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Synthesis, Characterization, Thermal, Bactericidal and Fungicidal Properties of Certain Main Chain Aliphatic-aromatic Random Copolyesters Possessing Chalcone Linkages in their Backbone

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Abstract:- In this paper, we report on the synthesis of five high molecular weight random copolyesters containing chalcone moieties in their main chain by the polycondensation of a chalcone diol with an aromatic diacid chloride (terephthalic acid) and four varying aliphatic diacid chlorides malonyl chloride, pimeloyl chloride, suberoyl chloride, azelaoyl chloride and sebacoyl chloride in a DMF/triethylamine medium. The chalcone used in the copolymerization process was prepared by an acid-catalyzed Claisen-Schmidt reaction. The synthesized aliphatic-aromatic random chalcone copolyesters were characterized by quantitative solubility and viscosity measurements which proved the copolyesters to have invariably high molecular weights. The microstructure of repeat units in the copolymer chain was established with the aid of FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques. The thermal analysis by the differential scanning calorimetry (*DSC*) gave the glass transition temperature (T_g), the melting temperature (T_m), and the isotropization temperature (T_i) indicating a semi-crystalline nature of copolyesters while the values of T_g (21.4°C) and T_m (108.8°C) concluded the copolyesters well suited for drug delivery applications. The inhibitory efficacy of the all five synthesized random copolyesters against the pathogenic bacteria (*B. subtilis & E. coli*) and the fungi (*A. niger & C. albicans*) was tested with the well diffusion method which demonstrated the copolyesters as good bactericidal and fungicidal agents but not as strong as the standard antibiotic, the *streptomycin* and the standard antifungals viz. the *clotrimazole* and the *fluconazole*.

Keywords:- *Random Aliphatic-Aromatic Copolyesters; Polycondensation; Chalcones; Copolymerization; Glass-Transition; Melting; Isotropization; Drug-Delivery; Bactericidal; Fungicidal.*

I. INTRODUCTION

The escalating global demand of plastic generate non-biodegradable waste, a threat to environment hence a subject of prime concern. To be specific, genotoxic biomedical waste (cytotoxic drugs, and vomit/urine/faeces from patients on cytotoxic drugs) due to its mutagenicity, teratogenicity, or carcinogenicity is a menace to the environment and has disastrous consequences upon human health and therefore be given utmost attention. Although, ways to reduce plastic products with a strong emphasis on recycling plastic waste already in action but the most prominent method to tackle this problem is the development and usage of biodegradable plastics.[1] For the same reason, development of biodegradable polymers (aliphatic polyesters) viz. poly(lactic acid), poly(butylene succinate), poly(propylene adipate), poly(ethylene succinate), poly(ε-caprolactone), poly(propylene sebacate), poly(3-hydroxybutyate), poly(propylene succinate) is on track from the past decade.[2-5]

Fungal and bacterial infections are the chief cause of high morbidity/mortality among human beings round the globe, especially in developing countries. The condition has been worsen with the emergence of multidrug drug resistance[6] for which the conventional antibiotics have failed and so as to cope with, the situation demands novel biologically active molecules or bioactive polymeric drugs. Ever since 2000, the use of polymer drugs began due to their pharmacological effect and their ability to deliver an existing antimicrobial drug. In 2002, amphiphilic copolymers, such as poly(norbornene), poly(β-amino acid), poly(methacrylate) and poly(hexamethylene biguanide) were synthesized through the copolymerization of cationic and hydrophobic monomers that mimic natural antimicrobial peptides and so could efficiently target multidrug resistance bacterial strains.[7] Later, in 2006, Whitesides lab employ heterobifunctional polymers to orchestrate surface of bacterial cell so that it can be recognized by neutralizing antibodies and phagocytosis by gram +ve bacteria.[8] Copolyesters, for example Eastman

Easter™, DuraStar™, and Eastman Tenite™ were historically been used for medicinal use, but in 2009, Eastman Titan™ dwell medicinal industry owing to its toughness, clarity and superior chemical resistance.[9] The credit goes to the 21st century in which biodegradable polymers developed that exerted significant cellular responses.[10]

As stated aliphatic polyesters the best choice due to biodegradability[11,12] but their low thermal and mechanical strength limit the usage on commercial scale. However, copolymerization[13,14] of aliphatic polyesters with aromatic analogues enhance their thermal and mechanical properties without sacrificing biodegradability[15]. Generally, water degrades all types of polyesters by cleaving main chain ester bonds but the hydrophobicity due to aromatic domains in aliphatic-aromatic polyester excludes H_2O from the environ of labile bonds and as a result only aliphatic segments consisting short methylene groups amongst the ester bonds degrade over the period of time.

Specifically, liquid crystalline random aliphatic-aromatic copolyesters incorporated with spacer units, say methylene groups in their backbone making the polymer flexible are drawing the attention of researchers due to their unique physicochemical properties that makes them perfect fit for high precision mouldings, high performance fibers, photoresists, temperature resistant performance materials, biomedical applications (sutures, bone pins, scaffolds, stents & drug delivery devices); despite of which their commercial sale is only 10 million lb. per year in the USA.[16] The quite low sale is attributed to their price as high as 20 times that of conventional thermoplastics (e.g. PET). However, blending polyesters with fillers derived from natural materials, like starch[17] and wheat gluten[18] reduce the cost but the incompatibility between the polyester matrix and the filler material may deteriorate the polymer's mechanical ability.

Chalcones, the 1,3-diphenylprop-2-en-1-one derivatives are the precursors of flavonoids and isoflavonoids that have low redox potential and so greater susceptibility to undergo electron transfer reactions. Chalcones either natural or synthetic demonstrate promising therapeutic efficacy viz., anticancer,[19] anti-inflammatory,[20] antiparasitic, antifungal,[21] antiulcerative,[22] antiprotozoal (antileishmanial, antitrypanosomal),[23] antituberculosis, antioxidant,[24] antimicrobial,[25] antigout, antimalarial,[26] antidiabetic, anti-HIV,[27] antimutagenic,[28] anticonvulsive,[29] antispasmodic and antiobesity. Among the natural chalcones: Xanthoangelol and 4-Hydrooxyderricin derived from the Ashitaba herb[30] are well known antioxidants and helpful in retarding the ageing; cinnamon derived methylhydroxy chalcone increase insulin response[31]; chalcone extracted from *Curcuma longa* reported as a chemopreventive agent[32]; and Xanthoangelol, Flavokawain A, Isoliquiritigenin, Isobavachalcone & Licochalcone already proved as powerful antitumor agents[33].

This strong pharmacology of chalcones is due to the large number of replaceable hydrogen atoms that allow an easy synthetic manipulation, presence of hydroxy and methoxy substituents and the versatile α, β-unsaturated carbonyl moiety that imparts Michael acceptor, oxidative & reductive, radical scavenging, thermal & photo-isomerization and photocrosslinking properties to chalcone.[34] As a Michael acceptor, chalcones interact with sulfhydryl of cysteines in proteins and other thiols (glutathione) and form 1,4-adducts that can change redox signaling and modulate: DNA synthesis, activation/inhibition of enzymes/transcription factors, expression of selective genes and regulation of cell cycle.[35] Chalcones not only have the ability to cure almost all microbial caused diseases but can treat infections in MDR 'ON' situations also for which the present day antibiotics have proved inferior. Chalcones either alone or in synergism with known antimicrobial agents can impair bacterial cell wall & DNA replication, hence remove MDR and prevents biofilm[36] formation without posing toxicity to normal mammalian cells.

The α,β-unsaturated carbonyl moiety act as a chromophore due to which chalcone forms crosslinked network when irradiated with UV-light.

Chalcone have been reported as biodegradable and biocompatible, though suitable for biomedical applications, such as sutures, pacemakers, chemopreventive drugs, controlled release drug delivery devices, implants and drug encapsulations. The relatively simple skeletal framework of chalcones in contrast to complex conventional drugs makes them the ideal choice to be incorporated in copolymers and design biodegradable and biocompatible polymers or polymeric drugs.

