J. Indian Inst. Sci., Sept–Oct. 1999, **79**, 431–442.

Poly(propylene fumarate)/*n*-vinyl pyrrolidone copolymer-based bone cement: Setting and *in-vitro* biodegradation

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Abstract

Two poly(propylene fumarate) oligomers, DAM-2, from diallyl maleate/1, 2-propylene glycol, and MA-2, from maleic anhydride/1, 2-propylene glycol, were synthesized. MA-2 was found to set to a crosslinked hard mass in comparatively lesser duration than that of DAM-2. *In-vitro* degradation studies in Ringers' solution, phosphate-buffered saline (PBS) and oxidative medium (30% hydrogen peroxide solution) reveal faster degradation with time during initial exposure followed by a steady state in weight loss. The PBS medium induces faster degradation after a lapse of 9 days in comparison with other media. Considering the hydrolytic degradation as major degradation pathway and the weight loss with time, the crosslinked product of MA-2/*n*-VP is relatively more stable undergoing slower degradation in comparison with that of DAM-2/*n*-VP, and could be promising for bone-cement application.

Keywords: Poly(propylene fumarate), *n*-vinyl pyrrolidone, bone cement, biodegradation.

1. Introduction

Biodegradable bone cements are used in orthopedic application[1, 2] and are designed to degrade *in vivo* in a controlled manner over a predetermined period.[3, 4] The advantages of degradable materials are: (1) They need not be removed after use by secondary surgery as degradation products formed are excreted from the body via natural pathways. (2) Progressive loss of degradable implant material will lead to regeneration of healing tissues. Bone cements having adhesive character, mechanical properties and biodegradability are used to repair bones.[5, 6] For success of this surgery, bone ends must be stabilized and bone stability must be maintained during healing and complete restoration of function with growth of new bone has to be established. Therefore, controlled biodegradation of bone cement formulation is an essential requirement. Aliphatic polyester is found to degrade in *in-vivo* environment.[7] The main mechanisms of biodegradation are hydrolytic, oxidative and environmental stress corrosion. Comonomer plays an important factor in crosslinking reaction, bonding strength and biodegradation in the case of hydrolytic and oxidative degradation of aliphatic polyesters. The present paper deals with the *in-vitro* biodegradation of poly(propylene fumarate)-N-vinyl pyrrolidone as a biodegradable cement for bone repair.

**For correspondence

2. Experimental

2.1. *Synthesis of poly(propylene fumarate), (PPF) oligomers*

2.1.1. *Synthesis of PPF oligomer (DAM-2) from diallyl maleate*

Diallyl maleate (9.81g) was taken in a three-necked RB flask. 1,2-propylene glycol (4.18 g) and *p*-toluene sulphonic acid (0.14 g) were added to it, the latter as a catalyst. The mixture was refluxed at 125°C for 1 h and the volatiles were removed under reduced pressure at 140°C for 30 min leaving behind DAM-2 resin as viscous brown liquid.

2.1.2. *Synthesis of PPF oligomer (MA2) from maleic anhydride*

Maleic anhydride (9.80 g) and 1, 2-propylene glycol (19.0 g) were taken in a three-necked flask and *p*-toluene sulphonic acid (0.57 g) was added as a catalyst. The mixture was refluxed at 140°C under nitrogen atmosphere for 3 h. After cooling the reaction mixture to room temperature, maleic anhydride (14.07 g) was added again to the flask and heated again at 200–220°C for 1 h in the absence of nitrogen atmosphere. The volatiles were removed under reduced pressure. The resin (MA2), collected from the flask was dissolved in dichloromethane (50 ml) and precipitated using petroleum ether. It was then vacuum-dried by rotary evaporation at a temperature of 70°C for 30 min to get an yellowish brown semi-solid.

