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Biodegradable brush-like graft polymers from poly(D,L-lactide) or poly(D,L-lactide-co-glycolide) and charge-modified, hydrophilic dextrans as backbone—Synthesis, characterization and *in vitro* degradation properties

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Brush-like graft polylactide (PLA) and poly(lactide-co-glycolide) (PLG) containing water soluble charged dextrans: dextran sulphate sodium (DSS) and diethylaminoethyl dextran chloride (DEAED) as backbones were synthesized in a bulk polymerization reaction using stannous octoate as catalyst. The polymers were characterized by n.m.r., g.p.c., LS, intrinsic viscosity measurement and d.s.c. methods. Brush-like graft PLA and PLG have different physico-chemical properties compared to linear polyesters such as PLA and PLG. Significantly accelerated degradation properties of the graft polymers were observed compared to linear PLG. A rapid decrease in polymer molecular weight and polymer mass demonstrates the influence of charged functionalities in the backbone. The nonlinear chain structure and an increased number of polar end groups accelerate the degradation and the apparent mass loss of the brush-like graft PLG when the weight average molecular weight (M_w) is still higher suggests a different mechanism from that of linear PLG. The polar groups in the polymeric backbone facilitate the cleavage of ester bonds. A discontinuous polymer mass loss in the case of linear PLG was not observed for brush-like graft polyesters. The charged polyelectrolyte backbone may also allow higher drug loading of parenteral delivery system with peptides and proteins due to ironic interactions. © 1997 Elsevier Science Ltd.

(Keywords: brush-like graft polyester; polyelectrolyte backbone; poly(lactide-co-glycolide))

INTRODUCTION

Biodegradable polymers represent a class of biomaterials with growing importance, especially for the field of biomedical applications, among which biodegradable polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL) and their respective copolymers, especially poly(lactic-co-glycolic acid) (PLG), are playing a prominent role[1]. These polyesters, produced by a ring opening polymerization, degrade in the body through hydrolysis of the main chain ester bonds to non-toxic cleavage products[2].

A well proven advantage of PLG polymers is the versatility of modifying polymer properties and performance characteristics by copolymerization. For application in controlled drug delivery, it is necessary to adjust drug release and polymer degradation rates by careful manipulation of monomer stereochemistry, comonomer ratio, polymer molecular weight. Because the mechanism of biodegradation is simple hydrolysis of the ester linkages, it is apparent that each of these factors plays an important role in the *in vivo* performance of PLG[3].

The drug release from PLA and its copolymers PLG, is, in general, controlled by both drug diffusion and polymer erosion. Linear random PLG with molar ratio of about 50/50 is widely used in controlled drug delivery, due to its fast degradation rate[4].

Despite considerable efforts, drug release from PLG devices are often not satisfactorily controlled. Release patterns deviating from an ideal 'infusion like' profile are not uncommon and especially hydrophilic drug candidates with $M_w > 500\,g\,mol^{-1}$, such as peptides and proteins, have shown *in vivo* plasma-level/time curves with clear discontinuities. Pharmacological effect and/or pharmacokinetic data were published recently on naferelin[5], tryptorelin[6], leuprorelin[7], IFN-β-implants[8], goserelin[9], leuprorelin microspheres[10], somatostatin analogues[11], and interleukin-2[12]. The observed *in vivo* drug release profiles have been described as 'polyphasic'[5] or 'triphasic'[13].

For the *in vivo* release pattern of biodegradable parenteral-depot systems, two phases of drug release can be distinguished. An initial phase during which release occurs predominantly by a pore-diffusion mechanism[14] through an interconnecting network formed by the dissolving drug substance itself. The

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second release phase is governed by polymer degradation. There is some controversy as to whether erosion of polymer itself[5] or water uptake[15] ultimately control the drug release is this phase. Similar release patterns of drugs with different molecular weights and hydrophilicities seem to be in evidence for erosion-control[16,17].

To overcome 'polyphasic' or 'biphasic' drug release profiles, many approaches were proposed, among which, the two most important rely either on increasing the hydrophilicity of PLG and/or on accelerating the polymer degradation rate. An increased hydrophilicity of PLG causes more rapid swelling of the polymeric matrix, thereby promoting drug diffusion. Blends of poly(vinyl alcohol) (PVA) and PLG were reported to show accelerated drug release rates[18]. ABA block copolymers consisting of PLG A-block and polyoxyethylene B-block were synthesized and studied for controlled release of macromolecules[17,19-21]. Further possibilities for an increase of polymer degradation are addition of accelerants[5], or changes of the polymer chain structure[21-23].

Star-shaped aliphatic polyesters of ϵ-caprolactone were obtained by Schindler and coworkers[21], when they initiated the polymerization by sugar alcohols, such as sorbital or ribitol. In the case of cross-linked hydrogels prepared from star-branched copolymers of capro- and valero-lactone with glycerol, an enzymatic surface erosion was observed[22]. Initial work done by Kissel and coworkers[23] on the synthesis of graft PLG polymers using different polyols, e.g. PVA, cyclodextrin and dextran acetate generated 'brush-like' polyesters exhibiting degradation profiles significantly different from that of linear PLG. Biphasic or polyphasic release profiles often observed with linear PLG were smoothed to a monophasic profile. Moreover, polymer degradation rate and mass loss (polymer-erosion) from microspheres were accelerated in comparison to PLG of similar M_w, due to more rapid water uptake and an accelerated formation of water-soluble degradation products caused by the structural modification of PLG. This material was used for biodegradable bromocriptine microspheres, yielding a continuous drug release profile over one month.

By introducing polyelectrolytes as backbones into brush-like graft PLG, a new concept to accelerate degradation of matrix and promote water-uptake due to the hydrophilicity of polyelectrolytes is proposed. An additional benefit could be the influence of charges on increasing the drug loading and modulation of peptide and protein release by ionic interactions between drug and polymeric matrix. Here, we report the synthesis and properties of 'brush-like' graft poly(lactide-co-glycolide) with polyelectrolytes: dextran sodium sulfate and diethylaminoethyl dextran chloride as backbone molecules.

