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Design, Synthesis and Characterization of Biodegradable Sorbitol Elastomers with Tunable Mechanical and Degradation Properties

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ABSTRACT

In this investigation we have synthesized a family of novel polyesters that are composed of structural units endogenous to the human metabolism such as Sorbitol, diethylene glycol, and diacids designated as poly (Sorbitol succinate-co-diethylene glycol succinate) (PSSaDEG), poly (sorbitol adipate-co-diethylene glycol adipate) (PSAaDEG), poly (sorbitol suberate-co-diethylene glycol suberate) (PSSuDEG) and poly (sorbitol suberate-co-diethylene glycol sebacate) (PSSeDEG) by catalyst-free melt polycondensation method. The synthesized pre-polymers were characterized by Fourier transform infrared and ^{1}H *and* ^{13}C *nuclear magnetic resonance spectra. Mechanical, swelling and degradation studies to evaluate the elastomeric and biodegradable properties. The results showed that PSADEG behaves like a thermoset and other three polymers PSSDEG, PSSuDEG and PSSeDEG are elastomeric in nature. Material properties of these polymers can be tuned by altering the diacid monomer and this study consistently proved that these elastomers can be used as scaffold material in the future after proving the non-toxic nature by cytotoxicity studies.*

Key words: *Catalyst free melt polycondensation, Sorbitol, Mechanical, Swelling and degradation studies.*

1. INTRODUCTION

Aliphatic polyesters are one of the most promising biodegradable materials because they are readily susceptible to biological attack. Many new uses such as absorbable bone plates, some surgical fixation devices, bioadsorbable surgical sutures and carriers for the controlled release of drugs have been found. Limiting factors for a broader use of synthetic aliphatic polyesters derived from diols and diacids are their poor mechanical properties and low melting temperature. At the same time, the high hydrolytic instability of these polymers resulted in a multitude of applications for this polymer class in the biomedical field starting with absorbable sutures [1].

Recently biodegradable aliphatic polyesters with elastomeric properties have received much attention as they can sustain and recover from multiple deformations causing irritation to the surrounding tissue. Numerous biodegradable elastomers have been synthesized due to their use in engineering of soft tissues like a blood vessel, heart valves, cartilage, tendon and bladder which possess elastic properties. Most of the biodegradable elastomers developed so far, require costly and complex synthetic procedures which translate into higher manufacturing cost that hinder their commercial and clinical use [2]. Synthetic polymers with less cost of production are essential to meet out the increased demand for tissue engineering.

In earlier works, several investigators have reported elastomers based on multifunctional monomers, in particular polyglycerol sebacate [3] xylitol glutamate sebacate [4] poly sorbitol adipate [5] sorbitol citric sebacate, sorbitol tartaric sebacate [6]. Besides some other biobased polyesters using castor oil and soyabean oil are attractive elastomers [7,8]. Among these elastomers, sorbitol based bioelastomers have been shown to offer a wide range of controllable mechanical profiles and biodegradability. Herein, we report on the synthesis of the new class of bioelastomers containing sorbitol as a common monomer which is metabolized in an insulin-independent manner in combination with diethylene glycol and aliphatic diacid by catalyst-free reaction.

2. MATERIALS AND METHODS

2.1. Materials

Sorbitol (S), succinic acid (SA), adipic acid (AA), suberic acid (Su), sebacic acid (Se), and diethylene glycol (DEG) (lancaster AR grade) were used as received. 1,4 dioxane and other solvents were purchased are analytical grade.

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2.2. Synthesis of Copolyesters

All the four polymers poly (sorbitol succinate-co-diethylene glycol succinate) (PSSaDEG), poly (Sorbitol adipate-co-diethylene glycol adipate) (PSAaDEG), poly (sorbitol suberate-co-diethylene glycol suberate) (PSSuDEG) and poly (sorbitol suberate-co-diethylene glycol sebacate) (PSSeDEG) were synthesized by the catalyst-free melt polycondensation technique by the following procedure. Appropriate molar amounts of monomers were melted in a round bottom flask at 150°C under a blanket of nitrogen gas and stirred for 2 h to prepare prepolymers. Then, the samples were transferred into polytetrafluoroethylene molds in a vacuum oven at 150°C for 5 days for further polyesterification. Four different polymers using four different diacids were synthesized in this study to investigate the effect of diacids on the physical and mechanical properties. The cured polymers were then stored in desiccators for further use. The schematic synthesis is shown in Figure 1. The resulting polymers were cross-linked at the reaction groups shown in Figure 1. The –OR groups in Figure 1 indicates both cross-linked or –OH groups.

