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REPORT NUMBER 4 of PHASE I

PREPARATION AND EVALUATION OF GLYCOLIC AND LACTIC ACID-BASED POLYMERS FOR IMPLANT DEVICES USED IN MANAGEMENT OF MAXILLOFACIAL TRAUMA

PART I

FINAL SCIENTIFIC REPORT

by

Richard G. Sinclair and Gilbert M. Gynn

February 16, 1972

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D. C. 20314

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13. ABSTRACT

Glycolide and L-lactide were synthesized and purified to monomer grade materials. Polymers and copolymers were prepared from the monomers, and the polymers were evaluated by flexural property measurements, DTA, and GPC. Rods were fabricated with 5mm X 10 in.dimensions by injection molding. Pellets, 2mm X 2mm, were fabricated. Similar pellets were also fabricated, incorporating C-14-labelled glycolic acid and tritium-labelled lactic acid moieties.

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February 16, 1972

Col. S. N. Bhaskar D.C.
Director, U.S. Army Institute of Dental Research
Walter Reed Army Medical Center
Washington, D.C. 20012

Contract Number: DADA17-'71 [illegible]-C-1053
Contractor: Battelle's Columbus Laboratories
Principal Investigator: R. G. Sinclair

Dear Col.Bhaskar:

Battelle's Columbus Laboratories is pleased to submit this final report on your program "Preparation and Evaluation of Glycolic and Lactic Acid-Based Polymers for Implant Devices used in Management of Maxillofacial Trauma". The report summarizes the work accomplished in the Phase I program and reported previously in monthly progress reports. As you know, the background developed during the Phase I program is being exploited by the scale-up and more extensive testing efforts of the Phase II program now in progress. Although the glycolide and lactide polymers and copolymers are difficult to prepare, we are pleased that we have been able to supply you with polymeric products suitable for use in your continued evaluation studies.

We wish you every success in developing therapeutic uses for these unique polymer types, and look forward to continuing our cooperation with you on the Phase II program. Your comments and questions are always welcome.

Sincerely yours,

Richard G. Sinclair
Polymer Chemistry Division

RGS:ejc

Enc. 2 copies to HDQA(SGRD-IDS)
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PHASE I--FINAL SCIENTIFIC REPORT

on

PREPARATION AND EVALUATION OF GLYCOLIC AND LACTIC ACID-BASED POLYMERS FOR IMPLANT DEVICES USED IN MANAGEMENT OF MAXILLOFACIAL TRAUMA

to

U. S. ARMY INSTITUTE OF DENTAL RESEARCH

Contract Number: DADA17-[redacted]-C-1053
'71

from

BATTELLE
Columbus Laboratories

by

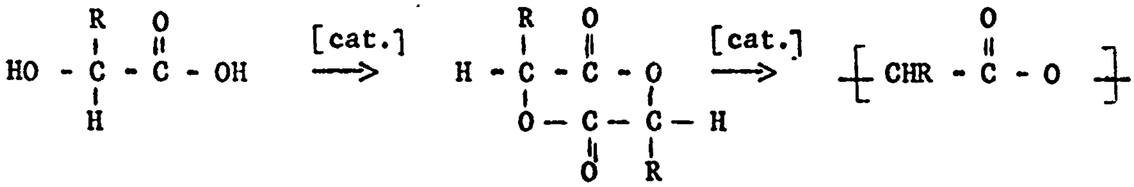
Richard G. Sinclair

November 1, 1971

INTRODUCTION

The United States Army Institute of Dental Research (USAIDR) wished to obtain certain fabricated items prepared from polyesters obtained by polymerizing glycolide and lactide monomers. Battelle prepared these monomers, polymerized them, evaluated the physical properties of the resulting polymers, and fabricated the polymers into useful items. The USAIDR currently is evaluating the items as sorbable, dental prosthetic devices. The polyesters have the advantage of being slowly absorbed by the body while supplying strong support to the area under repair. Since the implanted polyesters eventually disappear, they obviate the need for a second surgical operation after they have fulfilled their function.