2.2. *Characterization of PPF oligomers*

The PPF oligomers were analysed by infrared spectral analyses. Infrared spectrum was recorded using resin smear on sodium chloride window. A Nicolet (Impact 410) FTIR instrument was used for recording the spectrum. The molecular weight of these oligomers was determined by gel permeation chromatography using tetrahydrofuran as mobile phase. μ-Styragel columns (HR 2, HR 4E, HR 5E with size 7: 8 × 300 mm and flow rate 1 ml/min) and RI detector were used in a Waters Associates Instrument Version 2.15 for the analysis. Doughing time and time taken for setting of the oligomers were evaluated. The time required to form adhering fibers between a glass and the surface of the setting mass was noted as doughing time, and for total setting of the mixture at a particular temperature was taken as the setting time. Oligomers (3 g) were taken separately in two clean test tubes and benzoyl peroxide (0.3 g) was added to them. The doughing and setting times were noted at 37°C.

2.3. *Setting characteristics of mixtures of PPF oligomer and n-vinyl pyrrolidone*

Two mixtures, DAM-2/*n*-VP and MA-2/*n*-VP (1:1 w/w), were prepared by mixing equal amount of the PPF oligomer (DAM-2 or MA-2) and the comonomer *n*-vinyl pyrrolidone (*n*-VP). Doughing and setting times of the mixtures were evaluated as mentioned above using PPF oligomer (3 g), *n*-vinyl pyrrolidone (3 g) and benzoyl peroxide(0.3 g).

2.4. *Preparation and characterization of crosslinked products of PPF oligomer and n-vinyl pyrrolidone*

Crosslinked products, coded PDAM-2 and PMA-2, were prepared by curing the mixtures with benzoyl peroxide (5%) at 37°C. Infrared spectrum was recorded using a thin sheet of the

crosslinked product. The solubility of these products in different nonpolar and polar solvents was studied. The solvents used were benzene, toluene, carbon tetrachloride, chloroform, acetone, methanol, dioxane, dichloromethane and N, N-dimethyl acetamide. The thermal behaviour of the crosslinked products was studied by thermogravimetric analysis (TGA) and differential thermal analysis (DTA). The samples were heated to a maximum temperature range of 500°C at the heating rate of 10°C/min in inert nitrogen atmosphere. A Universal VI. 12E TA Instrument was used.

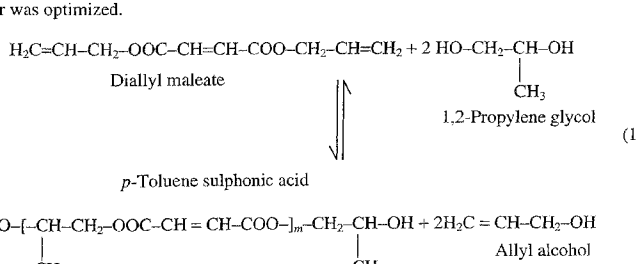
2.5. *Studies on in-vitro biodegradation of crosslinked products (PDAM-2 and PMA-2)*

The stability of the crosslinked products was determined by *in-vitro* aging in various simulated physiological media, PBS of pH 7.4, and Ringer's solution. Oxidation medium (30% hydrogen peroxide solution) was also used. The aging study was carried out at 37°C as reported earlier.[8, 9] Small pieces of the polymer sheets were accurately weighed and immersed in different media. The polymers were taken out on alternate days, dried, and their weight loss was determined. The weight loss(%) was plotted against duration of exposure (days). The relative aging stability was determined.

3. Results and discussion

3.1. *Synthesis of poly(propylene fumarate) oligomer DAM-2 from diallyl maleate*

The reaction between diallyl maleate and 1,2-propyleneglycol in the presence of *p*-toluene sulphonic acid is an equilibrium reaction (eqn 1). However, the formation of oligomer was ensured. The byproduct, allyl alcohol, was removed by vacuum distillation and the conversion to oligomer was optimized.