2.3. Characterization

2.3.1. Solubility test

Solubility of the copolyester samples was examined in 1,4 dioxane, chloroform, methanol, ethanol, ether, the tetra hydro furan, dimethyl formamide, water, dimethyl sulfoxide.

2.3.2. Fourier transform infrared (FTIR) spectrometry analysis

IR spectra of all the prepolymer samples were recorded using a Perkin-Elmer IR spectrometer in the range of 700 cm^{-1}-4500 cm^{-1}. The samples were embedded in KBr pellets.

2.3.3. Nuclear magnetic resonance (NMR) spectroscopic analysis

All the four prepolymers were dissolved in 1,4 dioxane and precipitated in water followed by filtration and drying. ^{1}H and ^{13}C NMR spectra of the polymer samples were recorded on a Bruker NMR (Bruker AXS Inc., Madison, WI) spectroscope at 400 MHz with deuterated dimethyl sulfoxide as a solvent and tetramethylsilane as an internal reference.

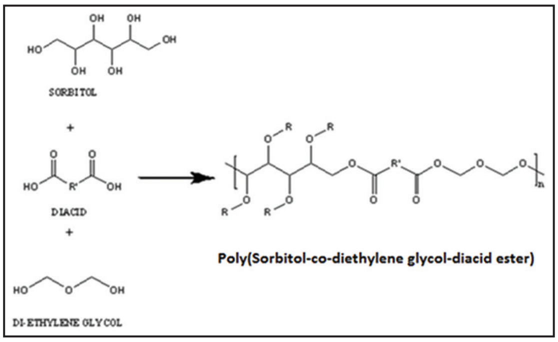


Figure 1: Schematic representation of synthesis of sorbitol polyesters. Diacid=Adipic acid, succinic acid, suberic acid/sebacic acid R’=-CH2 - of diacid; R=crosslinked copolymer.

2.3.4. In vitro degradation of polymers

Disc-shaped specimens (7 mm in diameter, about 1-1.5 mm thickness) were placed in a tube containing 10 ml phosphate buffer saline (pH 7.4) and 0.1 M NaOH to rapidly obtain relative degradation rates among samples. Specimens were incubated at 37°C in phosphate buffer solution (PBS) and 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 percentage mass loss (%M_{loss}) of the polymer was calculated from the following Equation (1)

$$\%M_{loss} = [(M_o-M_d)/M_o] \times 100\% \qquad (1)$$

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

2.3.5. Mechanical properties

The mechanical properties of polymers PSSaDEG, PSAaDEG, PSSuDEG and PSSeDEG were measured at room temperature with the universal testing machine (S.C. Dey Co., India) equipped with 500 N load cell and data acquisition software. The dog bone shaped polymer strips were prepared according to ASTM D 638 (35 mm^3 × 4 mm^3 × 2 mm^3, length × width × thickness = 1-2 mm) and pulled at a strain rate of 10 mm/min. The Young modulus was calculated from the initial slope of tensile stress versus strain. The crosslink density of the polymer sample was calculated with Equation (2) according to the theory of rubber elasticity [9].

$$n=E_0/3RT \qquad (2)$$

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).

3. RESULTS AND DISCUSSION

3.1. Solubility Studies

Solubility of synthesized polymers is shown in Table 1.

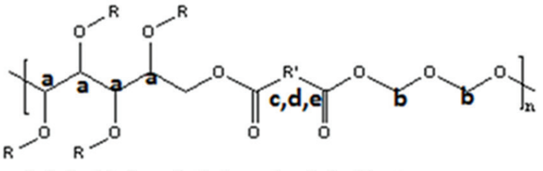
3.2. FTIR Spectroscopy Analysis

IR spectra recorded for the synthesized polyesters and are shown in Figure 2. The absorption peak around 1720 cm^{-1}, corresponding to ester (C=O) groups confirms the formation of ester bond [2,10,11] the peak assigned around 1250 cm^{-1} and 1180 cm^{-1} due to C-O stretching absorption of acid and the peak centered at 2940 cm^{-1} were assigned to methylene ($^{-}CH_2$) stretching absorption [12] from diacid, additional stretch around 1070 cm^{-1} and 892 cm^{-1} is associated with the vibration of ether bond existing between sorbitol and diethylene glycol and the vibrations within diethylene glycol. The broad peak centered at 3450 cm^{-1} were attributed to the hydrogen bonded hydroxyl groups [13,14] the weak band at 1380 cm^{-1} was probably due to C-O stretching in unreacted diacid [15].