Synthetically chalcones can be prepared by either of the reactions listed: Claisen-Schmidt condensation, Aldol condensation, Suzuki reaction, Wittig reaction, Friedel-Crafts acylation, Heck reaction, and Photo-Fries rearrangement.[37]

The advantage of chalcone chromophore over other photosensitive groups intend our interest to prepare aliphatic-aromatic random copolyesters containing chalcone moieties in their backbones. This work presents a straight forward technique i.e. solution polycondensation, to prepare random copolyesters by employing the chalcone [(*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one)] as the diol, an aromatic diacid chloride (terephthaloyl chloride), and four varying aliphatic diacid chlorides (malonyl/pimeloyl/suberoyl/azelaoyl/sebacoyl chloride) in the mole ratio of 2:1:1. The chalcone used in this study is prepared through the most versatile an acid-catalysed Claisen-Schmidt condensation method. The structure of repeat units is reported by the application of FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques, and their thermal stability through the differential scanning calorimetry. Since these chalcone copolyesters are biodegradable, biocompatible, and biologically active against microbes and fungi, therefore, herein we studied their thermal and biocidal behaviour in depth by assaying them against pathogenic bacteria (*B. subtilis* and *E. coli*) and fungi (*A. niger* & *C. albicans*) through well-diffusion method.

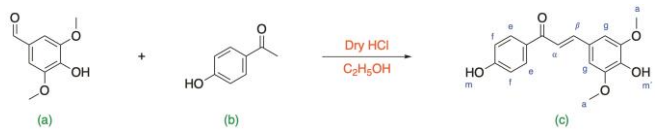
II. MATERIALS AND METHODS

A. *Materials (Heading 2)*

The Sigma-Aldrich AR grade 4-hydroxy-3,5-dimethoxybenzaldehyde, 1-(4-hydroxyphenyl)ethan-1-one, terephthaloyl chloride, pimeloyl chloride, malonyl chloride, suberoyl chloride, azelaoyl chloride, sebacoyl chloride were used for the synthesis of chalcone diols and five random copolyesters. The solvents viz., acetone, methanol, ethanol, triethylamine, dimethylformamide (DMF), dimethylsulphoxide (DMSO), dimethylacetamide (DMAc), chloroform, ethylacetate (EtOAc), benzene, n-hexane and water were purified and distilled prior to their usage. Sigma-Aldrich spectral grade deuterated DMSO containing TMS as internal standard was used as the reagent to record NMR spectra of copolyesters.

B. *Synthesis of the Chalcone, EHDP*

The chalcone diol EHDP was synthesized according to the acid-catalyzed Claisen-Schmidt condensation, Scheme 1. An equimolar mixture i.e. 2.0 g of 4-hydroxy-3,5-dimethoxybenzaldehyde and 1.5 g of 1-(4-hydroxyphenyl)ethan-1-one were dissolved in 100 mL of absolute alcohol with constant stirring. Subsequently, this alcoholic solution was then ice-cooled and thereafter passed dry hydrogen chloride gas for about an hour. The green precipitate of chalcone diol (*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (EHDP) crystallized out. Finally, the crude product was filtered, washed with distilled water, dried at room temperature and recrystallized from ethanol. Yield: 87.6%.



(a) 4-hydroxy-3,5-dimethoxybenzaldehyde
(b) 1-(4-hydroxyphenyl)ethan-1-one
(c) (*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1- one (**EHDP**)

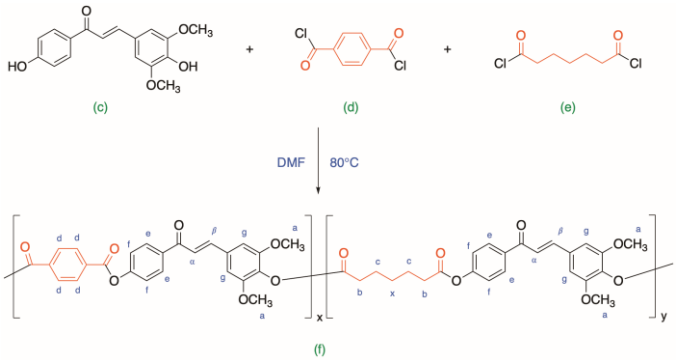
Scheme 1. An acid-catalyzed Claisen-Schmidt synthesis of the monomer diol, EHDP.

C. *Synthesis of the Copolyester, TPIH*

The five aromatic-aliphatic diacid chloride based random copolyesters were synthesized by the solution polycondensation. The ease of non-toxic chemical reaction made this inexpensive technique to prefer over the other reported methods of copolyester synthesis.

As an example, the synthesis of copolyester TPIH is described in Scheme 2. 1 mmol. (0.3 g) of chalcone diol, EHDP was dissolved in 15 mL of DMF in a polycondensation flask. After 5 minutes, 1 mL of triethylamine was added and stirred with the aid of magnetic-stirrer. Following the complete dissolution of the monomer, 0.5 mmol of each terephthaloyl chloride (0.1 g) and pimeloyl chloride (0.08 mL) was also added. The reaction temperature was raised and maintained at 80°C with continuous stirring for about 3 hours. Finally, the reaction mixture was allowed to cool down at room temperature and thereafter poured into 100 mL of distilled water, which made the requisite copolyester to precipitate out. The crude copolymer was then filtered, washed and air-dried.

Similar to the above procedure, four other copolyesters TMAH, TSUH, TNOH and TSEH were also synthesized employing the same chalcone diol EHDP and the aromatic diacid chloride but different aliphatic diacid chlorides, shown in the Table I; proposed structures of the copolyesters depicted in Figures 1g-j.



(c) (*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**EHDP**)
(d) terephthaloyl dichloride
(e) pimeloyl dichloride
(f) copolyester (**TPIH**)

Scheme 2. A polycondensation depicting the synthesis of the chalcone copolyester, TPIH.

TABLE I. CHALCONE DIOL AS MONOMER, AROMATIC AND ALIPHATIC DIACID CHLORIDES USED FOR THE SYNTHESIS OF FIVE COPOLYESTERS ALONG WITH THEIR RESPECTIVE CODES

Chalcone diol	**Aromatic diacid chloride**	**Aliphatic diacid chloride**	**Copolyester codes**
EHDP	Terephthaloyl chloride	Pimeloyl chloride	TPIH
EHDP	Terephthaloyl chloride	Malonyl chloride	TMAH
EHDP	Terephthaloyl chloride	Suberoyl chloride	TSUH
EHDP	Terephthaloyl chloride	Azelaoyl chloride	TNOH
EHDP	Terephthaloyl chloride	Sebacoyl chloride	TSEH

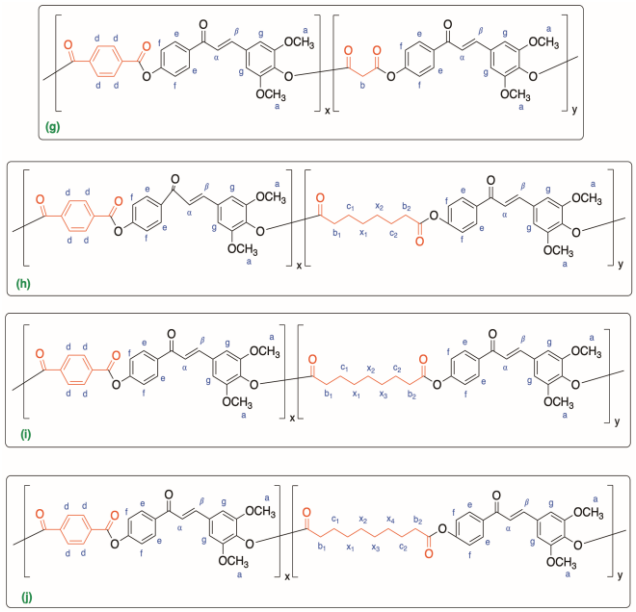


Fig. 1. Proposed structures of the copolyesters (g) TMAH, (h) TSUH, (i) TNOH, (j) TSEH.

III. CHARACTERIZATION METHODS

A. Solubility

Solubility of all the five chalcone copolyesters was qualitatively tested in various polar protic, polar aprotic and non-polar solvents viz., dimethylacetamide, dimethylsulphoxide, dimethylformamide, acetone, ethylacetate, chloroform, benzene, n-hexane, methanol and ethanol. 2-5 milligram of each copolymer sample was shaken with each of the above solvents and setup was placed aside for 6 hours with occasional shaking.

