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A Study on Xylitol Based Copolyester for In vitro Degradation Applications

Deepa K and Jaisankar V*

PG and Research Department of Chemistry, Presidency College, Chennai –600005,
Tamil Nadu, India.

Abstract : In this paper, we report on the synthesis and characterization of copolyesters from xylitol, lactic acid and sebacic acid through a catalyst free melt polycondensation method. The synthesized aliphatic random copolyesters were characterized by means of fourier transform infrared (FTIR), viscosity measurements, ^1H and ^{13}C nuclear magnetic resonance, differential scanning calorimetry (DSC) and gel permeation chromatography (GPC) studies. The effect of copolymer composition on the physical and thermal properties as well as degradation test was investigated. The mechanical properties evaluated for the polyester films in the tensile mode shows that the polymer has characteristics of elastomers and stiff thermosets. The degradation test was carried out in alkali medium. The phase behaviour of the polymers was studied by differential scanning calorimetry. As all the monomers used in these materials are component of other biomaterials, the synthesised xylitol based triblock copolyesters could be excellent candidates as future biomaterials.

Keywords : Catalyst free melt polycondensation, spectral and degradation studies.

Introduction

Recent developments in the synthetic biodegradable polymers have substantial interest for macromolecular science in both environmental and biomedical perspectives. Biodegradable polymers, including both natural and synthetic, have been extensively used for tissue repair purposes, including chitosan, collagen, hyaluronic acid (HA), polyester, polyanhydride, polyamide, polycarbonate, poly(amino acid), polyimide, polyphosphazene¹⁻³. Synthetic biodegradable polymers are preferred over natural polymers, metals and ceramics, because of their flexibility in tailoring the physical properties, tissue response, biodegradability and biocompatibility⁴⁻⁶. Biodegradable elastomers have been developed to overcome problems associated with biodegradable thermoplastic materials, such as rigid mechanical properties, bulk degradation and acidic degradation products in some cases⁷⁻⁸. They have been employed in a variety of biomedical applications such as drug delivery and tissue engineering⁹. Aliphatic functional polyesters are an important class of biomaterials for pharmaceutical and biological applications because of their biocompatibility, biodegradability, strength and elasticity¹⁰. The wide usage of polyesters among the biodegradable polymers can be ascribed to their myriad

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advantages¹¹. Sugar-based alcohols have been widely studied and used in the polycondensation of biodegradable polyesters¹². Xylitol was chosen for the present study because it is non-toxic and cytocompatible because sugar alcohols are endogenous to human metabolism¹³. In addition, it is hypothesized that the structure of xylitol will enhance the mechanical properties of the resulting polymers¹⁴ and the presence of several OH groups will increase the crosslinking resulting in a higher modulus¹⁵. Furthermore, the hydrophobicity of the xylitol-based polymers can be tuned.

In the present work, we report on the synthesis of the new class of biodegradable and bioelastomers polyesters was synthesized by performing an catalyst free melt polycondensation reaction of xylitol, lactic acid and sebacic acid. The synthesized polyesters were characterized by fourier transform infrared (FTIR), viscosity measurements, ¹H nuclear magnetic resonance (¹H NMR) and ¹³C nuclear magnetic resonance (¹³C NMR) spectra. The phase behaviour of the polymers was studied by differential scanning calorimetry (DSC). The molecular weight (M_w) and polydispersity index were determined by Gel Permeation Chromatography (GPC). *In vitro* degradation and swelling studies of the polyester were examined.

Experimental Details

Materials

Xylitol (99%; Sigma Aldrich), Lactic acid (Merck AR grade) and sebacic acid (Lancaster AR grade). All the other materials and solvents used were of analytical grade.

