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Diestrification and Biological study of Styrene Maleic Anhydride Copolymer with Alcohol and DMSO

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Abstract: SMA was modified with different alcohols and dissolves in DMSO it gives some interesting results. For the different conversions of esterified copolymers the propanol, butanol octanol, etc. alcohols was chosen for this work. Clearly it is observed that reaction rate was increase with the different chain length of the alcohols. The longer the aliphatic chain shows the greater the mobility of the chain and the more easily ester formed. If we compare aryl group containing alcohol the produce ester conversion was lower about 10-15% of ester. Tg and blood profile was also be studied for modified esters.

Keywords: Aliphatic alcohols, Esterification,Degree of esterification,Glass transition temperature,dimethyl sulfoxide.

Introduction

Synthesis of polymerizable acetales, sulfonate,esters[1] and carbamates[2] obtained from perfume alcohols. Pesticides and herbicides and the controlled release function of the monomers and polymers there of have been studied before. Perfume alcohols have also been supported to polymer backbones and the controlled release properties have been investigated.[3] Esterification of styrene maleic anhydride copolymers with some pure and mixture of alcohols have also been reported.[4,5]. SMA-ethanol[6] has been evaluate as enteric coating polymer for enthromycin tablets.

In this present article, we studied the reaction of an alternating copolymer of SMA(Styrene maleic anhydride) with alcohols; propyle, butyl etc. We determined the degree of esterification reaction in the solution by using tetrahydrofuran as solvent, at 25^0C without catalyst. The converted SMA was also treated with DMSO[7] and kept in descicator for 20 days for the double esterification.The conversions are compared in terms of the esterified copolymers esterification mechanism. We have also studied the glass transition temperatures of the copolymers have been measured and are compared in terms of the length of the alcohol chain. When SMA mixed with alcohol to give an ester by partial esterification now these ester was further treated with dimethyl sulphoxide an ester was obtained. SMA and dimethyl sulfoxide forms a polyelectrolyte (intermediate) gel by charge transfer interaction of DMSO with anhydride[6,7].

In this present communication we have studied the glass transition temperatures of the copolymers and are compared in terms of the length of the alcohol chain. The histopathology viz effect on Erythrocyte, Hb., Platelets, and TLC, DLC also studied.

Experimental

Styrene was supplied by Aldrich, its small amount was washed with aqueous Sodium hydroxide solution then distilled water followed by drying over anhydrous calcium chloride and finally distilled under vacuum for further use. Maleic anhydride was supplied by(s-d fine) was purified before use by recrystallization from anhydrous benzene and sublimation in vacuum.

Benzoyle peroxide (BPO) of analytical grade s.d-fine was purified by recrystallization in chloroform and methanol mixture. Aliphatic alcohols were purchased from Merk. Pure DMSO (Dimethyl sulfoxide)s-d fine was used for the synthesis, the used solvent acetone was analytical grade (s-d fine).

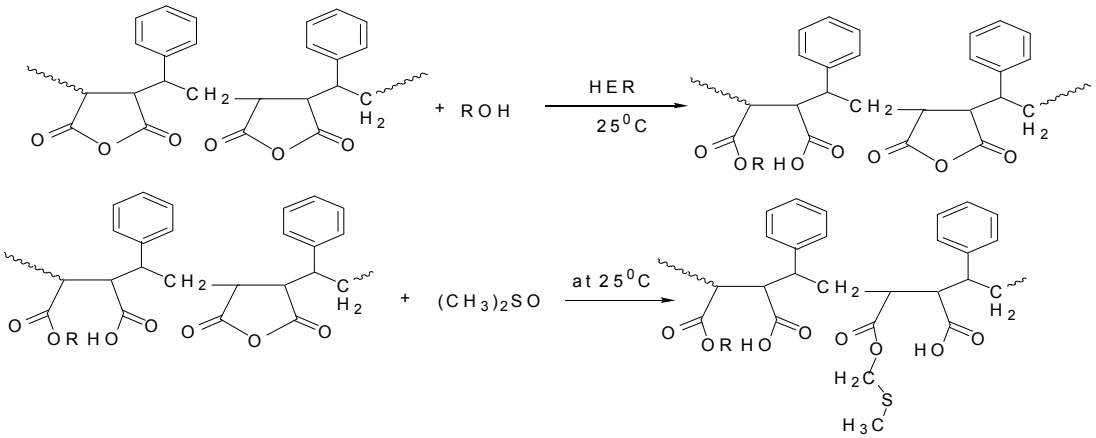
Infra red spectra were recorded on Perkin-Elmer Spectrum RX1in range 4000-450cm^{-1}, pellet were prepared with KBr disc. ^{1}HNMR spectra were recorded on Buker Avance 400MHz FTNMR in $(CD_3)_2SO$. Elimental analysis were determined with Carlo Erba 1108. Purity of polymer was done by infra red spectroscopy.

