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SYNTHESIS, CHARACTERIZATION AND COMPARISON OF BIODEGRADABLE ALIPHATIC COPOLYESTERS: POLY ETHYLENE GLYCOL OCTANEDIOL SEBACATE AND POLYETHYLENE GLYCOL DODECANEDIOL ADIPATE

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ABSTRACT

Biodegradable random aliphatic copolymers were synthesized through melt polycondensation with titanium tetra-isopropoxide $Ti(ipo)_4$ as a catalyst to produce polyethylene glycol octanediol sebacate (PEOSEB) and polyethylene glycol dodecanediol adipate (PEDDAD). The prepared copolymers were characterized by Fourier transform vibrational spectroscopy(FTIR), Nuclear magnetic resonance (NMR), Differential scanning calorimetry (DSC), Thermo gravimetric analysis (TGA) and Wide angle x-ray diffraction studies (WAXD). The viscosity measurements were studied using ubbelholde viscometer. Both the copolymers possessed antibacterial and antifungal properties. We have also reported the antioxidant behavior of these copolymers by DPPH method and hydrolytic degradation studies by phosphate buffer method.

Keywords: Biodegradable, Antioxidant and Hydrolytic degradation.

INTRODUCTION

Statistics reveal that around one-fourth of the polymers was found in municipal waste or landfills, that couldn't decompose physically by themselves thereby inflicting serious environmental problems[1]. Biodegradable aliphatic polyesters are the most frequently used materials for eco-friendly industrial applications. These polyesters possess thermal stability due to their glass transition and melting temperatures as previously reported[2]. Reports reveal that these biodegradable polymers are easily decomposed with the assistance of microorganisms[3,4]. Nowadays, biodegradation rate of acyclic copolymers was administered by increasing the quantity of ester groups within the main chain and additionally by determining its relative molecular mass[5,6].

Polyethylene glycol (PEG) is generally accepted as a biocompatible polymer, recommended by FDA (Food and Drug Administration). It is said to be inoffensive, soluble in organic solvents and cost-effective. Therefore it is widely used in biotechnical applications. PEG is a polyether which contains an oxygen atom as the polymer backbone and it interacts with cell membranes but is very harmful to active proteins and cells[7]. PEG helps in diminishing the collection of red blood cells and enhances the biocompatibility of PEG copolymers that are embedded as cardiovascular gadgets, for example, stents[8,9]. Reports declare that, this is the most utilized polymer in the biomedical field of drug delivery and the main remedial specialist that has a market endorsement for various drugs[10,11].

Fusako kawai *et al*[12] synthesized a newly isolated polyethylene glycol PEG - 20,000 from the acclimation of the strain N6 by coculture with Comamonas acidovorans. Behjat *et al*[13] synthesized few mixes of cellulose received from the base piece of kenaf plant, to obtain bio-composites with different thermoplastics, where PEG is used as a plasticizer. Huayu Tian *et al*[14] prepared synthetic biodegradable polymers which are widely used in biomedical fields and they are found to be bioactive and biocompatible. Peng Xue *et al*[15] synthesized biodegradable poly (ethylene succinate-co-diethylene

succinate) copolyesters with different diethylene glycol succinate compositions by two-stage melt polycondensation method. Hence based on their hydrophilic characteristics, we have a tendency to report PEG as an appropriate material for drug delivery[16,17].

The objective of the present work is to synthesize the aliphatic copolyesters from sebacic acid / adipic acid, PEG400 as a common monomer with 1, 8-octanediol / 1, 12-dodecanediol by melt polycondensation technique in the presence of Ti (IV) isopropoxide as a catalyst. The synthesized copolymers were outlined by dissolvability, inherent viscosity, spectral studies, and thermal analysis. The antibacterial and antifungal behavior of these copolymers were tested against E.Coli and Candida albicans bacteria. The antioxidant behavior of these copolymers was determined by DPPH method using UV spectrophotometer. Also, the hydrolytic degradation studies were observed at 37° C in the presence of phosphate buffer solution.

EXPERIMENTAL

Material and Methods

Sebacic acid, PEG 400 & Adipic acid were obtained from Merck and used as such. The diols 1, 8 - octanediol and 1, 12 -dodecandiol were purchased from Sigma - Aldrich. All other chemicals and reagents were analytical grade and used as received.

Preparation of Sebacate and Adipate Copolymers

The sebacate and adipate polymers were polymerised by reacting PEG400, sebacic / adipic acid and 1, 8 - octane / 1, 12 – dodecane diol by a two-step process in accordance with umare et al.[18] In the first phase, the reaction mixture was continuously purged out with nitrogen gas with an inlet adapter at 150° C for 2 hours. The transesterification catalyst Ti (IV) isopropoxide was added precisely in the previous phase to eliminate all the water molecules. Similarly, in the second phase, the reaction was again heated to 200° C for 1 hour under reduced pressure (<1Torr) to get the post-polymerized product and to discard the traces of water. The obtained copolyesters (*polyethylene glycol-co-octanediol sebacate*) and (*polyethylene glycol-co-dodecanediol adipate*) was purified by dissolving in a minimum amount of acetone and reprecipitated with ten folds of cold methanol with continuous stirring. The precipitate obtained was washed again and again with methanol, filtered, and dried at room temperature. The product obtained was a yellow solid with a yield of 95%.