EXPERIMENTAL

Materials and methods

D,L-Lactide and glycolide (Boehringer Ingelheim, Ingelheim, Germany, S-grade) were both recrystallized twice from ethyl acetate and dried at room temperature *in vacuo* (0.4 mbar) over P_2O_5 for 48 h. The melting points were 126°C and 83°C respectively. Dextran (Sigma, St. Louis, USA, M_w 500 000), dextran sodium sulfate (DSS, Sigma, M_w 5000, 8000 and 500 000) and diethylaminoethyl dextran chloride (DEAED, Sigma, M_w 500 000) were purified by the following method: charged dextran in 2% aqueous solution was reprecipitated by gradual addition of ethanol, after filtration, the purified dextran, DSS and DEAED were dried at 40°C *in vacuo* (0.4 mbar) over P_2O_5 for several days before polymerization to remove residual water. TGA (thermogravimetrical analyser) was used to determine residual solvents and water showing no detectable mass loss in the temperature range of 25–200°C under argon atmosphere. Stannous octoate (Aldrich, Milwaukee, WI, USA) was used without further purification.

Synthesis of the brush-like graft PLA and PLG with charged dextran as backbone

A 100 ml tri-neck flask charged with 28 g of D,L-lactide, 22 g of glycolide, and 50 mg of DSS was immersed into an oil bath, preheated to 170–200°C until the monomers melted. Under nitrogen and stirring, 200 mg of stannous octoate was injected at 170°C and reacted for 30 min. Subsequently, the bath temperature was lowered to 150°C, and the reaction was continued for additional 3.5 h. After cooling to room temperature, the product was dissolved in 100 ml of methylene chloride, washed with 200 ml of distilled water three times to remove unreacted DSS, then filtered, and precipitated in 400 ml of ethanol. The polymer was dried *in vacuo* at 30°C for 2 days until a constant weight was obtained. Both conversion of LA and GA were higher than 90%. The yields were in the range of 90% or higher.

Polymer synthesis for DEAED–PLG and dextran–PLG were carried out as described above for DSS, except that the temperature was kept constant at 150°C. The linear PLA and PLG were prepared under similar condition without dextran.

The products were characterized by ^{1}H n.m.r., g.p.c., d.s.c.[19], light scattering experiments (LS) and intrinsic viscosity measurement.

Endgroup analysis by potentiometric titration

An exactly weighed amount of polymer (*ca.* 1 g) was dissolved in 40 ml of a mixture of acetone and methanol (3/1 v/v). Subsequently, 10 ml of distilled water was added dropwise yielding a transparent solution. This solution was titrated with 0.02 N KOH–methanol solution to an endpoint of pH 8.5.

$$\text{Number of carboxylic endgroup } S = CV_{KOH}/56.1\,W_p \quad (\text{mmol g}^{-1}\text{ polymer}) \tag{1}$$

in which C is the concentration of basic solution, V_{KOH} is the volume of basic solution, and W_p is the weight of polymer.

In vitro *degradation of the graft PLG*

Preparation of films. Films were cast from 10% methylene chloride solution (w/v) on Teflon coated plates. Residual solvents were removed *in vacuo* at room temperature for two days until the constant weight was obtained and subsequently cut into $20 \times 10\,\text{mm}^2$ specimens. The film thickness was found to be $200 \pm 20\,\mu\text{m}$.

In vitro *degradation.* Films of the polymers immersed in 50 ml of 0.2 M phosphate buffer solution (pH 7.2) were stirred in a rotating metal block thermostat (Rotatherm, Liebisch, Germany) at 15 rpm and 37°C. At

preset intervals, the samples were recovered, and dried *in vacuo* to constant weight at room temperature. Molecular weight (g.p.c.) and mass loss (gravimetry) were determined.

Analytical methods

G.p.c. was carried out on Merck size exclusion columns (Lichrogel PS mix and Lichrogel PS 40, 10 μm), thermostatted at 25°C, using methylene chloride as solvent and a differential refractometer as detector (Merck RI 71). Molecular weights were calculated by the universal calibration method using polystyrene reference materials (Merck, M_w 3250; 5100; 19 600; 34 000; and 87 000). All n.m.r. spectra were obtained from $CDCl_3$ or CF_3COOD solution containing TMS as reference at 25°C on a JNMR-FX 100 or 400 (Jeol) spectrometer. D.s.c. measurement was carried out using a differential scanning calorimenter (Perkin Elmer DSC 7) in sealed aluminium pans under nitrogen atmosphere, Thermograms covering a range of 0–200°C were recorded at heating and cooling rate of 20°C min^{-1}.

Light scattering measurement in combination with g.p.c. was carried out on a miniDraw light scattering instrument (Wyatt Technology) with a SDV linear column (300 × 8 mm, 10 μm) and a K5 cell, THF as eluant with a flow rate of 0.700 ml min^{-1}, the wavelength of the laser light source was 690 nm and scattering angles were 45.6, 90.0 and 134.4°. Weight-averaged molecular weights and z-averaged mean square radii were calculated from light-scattering data using the method of Zimm[24]. Calculations were performed using the ASTRA software supplied by Wyatt Technology.

RESULTS AND DISCUSSION

Synthesis and properties of the graft polymers

The ring opening polymerization of cyclic lactones such as lactide and glycolide using Lewis acids as catalysts has been investigated by several groups[23,25]. The polymerization reaction has been interpreted as a 'coordination-insertion' type mechanism[26]. After activation of the cyclic ester-carboxyl function by Lewis acids, such as stannous octoate, co-initiators containing hydroxyl groups lead to ring opening of the lactone as outlined in *Figure 1*. Co-initiators frequently used to modulate the M_w of PLG and dodecanol[27] or in the simplest case water[28]. Using carbohydrates and sugar alcohols, such as D-glucose or mannitol star-graft polymer structures can be obtained[29]. The incorporation of the co-initiator was demonstrated by labelling-experiments. Endgroup-analysis using titrimetry and neutron-scattering data support the star grafted structure of the resulting polymers[22]. These polymers were shown to degrade faster than ungrafted linear PLG of comparable molecular weight. In the case of linear polyols, e.g. dextran or poly(vinyl alcohol) one would expect to obtain brush-like graft polyesters, containing relatively short PLG chains grafted on the polyol backbone. This structure modification is of interest, when both mechanical properties (chain stiffness) and fast degradation are desirable features of the biomaterial.