Synthesis

styrene maleic anhydride was prepared by according to the method described in the literature Oya[8] et al. Prepared SMA 2g (0.01mole) copolymer was added to 0.75ml.(0.01mole) of propanol and mixed well, the reaction mixture was kept in desiccator for 12 hrs. at 25^{0}C for best half esterification reaction. The modified SMA (Tg 245^{0}C) was checked by FTIR for determination of unreacted maleic anhydride moiety. Now modified SMA 0.26g (0.001mole) was mixed with 1ml.of DMSO and kept in desiccator with P_2O_5 for 20 days. DMSO was removed by vacuum evaporation. This resulted in the form of an adduct ester complex, this process was repeat for other alcohols. Elemental analysis for carbon, hydrogen and sulfur of ester complex were conducted (Table: I)
The 8 unknown compounds were synthesized according to given scheme I.

Determination of esterification degree

The conversion reaction was evaluated by lindt method. The two absorption band were chosen, the peak at 1680 1779cm^{-1}, the conversion p,was defiened as: $p=(1-A_t/A_0)X100$.



Scheme-I: Mechanism of the adduct formation

Table:I – Characterization of scheme-1

Comp. No.	R	Tg ^{0}C	Molecular Formula	Analysis % Cal. (Found)		
				C	H	S
I-A	C_3H_7	245	$C_{29}H_{34}O_8S$	64.20(64.28)	6.27(6.35)	4.82(5.15)
I-B	C_4H_9	239	$C_{30}H_{36}O_8S$	64.74(65.12)	6.51(5.78)	5.75(5.62)
I-C	C_5H_{11}	230	$C_{31}H_{38}O_9S$	65.25(65.40)	6.70(6.81)	5.60(5.42)
I-D	C_6H_{13}	224	$C_{32}H_{40}O_8S$	65.74(65.81)	6.80(6.75)	5.47(5.52)
I-E	C_8H_{17}	144	$C_{34}H_{44}O_8S$	66.65(66.65)	7.23(7.40)	5.22(5.24)
I-F	Isobutane	242	$C_{30}H_{36}O_8S$	64.94(64.98)	6.81(6.21)	5.45(5.42)
I-G	$C_6H_5CH=$	152	$C_{33}H_{34}O_8S$	67.99(67.01)	5.79(5.81)	5.41(5.64)
I-H	$CH_2=CHCH_2-$	240	$C_{29}H_{32}O_8S$	64.56(64.61)	5.78(5.81)	5.93(5.72)

R has been replaced by (A) C_3H_7, (B) C_4H_9(C) C_5H_{11},(D) C_6H_{13},(E) C_8H_{17},(F) Isobutane,(G) $C_6H_5CH_2$,(H) CH_2=CHCH one by one, resulting in the formation of 8 unknown compounds denoted by I - A to I – H.