PEOSEB

$$nOH-(CH_2)_n-OH+HOOC-(CH_2)_8-COOH+OH-(CH_2)_8-OH$$

$$\xrightarrow[-H_2O]{200^\circ C,\ Ti(IPO)_4} n[OH-(CH_2)_n-OOC-(CH_2)_8-COO-(CH_2)_8-O]_n$$

PEDDAD

$$nOH-(CH_2)_n-OH+HOOC-(CH_2)_4-COOH+OH-(CH_2)_{12}-OH$$

$$\xrightarrow[-H_2O]{200^\circ C,\ Ti(IPO)_4} n[OH-(CH_2)_n-OOC-(CH_2)_4-COO-(CH_2)_{12}-O]_n$$

Polymer Characterization and Instrumentation

Infrared spectroscopy was executed on an FTIR spectrophotometer (Shimadzu). Polymeric samples were pressed into KBr pellets directly for recording IR spectra. ^{1}H NMR spectra were recorded at 25° C using Bruker AVIII 500 MHz spectrophotometer with deuterated $CDCl_3$ as the solvent. The chemical shifts were reported using TMS as a reference. ^{13}C NMR was operated at 100 MHz and the chemical shifts were

reported using $CDCl_3$ as a solvent. DSC study was performed on (Perkin Elmer) DSC–Q100 instruments to quantify the thermal transitions of the copolymers at nitrogen atmosphere. The polymeric samples were weighed and placed in an air tightly closed aluminium pan, gathered inside the temperature varied from -50° C to 300° C at a heating rate of 10 degree celsius per minute. TGA analyses are executed by means of Perkin Elmer high-resolution thermobalance. Approximately 10 mg of the polymer samples were loaded into a platinum pan under a nitrogen atmosphere to avoid oxygen and moisture contamination. It is accessed from ambient temperature to 800° C at a heating rate of ten degree celsius per minute. The WAXD studies were carried out by a GE X-RAY 3003 diffractometer to collect the XRD patterns worked at 45kV and 30mA employed with Cu K_α filtered radiation (λ = 1.543Å). The crystallinity of the polymeric samples was found by scanning from 10° - 70°. The copolymers are completely dissolvable in chloroform and carbon tetra chloride, solvable in dichloromethane and tetrahydrofuran, partially soluble in acetone and DMF, nonsolvable in water and methanol.

Biological Studies

The antimicrobial studies of the random copolymers were determined by sabouraud dextrose agar (SDA) medium for fungi and Mueller-Hinton agar (MHA) medium for bacteria by well diffusion method respectively.

Antibacterial Activity

This activity was tested from Mueller Hinton Agar (MHA) medium through well diffusion method against two gram positive and gram negative human pathogenic microscopic organisms viz. *B. subtilis*, *S.aureus*, *E.coli*, and *Pseudomonas aeruginosa* species. Both the synthesized copolymers (PEOSEB and PEDDAD) reacted with four to five colonies of Mueller Hinton Agar (MHA) medium, incubated at 37°C for 12 hours.

The culture suspension turbidity was noted with a sterile saline solution, such that the final bacterial inoculum would contain 5×10^5 CFU/mL[19,20]. Using a sterile glass spreader the test organism were vaccinated on a well of 6 mm (dia) nutrient agar plates and disseminated uniformly with a sterile cork borer. A test compound of (50 µg) was added to each well, incubated at 37 °C for microbial analysis. The results were duplicated and displayed as means. The zone of inhibition (ZI) was measured with respect to standard antibiotic tetracyclin and DMSO as reference and control to find the accuracy[21].

Antifungal Activity

The antifungal activity was screened by well diffusion method on SDA medium. The medium was arranged and autoclaved at 15 lbs weight (121ºC) for 5 min, cooled to 50-55º C and filled with sterile petri plates to a uniform depth of 4 mm which is roughly proportionate to 25-30 ml in a 90 mm plate. Once the medium was stiffened, the standardized bacterial suspension was swabbed on the medium inside 15 minutes by altering the thickness of the inoculum and the plates were undisturbed for 3 to 5 min to assimilate the abundance moisture [22,23].

Antioxidant Activity

The antioxidant activity was determined by the use of stable free radical by DPPH scavenging method using UV-spectrophotometer for the synthesized compounds. DPPH in methanol (0.1 mm) was readied and 1.0 mL of this prepared solution was mixed with 1 mL of compounds solution at various concentrations. After incubation for 30 min, all the reaction mixtures were read with a spectrophotometer at 517 nm. A blank was prepared without compounds[24].

Hydrolytic Degradation

The hydrolytic degradation experiments were analyzed for the polyesters to determine its weight-loss percentage at pH 7.4 in a phosphate buffered solution at 37° C. The phosphate buffer solution was prepared by dissolving 4.710 g of KH_2PO_4 and 19.778 g of Na_2HPO_4 in 1000 ml distilled water.

RESULTS AND DISCUSSION

Viscosity and Solubility Measurements

Inherent viscosities of the copolymers were confirmed with the help of ubbelhode viscometer using chloroform as solvent at room temperature. The values of flow time of pure solvent and copolymer were found at a concentration of 1mg/ml[25]. The inherent viscosity and solubility of the copolymer are given in the Table-1.

Table-1: Inherent viscosity and solubility of copolymers PEOSEB and PEDDAD

S. No.	Polymer	Inherent Viscosity dl /g	Freely Soluble	Sparingly Soluble	Insoluble
1.	PEOSEB	0.3140	Chloroform, Carbon tetra chloride	Acetone	Water, Methanol
2.	PEDDAD	0.3254	Chloroform, Carbon tetra chloride	DMF	Hexane, diethyl ether

Spectral Studies

The FTIR spectrum of the copolymers PEOSEB and PEDDAD are shown in Fig.-1. These copolymers show a strong absorption band at 1733 cm^{-1} and 1736 cm^{-1} which corresponds to the stretching vibrations of carbonyl carbon of C=O group. The broad stretch at 3445 cm^{-1} and 3451 cm^{-1} was attributed to the presence of hydrogen-bonded carboxyl and –OH groups[26]. The significant peaks acquired at 1048 cm^{-1} – 1186 cm^{-1} and 1163 cm^{-1} confirms the presence of C-O stretching vibrations of the aliphatic copolymers[27]. The peaks obtained at 1466 cm^{-1}, 1461 cm^{-1} and 2928 cm^{-1} are ascertained to the stretching vibrations of the methylene carbon of its diols and diacids[13].

