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Incorporation of salicylates into poly(L-lactide)

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Summary

Recent studies have indicated that complications like swelling and inflammation of the surrounding tissue may occur in the late stage of the *in vivo* degradation of semi-crystalline PLLA bone fixation devices. Incorporation of an anti-inflammatory drug, like a salicylate, in the poly(L-lactide) chain might be a route to prevent these complications. In this study, it has been shown that it is possible to copolymerize L-lactide with di- and trisalicylide and to use salicylic acid as an initiator for the L-lactide polymerization or the L-lactide/ε-caprolactone copolymerization. Furthermore, PLLA was blended with poly(salicylic acid) and $Zn(salicylate)_2$ was synthesized and turned out to be a catalyst for the ring opening polymerization of L-lactide. The binary poly(L-lactide)/o-acetyl salicylic acid system has an eutectic composition for 52 % w/w of poly(L-lactide) in the mixture. Its eutectic melting temperature is 119 °C.

Introduction

Among several biodegradable polymers, poly(L-lactide) (PLLA), a semi crystalline polyester, is widely used in biomedical applications such as drug release systems (1), surgical sutures (2) and implants for fixation of bone fractures (3,4). This is due to the proven strength, biocompatibility and degradability by hydrolysis of PLLA.

The use of high molecular weight PLLA as a fracture fixation device in oral and maxillofacial surgery initially gave good results, healing of the bone fracture without clinically detectable complications took place. A serious problem, however, was the slow degradation rate of PLLA and complications such as inflammatory reactions and swelling, which showed up in the late stage of the degradation after an implantation period of 3 years of the device (5).

In order to lower the crystallinity of PLLA and to prevent or inhibit these unwanted reactions, incorporation of a biologically active drug with anti-inflammatory properties in the PLLA device might be a solution to this problem. Upon degradation of the PLLA the active component will be released. Recent studies showed that a decrease in the crystallinity of PLLA resulted in an acceleration of the degradation (6). Furthermore, much research has been done on the synthesis and behaviour of aspirin, derivatives of salicylic acid modified polymeric systems, which is because of the know analgesics and anti-inflammatory properties of the salicylates (7). In many of these systems the drug is attached by means of a hydrolytically degradable bond to the main chain of a polymer, as a means of increasing the duration of its activity (8–11). Less research has been

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done upon the incorporation of salicylates in the main chain of polymers which are to be used in the biomedical field (12-13).
The aim of this study is to investigate the possibility of incorporation of salicylates into PLLA by means of blending PLLA with poly(salicylic acid), poly(o-oxybenzoyl), copolymerization of L-lactide with the cyclic ester disalicylide (di-benzo- 1,5-dioxocin- 6,12-dion) and trisalicylide (tri-benzo-1,5,9-trioxacydodecin-6,12,18- trion), Figure 1, and by polymerization of L-lactide, and copolymerization of L-lactide/ε-caprolacton (50/50), initiated by the hydroxyl group of salicylic acid. Also Zn(salicylate)2 has been synthesized, and used as a catalyst in the ring opening polymerization of L-lactide. Furthermore the solidification and the melting behaviour of the guasi-binary system formed by poly(L-lactide) and the diluent o-acetylsalicylic acid has been investigated. It is know that eutectic solidification of polymers may lead to porous materials. This can be an important factor if the polymer is to be used as a surgical implant, as porosity determines tissue ingrowth (14-16).

