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Research Article

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Synthesis, Characterisation and Biomedical Application of Random Copolyester Using 1,4-Dithiane 2,5-Diol

Kalpana B* and Nanthini R

Department of Chemistry, Pachaiyapps's college, Chennai, India

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ABSTRACT

A New random linear copolyester Poly(1,4-dithiane 2,5-diol succinate-co-1,10 decane diol succinate), PDDS was synthesized by direct melt polycondensation method using 1,4-dithiane 2,5-diol and 1,10 decane diol and Succinic acid with Titanium tetra isopropoxide as catalyst. As the polymers with sulphur atom in the main chain has excellent properties and wider applications especially in making lens, it led us to synthesis a copolyester with sulphur moiety in main chain and study its biomedical property. A thorough literature survey revealed that 1,4-dithiane 2,5-diol is used as a monomer in the synthesis of polyurethane sealing compound and used as an biocontrol agent, crosslinking agent and chain extenders in polymerisation technique. The Synthesised copolyester PDDS was characterized by determining its inherent viscosity, Solubility, Glass transistion temperature (DSC), crystalline nature (XRD), FTIR, 1H-NMR and 13C-NMR spectroscopy. The biomedical properties such as antioxidant, antimicrobial and in vitro cytotoxicity against normal (Vero cell line) and cancer (A_{549} lung cancer cell line) by MTT Assay of synthesized copolyester PDDS were also studied.

Keywords: Copolyester; Polycondensation; 1,4-Dithiane 2,5-diol; Cytotoxic activity

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INTRODUCTION

Polyester with sulphur atom in main chain was produced by reaction between sulphonic diols such as 4,4‘ thiodiphenol with aliphatic diacid chlorides having methylene groups from 2 to 10. These polyesters possess high molecular weight and high thermo resistance [1-4]. The introduction of sulphur in main chain of linear polyester has a remarkable increase in adhesive property [5]. A polymerisable composition comprising of polythiol with high sulphur content and alicyclic polyisocyanate containing 1,4-dithiane derivative provides an optical material with high refractive index, high impact resistance and high heat resistance in an improved balance form [6]. Also a

polysulphide based resin having polythiol and a compound containing iso(thio)cyanato group has been produced using 1,4-dithiane derivates and the resin had extremely low dispersion properties and high refractive index and find wide application as a optical, glazing, coating and adhesive material [7]. A polyurethane (Diol+Isocyanate) biomaterial with sacrificial moiety susceptible to oxidation especially Sulphur containing moiety (1,4-dithiane 2,5-diol as a diol) in backbone of the polymer chain has increased tensile strength and modulus of elasticity and also degrade over time in an oxidizing environment or body, hence these biomaterial are used in making medical devices particularly for use as insulation on pacing leads [8]. It was further noticed that polyurethanes are widely used in implantable devices such as artificial hearts, cardiovascular catheters, pace maker lead insulations etc. [9]. As the literature survey reveals that polymers with sulphur atom has excellent properties, a copolyester using 1,4-dithiane 2,5-diol was prepared by direct melt polycondensation method and its characteristics and biomedical properties such as antioxidant, antimicrobial and cytotoxicity against normal and A_{549} cell line were studied.

EXPERIMENTAL SECTION

Materials and Methods

1,4-Dithiane 2,5-diol (Sigma Aldrich), Succinic acid (Sigma Aldrich), 1,10 decane diol (Sigma Aldrich) and Titanium Tetra isopropoxide (Lancaster) were purchased and used. All other solvents and chemicals (AR Grade) were used as such. The inherant viscosity was determined using ubbelohde viscometer. Perkin Elmer 883 spectrophotometer was used to record the FT-IR Spectra of synthesised copolyester. Using $CDCl_3$ as a solvent the 1H-NMR and 13C-NMR spectra for copolyester was recorded on a Bruker 400 MHz and Bruker 100 MHz Spectrometer respectively. DSC thermogram was recorded on DSC Q200 V23.10 Build 79 Differential Scanning Calorimeter. To study the crystalline nature of the synthesised copolyester Wide angle XRD was taken by Bruker B8 wide angle XRD with Cu/30 kv/15 mA. The *In vitro* cytotoxicity against normal (Vero cell line) and cancer (A_{549} lung cancer cell line) by MTT assay [10] and antioxidant activity by DPPH Scavenging Assay [11] and antimicrobial activity by Well diffusion method [12] have been determined.