We have extended this concept to charge containing polyols, because one might expect even faster degradation rates by these functionalities attached to the backbone. Moreover, many peptides and proteins containing charged amino-acids may interact with the charged backbone, yielding a higher drug loading and a decreased initial drug release. To investigate these hypotheses, we have prepared dextran sodium sulfate (DSS) and diethylaminoethyl dextran chloride (DEAED) containing polyesters using stannous octoate as catalyst. The properties of the resulting polymers are summarized in *Table 1*.

The solubility of DSS in the melt of lactide and glycolide is only limited, therefore, higher reaction temperatures (170–200°C) are needed and residual amounts of unreacted DSS are removed by exhaustive extraction with water to obtain pure polymers. The purified polymers are soluble in dichloromethane. The conversions of both monomers (lactide and glycolide) are high (>90%) and the synthesis poses no major difficulties.

DEAED dissolves quantitative in the monomer melt when the temperature exceeds 130°C. Again pure polymers are formed in good yield (~90%).

In the polymerization of lactide or glycolide initiated by a complex of stannous octoate and the charged dextran, the hydroxy group of the dextran functions as a co-initiator. The molecular weight of polymers is related to the concentration of DSS (*Figure 2*), indicating that DSS is directly involved in the polymerization. The same result was observed in the case of DEAED (*Table 1* sample Nos 9 and 10). Kricheldorf *et al.* suggested

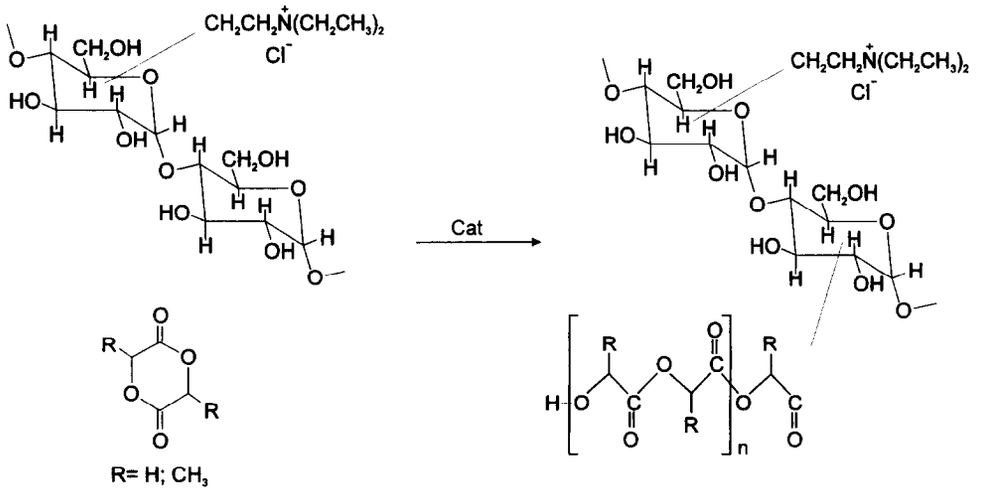

Figure 1 Synthesis of the graft polyester containing charged dextran

Table 1 Synthesis and properties of the graft polyesters

No.	Backbone	M_w	Monomer LA/GA	Initiator/Sugar[a]/M mol/mol/mol[b]	Reaction temperature (°C)	Reaction time (h)	Yield (%)	G.p.c. M_w	G.p.c. M_n	G.p.c. M_w/M_n	D.s.c. T_g °C
1	DSS	5000	50/50	0.85/7.6/1000	170	4	94	33000	11600	2.83	33
2	DSS	5000	50/50	0.85/4.4/1000	170	4	97	54000	25100	2.15	37
3	DSS	5000	50/50	0.85/3.0/1000	170	4	95	62000	32100	1.93	36
4	DSS	5000	50/50	0.85/1.5/1000	170	4	90	76000	45200	1.68	39
5	DSS	8000	50/50	0.80/3.2/1000	170	4	89	58000	23000	2.53	39
6	DSS	8000	75/25	0.80/3.2/1000	170	4	92	58000	25400	2.28	39
7	DSS	8000	100/0	0.80/3.2/1000	170	4	92	59000	31700	1.86	45
8	DSS	500000	100/0	0.20/2.1/1000	170	3.5	100	109000	77300	1.14	47
9	DEAED	500000	75/25	1.2/1.4/1000	150	0.6	91	143000	26800	5.35	40
10	DEAED	50000	100/0	1.2/1.4/1000	150	0.5	90	233000	78700	2.96	52
11	DEAED	500000	50/50	1.8/12/1000	150	12	99	42500	7300	5.81	35
12	DEAED	500000	75/25	1.8/7.8/1000	150	4	100	77000	14200	5.42	45
13	DEAED	500000	100/0	1.8/7.8/1000	150	4	96	87000	18900	4.60	53
14	DEAED	500000	100/0	1.3/12/1000	150	4	91	61000	13200	4.61	52
15	Dextran	500000	50/50	1.8/12/1000	170	4	95	43000	15300	2.81	37
16[c]	–		50/50					53700	14300	3.75	44

[a] DSS or DEAED or dextran
[b] The molecular weight of backbone is that of a unit ring with 1.5 charge group
[c] Linear PLG