3.3. NMR Spectroscopic Analysis

3.3.1. ^{1}H NMR analysis

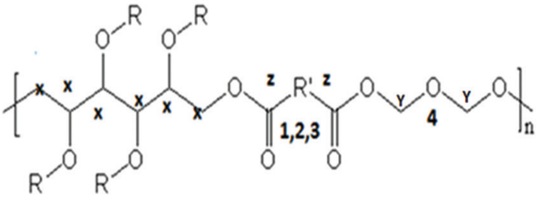
^{1}H NMR Spectra of all the synthesized polymer samples were recorded and shown in Figure 3. The peaks between 3.5 and 5 ppm were assigned to protons $–OCH_2[CH(OH)]_nCH_2O$- from sorbitol [10]. The peaks around 2.3 ppm, 1.6 ppm and 1.3 ppm shown in PSSuDEG and PSSeDEG were attributed to α, β and γ protons of diacids [16]. The peaks at 2.3 ppm and 1.6 ppm shown in PSAaDEG attributed to α and β protons and the peak at 2.3 ppm shown in PSSaDEG spectra were attributed to α protons of diacids. A peak around 3.5-4.5 ppm is due to methylene protons of diethylene glycol appeared in all the four spectra.



Poly Sorbitol-co-diethylene glycol-diacid ester

3.3.2. ^{13}C NMR analysis

^{13}C NMR spectra were recorded for the polyesters, and the corresponding assignments are given as follows. Sorbitol showed resonance peaks at 65.8, 66.1, 72.9, 74.3, 74.5, and 76.1 ppm in Figure 4 corresponds to 1-6 carbon atoms [6], in this first two peaks corresponds to the terminal carbon. The peaks in the region 60-65 ppm arose from carbons directly bonded to oxygen [17], either it may be a ($CO-OCH_2$) of diacid or it may be (CH_2-O-CH_2) of diethylene glycol, the peak around 173 ppm is due to COO- carbon of unreacted diacid. The peak at 35, 26, 30 ppm find in PSSuDEG and PSSeDEG spectra is due to α, β and γ carbon of suberic and sebacic acid. But the peak at 35, 26 ppm find PSAaDEG spectra corresponds to α and β carbons of adipic acid and only one peak at 30 ppm due to α carbons of succinic acid. Finally, a peak around 40 ppm is due to DMSO solvent.



Polyol(Sorbitol -co-diethylene glycol-diacid ester

3.4. In Vitro Degradation of Polymers

All the synthesized polyesters were tested for its degradation behavior in physiological conditions using PBS (pH 7.4) and in alkaline condition 0.1 M NaOH (pH 13.0) at 37°C. The results of the degradation are shown in Figure 5 as the weight loss of polymer with incubation time.

When we compare the degradation of the polymer in PBS Figure 5a and alkaline solution Figure 5b. Polyester undergo alkaline degradation rapidly than

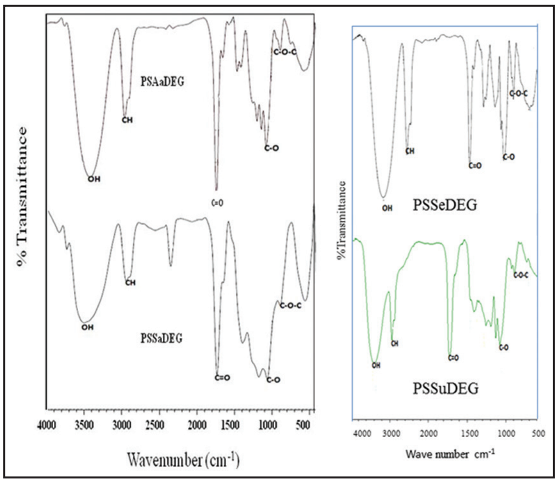


Figure 2: Infrared spectra of copolymers poly (sorbitol succinate-co-diethylene glycol succinate), poly (sorbitol adipate-co-diethylene glycol adipate), poly (sorbitol suberate-co-diethylene glycol suberate) and poly (sorbitol suberate-co-diethylene glycol sebacate).

Table 1: Solubility of the copolyesters.

Polyester	Acetone	1,4 dioxane	$CHCl_3$	DMSO	Methanol	Ethanol	Water
PSSaDEG	++	+++	+++	+++	---	---	---
PSAaDEG	++	+++	+++	+++	---	---	---
PSSuDEG	++	+++	+++	+++	---	---	---
PSSeDEG	++	+++	+++	+++	---	---	---

+++: Free soluble, ++: Partially soluble, ---: Insoluble. PSSaDEG: Poly (sorbitol succinate-co-diethylene glycol succinate), PSAaDEG: Poly (sorbitol adipate-co-diethylene glycol adipate), PSSuDEG: Poly (sorbitol suberate-co-diethylene glycol suberate), PSSeDEG: Poly (sorbitol suberate-co-diethylene glycol sebacate), DMSO: Dimethyl sulfoxide degradation in PBS solution as base catalysis causes faster chain cleavage than polymer swelling [18].