Synthesis of polyesters

The copolyester poly (xylitol lactate sebacate) (PXLSe) was synthesised by the catalyst free melt polycondensation technique as reported as earlier¹⁶. The polycondensation flask was a three neck flask equipped with a nitrogen inlet, a condenser and a thermometer. A magnetic stirrer was used to stir the reaction mixture. The appropriate molar amounts of monomers were melted in a round bottom flask and the temperature of the reaction mixture is raised to 120°C in 20 min. Then, the temperature is gradually raised in 10°C steps every minute to the fixed reaction temperature of 160°C under a blanket of nitrogen gas and stirred for 7 hrs to remove water being the esterification by product. The resulting crude copolymer was dissolved in DMSO and then poured into excess of dry coldmethanol to purify the polyester. Then, the polyester was transferred into polytetrafluoroethylene molds in a vacuum oven at 80 °C for 7 days for further post polymerization process. The obtained yield of polymer was 90%. The cured post-polymerisation was dried in a dessicator for further characterisation. The schematic synthesis is shown in Figure 1.

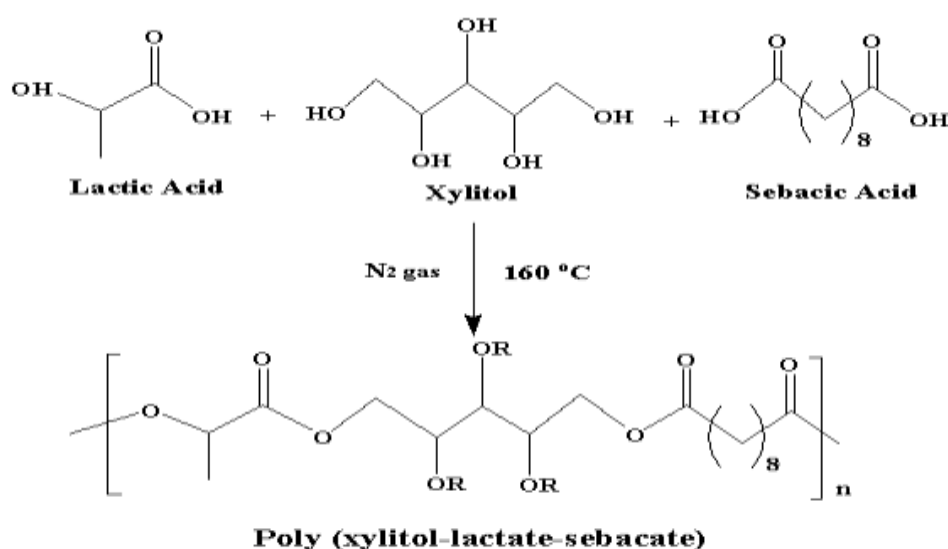


Figure. 1. Scheme of the synthesis of copolyester, (PXLSe)

Characterization

Solubility

Solubility of the copolyester samples was examined in 1,4 dioxane, chloroform, methanol, ethanol, acetone, hexane, toluene, tetrahydrofuran, dimethyl formamide, water, dimethyl sulfoxide.

Inherent viscosity

The inherent viscosity [η_{inh}] of the random polyesters was determined in dimethyl sulfoxide using Ubbelohde viscometer in which the pure solvent had a flow time of 60 seconds. The polyesters were dissolved in DMSO to prepare 1% wt solution at room temperature.

Fourier-Transform Infrared (FTIR) Spectroscopy

Fourier transform infrared spectroscopy (FTIR) of the polyester was performed with a Perkin-Elmer IR spectrometer. All the spectra were acquired on an average of about 12 scans with a resolution of 4 cm^{-1} over the range of $400\text{--}4000\text{ cm}^{-1}$. The samples are embedded in KBr pellets.

Nuclear magnetic resonance spectroscopic analysis (^1H and ^{13}C NMR)

^1H and ^{13}C NMR spectra of the polyester were performed with a BrukerAvance NMR Spectrometer (400 MHz). The prepolymers were prepared by dissolving them in deuterateddimethylsulfoxide (DMSO- d_6) calibrated against internal standards and the chemical shift values are reported in parts permillion (ppm).

Differential Scanning Calorimetry (DSC)

The DSC was performed with a TA Instruments Q2000 to determine the thermal properties of the polyester. Polyester (3 to 5 mg) loaded in an aluminum pan were subjected to heating and cooling cycles of -40°C to 500°C and the temperature was ramped up by $10^\circ\text{C min}^{-1}$ under a N_2 flow of 50 mL min^{-1} .