Histopathology:

For histopathological investigations 30 male Charles foster stain of albino rat of about 175-200g body weight were used for the study.15 days quarantined (acclimatized) rats were kept in husbandry condition of 22-25^{0}C room temperature, 50-70% relative humidity and 12hr. light and 12 hr. dark photoperiod. The animals were kept in identical environmental condition and were mentioned in pellet diet and water (24hrs.).The selected 24 male rats were divided into 4 groups of 6 rats, II, III, IV group served as treated, while Ist group served as control group.

For implantation of the complex, lower abdominal area was chosen, minor incision with the help of sharp sterile blade was given of the size 0.5cm.The polymer complex was injected into the lumen. Different doses of complex as stated in (Table-3) were given and skin wound was stitched, dressed up neosprin antibiotic powder, all the rats were kept under strict watch till the healing was completed. Different hematological parameters were recorded in the control as well as the complex treated rats as follows: Total leukocyte count (10^3/cumm), Total Erythrocyte count (RBC) (10^6cumm), Hb gm%., Platelet count (10^3cumm) (Table-I). Liver was removed for histological examination. All readings were obtained by standard methods of histopathology.

Table:II - Spectral data of scheme-1

Comp. No.	R	IR (ν_{max} cm^{-1}) KBr	1HNMR (δppm) d_6 DMSO
I-A	C_3H_7	3020(C-Hstr)aromatic,1680(C=Cstr) aromatic, 1779(C=Ostr) ester,1260(C-Ostr), 1448(C-Hbend) methylene, 3350 (O-Hstr)H bond .	1.2-1.4(multip.,9H),1.6(sextent,2H), 4.3 (t, 2H),2.2(d,1H),10.1(s,2H)Hbond, 2.4 (q,3H) ,3.4 (s,2H), 1.1(s,3H), 7.2 (s, 10H, Ar)
I-B	C_4H_9	3002(C-Hstr)aromatic,1680(C=Cstr) aromatic, 1780(C=Ostr) ester,1260(C-Ostr), 1410 (C-Hbend) methylene, 3460 (O-Hstr)H bond .	1.1(t,3H),3.8(t,2H),2.1(d,1H),1.3-1.4 multi,7H),10.2(s,2H)Hbond,2.4(q,3H), 3.4(s,2H),0.9(s,3H),1.6(q,1H),7.1(s, 10H, Ar),1.6(p,2H)
I-C	C_5H_{11}	3002(C-Htr)aromatic, 1665(C=Cstr) aromatic, 1748(C=Ostr)ester,1255(C-Ostr), 1410(C-Hbend) methylene, 3380 (O-Hstr)H bond.	1.4(multi.7H),1.1(t,3H),4.3(t,2H),2.2(d,1H), 1.3(multi.,4H),10.1(s,2H)Hbond,2.4(q,3H), 3.5(s,2H),1.1(s,3H),1.6(d,1H),7.2(s,10H,Ar)
I-D	C6H13	3018(C-Htr)aromatic, 1600(C=Cstr) aromatic, 1755(C=Ostr)ester,1248 (C-Ostr),1408(C-Hbend)methylene, 3358(O-Hstr)H bond.	1.4(multi.8H),1.2(t,3H),4.4(t,2H),2.3(d,1H), 1.1(s,3H),10.1(s,2H)Hbond,2.4(q,3H),3.6(s, 2H),1.1(s,3H),1.4(q,1H),7.2 (s,10H,Ar), 1.3(t,2H).
I-E	C8H17	3018(C-Htr)aromatic,1600(C=Cstr) aromatic, 1755(C=Ostr)ester,1248 (C-Ostr), 1400(C-Hbend) methylene, 3458 (O-Hstr)H bond	1.0(t,3H),4.2(t,2H),2.3(d,1H),10.1(s,2H)Hb ond,2.4(q,3H),3.4(s,2H),1.2(s,3H), 1.7(d,2H),1.4(q,1H),6.8(s,10H,Ar),1.3 (t,2H). 1.4-1.5(multi.,13H),
I-F	Isobutane	3010(C-Hstr)aromatic, 1660(C=Cstr) aromatic, 1740(C=Ostr)ester,1260(C-Ostr), 1470(C-Hbend) methylene, 3300 (O-Hstr)H bond	1.3(s,9H),2.0(d,1H),1.4(2H,overlap),9.8(s,2 H)Hbond,2.4(q,3H),1.3(4H,overlap),3.4(s,2 H),1.1(s,3H) (s,10H,Ar),
I-G	C6H5CH2	3040(C-Hstr)aromatic, 1040(O-Cstr), 1661(C=Cstr)aromatic,1760(C=Ostr) ester, 1430 (C-Hbend) methylene, 3390 (O-Hstr)H bond.	2.7(s,2H),7.2(s,15H,Ar)overlap,2.3(d,1H),1. 5(d,1H),9.8(s,2H)Hbond,2.2(q,3H),1.3(d,2 H),3.4(s,2H),0.9(s,3H),1.4(q,1H), 1.3(t,2H)
I-H	CH2=CH-CH2-	3013(C-Hstr)aromatic, 1248(O-Cstr), 1670, 1647(C=Cstr)aromatic, 1745 C=Ostr) ester,1445(C-Hbend) methylene, 3410 (O-Hstr)H bond.	4.7(d,2H),5.3(p,1H),4.3(d,2H),2.2 (q,3H),10.5(s,2H)Hbond,1.6(d,1H),2.4 (d,1H),1.3(d,2H),3.4(s,2H),1.3(t,2H), 7.2(s,10H,Ar)overlap,1.1(s,3H),1.4 (q,1H).

