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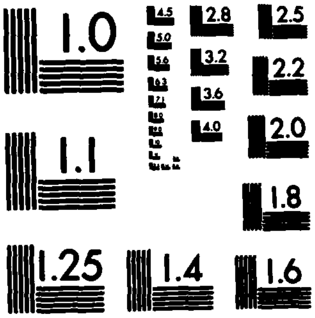

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Development of Repair Materials for Avulsive Combat-Type Maxillofacial Injuries

Annual and Final Report

D. L. Wise
R. L. Wentworth
J. E. Sanderson
S. C. Crooker

August 1982

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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Dynatech R/D Company
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The objectives for the project to develop a repair material for avulsive combat-type maxillofacial injuries have been achieved. A composition containing poly-(propylene fumarate), an unsaturated crosslinkable polymer made from fumaric acid, one of the Krebs Cycle acids, and propylene glycol, a commonly used diluent in parenteral drug formulations, along with benzoyl peroxide, vinyl pyrollidone, and an inert filler such as calcium sulfate (gypsum) has been shown to be easily workable by hand, to solidify in 15 minutes at physiological temperatures, and to have physical properties

suitable for the intended application. An additional component which may be required to provide adequate shelf-life is a food grade anti-oxidant such as Tenox (TBHQ). The results obtained with this composition to date suggest that this material is ready for in vivo evaluation in a suitable animal model.

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Section 1

SUMMARY

The objectives for the project to develop a repair material for avulsive combat-type maxillofacial injuries have been achieved. A composition containing poly-(propylene fumarate), an unsaturated crosslinkable polymer made from fumaric acid, one of the Krebs Cycle acids, and propylene glycol, a commonly used diluent in parenteral drug formulations, along with benzoyl peroxide, vinyl pyrollidone, and an inert filler such as calcium sulfate (gypsum) has been shown to be easily workable by hand, to solidify in ~15 minutes at physiological temperatures, and to have physical properties suitable for the intended application. An additional component which may be required to provide adequate shelf-life is a food grade antioxidant such as Tenox (TBHQ). The results obtained with this composition to date suggest that this material is ready for in vivo evaluation in a suitable animal model.

Section 2

INTRODUCTION

The potential of polymeric materials for surgical repair has been appreciated by surgeons, dentists, and medical researchers, and promising development has been reported. Some of the aims of work to date have been attainment of biodegradability, flexibility of formulation for tailoring at the surgical site, and achievement of ultimately acceptable esthetic results. The need for such materials is especially acute in the treatment of avulsive maxillofacial wounds in military situations. In these applications, there are encountered not only the exacting surgical demands of maxillofacial wound treatment but the special logistical demands of military utilization. Thus the state of development of surgical repair materials to date, while promising, has not yet been brought to a satisfactory stage.

The work under contract no. DAMD 17-80-C-0186, was based on the use of biocompatible, biodegradable polymers synthesized from substances occurring in the so-called Krebs cycle of metabolism. Chemical qualities of these polymers include the possibility of formulating them in a molecular weight range well-suited for preparing pastes or moldable putties. In addition, certain members of this class of polymers possess unsaturation, or potential for controlled crosslinking. Under proper control this crosslinking characteristic may be exploited to convert a formable mass to a rigid structure having good physical properties, but retaining the quality of biodegradability. Previous work to apply these materials to the sustained release of drugs has experimentally confirmed their biodegradability as well as revealing the preparative procedures required to provide the desired surgical repair materials. Separation of the desired fraction may be carried out by fractional precipitation. For example, a solution of polymer in methylene chloride blended with ethyl ether will yield a precipitate of high molecular weight polymer. The remaining low molecular weight material may also be recovered for use.

In the application of poly(propylene fumarate) as a biodegradable matrix for the sustained delivery of drugs, experience had previously been gained in the rate of dissolution through hydrolysis of these materials. This hydrolysis of the polyester structure has been studied in vitro through exposure of sample formulations to pH 7 buffer at 37°C. In an experiment which may be cited as an example, 1/16 inch diameter spheres of poly(propylene fumarate) of molecular weight 34,000 required exposure in vitro for 180 days to reach complete dissolution. Analysis of the data obtained in these experiments indicated that the hydrolysis proceeded at the surface of the particles rather than within the particles. Other dissolution tests, performed with particles of different dimensions, confirmed this picture of the mode of hydrolysis.

Another component, the utility of which was not appreciated initially, is a reactive monomer. The purpose of including such a component is to provide the mobility necessary to facilitate cross-linking of the polymer chains.

The chemistry of the system proposed for development includes provision for converting the plastic material applied to the wound to a solid form. The conversion is carried out by initiating chemical cross-linking between the polyester molecules in the formulation. This crosslinking is possible due to the presence in these polyesters of vinyl unsaturation in the fumarate portion of the molecule. Addition to the mixture of a free radical generator, such as a peroxide, leads to the desired crosslinking. Only a modest degree of cross-linking is desired--just sufficient to convert the mass from a plastic mass to a solid. The crosslinking must not be so extensive and thorough that the resulting solid becomes non-biodegradable.

The action desired is very much like that obtained in the preparation and use of bone cements, for example, those used to bond artificial hip joints to the femur. One such bone cement is prepared by mixing methyl methacrylate with benzoyl peroxide to form a reactive paste. Within a few minutes the free radicals generated by the peroxide cause crosslinking of the unsaturated chemical bonds in the methyl methacrylate molecules and a solid mass results. Benzoyl peroxide is a prime candidate for investigation as a crosslinking agent in the proposed surgical repair composition. It was anticipated that benzoyl peroxide, a material already approved in medical applications, will perform adequately. However, other substances are available for use if benzoyl peroxide proved inadequate.