B. Inherent Viscosity

The inherent viscosity ($\eta_{inh.}$) of all the synthesized copolymers was determined in DMAc solution using Ubbelohde Viscometer at 30°C. 0.1 gdL^{-1} copolymer solutions were prepared by dissolving 25 mg of pure dry random copolyester in 25 mL of dimethylacetamide in each case. These solutions prepared were kept aside for at least 12 hours with intermittent shaking prior to their placement in the viscometer. The intrinsic viscosity was then calculated using (1):

$$\eta_{inh.} = ln(t/t_o)/C \quad (1)$$

where t is the flow time of the polymer solution, t_o is the flow time of the pure solvent and C is the concentration of the copolyester solution.

C. Spectral Characterization

The microstructure of chalcone diol and the repeat units of all random copolyesters synthesized was investigated by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques. FT-IR measurements were taken in the form of KBr-pelleted copolyester samples on a Perkin-Elmer FT-IR Spectrometer at 4 cm^{-1} resolution in the range of 4000 to 400 cm^{-1}.

Bruker AV III 500 MHz NMR instrument operating at 500 MHz and 75 MHz was used to record ^{1}H-NMR and ^{13}C-NMR spectra of chalcone and chalcone containing copolyesters, at room temperature, in DMSO-d6 as a solvent spiked with TMS as an internal standard.

D. Thermal Characterization

DSC thermogram of the copolyester TPIH was recorded on a Netzsch–DSC 200 F3 Maia instrument at a heating rate of 10°C per minute in an inert atmosphere of nitrogen. To an approximation 3-6 mg of the copolymer sample was used for DSC measurement.

E. Methods for Determining Biological Efficacy

Antibacterial Efficacy: To test the antibacterial efficacy, the five chalcone containing copolyesters were examined against *Bacillus subtilis* and *Escherichia coli* using the agar well-diffusion method. Different concentrations of the test compounds say 25, 50, 75 and 100 µg/mL were prepared in DMSO. Target pathogens were cultured in Mueller Hinton Agar (MHA) medium, past 24 hours of which, the suspensions were adjusted to standard subculture dilution. The Petri dishes containing agar medium were then inoculated with freshly prepared microbial inoculum over the entire agar surface. Agar wells with a diameter of 6 millimeters were made with the aid of a sterile stainless steel cork borer. The antibiotic *streptomycin* (10 µg) was used as the positive reference standard to determine the sensitivity of each target microbial species. A 20-100 µL volume of the test solution at desired concentration was introduced into the well, after which the agar plates were incubated at 37°C for 24 hours. The diameter of the clear zone around the well was then measured and expressed in millimeters.

Antifungal Efficacy: *Candida albicans* and *Aspergillus niger* were used to test the antifungal activity of copolyesters TPIH, TMAH, TSUH, TNOH and TSEH by the well-diffusion method. The fungal strains were cultured on Sabouraud dextrose agar, incubated at 37°C for 24 hours and maintained for 5 days on potato dextrose agar (PDA) slant. Sterilized Sabouraud dextrose agar medium was then inoculated with a 72 hour old 0.5 milliliter fungal suspension in a separate flask. After which, 25 mL of the inoculated medium was evenly spread in a sterilized Petri dish and kept aside to set for 2 hours. The cups 6 mm in diameter were punched in Petri dish and filled with 100 µL (2 mg/mL) of test solution of desired concentration, for instance 25, 50, 75 or 100 µg/mL. The plates were then incubated at 37°C for 72 hours. The standard antifungal drugs *clotrimazole* and *fluconazole* were used as the positive control. On completion of the incubation period, the diameter of inhibition zone was measured in millimeters.

IV. RESULTS AND DISCUSSION

A. Solubility

Qualitative solubility test of all the five copolyesters when performed in different solvents disclosed that the copolymers were soluble in polar aprotic solvents, for instance dimethylacetamide, dimethylsulphoxide, dimethylformamide at room temperature, partially soluble in moderately polar solvents, say acetone, ethylacetate & chloroform but insoluble in non-polar solvents, such as benzene, hexane and hydroxyl

containing or polar protic solvents i.e. methanol and ethanol. The insolubility is owed to the highly rigid aromatic nature of polymers. It is noticed that the solubility decreases with an increase in the molecular weight of solute and as such the affinity between the solute and the solvent is high when the two have similar polarity, represented in the Table II.

TABLE II. SOLUBILITY TREND OF CHALCONE COPOLYESTERS

S.No.	Polymer code	DMAc	DMSO	DMF	Ac_2O	EtOAc	$CHCl_3$	C_6H_6	C_6H_{12}	MeOH	EtOH
1	TMAH	++[a]	++[a]	++[a]	+-[b]	+-[b]	+-[b]	--[c]	--[c]	--[c]	--[c]
2	TPIH	++ [a]	++ [a]	++ [a]	+- [b]	+- [b]	+- [b]	-- [c]	-- [c]	-- [c]	-- [c]
3	TSUH	++ [a]	++ [a]	++ [a]	+- [b]	+- [b]	+- [b]	-- [c]	-- [c]	-- [c]	-- [c]
4	TNOH	++ [a]	++ [a]	++ [a]	+- [b]	+- [b]	+- [b]	-- [c]	-- [c]	-- [c]	-- [c]
5	TSEH	++ [a]	++ [a]	++ [a]	+- [b]	+- [b]	+- [b]	-- [c]	-- [c]	-- [c]	-- [c]

[a] ++ soluble
[b] +- *soluble on warming*
[c] — *insoluble*

B. Intrinsic Viscosity

The aliphatic-aromatic chalcone copolyesters synthesized so found to have high molecular weights as depicted by their inherent viscosity values viz. 1.18–1.98 dLg^{-1} (Table III), calculated by using dimethylacetamide as the solvent. Inherent viscosity values of chalcone containing copolyesters increase with an increase in the length of their aliphatic segments. High inherent viscosity values attributed to substituent methoxy which enhance solute-solvent interactions and in a way disrupt the macromolecular chain of copolyesters. Inherent viscosity values increase with the length of incorporated methylene spacer which in turn might be due to an increase in the molecular weight of the synthesized chalcone copolyesters, hence the copolyester derived from malonyl chloride has the least $\eta_{inh.}$ value among the all five copolyesters. Contrary to this, the viscosity of TSUH found to be higher than that of TNOH due to an 'odd-even' effect, the former being derived from suberoyl chloride having an even number of carbon atoms as compared to the azelaoyl chloride with an odd number of carbons.

TABLE III. CALCULATED INTRINSIC VISCOSITY VALUES OF COPOLYESTERS USING DMAC AS SOLVENT AT 30°C.

S.No.	Copolyester Code	$\eta_{inh.}$ at 30°C in dL/g
1	TMAH	1.18
2	TPIH	1.79
3	TSUH	1.88
4	TNOH	1.81
5	TSEH	1.98

C. FT-IR Analysis

The fourier transform infra-red spectra of the chalcone EHDP and the all five copolyesters are shown in Figures 2–6 and the values of their characteristic spectral absorptions in the Tables IV and V, respectively.