Table III: Absorbance value for the esterification reaction, conversion % (p) calculation for propanol

IR Absorption (cm^{-1})	Initial Abso (A_0)	$A_{2hrs.}$	$A_{4hrs.}$	$A_{8hrs.}$	$A_{20hrs.}$	$A_{24hrs.}$
1779	*1.987*	1.984	0.821	0.572	1.301	0.467
1680	0.387	0.311	0.187	0.156	0.152	0.331
1779/1680	5.134	6.371	4.390	3.667	2.541	1.410
At/A0	-	1.240	0.845	0.714	0.494	0.274
%	-	0	15.5	29	50	73

RESULTS AND DISCUSSION

It has been well known that both St and Ma copolymerize usually in an alternating way resulting in a poly (St-Ma) alternating polymer (SMA) with a highly regular structure. SMA is a type of important functional co-polymer as its anhydride group on the backbone chain can react with other reagents, such as alcohol, amine, water DMSO etc. to produce many derivatives. To ascertain the structure of the polymer complex, both FTIR,^{1}HNMR spectra were registered and evaluated. The conversion of esterification of the copolymers with propanol, butanol and other alcohols gives modified copolymers. This conversion was obtained under the experimental conditions described in the experimental section.

The esterification reaction was followed by 1779cm^{-1} and 1680cm^{-1} peaks which correspond to C-O-C stretching absorbance of maleic anhydride and C=C vinyl stretching of styrene respectively. Spectra shows clearly the decreasing of the 1779cm^{-1} band, from the initial copolymer esterified with n-butanol up to 24 hrs. of reaction time. When compared the different conversion was observed for the copolymers esterified with the alcohols viz propanol, butanol octanol studied in this work. It is observed that the reaction rate increases with the different chain length of the alcohol.

By considering the kinetics of the esterification reaction the propanol and octanol have some difference in conversion after 4 hrs. of reaction time. In the case of propanol, actually there is very low(~15.5%) conversion to the ester at this time, while with octanol a 18% of the ester has been formed. A similar situation occurs at 8 hrs. with propanol only 29% of ester formed and with octanol 50% of ester has been reached. These extreme case demonstrates the influence of the aliphatic length of the alcohol towards the esterification, which appears to be favoured by the longer chain aliphatic alcohol. The longer the aliphatic chain, greater is the mobility of the chain and the more easily formed ester. If we compare the aryl group containing alcohol it gives only lower ester conversion i.e to the extent of 10-15% of ester.