As a major objective of this program, glycolide and lactide monomers were to be prepared and polymerized. The monomers are generally prepared by the catalytic dehydration of lactic acid or glycolic acid. The products, lactide or glycolide, respectively, must be



$$HO-\overset{R}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH \xrightarrow{[cat.]} \begin{array}{ccccccc} & R & & O & & & \\ & | & & \| & & & \\ H- & C & - & C & - & O & \\ & | & & & & | & \\ & O & - & C & - & C & -H \\ & & & \| & & | & \\ & & & O & & R & \end{array} \xrightarrow{[cat.]} \left[CHR-\overset{O}{\overset{\|}{C}}-O \right]$$

R = H, glycolic acid. . . . . .glycolide
R = CH_3, lactic acid. . . . . .lactide

highly purified to monomer-grade purity before polymerization.

A further objective of the Phase I Program was to fabricate each of five different polymer/copolymer compositions into rods and pellets. In addition, a final objective was to provide the same polymers in pellet form, incorporating C-14 and H-3 labels for use in subsequent absorbtion-rate evaluations by USAIDR.

SUMMARY

During this program, glycolide and lactide monomers were synthesized, a number of polymers were prepared and characterized, and processing and fabrication data were obtained on the polymeric products. Homopolymers and copolymers of glycolide and L-lactide were prepared as outlined in our proposal. The polymers were evaluated by differential thermal analysis (DTA), gel permeation chromatography (GPC), dilute solution viscometry, and flexural property measurements. In addition, these data were compared to similar data obtained on the polymer supplied by the Army Dental Research Center, referred to in this report as the standard polymer (SP).

The first group of experimental polymers prepared by Battelle was found to have mechanical properties comparable or superior to those of the SP. Certain other key properties, such as molecular weights, apparent degrees of crystallinity, and melting points of some of the copolymers also were found to be similar to those of SP.

A second series of polymers and copolymers was prepared using much milder polymerization conditions than utilized in our first polymer preparations. The products of the second series of polymers were of excellent quality as evidenced by their color and the results of thermal analyses, molecular weight characterizations, and physical property measurements. Difficulties were encountered in fabricating the polymers into rods due to the formation of voids and bubbles in their crystalline matrices. These problems were overcome by modifications of fabrication techniques which eventually permitted successful injection molding of the desired polymer specimens. Rods of each of the polymer compositions were shipped to you on June 22, 1971.

Small pellets have been relatively easy to fabricate. Two hundred pellets of each polymer type were shipped to you. C-14-labelled glycolic acid and tritium-labelled lactic acid were synthesized into glycolide and lactide which were then purified and converted into the appropriate labelled homopolymer and copolymer compositions. The labelled polymers were pressed into pellets and mailed to you.

Details of Experimental Work

First Series of Polymers. Monomers and catalyst (0.01 mole percent) stannous octoate were charged into ampoules in a dry bag, evacuated, and the ampoule sealed with a torch. The monomers were stirred and heated at 115 C for 3 hours, which partially effects polymerization before the stirrer stalls. Final polymerization was carried out at 190 C over 24 hours. The polymers were light brown in the case of the poly(glycolide) with increasing color in the case of the polymers incorporating more lactide.

The mechanical properties of the homopolymers and copolymers of glycolide and lactide have been found to vary with composition. The composition, in turn, appears to correlate with degree of crystallinity. The data shown in Table 1 compare the flexural strength properties of the first series of polymers prepared. For this series, flexural strength does not appear to be greatly dependent on molecular size or relative amounts of crystallinity. Past experience has shown that large differences in degree of crystallinity of polymers do cause variations in modulus particularly, and that large differences in molecular size have more effect on strength properties.