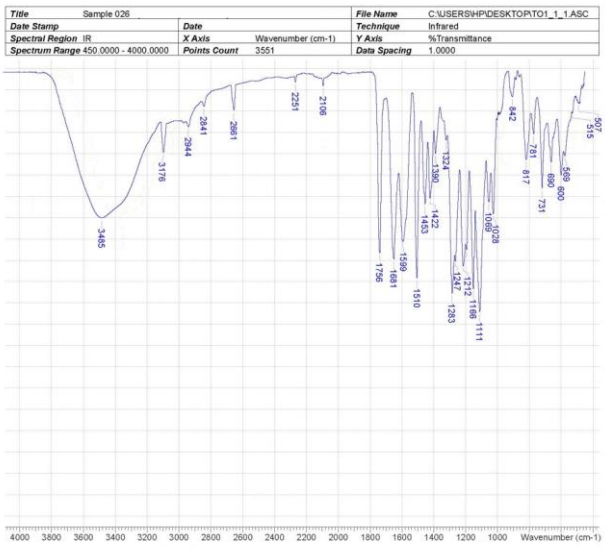


Fig. 2. FT-IR spectrum of the copolyester TMAH

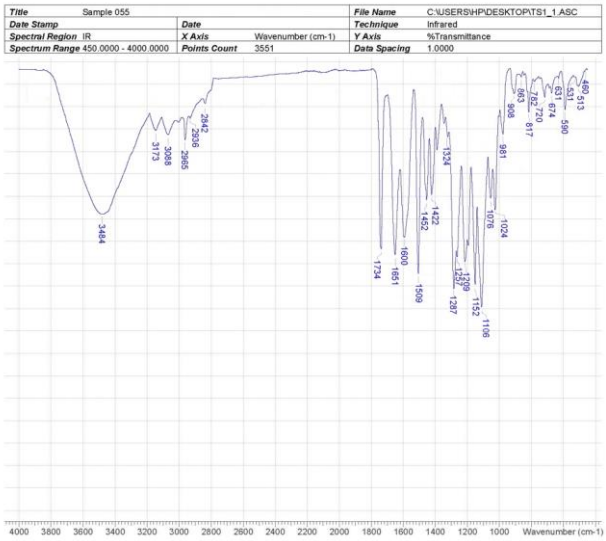


Fig. 3. FT-IR spectrum of the copolyester TPIH

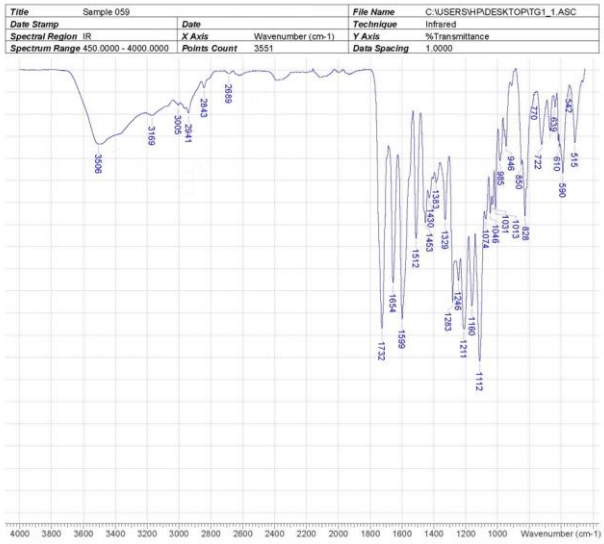


Fig. 4. FT-IR spectrum of the copolyester TSUH

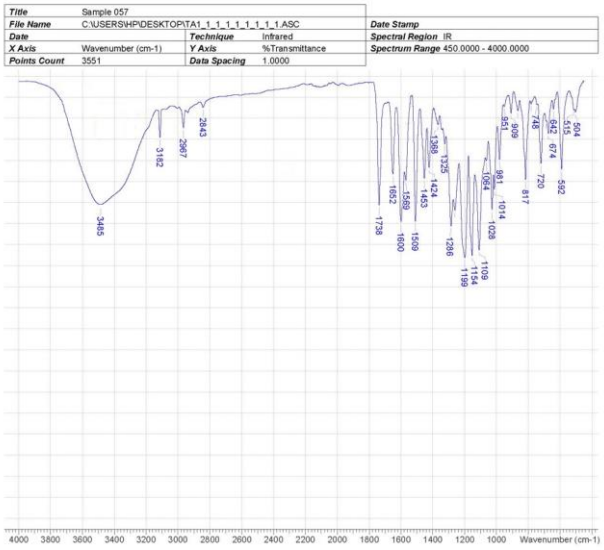


Fig. 5. FT-IR spectrum of the copolyester TNOH

TABLE IV. CHARATERISTIC ABSORPTIONS IN FT-IR SPECTRA OF THE CHALCONE, EHDP AND THEIR ASSIGNED FREQUENCIES.

Chalcone	Frequencies (in cm^{-1}) of Various IR-Bands										
	Broad H-bonded ν_{O-H}	ν_{C-H}	*Aliphatic*				*α,β-Unsaturated* $\nu_{C=O}$	*Aromatic* $\nu_{C=C}$	*Aryl alkyl ether* $\nu_{as\ C-O-C}$	*Aryl alkyl ether* $\nu_{s\ C-O-C}$	*Weak combination and overtone bands*
			ν_{as} C-H		ν_{s} C-H						
			CH_3	CH_2	CH_3	CH_2					
EHDP	3485	3174	2965	2985	2842	2936	1646	1602,1567, 1509,1451	1256	1025	2000-1667

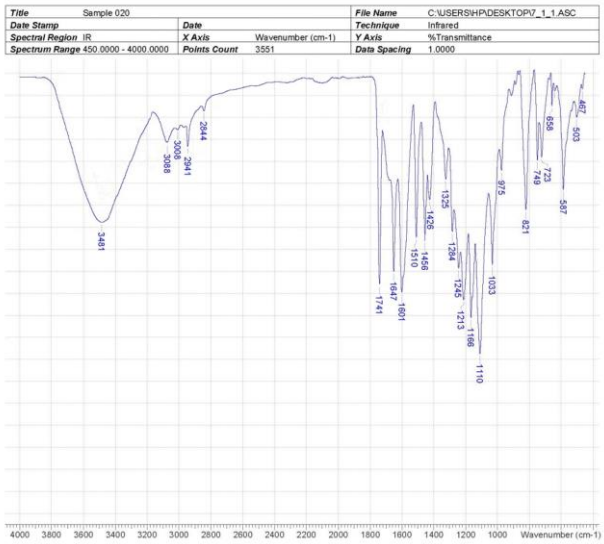


Fig. 6. FT-IR spectrum of the copolyester TSEH

Figures 1g-j, -C(=O)-O- is flanked by two phenyl groups out of which (i) the one conjugated with -C=O- group lowers the normal $\nu_{C=O\ ester}$ frequency by 40-15 cm^{-1} while, (ii) the other phenyl group conjugated with -C-O- group raises the stretching frequency of normal $\nu_{C=O\ ester}$ by the same amount. The combined effect of (i) and (ii) is that a band corresponding to $\nu_{C=O\ ester}$ appears in the range 1756–1732 cm^{-1} and as can be seen in IR spectra of the copolyesters, Figures 1.2-1.7. The appearance of a band between 1681–1647 cm^{-1} corresponds to stretching vibration of an α,β-unsaturated carbonyl group. Thus, there are two types of carbonyl groups incorporated in the copolyesters, the one bestowed from dicarboxylic acid and the other from chalcone part. The frequency of ester carbonyl group is higher than that of enone carbonyl group due to electron withdrawing nature of oxygen adjacent to the former carbonyl moiety.

TABLE V. CHARACTERISTIC ABSORPTIONS IN FT-IR SPECTRA OF COPOLYESTERS AND THEIR ASSIGNED FREQUENCIES

S.No.	Polyester Code	Frequencies (in cm^{-1}) of Various IR-Bands									
		End O-H group ν_{O-H}	*Aromatic* $\nu_{=C-H}$	*Aliphatic* ν_{C-H}	*Ester* $\nu_{C=O}$	*α,β-Unsaturated* $\nu_{C=O}$	*Aromatic* $\nu_{C=C}$	*Aryl alkyl ether* $\nu_{as}{}^{d}$ C-O-C	*Aryl alkyl ether* $\nu_{s}{}^{e}$ C-O-C	*Aromatic ester* $\nu_{as}{}^{d}$ C-C(=O)-O	*Aromatic ester* $\nu_{as}{}^{d}$ O-C=C
1.	TMAH	3485	3176	2944, 2841	1756	1681	1599,1510, 1453	1212	1028	1283	1111
2.	TPIH	3484	3088	2965, 2936, 2842	1734	1651	1600,1509, 1452,1422	1209	1024	1287	1106
3.	TSUH	3506	3005	2941, 2843	1732	1654	1599, 1453,1430	1211	1046	1283	1112
4.	TNOH	3485	3082	2967, 2843	1738	1652	1600,1569, 1509,1453	1199	1028	1286	1109
5.	TSEH	3481	3088, 3008	2941, 2844	1741	1647	1510,1456, 1426	1213	1033	1284	1110

[d] ν_{as} → asymmetric stretching
[e] ν_{s} → symmetric stretching

Two bands, one in the range 1213–1199 cm^{-1} and another in between 1046–1024 cm^{-1} appears due to asymmetric and symmetric stretching of C-O-C bond, confirming the existence of $-OCH_3$ groups in the copolyesters. The absorptions in between 1287–1283 cm^{-1} ($\nu_{as\ C-C(=O)-O}$) and 1112-1106 cm^{-1} ($\nu_{as\ O-C=C}$) in the FT-IR spectra of copolyesters corresponds to two asymmetric coupled vibrations for esters of aromatic acids. A set of bands from 2967 to 2841 cm^{-1} as appeared in the infra-red spectra of all five copolyesters are mainly due to stretching vibrations of aliphatic C-H bonds (associated with $-CH_3$ and $-CH_2$ groups), while absorption in between 3176–3005 cm^{-1} is due to stretching of aromatic C-H bonds. Four absorptions from 1600–1422 cm^{-1} implies aromatic C=C bonds confirming that the copolyesters consists of aromatic domains in addition to aliphatic segments. A broad band in the range 3506–3481 cm^{-1} indicates that to the chalcone and the copolyesters a hydrogen bonded O-H group is attached.