Synthesis of Copolyester

In a three necked round bottom flask 1,4-dithiane 2,5-diol (0.01 mole), Succinic acid (0.02 mole) and 1,10 decane diol (0.01 mole) is taken and the left inlet is connected to nitrogen cylinder, middle inlet to the guard tube and the right inlet is closed with stopper. Then the mixture heated in an oil bath, after complete melting of mixture about 0.8 ml of Titanium Tetra isopropoxide is added and the temperature is maintained at 185°C for one hour with stirring. The temperature is then increased to about 194°C and maintained at that temperature for two hours. The crude copolyester obtained is dissolved in chloroform and poured in ice cold methanol to reprecipitate the pure polyester as shown in Figure 1.

RESULTS AND DISCUSSION

Solubility and Viscosity Measurement

Solubility of the copolyester PDDS in solvents like DMF, DMSO, THF and $CHCl_3$ was determined and it has been fouud to be soluble in almost all the solvents. The inherent viscosity of the Copolyester PDDS was determined using Ubbelohde viscometer. By determining the flow time of the solvent and 1% solution of the copolyester in $CHCl_3$ at room temperature, the inherent viscosity was found to be 0.9774 dL/g.

FT-IR Spectral Analysis

The IR spectra recorded for copolyester are presented in Figure 1. The IR spectra of the synthesized copolyester showed a strong absorption band at around 1701.12 cm^{-1}, which is characteristic absorptions of carbonyl stretching vibration of ester groups and thus confirmed the formation of polyesters. The absorption band at 2986.07 was assigned to methylene (-CH_2-) groups for the diacids/diols while the band at 1122, 573.15 and 947 cm^{-1} was attributed to C-O-C asymmetric stretching, C-S stretching and aliphatic C-C stretching respectively.

^{1}H-NMR and ^{13}C-NMR Spectral Analysis

The ^{1}H-NMR and ^{13}C-NMR Spectra of the copolyester PDDS are shown in Figures 2 and 3. The assignments of characteristic peak in the ^{1}H-NMR and ^{13}C-NMR spectra of the copolymer are given the Tables 1 and 2 respectively. All these chemical shift values show the random distribution of monomers in the synthesized copolyester.

DSC Analysis

The DSC thermogram of the synthesied copolyester PDDS are presented in Figure 4. The thermogram shows the glass transition temperature as – 50°C and the melting point temperature as 66.13°C.

X-ray Diffraction Studies

The Wide angle XRD determines the degree of crystallinity of the polymer. The diffractogram of the synthesized PDDS are shown in Figure 5. The diffractogram shows that the synthesized copolyester is amorphous in nature.

Antioxidant Analysis

Table 3 shows the DPPH scavenging activity of the copolyester PDDS. Antioxidant compounds are used as food additives and in preventing lifestyle related diseases and ageing [13]. Lower the value of IC_{50}, greater is the antioxidant property. The IC_{50} value (111.64) of the synthesized copolyester by DPPH Scavenging Assay shows that it has good antioxidant property.

Antimicrobial Activity

The antimicrobial activity of Copolyesrer PDDS against two gram negative and gram positive bacteria by well diffusion method is given in the Table 4 and Figure 6. The copolyester exhibits inhibition range from 10.0-14.0 mm for the human pathogens which shows that the synthesized copolyester PDDS have excellent antimicrobial activity.

