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Biodegradable poly(propylene fumarate) was synthesized and characterized for application as a moldable bone repair material which could be placed in a bone defect and subsequently cured to a hardened consistency within 30 to 35 minutes. Curing was accomplished by cross-linking with vinyl pyrolidone in the presence of benzoyl peroxide. In vitro degradation studies of the set material did not appear to demonstrate degradation rates conducive to mediating bone repair. In vivo studies were also negative. However, the data suggest that poly(propylene fumarate) has potential as a moldable bone repair material and further research will be required.

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SYNTHESIS OF A MOLDABLE BIODEGRADABLE BONE REPAIR MATERIAL CHARACTERIZATION AND IN VIVO EVALUATION OF CROSS-LINKED POLY (PROPYLENE FUMARATE)

FINAL REPORT

AUGUST 1987

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In conducting research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources National Research Council.

SYNTHESIS AND CHARACTERIZATION OF CROSS-LINKED POLY(PROPYLENE FUMARATE)

INTRODUCTION

Past efforts in the development of biocompatible and biodegradable materials for use as temporary replacement for lost soft tissue and/or bone following trauma have produced homo- and co-polymers of lactic and glycolic acids (1-3). Over the years, the polyesters from these organic acids have also found application as bioresorbable sutures and controlled-release devices for biologically active agents (4-7). Their biodegradability is largely attributed to the chemical property of ester linkages to undergo hydrolysis in an aqueous environment. As the polymer is hydrolyzed to oligomers or monomers, these low molecular-weight, water-soluble products diffuse and can be eliminated by the excretory mechanisms of the host organism. Secondary degradation mechanisms can also take effect as the smaller molecules become substrates of enzymes. Phagocytic activity can also contribute to biodegradation, if the polymer is not compietely biocompatible and is considered by the host to be a foreign substance.

While copolymers of lactic and glycolic acids have been found to be highly effective as bone replacement materials (8), their chemical nature dictate that they be used as solids which are pre-shaped and/or carved to fit a bone defect at the time of surgery. This can be time consuming procedure. Thus, research and development of a biocompatible polymer which could be prepared in a putty-like consistency, easily formed into a bone defect and rapidly hardened in situ, is highly desirable. In this regard, poly(propylene fumarate), or PPF for short, is a desirable polymer because it is derived from two known biocompatible compounds, fumaric acid and propylene glycol. Fumaric acid is a Kreb's cycle intermediate which has an unsaturation in addition to its carboxylic acid functionalities, whereas propylene glycol is a diol which

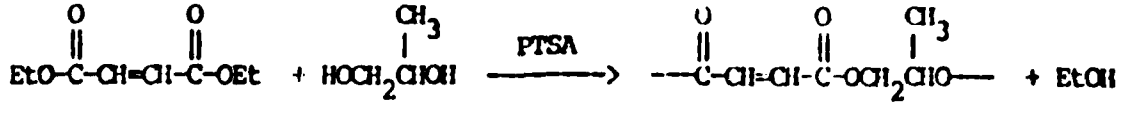
can be enzymatically converted to pyruvic and acetic acids (9) before being shunted to the Kreb's cycle. Because of the presence of an unsaturation in the fumarate moeity, the solid polymer can be prepared into a putty-like consistency by the addition of a liquid cross-linking agent. In this form, incorporation of particulate osteogenic materials into the polymer is facilitated to afford a biodegradable bone-forming implant which can be shaped and formed at the time of surgery.

Although the first deliberate synthesis of PPF was in 1981 by Wise (10) under contract to the U.S. Army Institute of Dental Research, some form of PPF synthesis was initiated in 1961 when Szmercsanyi (11) reported the qualitative results of the reaction of maleic anhydride with propylene glycol (Equation 1).

PPF

Equation 1

Andreis (12, 13), later determined and confirmed that 95% of maleic anhydride was converted under certain conditions to fumarate as it reacted with propylene glycol. The para-toluenesulfonic acid-catalyzed synthesis of PPF developed by Wise, which reacts the diethyl ester of fumaric acid with propylene glycol to liberate ethanol, proved to be irreproducible (Equation 2). Thus, synthetic efforts were undertaken at USAIDR.



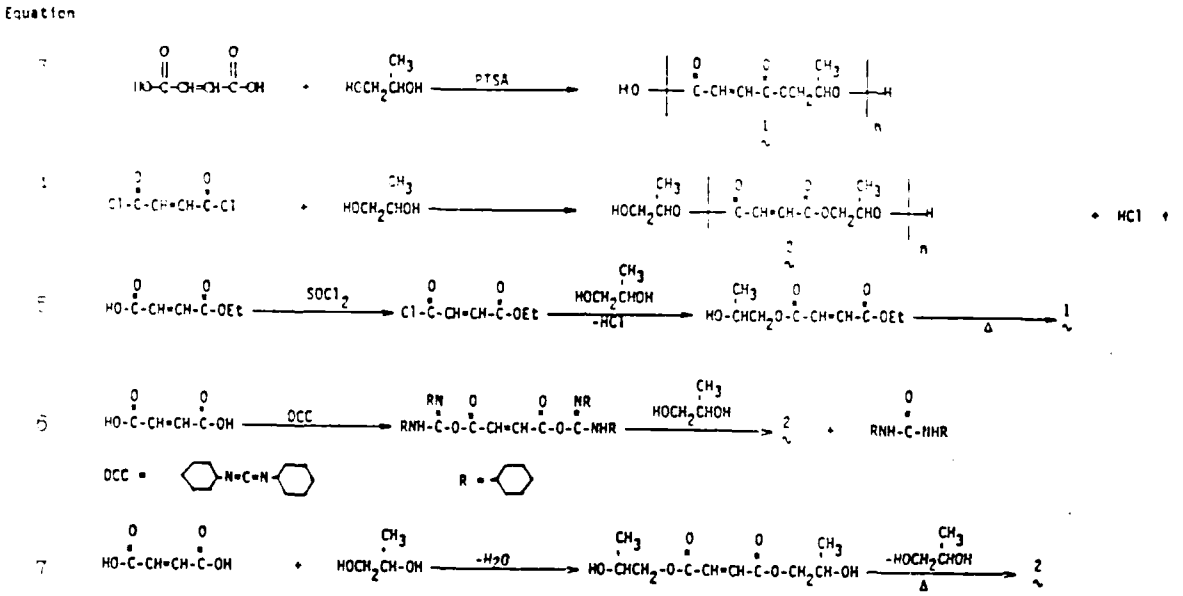
PPF

Equation 2

To date, different synthetic methods (see TABLE 1) for PPF have been attempted at USAIDR (16) where the acid catalyzed polycondensation (Equation 3) of fumaric acid with propylene glycol to liberate water is the most reproducible. The polymer from the reaction was used in model studies to determine its curing behaviour in order to develop formulations for the moldable implant.

TABLE 1

Equation



EXPERIMENTAL

MATERIALS. The chemicals whose commercial sources are not given were purchased from Aldrich Chemical Co. Fumaric acid was purified by recrystallization from methanol. Propylene glycol was fractionally distilled from 4A molecular sieves under reduced pressure.

INSTRUMENTATION. IR specta were recorded on a FTIR Perkin-Elmer Model 1550 spectrophotometer using a diffuse reflectance accessory and a Perkin-Elmer Model 7500 professional computer for spectral enhancement. NMR spectra were recorded on a Varian EM360 spectrometer. Chemical shifts are reported relative

to Me_4Si. GPC was performed in 0.2M LiBr in dimethyl formamide at a flow rate of 1 mL per minute with a Waters 6000A liquid chromatograph using a mixed bed Jordi-Gel polystyrene/divinylbenzene column in the 10^3 to 10^7 permeability range which is heated to 80°C. Thermal analysis by DSC was performed on a Perkin Elmer DSC-4 differential scanning calorimeter equipped with a control and programming unit and a calorimetric cell that allows scans from ambient temperatures to 400° to determine the glass transition and melting temperatures, the heat related to the during and post-curing processes, and the kinetics of the overall reaction. Thermograms were produced by scanning the samples from 50 to 250°C at four different scan rates (10 - 40°C-min^{-1}). The DSC cell was calibrated for temperature and heat of fusion using indium as standard. The sample weight used was 5.0 mg. Runs were always made using an empty sample holder as reference.

SYNTHESIS OF PPF. All the polymerization reactions were carried out under a dry nitrogen atmosphere using various fumaric acid derivatives with one equivalent or, in certain cases, varying excesses of propylene glycol. One of the objectives in the synthesis was to develop a means of controlling number average molecular weight M_n and molecular weight distribution. Since these parameters have a direct effect on the degradation rate of the polymer and on its cross-linking properties, several methods of polycondensation were investigated. Table 2 in the next page is a summary of the polycondensation methods. Since Equation 3 was the most fruitful and reproducible of all the methods, its synthesis will be described in detail: The polycondensation reaction was performed by a comonomer-feed technique in which fumaric acid was added in portions to the reaction mixture. The apparatus for conducting the reaction was set up as shown in Figure 1 (Page 6). At a one mole scale, 117 g of fumaric acid was added with a powder addition funnel to a mechanically

TABLE 2. SUMMARY OF POLYCONDENSATION METHODS

METHOD	FUMARATE DERIVATIVE	SOLVENT	TEMPERATURE	TIME	CATALYST
Transesterification (Eq. 2)[10]	Diethyl Fumarate	Bulk	200°C	24 h	PTSA[d]
Acid Chloride (Eq. 4)	Fumaryl Chloride[c]	Bulk	0°C	24 h	None
Acid Chloride-Semiester (Eq. 5)	Fumaryl-Chloride-mono-ethyl ester[a,c]	Bulk	0°,then 200°C	24 h	None
Carbodiimide (Eq. 6)	Fumarate Dicarbodiimide[b,c]	THF	67°C	24 h	None
Esterification (Eq. 3,7)	Fumaric Acid	Propylene Glycol	200°C	24 h	None

a. Synthesized by treating fumaric acid-mono-ethyl ester with thionyl chloride.
b. Generated *in situ* from fumaric acid and dicyclohexyl carbodiimide.
c. Comonomer-feed technique used.
d. Para-toluene sulfonic acid.