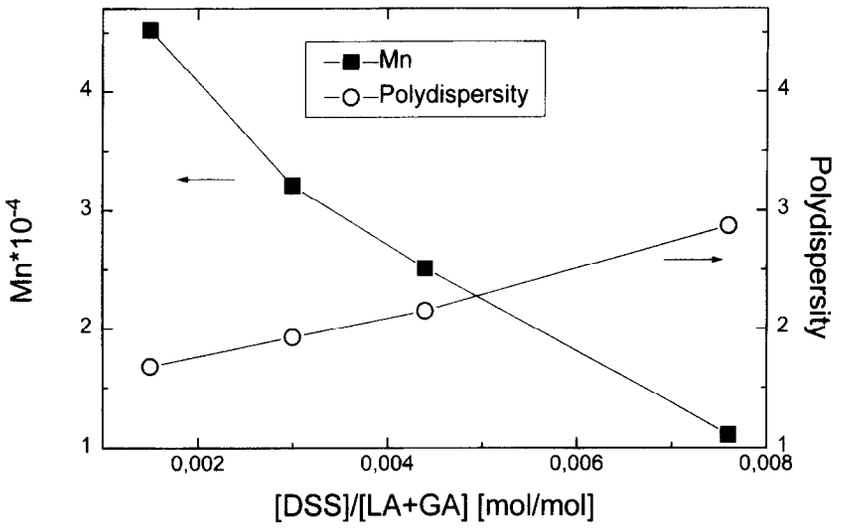

Figure 2 Influence of the concentration of dextran sodium sulfate (relative to monomers) on the molecular weight of DSS–PLG (50/50) (*Table 1* Nos 1, 2, 3 and 4)

recently[28] that ring opening polymerizations of L-lactide using stannous octoate proceeds via a complex-insertion-polymerization mechanism, in which alcohols function as efficient co-initiators, initiating most of the growing PLA chains, as shown by n.m.r. spectroscopy.

Figure 3a shows the ^1H n.m.r. spectrum of ungrafted diethylaminoethyl-substituted dextran in CF_3COOD. This relatively complex DEAED spectrum is also seen in *Figure 3b* after grafting with D,L-lactide. The signals of the polylactide appear at $\delta = 2.16$ ppm (CH_3) and 5.87 ppm (CH). Small signals can be found, $\delta =$ 1.00 ppm corresponding to the CH_3 of DEAED charged group. The proton signals of the dextran ring appear as complex multiplet at $\delta = 4.3$–4.9 ppm. In addition the methyl group CH_3 of lactyl at the grafted unit and the terminal unit contributes signals at $\delta = 2.35$ and 2.02 ppm respectively.

The influence of the impurities in the charged dextran to the polymerization was shown in the g.p.c. traces of DEAED–PLAs with the original or different purified DEAED (*Figure 4*). Because of residual water or other impurities in the charged dextran which may form a co-initiator, g.p.c. trace of DEAED–PLA with original DEAED as co-initiator show two separate peaks (A), one with higher molecular weight corresponding to the graft polymer initiated by the charged dextran and a second one with lower molecular weights corresponding to linear polymeric chains initiated by the impurities, e.g. water, which located at the same elution volume as the g.p.c trace of the linear PLA initiated by stannous octoate. The ratio of the linear polymer to the graft counterpart can be reduced by the purification of the backbone by reprecipitation and removal of volatile impurities *in vacuo* (B). After elimination of water and