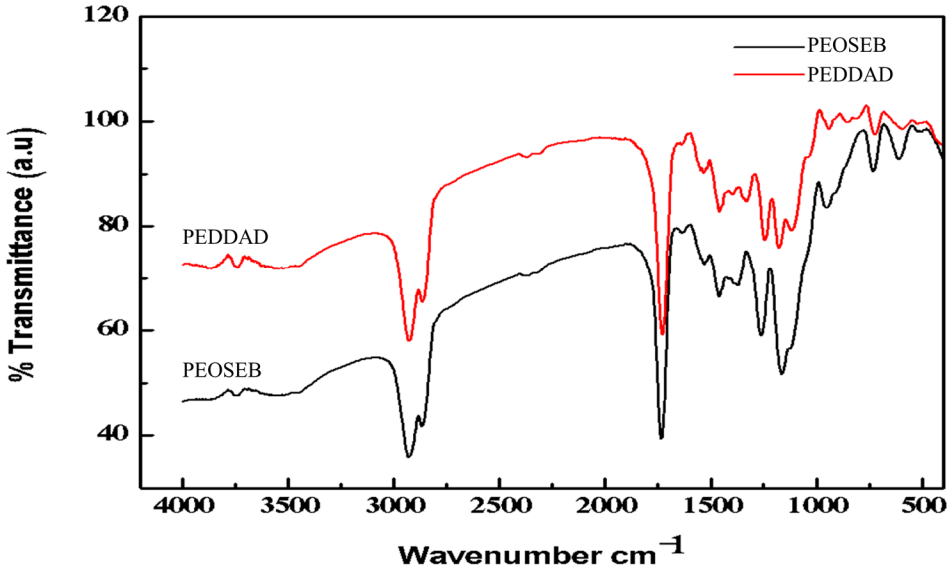

Fig.-1: FTIR Spectrum of PEOSEB and PEDDAD

^{1}H NMR Spectral Data of Copolymers PEOSEB and PEDDAD

The ^{1}H NMR spectrums of these copolymers are shown in Fig.-2 and 3. The peaks present at 1.61 ppm, 1.30 ppm - 1.32 ppm and 1.54 ppm - 1.61 ppm were assigned to the methylene protons of octane diol and dodecane diol[28]. The multiple peaks observed from 3.65 ppm -3.69 ppm, 3.58 ppm -3.64 ppm, 2.25 ppm - 2.31 ppm and 2.25 ppm - 2.29 ppm could be due to the proton signals attached to the carbonyl carbon of

ester oxygen atom and methylene protons of the acid group[29,30]. In addition, the multiplets observed at 4.05 ppm – 4.22 ppm and 4.14 ppm – 4.17 ppm corresponds to the methylene proton attached to the -OH group[31,32].