Figure 1. Schematic of Apparatus for Polymer Synthesis

A. Stirrer Motor

B. Powder Addition Funnel

C. Vigreaux Column

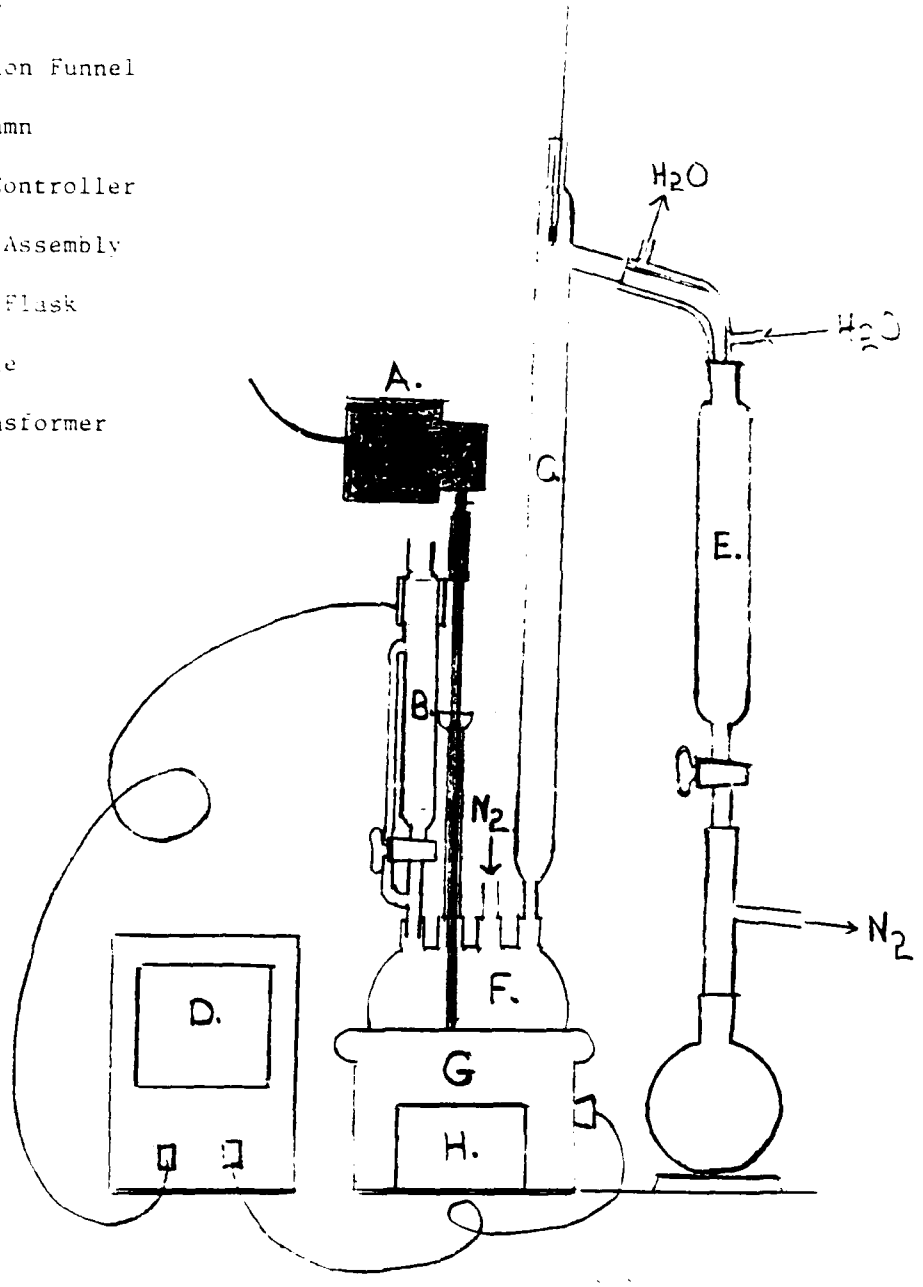
D. Temperature Controller

E. Distillation Assembly

F. Round-Bottom Flask

G. Heating Mantle

H. Variable Transformer



stirred mixture of 790 mg of para-toluenesulfonic acid and 80 mL of propylene glycol, with the stirring and temperature set at 60 rpm and 109°, respectively. The addition of fumaric acid was at such a rate that the previous portion of the powder dissolved before the next portion was added. When the powder no longer dissolved, addition was interrupted, and the reaction temperature was increased to 158°C. The fumaric acid re-dissolved, and condensate, which is composed of water and propylene glycol, is distilled over a boiling point range of 122° to 137°C. When the addition was completed, the powder addition funnel was replaced with a glass stopper, and heating was continued for 16 hours. Without terminating the heating and the flow of nitrogen, the apparatus was reconfigured for simple vacuum distillation by the removal of the Vigreaux column and the graduated pressure-equilibrating addition funnel. With the stirring and temperature maintained at 60 rpm and 158°C, respectively, nitrogen flow was terminated, and vacuum (1mm Hg) was applied for 2 hours to remove unreacted propylene glycol. At the end of the reaction, stirring and heating were discontinued and vacuum was released by purging with dry nitrogen gas. Before the raw polymer became solidified from cooling, the stirrer motor was raised to suspend the stirrer blade above the surface of the contents of the flask. When a temperature of 30°C or lower was reached, the raw polymer was dissolved with mechanical stirring in methylene chloride, treated with decolorizing charcoal, and vacuum-filtered through a Celite pad in a medium fritted funnel. The filtrate was then shaken with 500 mL of 80% aqueous methanol in a separatory funnel to extract unreacted starting material. After the layers separated, the top layer was discarded and the extraction was repeated with the same volume of 80% aqueous methanol. The lower methylene chloride layer was isolated, dried over anhydrous calcium chloride and rotary evaporated. The remaining syrup was transferred into a crystallizing dish and dried under vacuum overnight at room temperature. The

polymer foamed, and after 24 hours under vacuum, the polymer was crushed with a mortar and pestle, and then stored in a brown bottle in a vacuum desiccator.

CROSS-LINKING OF PPF. Cross-linking experiments were performed on the purified PPF to optimize the handling properties of the putty. Before proceeding into the development of an osteogenic composite, the initial objective in this section was to determine the optimum mixing ratio of the initiator, the cross-linking agent, and the polymer. Thus, according to the amounts given in Table 3, benzoyl peroxide (BPO) was dissolved in N-vinyl-2-pyrrolidone (NVP).

TABLE 3

Composition of Samples

Sample Number	PPF[1] (mg)	NVP[2] (uL)	BPO[3] (mg)	Group Number
1	500	12.5	5.0	II
2	500	25.0	5.0	II, I
3	500	37.5	5.0	II
4	500	50.0	5.0	II, III
5	500	25.0	4.0	I
6	500	25.0	2.5	III, I
7	500	25.0	1.0	I
8	500	25.0	0	I
9	500	12.5	1.25	III
10	500	37.5	3.75	III

1. Poly (propylene fumarate)
2. N-vinyl-2-pyrrolidone
3. Benzoyl peroxide

Group I: Constant NVP:PPF ratio (5%) and variable BPO concentration (0 to 1%).
Group II: Constant BPO:PPF ratio (1%) and variable NVP concentration (2.5 to 10%).
Group III: Variable NVP and BPO concentrations, but constant NVP:BPO ratio (10:1).

When the BPO was observed to be in solution, the polymer was added and mechanically mixed into the solution with a spatula. When the solution was completely embibed by the polymer, the mixture was worked by hand into a moldable mass. Table 4 is a summary of the observations made during the mixing.

TABLE 4

Mixture Characteristics

Sample Number	Mixing[1] Time (min)	Tacky (Yes/No)	Elastic (Yes/No)	Setting[2] Time (min)
1	5	No	No	<1
2	4	No	No	<1
3	4	No	No	4
4	2	Yes	No	20
5	5	No	No	<1
6	5	No	No	<1
7	5	No	No	<1
8	5	No	No	<1
9	5	No	No	<1
10	2	Yes	Yes	25

1. Mixing time is the time required for the components to be agglomerated.
2. Setting time is the time required after complete mixing to achieve a difficultly moldable state.

IN VITRO DEGRADATION. The unused amounts from the thermal analysis were weighed, placed in 20 mL of phosphate buffer (pH 7.2), and kept at ambient conditions. Periodically, the samples were removed from the buffer, dabbed on absorbent paper to rid of excess fluids, weighed, and replaced in a fresh amount of buffer solution to continue its course of degradation before the next weighing. Degradation and re-weighing were performed until no solid matter can be obtained for weighing. Figures 2-4 are a summary of the data obtained from this portion of the investigation.