As the length of the diacid in the polyester increases, hydrophobicity and crosslink density of the polyester increases which in turn decreases the degradation rate was observed in the synthesized polyester [2,19]. So the degradation rate decreases in the following order PSSaDEG>PSAaDEG>PSSuDEG>PSSeDEG in both in PBS and 0.1 M NaOH solution.

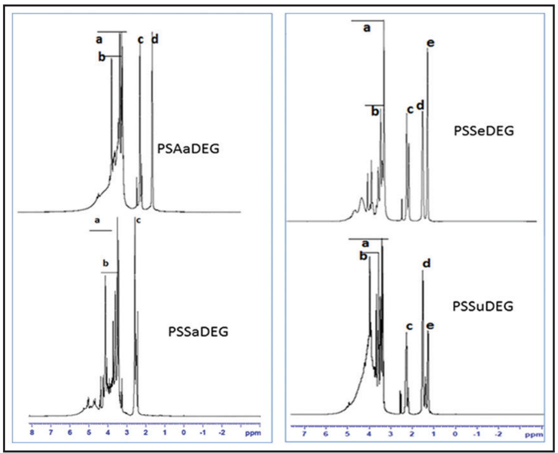


Figure 3: ^{1}H Nuclear magnetic resonance spectra for poly (sorbitol succinate-co-diethylene glycol succinate), poly (sorbitol adipate-co-diethylene glycol adipate), poly (sorbitol suberate-co-diethylene glycol suberate) and poly (sorbitol suberate-co-diethylene glycol sebacate) polymers.

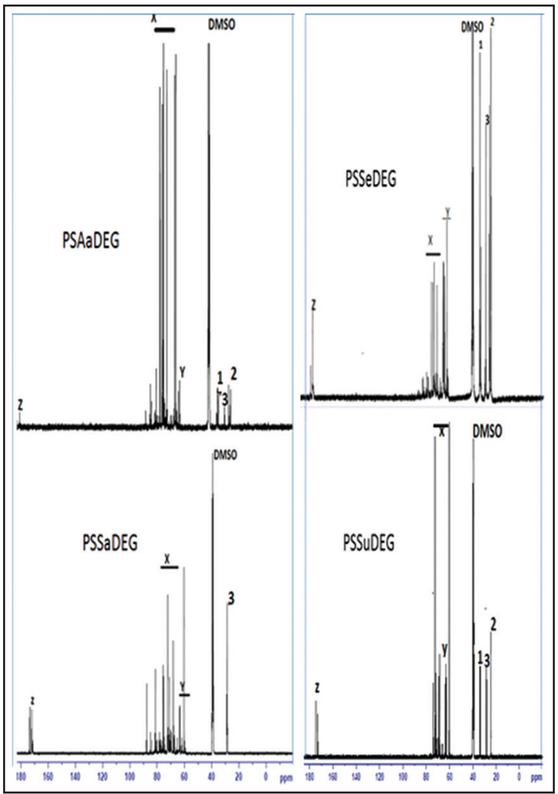


Figure 4: ^{13}C Nuclear magnetic resonance spectra for poly (sorbitol succinate-co-diethylene glycol succinate), poly (sorbitol adipate-co-diethylene glycol adipate), poly (sorbitol suberate-co-diethylene glycol suberate) and poly (sorbitol suberate-co-diethylene glycol sebacate) polymers.

3.5. Mechanical Properties

Tensile tests of the polymers exhibited characteristics similar to that of elastomers. The variation of the tensile stress with strain for the polymers is shown in Figure 6. The average Young's modulus, tensile strength, cross-link density and percentage elongation at break were reported in Table 2.

The Young's modulus, tensile stress and cross-link density decreases, but percentage elongation at break increases with decrease in chain length of diacid in a polymer. This increase in crosslink density with respect to length of the diacid was already proved by degradation studies. All polymers, showed stress versus strain plots of Young's modulus and tensile stress ranges from 3.84 to 1.77 Mpa and 0.57 to 0.78 MPa were intermediate between cancellous bone and cortical bone and therefore it could be useful for bon tissue engineering and osteosynthesis applications [6].