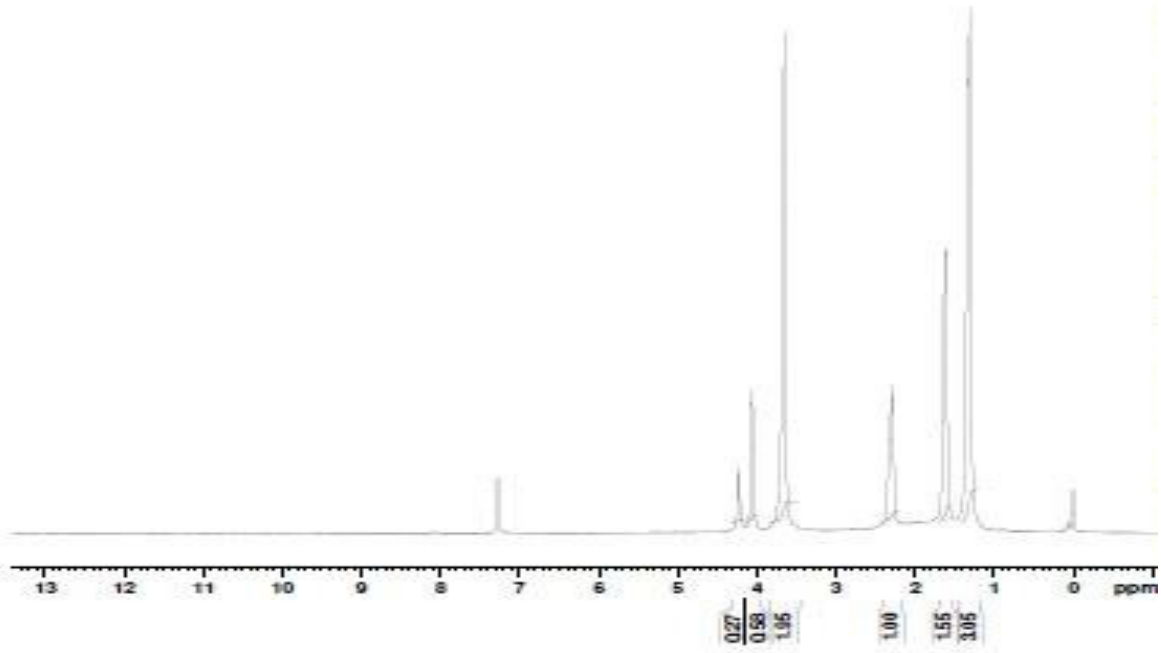

Fig.-2: ^{1}H NMR spectrum of PEOSEB

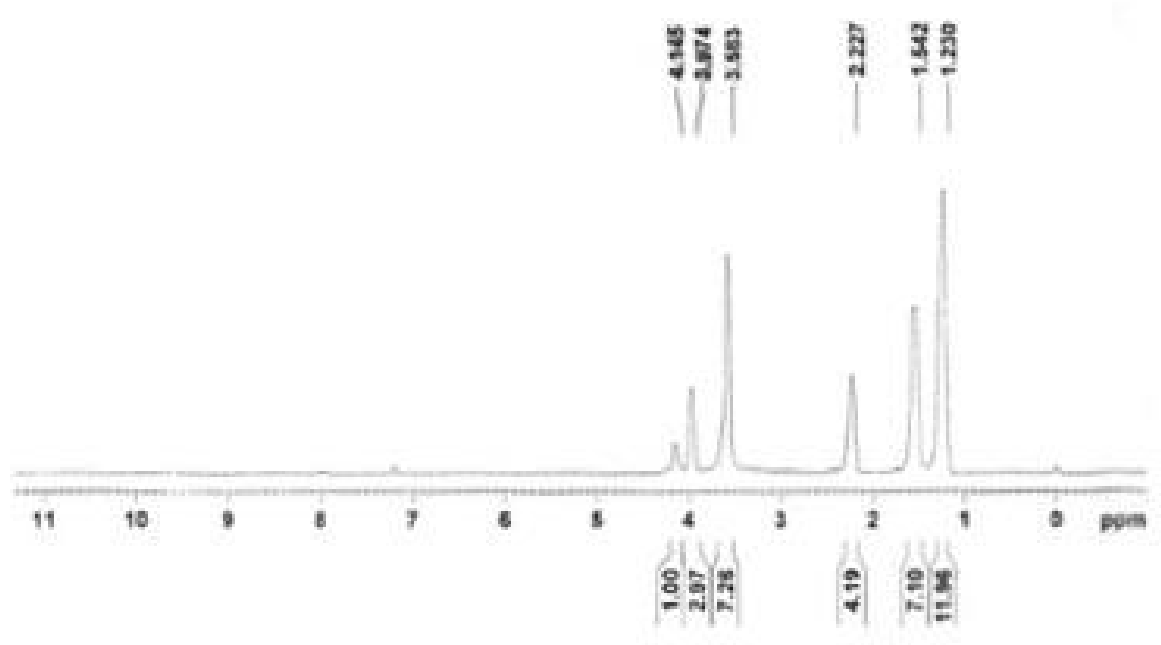

Fig.-3: ^{1}H NMR spectrum of PEDDAD

Fig.-4 and 5 show the ^{13}C NMR spectra of the purified copolymers. The peaks appeared at 173.7 ppm - 173.9 ppm and 173.8 ppm confirms the presence of carbonyl groups of sebacate and adipate copolymers respectively[33,34]. The ^{13}C peaks commonly obtained in the upfield region 24.7 ppm - 24.5 ppm reveals the presence of carbon atoms of sebacic and adipic acid[35,36]. The signals commonly noticed from 64.3 ppm - 70.5 ppm, 63.3 ppm - 69.1 ppm and 62.6 ppm - 68.5 ppm were ascertained to the methylene carbons attached to the carbonyl carbon of ester group and methylene carbons attached to –OH group[37,38].

