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Synthesis and Characterization of Chitosan-g-poly-(D, L-lactic acid) Copolymer

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Abstract: Biodegradable chitosan-g-poly (D, L-lactic acid) copolymers were prepared *via* two methods. (1) The lactide was grafted onto hydroxyl groups of chitosan by using macromolecular initiator sodium of trimethylsilyl-chitosan, (2) poly (D,L-lactic acid)(PLA) with low molecular weight can be linked to the amino group by coupling activated PLA to trimethylsilyl-chitosan. Two graft copolymers had hydrophilic-hydrophobic character and can be applied as carriers for drug delivery.

Keywords: Poly (D, L-lactic acid), chitosan, graft copolymer, coupling, macromolecular initiator.

Recently, new biodegradable materials based on hydrophobic polyester and hydrophilic polysaccharide have attracted much attention because of the application of ecological situation[1~3]. Chitosan is a cationic polysaccharide with non-toxicity, biocompatibility, it has been widely applied in pharmaceutical research as a carrier for drug delivery and biomedical materials[4~5]. However, the insolubility in general solvents except for acid aqueous solution has limited its extensive studies. Poly (D, L-lactic acid) (PLA) and its copolymers have been applied for biomaterials. However, strong hydrophobic PLA limited its application in soft tissue and drug-controlled release. We found that chitosan (deacetylation degree 50%) can be dissolved in dimethyl sulfoxide (DMSO), by trimethylsilylation of its hydroxyl groups, PLA was grafted amino groups or hydroxyl groups of chitosan by various methods. These hydrophilic-hydrophobic biodegradable materials could be applied as drug carriers.

Preparation of chitosan with deacetylation degree 50% was an important procedure[6]. In brief, 80 mL 10% aqueous acetic acid including 3 g chitosan (deacetylation degree of chitosan 90%, M_w=1.5*10^5) was poured into mixture of 10 mL acetic anhydride and 1 L pyridine. The reaction was stirred for 24 hours, then pH value was adjusted to 7, finally the white flake product was filtrated and dried at room temperature.

In order to control the number of hydroxyl groups and achieving solubility in organic solvents, we prepared trimethylsilyl-chitosan (TMS-chitosan) adopting hexa-methyldisilazane (HMDS) as a silylating agent. The TMS-chitosan was carried out in nitrogen-purged flask as follows. 1 g chitosan was dissolved in 50 mL DMSO

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completely. Then 3-6 g HMDS and 0.5 g triethylamine were added. The reaction mixture was maintained at 50 ºC for 16 hours under stirring. The product was precipitated by acetone and washed with ethyl ether. The purified product was characterized by ^{1}HNMR and FT-IR spectra. The signals of ^{1}HNMR ($CDCl_3$, δ ppm) showed protons of trimethylsilyl (TMS) group at δ 0.1 and protons of chitosan at δ 4.8. The peak of δ4.8 disappeared when the chitosan was completely protected (**Figure 1**). The trimethysilylation of chitosan was further evidenced by FT-IR (KBr, cm^{-1}) spectrum. New absorption related to TMS group could be detected at 841, 1049 and 1251 cm^{-1}.

Lactide could be grafted onto hydroxyl groups of chitosan by ring-opening polymerization. The procedure must be carried under dry condition as follows. 100 mg TMS-chitosan was dissolved in 25 mL dry DMSO at room temperature. Then 9.6 mg

Figure 1 The ^{1}H NMR spectrum of TMS-chitosan

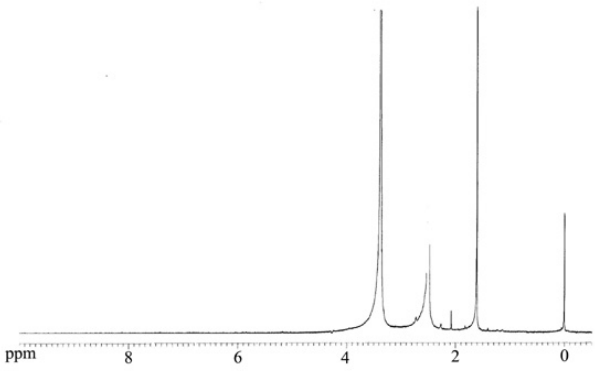
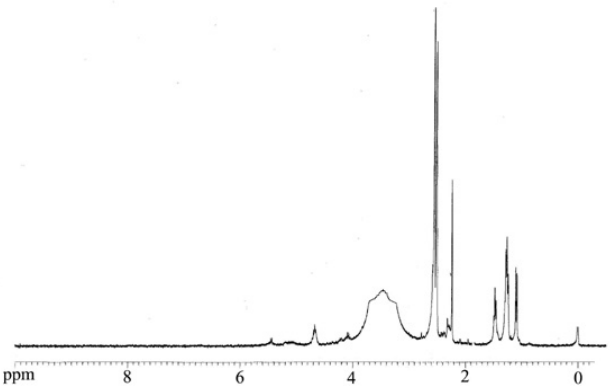