TABLE 1. EVALUATION DATA OF GLYCOLIDE--LACTIDE POLYMERS

Sample Number	28750-6-1	28750-6-2	28750-6-3	28750-6-4	28750-6-5	SP[(a)]
Glycolic/Lactic ratio[(b)]	100/0	75/25	50/50	25/75	0/100	--
Relative molecular size[(c)]	-- (d)	-- (d)	4.60	5.00	8.50	7.80
Percent residual monomer[(e)]	-- (d)	-- (d)	1.6	2.85	4.5	<0.1
Softening range, C[(f)]	180-200	55-60	55-60	55-60	55-60	
DTA melting points, C[(g)]	230	58	58	58	60;160, dual crystallinity	60
DTA crystallinity	High	Moderate	Low	Low-to moderate	Moderate	Moderate
Flexural strength, Kps[(h)]	13.1 14.9 16.7 16.9	20.0 21.9 22.1	14.2 14.0 13.1 16.4 12.7	14.0 10.9 11.2 14.7 15.0 15.6	13.5 14.6 13.4 13.0	12.0 13.6
Tangent modulus[(h)] of elasticity x 10^5 psi	10.1 10.9 9.75 9.22	7.26 7.58 7.67	5.95 5.85 a6.08 6.29 6.36	5.63 5.95 5.62 5.86 5.23 5.77	4.74 4.79 4.96 4.57	5.23 5.11

(a) Standard polymer received from the Army Dental Research Center.
(b) Weight ratio of glycolide to lactide charged into the polymerizations.
(c) Molecular weight, times 10^{-4}, at the maximum of the GPC curve, as referred to polystyrene standards. These values indicate relative molecular sizes rather than the molecular weights of the polymers.
(d) Not soluble in the GPC solvent used.
(e) GPC estimate, based on the detector response for both monomers and the assumption that the relative amounts of each monomer is the same as was charged into the polymerization.
(f) Temperature range on Fisher-Johns melting point apparatus at which the polymer becomes rubbery.
(g) Midpoint of DTA melting endotherms which were first order phase transitions; Polymer Sample Number 28750-6-5 showed two melting points.
(h) ASTM D790, using a span to depth ratio of 10:1. Replicate values shown vary, depending on molding conditions for preparing test specimens.

All of the polymers prepared exhibited flexural strengths as good as or better than that of SP sample. The second series of polymers prepared (described below) showed essentially the same trends, and the choice of copolymer composition probably depends upon the results of in vivo absorption studies. Fabrication techniques were developed that permit the molding and processing of the various polymers into the desired shapes. The 100 percent glycolide polymer was found to have a significantly higher melting range than the other polymers and was more difficult to process.

Second Series of Polymers. A second series of five polymers was prepared, varying in composition as shown in Table 2. The polymerizations were performed in sealed glass ampoules from carefully purified glycolide and lactide monomers, using anhydrous, 0.01 mole percent, stannous octoate catalyst. Glycolide is normally polymerized at 200 C and lactide at much lower temperatures because of its higher reactivity and tendency to thermally degrade. Therefore, the various monomer compositions were polymerized using lengthy reaction periods at 115 C, in order to accomodate both types of monomer problems. The homopolymer of glycolide was a buff-colored, opaque solid due to its crystalline nature. The homopolymer of lactide was a snow-white crystalline solid. The other three copolymers were translucent and amorphous in appearance. The polymers were pulverized and vacuum heated to remove deleterious surface moisture and any residual monomer. Those polymers which were soluble were evaluated by gel permeation chromatography (GPC) and dilute solution viscometry. The results indicated very high molecular weights and, therefore, promised good physical properties. Residual monomer percentages were nondetectable or nearly so, probably of the order of 0.5 percent or less.

Specimens of each polymer were heated in air on a hot stage, and qualitative effects such as onset of rubbery behavior and complete melted temperature were noted. Differential thermal analysis (DTA) was performed on each polymer, and significant differences were observed. The polyhomoglycolide was sharp melting and very crystalline. The virgin polymer melted

TABLE 2. EVALUATION DATA OF GLYCOLIDE-LACTIDE POLYMERS

Sample Number	28750-11-1	28750-11-2	28750-11-3	28750-11-4	28750-11-5
Glycolide/Lactide ratio(a)	100/0	75/25	50/50	25/75	0/100
Relative molecular size,(b) x 10^{-4}	--	--	4.20	10.0	8.50
Percent residual monomer(c)	--	--	< 0.5	< 0.5	< 0.5
Solution viscosity dl/g(d)	--	1.74	2.50	1.72	1.80
Softening range, C(e)	215-219	130-198	60-160	64-136	155-193
DTA melting points, C(f)	218; 228	50; 192	50	144	192
DTA crystallinity	High	Moderate	Low	Moderate	High
Tensile strength, psi(g)	14,477	9,278	7,168	7,048	7,036
Flexural strength/ Modulus(h)	--	--	--	--	14,181/4.76x10^{5}

(a) Weight ratio of glycolide to lactide used in the polymerizations.