Gel Permeation Chromatography (GPC)

The molecular weight and polydispersity was characteristics by GPC and its carried out with Malvern Viscotek TDA 305, Apparatus Tetra detection Gel Permeation Chromatography, using tetrahydrofuran as the mobile phase (eluent), and flow rate 1ml.min^{-1} at 25°C .

Mechanical properties

The mechanical properties of the polyesters were measured in tensile mode at room temperature using (S.C. Dey Co., India) Universal Testing Machine (UTM) equipped with data acquisition software. Dog-bone shaped specimens ASTM standard D 638 ($35\text{ mm}^3 \times 4\text{ mm}^3 \times 2\text{ mm}^3$, length \times width \times thickness = 1-2 mm) were prepared and tested at a strain rate of 10 mm/min. The stress strain curve for the polymers was obtained by providing the actual values of thickness and width as input to data acquisition software. The Young modulus of the polymer was calculated from the initial slope of stress versus strain curve. The tensile strength and the maximum elongation percentage were obtained from the curve matching the maximum stress and strain at break. The crosslink density of the polymer sample was calculated with Equation (1) according to the theory of rubber elasticity¹⁷.

$$n = E_0/3RT \quad (1)$$

Where n is the number of active network chain segments per unit volume (mol/m^3), E_0 is the Young's modulus (Pa), R is the universal gas constant (8.314 J/mol.K), and T is absolute temperature (298 K).

In vitro degradation

The square shaped polymer specimen of side 7-10 mm and 1.5-2 mm thickness has been immersed in 0.1 M NaOH to rapidly obtain relative degradation rates among samples. Specimen were incubated at 37°C in NaOH solution for predetermined times, respectively. After incubation, samples were washed with distilled

water, incubated in ethanol overnight, and dried to a constant weight. The percent degradation of the polymer in NaOH solution has been calculated from the following Equation (2).

$$\%M_{\text{loss}} = [(M_0 - M_d) / M_0] \times 100\% \quad (2)$$

Where M_0 and M_d are the masses of the polymer sample at the initial and given times.

Results and Discussion

Solubility studies

Solubility of synthesized polymers is shown in Table 1.

Table 1: Solubility studies of polyesters

Polyester	1,4 Dioxane	DMF	DMSO	Methanol	CHCl ₃	THF	Ethanol	Hexane	Toulene	Acetone	water
PXLSe	(+++)	(+++)	(+++)	(+++)	(+++)	(+++)	(+++)	(---)	(---)	(---)	(---)

(+++) **Free Soluble**; (++) **Partially soluble** and (---) **Insoluble**.

PXLSe: Poly (xylitol lactate sebacate) **DMF:** Dimethyl formamide, **DMSO:** Dimethyl sulfoxide, **THF:** Tetrahydrofuran.

Inherent Viscosity

The inherent viscosity of the synthesised polyesters was measured in Dimethyl sulfoxide (DMSO) using Ubbelohle viscometer. The inherent viscosity value of the synthesised polyester is 0.99dL/g.

Fourier-Transform Infrared (FTIR) Spectroscopy

IR spectra recorded for the synthesized polyesters and are shown in Fig.2. The absorption peak around 1728cm^{-1} , corresponding to aliphatic ester (C=O) groups confirms the formation of aliphatic ester bond and 727cm^{-1} (ring C-H out of plane bending). The C-H symmetric stretching of aliphatic-CH₂- group was observed at 2931cm^{-1} . Strong vibrational modes observed at 1238cm^{-1} and 1119cm^{-1} are associated with C-O-C asymmetric stretching modes of aliphatic esters. A broad stretch was also observed at approximately 3357cm^{-1} , which was attributed to hydrogen-bonded hydroxyl groups and 3079cm^{-1} (CH₃ stretch)¹⁸.