FIGURE 2 DEGRADATION OF GROUP I SAMPLES

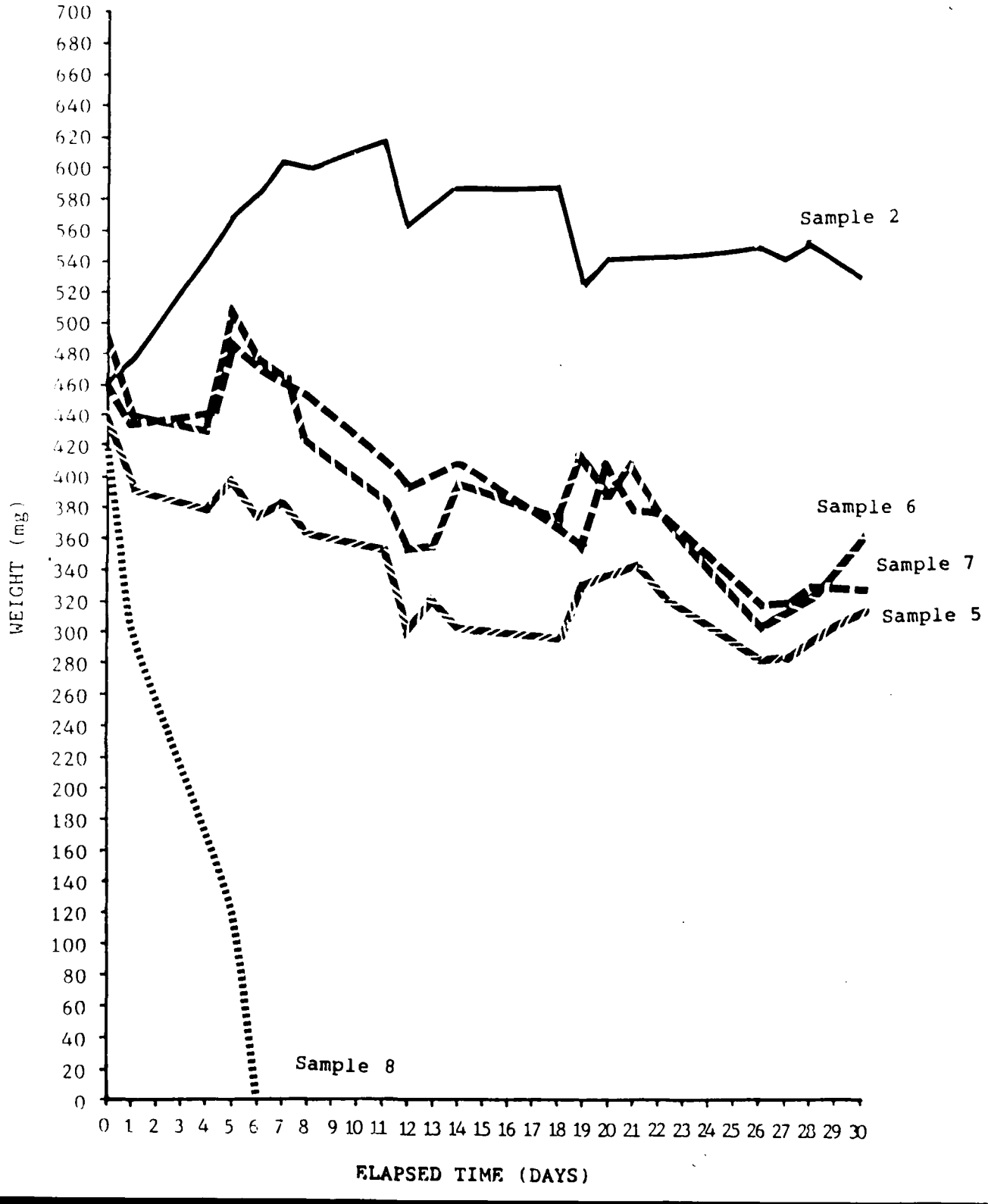


FIGURE 3. DEGRADATION OF GROUP II SAMPLES

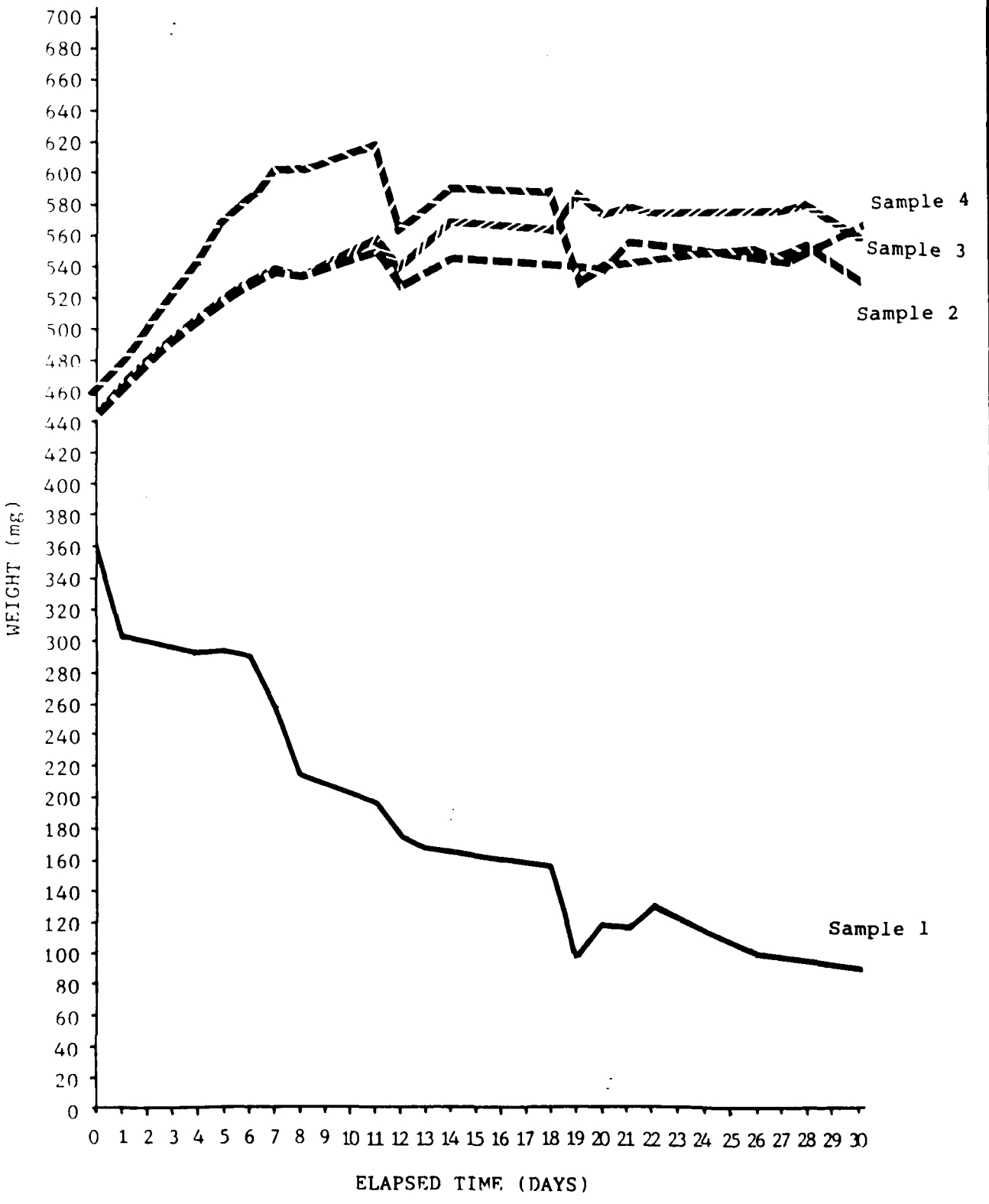
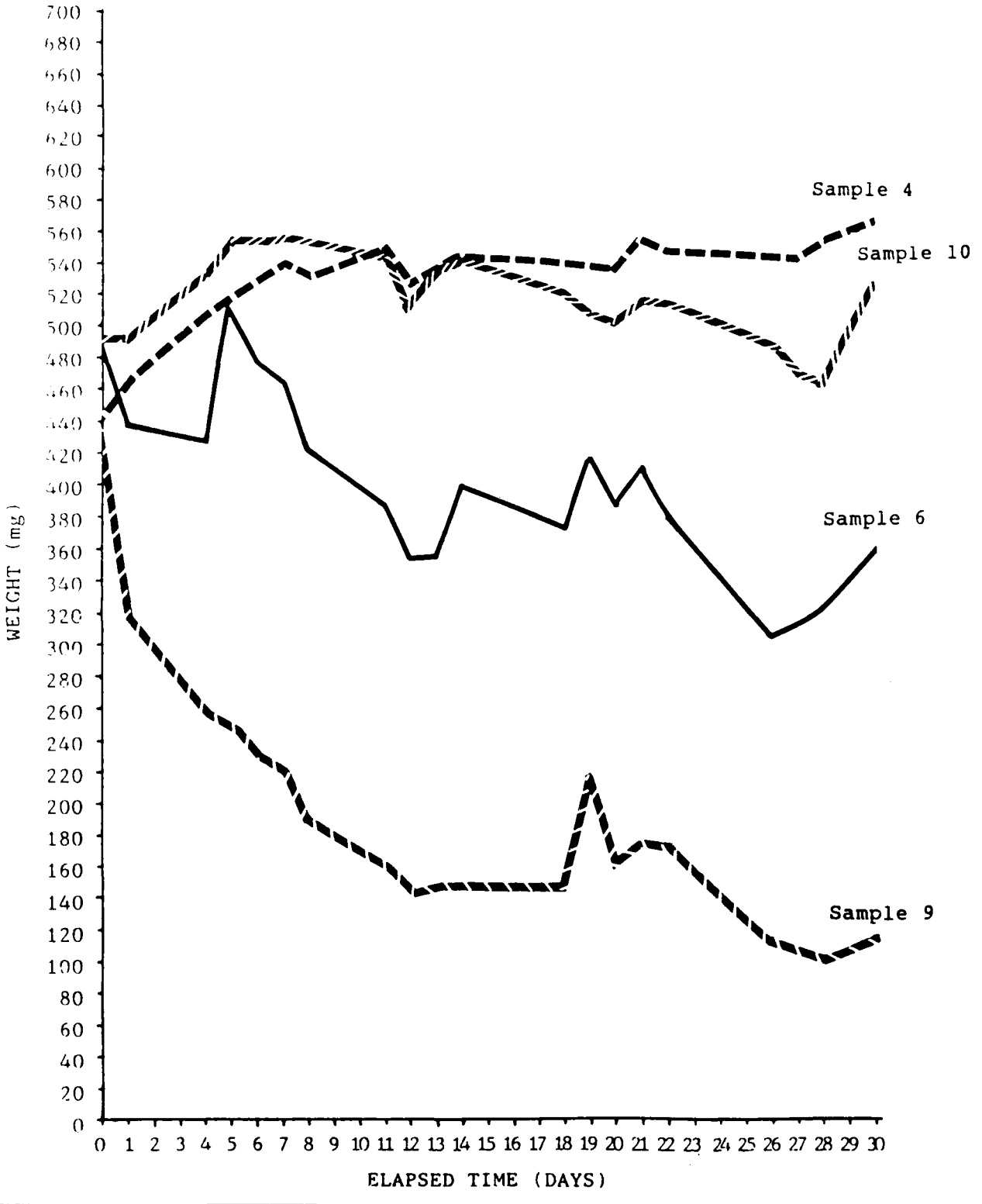