In summary, the desired composition contains four components:

1. a polymeric binder having chemical unsaturation susceptible to crosslinking;

2. a reactive monomer capable of facilitating cross-linking of the polymeric binder;

3. a filler material which will convert the material to a workable paste or putty suitable for emplacement by the surgeon; and

3. a reagent capable of initiating crosslinking to the extent needed to convert the putty to a solid.

These components must, of course, combine to produce a material having the biocompatibility and biodegradation qualitities desired. It must adhere to bone and exhibit adequate physical strength.

The foregoing discussion has presented the technical basis for creating the necessary polymeric binder and filler. The program is concerned with the composition of the paste or putty to be formed from the four classes of ingredients. It will be appreciated that if the liquid components are blended with the powdered ingredients, a certain minimum proportion of liquid must be added to the powder before a coherent mixture is obtained. If the proportion of fluid is then increased, the mass will take on plastic qualities, and it will exhibit a yield value, that is, it will require some minimum force to deform it. Still further addition of fluid will render the mixture more plastic and the yield value will decrease. A proportion of fluid finally will be reached at which the mass has no yield value. Such a mixture now may flow in the undisturbed state. The range of proportions of liquid and solid between establishment of coherence and loss of yield value is the plastic range of such mixtures. Within this range, useful workability will be found. However, within the plastic range there may exist compositions which will lose cohesion if deformed excessively or if deformed at an excessive distortion rate. Other compositions in the plastic range may possess little mechanical strength. Another quality of such mixtures that will vary as the proportion of liquid is varied, is the wetting of surfaces to which the mixtures are applied. Either the extent of wetting or the rate of wetting may change as the composition in the plastic range is changed. This property is of concern with respect to developing adhesion between bone and a surgical repair material.

In formulating to obtain a plasticity which will be totally satisfactory to surgeons using the proposed repair material the principal variables of concern are the size, shape, and proportion of the particles of filler and crosslinking agent added to the liquid carrier material. Experience indicates that the finer the particle and the more asymmetric the particle shape the more profound its influence on developing and changing plastic flow in mixtures with fluids. Thus, it may be necessary to have large proportions of large, spherical particles in order to obtain a plastic mixture. The effect on plasticity of changes in the proportions of such particles may be small. In contrast, low volumetric concentrations of fine, asymmetric particles may affect plasticity profoundly. Needle-shaped, platy particles, or agglomerations of spherical particles, for example, are effective in developing plasticity of mixtures with fluids. Clearly, the formulation of a surgical repair composition of satisfactory handling and application qualities requires tailoring of the properties of the filler particles.

Section 3

MATERIALS AND METHODS

3.1 Materials

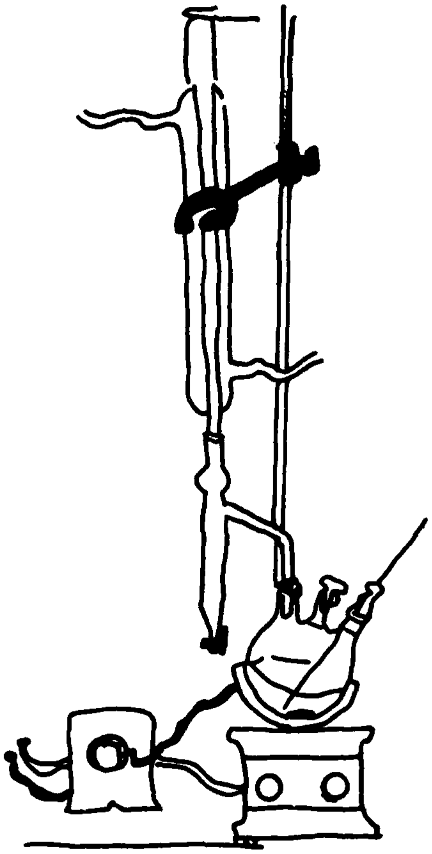
Reagents used in the synthesis of poly(propylene fumarate) were readily obtained from commercial laboratory suppliers. Diethyl fumarate (Kodak 1430), propylene glycol (Fisher P-354) and p-toluenesulfonic acid (Fisher A-320) were all successfully used as delivered without futher purification. Initiators used in crosslinking studies, solid benzoyl peroxide (Alfa 13633) and liquids such as t-butyl hydroperoxide, methyl ethyl ketone peroxide, di-t-butyl peroxide, and t-butyl perbenzoate (all from Lucidol) were available for immediate use. Accelerators, also referred to as promoters, for the crosslinking initiators such as N,N-dimethyl aniline (Fisher A-746), NN-dimethyl-p-toluidine (Eastman 646), and Cobalt Naphthenate (Pfaltz and Bauer C23710) were employed to help speed the crosslinking reaction. Polylactic acid and high molecular weight poly(propylene fumarate) were synthesized at Dynatech to be used as organic fillers. Inorganic fillers such as calcium carbonate (Fisher C-62) sodium bicarbonate (Fisher S-233) and calcium sulfate (Mallinckrodt 4300) were employed to be easily leached from the crosslinked mixtures. Acetone and methylene chloride, used as solvents for PPF and anhydrous ether used for precipitation of high molecular weight-PPF were likewise readily available from laboratory suppliers. N-vinyl-2-pyrrolidinone was obtained from Aldrich Chemical and was normally used without purification. Tertiary butyl hydroquinone (Tenox TBHQ) used as an antioxidant was obtained from Eastman Chemicals.

3.2 Methods

Low molecular weight poly(propylene fumarate) was synthesized in a one liter flask fitted with a reflux condenser and a Barrett Trap. See Figure 3-1. As the ethanol is distilled and removed, it was collected from the receiver of the Barret Trap as a means of measuring completion of the reaction.