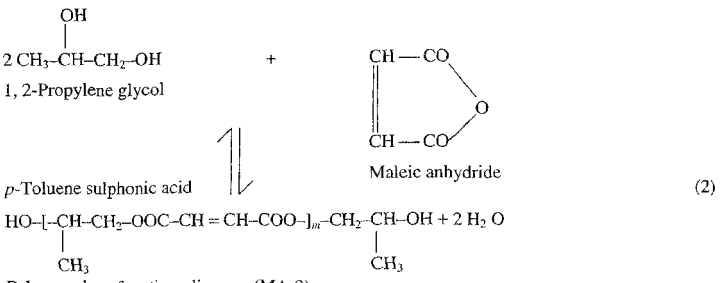


(1)

Polypropylene fumarate oligomer (DAM-2)

3.2. *Synthesis of poly(propylene fumarate) oligomer MA-2 from maleic anhydride*

Maleic anhydride and 1, 2-propylene glycol undergo bulk polymerization in the presence of *p*-toluene sulphonic acid (eqn 2).

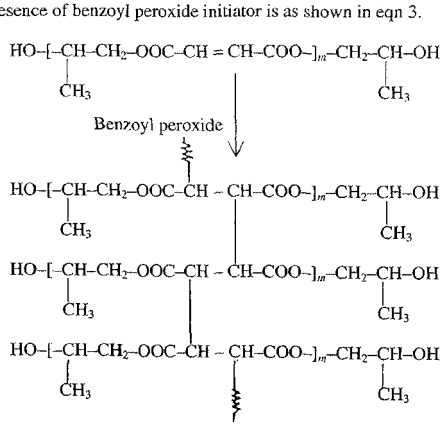


(2)

3.3. *Characterization of oligomers and mixtures of PPF oligomer and n-vinyl pyrrolidone*

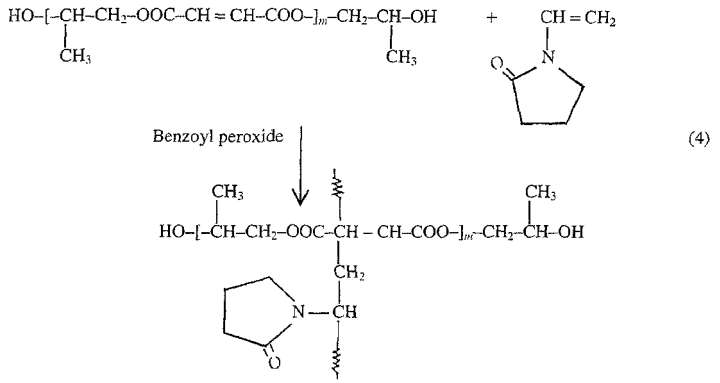
The FT-IR spectral data of oligomers DAM-2 and MA-2, given in Table I, reveal responses for prominent groups, unsaturated double bonds, ester, hydroxyl groups in DAM-2 and MA-2 oligomers. The peaks at 989.21 cm^{-1} for DAM-2 and at 981.85 cm^{-1} for MA-2 are due to the formation of fumarate groups. The molecular weights of DAM-2 are Mn 7579, Mw 8571 and polydispersity 1.1309, and of MA-2 are Mn 8309, Mw 9981 and polydispersity 1.2013.

The essential properties of a hard-tissue adhesive (bone cement) are short setting time and controlled biodegradability. Setting characteristics is a measure to testify the quality of adhesive. The setting reaction (curing) of the oligomer takes place by crosslinking through unsaturated double bonds via free radical mechanism. Self-crosslinking in poly(propylene fumarate) oligomers in the presence of benzoyl peroxide initiator is as shown in eqn 3.



(3)

An important factor in the crosslinking of unsaturated groups of poly(propylene fumarate) oligomer as a crosslinked product is the degree of conversion of maleate isomer into fumarate isomer during vacuum-condensation reaction. Poly(propylene fumarate) has greater hardness and a higher heat-distortion temperature than its maleate counterpart, whereas the reverse is true for impact strength. This is explained by the higher reactivity of fumarate as compared with the maleate ester. The propylene glycol content increases the hardness of the polyester resin.[10] With the addition of the vinyl monomer (*n*-vinyl pyrrolidone) and initiator, benzoyl peroxide, crosslinking between PPF and *n*-VP takes place leading to a crosslinked copolymeric product. Crosslinking reaction of poly(propylene fumarate) oligomer with the comonomer *n*-vinyl pyrrolidone is shown in eqn 4.