FIGURE 4 DEGRADATION OF GROUP III SAMPLES



IN VIVO EVALUATION. Cross linked polypropylene fumarate alone and in combination with demineralized bone matrix(DBM) was evaluated in rats and rabbits. At the time of surgery powdered PPF was mixed with N-vinyl-2-pyrolidone(NVP)and benzoyl peroxide (BPO) in the ratio and mixing time shown for sample number 4 tables 3 and 4. If the PPF mixture alone was used the mixture was allowed to reach a non-tacky, putty-like consistency before placing the mixture in a prepared bone defect in an experimental animal. Mixtures were made in ratios of either 50:50 by weight or 70:30 by weight of the PPF mixture to DBM. The DBM used was prepared from rat or rabbit bone according to Urist (17). When a PPF-DBM mixture was used the PPF-NVP-BPO mixture was first prepared and allowed to set for 2 to 3 minutes. The DBM was then folded into the PPF mixture until a consistent mix was obtained. The DBM particles were in the size range of 50 to 300 microns. The setting times for the PPF mixture versus the PPF mixture plus DBM were approximately the same ($\pm$1-2 minutes).

After achieving suitable anesthesia using sodium pentobarbital (3-5mg/100gm of body weight,ip) 3 cranitomy defect of 2.5mm diameter were made in the parietal bones of 36 rats. One defect remained untreated, one defect received the PPF mixture alone and the third defect received the PPF mixture with DBM added in a 50:50 ratio. Six animals were sacrificed at 7, 14, 21, 28, 60 and 75 days. Bone recovered from each site on each animal was imbedded in polymethyl methacrylate and stained with goldners trichrome stain. In every case the animal was not closed at initial surgery until the mixtures placed in the experimental sites resisted mild pressure with a metal probe. It was noted that care had to be taken to minimize bleeding during placing of the experimental mixtures. Excessive mixing with blood tended to inhibit the setting process. Samples of freshly set mixtures of

PPF and PPF plus DBM were also placed in the gluteal muscle of each rat and recovered at the time of sacrifice for a qualitative evalutation of consistency and size.

Tissues taken at 7 to 28 days post implantation did not show an immunogenic response. However, bone fill and implant degradation were extremely slow. At 56 days the control defects show good bone fill with healing nearly complete. The experimental sites show small amounts of bone beginning to fill the defects with the site containing DBM displaying somewhat more bone than the sites containing only the PPF mixture. At 75 days post-implantation there was still a great deal of the implant materials left in the experimental sites. The apparent lack of degradation in vivo appears to be in agreement with the in-vitro results shown in Figure 3 for sample #4 (The sample #4 formulation was used in this study for all implants).

There is some indication that the addition of DBM to the PPF mixture may stimulate bone regeneration. A subsequent study done in rabbits used implants consisting of a 70:30 mix of DBM to PPF mixture .

Ten adult male New Zealand white rabbits randomly selected were anesthelized using xylocaine/ketamine supplemented with 1.8ml 2% lidocaine HCL with 1:100,000 epenephrine. The hair around the inferior border of the right and left mandiular ramus was removed with a depilatory agent and the area scrubbed with povidone iodine. Before surgery 150,000 units of Flocillin^{R} were administered intra-muscularly. An incision was made over the lower end of each ramus of the mandible to expose a free, flat bone surface. An 8mm diameter defect was made in each ramus. One side was used as an untreated control and the other received a 70:30 mixture of DBM plus PPF mixture prepared at the time of surgery and allowed to set to a stiff

putty-like consistency before insertion into the defects. Two Animals were sacrificed at 14, 28, 56, and 112 days after implantation. Bone recovered from each defect site was imbedded in polymethyl methacrylate and stained with Goldners trichrome stain.

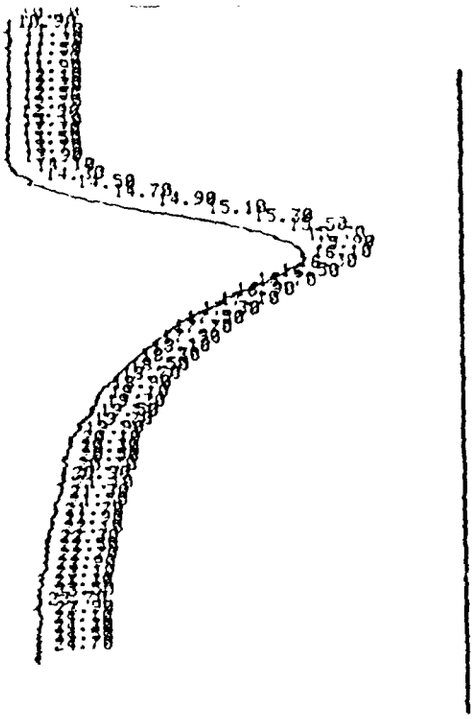
Tissues taken at 14 and 28 days show good bone fill in the control sites with approximately 50% fill at 56 days. The experimental site showed mostly connective tissue up to 28 days post-implantation and some bone fill at 56 days around the periphery of the defect. The central portion of the implants looked like oatmeal and could be easily crumbled out of the defect starting at 28 days after implantation. At 112 days post-implantation about 30 to 40% of the defect had bone fill with the remainders of the defect containing dense connective tissue. Remains of the implants could still be seen.

RESULTS AND DISCUSSION

All the procedures attempted produced the polymer, but only the comonomer feed technique produced the PPF in its usable form and was easily duplicated. The polymer appears as a light yellow free flowing powder. It is soluble in chloroform, methylene chloride, acetone, dimethylformamide, and ethyl acetate, but is insoluble in water and methanol. Following its synthesis, the polymer was characterized by thermal, chromatographic and spectroscopic means. The PPF synthesized by the above procedure generally has a number-average molecular weight of 3,000. Attempts to produce polymers in its pure form above this molecular weight have proven to be difficult because of viscosity and gelation problems. When the raction is observed to be gelling, stirring becomes almost impossible and the polymer is no longer soluble for work-up. However, lower molecular weights have been obtained by changing reaction parameters such as temperature, time, and concentration. Figure 5 is a typical chromatogram of the polymer. Note that the GPC curve is not completely symmetrical and that it is skewed towards the lower molecular weights. This causes the number average molecular weight to be lower. Continuous extraction and re-precipitation techniques have been attempted and have not been successful at removing the lower molecular weights. There are preparative liquid chromatographic techniques available, but they are not cost effective and can accept sample loads of only a few grams.