Thus, the FT-IR data evidenced the formation of the ester linkage which is must in the polymerization and marks the presence of chalcone diol and diacid chloride units in the polymer.

D. ^{1}H-NMR Analysis

The ^{1}H-NMR spectra of all the five copolyesters synthesized are depicted in the Figures 7–11 and the types of protons inferred from them together with their chemical shift values in ppm downfield from tetramethylsilane are tabulated in the Table VI.

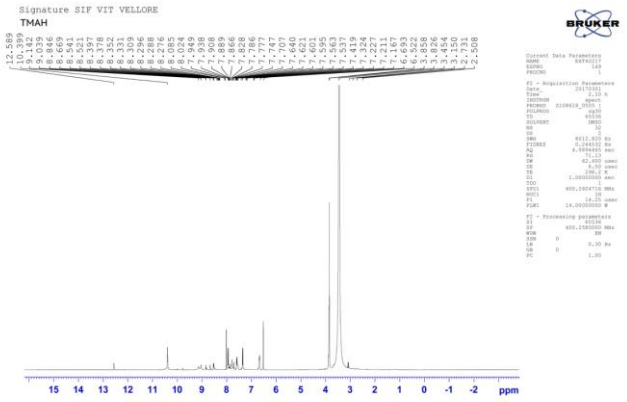


Fig. 7. 1H-NMR spectrum of the copolyester TMAH

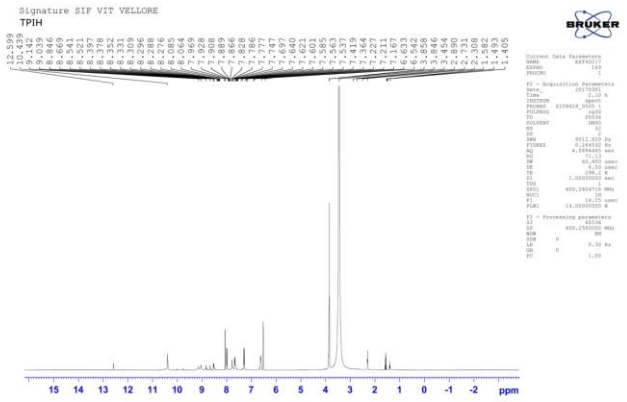


Fig. 8. 1H-NMR spectrum of the copolyester TPIH

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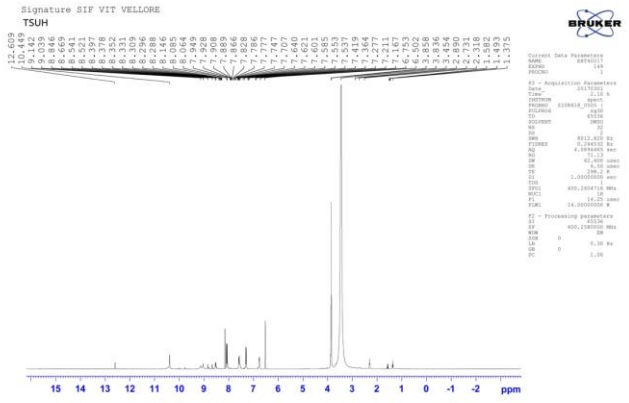

Fig. 9. 1H-NMR spectrum of the copolyester TSUH

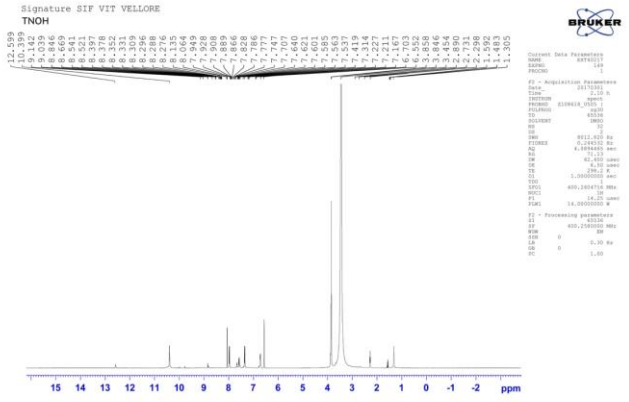

Fig. 10. 1H-NMR spectrum of the copolyester TNOH

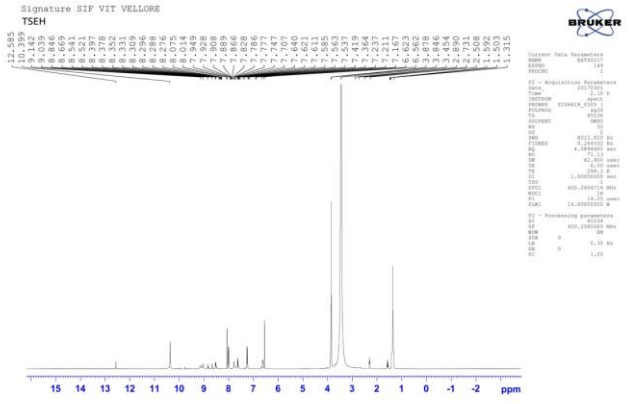

Fig. 11. 1H-NMR spectrum of the copolyester TSEH

Fig. 12.

Chalcone EHDP: ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.86 (6H, s, H_a), δ 6.40 (2H, s, H_g), δ 7.81 (2H, d, H_e, J_{HeHf} = 6 Hz), δ 6.80 (2H, d, J_{HfHe} = 6 Hz), δ 6.68 (1H, d, H_α, $J_{H\alpha H\beta}$ = 15.1 Hz), δ 7.61 (1H, d, H_β, $J_{H\beta H\alpha}$ = 15.1 Hz), δ 9.11 (1H, s, $H_{m'}$), δ 10.23 (1H, s, H_m).

$C_{m'}$-proton (δ 9.11) absorbs at high frequency as compared to C_m-proton (δ 10.23) which implies that former is flanked by some electron donating group deshielding the proton and so is in agreement with the proposed structure of chalcone in Scheme 1c, holding two -OCH_3 groups ortho to $C_{m'}$-proton.

Copolyester TMAH (Figure 7): ^{1}H-NMR (400 MHz, DMSO-d6): δ 3.15 (2H, s, H_b), δ 3.15 (12H, s, H_a), δ 6.52 (4H, s, H_g), δ 6.69 (2H, d, H_α, $J_{H\alpha H\beta}$ = 15.4 Hz), δ 7.32 (4H, d, H_f, J_{HfHe} = 7 Hz), δ 7.59 (2H, d, H_β, $J_{H\beta H\alpha}$ = 15.4 Hz), δ 7.93 (4H, d, H_e, J_{HeHf} = 7 Hz), δ 8.0 (4H, s, H_d), δ 10.27 (end phenolic -OH protons), δ12.58 (end carboxylic acid proton).

