DEVELOPMENT OF REPAIR MATERIALS FOR AVULSIVE COMBAT-TYPE MAXILLOFACIAL INJURIES (U) DYNATECH R&D CO CAMBRIDGE MASS D L WISE ET AL. NOV 81 DYNATECH-172
Development of Repair Materials for Avulsive Combat-Type Maxillofacial Injuries

Annual Report

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

November 1981

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

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Dynatech Project No. WRA-6
Dynatech Report No. 2172

Dynatech R/D Company
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Cambridge, Massachusetts 02139

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Biodegradable Polymer, Avulsive Maxillofacial Injuries

The progress in the current program to produce a biodegradable material for maxillofacial reconstruction based on poly(propylene fumarate) is essentially on schedule. The various organic components required, liquid and solid poly (propylene fumarate) and solid polyactic acid have been prepared. These have been formulated, along with inorganic fillers, into pastes which have handling properties suitable for maxillofacial reconstruction, similar to modeling clay. These pastes have been crosslinked into solid materials which appear to have sufficient rigidity and strength for the intended application. Leaching...
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The current primary technical hurdle is to find an acceptable curing system that will harden the material in 10-15 minutes at physiological temperatures. The best rates to date have been achieved using benzoyl peroxide as the initiator, but this material exhibits compatibility problems with the composition. Current work is focused on the use of t-butyl perbenzoate, and although satisfactory rates have not been achieved to date with this material, recent progress suggests that success is imminent. Alternatively, work can be resumed to obviate the compatibility problems associated with benzoyl peroxide.

Once the curing rate hurdle is overcome, it is then only necessary to document the efficacy of the formulation as much as is practical prior to in vivo testing.
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Section 1

SUMMARY

The progress in the current program to produce a biodegradable material for maxillofacial reconstruction based on poly(propylene fumarate) is essentially on schedule. The various organic components required, liquid and solid poly(propylene fumarate) and solid polylactic acid have been prepared. These have been formulated, along with inorganic fillers, into pastes which have handling properties suitable for maxillofacial reconstruction, similar to modeling clay. These pastes have been crosslinked into solid materials which appear to have sufficient rigidity and strength for the intended application. Leaching studies suggest that the biodegradability of these materials has been preserved after cross-linking and that the use of an inorganic filler which is leached from the composite fairly rapidly will provide channels for bone regeneration.

The current primary technical hurdle is to find an acceptable curing system that will harden the material in 10-15 minutes at physiological temperatures. The best rates to date have been achieved using benzoyl peroxide as the initiator, but this material exhibits compatibility problems with the composition. Current work is focused on the use of t-butyl perbenzoate, and although satisfactory rates have not been achieved to date with this material, recent progress suggests that success is imminent. Alternatively, work can be resumed to obviate the compatibility problems associated with benzoyl peroxide.

Once the curing rate hurdle is overcome, it is then only necessary to document the efficacy of the formulation as much as is practical prior to \textit{in vivo} testing.
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 current work, under contract no. DAMD 17-80-C-0186, is 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 has been gained in the rate of dissolution through hydrolysis of these materials. This hydrolysis of the polyester structure has been studied \textit{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 \textit{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.

The physical extent of a surgical repair/augmentation material applied in treatment generally will be significantly greater than the dimensions of the test samples cited above. In addition it is judged that a duration shorter than six months in the undegraded state will be preferable in wound treatment. Shorter lifetime before dissolution, both inherently and with respect to physical extent may be attained through formulation with lower molecular weight material. This goal is consistent with that of preparing a viscous fluid suitable as the base for a putty or paste. It is estimated that the proper balance of properties will be attained in a material having a molecular weight of 10,000 or less.

One possible approach is to use particles of solid poly(propylene fumarate) as the filler material which enables preparation of a putty or paste from the viscous, lower molecular weight polymer. Although the higher molecular weight polymer to be used as filler will have an inherently slower dissolution rate attributable to its higher molecular weight, it can be arranged for such filler to hydrolyze at an acceptably rapid rate by regulating the particle size. For example, the 1/16 inch spheres referenced above, when ground, yielded a powder of 150 micron particle size which underwent complete dissolution in 20 days. Other possible filler materials
are polylactic acid and inorganic materials such as calcium carbonate or calcium sulfate.