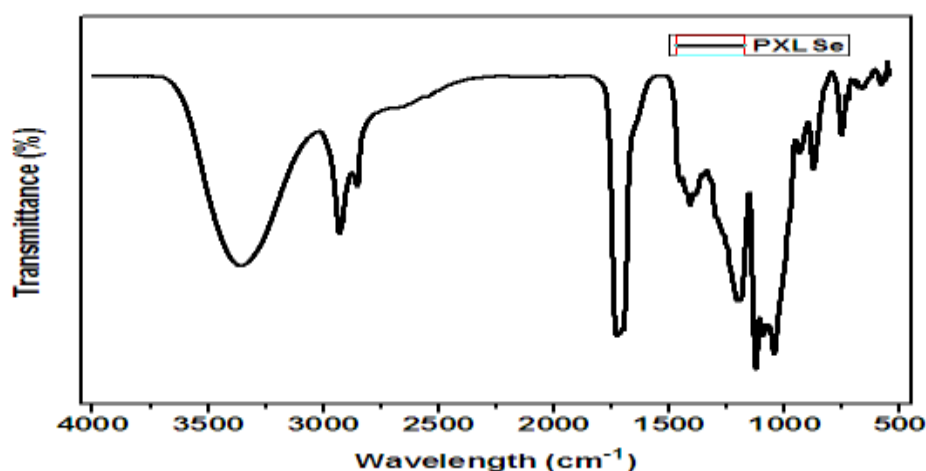


Fig. 2. FTIR spectra of PXLSe

Nuclear magnetic resonance spectroscopic analysis (^1H and ^{13}C NMR)

^1H - NMR Spectroscopy

^1H -NMR Spectra of the synthesized polymer samples were recorded and shown in Fig 3(a). The peak located at 3.37 ppm and 3.89 ppm corresponds to central and terminal methine ($-\text{CH}-$) protons of xylitol and ($-\text{CH}_2-$) methylene protons at 4.23ppm from xylitol. The peak 2.25-2.45 ppm is due to terminal methylene protons ($-\text{CH}_2-$) from dicarboxylic acid. The protons from central methylene units of dicarboxylic acids showed peaks at 1.29-1.6 ppm¹⁹ depending upon the presence of suberic acid.

^{13}C - NMR Spectroscopy

^{13}C -NMR spectra were recorded for the polyesters, and the corresponding assignments are given as follows in Fig.3 (b).A doublet peak at 173 ppm is due to carbonyl carbon atom of the ester group. The peak at 40 ppm is due to residual d_6 -DMSO. The peak at 68.4-68.7 ppm methylene carbon attached to oxygen, $-\text{O}-\text{CH}_2$ and the peak at 33-43 ppm methylene carbon attached to ester, $-\text{O}-\text{CH}_2$. The central and terminal methylene carbons of dicarboxylic acids are 23-30 ppm.