The NMR spectrum of PPF indicates that the methyl groups of the propylene moeity, which are the pendant groups of the polymer, are not evenly spaced along the polymer chain. Note in the spectrum (Figure 6) that the methyl peaks at 1.30 ppm appears as a triplet. This is the result of two doublets that are over-lapping. In poly(d,l-lactic acid) where the methyl groups are equidistant along the polymer chain, the NMR spectrum of this polymer shows two distinct

FIGURE 5



SAMPLE POSITION 01 SINGLE MODE WISP REPORT

INJECTION VOLUME 0035
NUMBER OF INJECTIONS 1 INJECTIONS REMAINING 0
RUN TIME 00:25 EQUILIBRATION DELAY 00:00
NON-DEFAULT SYS MSG'S: 6500-0030 PSI,7048
WISP CODES GENERATED:

OCT. 31, 1985 09:30:44 CHART 1.00 CM/MIN
RUN #45 CALC #1
COLUMN SOLVENT OPR ID: 6

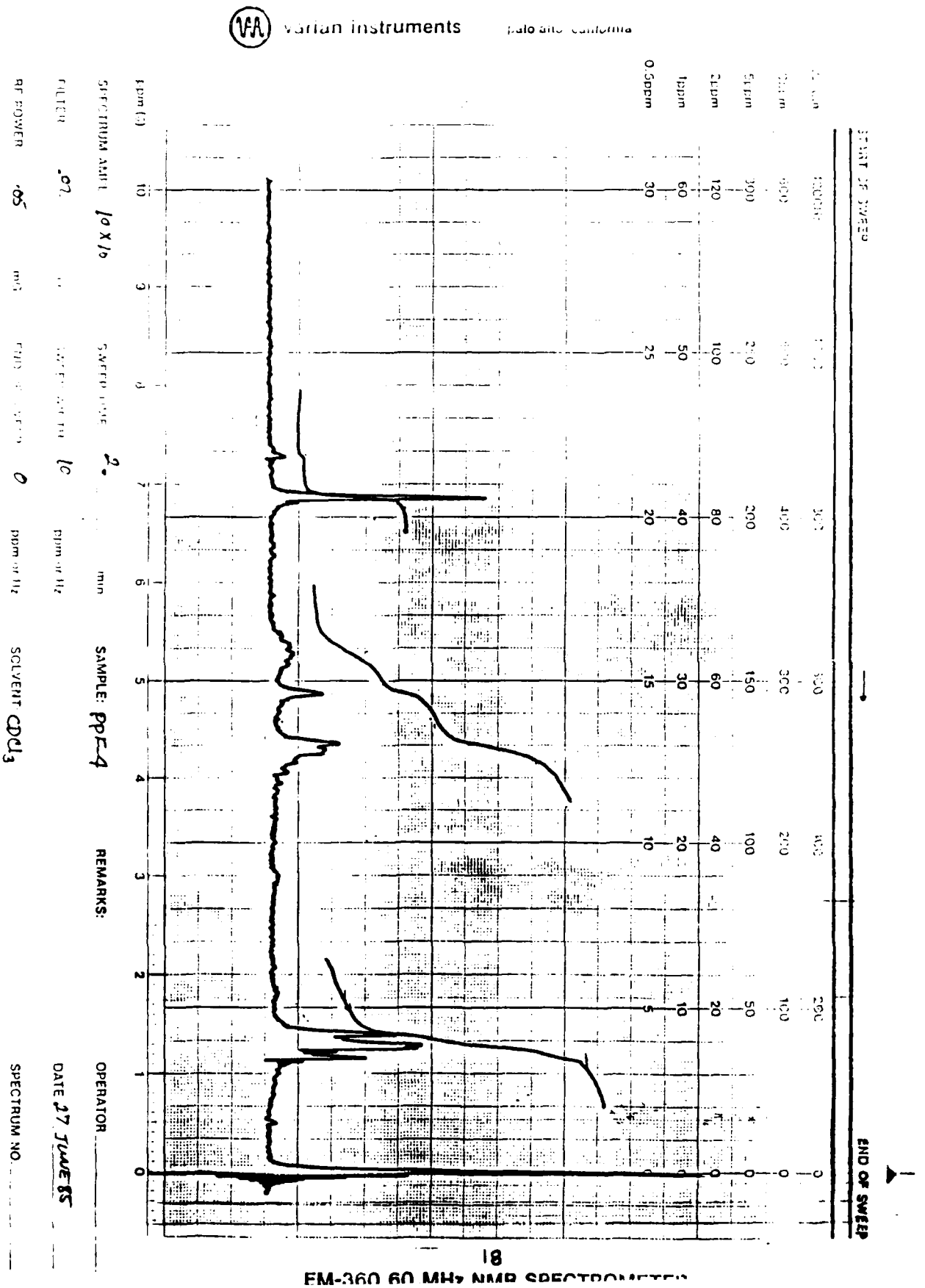
GPC QUANTITATION

RT	AREA	MOL WT	A/MW	
14.30	21363	0.103133E5	0.207140E1	F
14.50	52523	0.845005E4	0.621570E1	F
14.70	98663	0.702100E4	0.140525E2	F
14.90	164860	0.592623E4	0.278186E2	F
15.10	239401	0.508133E4	0.471138E2	F
15.30	316096	0.445560E4	0.709435E2	F
15.50	374996	0.397471E4	0.943454E2	F
15.70	412227	0.360973E4	0.114198E3	F
15.90	439044	0.336132E4	0.130616E3	F
16.10	443644	0.320248E4	0.138531E3	F
16.30	428514	0.313607E4	0.136640E3	F
16.50	399284	0.314406E4	0.126996E3	F
16.70	366219	0.324613E4	0.112817E3	F
16.90	329886	0.344348E4	0.958001E2	F
17.10	305220	0.376271E4	0.811170E2	F
17.30	274769	0.426380E4	0.644422E2	F
17.50	247431	0.496901E4	0.497948E2	F
17.70	229839	0.600287E4	0.382881E2	F
17.90	210153	0.751771E4	0.279543E2	F
18.10	192371	0.976532E4	0.196994E2	F
18.30	176225	0.131785E5	0.133721E2	F
18.50	160133	0.184993E5	0.865616E1	F
18.70	146625	0.270447E5	0.542157E1	F
18.90	131425	0.412451E5	0.318643E1	F

NO-AVG 0.430808E4
WT-AVG 0.630043E4
Z-AVG 0.138092E5
VIS-AVG 0.629965E4

DISPERSITY 0.146246E1
INTRINSIC VISCOSITY 0.629839E-2

FIGURE 6



EM-360 60 MHz NMR SPECTROMETER

types of methyl doublets which accounts for the two types of methyl groups in the syndiotactic polymer (14, 15). Previous NMR analysis by Andreis (12, 13) on a similar polycondensation reaction where maleic anhydride was polyesterified with propylene glycol confirms the NMR observation on PPF. Because of the lack of order in the spatial interval of the pendant methyl groups, and that the propylene glycol used was a racemic mixture, PPF cannot assume a crystalline structure, and thus, it is amorphous. This is confirmed by DSC when no glass transition temperature (Tg) was observed (Figure 7). The absence of a Tg can also be attributed to partial cross-linking during the reaction and/or work-up. There is an indication in the NMR spectrum that partial cross-linking may be occurring because of a lower-than-expected integration of the fumarate protons at 6.8 ppm. Although it was expected that the molar ratio of fumarate to propylene glycol may be less than one because of a lower degree of polymerization, the ratio calculated from the NMR spectrum does not equate to a degree of polymerization that is consistent with the molecular weight obtained by GPC.

Although the molecular weight of the polymer was low and despite its other inherent properties observed by NMR and DSC, PPF was found to be processable under the conditions prescribed. As shown in Table 4 earlier, the formulations had more or less different handling properties. For example, in the Group II samples where only the amounts of NVP used varied, an insufficient amount of the cross-linking agent resulted in a longer mixing time but shorter setting time. In the other extreme, excess N-vinyl-2-pyrrolidone added resulted in quicker agglomeration, but longer setting time. This was to be expected because there was more liquid available to coat the particles of polymer. The N-vinyl-2-pyrrolidone also acts as a plasticizer which would make the composition softer with increasing concentrations. In the Group I samples where only the amounts of BPO used varied, the trend was not as

