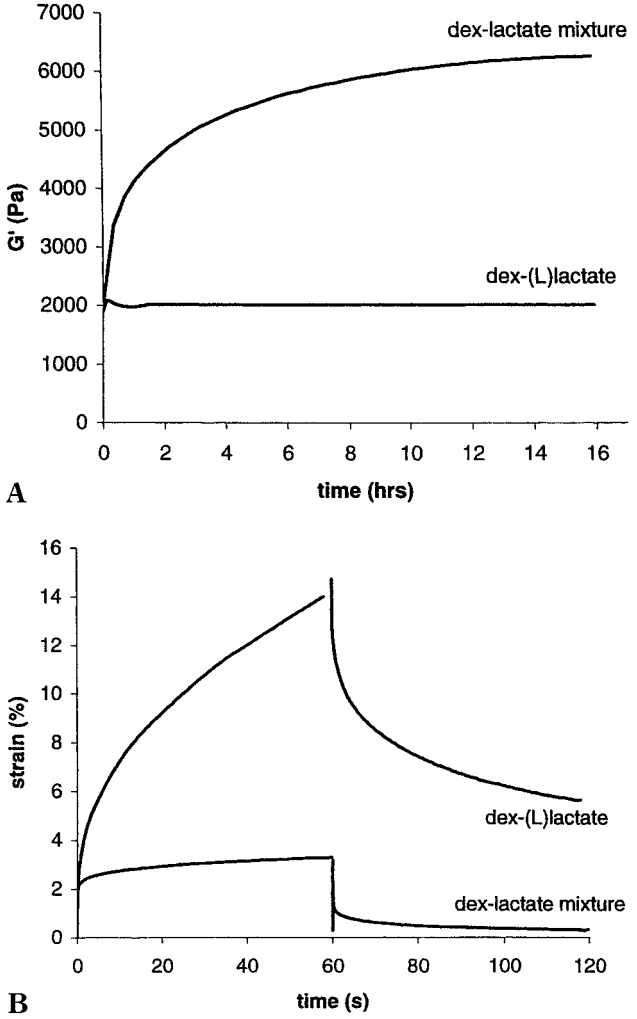

Figure 6. Storage modulus as a function of the time of dex−(L)lactate and the mixture of dex−(L)lactate and dex−(D)lactate (DP_{av} 12, DS 5, 80% water at 20 °C) (A) and the creep of corresponding dex−(L)lactate and the mixture of dex−(L)-lactate and dex−(D)lactate at 20 °C (B).

associate with each other. Mixing of dex−lactates with higher degrees of polymerization resulted in formation of a gel as reflected by a substantially greater value for G' of the mixture compared to the G' for one of the isomers (compare open and closed symbols, Figure 7A). As Figure 7B shows, stronger gels were obtained by increasing the degree of substitution and by decreasing the water content of the system.

Monodisperse Lactic Acid Oligomers Grafted to Dextran. Rheology. Monodisperse lactic acid oligomers, with a degree of polymerization ranging from 8 to 12, were coupled to dextran to determine the effect of the lactic acid chain length on the gel formation. Mixtures of dex−(L)lactate and dex−(D)lactate with the same degree of polymerization of the lactic acid oligomers were investigated for their ability to form a gel (Table 1). From these data it can be seen that mixtures of dex−(L)lactate and dex−(D)lactate with a DP lower than 11 did not result in a hydrogel, even when a high degree of substitution (DS 17) or low water content (70%) was used. On the other hand, for dex−lactate DP 11 or 12, an increase in G' was observed after mixing the dex−(L)lactate and dex−(D)lactate product, and a hydrogel was formed. Gel formation was confirmed by a creep experiment, which showed an almost elastic behavior of the mixture. A gel was also obtained with