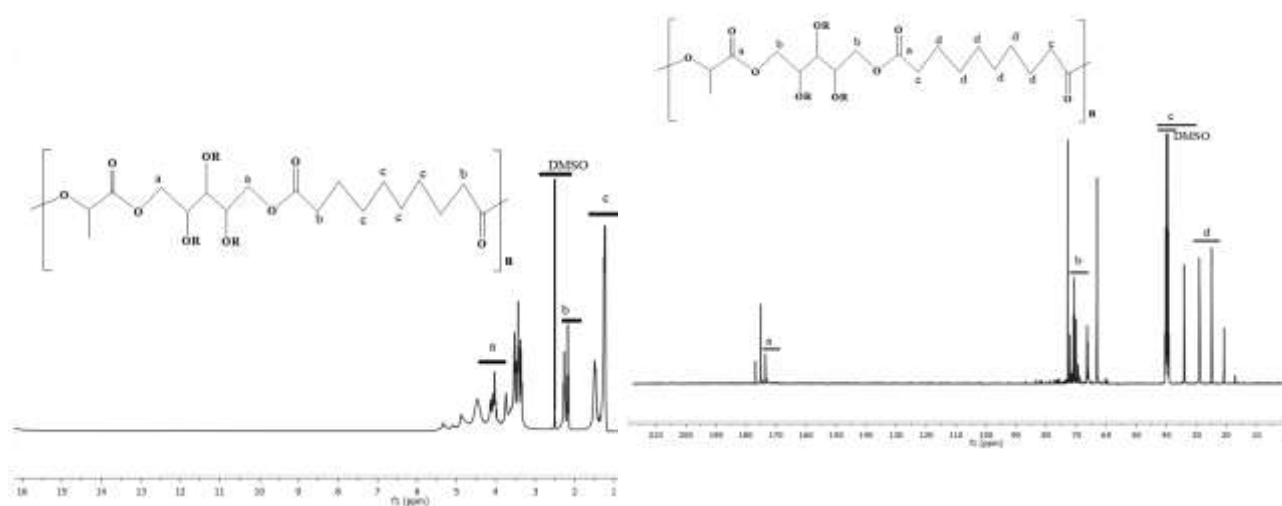


Fig 3. (a) ^1H -NMR and (b) ^{13}C -NMR of copolyester of PXLSe

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) thermograms of the synthesised copolyester (PXLSe) are shown in Fig.4. As listed in Table 2, the glass transition temperature (T_g) of the polyesters (PXLSe) is $-25.1\text{ }^\circ\text{C}$ respectively. It's showed below room temperature, a characteristic feature that determined their elastomers like behavior²⁰. From Tables 2, we can clearly see the melting temperature (T_m) of the polyesters (PXLSe) is $275.12\text{ }^\circ\text{C}$. Thus, these materials are elastomeric in nature which is one of requirement for biomaterials.

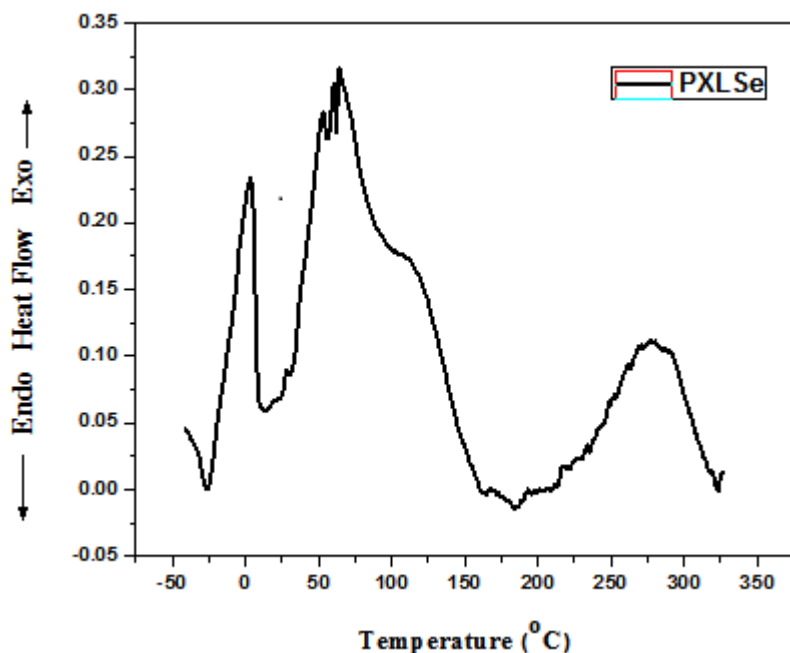


Fig.4. DSC spectra of PXLSe

Table 2. DSC and Mechanical properties of polymer

Polyester	Tg(°C)	Tm (°C)	Tensile stress (Mpa)	Young's modulus (Mpa)	Elongation at break %
PXLSu	-25.1	275.12	3.28	0.104	111.5

Gel Permeation Chromatography (GPC)

Gel permeation chromatography has its greatest value for measuring the molecular weight and polydispersity of synthetic polymers. This method depends on distribution coefficients, relating the selective distribution of an analysis between the mobile phase and stationary phase. It gives an idea of number average and weight average molecular weight²¹. The chromatograms in Figs.5 show Mn, Mw values which are tabulated in Table.3.