Copolyester TPIH (Figure 8): ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.40 (2H, q, H_x, J_{HxHc} = 8 Hz), δ 1.49–1.58 (4H, m, H_c), δ 2.30 (4H, t, H_b, J_{HbHc} = 7 Hz), δ 3.85 (12H, s, H_a), δ 6.54 (4H, s, H_g), δ 6.63 (2H, d, H_α, $J_{H\alpha H\beta}$ = 15.1 Hz), δ 7.29 (4H, d, H_f, J_{HfHe} = 6 Hz), δ 7.69 (2H, d, H_β, $J_{H\beta H\alpha}$ = 15.1 Hz), δ 7.96 (4H, d, H_e, J_{HeHf} = 6 Hz), δ 8.08 (4H, s, H_d), δ 10.43 (end phenolic -OH protons), δ12.59 (end carboxylic acid proton).

Quintet at δ 1.40 integrating four two H_x protons, with J_{HxHc} value of 8 Hz indicating vicinal coupling; a multiplet in the range δ 1.49–1.58 corresponding to two four H_c protons; a triplet at δ 2.30 representing four H_b protons with a vicinal coupling constant of 7 Hz; and as such no virtual coupling is seen.

Copolyester TSUH (Figure 9): ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.37 (4H, distorted q, H_x, J_{HxHe} = 6 Hz), δ 1.49–1.58 (4H, m, H_c), δ 2.31 (4H, t, H_b, J_{HbHc} = 6 Hz), δ 3.83 (12H, s, H_a), δ 6.50 (4H, s, H_g), δ 6.75 (2H, d, H_α, $J_{H\alpha H\beta}$ = 15.6 Hz), δ 7.27 (4H, d, H_f, J_{HfHe} = 7 Hz), δ 7.55 (2H, d, H_β, $J_{H\beta H\alpha}$ = 15.6 Hz), δ 8.06 (4H, d, H_e, J_{HeHf} = 7 Hz), δ 8.14 (4H, s, H_d), δ 10.24 (end phenolic -OH protons), δ12.60 (end carboxylic acid proton).

A quintet at δ 1.37 for four H_x protons is somewhat distorted because methylene protons are very close in chemical shifts and are strongly coupled to one another and act as conglomerate of spins in coupling to H_c protons. Note: Sets labelled as x_2 (or x_1) are chemical shift equivalent as for which Δν/J is zero. Since H_x, H_c and H_b protons forms an ABX spin system, H_c protons appears as a distorted multiplet, δ 1.49–1.58. The severe distortion of the H_c proton signal which is formally coupled only to the adjoining CH_2 (x_2) group, is a result of the "conglomerate" coupling. H_b protons shows clean triplet because c_2 protons are somewhat deshielded i.e. separated from other CH_2 groups, thus there is no virtual coupling.

Copolyester TNOH (Figure 10): ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.30 (6H, broadened distorted q, H_x, J_{HxHe} = 8 Hz), δ 1.48–1.59 (4H, m, H_c), δ 2.29 (4H, t, H_b, J_{HbHc} = 6 Hz), δ 3.85 (12H, s, H_a), δ 6.55 (4H, s, H_g), δ 6.70 (2H, d, H_α, $J_{H\alpha H\beta}$ = 15.3 Hz), δ 7.31 (4H, d, H_f, J_{HfHe} = 8 Hz), δ 7.58 (2H, d, H_β, $J_{H\beta H\alpha}$ = 15.3 Hz), δ 7.94 (4H, d, H_e, J_{HeHf} = 8 Hz), δ 8.13 (4H, s, H_d), δ 10.39 (end phenolic -OH protons), δ12.59 (end carboxylic acid proton).

A broad distorted signal, δ 1.30 appears for six H_x protons. Reason: CH_2 groups (or H_x protons) are very similar in chemical shift and strongly coupled to one another therefore act as conglomerate of spins in coupling to H_c protons. Also, distorted quintet, δ 1.48-1.59 for four H_c protons is a characteristic of a strongly coupled hydrocarbon chain. The four H_b protons shows clean triplet, δ 2.29 because H_c protons are somewhat deshielded i.e. separated from other CH_2 groups (x proton sets) which are strongly coupled; there is no virtual coupling.

Copolyester TSEH (Figure 11): ^{1}H-NMR (400 MHz, DMSO-d6): δ 1.31 (8H, broad, H_x), δ 1.50–1.59 (4H, m, H_c), δ 2.30 (4H, t, H_b, J_{HbHc} = 7 Hz), δ 3.87 (12H, s, H_a), δ 6.56 (4H, s, H_g), δ 6.62 (2H, d, H_α, $J_{H\alpha H\beta}$ = 15.5 Hz), δ 7.23 (4H, d, H_f, J_{HfHe} = 10 Hz), δ 7.61 (2H, d, H_β, $J_{H\beta H\alpha}$ = 15.5 Hz), δ 8.01 (4H, d, H_e, J_{HeHf} = 10 Hz), δ 8.07 (4H, s, H_d), δ 10.39 (end phenolic -OH protons), δ12.58 (end carboxylic acid proton).

δ 1.31, a broad signal appears for 8 protons (H_x). The broadness of the resonance likely corresponds to slight differences in ^{1}H-NMR chemical shifts between methylene protons. The H_x protons are very similar in chemical shift and are strongly coupled to one another and act as conglomerate of spins in coupling to H_c protons. δ 1.50 – 1.59 for H_c protons appears as a multiplet (distorted quintet) due to coupling with H_b (classical triplet at δ 2.30) and H_x protons. The distortion of signal of H_c protons is a result of "conglomerate" coupling or virtual coupling and is a characteristic of strongly coupled hydrocarbons.

TABLE VI. TYPES OF PROTONS AS PREDICTED BY ^{1}H-NMR SPECTRA OF COPOLYESTERS AND THEIR CHEMICAL SHIFT VALUES (δ).

Chemical Shift (δ)	Types of Protons
1.30 – 1.58	Methylene
3.82 – 3.87	Methyl
6.62 – 6.75	α-ethylenic
6.50 – 8.14	Aromatic
7.55 – 7.69	β-ethylenic
10.24 – 10.43	End phenolic OH
12.58 – 12.60	End carboxylic acid

The H_α and H_β protons occur as two doublets with a large $J_{H\alpha H\beta}$ value (15.1–15.6 Hz), revealing the trans geometry for the chalcone and the copolyesters. No trace for the unfavorable Z-isomer was detected in the ^{1}H-NMR spectra. The instability of the Z-configuration may be due to the strong steric interaction between the carbonyl group of the enone system and the ring attached to the ethylenic β-carbon atom. The H_β protons showed absorption at a higher frequency than that of ethylenic α-protons. This may possibly be due to the delocalization of the π-electron density of the enone system which made the existence of a positive formal charge on the ethylenic β-carbon. The spectra showed methoxy protons as a singlet in the range δ 3.82 – 3.87. The backbone methylene protons, namely H_b & H_c derived from dicarboxylic acid moieties viz. malonyl, pimeloyl, suberoyl, azelaoyl and sebacoyl chlorides were noticed as triplet and in the range δ 2.29 – 3.15 and multiplet in the range δ 1.48 – 1.59 with J value around 6-7 Hz indicating coupling between vicinal protons. Thus, the ^{1}H-NMR data deduce the presence of methylene spacers in the backbone of copolyesters making them considerable flexible.

The chalcone EHDP and polyesters (TMAH, TPIH, TSUH, TNOH and TSEH) showed a number of signals in the range δ 6.50 – 8.14; reason being the presence of more number of aromatic protons in different chemical environments. A singlet between δ 8.0 – 8.14 corresponds to 4 Ar-H_d protons. The frequency of this signal is higher than that of normal benzene absorption due to the attachment of two electron withdrawing groups (i.e. keto groups). Also, 2 Ar-H_g protons ortho to methoxy groups resonate in the range δ 6.50 – 6.55 giving singlet which is upfield to normal benzene proton absorption (δ 7.37) because of extra electron density via resonance due to -OCH_3 groups which shield the H_g protons, especially at ortho/para positions.

A doublet between δ 7.93 – 8.06 corresponds to 2 Ar-H_e protons, the absorption being further downfield than that of normal benzenic proton absorption (δ 7.37) due to withdrawal of electron density via resonance because of the presence of ortho carbonyl moiety which deshields 'H_e' protons, particularly at ortho/para positions. 2 Ar-H_f protons (ortho to –C(=O)O– moiety) resonate between δ 7.23 – 7.32 giving doublet; absorption upfield to normal benzene absorption since lone pair of electrons on oxygen attached ortho to H_f protons participate to both ring and as well to ester bond during resonance. Also, the value of coupling constant between H_e and H_f protons lying in between 6-10 Hz indicate an ortho coupling.