(4)

The setting time of the blends of DAM-2/*n*-VP and MA-2/*n*-VP extended to slightly higher duration with the addition of comonomer, *n*-vinyl pyrrolidone (Table II). The increased

Table I
Infrared spectral responses for poly(propylene fumarate) oligomers

Spectral responses	Peak position (cm^{-1})	
	DAM-2	MA-2
–OH (hydrogen bonded)	3434.96	3290
=C=O (stretching of ester)	1732.45	1729 02
C–H (stretching of saturated)	2883.94	2986.56
C–H (stretching of –CH=CH–)	1645.1	1643.53
$–CH_3$ (symmetric stretching)	1398.32	1370
$=CH_2$ (stretching)	2939.33	2986.56
–C–O– (stretching)	1269.25	1180
C–H bending (*trans* CH=CH)	989.21	981.85
$–CH_2–$ scissoring and $–CH_3$ asymmetric bend	1455 73	1460

Table II
Setting characteristics of DAM-2 and MA-2 oligomers and mixtures

Sample	Weight composition (g)			Doughing time (h)	Setting time (h)
	Oligomer	Benzoyl peroxide	*n*-VP		
Oligomer					
DAM-2	1	0.1	–	12	25
MA-2	1	0.1	–	1	20
Blend					
DAM-2/*n*-VP	1	0.1	1	7	21
MA-2/*n*-VP	1	0.1	1	0.5	10

setting time with *n*-vinyl pyrrolidone is due to the chain propagation reaction at 37°C. Comparing with the setting reaction of DAM-2 oligomeric resin, the MA-2 resin sets in shorter duration (Table II). This may be due to higher concentration of fumarate units in MA-2 oligomer

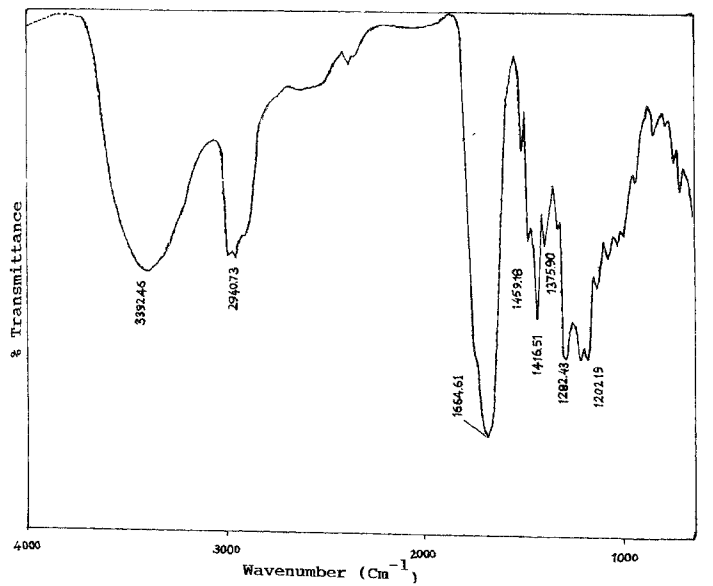


FIG. 1. FT–IR spectrum of PDAM-2.

Table III
Degradation of PDAM-2 and PMA-2 in different media

Media	Weight loss (%) at different durations of exposure (days)						
	3	5	7	9	11	13	15
PDAM-2							
PBS	39.44	53.24	53.24	53.24	Deformed	–	–
Ringers solution	57.45	60.43	60.80	60.85	60.85	60.85	60.85
30% H_2O_2 solution	34.03	41.00	43.64	44.55	44.55	44.55	44.55
PMA-2							
PBS	34.72	53.13	53.13	53.13	Deformed	–	–
Ringer's solution	44.66	49.48	55.69	60.11	61.25	61.25	61.25
30% H_2O_2 solution	43.22	48.06	49.61	52.21	54.46	56.01	56.01

than in DAM-2 oligomer. It has been reported by Melville *et al.*[11] that at a temperature of about 190°C, isomerization reaction takes place and for maleic acid the *cis* configuration is changed into less strained more planar *trans*-fumarate configuration. However, at this tempera-