From the above discussions it is revealed that a partial esterification reaction occurs without any catalyst. One mole of alcohol attacks on one anhydride moiety, C-O-C rupture and produce a mole of ester and one anhydride moiety remains unreactive as is seen in the FTIR spectrum. The Peaks due to unreacted anhydride group (1855,1790cm^{-1}) in the FTIR spectrum are clearly seen, These unreacted anhydride moiety reacts with dimethylsulfoxide to perform Pummrer reaction by charge transfer interaction.

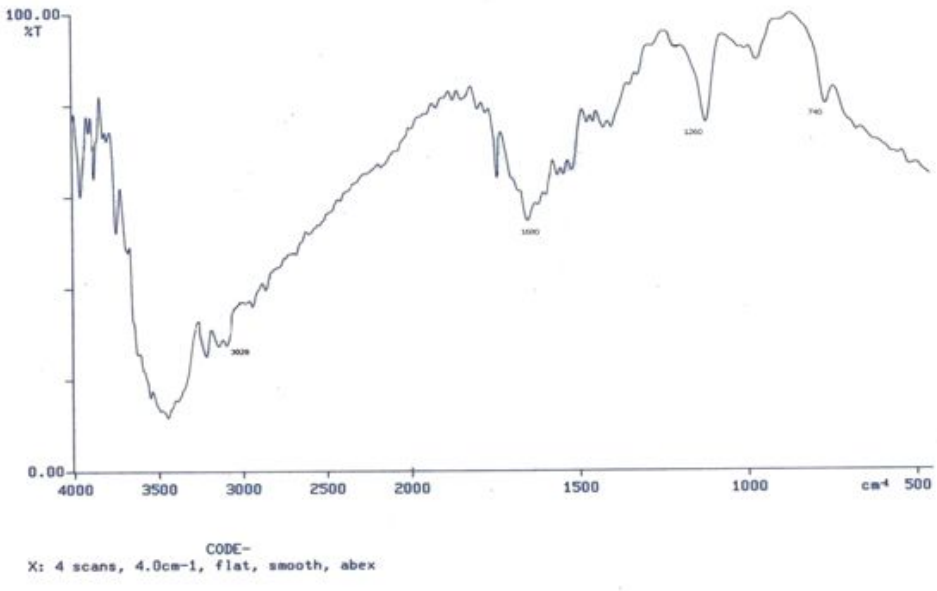
In the ^{1}HNMR spectrum of copolymer and products (3A-H), broad overlapping peaks between 1.1and 2.4δ ppm and peaks between 6.8-7.2δ ppm are due to methylene /methine and aromatic ring hydrogens of styrene respectively. Product (3A-H) showed peak between 2.2-3.4δ ppm and at about 3.8 δppm due to Ar-CH_2 and Ar-C-CH_2-O respectively. Peaks at 9.8-10.3 δppm showed typical peak of carboxylic group present in molecule.

Table-IV: Recording of Haematological parameter (Mean, ±SD) of modified ester treated rats.