(b) Relative molecular weights at the maximum of the GPC curve, as referred to polystyrene standards.

(c) GPC estimate.

(d) Solvent, hexafluoroisopropanol; temperature, 25 C; concentration 0.1 g/dl.

(e) Temperature range on Fisher-Johns melting point apparatus in which sample proceeds from a rubber to a melt.

(f) Midpoint of differential thermal analysis melting endotherms which were first order phase transitions. Some samples exhibited two melting points.

(g) Instron tests, average of 5 values on 0.5 x 4 x .005 inch samples.

(h) Similar to Table 1.

at 228 C while the remelted sample showed a new morphological form melting at 218 C. The polyhomolactide was also a highly crystalline material while the other three copolymers showed much lower extents of crystallinity.

Although no attempt was made to orient the polymer samples (or induce crystallinity by mechanically stretching the polymers), tensile strengths were found to be quite good. The values shown in Table 2 would compare favorably with similar values for nylon or polycarbonate. They would be lower than oriented Mylar, of course. The bulk properties of Samples 28750-11-2, -11-3, and -11-4 are such that the polymers show a qualitative tendency to flow under pressure. The other two polymers, Samples 28750-11-1 and -11-5 showed brittle fracture under pressure. The tensile strengths shown in Table 1 represent a brittle fracture value for Samples 28750-11-1, -11-3, and -11-[illegible] and a more ductile-type failure with the other two samples. It should be noted that the glycolide sutures are plasticized in order to obtain the elongation properties necessary for surgeon's knots.

The above polymers were subsequently fabricated into rods, 5 mm in diameter by 25 cm long, and pellets 2 mm in diameter by 2 mm in length. For each polymer composition two rods and 200 pellets were shipped to the USAIDR.

Radioactive Polymers. Glycolide-1-C-14 was prepared from glycolic acid-1-C-14 essentially by the method of Lowe(1). Pure white, crystalline glycolide monomer was obtained in 59 percent yield after recrystallization. L-(-)-lactide-2-H-3 was prepared from L-(+)-lactic acid-2-H-3 by the method of Selman(2). Pure-white crystalline needles were obtained in 83 percent yield.

After carefully drying monomers, catalyst, and apparatus, the polymerization was carried out for 128 hours in vacuum-sealed ampoules at 140 to 150 C. The labelled polymers proved to be more brittle than the previously prepared (unlabelled) polymers. However, their physical properties were much improved by heating the pulverized polymers in a sublimator with stirring. Unreacted monomer and low-molecular weight materials were removed from the polymers during this process. The purified polymers were then pulverized

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(1) C.E. Lowe, U.S. Pat. 2,668,162 (DuPont, 1954), or W.R. Sorenson and T.W. Campbell, "Preparative Methods of Polymer Chemistry", p. 246, 1st Ed., Interscience Pub., N.Y. (1961).

(2) S. Selman, U.S. Pat. 3,322,791 (Ethicon, 1967).

and molded into pellets in a press. The 100 percent glycolide polymer pellets were prepared by both slow cooling and quenching to obtain polyglycolide samples having different degrees of crystallinity. The 75/25, 50/50, and 25/75 glycolide-lactide polymers have not been observed to be very crystalline. They were quenched after molding into pellets. The 100 percent lactide polymer, which is very crystalline, does not exhibit the differences in crystallinity due to slow cooling versus quenching shown by the polyglycolide. The pellets from the polyactide polymer were prepared, therefore, using only a quenching technique.

The labelled pellets were shipped to you on August 16, 1971. The compositions and calculated values for the C-14 and H-3 activities of the several polymer samples are shown in Table 3.

TABLE 3. COMPOSITION AND APPROXIMATE ACTIVITY OF POLYMERS

Sample No.	28750-32-1	-32-2	-32-3	-32-4	-32-5
Glycolide/Lactide	100/0	75/25	50/50	25/75	0/100
dpm/pellet of C-14	6.35x10^4	4.7^6x10^4	3.17x10^4	1.59x10^4	0
dpm/pellet of H-3	0	5.17x10^5	1.03x10^6	1.55x10^6	2.07x10^6

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