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 crosslinking between the polyester molecules comprising the fluid component of 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 crosslinking 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, e.g., urea peroxide, are available for use if benzoyl peroxide proves inadequate.

The reactivity of the crosslinking agent poses a problem in the procedure for preparing the proposed mixtures for application. In general, it is foreseen that the crosslinking agent will be mixed with the other ingredients just before use. The proportions required, however, will be small, yet uniform blending must be attained in a short time. Furthermore, the proposed agent, benzoyl peroxide, is a dry ingredient which will contribute to the plasticity of the paste prepared. Development work will
be required to determine whether point-of-use blending of a mixture of the powdered ingredients with the liquid is preferable, or whether partial or complete pre-blending of the filler and liquid is more practical. Suspension of the peroxide crosslinking agent in an acceptable inert fluid may prove desirable.

In summary, the desired composition will contain three components:

1. a viscous liquid carrier material having chemical unsaturation susceptible to crosslinking;
2. a filler material which will convert the liquid 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 qualities desired. It must adhere to bone and exhibit adequate physical strength.

The foregoing discussion has presented the technical basis for creating the necessary liquid carrier material and the powder filler. The program is concerned with the composition of the paste or putty to be formed from the three classes of ingredients. It will be appreciated that if the liquid is 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 further 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 Napthenate (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.

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 was 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 Vigreaux distillation column and standard distilling head fitted with a drip tip collection adapter. The reaction is allowed to proceed until no more ethanol is collected at the reaction temperature of 220°C. At this point, the distilling head and Vigreaux column are removed from the flask and a vacuum adapter and vacuum trap are added to the system. A mechanical vacuum pump fitted with a bleeder valve to control vacuum and to eliminate bumping is then used to strip volatile material from the reaction mixture. When vacuum is first applied, the reaction mixture is a light yellow, clear, freely flowing liquid. After ~1 hr of applied vacuum, the pot material becomes a dark brown, opaque mass. This pot material is then dissolved at room temperature in CH₃Cl₂ and this solution is precipitated in anhydrous ethyl ether to collect the product, which is then vacuum dried at room temperature.

Crosslinking studies on unfilled PPF using liquid initiators are performed by weighing the desired amount of LHW-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.

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 not sufficiently high to destroy the inherent biodegradability of the polymer.

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, \(M_n\), 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 \(\mu\) 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.
<table>
<thead>
<tr>
<th>SPECTRUM NO.</th>
<th>ORIGIN</th>
<th>LEGEND</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>012407-1</td>
<td></td>
<td>1.</td>
<td>PPE from 012407-1</td>
</tr>
<tr>
<td>SAMPLE - PPE is</td>
<td></td>
<td>2.</td>
<td>Sun next on HCl cells</td>
</tr>
<tr>
<td>Straight from jet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no crystal attempts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>made.</td>
<td>Purity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHASE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATE 3/31/81</td>
<td>OPERATOR</td>
<td>SCC.</td>
<td></td>
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The diagram represents the IR Spectrum of Poly (Propylene Fumarate) with the following wavelength values:

- Wavelength (Microns): 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
- Absorbance: 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0

The spectrum includes peaks and troughs at various wavelengths indicating the absorption characteristics of the sample.
Figure 3.3
Gel Permeation Chromatogram of PPF 013505-1
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.
4.1 Polymer Synthesis

Poly(propylene fumarate) is synthesized from diethyl fumarate and propylene glycol by transesterification using p-toluenesulfonic acid as a catalyst. To date, 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 (172 g diethyl fumarate, 76 g propylene glycol, 0.5 g 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 was continued in this manner until the pot temperature reached 220°C, about

Table 4.1
SUMMARY OF REACTION CONDITIONS AND PRODUCTS FOR LMW-POLY(PROPYLENE FUMARATE)