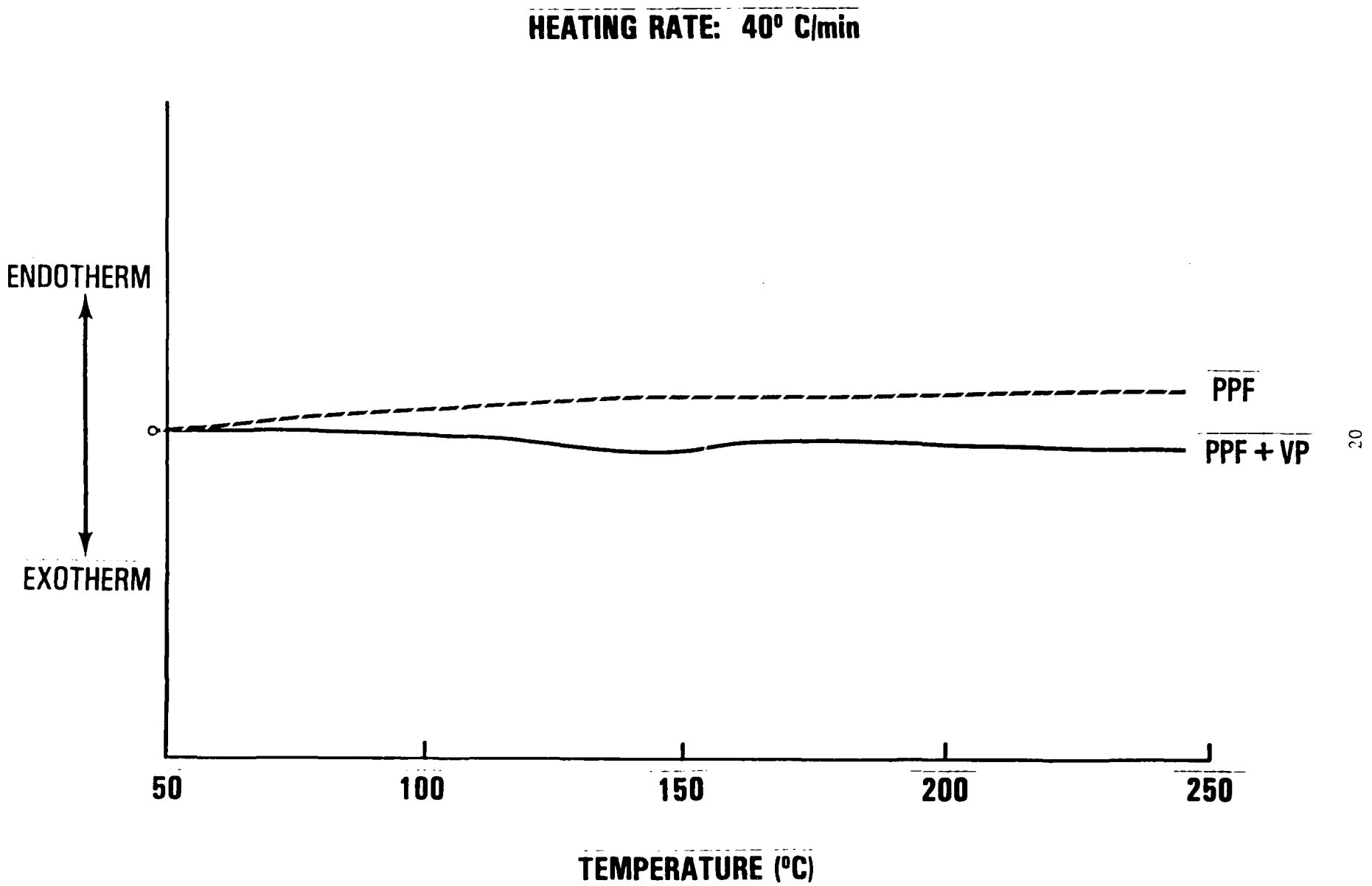

HEATING RATE: 40° C/min
ENDOTHERM
EXOTHERM
0
PPF
PPF + VP
50
100
150
200
250
TEMPERATURE (°C)

FIGURE 7

pronounced. In this group, there was little or no variation in the mixing and setting times. Therefore, it would appear that these two time-variables were more dependent on NVP concentrations. The Group III samples, where NVP to BPO ratio was kept constant but were varied in concentration relative to PPF, only reinforced the apparent dependency of the mixing and setting on NVP concentrations.

A comprehensive thermal analysis was performed on the formulations to determine the extent of cross-linking. Table 5 in the next page is a complete summary of the data obtained from DSC experiments. Although the actual curing of the thermoset was conducted at room temperature, data from the four different heat rates can be extrapolated to $0^{\circ}C\text{-}min^{-1}$ heat rate to determine whether curing could still occur at room temperature. In the Group I series, variation in the BPO concentrations has little effect on the three curing parameters (temperatures of initiation, peak, and completion) with the exception of the sample with no BPO. The absence of an initiator forces the mechanism of cross-linking to proceed through a different pathway because of the lack of initiator-generated free radicals. In the Group II series, increasing NVP amounts generally decreases all three curing parameters. In the Group III series, increasing amounts of NVP and BPO has little or no effect on the completion temperature of curing, whereas the peak and initiation temperatures of curing are lowest at 10% NVP and 1% BPO. In comparing the curing times of each sample at different heat rates (Figures 8-10), Group I samples seem to indicate that increased BPO concentrations are not desirable because it was accompanied by an increase in curing times. In the Group II samples, a minimum curing time was observed at 7.5% NVP. Therefore, this concentration of NVP would be the baseline from which the development of a moldable implant would begin. The plot of the cure times of the Group II samples appears to be

TABLE 5. Curing Characteristics of PPF:NVP at Various Scan Rates

Sample Number	Heating Rate (°C/min)	Initiation of Curing (°C)	Peak (°C)	Completion (°C)	Cure Range (°C)	Cure Time (sec)	Δ H (cal/g)
1	10	90	132	162	72	432	50.1
	20	97	143	170	73	219	43.8
	30	92	146	180	88	177	50.6
	40	100	150	188	88	132	40.9
2	10	90	136	164	74	444	22.2
	20	90	140	170	80	240	42.2
	30	93	144	180	87	177	41.4
	40	96	146	182	86	129	40.0
3	10	88	130	152	64	384	17.7
	20	95	136	167	72	216	25.9
	30	95	140	170	75	150	22.5
	40	100	144	178	78	117	29.3
4	10	80	127	153	73	438	31.5
	20	85	128	163	78	236	39.2
	30	88	134	170	82	165	42.9
	40	88	136	174	86	129	40.0
5	10	83	129	155	72	432	34.6
	20	87	135	165	78	232	32.5
	30	93	140	173	80	160	32.0
	40	96	142	180	84	126	31.5
6	10	86	127	154	68	408	24.5
	20	90	137	160	70	210	25.2
	30	95	140	172	77	156	26.5
	40	96	142	178	82	123	33.2
7	10	88	127	147	59	354	12.7
	20	90	132	159	69	210	13.9
	30	89	140	163	74	147	11.8
	40	100	142	172	72	98	20.4
8	10	90	110	130	40	240	3.8
	20	90	117	143	43	160	3.2
	30	114	140	158	44	88	2.1
	40	104	134	156	52	78	6.2
9	10	84	132	150	66	396	17.4
	20	88	140	160	72	216	18.6
	30	90	144	170	80	160	28.8
	40	110	148	180	70	90	11.0
10	10	88	130	152	64	372	28.3
	20	92	134	164	72	216	33.7
	30	92	142	172	80	160	29.8
	40	100	146	178	78	107	27.8