Figure 3.1

Apparatus for Synthesizing Low Molecular Weight Polyesters



The apparatus used for synthesis of high molecular weight poly(propylene fumarate) was similar to that in Figure 3.1 with the exception that instead of a Barret Trap and reflux condenser, the flask is fitted with a 25 cm. Vigreaux distillation column and standard distilling head fitted with a drip tip collection adapter. The reaction is allowed to proceed until no more distillate is collected at the reaction temperature of 250°C. At this point, approximately 175 ml of distillate will have been removed from a 2 mole reaction (i.e. diethyl fumarate, 344 g, propylene glycol, 152g, p-tolunesulfonic acid, 1g). The reaction mixture is then cooled to < 100°C, the Vigreaux column is removed, and a vacuum pump is attached to the system. The reaction mixture is then reheated to 220°C under full vacuum ~1mm Hg) over a period of about four hours. At this time an additional 75 ml of distillate will have been collected. The reaction mixture is then cooled, dissolved in methylene chloride, and fractionally precipitated with ether in a separating funnel. The lower layer is washed with additional ether and dried under vacuum at room temperature to give a white to yellow powder melting at 80°C.

Crosslinking studies on unfilled PPF using liquid initiators are performed by weighing the desired amount of LMW-PPF, after warming in a water bath, into either nickel or stainless steel 50 ml crucibles. The crucibles are placed on a hot plate and the PPF gently warmed until easily stirred. At this point the appropriate amount of promoter is added to the PPF and thoroughly mixed. The initiator is then added while the mixture is still warm and also thoroughly mixed. This warm mixture is then put into a small test tube for use in 37°C oil shaker bath or in an aluminum foil weighing dish before placing the sample in a laboratory oven for elevated temperature studies.

Crosslinking studies are made in much the same manner for filled PPF samples. The PPF is added to the crucible, warmed and mixed with the promoter. Then the filler is gradually added and mixed thoroughly. When no more filler can be added because the mixture was too "stiff" to stir, the material is removed from crucible to a Petrie dish containing the remainder of the filler. The material is then kneaded by hand like bread dough to mix the remaining filler. The resulting ball of material is then weighed into portions needed for crosslinking studies. The appropriate amount of liquid initiator is added to the surface of the portion being crosslinked. The material is then worked by hand to mix the initiator with the sample thoroughly. The sample is then put into a test tube or an aluminum foil weighing dish prior to being crosslinked.

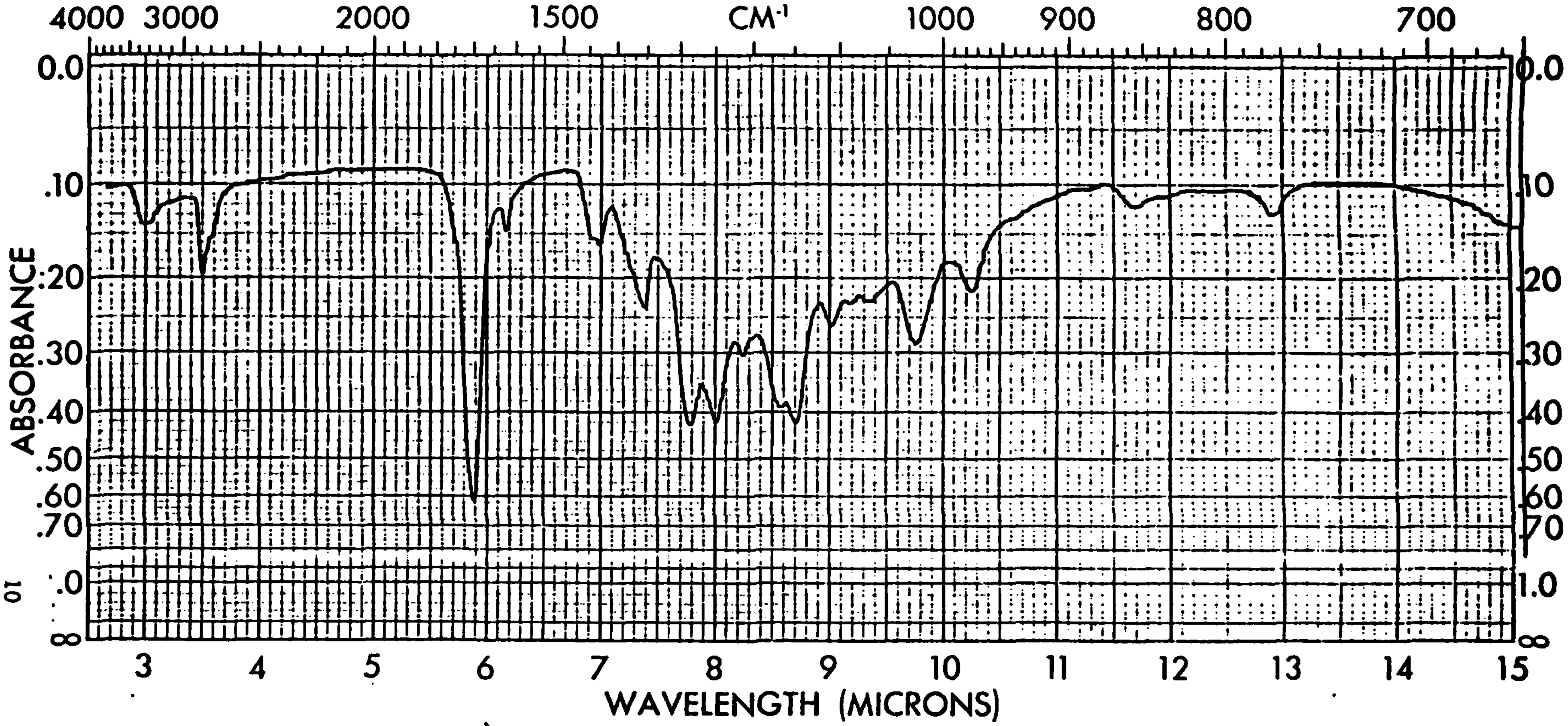
Formulas containing only solid poly(propylene fumarate) may be mixed either of two ways. First, the PPF can be dissolved in the monomer component to form a plastic mass which is then filled by the kneading technique described earlier. Alternatively, the monomer component may be adsorbed on the filler prior to blending with the PPF. This method gives a dry powder precursor which does not form a plastic mass until the initiator monomer solution is added.