<table>
<thead>
<tr>
<th>Run #</th>
<th>Type</th>
<th>Reaction Time</th>
<th>Maximum Temperature</th>
<th>Diethyl Fumarate</th>
<th>Propylene Glycol</th>
<th>Remarks</th>
</tr>
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<tbody>
<tr>
<td>07778-1</td>
<td>Silicone Oil Suspension</td>
<td>53 hrs.</td>
<td>170-180°C</td>
<td>0.8</td>
<td>0.8</td>
<td>Opaque orange-yellow containing both viscous liquid and gel.</td>
</tr>
<tr>
<td>011366</td>
<td>S.O.S.</td>
<td>61 hrs.</td>
<td>180°C</td>
<td>0.8</td>
<td>0.8</td>
<td>Orange-yellow, viscous tacky liquid. Mn ≈ 550 by end group titration.</td>
</tr>
<tr>
<td>012407-1</td>
<td>S.O.S.</td>
<td>80 hrs.</td>
<td>170°C</td>
<td>0.8</td>
<td>0.8</td>
<td>Orange-yellow opaque liquid.</td>
</tr>
<tr>
<td>012432-1</td>
<td>Neat</td>
<td>39 hrs.</td>
<td>245°C</td>
<td>0.8</td>
<td>0.8</td>
<td>A red, clear liquid, extremely tacky and very viscous.</td>
</tr>
<tr>
<td>012437-1</td>
<td>Neat</td>
<td>8.5 hrs.</td>
<td>210°C</td>
<td>0.6</td>
<td>0.9</td>
<td>Light-yellow, clear liquid, least viscous of all runs</td>
</tr>
<tr>
<td>012709-1</td>
<td>Neat</td>
<td>19 hrs.</td>
<td>239°C</td>
<td>0.76</td>
<td>0.76</td>
<td>Reddish-amber, clear liquid, not quite as viscous as Run #012432-1.</td>
</tr>
<tr>
<td>013505-1</td>
<td>Neat</td>
<td>14 hrs.</td>
<td>245°C</td>
<td>1.0</td>
<td>1.0</td>
<td>Reddish-amber, clear liquid</td>
</tr>
</tbody>
</table>
eight hours. Then the column was removed and the remaining volatile components of the reaction mixture were 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 vacuum at room temperature for 48 hours. Giving a yellow, free flowing powder which melted at about 75°C. The yield of final product was about 35 percent.

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

\[
\text{CH}_3 \quad \text{H} \quad (O - \text{C} - \text{CO})_n \text{OH} \quad \text{H}
\]

contains a hydrogen atom which should be readily extractable by a free radical.

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 CaCO₃ 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 suggests that the ultimate composition may contain high molecular weight PPF as filler 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 are 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 compatibility advantages of t-butyl hydroperoxide, the primary initiator candidate is t-butyl perbenzoate (Lucidol). As can be seen from the structures in Figure 4.1, t-butyl perbenzoate is a hybrid of the two previous initiators.

Figure 4.1
Free Radical Initiators

Benzoyl Peroxide

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{C} \\
\text{CH}_3 & \quad \\
\end{align*}
\]

\text{t-butyl perbenzoate}

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{C} & \quad \text{OC} \\
\text{CH}_3 & \\
\end{align*}
\]

\text{t-butyl hydroperoxide}
Results to date suggest that t-butyl perbenzoate may be the ultimate choice of initiator, but more formulation studies are required before satisfactory rates at physiological temperatures are obtained.

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 NaHCO₃ or CaSO₄. 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. Therefore, more work must be done to obtain hard, brittle products such as these but at physiological temperatures.