Parameter	Group -I			Group-II			Group-III			Group-IV		
	Initial	Mid Term	Final	Initial	Mid Term	Final	Initial	Mid Term	Final	Initial	Mid Term	Final
TLC	2.70	3.58	5.48	6.00	6.33	5.81	5.61	5.58	5.45	6.18	6.78	6.61
x 10^3 cumm	0.78	0.81	0.73	0.83	0.86	0.69	0.67	0.72	0.68	0.59	1.15	1.14
RBC	6.32	5.50	5.76	6.27	6.14	6.1	6.04	6.18	6.5	6.19	6.43	6.65
x10^6cumm	1.12	0.37	0.62	0.79	0.50	0.78	0.67	0.62	0.52	0.60	0.82	0.53
Hb.	13.36	12.33	12.8	13.56	13.43	13.73	11.46	12.58	13.66	13.05	13.48	14.26
gm%	1.67	1.88	1.82	1.49	1.62	1.64	1.40	1.35	1.58	1.55	1.44	0.95
Plt.	519	512	522.83	619	612	622.83	638.5	674.83	67.1	582.83	705	694.5
X10^3cumm	88.18	76.40	64.14	89.18	86.40	74.14	84.52	90.14	67.15	65.58	165.8	70.74
DLC % **P**	21.83	21.33	22.16	24.66	26	22.5	19.33	22.5	24.33	18.83	23	24.66
	4.26	4.17	6.61	3.88	7.40	6.25	6.25	4.17	2.2	3.48	5.60	8.14
L	79.33	75.33	73.66	72.5	69.66	73.16	77.5	74.5	71.66	77.83	75.5	72.16
	6.74	5.71	7.86	5.52	6.77	5.74	3.61	7.14	3.71	3.71	6.71	8.32
M	1.50	2.0	1.5	1.5	1.5	2.0	2.0	1.66	2.5	2.16	1.5	1.66
	0.54	0.89	0.40	0.40	0.83	0.48	1.09	0.81	1.04	0.75	1.04	1.03
E	0.83	0.83	0.5	0.50	0.66	0.66	0.66	0.83	0.1	0.5	0.83	0.83
	0.75	0.75	0.54	0.54	0.81	0.51	0.51	0.75	1.89	0.54	0.75	0.75
B	0.5	0.50	0.33	0.5	0.50	0.66	0.66	0.5	0.5	0.66	0.5	1.66
	0.54	0.54	0.50	0.5	0.54	0.51	0.51	0.54	0.54	0.51	0.54	1.51

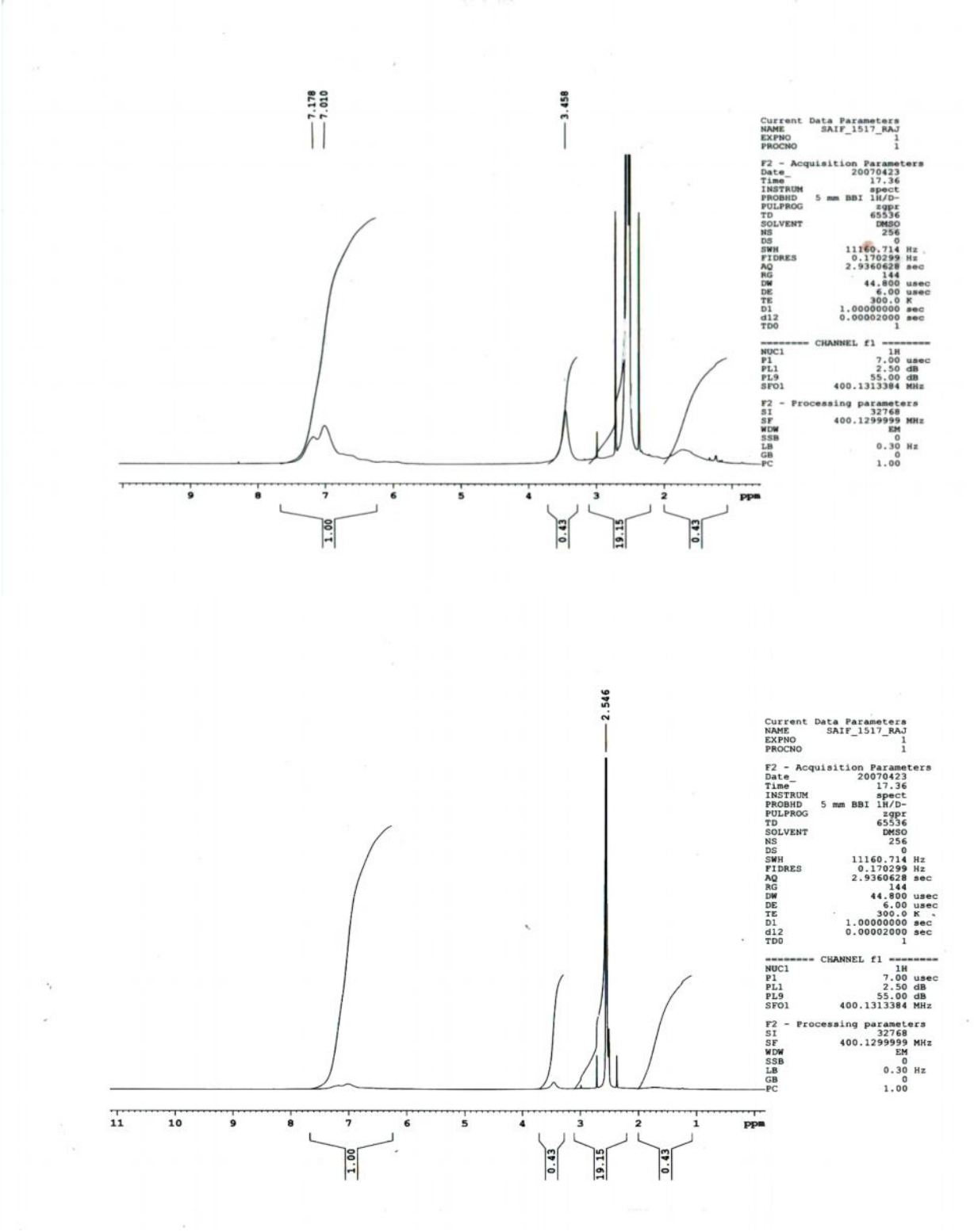
P- Neutrophils, **L** - Lymphocytes, **M** - Monocytes , **E** - Eosinophiles , **B** - Basophiles
Dose Schedule- Group-I Control: 0.03ml DMSO , **Group -II** Low Dose: 0.5mg. modified ester + 0.03ml DMSO
Group-III Mid Dose: 2.0mg. modified ester + 0.03ml.DMSO,
Group-IV High Dose 4.0mg. modified ester + 0.03ml.DMSO