Cross-linking studies on these materials were carried out by packing the material in a large polyethylene pipet tip, usually with the assistance of vacuum. The pipet tip is then put into a test tube which is suspended in an oil bath at 37°C. Once cross-linked the pipet tip is split and the rigid sample is removed. The resulting cylinder is cut into discs with a hacksaw and then polished with emery cloth to remove sawmarks and to facilitate examination for uniformity.

Once synthesized, the poly(propylene fumarate) is characterized in several ways. Infrared spectra are obtained by running the liquid polymer on NaCl cells. Figure 3.2 shows a typical IR spectrum of LMW-PPF. Once the PPF is crosslinked, spectra are taken to compare relative intensity of the peak at ~ 1600 cm^{-1} (due to fumarate double bond) to that of the relative intensity of the same peak for the non-crosslinked material. In most cases, the peak of crosslinked material is not significantly less intense than that of non-crosslinked PPF. This indicates that the degree of crosslinking is low and probably not sufficient to destroy the inherent biodegradability of the polymer.

Figure 3-2

IR Spectrum of Poly (Propylene Fumarate) #012407-1



SPECTRUM NO. 012433-2

SAMPLE – PPF is straight from jar no crosslink attempt made -

ORIGIN

PURITY

PHASE

THICKNESS

LEGEND

1.

2.

DATE 3/31/81.

OPERATOR SCC

REMARKS PPF from 012407-1 run neat on NaCl cells

SPECTRUM NO.

SAMPLE

Another method of characterization that was performed is viscometry. These measurements are made at 24°C using a Brookfield LVF viscometer equipped with a #4 spindle at 0.3 RPM. Viscosity of low molecular weight PPF is an important parameter to monitor because of the importance of the handling properties of the final composition.

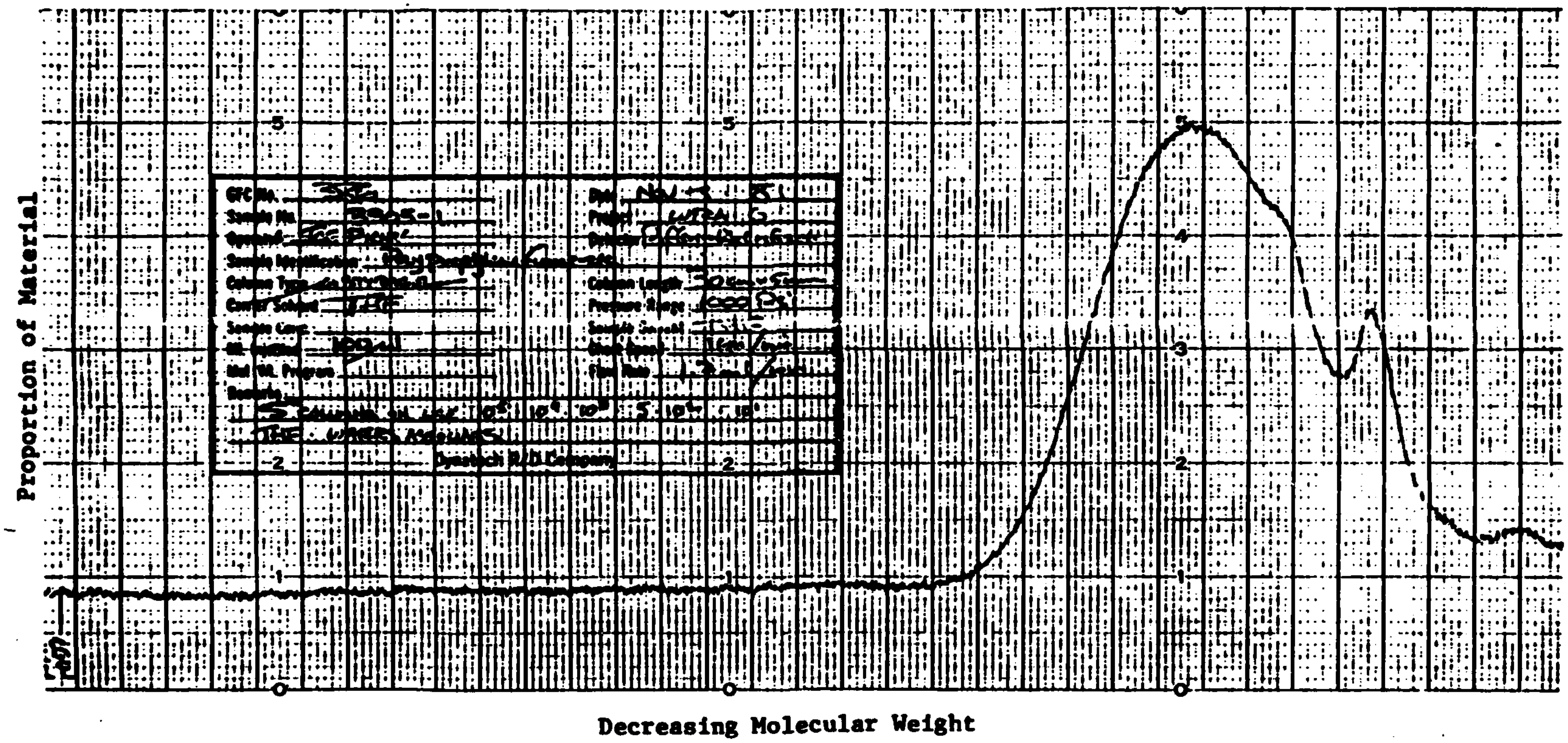
Several attempts have been made to determine the number average molecular weight, Mn, for PPF by endgroup titration. Samples were dissolved in excess 1.0 N NaOH overnight and then back titrated with 1.0 N HCl solution to determine the apparent equivalent weight. None of these attempts gave satisfactory results. A more reliable determination of molecular weight was obtained by Gel Permeation Chromatography using Waters μ Styrogel Columns. Figure 3.3 shows a typical chromatogram.