4.4 Leaching Studies

Samples of calcium carbonate-filled crosslinked poly(propylene fumarate), as previously described, were subjected to several sets of leaching conditions to assess the biodegradability of the composition. First, a sample was heated to 60°C in NaOH and dissolved immediately, leaving only a white, fluffy residue, presumably calcium carbonate. This experiment suggests that crosslinking has not destroyed the ultimate biodegradability of the composition. Another sample was placed in a flask containing a pH 1 HCl•KCl buffer solution at 37°C (shaker bath). This sample, after twenty-five days was observed to have floated to the surface of the solution, presumably as a result of leaching of the calcium carbonate filler, leaving carbon dioxide bubbles in its place. When the sample was dried and weighed, it was found to have lost 30 percent of its original
weight. This experiment indicates that the inorganic filler can be leached out of the composition, but it also suggests that calcium carbonate will be leached out too slowly under physiological conditions. As confirmation of this, a second sample leached in phosphate buffer at pH 7 did not float in thirty-five days.

Samples of crosslinked PPF filled with 70 percent sodium carbonate or sodium bicarbonate were leached completely in pH 7 buffer in approximately 24 hrs leaving only a non-self supporting polymer residue behind. A more recent leaching study was performed using calcium sulfate at 70 percent loading by weight as the inert filler. Calcium sulfate has a water solubility of 0.35g/100 ml at 20°C and based on the results of the previous leaching experiments would be expected to exhibit a leaching rate intermediate between calcium carbonate and the sodium salts, or about ten days. However, initial leaching studies in pH 7 phosphate buffer at 37°C showed no evidence of appreciable loss of filler after 14 days. Leaching studies were continued using distilled water as the leaching medium and a satisfactory leaching rate is being observed by precipitating sulfate from the leachate with barium chloride. The conclusion is that the phosphate in the buffer solution is exchanging with the sulfate in the composite, rendering the filler less soluble than was expected. Future leaching experiments with calcium-containing fillers will be performed in a non-phosphate-containing buffer.
Section 5

PROJECT STATUS

Figure 5.1 shows the project schedule as originally proposed. To date all of the preparative stages have been completed satisfactorily. Although some improvement in the yield of the high molecular weight PPF preparation would be desirable, any effort in this direction can be carried out in parallel with the main thrust of the program. The formulation stages are also sufficiently advanced to proceed with the remainder of the program with the exception of curing agent selection. To date only benzoyl peroxide has given set rates approaching the 10-15 minute goal at physiological temperatures, and this initiator exhibits compatibility problems, as outlined earlier. However, current work with t-butyl perbenzoate using a composition containing some high molecular weight poly(propylene fumarate) as filler shows promise in producing a sufficiently quick setting formulation. An alternative approach, if required, is to readdress the compatibility problems of benzoyl peroxide.

Satisfactory paste formulations have been proposed which can be worked by hand. Rigid samples of several of these formulations have been prepared, albeit by crosslinking for extended times or elevated temperatures. Solubility of these materials in sodium hydroxide suggests that their biodegradability has been preserved. Their rigidity and strength, although not evaluated quantitatively as yet, appear to be satisfactory for the current application. Progress toward achieving a formulation with satisfactory in vitro degradation properties is nearly adequate. In short, the program is essentially on schedule.
Figure 5.1
PROJECT SCHEDULE

Polymers Preparation
P1 Raw Material Procurement
P2 Liquid Preparation
P3 Solid Fumarate
P4 Solid Polylactide Acid

Formulation
F1 Particle Size/Shape Selection
F2 Paste Preparation
F3 Curing Agent Selection
F4 Optimize Formula
F5 Further Optimization

Evaluation
E1 Rapid Hydrolysis
E2 Adhesion Tests
E3 Physical Tests
E4 In Vitro Tests
E5 In Vitro Tests II
E6 Submission to Contracting Officer

Sample Preparation
S1 In Vitro Samples
S2 In Vitro Samples II
S3 Final Sample Preparation

Reporting
Q Quarterly
AR Annual Report
FR Final Report
APPENDIX

United States Patent [19]
Wise

[54] SUSTAINED RELEASE OF
PHARMACEUTICALS FROM POLYESTER
MATRICES

[75] Inventor: Donald L. Wise, Belmont, Mass.