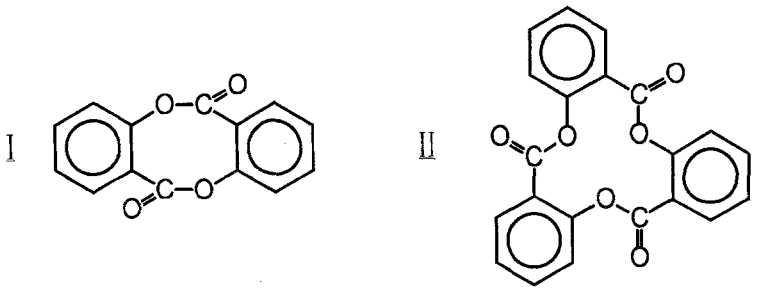

Figure 1: *Structural formulae of disalicylide (I) and trisalicylide (II).*

Experimental

(Co)polymerizations: Aspirin, o-acetylsalicylic acid (Janssen Chimica; Belgium), was used without further purification and slowly heated above its melting point (ca. 137 °C) at 21 mm Hg pressure in order to prepare poly salicylic acid. Acetic acid was distilled off under N_2 for one hour. Next the temperature was slowly increased to 190 °C and maintained for two hours. The distillation took place until no more acetic acid was formed.
Depolymerization of the polycondensate poly(o-oxybenzoyl) was carried out at 330 °C (15 mm Hg pressure) in a heated tube-oven. Purification of the sublimate and isolation of the di- and trisalicylide occurred by means of refluxing in chloroform (3 hours) and recrystallization (-15 °C) from pure chloroform and acetone.
Copolymers of L-lactide with di- and trisalicylide were prepared by dissolving the salicylate in the lactide melt, and using stannous octoate $Sn(Oct)_2$ as a ring opening catalyst. The polymerizations were carried out in silanized polymerization vessels under N_2 at 110 °C for 7 days. The copolymers were purified by precipitation using chloroform as the solvent and methanol as the precipitant.
L-lactide (Purac Biochem; The Netherlands) was recrystallized from sodium dried toluene. ε-caprolactone (Janssen Chimica, Belgium) was purified by drying over CaH_2 and distillation under reduced nitrogen atmosphere. The

salicylic acid (Merck; Germany) initiated polymerization of L-lactide and L-lactide/ε-caprolactone (50/50) in bulk took place by ring opening with $Sn(Oct)_2$ as a catalyst according to standard procedures (17). The molecular weight of the salicylic acid initiated polymers was determined by means of titration with KOH solution. Polymerization of L-lactide with $Zn(salicylate)_2$ as a catalyst occurred also according to these standard procedures.

Blends and $Zn(salicylate)_2$ catalyst: Blends of poly(L-lactide) and poly(o-oxybenzoyl) were prepared by dissolving the two polymers (ca. 7 g) in chloroform (160 ml) followed by precipitation in methanol and drying in a vacuum oven.

$Zn(salicylate)_2$ was prepared by reaction of ZnO (0.064 mole) with salicylic acid (0.128 mole) in water (250 ml) at (90 °C; 8 hours) followed by filtration and crystallisation at - 15 °C.

Eutectic solidification: Poly(L-lactide) was precipitated according to standard procedures and had a $\overline{M}w/\overline{M}n$ ratio of 2.0. The viscosity-average molecular weight of the polymer was $4 * 10^5$, and its melting peak 189.1 °C. Aspirine was recrystallised twice from o-xylene. Its melting temperature was 138.2 °C. Di-chloromethane was used to dissolve and mix the proper amounts of poly(L-lactide) and aspirine, afterwards the solvent was evaporated. For further homogenization the mixtures were kept at a temperature 10 °C higher than the melting temperture of the highest melting component for 15 minutes. The samples were then quenched to room temperature. Melting characteristics were obtained with a Perkin Elmer DSC-7 apparatus using 6 mg samples and a scan speed of 10 °C/min.

Compression Moulding and Characterization: (Co)polymer conversions and compositions were determined by 300 MHz ^1H NMR of solutions in deuterated chloroform. Thermal properties were measured on a Perkin-Elmer DSC-7 at a heating rate of 10 °C per minute. Tensile testing specimens were moulded to 6*50*2 mm at 200 °C and rapidly cooled to room temperature. The stress-strain behaviour was examined at room temperature with an Instron 4301 tensile tester, at a crosshead speed of 10 mm per minute.

Results and discussion

Polymerization of L-lactide with di- and trisalicylide: Polycondensation of aspirin (ca. 63.5 g) gave, as previously was shown (18,19), a yellow, brittle transparent, amorphous poly(o-oxybenzoyl) and acetic acid (19.3 g). The glass transition temperature of the polycondensate was found to be Tg = 76.8 °C. Depolymerization of this polycondensate on heating in vacuo yielded a white semi-crystalline sublimate, from which di- and trisalicylide could be isolated. An amount of 7 g of the sublimate was dissolved in boiling chloroform and after crystallization upon cooling 2.4 g (16.8 %), disalicylide was obtained as colourless, twinned rhombs m.p. 232.6 °C (Found: C, 69.2 %; H, 3.4 %: Calc. for $C_{14}H_8O_4$: C, 70.0 %; H 3,4 %); ^1H NMR ($CDCl_3$): 7.4 - 8.0 ppm (m, 8H, $C_{12}H_8$). Recrystallization of the chloroform residue after acetone addition gave 1.9 g (13.3 %) trisalicylide as colourless needles m.p. 198.4 °C (Found: C, 70.0 %; H, 3.3 %: Calc. for $C_{21}H_{12}O_6$: C, 70.0 %; H 3.4 %); ^1H NMR ($CDCl_3$): 7.4 - 8.0 ppm (m, 12H, $C_{18}H_{12}$).