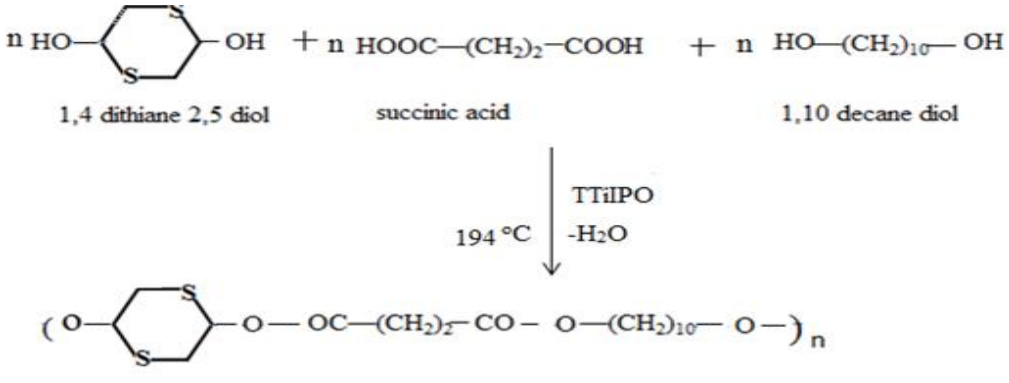
Cytotoxic Activity

The MTT assay of the PDDS against the normal and A_{549} cell line at various concentrations were carried out and the results are given in Tables 5 and 6. The concentration required for 50% inhibition of viability IC_{50} were determined graphically as shown in Figure 7. The affected normal and A_{549} cells at various concentrations is shown in Figures 8 and 9. The effect of the PDDS on the normal and A_{549} cell line was expressed in terms of % cell viability. It is explicit from Tables 5 and 6 that, low concentration of PDDS induced more anticarcinogenic activity on A_{549} cell line than normal vero cell line.

CONCLUSION

The Copolyester PDDS was synthesised by direct melt polycondensation method and it showed good solubility in various organic solvents. The probable structure of the copolyester was confirmed by FT-IR and NMR spectroscopy. The inherent viscosity of PDDS indicates that it possess high degree of polymerisation. The X-ray diffractogram of

copolyester revealed that it is amorphous in nature. The excellent antioxidant, antimicrobial and cytotoxic activity of copolyester indicates that it has versatile application in biomedical field.



poly(1,4 dithiane diol succinate-co-1,10 decane diol succinate)