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260/75 R
[51] Int. Cl. A61K 9/22; A61K 31/74
[58] Field of Search 128/260, 335.5; 424/19-22, 78-83, 32, 33; 260/750 R, 78.5

[56] References Cited
UNITED STATES PATENTS
3,737,521 6/1973 Born 424/22

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[57] ABSTRACT
A novel class of polymer-based products for use in physiological environment, e.g. for use as sutures or implanted, medicine-bearing compositions for use in controlled-rate medication, or the like. The advantageous polymers on which these products are based are condensation polymers formed of Krebs cycle acid-type compounds and a physiologically-tolerable polyol type compound such as glycerol or the like.

8 Claims, No Drawings
SUSTAINED RELEASE OF PHARMACEUTICALS FROM POLYESTER MATRICES

BACKGROUND OF THE INVENTION

It has previously been known to use polyamino acid-type materials and polyglycolic acid-type materials (for example, polylactides) for use in physiological environments, especially for sutures which degrade into physiologically-tolerable degradation products. Some of these materials have been suggested for use as medicinal implants. However, it has proved difficult or impossible to achieve both relatively short-term and straight-line release-rate characteristics from matrices formed of such polymer products. Moreover, these products are relatively expensive.

Therefore, the problem facing the present inventors was one of providing physiologically-tolerable polymers which could be advantageously utilized in making improved products for use in physiological environments.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compositions which have particular utility in sustained delivery of active medicinal agents in a physiological environment.

Another object of the invention is to provide novel polymeric materials useful as matrices with the medicinal agents to form the compositions of the inventions. Another object of the invention is to provide sustained-release compositions of the type wherein the matrix is metabolized or degraded to an excretable form utilizing the Kreb's Cycle, i.e. the so-called "citric acid cycle" or "tri-carboxylic acid (TCA) cycle."

Another object of the invention is to provide a novel process for making medicinal articles for use in sustained delivery applications.

Still another object of the invention is to provide a novel class of polymers. A further object of the invention is to provide polymer-based medicinal articles which are exceptional in their ability to release, at an unusually constant rate, medicinal compounds which are incorporated within the polymer.

Other objects of the invention will be obvious to those skilled in the art on their reading of the instant disclosure.

The above objects have been achieved by the manufacture and utilization of polyester matrices or polyamide matrices based on the reaction of the di- and tri-carboxylic acids of the type which occur in the Krebs cycle. These acids include citric, cis-aconitic, isocitric, α-ketoglutaric, succinic, fumaric, malic, and oxaloacetic. The preferred procedure is to react these acids or the physiologically tolerable homologues thereof with a biologically compatible polyol compound, e.g. glycerol, or a compound based on such a polyol, e.g. an ester of glycerol. Among the physiologically-tolerable polyols useful in the invention are glycerol, mannitol, sorbitol, and the like, but glycerol and glycerol-derived compounds are preferred reactants.

The molecular weights of polymers of the invention are usually between 20,000 to 200,000. Some limited crosslinking is usually present and, in all cases, the polymer is a solid material capable of assuming shape and maintaining its structural integrity, i.e. not disintegrating, in the physiological environment during its useful release-moderating life. Therefore, it degrades to products which are readily disposed of by normal bodily functions.

Among the reactions which may be utilized in forming compositions according to the invention are those wherein the Krebs-acid compound is reacted with a triester such as traceticin, or with a monoester such as monoacetin, or with glycerol itself. The Krebs-acid compound may be utilized in any convenient form, e.g. in the form of an anhydride, a diacid chloride, in a salt form such as the di-sodium salt form, or the like.

The precise reaction may be selected in view of the ease with which it permits production of polymer of desired properties. In general, a triester such as traceticin is less reactive and can be advantageously used to produce flexible or relatively low molecular weight products. There are other procedures which are useful in optimizing preparation of the polymers. When utilizing monoesters like the monoacetins, it is believed to be desirable to select one wherein the two hydroxyl groups have similar reactivity, e.g. as in β-monoacetin.

Such a procedure will allow one to obtain longer linear polymers. Moreover, when glycerol is used as a reactant, maintenance of the reaction temperature below about 180°C will tend to suppress undesired reactions with hydroxyl groups other than the primary hydroxyl groups. Moreover, it is sometimes advantageous to utilize the diacid form of the Kreb's-cycle compounds to avoid water of reaction being formed and to lower the polymerization temperatures. Interfacial polymerization appears to be a particularly desirable approach to preparing polymers with the diacid compounds.