FIGURE 8. CURING TIME OF GROUP I SAMPLES

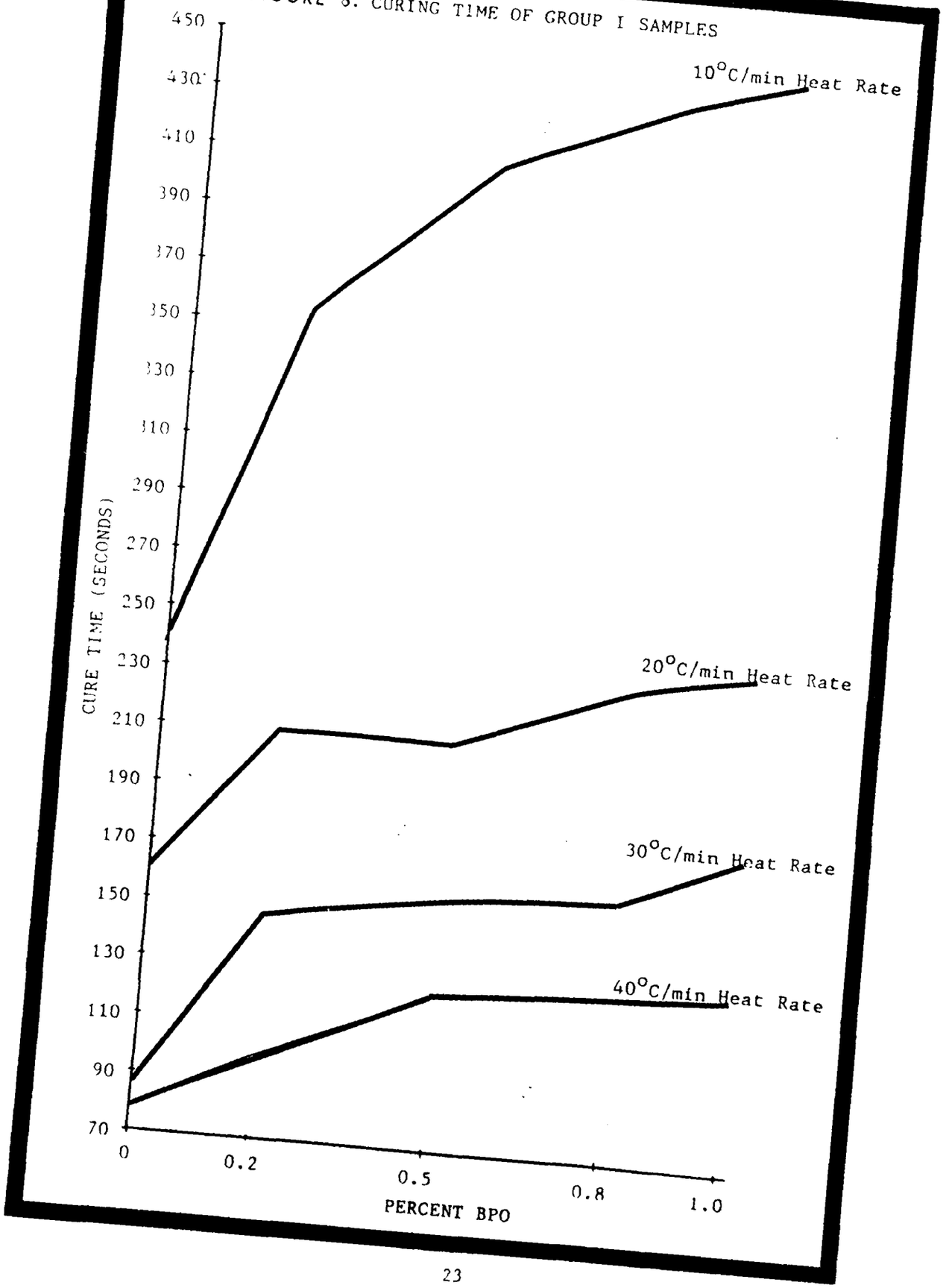


FIGURE 9. CURING TIME OF GROUP II SAMPLES

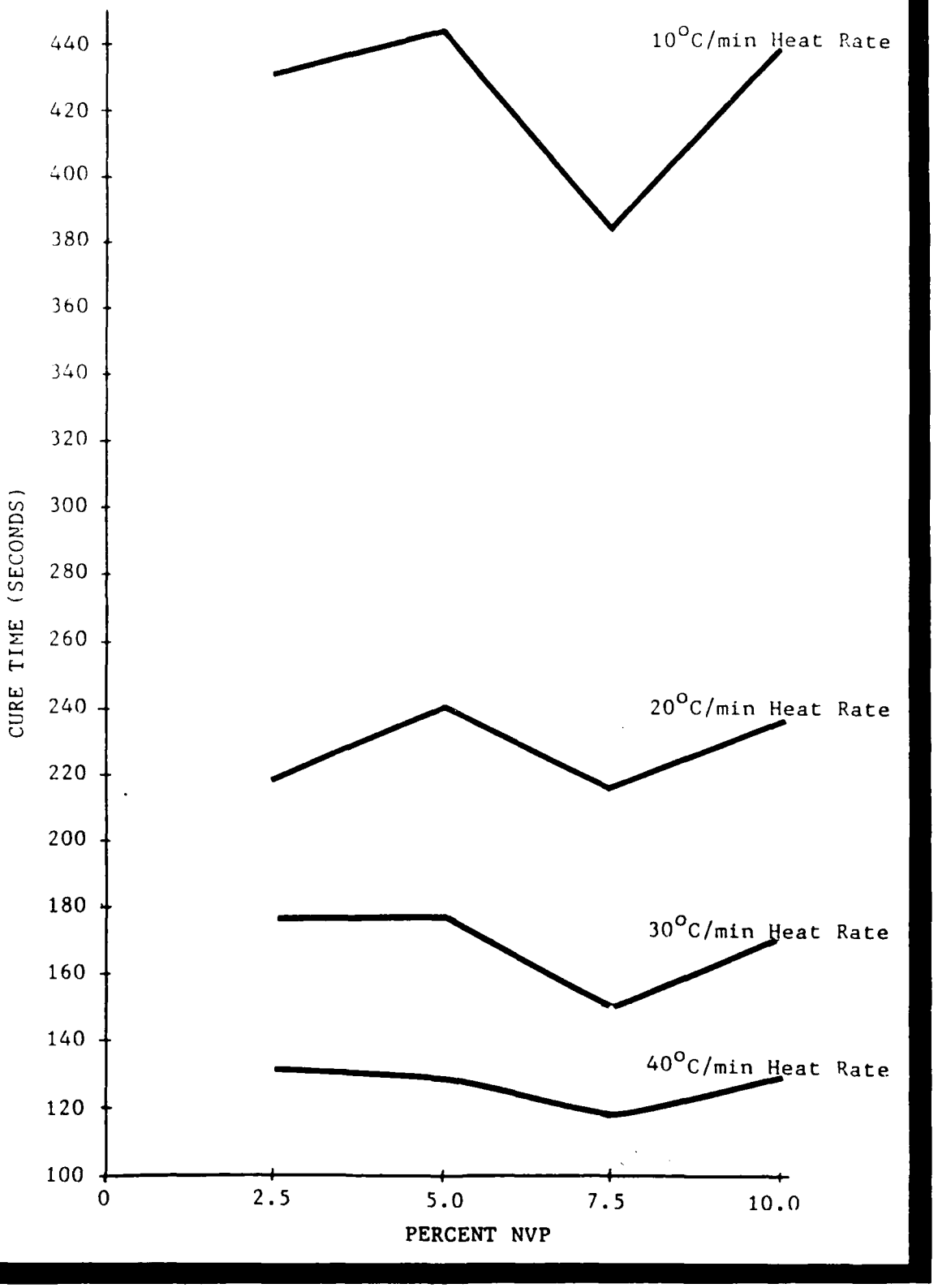
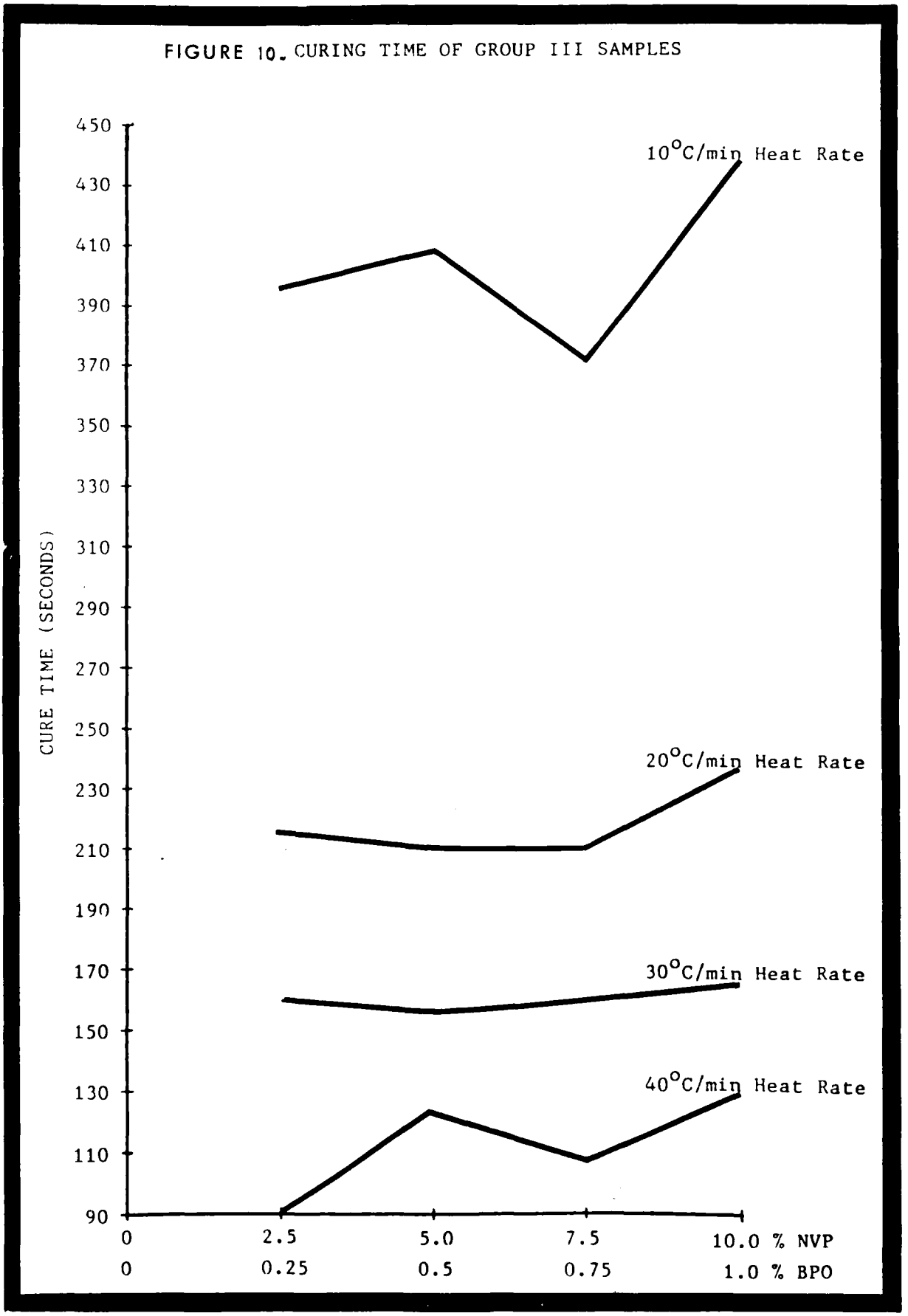


FIGURE 10. CURING TIME OF GROUP III SAMPLES



a hybrid of the Groups I and II cure time plots, but it is more characteristic of the Group II plot, which again indicates a greater dependence on NVP concentrations. The cure ranges plots (Figure 11) parallels the cure time plots since these two parameters are interrelated. In choosing the most desirable concentrations of NVP and BPO, one must consider the thermodynamics of the cross-linking reaction. The concentration of the initiator and cross-linking agent must be at a level such that the heat of curing is maximized (requires least energy). By plotting the heats of curing (Figure 12) of the three groups and locating a region where their heats of curing are maximized with regard to each other, it would appear that the most desirable concentrations for NVP and BPO are 5 to 10% and 0.6 to 1.0%, repectively.

In the in vitro degradation experiments, the degradation data as summarized in Figures 2-4 (Pages 10-12) on the three groups indicate that thermoset does not have a constant degradation rate. With the exception of Sample 8 in Group I, which was absent of BPO, all the samples undergo periods of weight gain and weight loss. The swelling behaviour is evidence of a cross-linked system, but its absence in Sample 8 does not necessarily mean the absence of cross-linking. When comparing samples with Group I, it should be noted that only Sample 2, which had the greatest amount of BPO (1%), gained weight during the first day. This observation supports the use of BPO in less than 1% concentrations. It would appear that the concentration of NVP should not be above 5% because all the samples in Group II above this concentration exhibited wieght gains during the first day. However, Sample 10 in Group III, which had 7.5% NVP and 0.75% BPO, showed neglible (<0.2%) weight increase on the first day, which is misleading because it would subsequently gain weight until its weight has increased by 13%. Since some of the samples would break apart into several pieces, it is difficult to measure the dimensions of a degrading sample, and thus, weighing became the obvious alternative. It