Scheme-1

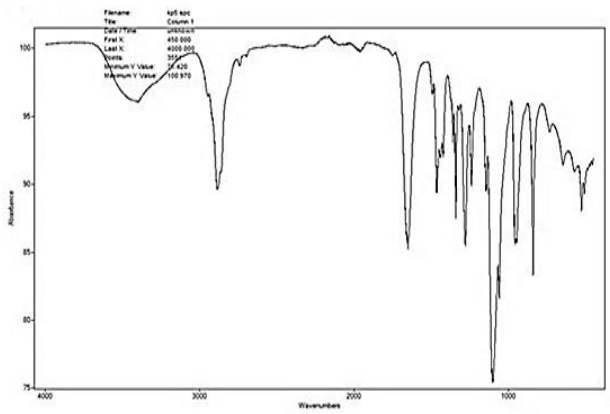


Figure 1. FT-IR spectra of PDDS

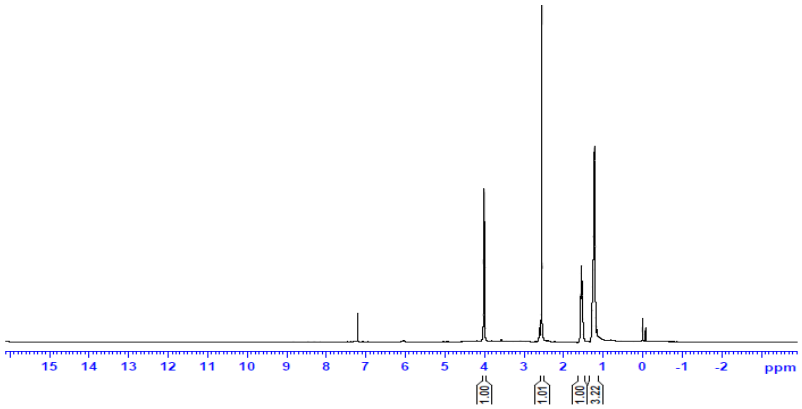


Figure 2. ^{1}H-NMR Spectrum of the PDDS

Table 1. ^{1}H-Nmr Spectral data of the PDDS

Chemical Shift in ppm	Type of Proton
1.172-1.216	-CH_2- protons
1.514-1.564	-C-CH_2-CO protons
2.552-2.591	-CH_2-CO- protons
3.991	C-CH_2-S protons
4.008-4.024	C-CH_2-O protons
7.205	$CDCl_3$ Solvent

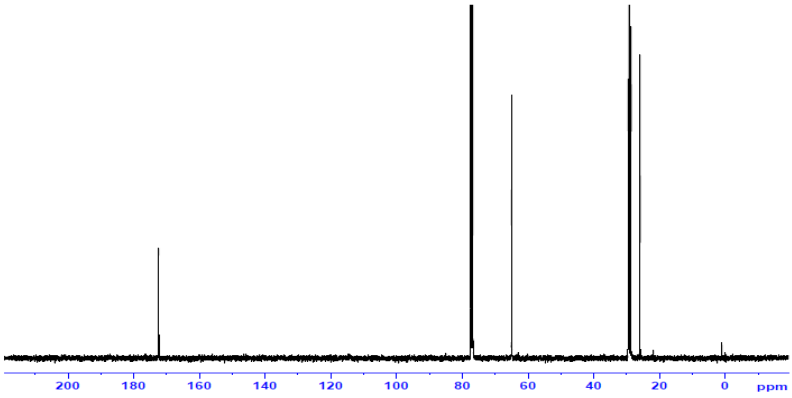


Figure 3. ^{13}C-NMR spectrum of PDDS

Table 2. ^{13}C-NMR spectral data of PDDS

Chemical Shift in ppm	Carbon Assignment
21.79-25.86	-CH_2-
28.57-29.42	-CH_2-S-
63.03-64.98	-CH-S-
76.73-77.36	-CH_2-O-
172.27-172.45	-C=O (ester group)