Figure -I FTIR spectra of propanol modified ester



The alcohol derived copolymers were also thermally characterized. The Tg shows that a comparison of Tg for the copolymer esterified with the different alcohol. The Tg ranged from 144 - 245^{0}C for propanol and octanol respectively. As expected, The Tg are influenced by the aliphatic side chain of the alcohol which provides a higher freedom degree and movement to the polymer structure. For this reason, we found the lowest Tg with the longer alcohol chain, octanol at 144^{0}C, while the shorter one, propanol would give a more rigid structure and its Tg should be the highest, as it was found 245^{0}C. The other Tg value are shown between 144-245^{0}C.

Figure -II A, B ^{1}H NMR Spectra of of propanol modified ester



Histopathological study has revealed that the total leucocytes count increased 7.6-2.1% at low dose, 13.6-7.8% at mid dose and 17.0-10.5% at high dose in mid term and final reading was recorded in treated group rats in comparison to control dose .While Red blood cell count also increased in treated group rats below control group rats. RBC increased 9.6-5.5%in low dose, 10.3-12.2% at mid dose and 14.8% at high dose in mid term, Hemoglobin also increased 6.3-6.7% at low dose 14.64-10.5% at high dose, pellet count and differential leucocytes count are also increased in comparison to control dose of control group rats (Table-III).

Conclusion

The conversion of esterification of the copolymers with propanol, butanol and other alcohols gives modified ester (Scheme-I). This conversion was obtained under the experimental condition described in the experimental section. The Spectra show clearly the decreasing trend of the 1779 cm^{-1} band, from the initial copolymer esterified with n-butanol up to 24 hrs of reaction time. A comparative study of the different conversions obtained for the copolymers esterified with propanol, butanol, octanol the alcohols clearly shows that reaction rate increases with the different chain length of the alcohol. We believe that the results obtained fully agree with the mechanism.

In histological study the polymeric ester has one exposure level, NOEL (No observable adverse effect level) the high dose that did not cause any clinical adverse effect.

Acknowledgements

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