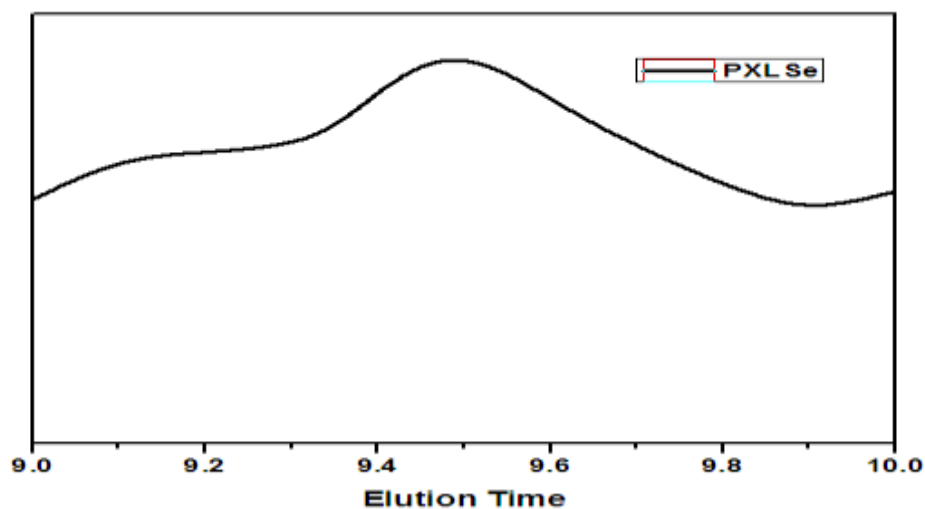


Fig.5.GPC of copolyester of PXCSu

Table 3: GPC of copolyester PXLSe

Copolyester	(\overline{Mn}) (g/mol)	(\overline{Mw}) (g/mol)	Polydispersity Index $(\overline{Mw}) / (\overline{Mn})$	Degree of polymerisation
PXLSe	1086	1272	1.17	29.77

In vitro polymer degradation

In vitro degradation of aliphatic polyesters was confirmed in 0.1M NaOH (pH 13.0) medium. From the Fig. 6, shows that the polymer completed 100% alkaline degradation with in 24hrs in 0.1M NaOH solution due to surface erosion. Hence, it is used to study the drug release pattern of synthesized polyesters²².

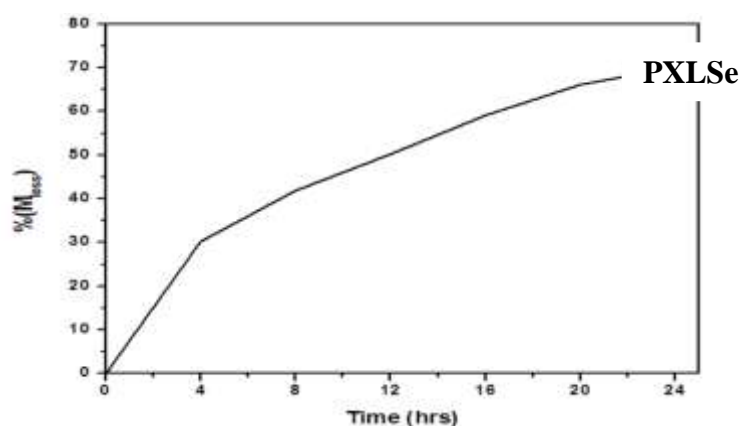


Fig.6. Tensile stress versus strain curves for the polymers (PXLSe)

Conclusion

Poly (xylitol lactate sebacate) elastomers exhibit controllable biodegradation and mechanical properties via a simple, safe and cost-effective catalyst free melt polycondensation reaction. The copolyesters were synthesized from xylitol, lactic acid and sebacic acid by a catalyst free melt polycondensation. The chemical structures of the synthesized polymers were characterized using FTIR and (¹H and ¹³C) NMR. Physical properties such as mechanical properties, and *in vitro* degradation were evaluated. Thermal methods of analysis (DSC) helped determine the glass transition temperature and melting temperature of the copolyesters. The molecular weight of polyester was determined by GPC. The biodegradation of these polyesters was carried out in alkali medium using the 0.1N NaOH. The results clearly indicated that the length of the polymer chains would be the major controlling factor on the biodegradability of polyesters. Thus, the degradation of polyesters was influenced by the polyester composition, polyester properties such as molecular weight, melting temperature and the glass transition temperature.

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