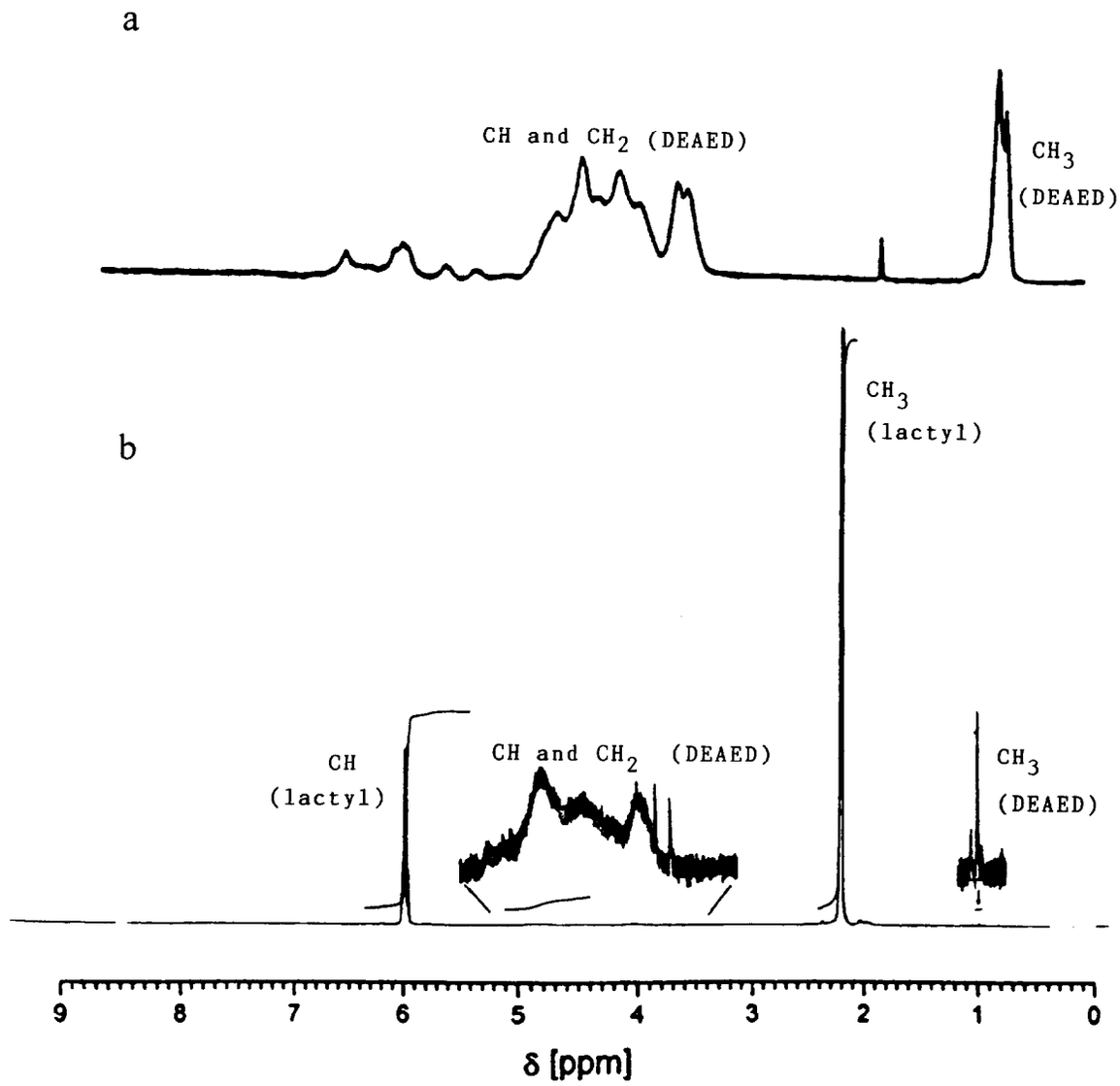

Figure 3 ^{1}H n.m.r. spectrum of DEAED and DEAED–PLA. (a) DEAED in CF_3COOD, (b) DEAED–PLA in CF_3COOD

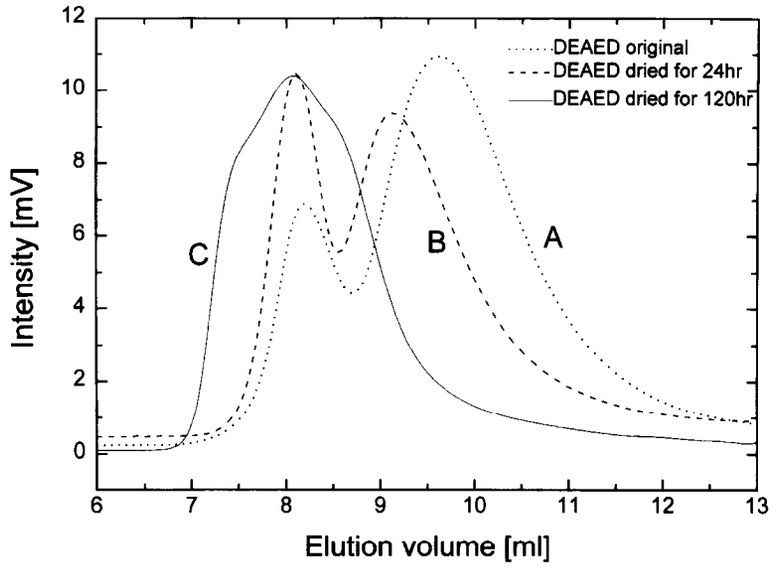

Figure 4 G.p.c. traces of DEAED–PLA initiated by unpurified and purified DEAED

other impurities, a single peak in the g.p.c. trace (C) was found, demonstrating that the graft polymer contain only traces of linear PLA. The polydispersity of the polymers was increased, however, probably due to the high viscosity of the bulk reaction medium, leading to impaired diffusion of monomers and the high reaction temperature.

The molecular weight of the graft PLG determined by g.p.c. is lower than that calculated from the initial molecular weight of the dextrans used and the ratio of the monomer to the dextrans. The hydrodynamic radii of the graft PLG are smaller than those of linear PLG leading to a lower estimate of the relative molecular weight compared to linear polystyrene standards using g.p.c. When determining the absolute molecular weight of graft PLGs using a laser light scattering detector these deviations become obvious, as shown in *Table 2*. Another factor contributing to an increase in polydispersity is the thermal instability of charged dextran at high temperatures. The inherent viscosities of DSS (M_w 500 000) decreased considerably after 2 h exposure to 170°C to *ca.* 20% of the original value. Addition of monomers (LA or GA) even accelerated this thermal degradation process. Dextran and DEAED show similar degradation behaviour. The degradation in the molecular weight of the backbone ultimately leads to a lower molecular weight of the graft PLA or PLG.

Limited solubility of DSS in the monomer melt yields a lower content of the backbone in graft polymer. The low content of DSS and the complex ^{1}H n.m.r. spectrum of the DSS backbone make an assignment of n.m.r signals very difficult. The number of carboxylic endgroups in the graft polymer, as determined by potentiometric titration, is lower than that of linear PLG, offering indirect evidence for the incorporation of DSS (*Figure 5*). This number in the carboxylic end group depends on the molecular weight of DSS–PLG, as well as DEAED–PLG, suggesting that the terminal group is not a carboxylic functionality. In accordance with the complex-coordination mechanism one would expect a graft polymer with terminal hydroxyl groups[28]. The complexity of polymerization reaction and additional transesterification or depolymerization reactions may yield, however, some carboxylic-terminated molecules. Therefore, relatively low acid value of the grafted polymer independent of the molecular weight are obtained.