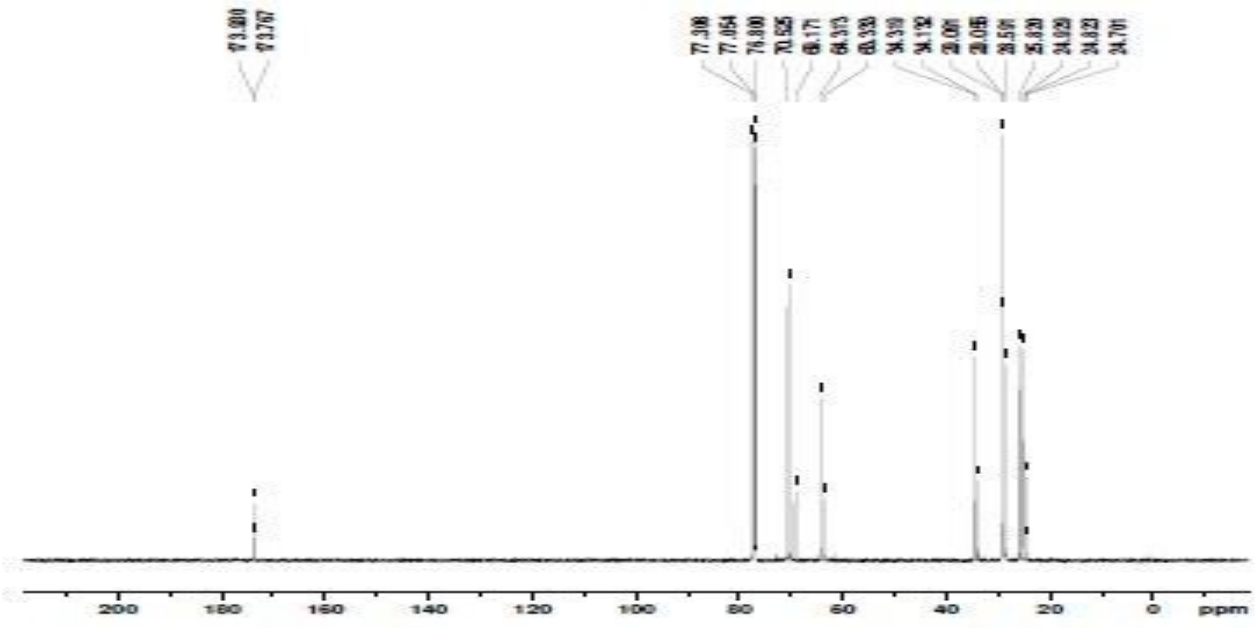

Fig.-4: ^{13}C NMR spectrum of PEOSEB

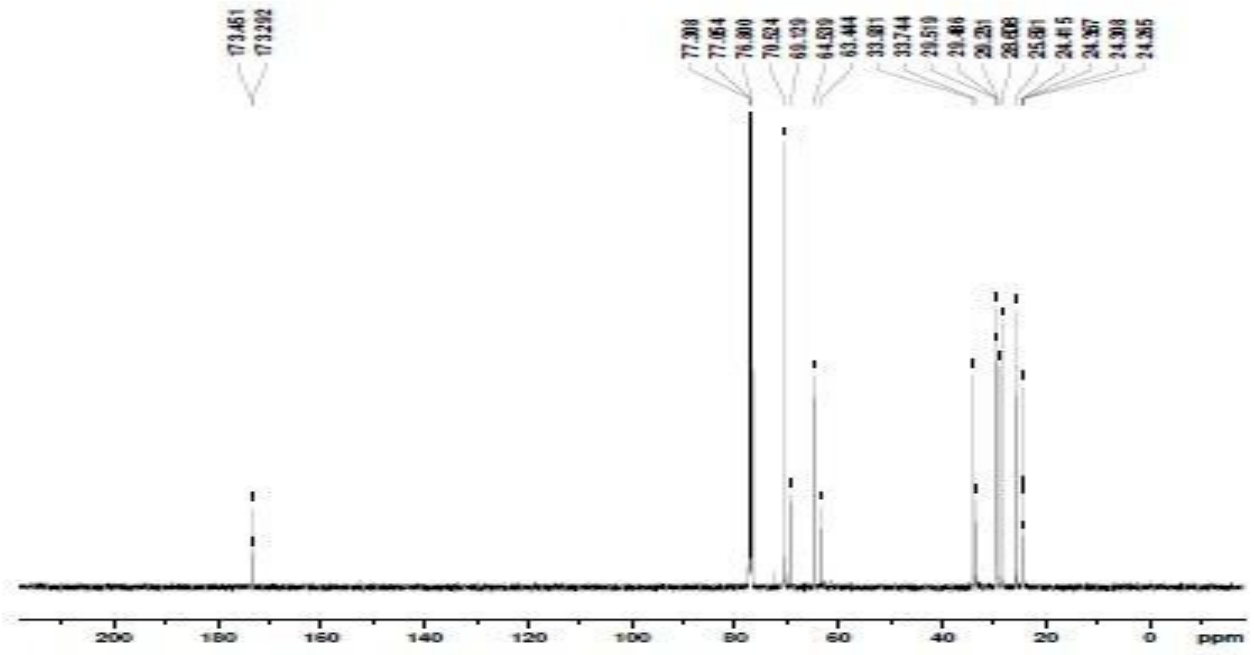

Fig.-5: ^{13}C NMR spectrum of PEDDAD

Thermal Analysis

The DSC thermograms of the aliphatic copolymers were plotted from -50° C to 300° C employed under a nitrogen atmosphere at a constant heating rate of 10 degree celsius per minute. The DSC thermogram of the copolymers exhibited melting temperatures(T_m) at about 57.37° C and 57.84° C for PEOSEB and PEDDAD which produced only endothermic peaks[33,34]. The thermograms of these copolymers are displayed in Fig.-6 and 7. The glass transition temperatures (T_g) for PEOSEB and PEDDAD were found to be -40° C and -38° C which induced chain flexibility due to its low temperature. Both the copolymers can be effectively used in drug release behavior because of its low glass transition temperature[26].