Figure 2 The ^{1}H NMR spectrum of chitosan-g-PLA



sodium *t*-butoxide was added in above solution, stirring for 1 hour, hydroxyl groups were reacted with sodium *t*-butoxide to convert into macromolecular initiator. Finally 2.16 g lactide was added to the solution and kept for 2 hours. Polymerization was terminated and deprotected by addition 2 mL 1 mol/L HCl aqueous solution. The grafted copolymer was precipitated by acetone and washed with ethyl ether. By measuring gravimetry of the grafted copolymer, molecular weight of the copolymer was hardly increased after adding lactide due to the limited activity of the macromolecular initiator. The deprotected grafted copolymer was characterized by ^{1}H NMR spectrum (**Figure 2**). The signals of ^{1}HNMR ($CDCl_3$, δ ppm) at 4.1 and 5.15 showed the existence of terminal and internal proton signal of PLA. The signal of methyl proton linked amide ($NHCOCH_3$) was observed at 2.1 ppm.

PLA could be linked to amide group of the chitosan. Firstly, PLA (M_n=80) was synthesized by polycondensation of D,L-lactic acid using Sn $(Oct)_2$[7]. To couple the PLA onto chitosan, the PLA was activated by dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide in $CHCl_3$. The PLA was added to the DCC solution by stirring for 2 hours, then the N-hydroxysuccinimide was added for 8 hours, thereafter the precipitation was filtrated and $CHCl_3$ was evaporated under reduced pressure, finally the activated PLA was washed with ethyl ether. The reaction of the activated PLA coupling onto chitosan with complete protection of TMS group was carried out at 50° C in dry DMSO. The product was deprotected by 1 mol/L HCl aqueous solution. At last, the coupled copolymer was precipitated by acetone.

The structural difference between activated PLA and PLA was due to the formation of ester bond with NHS (**Figure 3**). The signals of^1 HNMR ($CDCl_3$, δ ppm) at 2.65 showed its formation. For preventing degradation, the coupled copolymer was prepared at mild reaction condition (30-50 ℃) and shorter reaction time (6-12 hours). The coupled PLA was characterized by ^{1}H NMR spectrum (**Figure 4**).

Figure 3 The ^{1}H NMR spectrum of activated PLA

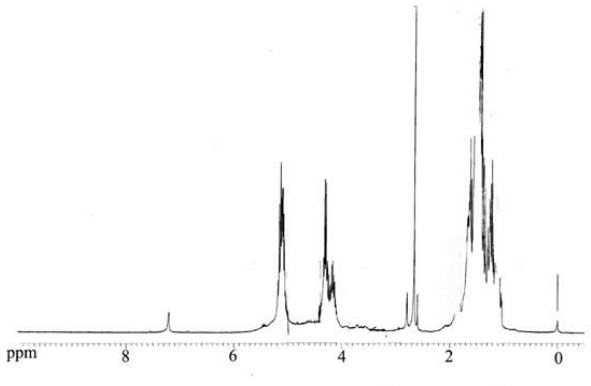
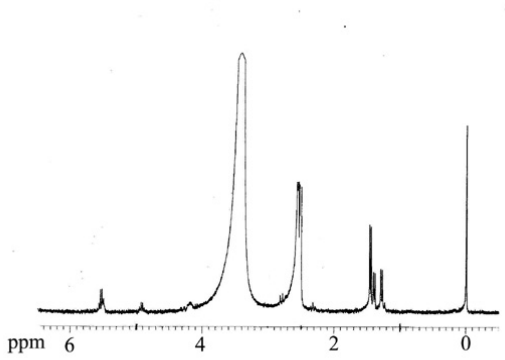


Figure 4 The ^{1}H NMR spectrum of activated PLA grafted chitosan



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