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MANAGEMENT OF HARD TISSUE AVULSIVE WOUNDS AND
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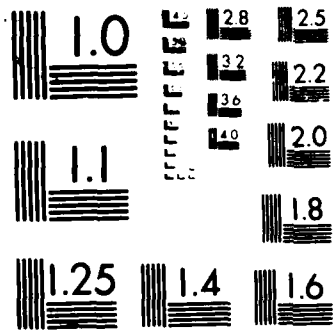
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MANAGEMENT OF HARD TISSUE AVULSIVE WOUNDS
AND MANAGEMENT OF OROFACIAL FRACTURES

Annual Report

May 31, 1984

Supported by

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<p>Research studies were conducted to produce and evaluate a high-quality directional porosity resorbable calcium phosphate ceramic material for use in the management of hard tissue avulsive wounds and orofacial fractures. The previous efforts demonstrated that directional porosity would allow adequate ingrowth of bone through the biomaterial prior to loss of mechanical integrity of the biomaterial.</p> <p>The overall objective is to produce a completely resorbable biomaterial which will promote bone formation and via a bone remodeling-biodegradation process be completely replaced by bone. It should be pointed out that the dynamics of this situation are complex. The biomaterial should allow bone ingrowth and provide mechanical integrity during the remodeling, biodegradation process. The dissolution of the biomaterial and bone formation need to proceed in a parallel and controlled fashion, so that mechanical integrity of</p>					
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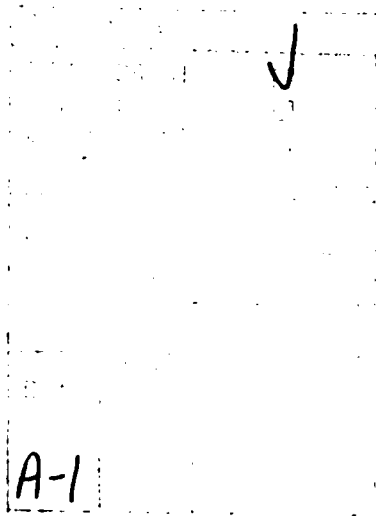
the area under repair is not lost. In early studies, omnidirectional structural material would, depending upon the chemical composition, either: not entirely biodegrade, or would degrade until mechanical integrity was lost. Unidirectional materials, as reported previously in our Annual Reports for Contract No. DADA17-69-C-9118 (dated May 31, 1981 and May 31, 1982) were free of these problems; ingrowth and subsequent bioresorption without loss of implant integrity was noted.

"First Generation" Unidirectional Material utilized to prove the concept, had low pore density and poor mechanical strength. The materials utilized the second in vivo investigation were calendered or rolled to form a serrated surface and then stacked and sintered together to form a unique unidirectional porosity as required by the particular implant situation. We have termed this the "second generation" material. The technique allows directional porosity material to be formed in blocks of high-strength material with continuous pores of large diameter. The pores can be specifically oriented, and the surrounding material can be made dense enough to provide a high-strength scaffold.

Numerous attempts were made in this year's activities to reproduce a material that had previously been successfully manufactured and reported in the Annual Report of Contract DAMD17-82-C-2168 on May 19, 1983. The previous supply of calcium carbonate required as the starting material in the formulation of tricalcium phosphate was no longer available. Substitution of material with reagent-grade calcium carbonate from several other manufacturers produced unsatisfactory results. X-ray diffraction analyses and atomic absorption spectrometry yielded no pertinent information that should indicate why certain calcium carbonates would not provide proper yields of tricalcium phosphate. Finally, one source of material was found that provided appropriate results of a high yield tricalcium phosphate. Tapes were successfully extruded; however, the tapes produced by a hot extrusion using the new calcium carbonate would not successfully bond together and produce the same high quality tricalcium phosphate that had been previously produced. Consequently, the rest of the year's activities concluded with an intensive evaluation of the extrusion process to ascertain why the previously utilized extrusion and sintering techniques cannot be reproduced. That indicates that minor changes in the binder concentrations are negatively affecting the results.

15.

Biodegradable Ceramics
Bioresorbable Ceramics
Tricalcium Phosphate



SUMMARY

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The overall objective is to produce a completely resorbable biomaterial which will promote bone formation and via a bone remodeling--biodegradation process be completely replaced by bone. It should be pointed out that the dynamics of this situation are complex. The biomaterial should allow bone ingrowth and provide mechanical integrity during the remodeling, biodegradation process. The dissolution of the biomaterial and bone formation need to proceed in a parallel and controlled fashion, so that mechanical integrity of the area under repair is not lost. In early studies, omnidirectional structural material would, depending upon chemical composition, either: not entirely biodegrade, or would degrade until mechanical integrity was lost. Unidirectional materials, as reported previously in our Annual Reports for Contract No. DADA17-69-C-9118 (dated May 31, 1981 and May 31, 1982) were free of these problems; ingrowth and subsequent bioresorption without loss of implant integrity was noted.

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FOREWORD

No animal research was included in this research. However, previously conducted studies adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BACKGROUND, PROBLEM AND APPROACH

Historically, various techniques have been employed for the repair or treatment of osseous diseases, defects, and wounds. Autogeneous bone grafting remains the most satisfactory approach, but is not without the disadvantages associated with double surgeries, limits in structural properties, and the limitations imposed on the repair of massive osseous defects.

Since April, 1969, Battelle's Columbus Laboratories has been conducting research under contract to the U.S. Army Institute of Dental Research (USAIDR), to develop resorbable ceramics for potential application in the repair of hard tissue avulsive wounds. The basic materials have been calcium phosphates. These materials were selected because they contain two of the essential elements of the natural bone mineral phase, calcium hydroxyapatite.