Two copolymerizations at 110 °C of L-lactide with the cyclic esters di- and trisalicylide by means of ring opening with $Sn(Oct)_2$ gave slightly-yellow, crystalline copolymers. The thermal properties of the as-polymerized copolymers are given in Table 1.

Table 1

Thermal properties of as-polymerized copolymers of L-lactide and cyclic salicylides.

comonomer	mole %	ΔH (J/g)	Tm (°C)	Tg (°C)
—	0.0	72.1	192.4	57
trisalicylide	1.6	50.9	169.0	—
disalicylide	4.9	41.1	164.2	58

A decrease in the crystallinity and the melting temperature of the PLLA is observed upon copolymerization with cyclic salicylides. The incorporation of o-oxybenzoyl groups from di- or trisalicylide was checked with ^{1}H NMR. Figure 2 shows the NMR spectrum of the poly(L-lactide/trisalicylide) copolymer after precipitation. Obviously trisalicylide (and disalicylide, spectrum not shown) has been incorporated into PLLA chains, giving four peaks at 7.3 to 8.0 ppm which can be assigned to the aromatic protons of the o-oxybenzoyl groups. The peaks at 5.1 and at 1.55 ppm respectively correspond to methyne and methyl protons of the lactide units.

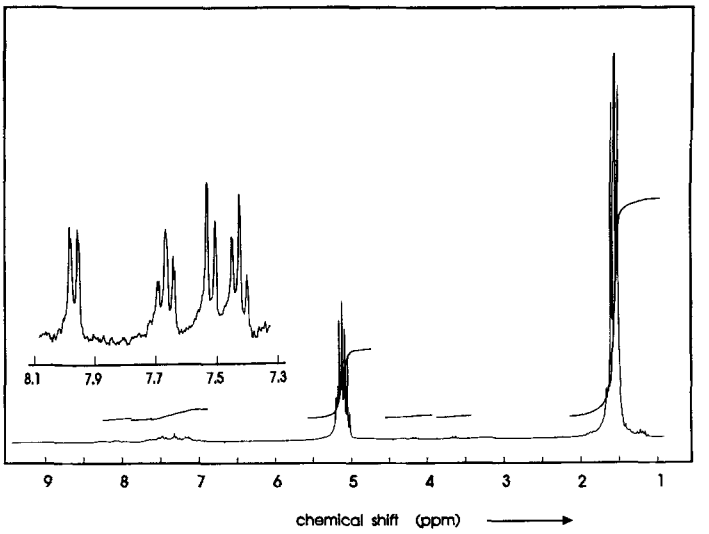

Figure 2: *^{1}H 300 MHz spectrum of the purified poly(L-lactide/trisalicylide) copolymer.*

The hydrolytic degradation of these degradable copolymers by cleavage of the ester bonds yields the release of lactic acid and salicylic acid. Because of the release of salicylic acid and its anti-inflammatory properties, unwanted inflammatory reactions (ref. 5) might be prevented. These copolymers might also be a route to control the rate of release of salicylic acid and could therefore be used as a controlled drug release system.

Unfortunally incorporation of o-oxybenzoyl groups by means of a transesterification reaction of PLLA ($\overline{Mn}$ = 4 * 10^5) with o-acetylsalicylic acid using different types of catalysts did not succeed. No incorporation took place.

Blends of PLLA with Poly(o-oxybenzoyl): Two blends of high molecular weight PLLA ($\overline{Mv}$ = 5 * 10^5) and poly(o-oxybenzoyl) ($\overline{Mn}$ = 2050) were made by dissolving the polymers in chloroform, giving a sligthly pink solution. After precipitation and compression moulding, the blends showed a marble-like structure. This can presumably be attributed to some degradation of PLLA as a result of the presence of the carboxylic end groups of poly(o-oxybenzoyl). The results of the mechanical testing of the blends are given in Table 2.

Table 2

Mechanical properties of poly(L-lactide)/poly(o-oxybenzoyl) blends.

weight % poly (o-oxyben.)	σ (MPa)	ε (%)
0.0	72.3	7.1
17.3	53.2	4.4
28.1	36.6	5.7

It shows that a negative effect on the tensile strength occurs with an increase in the amount of poly(o-oxybenzoyl). This can be attributed to the stiff o-oxybenzoyl units and the degradation of the PLLA. Further optimization of processing conditions and increase of the molecular weight of the poly(o-oxybenzoyl) is expected to improve the mechanical properties of these blends.