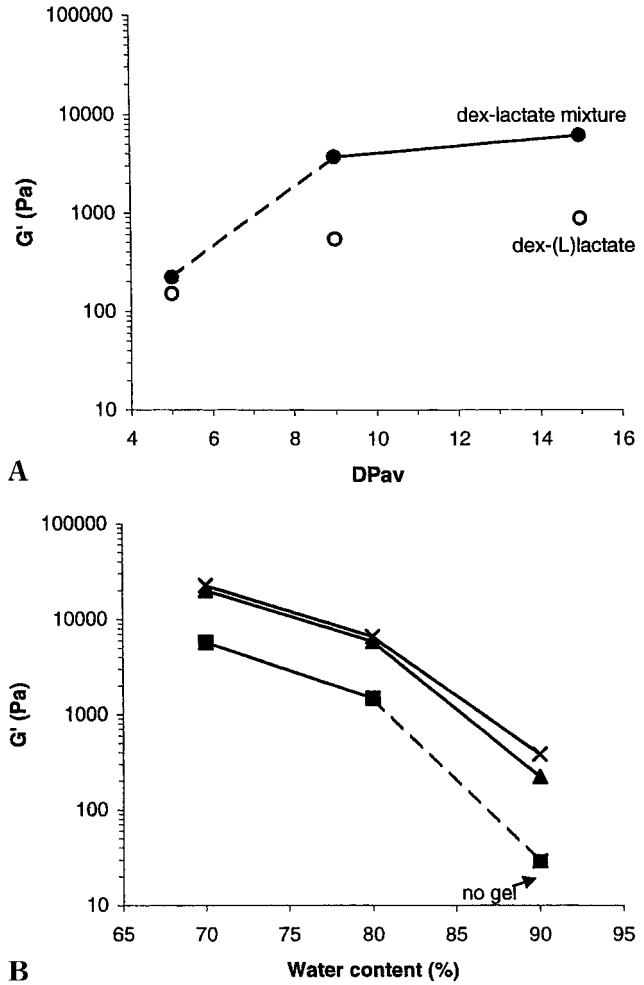

Figure 7. Influence of DP on the storage modulus of dex−(L)lactate (open symbols) and of the dex−lactate gels (closed symbols) at fixed DS (DS 5) and water content (80%) (A) and the influence of the water content and the DS on the storage modulus of dex−lactate gels with DP_{av} 9, DS 3 (■), DP_{av} 9, DS 13 (▲), and DP_{av} 12, DS 5 (×) (B).

Table 1. Rheology and PAS Data of the Mixtures of Monodisperse Dex−(L)Lactate and Dex−(D)Lactate[a]

			rheology	PAS	
DP	DS	% water	creep	gelation	stereocomplex
8	17	70	V	−	−
8	17	80	V	−	−
10	6	70	V	−	+/−
10	6	80	V	−	−
10	15	70	V	−	+
10	15	80	V	−	−
11	17	80	E	+	++
12	8	80	E	+	++

[a] V = mainly viscous; E = mainly elastic.

dex−(L)lactate DP 12 and DS 17, most likely because of homocrystallization of the oligomer.[30]

FTIR Transmission and Photoacoustic Spectrometry. Infrared spectroscopy was applied to investigate the possible stereocomplex formation in the monodisperse dex−lactate gels. It was recently shown by Vert et al.[41] that IR spectroscopy can be used to distinguish between 10_3 and 3_1 helical conformations of the crystalline homopolymer of poly(lactide) (PLA) and the PLA stereocomplex, respectively.[42,43] Since sharp IR-band shapes were observed for the monodisperse products, they were used for interpretation purposes. FTIR−transmission spectra of the free monodisperse lactic acid oligomer (DP 8) and its corresponding blend, which form stereocomplexes upon mixing,[30] were recorded (Figure 8). In the stereocomplex, the most pronounced difference was the disappearance of the absorption peak at 1270 cm^{-1} ($\delta(CH_3)$, ν(COC), indicated by the dotted line). This is in agreement with the results obtained from the polydisperse poly(lactic acid), as previously published.[41]

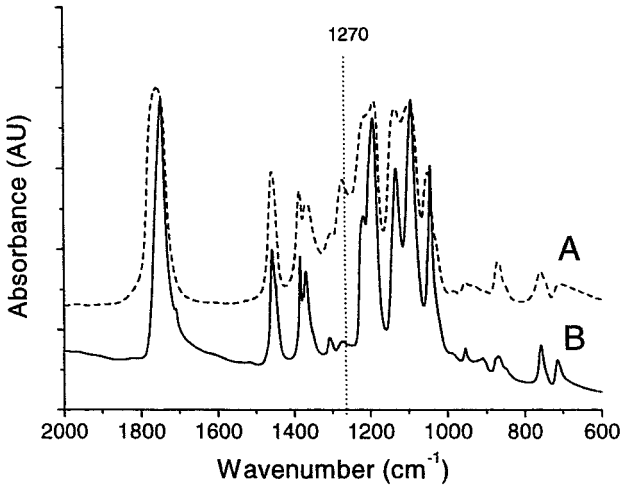

Figure 8. FTIR spectra of monodisperse (L)-lactic acid oligomer DP8 (A) and corresponding blend (B).