However, it should be realized that the general technology for forming condensation polymers of polyols and polyacid is very well known to those skilled in the art. The primary contribution of the present inventors is the selection of polymeric building blocks such that, on decomposition of the polymer in a physiological environment, the degradation products will be easily disposed of by the body. Moreover, it has been discovered that these polymers, when utilized as matrices of pre-selected shapes, provide means to form compositions from which medicines (and by the term "medicine" is meant treating agents generally) can be released in the body at a surprisingly stable and predictable rate over relatively short time periods. For example, it is possible to deliver 75 to 90 percent or more of a medicine within a 30-day treatment period with a substantially constant release rate, i.e. a release rate which does not differ from a ± 10 percent delivery rate during that period.

ILLUSTRATIVE EXAMPLE OF THE INVENTION

In order to point out more fully the nature of the present invention, the following working example is given as an illustrative embodiment of the present process and products produced thereby.

In the following examples, the material known as hydrocortisone (11α, 17α, 21-trihydroxy-4-pregnene-3, 20-dione) was used as an active agent because there appears to be substantially no chemical interaction between the treating agent and the polymeric matrices illustrated. It is believed that those skilled in the art can interpret the examples as illustrative of treating agents generally.

The active agent was dissolved in ethyl alcohol, and a known amount of radioactive-carbon-tagged hydrocor-
tisone was added to the solution. The solvent was evaporated to yield an active agent of uniform radioactive concentration. This agent was comminuted and the resulting finely-divided active agent blended with polymer in a jar mill. The resulting uniform blend was sintered or milled into shaped medicinal articles. Sintering is merely a fusing of drug and polymer with heat and pressure, usually at temperatures from about 150° to about 200°C. Mulling was used where the polymer was soft enough to form a cohesive mixture using only the mulling action.

In Vitro Testing of Physiological-Release Characteristics

The samples prepared were weighed and placed in 50 ml of an aqueous solution buffered to a pH of 7 with monobasic and dibasic potassium phosphates (i.e. with Sorenson's buffering solution). The liquid was agitated and maintained at 37°C. Samples of the liquid were removed from time to time and were evaluated by radioactive scintillation analysis to determine the amount of cortisone released.

EXAMPLE 1

The following procedure is followed in preparing a polymer from fumaric acid and α-monooacetin by solution polymerization.

A 2000 ml, round-bottom flask is enclosed in an electric heating mantle and equipped with a means to pass nitrogen purge gas over its contents. The flask is also equipped with a Dean Stark trap, a reflux condenser, and a bubbler to aid in regulating nitrogen flow. The flask was charged with 100 ml of dimethylformamide (DMF) for use as a solvent reaction medium. The solvent is refluxed at 153°C until the Dean Stark trap is full to assure the absence of water in the system. After an hour at reflux, the solvent was cooled to 50°C. Then the reactants are added to the solvent.

| Fumaric acid | 10 grams |
| Monooacetin | 9.57 grams |
| Potassium methoxide | 0.1 grams |

The mix was allowed to reflux for 5 hours and 25 minutes at 153°C. A clear, pale yellow solution formed during this period. It was soluble in water and insoluble in hexane. When the DMF was distilled from the solution over a period of about 3 hours, a brown solid condensation polymer of fumaric acid and monooacetin was left in the flask.

EXAMPLE 2

A polymer of L-Malic acid and monoacetin was also prepared by a suspension, sometimes called "pearl," polymerization method. The "solvent" used as the suspending medium was Stoddard solvent, the catalyst was potassium methoxide, and the reaction temperature was 150°C.

The charge to the reactor, made after the medium reached temperature, was as follows:

| Stoddard solvent | 120 ml |
| Malic Acid | 10 grams |
| Monoacetin | 8.5 ml |
| Potassium methoxide | 0.1 grams |

The catalyst was added last. The reaction was carried out for 6 hours at about 150°C and under continuous agitation.