Laser light scattering is an effective method to investigate the molecular architecture of polymers. The linear and graft polylactide were characterized by light scattering using a light scattering detector in combination with size-exclusion chromatography. The weight average molecular weight and the *z*-averaged hydrodynamic radius (R_w) of gyration which is defined as the square root of the weight average of the mean square radius $(r^2)_i$ are shown in *Table 2*. Because of insufficient solubility of DEAED–PLA in THF, the measurement was conducted in methylene chloride. The gyrative radius of the polymer is a physical property depending on

Table 2 Molecular weight of the polymers by g.p.c. (RI detector) and light scattering measurements

	G.p.c.[a]			LS[b]			
Samples	$M_w \times 10^{-5}$	$M_n \times 10^{-5}$	D	$M_w \times 10^{-5}$	D	R_w (nm)	α
PS standard	–	–		3.60	1.30	22.8	0.596
linear PLA1	1.34	0.89	1.51	1.32	1.55	26.0	0.556
linear PLA2	3.07	1.29	2.38	4.81	1.35	27.6	0.560
DSS–PLA	1.09	0.77	1.41	6.23	–	29.6	0.155
DSS–PLG	0.33	0.12	2.83	0.57	1.37	11.4	0.186
DEAED–PLA	2.33	0.79	2.96	108[a]	1.81[a]	74.5[a]	0.141[a]

[a] Dichloromethane as eluent
[b] In tetrahydrofuran

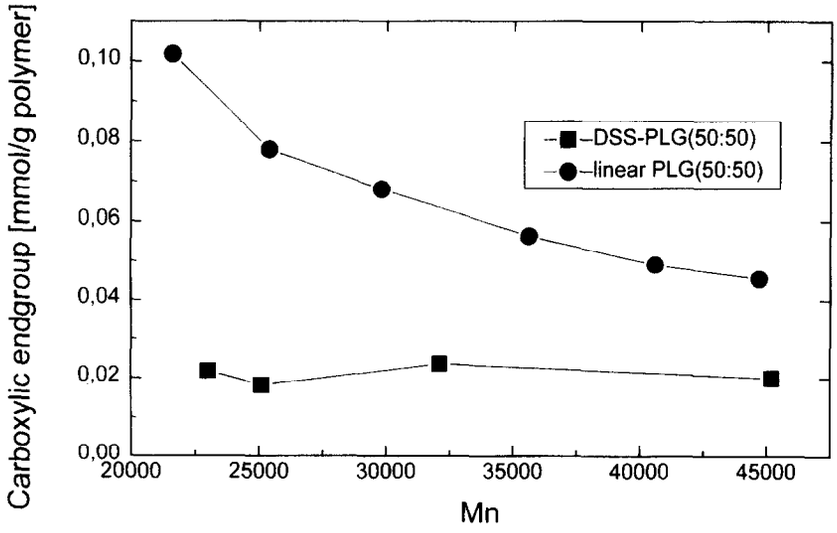

Figure 5 Acidic value analysis of linear or graft (*Table 1*, Nos 2, 3, 4 and 5)

the molecular architecture and average molecular weight. *Figure 6* shows the relation of weight average radius of gyration (R_w) with M_w of linear and graft PLA, as well as standard polystyrene, the linear and graft PLA shows a good correlation between R_w and M_w described by

$$R_w = A\, M_w^{\alpha} \tag{2}$$

in which A is a constant and α is correlated to the architecture of the polymer chain. In dilute solution the polymer architecture can be classified as rod, random coil or sphere, depending on the hardness and stiffness of the polymer chain. Linear macromolecules with rigid chains show a larger radius R_w and α value (rod-like), while flexible graft polymers have smaller R_w and α values than the former and show random coil or sphere shape in dilute solution[30]. A significant difference between linear and graft PLA is shown in *Figure 5*. A smaller hydrodynamic radius and α value of the graft PLA compared to linear PLA, can be regarded as evidence of the brush-like structure of the graft PLA, because it is known that the graft polymers exhibit a smaller hydrodynamic volume than their linear counterparts[30].

Evidence for the branch architecture can also be obtained from the determination of the intrinsic viscosities. *Figure 7* shows the relationship between intrinsic viscosities of linear and graft PLG (75/25) in THF solution (vs.) the weight average molecular weights (g.p.c.). The intrinsic viscosities of the graft PLGs are smaller than those of linear polyesters of comparable molecular weight. This is in agreement with the finding reported by others[2,31]. As in the case of the radius of gyration, ratios of the intrinsic viscosity of the graft polymer to the corresponding linear polymer properties can be formed, assuming similar molecular weights[32]

$$g = [\eta]_g/[\eta]_l \tag{3}$$

This ratio g is comparable to the ratio of the hydrodynamic radius of the branched species to corresponding linear polymer having the same molecular weight[32]. The ratio g depends on the number of branches, is, however, also influenced by the solvent. By the extension of the plots in *Figure 7*, in the range of molecular weight in *Table 1*, the value of g of DSS–PLG to linear PLG is from 0.83 (M_w 30 000) to 0.80 (M_w 140 000), and that of DEAED–PLG

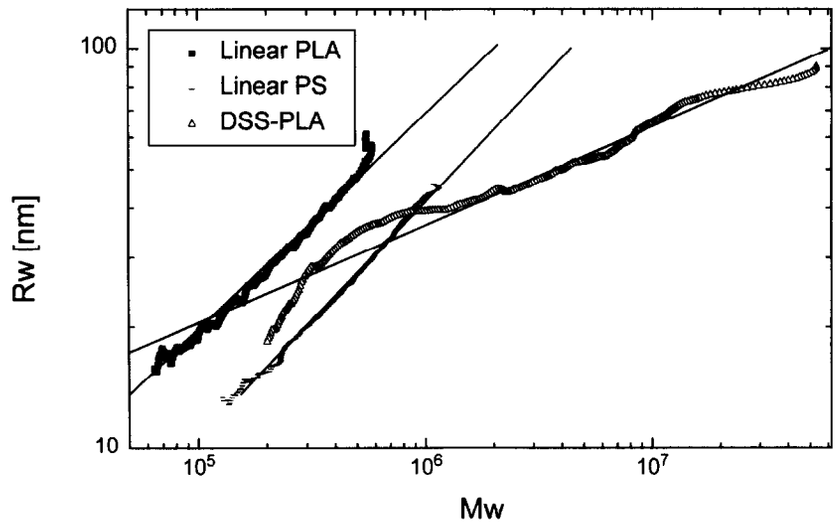

Figure 6 Relation of the gyration sizes and M_ws of different polymers in THF solution measured by light scattering