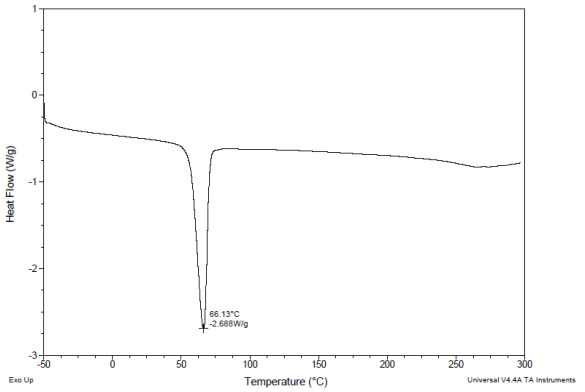


Figure 4. DSC Thermogram of PDDS

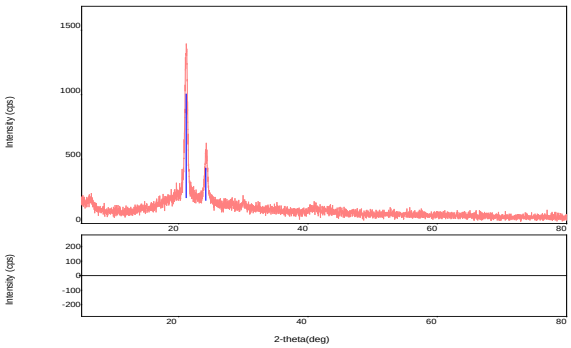


Figure 5. X-Ray Diffractogram of PDDS

Table 3. *In vitro* Antioxidant Activity of PDDS by DPPH Scavenging Assay

Conc. Of Compounds (µg/mL)	Percentage of inhibition
1000	72.92 ± 4.94
500	70.11 ± 5.28
250	63.38 ± 3.62
125	55.98 ± 2.29
62.5	47.59 ± 1.93
31.25	36.46 ± 1.15
15.62	24.09 ± 0.98
IC_{50} (µg/mL)	111.64

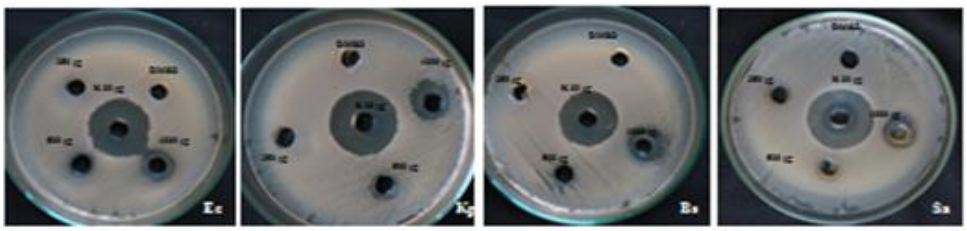


Figure 6. Antimicrobial activity of *Escherichia coli*, *Klebsiella pneumonia*, *Bacillus subtilis* and *Staphylococcus aureus*

Table 4. Antimicrobial activity of PDDS by well diffusion method

Human Pathogens	**Concentration (in µg/mL)**	**Zone of inhibition in mm (Percentage of Inhibition)**	**Standard Drugs Tetracycline/(30 µg/mL)**	**Types of Organisms**
Escherichia coli	1000	12 ± 0.84 (13.33 ± 0.93)	18 (20)	Gram negative Bacteria
	500	11 ± 0.77 (12.22 ± 0.85)		
	250	-		
Klebsiella pneumoniae	1000	14 ± 0.98 (15.55 ± 1.01)	24 (26.66)	
	500	12 ± 0.84 (13.33 ± 0.93)		
	250	-		
Bacillus subtilis	1000	13 ± 0.91 (14.44 ± 1.01)	32 (35.55)	Gram Positive Bacteria
	500	-		
	250	-		
Staphylococcus aureus	1000	14 ± 0.98 (15.55 ± 1.01)	31 (34.44)	
	500	10 ± 0.70 (11.11 ± 0.77)		
	250	-		

Table 5. Cytotoxic Activity of PDDS on Vero (normal) cell line

Concentration of compounds (µg/ml)	(%) Cell viability
1000	51.37
500	58.64
250	63.41
125	69.06
62.5	74.71
31.2	80.49
15.6	88.83
7.8	92.60
Cell control	100
IC 50 value (µg/mL)	1143.90

Table 6. Cytotoxic Activity of PDDS against Lung cancer (A_{549}) cell line

Concentration of compounds (µg/ml)	(%) Cell viability
1000	20.52
500	34.80
250	42.05
125	51.39
62.5	62.58
31.2	69.66
15.6	78.58
7.8	86.55
Cell control	100