The polymer was recovered by distilling of excess solvent, filtering, washing with hexane, air drying, and then placing under a vacuum for several hours. A tacky pliable polymeric solid was recovered and identified as a polyester resin.

EXAMPLE 3

A pearl polymerization similar to that described in Example 2 was carried out but using the following reaction mix:

- 120 ml of silicone oil
- 10 grams of citric acid
- 5.34 ml monoacetin
- 0.465 ml N-butyl lithium

The reaction was run for about 2.5 hours at 145°C. A sticky, yellow polyester polymer was recovered.

EXAMPLE 4

A quantity of 0.82 grams of the polymer of Example 3 was milled with 0.1655 grams of 14C-labelled hydrocortisone. 0.261 grams of the resulting composition was shaped in the form of a football-shaped pellet and placed in an extraction thimble for in vitro testing. See FIG. 1 for a curve descriptive of the release rate.

EXAMPLE 5

A quantity of 0.35 grams of the polymer of Example 3 was milled with 0.175 grams of 14C-labelled hydrocortisone. 0.259 grams of the resulting composition were shaped in the form of a football-shaped pellet and placed in an extraction thimble for in vitro testing. See FIG. 2 for a curve descriptive of the release rate.

EXAMPLE 6

The following procedure was carried out in preparing a condensation product from succinic anhydride and glycerol.

A round-bottom, 250 ml indented flask was equipped as described in Example 1 but also with a stirrer. A quantity of 120 ml of silicone oil was charged to the flask. To the silicone reaction medium was added:

- 10 grams of succinic anhydride
- 7.3 grams of glycerol
- 0.05 grams of para-toluenesulfonic acid

The temperature was raised rapidly to 163°C. The reaction continued for 1.5 hours at 163°C. Then the temperature was lowered to 90°C for two more hours and the stirring was continued. After this time the contents of the flask were cooled, and the reaction product, in the form of small yellow polymeric pearls of about 1/10 inch in diameter, was filtered, washed with hexane, air dried, and put under vacuum overnight.

EXAMPLE 7

A quantity of 0.919 grams of the polymer of Example 6 was milled with 0.229 grams of labelled hydrocortisone. A sample of 0.6283 grams of the resulting composition was shaped as a football-shaped pellet preparatory to in vitro testing. See FIG. 1 for a curve descriptive of the release rate.

EXAMPLE 8

A quantity of 0.316 grams of the polymer of Example 6 was milled with 0.1810 grams of labelled hydrocorti-
A sample of 0.2702 grams of the resulting composition was shaped into the form of a football-shaped pellet. See FIG. 2 for a curve descriptive of the release rate of the hydrocortisone.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the scope of the invention which might be said to fall therebetween.

What is claimed is

1. A shaped implantable solid article, formed of a composition comprising a pharmaceutical agent, in a matrix, said pharmaceutical agent being adapted for controlled diffusion from said matrix upon implantation, said matrix being formed essentially of a polyester, having an average molecular weight of up to 200,000 formed by the polymerization of a first reactant which is monoacetin, triacetin, glycerol, mannitol, or sorbitol with (2) at least one of a second reactant which is fumaric acid, L-malic acid, citric acid cis-aconitic acid, isocitric acid, alpha-ketoglutaric acid, succinic acid, oxaloacetic acid, or the anhydrides, acid chlorides or disodium salts of said acids.

2. An implantable article as defined in claim 1 having a consistent diffusion rate of said pharmaceutical agent from said matrix until less than about 10 percent of said agent remains within said matrix.

3. An implantable article as defined in claim 1 wherein said polyol is triacetin or monoacetin.

4. A composition as defined in claim 2 wherein said second compound is citric acid, or succinic acid.

5. An implantable article as defined in claim 4 wherein said polyol is triacetin or monoacetin.

6. An implantable article as defined in claim 3 wherein said pharmaceutical agent is a steroid.

7. A composition as defined in claim 5 wherein said second compound is citric acid or succinic acid.

8. An implantable article as defined in claim 5 wherein said pharmaceutical agent is a steroid.