Another method to determine whether a crosslinked sample is sufficiently crosslinked to prevent biodegradation, is to place a sample in a one liter flask with 250 ml of 1N NaOH solution. The flask is fitted with a reflux condenser and heating mantle. Dissolution, as soon as heating is begun, suggests that the sample will be ultimately biodegradable at neutral pH and body temperatures.

In vitro leaching tests are made to determine biodegradability and rate of leaching of filler. Weighed samples are placed in stoppered 250 ml Erlenmeyer flasks along with 200 ml of leaching solution, i.e., pH = 7 buffer, or pH = 1 buffer or in some cases distilled water. Recently 1.5 mm beads have been molded in a transfer mold and crosslinked at 37°C. Five of these beads are then placed in a 10 x 50 mm Whitman cellulose extraction thimble and suspended in 50 ml of distilled water in test tubes. The test tubes are then placed in a 37°C shaker bath. The distilled water is checked regularly for pH and is changed when deviations from neutrality are observed or when a substantial precipitate is found with barium chloride.

Figure 3-3

Gel Permeation Chromatogram of PPF 013505-1



Section 4

RESULTS AND DISCUSSION

4.1 Polymer Synthesis

Poly(propylene fumarate) is synthesized from diethyl fumarate and propylene glycol by transesterification using p-toluenesulfonic acid as a catalyst. Several runs have been made to produce a low molecular weight polymer for use as the fluid component of the composition. These materials were prepared initially by suspension polymerization in silicone oil, but better results have been obtained by bulk polymerization. Suitable material is produced for this application by removing 105 ml of distillate from a one mole (172g diethyl fumarate, 76g propylene glycol, 0.5g PTSA) reaction. This product has a viscosity of $\sim 1 \times 10^6$ cps when measured at 24°C using a Brockfield LV #4 spindle at 0.3 RPM.

The distillate is not all ethanol when collected in this manner. Infrared analysis indicates that the distillate, which comes over at 140°C contains approximately 10 percent diethyl fumarate. This analysis is consistent with an estimate of the composition based on the vapor pressures of ethanol and diethyl fumarate at 140° C.* Properties of several batches of low molecular weight PPF are shown in Table 4.1.

Loss of diethyl fumarate in the synthesis of low molecular weight poly(propylene fumarate) is not a serious problem, but it is where high molecular weight polymer is the goal. In order to synthesize solid, high molecular weight PPF for use as a filler in the composition, a distillation column is employed. When this is done, the distillate comes over at 78°C, indicating that it is nearly pure ethanol. Distillation is continued in this manner until the pot temperature reaches 250°C, about

---

* Perry, R. H. and Chilton, C. H. 1973. Chemical Engineers Handbook, 5th ed., McGraw Hill: New York. p. 3-49.

Table 4-1

SUMMARY OF REACTION CONDITIONS AND PRODUCTS FOR LMW-POLY(PROPYLENE FUMARATE)

Run #	Type	Reaction Time	Maximum Temperature	Diethyl Fumarate	Propylene Glycol	Remarks
07778-1	Silicone Oil Suspension	53 hrs.	170-180°C	0.8	0.8	Opaque orange-yellow containing both viscous liquid and gel.
011366	S.O.S.	61 hrs.	180°C	0.8	0.8	Orange-yellow, viscous tacky liquid. $\overline{M}_n \cong 550$ by end group titration.
012407-1	S.O.S.	80 hrs.	170°C	0.8	0.8	Orange-yellow opaque liquid.
012432-1	Neat	39 hrs.	245°C	0.8	0.8	A red, clear liquid, extremely tacky and very viscous.
012437-1	Neat	8.5 hrs.	210°C	0.6	0.9	Light-yellow, clear liquid, least viscous of all runs
012709-1	Neat	19 hrs.	239°C	0.76	0.76	Reddish-amber, clear liquid, not quite as viscous as Run #012432-1.
013505-1	Neat	14 hrs.	245°C	1.0	1.0	Reddish-amber, clear liquid

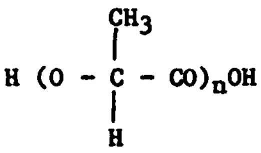
five hours. Then the column is removed and the remaining volatile components of the reaction mixture are stripped off under vacuum. After cooling, the resultant solid mixture was dissolved in methylene chloride and precipitated in diethyl ether. The precipitate was then dried under vacumm at room temperature for 48 hours. Giving a yellow, free flowing powder which melted at about 75°C. The yield of final product is about 35 percent. The low molecular weight material remaining in solution may be isolated by evaporation and revacuum distilled to produce additional high molecular weight product.

4.2 Filler Selection

Initial crosslinking studies on filled samples of PPF were run using polylactic acid as a filler. These experiments were unsuccessful, presumably because polylactic acid contains a hydrogen atom which should be readily extractable by a free radical.