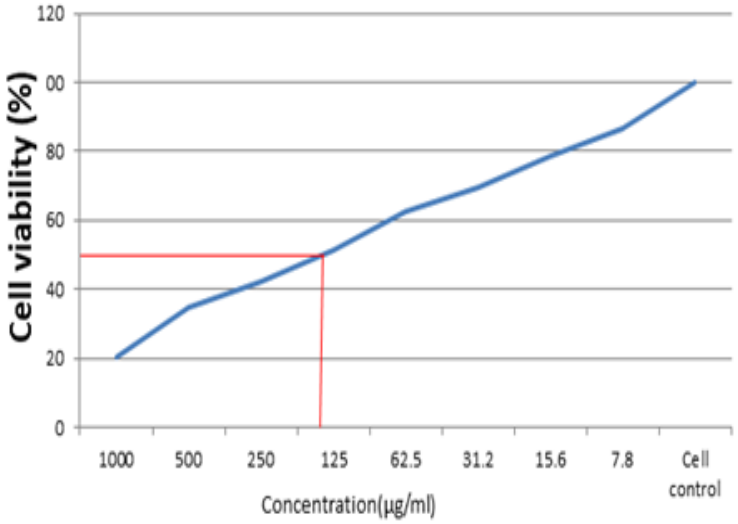


Figure 7. Graphical representation of activities of PDDS in MTT Assay

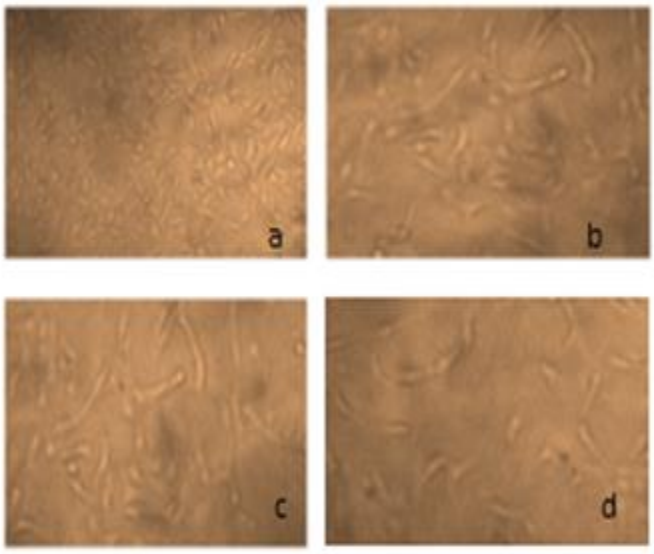


Figure 8. *In vitro* cytotoxic activity of PDDS on Normal vero cell line at different concentrations (a) Normal cell, (b) 7.8 µg/ml, (c) 500 µg/ml and (d) 1000 µg/ml

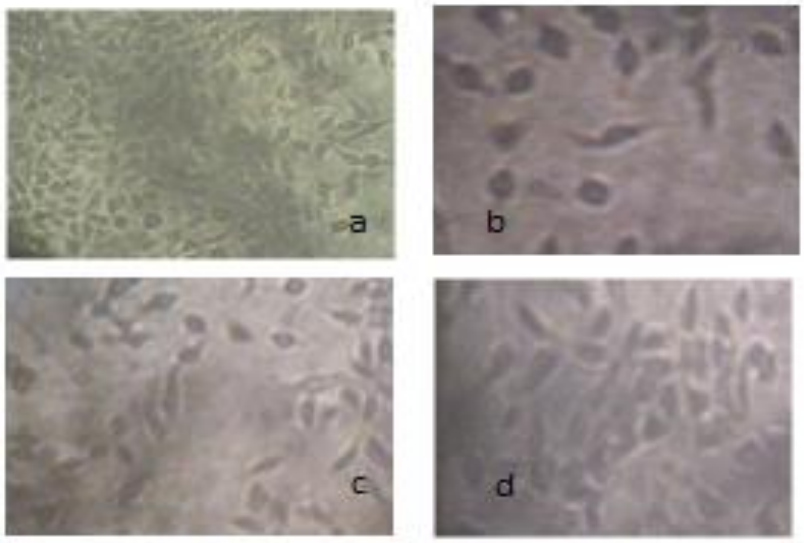


Figure 9. *In vitro* cytotoxic activity of PDDS on A_{549} (lung cancer) cell line at different concentrations (a) Normal cell, (b) 1000 µg/ml, (c) 125 µg/ml and (d) 7.8 µg/ml

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