4. CONCLUSION

Sorbitol elastomers composed of structural units endogenous to the human metabolism which was systematically synthesized from sorbitol, diethylene glycol and various diacid which exhibit controllable mechanical and degradation properties. Results on effects of diacids on properties of the copolyesters indicate that Sebacic acid provides copolymers with highest crosslink density, compared to that of shorter chain diacids, due to its optimum methylene flexibility and the reactivity of acidic groups with alcohol groups. Types of diacids and aliphatic content in the copolymer chain play a key role in degradation behaviors and mechanical properties of the samples by imposing different degree of chain flexibility. These elastomers may find applications in tissue engineering such as

Table 2: Tensile strength, Young's modulus, elongation at break values.

Polymer	Tensile stress (Mpa)	Young's modulus (Mpa)	Elongation at break %	Cross-link density n (mol/m^3)
PSSaDEG	0.57	1.77	87.0	238.1
PSAaDEG	0.63	2.46	19.8	331.0
PSSuDEG	0.75	3.59	15.5	484.2
PSSeDEG	0.78	3.84	15.3	516.6

PSSaDEG: Poly (Sorbitol succinate-co-diethylene glycol succinate), PSAaDEG: Poly (sorbitol adipate-co-diethylene glycol adipate), PSSuDEG: Poly (sorbitol suberate-co-diethylene glycol suberate), PSSeDEG: Poly (sorbitol suberate-co-diethylene glycol sebacate)

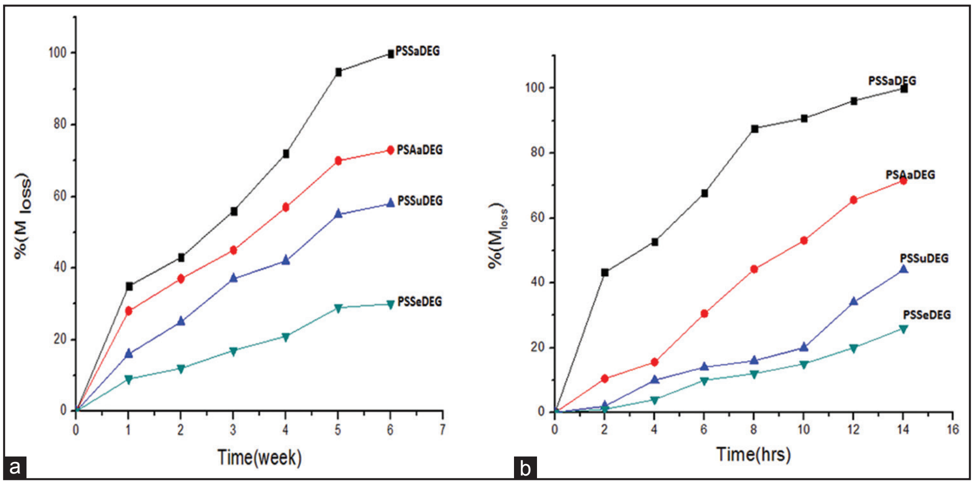


Figure 5: *In vitro* degradation of the polymers: (a) more than 1 week in polybutylene succinate at 37°C, (b) less than a day in 0.1 M NaOH solution at 37°C.

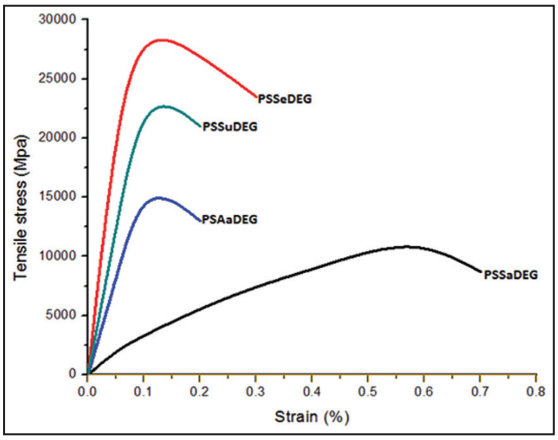


Figure 6: Tensile stress versus strain curves for all the polymers poly (sorbitol succinate-co-diethylene glycol succinate), poly (sorbitol adipate-co-diethylene glycol adipate), poly (sorbitol suberate-co-diethylene glycol suberate) and poly (sorbitol suberate-co-diethylene glycol sebacate)

blood vessels, heart muscle and soft tissues in general as diacid act as a cross-linker, could be increased or decreased to produce stronger and weaker elastomers with a wide range of tensile strength and Young's modulus values suitable for tissue engineering.

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***Bibliographical Sketch**

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