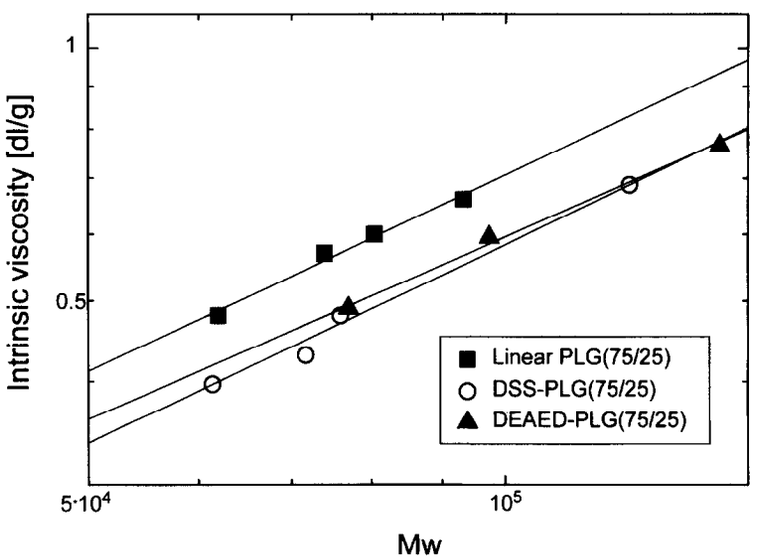

Figure 7 Relation of the intrinsic viscosities of M_ws of the linear and graft PLG in THF

to a linear one is 0.89 (M_w 30 000) to 0.82 (M_w 250 000). These data demonstrate the smaller hydrodynamic volumes of DSS- and DEAED–PLG due to the graft architectures and agree with the results of n.m.r., acidic value analysis and LS measurement.

Thermal properties of the grafted polymer were determined using differential scanning calorimetry (d.s.c.). The glass transition temperature (T_g) of the grafted polymers was decreased by 5–10°C, compared to corresponding linear PLG (*Table 1*). The increase in steric hindrance due to the nonlinear structure seems to decrease van der Waal's interactions between the polymer chains and therefore depresses the glass transition temperature T_g. In the case of L-lactide, used for DSS–LPLA, the melting temperature T_m is lowered by *ca.* 20°C, and the crystallinity is reduced to 25%, compared to that of linear LPLA (37%)[3].

In vitro *degradation*

The molecular weight of brush-like polyesters was determined by g.p.c. after immersion in phosphate buffer solution (pH 7.2) at 37°C (*Figures 8* and *9*). A rapid decrease of the molecular weights and mass loss are observed significantly different from that of linear PLA and PLG. The possible factors contributing to the accelerated degradation in buffer solution are the nonlinear chain structure, the charges on the backbone and the increased number of the terminal polar groups due to the graft architecture.

Figure 10 shows the influence of steric structure and charge on the degradation of graft PLG (50/50). Significant acceleration of the degradation of DEX–PLG indicates that the nonlinear chain structure of the graft polymers increase the steric hindrance and reduces van der Waal's interaction of molecules and T_g, the permeability of water is improved[21].

The charges on the backbones also shows the influence on the degradation of graft polymers (*Figure 10*). Both positive or negative charged functionalities may interfere with the hydrolysis of ester bonds of PLA and PLG. Especially, PLG is more sensitive to hydrolysis, due to its random chain structure[33], lower T_g, and chain flexibility which increases the probability of the polar ion attacking ester linkage. Compared to the random hydrolysis of linear PLA and PLG, in the case of the brush-like polyesters, the cleavage of chains could preferentially occur in the vicinity of the polar group on the backbone or graft point. This leads to a noticeable acceleration of the decrease in molecular weight, the destruction of nonlinear architecture, and formation of linear polymer with lower molecular weights.

The nonlinear structure of the brush-like graft PLA and PLG is also expected to promote effectively the permeability of water into the polymer matrix, due to an increase of hydrophilicity resulting from polar terminal endgroups and charged functionalities on the backbone.

The graft polymers consisting of the more hydrophobic PLA show slower degradation rates in the initial period up to 10 days, compared to PLG. This can be explained by higher T_g and hydrophobicity of matrix, and reduced water uptake. When the polymer degrades, a gradual decrease of T_g is seen. The diffusion coefficient of water is then increased and polymer degradation accelerates, until the destruction of nonlinear architecture leads to the formation of linear PLA.

The polymer mass loss of the graft PLG is substantially accelerated during degradation in buffer solution, even when the molecular weight is still high. In the case of linear PLG (50/50) no mass loss is observed before M_n reached values of *ca.* 700–2000 Da[15]. It is interesting to note that the erosion (mass loss) of the graft PLG is different from this behaviour possibly due to the fact that water soluble oligomers are produced more rapidly. The large number of hydroxy groups in the charged dextran backbones leads to many short branches. These short branches degrade in water yielding soluble segments of polyesters after a few cleavage steps. This is a possible explanation for the differences in the decrease of the molecular weights of the linear and graft PLG. The influence of charges on the degradation behaviour becomes apparent when we compare with DEX–PLG (50/50) (*Figure 10*). In this case a significant effect on the mass loss is observed which we attribute to a combination of catalytic cleavage of the pending PLG chains and a higher water content in the matrix.