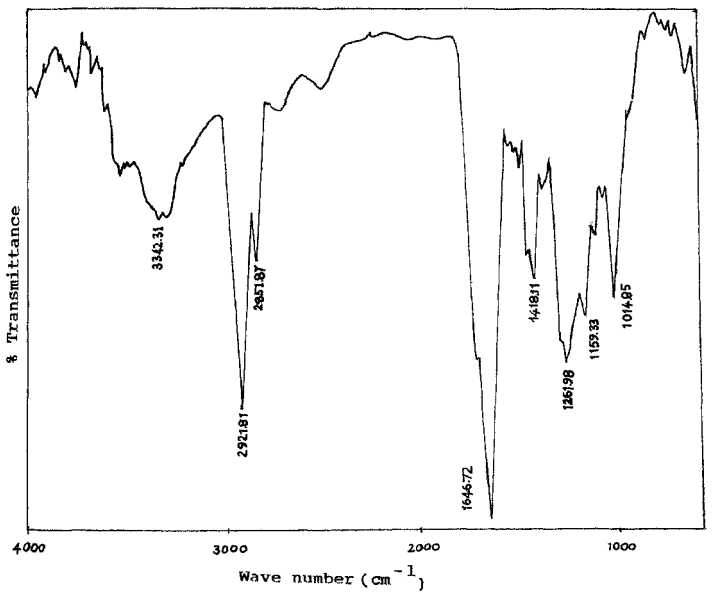


FIG. 2. FT–IR spectrum of PMA-2.

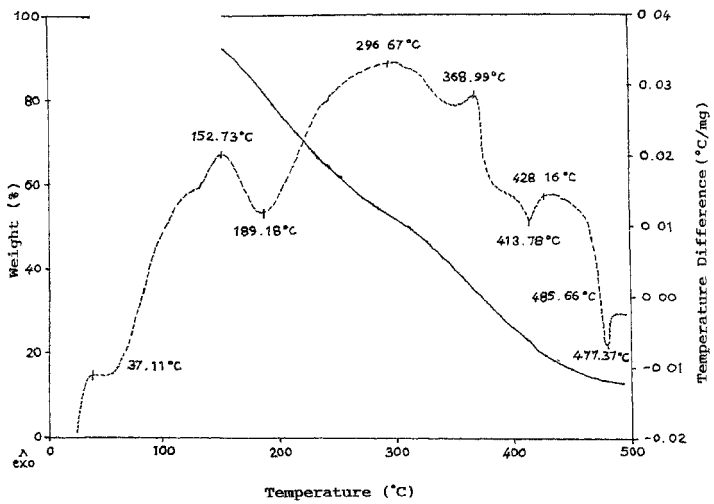


FIG. 3. TGA and DTA curves of PDAM-2.

ture and duration of 15–18 h, maleic anhydride also enters side reaction with glycols, which reduce the degree of unsaturation. Such side reactions give crosslinked product. In the present investigation, no crosslinked product was obtained along with poly(propylene fumarate) resin during the vacuum-condensation reaction.

3.4. *Characterization of PDAM-2 and PMA-2*

3.4.1. *Infrared spectral studies*

The absence of peak (Figs 1 and 2) at 1645 cm^{-1} and 989.21 cm^{-1} for PDAM-2 indicates the consumption of reactive fumarate groups and completion of crosslinking reaction at C = C bond of fumarate groups. The ester group shifted to lower wavelength. The strong peak at 1664.61 cm^{-1} is due to hydrogen-bonded ester groups and *n*-VP units. The new peaks at 1491, 51, 1375.90 cm^{-1} in PDAM-2 are due to *n*-VP units. The presence of peak at 1646.7 cm^{-1} for PMA-2 reveals the presence of unreacted alkenic groups. However, the disappearance of the peak of fumarate double bonds at 981.85 cm^{-1} indicates the completion of crosslinking through fumarate units. The ester group also appeared at lower wavelength as in PDAM-2 product. IR spectral analyses reveal the crosslinked nature of the product.