Salicylic acid initiated PLLA polymerization and Zn(salicylate)2 as a catalyst: The polymerization of L-lactide in the presence of Sn(Oct)2 proceeds via a coordinated insertion mechanism (17,20), small amounts of H2O or hydrolyzed monomers cannot completely be excluded and might be the true initiator of the polymerization (21,22). It is generally accepted that the ring opening reaction of lactide can be initiated by alcohols (23). A small quantity of alcohol acts as a molecular weight control agent. Using salicylic acid in the ring opening polymerization of L-lactide, initiation will preferentially take place at the hydroxy group attached to the aromatic ring, although initiation by the carboxylic group cannot completely be excluded (24,25).

Using this concept, an amorphous low molecular weight PLLA (Tg = 46 °C) was synthesized using 5.2 mole % salicylic acid as the initiator. The molecular weight of the polymer determined by means of titration with a KOH solution was $\overline{Mn}$ = 2609 (calc. $\overline{Mn}$ = 2769). Evenso an amorphous waxy low molecular weight copolymer of L-lactide and ε-caprolactone (50/50) was synthesized

($\overline{Mn}$ = 2544) using 5.2 mol % salicylic acid. Obviously, it is possible to incorporate salicylic acid endgroups into poly(L-lactide) (co)polymers. Polymers of these kind might be used for the controlled release of salicylic acid as the salicylic acid initiator will be released upon hydrolysis.

Although $Sn(Oct)_2$ is a suitable and often used catalyst for the polymerization of L-lactide (it is also FDA approved), use of a zink containing catalyst instead of tin might prove to be less toxic in the human body. $Zn(salicylate)_2$ was synthesized by reaction of ZnO and salicylic acid to form a Zn-salt (25). Reaction of ZnO with salicylic acid resulted in large brown crystals (Found: Zn, 17.2 %; C, 49.5 %; H 3.8 %: Calc. for $Zn(C_7H_5O_3)_2$: Zn, 19,3 %; C, 49.5 %; H, 2.9 %). The Zn-salicylate showed catalytic activity. Polymerization of L-lactide with 1.0 mole % $Zn(salicylate)_2$ yielded a brittle, crystalline, low molecular weight polymer with a melting temperature of 153.0 °C and a heat of fusion of 39.1 J/g. Conversion of the monomers measured by ^1H NMR was 97.09 %.

Eutectic solidification of the poly(L-lactide)/o-acetylsalicylic acid system: Figure 2 shows the phase diagram for poly(L-lactide)/o-acetyl-salicylic acid mixtures.

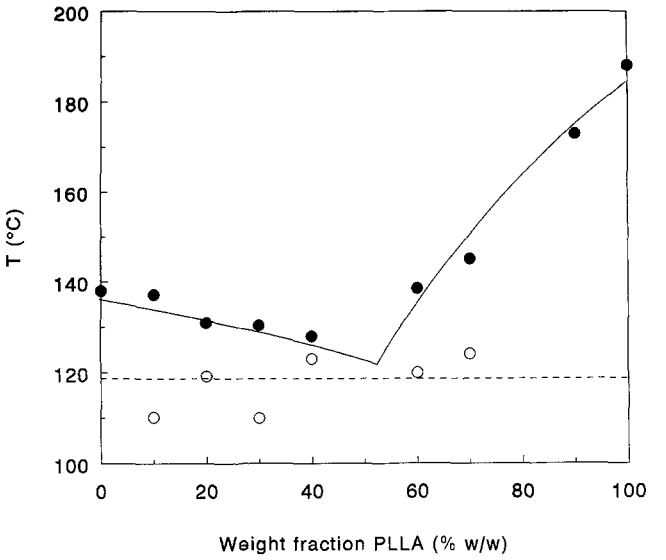

Figure 3: *Phase diagram for the poly(L-lactide)/o-acetylsalicylic acid system.*

The mixtures formed an eutectic composition for 52 % w/w of poly(L-lactide) with an eutectic melting temperature of 119 °C. However as o-acetyl-salicylic acid polymerizes quite easily, it is not possible to distinguish if the minimum in the curve for the poly(L-lactide)/o-acetyl- salicylic acid system is due exclusively to eutectic crystallization.

Conclusions

The results presented in this study show that along different ways it is possible to incorporate salicylates into PLLA. These polymers might be used as bone-fracture fixation devices. The whole polymeric system is expected to eventually degrade and release lactic- and salicylic acid upon degradation (hydrolytic or enzymmatic).
Besides load bearing devices, the modified PLLA polymers might probably also be used as a controlled release system for salicylic acid. For this purpose, also copolymers of L-lactide and other lactones can be used. Furthermore the poly(L-lactide)/o-acetylsalicylic acid system formed an eutectic composition for 52 % w/w of poly(L-lactide) with an eutectic melting temperature of 119 °C.

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