Figure 4-1

Polylactic Acid



$$H\ (O - \overset{\displaystyle CH_3}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}} - CO)_nOH$$

Subsequently, as a result of the need for rapidly developing porosity in the material to facilitate intrusion of new tissue being pointed out by the contracting agency, inorganic fillers have been investigated. PPF loaded with up to 40 percent by weight of calcium carbonate has been crosslinked successfully to produce rigid materials. This appears to be the maximum level of $CaCO_3$ that can easily be worked by hand at room temperature. However, because of the density difference between calcium carbonate and PPF, the calcium carbonate represents less than 20 percent of the composition by volume. In a final formulation, the filler should represent a higher volume percent of the composition to give the handling properties required for this application. Higher filler loadings were obtained by warming the polymer to ~ 80°C before mixing in the filler. At the same time, sodium carbonate and sodium bicarbonate were used to increase the leaching rate of the inorganic filler. Warm blending followed by hand kneading was successful in increasing the loading level to 70 percent by weight or slightly over 50 percent by volume. This material even after a liquid initiator and accelerator were blended in had suitable handling properties for maxillofacial reconstruction.

As the leaching results to be presented later will indicate, these fillers were leached too rapidly. The next inorganic filler to be tried was calcium sulfate. Filling of low molecular weight PPF with calcium sulfate at the same weight percentage as before also gave a putty with handling properties suitable for maxillofacial reconstruction and when crosslinked gave a material remarkably bonelike in appearance.

High molecular weight PPF has been investigated as a filler for low molecular weight PPF. Remarkably, this material gives a composition with suitable handling properties at a loading of about 30 percent. This composition has other interesting properties, to be discussed later, which suggested that the ultimate composition would contain high molecular weight PPF along with one of the more rapidly leached inorganic fillers.

4.3 Crosslinking Studies

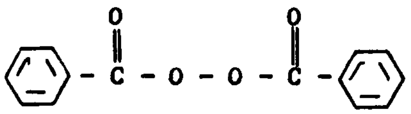
In these studies, methyl methacrylate has been used as a control. Crosslinking studies are normally carried out in 16 x 150 mm test tubes in a 37°C bath. Under these conditions, methyl methacrylate containing 3.0 percent benzoyl peroxide and 0.5 percent NN-Dimethyl aniline accelerator, polymerized in approximately 60 minutes. Poly(propylene fumarate), when the benzoyl peroxide is predissolved in a small amount of a mutual solvent, methylene chloride or acetone, crosslinks somewhat faster than the methyl methacrylate under the same conditions. Unfortunately, filled samples prepared in this way produce only a rubbery material, possibly as a result of plasticization by the solvent. Attempts to remove the solvent after mixing but before crosslinking gave no significant improvement.

In order to overcome the apparent difficulties associated with the need to predissolve benzoyl peroxide, other initiators, particularly liquid initiators were being investigated. The first of these to be investigated was t-butyl hydroperoxide (Lucidol HEPV251). Although t-butyl hydroperoxide is one of the more thermally-stable peroxide initiators, its use obviated many of the difficulties observed with benzoyl peroxide. When crosslinked at 210°C for one hour, a material of sufficient strength and rigidity for use in this application was obtained. Similar results were obtained at 150°C for one hour. This was the first crosslinked material produced in this program that approaches the physical requirements for maxillofacial reconstruction.

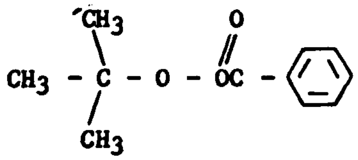
In order to combine the rapid polymerization properties of benzoyl peroxide with compatability advantages of t-butyl hydroperoxide, the primary initiator candidate then became t-butyl perbenzoate (Lucidol). As can be seen from the structures in Figure 4-2, t-butyl perbenzoate is a hybrid of the two previous initiators.

Figure 4-2

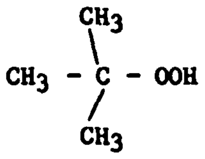
Free Radical Initiators



Benzoyl Peroxide



t-butyl perbenzoate



t-butyl hydroperoxide

Initial attempts at crosslinking both filled and unfilled samples of PPF using t-butyl perbenzoate as an initiator and NN-dimethyl aniline or NN-dimethyl-p-toluidine as promoters were not particularly successful. However, when cobalt napthenate was used as the promoter, or if you will, accelerator, results were markedly improved. At a promoter concentration of 1.0 percent wt. (of total PPF content) and t-butyl perbenzoate at 2 percent, unfilled samples of PPF crosslinked into a hard, rubbery solid in 20 minutes at ~ 110°C and the same result occurred at 37°C in less than 22 hrs. Using the same conditions as above, hard, brittle samples were obtained at 110°C when the PPF had been filled with inorganic fillers such as $NaHCO_3$ or $CaSO_4$. However, due to handling problems, it was impossible to run these filled samples at 37°C. Similarly, PPF filled with powdered high molecular weight PPF crosslinked into a hard sample, looking like peanut brittle when crosslinked at 110°C for 20 minutes. When the above reactions were tried at 75°C, the samples obtained were hard and brittle only after being in the oven overnight.

Subsequently an extensive study was performed to develop a formulation based on t-butyl perbenzoate that would crosslink rapidly at 37°C. The results of many of these experiments are shown in Table 4.2. Based on these experiments it was concluded that the crosslinking times were 0-1 hr. at 110°C, 2-5 hrs. at 60°C, and 12-24 hrs. at 37°C, and that the crosslinking times were relatively independent of the actual initiator formulation used.

Since some of the initiator compositions used, particularly those based on methyl ethyl ketone peroxide (Lucidol DDM-9), should have given almost explosive crosslinking rates it became apparent that initiation was not the rate limiting step. It appeared likely that free radical propagation may be rate limiting. In order to test this hypothesis new formulations were prepared based on the use of high molecular weight poly(propylene fumarate) in conjunction with an unsaturated monomer acting as solvent. The principle is that monomer can diffuse between the polymer chains to effect crosslinking, whereas diffusion was restricted at physiological temperatures in previous formulations employing low molecular weight polymer.