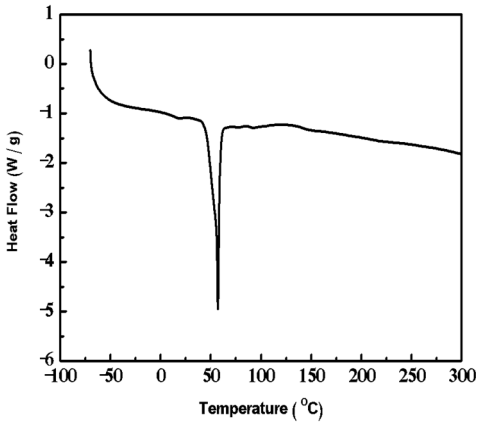

Fig.-6: DSC spectrum of PEOSEB

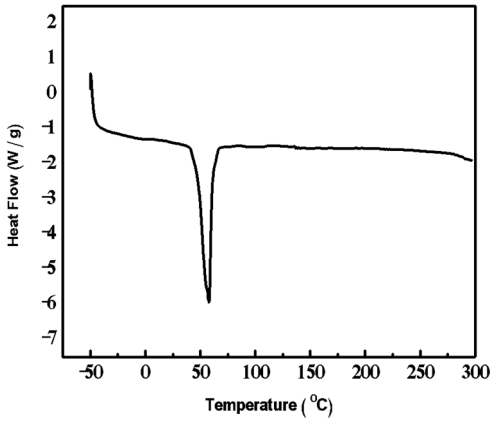

Fig.-7: DSC spectrum of PEDDAD

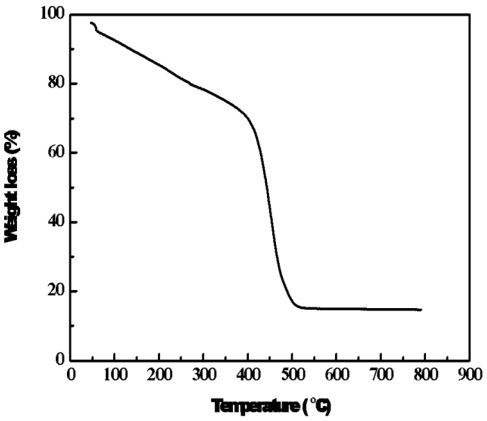

Fig.-8: TGA spectrum of PEOSEB

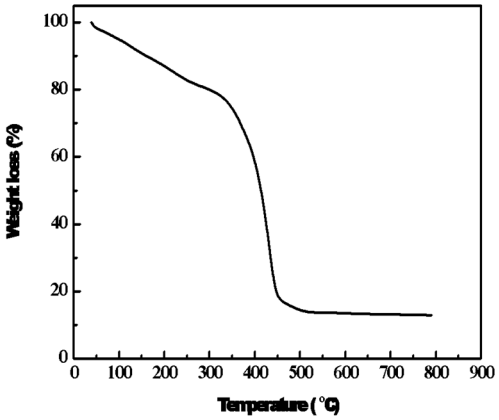

Fig.-9: TGA spectrum of PEDDAD

The thermal studies were also conducted for each copolymer by TGA instrument at a heating rate of 10 degree celsius per min in nitrogen atmosphere are displayed in Fig.-8 and 9. From the results of TGA both the copolymers undergo single stage decomposition with an initial decomposition temperature (Td) of 277.57° C and a final decomposition temperature of 411.77° C for PEOSEB. Similarly, for PEDDAD the decomposition temperature commences at 248.76° C and ends at 343.54° C, and it is observed that both the copolymers are thermally stable. The temperature difference occurs due to the inclusion of other monomer units into the polymeric chain.

X-ray Diffraction Analysis

In this paper, the crystalline structure of the copolyesters was investigated by wide-angle x-ray diffraction method, displayed in Fig.-10 and 11. It is proposed that the sebacate polymer showed sharp reflection peaks at 2θ = 21.32°, 24.23°and 43.99° indicating the formation of crystalline peaks[35,36]. Similarly, the peaks of interest for adipate polymers are at 21.63° and 24.23° proving its crystallinity. The length of the flexible space groups increases with increase in diffraction peak intensity. This is in accordance with the study of Chen et al[37,38]. Reports reveal that flexibility of the copolymers proves its crystallinity[39]. Hence, from the x-ray diffraction studies, it is observed that both the copolymers were found to be crystalline.

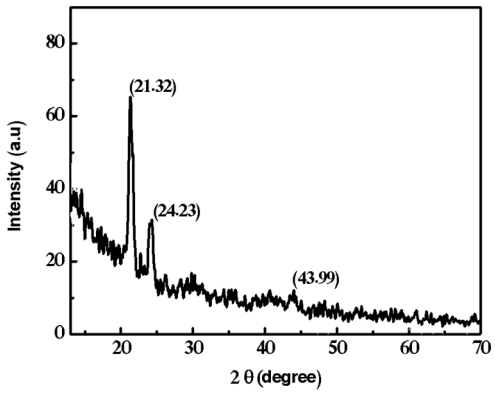

Fig.-10: XRD spectrum of PEOSEB

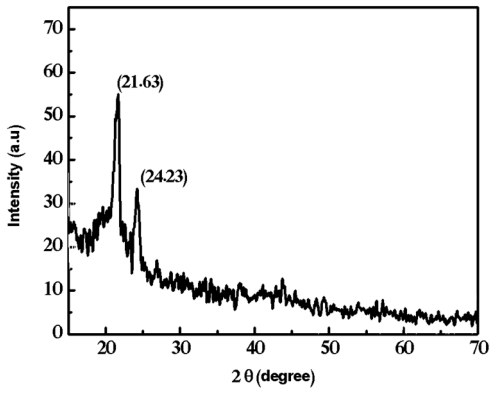

Fig.-11: XRD spectrum of PEDDAD

Antibacterial Activity

the antibacterial and antifungal activity of the copolymers were analyzed by agar well diffusion assay using four bacterial strains viz. *E.coli* and *P.aeruginosa , Bacillus subtilis* and *Staphylococcus aureus* and the images are displayed in Fig.-12 and 13. From the results of Table-2, the two copolymers exhibited moderate to good antimicrobial activity. While comparing the sebacate and adipate polymer with the standard drug tetracyclin, the adipate polymer showed more activity towards the gram-negative bacteria (*E. coli and P. aeruginosa*). Similarly, in the comparison with gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), the rate of inhibition was found to be higher for adipate polymer than sebacte polymer[40,41]. From the results of Antifungal data against *Candida Albicans*, the sebacate polymer alone was active at higher concentrations and adipate polymers showed nil activity. The inhibition % was computed by:

$$\text{Percentage of inhibition} = [\text{Zone of inhibition} / \text{Dia. of the petriplate}] \times 100$$

Table-2: Antimicrobial activity of PEOSEB & PEDDAD compounds against human pathogens by well diffusion method