A very intense signal (HOD peak) at δ 3.405 was mainly due to dissolved water in the DMSO-d6 being used as the solvent, and the signal observed at δ 2.508 was due to residual proton in the otherwise deuterated solvent and so also called as residual proton peak or residual solvent signal.

E. Stereochemistry

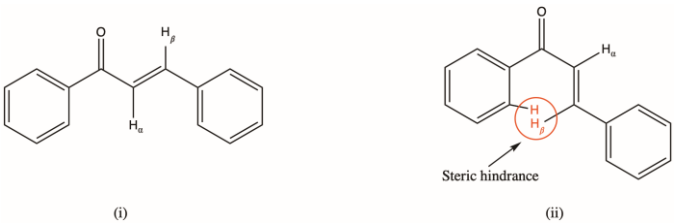

Fig. 13. (i) The thermodynamically favorable E-s-cis and, (ii) the thermodynamically unfavorable E-s-trans, conformations of a chalcone.

E-s-cis conformation might be more predominant for chalcone and copolyesters which have unsubstituted enone system. The E-s-trans conformer is thermodynamically unfavorable due to steric interaction between the hydrogen atom on the ethylenic β-carbon and the one present at the ortho position of the aromatic substituent linked to the carbonyl carbon, as seen in the Figure 4(ii). Such steric

hindrance between the hydrogen atoms render the E-s-trans conformer to be non-planar leaving the E-s-cis conformer in planar state where no such steric hindrance is present in Figure 4(i). This non-planarity of the E-s-trans conformer weakens the delocalization of π-electrons through the enone system in comparison to E-s-cis conformer, thus increasing the double bond characters of C=O and C=C groups.

F. ^{13}C-NMR Analysis

Structures of copolyesters proposed by their FT-IR and ^{1}H-NMR spectra were confirmed by their ^{13}C-NMR spectra, which not only gives chemical shift values of non-equivalent carbons but also their relationship with hydrogens. The ^{13}C-NMR spectra of random copolyesters are shown in Figures 13–17 and the chemical shift values (in ppm) of non-equivalent carbons in the Table VII.

The absorptions in the range 163.46 – 173.27 ppm and 187.57 – 189.7 ppm were due to carbonyl carbon of ester and carbonyl carbon of chalcone and so confirmed the formation of polyester. The α,β–unsaturation in the chalcone moiety rendered the carbonyl carbon to absorb a bit downfield to the ester carbonyl carbon.

The α- and the β-carbons of the vinylic double bond were noticed at 121.29–121.87 and 144.46–148.66 ppm, latter being more downfield due to the polarization of the -C_α=C_β- bond caused by the carbonyl group thus reducing the electron density at β-position.

Unsubstituted aromatic carbons of chalcone moiety showed signals in between 103.16–130.89 ppm while substituted ones in the range 125.73–155.39 ppm, indicating that the substituents are electron withdrawing.

Methoxy carbons were verified by the appearance of peak in the 55.8–60.8 ppm range, while the resonance signal in between 24.7–41.6 ppm is due to methylene carbons. This indicates that the formed copolyesters are flexible enough since the methylene groups covalently incorporated in their backbones as spacers.

The appearance of a septet at 40.53–39.27 ppm is due to the deuterated dimethylsulphoxide used as the solvent.

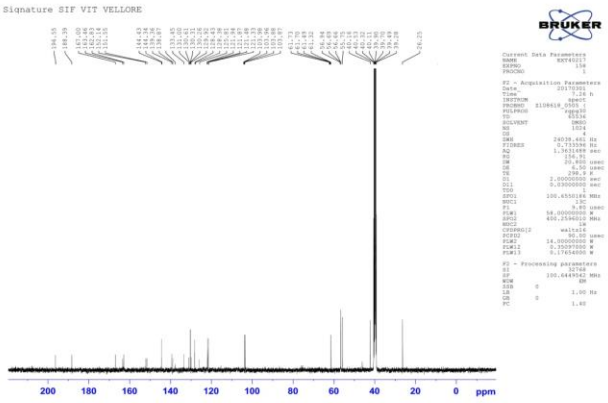

Fig. 14. The ^{13}C-NMR spectrum of the copolyester TMAH

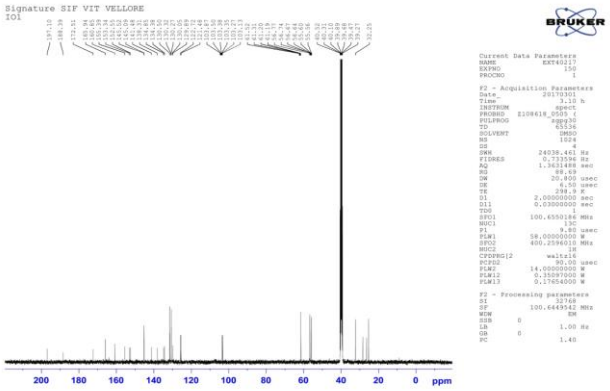

Fig. 15. The ^{13}C-NMR spectrum of the copolyester TPIH

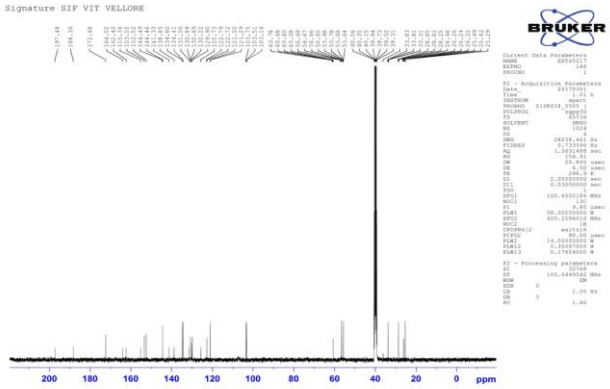

Fig. 16. The ^{13}C-NMR spectrum of the copolyester TSUH

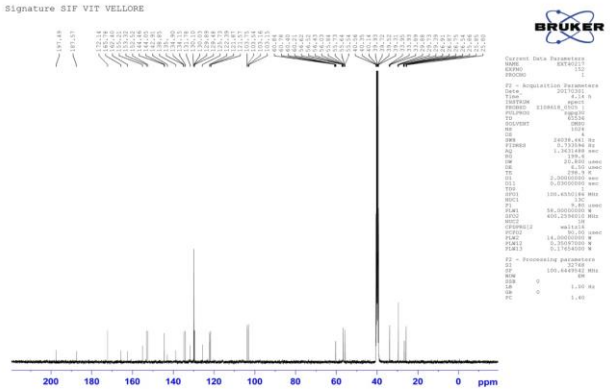

Fig. 17. The ^{13}C-NMR spectrum of the copolyester TNOH

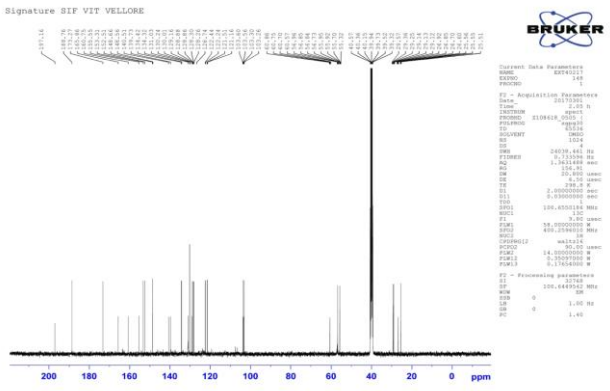

Fig. 18. The ^{13}C-NMR spectrum of the copolyester TSEH

TABLE VII. TYPES OF CARBONS AS INFERRED FROM ^{13}C-NMR SPECTRA OF THE COPOLYESTERS AND THEIR CORRESPONDING CHEMICAL SHIFT VALUES.