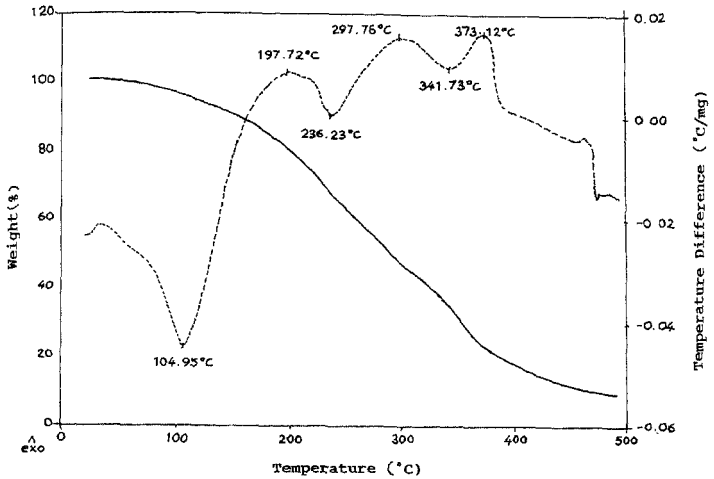


FIG. 4 TGA and DTA curves of PMA-2

3.4.2. *Solubility*

The crosslinked products are insoluble in benzene, carbon tetrachloride, chloroform, and acetone and sparingly soluble in methanol, dioxane and dimethyl acetamide. However, PDMA-2 is sparingly soluble in toluene while PMA-2 is insoluble. This suggests that PMA-2 has attained a highly crosslinked state in comparison with that of the former.

3.4.3. *Thermal studies*

The TGA–DTA curves (Figs 3 and 4) give the variation in softening temperature. PMA-2 shows the softening point predominantly at 104.95°C, whereas it is only clearly established in PDAM-2. PMA-2 and PDAM-2 show decomposition peak at 197.72 and 152.7°C, respectively.

TGA shows the difference in the thermal decomposition history of the two polymers. The initial weight loss may be attributed to the first-stage degradation by chain scission. The second decomposition temperature in the case of PMA-2 is 297.76°C and 296.67°C in the case of PDAM-2. The former left a residue of 9% at 491.96°C, while the latter gives 13% at the same temperature. A comparison of the intial decompositions shows that degradation starts at low temperature in the case of PDAM-2 revealing low stability in comparison with that of PMA-2.

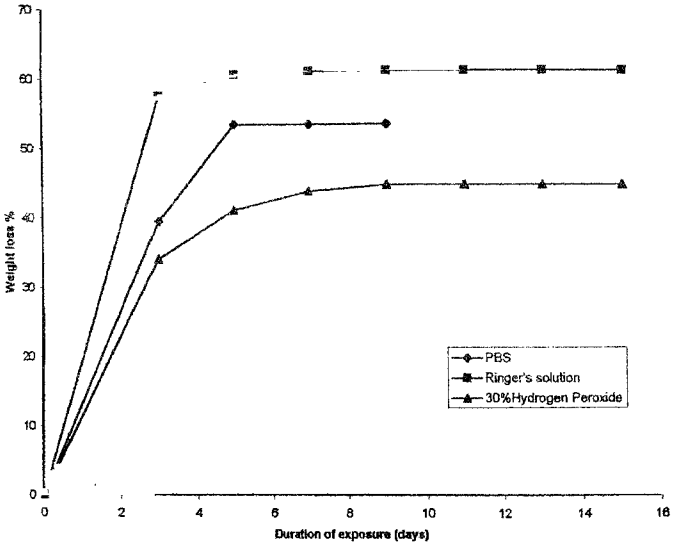


FIG. 5. Biodegradation of PDAM-2 in simulated physiological media.

3.5. *Studies on in-vitro biodegradation of PDAM-2 and PMA-2*

The *in-vitro* aging studies reveal degradation in simulated body fluids, Ringer's solution, PBS and oxidative medium hydrogen peroxide. Ringer's solution and PBS medium can induce hydrolytic degradation through ester hydrolysis. Degradation in hydrogen peroxide medium is due to oxidative degradation.