FIGURE 11. CURE RANGE AT VARYING HEAT RATES

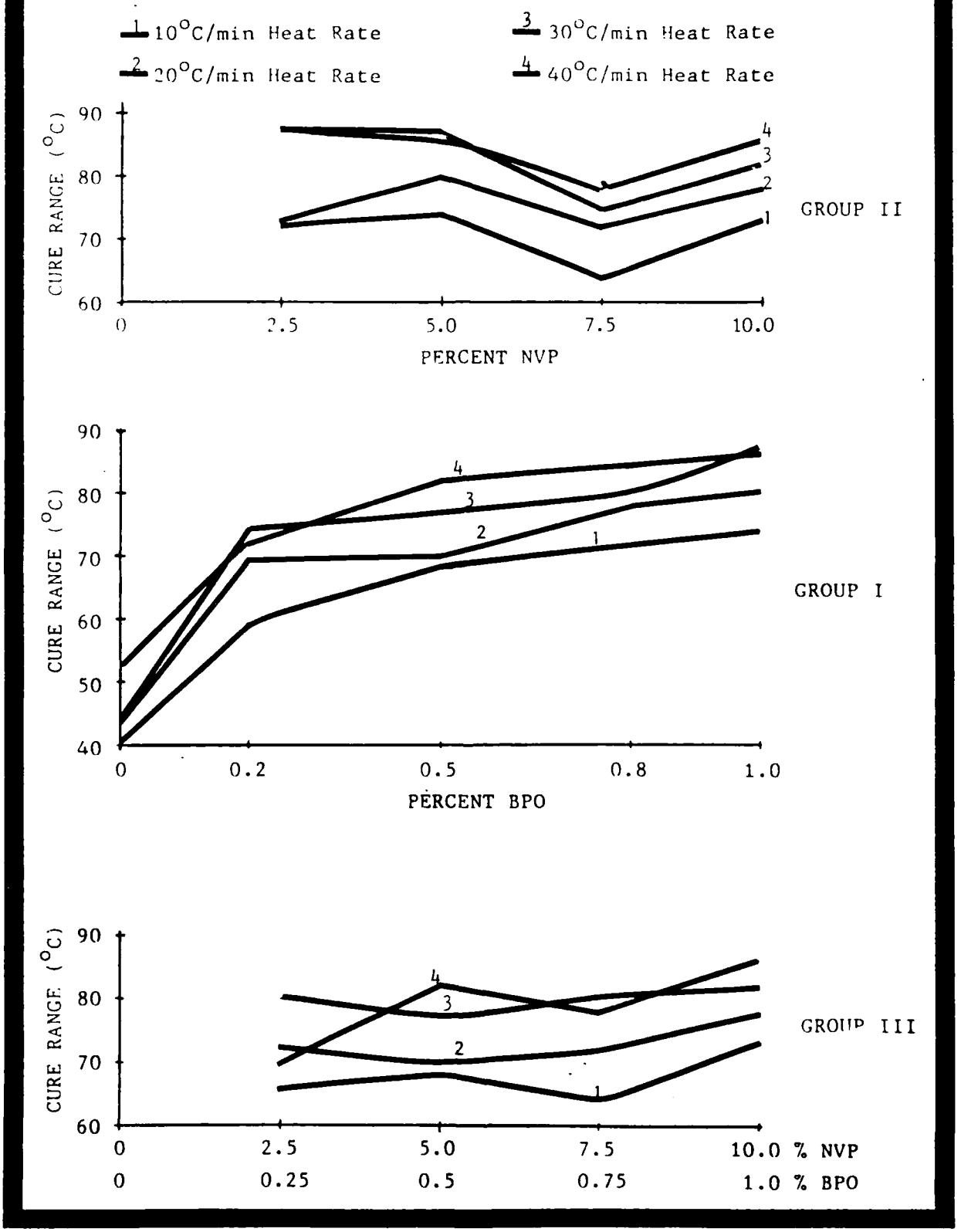
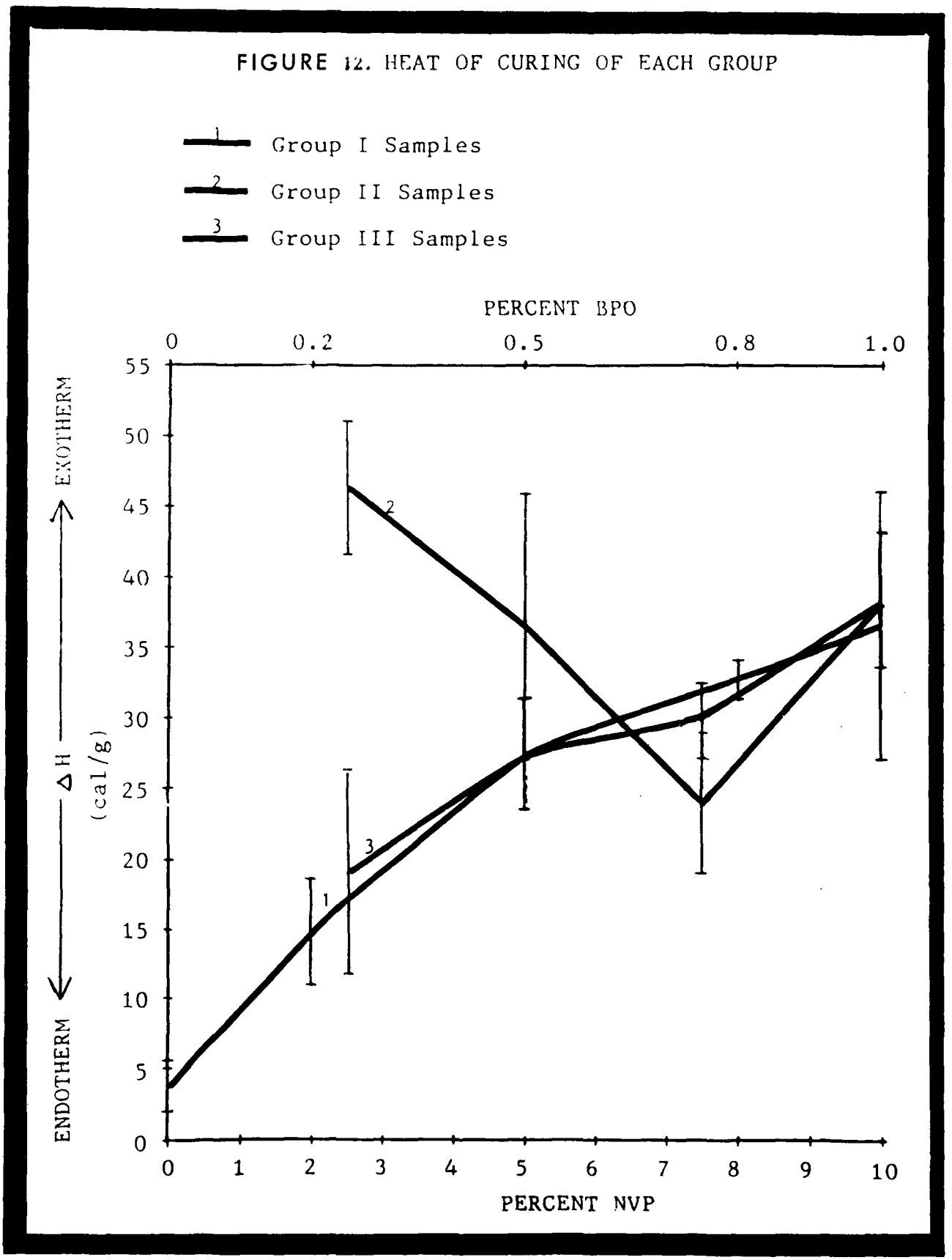


FIGURE 12. HEAT OF CURING OF EACH GROUP



appears that as a sample swelled, its density decreased as evidenced by its more buoyant tendency. Therefore, an increase in weight coupled by a decrease in density translates to a greater increase in volume relative to that of the weight. Thus, the moldable implant must be formulated such that the degradation rate would negate volume increases due to swelling. With this consideration, none of the formulations are ideal because of either too rapid or fluctuations in their degradation rate.

CONCLUSIONS

PPF appears to be a good candidate for developing biodegradable, moldable implant. The polymer synthetic procedure is reproducible and efficient. Although the procedure is only for producing PPF at a low molecular weight, polymer engineering becomes a more important aspect in the development of the moldable implant because adjusting formulations is more facile than changing reaction conditions. By adjusting the cross-linking agent, initiator, and polymer ratio, one can tailor the properties of the composite. For example, increasing the initiator concentration, relative to the other components, would increase the cross-link density and decrease the distance between cross-linked chains. This would affect the amount of water that the mixture can absorb, and thus, its degradation rate. Furthermore, the higher cross-link density translates to a higher number of fumarate residues that have become saturated at their carbon-carbon double bond. As a result of this saturation, the adjacent ester linkages become deactivated towards hydrolysis. On the other hand where the amount of cross-linking agent is increased, the result is an increase in the cross-link distance between the bonded polymer chains. This allows the composite to swell to a larger extent in an aqueous environment. Thus, in the development of the moldable implant, fine tuning the balance of the components to achieve the desirable property is a more advanta-

geous route because of its simplicity, instead of adjusting reaction conditions to achieve the same effect. The *in vivo* experiments done to date did not have a favorable outcome. The degradation rate of the PPF mixture was too slow and apparently after a length of time the material begins to crumble. This may be related to fluid imbibition which seems to cause swelling of the polymer with concomitant disintegration. The tendecy to crumble was particularly noticeable in mixtures of PPF with DBM. The inclusion of DBM in the polymer appears to be conducive to bone ingrowth into the implants, but the control defects which remained untreated healed far better than the experimental defects. There does not appear to be any significant advantage to using the PPF to fill defects that would heal if left untreated. However, in the case of non-healing defects the PPF may have an application . It is obvious from the *in vivo* work that the degradation rate of PPF with or without added DBM must be improved. While PPF shows potential for the applications we have intended, it has not yet been configured into an acceptable formulation.

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