Chemical Shift (δ)	Types of Carbons
24.7–41.6	Methylene carbon
55.8–60.8	Methoxy carbon of chalcone
121.29–121.87	α-carbon chalcone
144.46–148.66	β-carbon chalcone
163.45–173.27	Carbonyl carbon ester
187.57–189.7	Carbonyl carbon chalcone
103.16–130.89	Unsubstituted aromatic carbon chalcone
125.73–131.78	Aromatic carbon attached to β-carbon of chalcone
129.16–162.83	Aromatic carbon attached to esteric oxygen
133.45–142.91	Aromatic carbon to which carbonyl carbon attached
138.31–155.39	Aromatic carbon to which methoxy group attached

G. Thermal Analysis by Differential Scanning Calorimetry

The heating curve displayed in the DSC thermogram, Figure 18, showing the thermal transition for the copolyester TPIH has an endothermic melting (T_m) peak at 108.8°C with the corresponding enthalpy (ΔH_m) of 71.44 J/g. Also, the thermogram reveals 21.4°C as the glass transition temperature (T_g) as well as isotropization temperature or clearing temperature (T_i or T_{cl}) of 362.4°C. Since the DSC thermogram for the copolyester TPIH exhibit both glass transition, and melting temperature it is concluded that TPIH is semi-crystalline in nature i.e. it possess both amorphous and crystalline domains. The low T_g value of 21.4°C indicates that the backbone of the TPIH is considerable flexible. Thus, T_g and T_m values lie within the temperature range in which the copolymer TPIH is suitable for drug delivery application.

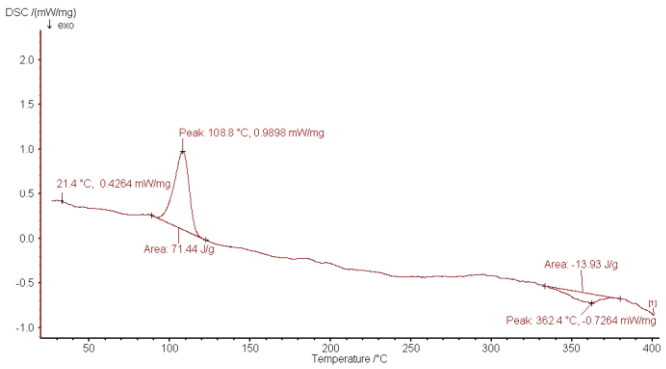

Fig. 19. The DSC thermogram of the copolyester TPIH

H. Antibacterial Efficacy

The results of the antibacterial activity of the five copolyesters are shown in the Table VIII. It has been observed that all the copolyesters were active against the test microorganisms with moderate antibacterial efficacy against the *B. subtilis* while a stronger inhibitory effect against the *E. coli*, but less than the standard *streptomycin*. This bactericidal activity was found to increase with an increase in the copolymer concentration.

TABLE VIII. INHIBITORY EFFECT OF DIFFERENT CONCENTRATIONS OF TEST COPOLYESTERS UPON THE GROWTH OF *BACILLUS SUBTILIS* AND *ESCHERICHIA COLI* AND THEIR COMPARISON WITH THE STREPTOMYCIN.

Test Copolyester Code	Zone of Inhibition (diameter in mm) for the Following Test Microorganisms									
	Bacillus subtilis					*Escherichia coli*				
	25 μg	*50 μg*	*75 μg*	*100 μg*	*Streptomycin 10 μg*	*25 μg*	*50 μg*	*75 μg*	*100 μg*	*Streptomycin 10 μg*
TMAH	–[f]	–[f]	7	9	19	12	14	16	16	20
TPIH	–[f]	–[f]	6	8	19	9	12	15	16	20
TSUH	–[f]	–[f]	6	8	19	12	14	16	17	20
TNOH	–[f]	–[f]	7	9	19	–[f]	13	9	17	20
TSEH	–[f]	–[f]	7	9	19	–[f]	–[f]	10	10	20

[f].(–) = Inactivity

[g].

I. Antifungal Efficacy

The antifungal activity of the synthesized copolyesters viz. TMAH, TPIH, TSUH, TNOH & TSEH as determined by the well diffusion method is shown in the Table IX. All the copolyesters inhibit the growth of *Candida albicans* whereas only TMAH and TSUH were effective against the *Aspergillus niger*. Fluconazole subdued the growth of *Aspergillus niger* by 27 mm while Clotrimazole suppressed *Candida albicans* by 15 mm. The Table 8 also demonstrated that the fungicidal activity of the copolymers be more effective when their concentration was increased.

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TABLE IX. INHIBITORY EFFECT OF DIFFERENT CONCENTRATIONS OF TEST COPOLYESTERS AGAINST *CANDIDA ALBICANS* AND *ASPERGILLUS NIGER* AND THE COMPARISON OF RESULT WITH THE STANDARD ANTIFUNGAL DRUGS VIZ. *FLUCONAZOLE* AND *CLOTRIMAZOLE*

Test Material	**Zone of Inhibition (diameter in mm) For the Following Fungi**							
	Candida albicans				***Aspergillus niger***			
	25 µg	**50 µg**	**75 µg**	**100 µg**	**25 µg**	**50 µg**	**75 µg**	**100 µg**
TMAH	17	17	19	19	–[g]	–[g]	7	9
TPIH	16	16	18	18	–[g]	–[g]	–[g]	–[g]
TSUH	15	17	19	19	–[g]	–[g]	–[g]	7
TNOH	13	15	17	17	–[g]	–[g]	–[g]	–[g]
TSEH	14	17	15	18	–[g]	–[g]	–[g]	–[g]
Fluconazole **25 µg**					27			
Clotrimazole **25 µg**	15							

[h](–) = No activity

V. CONCLUSION

The solution polycondensation method employed for the synthesis of five random chalcone containing copolyesters viz. TMAH, TPIH, TSUH, TNOH and TSEH using different aliphatic diacid chlorides (malonyl chloride, pimeloyl chloride, suberoyl chloride, azelaoyl chloride & sebacoyl chloride), an aromatic diacid chloride (terephthaloyl chloride) and a chalcone diol [(*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (EHDP)] resulted in high molecular weight copolymers with moderate to good yield.

The solubility of the copolymers synthesized so far decreased with an increase in their molecular weights. Contrary to it, the solubility increased as the number of incorporated methylene spacers increase making the polymer backbone more flexible. The all five random chalcone polymers were soluble in polar aprotic solvents (dimethylsulphoxide, dimethylacetamide & dimethylformamide), partially soluble in moderately polar solvents (acetone & ethylacetate) and insoluble in non-polar solvents/polar protic solvents (benzene, n-hexane, methanol & ethanol). It can be concluded that the affinity between the polymer and the solvent was high when the two were of similar polarity.

The intrinsic viscosity values falls under the range 1.18–1.98 dLg^{-1} at 30°C which indicated that the degree of polymerization was high for the all five synthesized chalcone copolyesters. The intrinsic viscosity follow a similar trend as do the solubility i.e. $\eta_{inh.}$ values increase with an increase in the length of incorporated methylene spacer chain, except TSUH & TNOH pair which is in disagreement due to the Odd-Even effect. Thus, the copolyester fabricated by employing malonyl chloride as an aliphatic diacid unit would be of lowest $\eta_{inh.}$ value, which is found so in the present case. The inherent viscosity values also indicated the random chalcone copolyesters possess reasonably high molecular weights.

The types of functional groups and nature of mesogenic units present in the chalcone containing polymers indicated by the characteristic absorptions in their fourier transform-infrared, proton & ^{13}C NMR spectra confirmed the formation of copolyester in the thermodynamically more stable E-s-trans conformation.

The differential scanning calorimetry data of copolymers consists both glass transition (T_g) and melting temperatures (T_m) concluding at least two-phase structure of copolyesters i.e. chalcone containing random copolyesters consists of both crystalline and amorphous segments. T_g and T_m values lie within the temperature range in which the copolymers are suitable for the drug delivery application.

The antibacterial and antifungal assay of five random chalcone incorporated copolyesters against the pathogenic bacteria *(Bacillus subtilis & Escherichia coli)* and fungi *(Candida albicans* & *Aspergillus niger)* proved the all five copolyesters as good antibacterial and antifungal agents with moderate efficacy against *B. subtilis & A. niger* while a strong inhibitory activity against *E. coli* & *C. albicans* but no stronger than the standard drugs like *streptomycin, fluconazole* and *clotrimazole.*

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