The data on aging studies of PDAM-2 (Fig. 5) show faster degradation during initial aging followed by slow degradation reaching a steady-state condition during subsequent aging. Among the aging media, higher initial weight loss was noticed in Ringers solution. In PBS medium, PDAM-2 was completely deformed after 10 days of aging. Aging in 30% hydrogen peroxide solution also reveals appreciable degradation. The degradation in hydrogen peroxide could be through oxidation at the residual unreacted alkenic groups. The data on degradation of PMA-2 (Fig. 6) show a similar trend of faster degradation during initial aging followed by slow degradation reaching a steady-state condition during subsequent aging. The maximum initial weight loss was also noticed in Ringer's solution as well as in hydrogen peroxide medium.

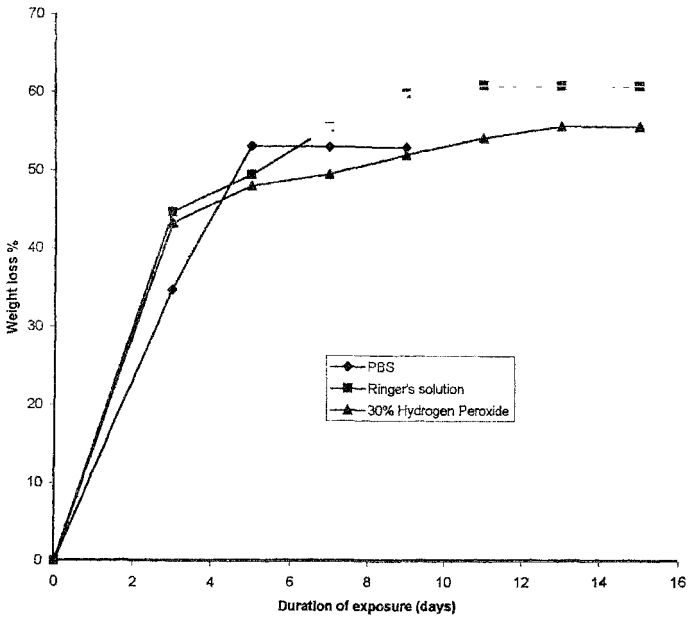


FIG. 6. Biodegradation of PMA-2 in simulated physiological media

Comparing the intial degradation, higher weight loss was observed with PDAM-2 in Ringer's solution and PBS media in comparison with that of PMA-2. Comparing the initial degradation in oxidative medium, a reverse trend was noticed. The higher weight loss of PMA-2 in oxidative medium is attributed to the presence of more unreacted alkenic groups as noticed in the IR spectral analysis. The degradation in Ringers solution in the case of crosslinked product PDAM-2 reached a steady state after 7 days of exposure, whereas it took 11 days for PMA-2. Considering the hydrolytic degradation as the major degradation pathway in the present products, the weight loss data observed at the beginning of aging in hydrolytic media reveal that PMA-2 product is relatively more stable in comparison with PDAM-2 product.

4. Conclusion

Poly(propylene fumarate) oligomers were synthesized using two diifferent monomers, diallyl maleate/1,2-propylene glycol and maleic anhydride/1,2-propylene glycol. The poly(propylene fumarate) oligomer MA-2 synthesized from maleic anhydride was found to set in lesser dura-

tion in comparison with that of DAM-2 synthesized from diallyl maleate. The setting studies reveal that poly(propylene fumarate) mixure, MA-2/*n*-VP, has fast setting characteristics.

The *in-vitro* degradation studies of the crosslinked products reveal faster degradation with time during initial exposure followed by a steady-state of weight loss. Comparing the effect of the media, Ringer's solution, PBS and hydrogen peroxide solution, PBS induces faster degradation after a lapse of 9 days. In other media, the product undergoes sustained degradation, which involves longer duration for complete disappearance of the material. PMA-2 undergoes slow degradation in comparison with PDAM-2. The studies reveal that MA-2/*n*-VP-based bone-cement formulation could be a more promising adhesive.

Acknowledgements

The authors are grateful to the Head, Biomedical Technology Wing and Director, Sree Chitra Tirunal Institute for Medical Sciences and Technology for facilities.

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