CONCLUSIONS

The graft brush-like polyester of lactide and its random copolymers with glycolide containing negatively charged

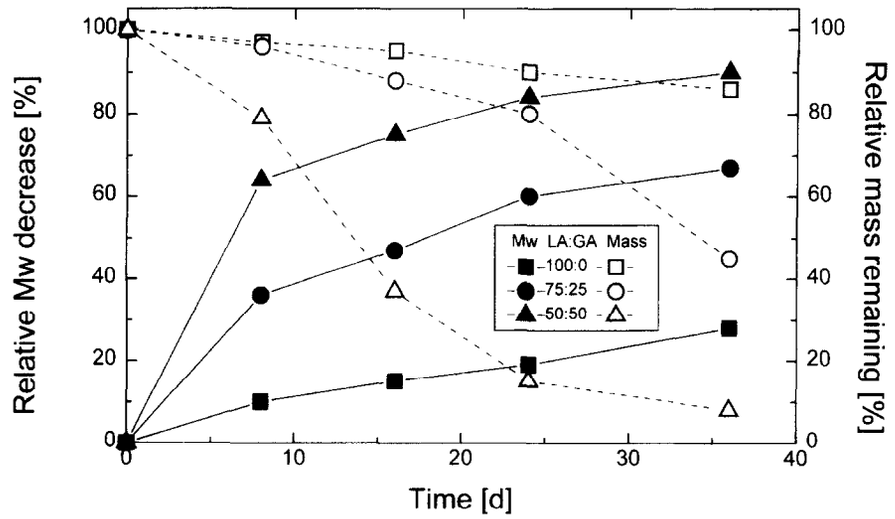

Figure 8 *In vitro* degradation of DEAED–PLG in phosphate buffer (pH 7.2) (*Table 1*, Nos 11, 12 and 13)

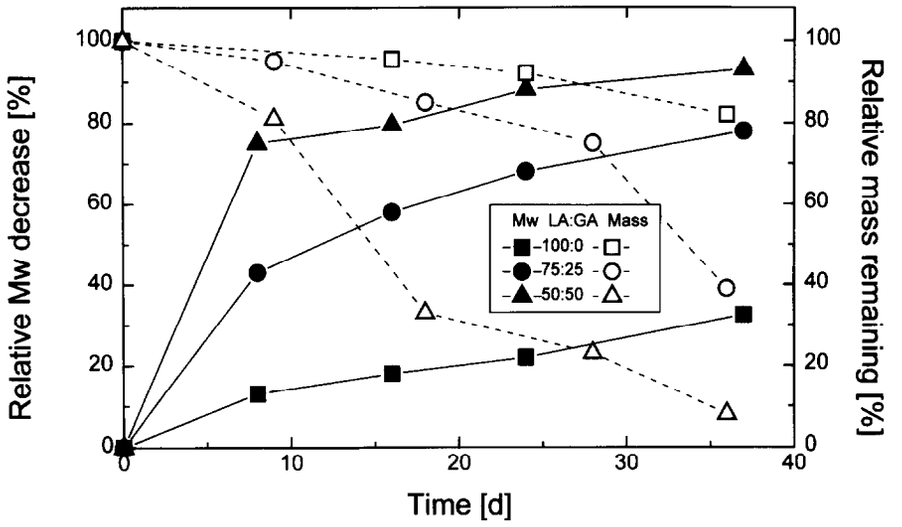

Figure 9 *In vitro* degradation of DSS–PLG in phosphate buffer (pH 7.2) (*Table 1*, Nos 5, 6 and 7)

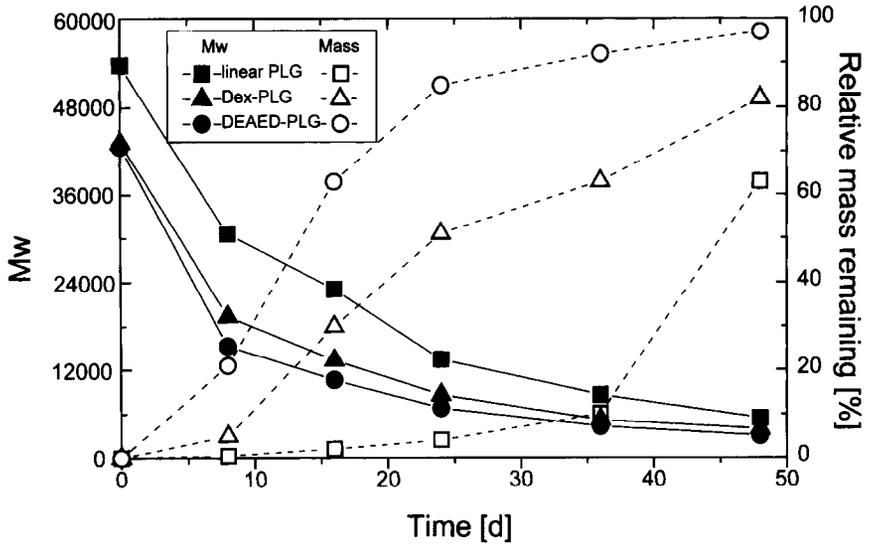

Figure 10 Influence of steric structure and charge on the degradation of PLG (50/50) (*Table 1*, Nos 11, 15 and 16)

dextran sodium sulfate and positively charged diethylaminoethyl dextran chloride as backbones were synthesized by bulk polymerization using stannous octoate as catalyst.

The graft polymers were characterized by n.m.r., g.p.c. LS, intrinsic viscosity measurement and d.s.c. The incorporation of charged dextran is demonstrated by ^{1}H n.m.r. spectra, the acidic value analysis and the relation of polymer properties and the reaction condition. Light scattering and intrinsic viscosity measurements show that the graft polymers have smaller radii of gyration which are less dependent on M_w, this difference demonstrates that the graft PLG has a different architecture from the linear one. T_g of the graft PLG is decreased by *ca.* 5–10°C due to nonlinear architectures.

The degradation of the graft polyesters show a different mechanism from that of linear PLG. An accelerated decrease in both molecular weight and polymer mass demonstrates the effects of the charged functionalities and nonlinear chain structure on the degradation behaviour of the graft polyester. The unusual decrease in the mass suggests the existence of many short branches in the graft polymer.

Biodegradable graft PLG with polyelectrolytes as backbone offer the possibility to manipulate release and compatibility of hydrophilic drug substances in a more flexible way than commonly used linear PLG, and may offer a possibility to overcome 'polyphasic' or 'biphasic' drug release profiles from biodegradable delivery systems due to faster erosion of the polymer. The introduction of charges into the polymer backbone may improve the compatibility of the polymer to sensitive drugs, such as protein and nucleic acids. Parenteral protein delivery and gene transfer systems could benefit from such an approach.

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