After rheology measurement, the dex−*(monodisperse)*lactate products were dried at ambient temperature. Next, IR spectra of these dried products were recorded with the PA-detection method, which turned out to be qualitatively comparable to FTIR−transmission method. Figure 9 shows that similar IR spectra were obtained for the dex−(L)lactate with DP 8 and DP 11, as well as for the dex−lactate mixture with DP 8, in which no gelation occurred (Table 1). Interestingly, for the dex−lactate mixture with DP 11 (rheology experiments demonstrated the formation of a gel, Table 1) some clear IR-frequency shifts were observed in the IR spectrum. The observed shift from 1270 to 1260 cm^{-1} (Figure 9B) can likely be ascribed to the formation of stereocomplexes in the dex−lactate mixture. In Table 1, the presence of stereocomplexes, as detected by IR−PA, in different dex−lactate mixtures is given. For systems with DP 11 and 12, gelation (based on rheology) was clearly associated with the presence of stereocomplexes. Interestingly, the dex−lactate mixtures with DP 10 (DS6 and DS15) and a water content of 70% showed the same IR-frequency shift (from 1270 to 1260 cm^{-1}) as well, although for these mixtures no hydrogels were formed according to the rheology data. This indicates that stereocomplexes are formed in the dex−lactate mixture with DP 10 and a water content of 70%. However, only a few physical interactions (stereocomplexes) may be present, which are not sufficient to form an elastic network. For the free lactic acid oligomers a minimum DP of 7 is required for the stereocomplexation.[30] Obviously, for dex−lactates, longer lactic acid chains are required to obtain the parallel orientation[42] of at least seven lactic acid units of opposite chirality needed for the formation of stereocomplexes.

Conclusions

In this paper, we show that stereocomplex formation between enantiomeric lactic acid oligomers grafted to dextran yields a hydrogel. The physical cross-links are

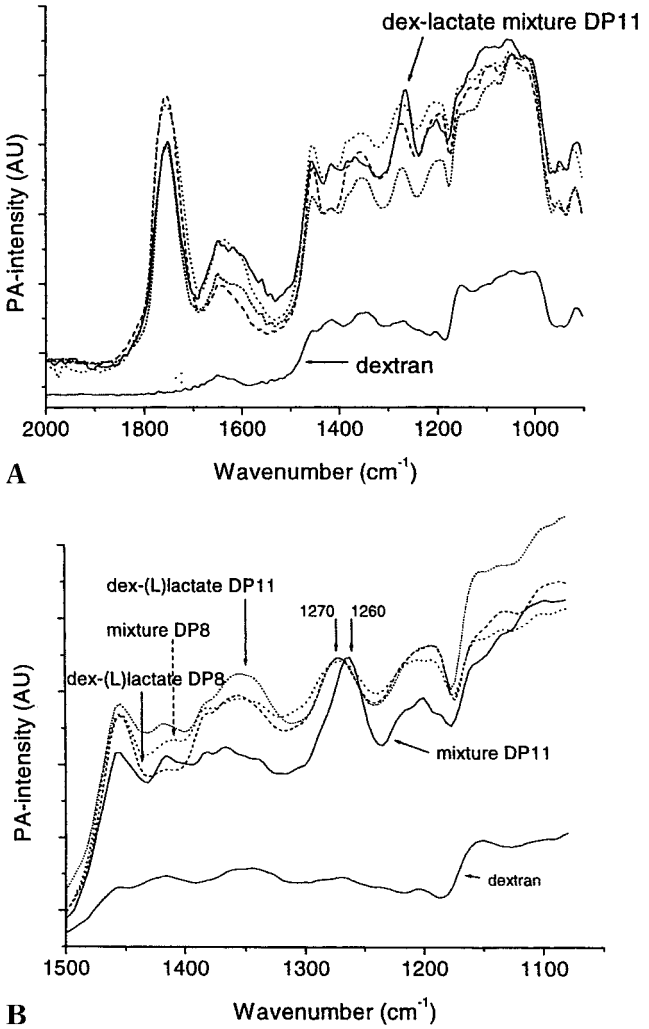

Figure 9. FTIR−PAS spectra of dex−(L)lactate DP8, dex−(L)lactate DP11, a mixture of dex−(L)lactate and dex−(D)-lactate DP8, and a mixture of dex−(L)lactate and dex−(D)lactate DP11 (A) and magnification from 1500 to 1050 cm^{-1} (B).

formed in an aqueous environment. It is expected that the hydrogel will possess a good biocompatibility and is fully degradable. As degradation products, lactic acid (an endogenous compound) and dextran (a well-known nontoxic pharmaceutical polymer used as plasma expander) are expected. It is shown that the hydrogel characteristics can be easily modulated as a function of the degree of polymerization, the degree of substitution and the water content. The hydrogel system presented in this paper opens unique possibilities, e.g., to encapsulate proteins in an aqueous environment, avoiding the use of cross-linking agents and organic solvents, which could adversely affect the integrity of the protein.

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