Human Pathogens	Concentration (in µg/mL)	Zone of inhibition in mm (Inhibition %)			
		PEOSEB	PEDDAD	Standard Drugs Tetracycline/Fluconazole (30 µg/mL)	
Escherichia coli	1000	15	-	18	Gram negative Bacteria
	500	11	-		
	250	-	-		
Pseudomonas aeruginosa	1000	12	16	24	
	500	-	13		
	250	-	12		

Bacillus subtilis	1000	-	-	32	Gram Positive Bacteria
	500	-	-		
	250	-	-		
Staphylococcus aureus	1000	-	17	31	
	500	-	12		
	250	-	10		
Candida albicans	1000	14	-	20	Fungi
	500	12	-		
	250	-	-		

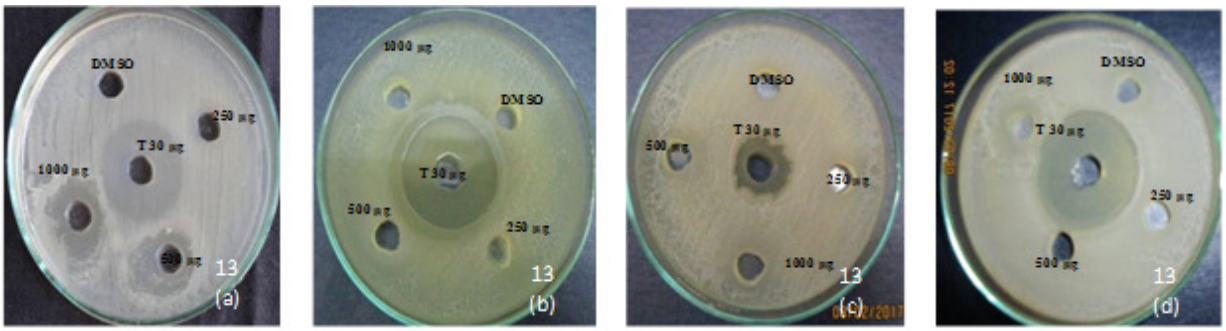

Fig.-12 (a-d): Antibacterial activity of synthesized compounds (a) PEOSEB-Ec, (b) PEOSEB-Bs, (c) PEDDAD-Pa (d) PEDDAD-Sa

Ec-*Escherichia coli,* Bs- *Bacillus subtilis,* Pa- *Pseudomonas aeruginosa,* Sa- *Staphylococcus aureus,* T-30µg-Tetracycline

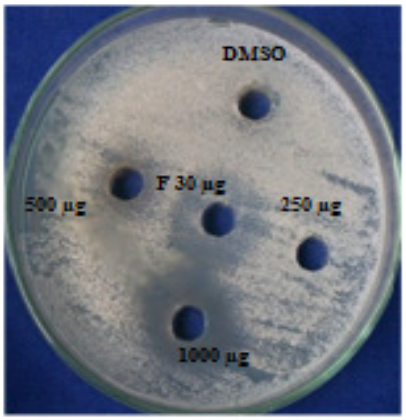

Fig.-13: Antifungal activity of synthesized compound PEOSEB against Candida albicans F-30µg- Fluconazole

Antioxidant Results for the Synthesized Copolymers

The antioxidant activity was evaluated for PEOSEB and PEDDAD by DPPH assay. The rate of discoloration demonstrates the scavenging potential and donates hydrogen to the synthesized antioxidant copolymer with a decrease in absorbance from the DPPH radical[17]. The amount of scavenging potential from a purple color to yellow color was well observed for PEOSEB and PEDDAD at 517 nm[42]. The radical scavenging activity was found to be 89.45% (1000 µg/ml) for PEOSEB and 91.72% (1000 µg/ml) for PEDDAD. A graph is plotted between concentration (µg/ml) and inhibition %, shown in Fig.-14. From the results; it is significant that PEDDAD is a good radical scavenging molecule. Also, the IC 50

(Inhibitory concentration at 50%) value was calculated for both the copolymers. The IC 50 value for PEOSEB was recorded at 29.25 µg/ml comparatively; the IC 50 value for PEDDAD was recorded at 29.74 µg/ml. From the results of IC 50 value, it is explicit that both the copolymers exhibit intense antioxidant activity as shown in Table-3. The scavenging activity was determined by:

$$\text{Scavenging activity (\%)} = [(\text{control optical density} - \text{sample optical density}) / \text{control optical density}] \times 100$$

Further, the selected compounds can be evaluated for antiproliferative activity against cancer cell lines. Antioxidants react with DPPH to form DPPH-H stable free radical. The absorbance decreases from DPPH radical to the DPPH-H form. The rate of discolorations illustrates the scavenging potential of the antioxidant compounds in terms of hydrogen donating ability.