Table 4-2

CORSSLINKING OF POLY(PROPYLENE FUMARATE) WITH t-BUTYL PERBENZOATE

Sample No.	t-Butyl Perbenzoate Concentration	Promoter Concentration	Filler Concentration	Temperature	Reaction Time	Results
013510-3	3.5%	0.5% dimethylaniline	62%$NaHCO_3$	108°C	1 hr	Soft @ oven T. Hard & brittle RT.
013512-3	3.0%	1% DMA	none	107°C	1½ hr	Soft @ oven T. Hard & brittle RT.
013514-1	2%	0.5% cobalt naphthenate	none	108°C	1½ hr.	Rubbery @ oven T. Hard & brittle RT.
013516-2	3.5%	0.5% CoN	71%$NaHCO_3$	108°C	¼ hr 1 hr	Soft @ oven T. Hard @ oven T.
013518	3.5%	0.5% CoN	71%$NaHCO_3$	108°C	2 hr.	Hard @ oven T.
013522-1	1%	1% CoN	none	37°C	6 hr. 22 hr.	Soft Hard
013522-2	1%	1% CoN	none	114°C	2/3 hr.	Rubbery
013524-1	2%	1% CoN	none	37°C	18 hr.	Hard
013524-2	2%	1% CoN	none	37°C	6 hr. 18 hr.	Soft Rubbery
013526-1	2%	1% CoN	none	37°C	18 hr.	Hard
013526-2	2%	1% CoN	none	110°C	1/3 hr.	Rubbery

Table 4-2 (Continued)

Sample No.	t-Butyl Perbenzoate Concentrate	Promoter Concentration	Filler Concentration	Temperature	Reaction Time	Results
013528-1	2%	1% CoN	70% $NaHCO_3$	110°C	2/3 hr.	Hard, not brittle
013530-1	2%	1% CoN	70% $CaSO_4 \cdot 2H_2O$	110°C	½ hr.	Hard & brittle
013533-1	2%	1% CoN	70% $CaSO_4 \cdot 2H_2O$	75°C	2 hr. 52 hr.	Soft Rock hard
013541-1	2%	0.6% CoN	36% HMW PPF	22°C	24 hr.	No reaction
013541-2	2%	0.6% CoN	36% HMW PPF	108°C	1/3 hr.	Hard & brittle
013549-1	2%	3% CoN	28% $NaHCO_3$	58°C	2 hr.	Rubbery
013954-1	4%	3% CoN	62% $CaSO_4 \cdot 2H_2O$	60°C	5 hr.	Rubbery
013970-1	4% Old Sample	2% CoN	none	110°C	½ hr.	Hard & brittle
013970-2	4% New Sample	2% CoN	none	110°C	½ hr.	Hard & brittle
013974-1	2%	3% CoN	50% HMW PPF	108°C	½ hr.	Hard & brittle

Experiments to test this approach to putty formulation from high molecular weight poly(propylene fumarate) were carried out with the reactive monomers styrene, diethyl fumarate, and N-vinyl-2-pyrrolidone. Benzoyl peroxide is soluble in these substances. Compositions containing styrene and vinyl pyrrolidone were found to cross-link rapidly at physiological temperatures with benzoyl peroxide, the vinyl pyrrolidone without the use of an accelerator. The use of low molecular weight poly(propylene fumarate) in similar formulations also gave rapidly cross-linking formulations, but suffered from a lack of physical strength. Note that in the lattermost formulation fluid, low-molecular weight poly(propylene fumarate) acted as solvent for initiator, but the solid high molecular poly(propylene fumarate) did not dissolve in the low molecular weight material.

Samples in the form of discs have been prepared by solidifying the composition in a polyethylene tube. Once hard, the tube is removed and the cylinder of polymer is cut into discs approximately 1/2" in diameter and 1/8" thick with a hacksaw. The surfaces of the discs were then polished with emery cloth.

The formulation is:

Putty Composition

$CaSO_4 \cdot 2H_2O$	12 g
HMWPPF	4 g
Vinyl pyrollidone	1 g

Initiator Formulation

Benzoyl peroxide	0.12 g
Vinyl pyrollidone	0.5 g

To the best of our knowledge, all of these components are physiologically acceptable, and we believe that this formulation offers a basis upon which optimization studies may be based. It has been demonstrated that the organic portion of the composition is completely dissolved by warm 1.0 N NaOH.

4.4 Physical Properties

Lot number 015451-1 of formulated poly (propylene fumarate) was crosslinked at 37°C. Sixteen hours later the resulting rod was removed from the pipet tip and cut into five ~1/2" segments using a hacksaw. The ends of each piece were squared on a lathe using a facing tool. Each segment was measured for hardness using a Shore D-2 hardness tester. The results are given in Table 4-3.

Table 4-3

Reading No.	Hardness
1	81
2	85
3	86
4	86
5	82

Average = 84 ± 2.3

Figure 4-3 shows the relationship between Shore D hardness and Rockwell C hardness. These results are in the range of acrylics and other rigid polymers.

The same samples were used to determine the compression strength of the material. The samples were measured using a Vernier caliper and were tested using an Instron tester at a head speed of 0.1"/min. The results of these determinations are given in Table 4-4. Although these results are somewhat less than would be observed for acrylic bone cements, which would run approximately 10,000psi under the same conditions, they are probably adequate for a temporary application such as maxillofacial injury repair.