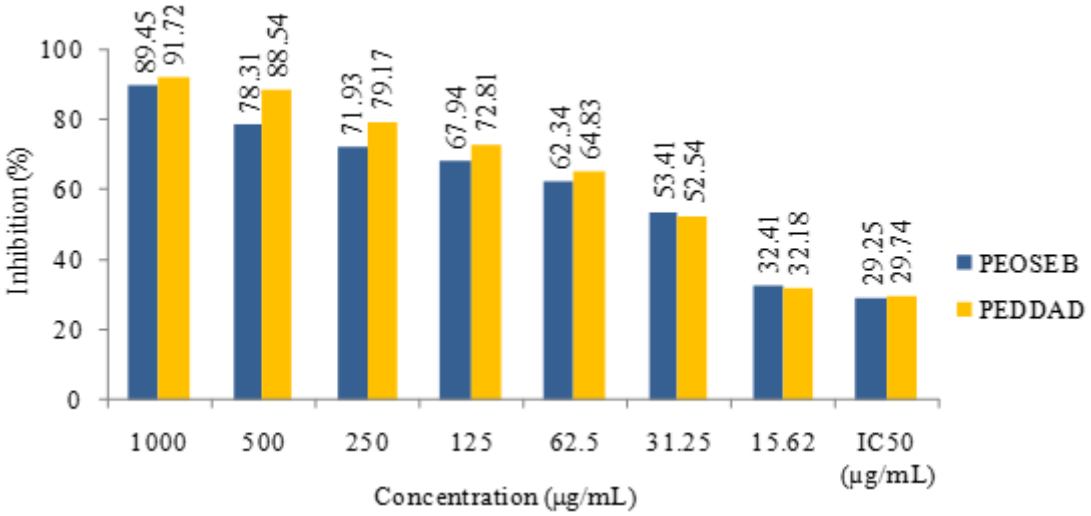

Fig.-14: Inhibition % and scavenging activity of PEOSEB and PEDDAD

Table-3: Antioxidant values of PEOSEB & PEDDAD conc. of compounds (µg/mL)

Inhibition %									
		1000	500	250	125	62.5	31.25	15.62	IC50 (µg/mL)
	PEOSEB	89.45	78.31	71.93	67.94	62.34	53.41	32.41	29.25
	PEDDAD	91.72	88.54	79.17	72.81	64.83	52.54	32.18	29.74

Hydrolytic Degradation

Although there are various ways for analyzing the polymer biodegradation, an initial test was approached by phosphate buffer solution at pH (7.4) to determine the hydrolytic degradation of polymers. The polymer samples were hydraulically pressed in the form of a disc (10 mm in diameter), wholly soaked in the above solution at body temperature (37° C) using about 0.2 g from both of the copolymers[43,44].
The %weight loss was measured at different time intervals by using the following equation:

$$\% \text{ Weight Loss} = Wo - Wt / Wo * 100$$

Where, Wo = Initial weight of the disc and Wt = Weight of degradable disc at a time (t).

The comparative study was done by measuring the weight loss for the copolymers on the 1st, 5th, 10th and 15th day and the results were tabulated in Table-4. A graph is plotted between degradation of time (in days) and % weight loss for both the copolymers PEOSEB and PEDDAD, which are shown in Fig.-15. From the results it is evident that the sebacate copolymer degrades very faster than the adipate copolymer due to variation in their melting points[45,46].

Table-4: % weight loss for sebacate and adipate polyesters in sodium phosphate buffer solution at (pH = 7.4, 37° C)

Name of the Compounds	Initial weight (g) 0th Day	Weight Loss (%) on Different Days			
		1st Day	5th Day	10th Day	15th Day
PEOSEB	0.2	0	37	53	90
PEDDAD	0.2	0	33	56	81

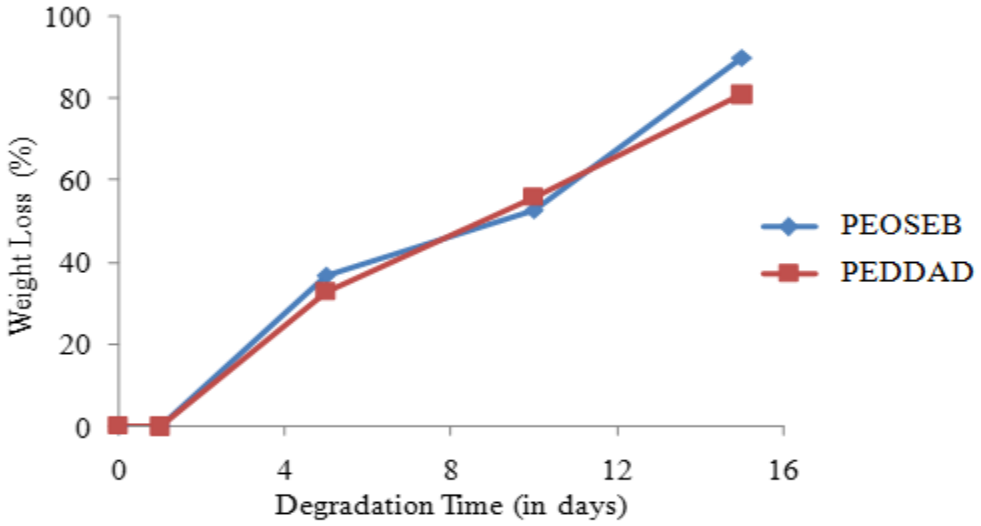

Fig.-15: Weight Loss of PEOSEB and PEDDAD polyesters prepared in Phosphate buffer solution (pH = 7.4, 37^{0}C)

CONCLUSION

Biodegradable Random Aliphatic Copolyesters namely Polyethylene glycol octanediol sebacate and Polyethylene glycol dodecanediol adipate were successfully synthesized by direct melt polycondensation technique using titanium tetra-isopropoxide as a catalyst for their respective diols and diacids. The application of this copolyester quietly depends upon its dissolvability in common solvents. The resulting structure of the repeating units was confirmed on the basis of NMR spectral data. The polymeric chain flexibility is found due to its low glass transition temperature analyzed by DSC and TGA studies. The thermal stability analysis also confirms the decomposition temperatures, which are widely used in drug delivery applications. From the antimicrobial studies, it is observed that the rate of inhibition was found to be higher for adipate polymer than sebacate polymer. From the antifungal data, the sebacate polymer alone was active at higher concentrations and adipate polymer showed nil activity. From the results of the antioxidant study, it is explicit that both the copolymers exhibit intense antioxidant activity. From the results of hydrolytic degradation it is evident that the sebacate copolymer degrades very faster than the adipate copolymer due to variation in their melting points.

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