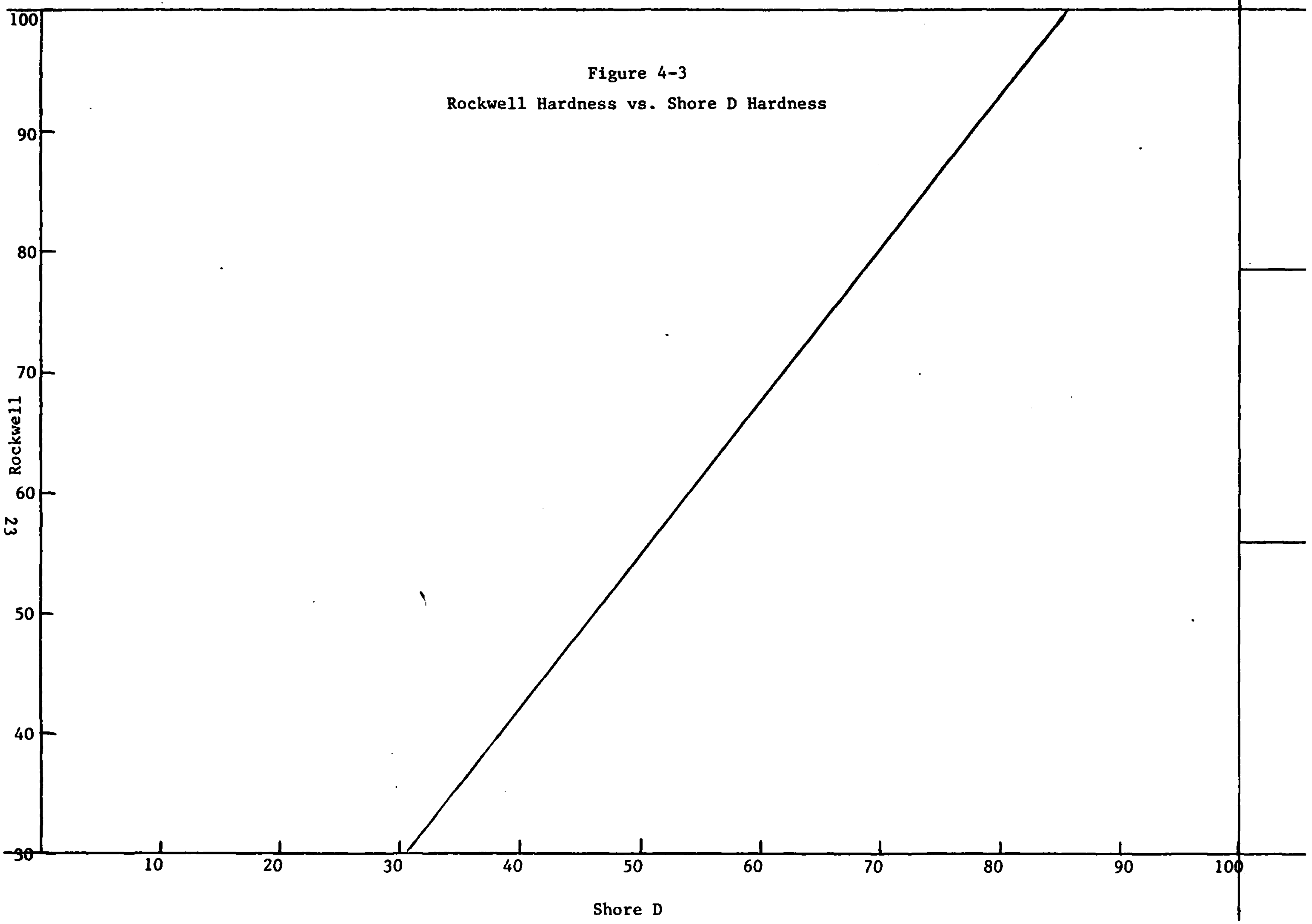


Figure 4-3

Rockwell Hardness vs. Shore D Hardness

Table 4-4

DYNATECH R/D COMPANY

MECHANICAL PROPERTIES DATA REDUCTION SHEET

JOB: WRA-6 **DATE:** 07/28/82 **MATERIAL:** Crosslinked PPF **LOT NO.:** 015454-1

CONDITIONING: Specimens <24 hrs old **TEST MODE:** Compression **LOAD CELL RANGE:** 0-X-2000 lbs.

CHART SPEED: 1"/min. **CROSSHEAD SPEED:** 0.1"/min.

Sample Number	Length in.	Width in.	Thick-ness in.	Area in.^{2}	Gage Length in.	Load lbs.	Strength lbs.in^{-2}	Deform-ation in.	Elonga-tion %	Modulus lbs.in^{-2}		Comments
- A	0.510"	0.435" 0.450"		0.154"								Result not obtained
- B	0.475"	0.459" 0.471"		0.170"		1350	7950					Head Speed, 1 in/min
- C	0.525"	0.400" 0.412"		0.129"		860	6667					0.1 in/min.
- D	0.510"	0.376" 0.390"		0.115"		740	6435					0.1 in/min.
- E	0.499"	0.419" 0.429"		0.141"		1000	7082					0.1 in/min.

The strength could probably be improved by increasing the molecular weight of the polymer or by increasing the ratio of polymer to filler.

4.5 Leaching Studies

Beads 1.5 mm in diameter of calcium sulfate-filled polypropylene fumarate similar to the composition described were transfer molded and crosslinked at 37°C. Five beads were weighed into each of three Whatman extraction thimbles and were suspended in testtubes of distilled water (50 mℓ). The tubes were put in a shaker bath at 37°C. After sixteen days, a weight loss of 50% was detected by drying and weighing one set of beads. This weight loss is presumed to be a result of leaching of the calcium sulfate filler from the beads. It is interesting to note that the beads maintained their structural integrity even in the light of a 50% weight loss. This result suggests that the polymeric fraction of the composition is in the form of the continuous matrix surrounding the particles of calcium sulfate.

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