In vivo studies were conducted initially at USAIDR, using the sintered porous materials and slurries prepared at Battelle from tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ and other calcium orthophosphate powders CaHPO_4 and $\text{Ca}(\text{H}_2\text{PO}_4)_2$, to evaluate the potential use of calcium phosphates to both facilitate repair of bone defects and to determine the best material for future exploration(1-3). The implant studies indicated that calcium phosphates consisting essentially of the mineral phases $\text{Ca}(\text{PO}_3)_2$, $\text{Ca}_3(\text{PO}_4)_2$, and CaHPO_4 are well tolerated by the tissue, appeared to be nontoxic, resorbable, and permitted rapid invasion of new bone.

Of the various porous calcium phosphate materials investigated, tricalcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$, was selected for continued development and evaluation since it was easy to fabricate and was found to be both biocompatible and resorbable. Emphasis has been directed toward producing porous materials consisting of single-phase tricalcium phosphate(4-7). Research on granular formations of tricalcium phosphates (TCP) continued at USAIDR. Basic research at Battelle-Columbus was focused on producing practical large segment replacement implants from TCP.

To provide basic resorption rate data on the in vivo behavior of solid tricalcium phosphate bioresorbable ceramics, implant studies were initiated in 1975 at Battelle-Columbus using the rabbit calvarium model(8). Early samples of tricalcium phosphate were implanted as a control and samples

of two new materials were implanted for comparative observation. These new materials were prepared using improved processing techniques derived in previous materials development studies and represented significant improvements in the structural characteristics of porous tricalcium phosphate. The characterization of the materials involved and the results of the in vivo studies were the subject of the fifth report(8).

These results indicated that the improved material exhibited significant increases in resorption rate. In fact, the material resorbed so rapidly that after the ninth month the implant appeared to be granulated and was invaded with connective tissue. This result does not imply lack of biocompatibility, but does suggest that such rapid degradation can be deleterious in stress-bearing situations.

To determine the effects of structural variations on resorption rate, experimental porous implants were prepared using a single tricalcium phosphate powder with different pore size distribution. Three materials were prepared for in vivo evaluation. These studies demonstrated that orientation of pore structure is a more important variable than pore size distribution(9). The study indicated that a higher density material of the stoichiometric chemistry with directional porosity is probably the desired material.

The seventh report(10) demonstrated that the concept of directional porosity could provide a satisfactory result; adequate ingrowth of bone to provide mechanical integrity prior to loss of mechanical integrity of the tricalcium phosphate. These results were corroborated by Tortorelli(11). The material used in these experiments was far from ideal; consequently, a better method of production was sought. The eighth report outlines the development of a better material, the second generation material, and early phases of its in vivo evaluation(12). The ideal material should minimally inhibit the ingrowth of bone; consequently, large pores and a high pore density are desirable. The ideal material should also be of high strength and should have mechanical properties approaching bone. Consequently, a material of high density in the non-porous regions was sought. It was also deemed desirable to have a material that could be readily manufactured with the pore alignment and size required for a particular application.

The present report outlines the development of a higher quality "third generation" material which more closely approaches properties required for an ideal material.

MATERIALS AND METHODS

Preparation of Tricalcium Phosphate Material

A major portion of this year's activity was to reproduce material that had been successfully manufactured and reported on in the May 19, 1983 Annual Report(13). The method was identical to that listed in the above cited report. Fischer Scientific certified ACS calcium catalog number C65 had previously been obtained and used in conjunction with Fischer reagent-grade phosphoric acid for the production of tricalcium phosphate. Phosphoric acid was diluted to the proper concentration, heated while stirring, and calcium carbonate was slowly added. After two hours of stirring, mixtures were heated overnight and placed on glass trays and vacuum dried to complete dryness. Following production of these batches, X-ray diffraction analysis was routinely performed by the Battelle-Columbus Analytical Laboratory. Precipitation of the two components was performed at a temperature of 180°F. Vacuumed drying was performed at 220°F. Since the above mentioned Fischer material is no longer available, sample calcium carbonates were obtained from Alpha Products and Mallinckrodt Chemical Company, and the previously utilized techniques were employed. The X-ray diffraction analysis was performed on the precipitated samples as well as those calcined at 1550°F for 3½ hours. Unfortunately, the pattern strengths for samples produced from both the Alpha and Mallinckrodt indicated poor conversion to whitlockite (tricalcium phosphate). There was a contamination with hydroxylaptite. Obviously both the Mallinckrodt and Alpha materials were producing unsatisfactory conversion rates. Attempts were made to find further sources of calcium carbonate that would give adequate yields. Fischer C64 material produced a satisfactory 100 percent to beta whitlockite (beta tricalcium phosphate). However, the Baker material was only 39 percent converted to Beta whitlockite. Optical

emission spectroscopy was performed in an attempt to understand why certain calcium carbonates would not produce proper conversion to tricalcium phosphate. The results yielded only minor impurities which should not interfere with the chemical conversion. The specific surface area of the various received materials were evaluated to see if surface area differences would have any effect upon conversion. However, no remarkable differences were noticed. The optical emission spectroscopy of the previously successful Fischer C64 material indicated a higher percentage of the silicon, iron and magnesium as seen in materials. In addition, spark source analysis for impurities were performed with Fischer C64, C65, Mallinckrodt, and Alpha materials. Again some minor differences were found especially in trace contaminations of strontium, potassium and phosphorus. Interestingly, the greatest difference in these trace contaminant differences were found between Fischer C64 and C65, the only two materials which provided successful results.

It was decided not to expend any more project funds attempting to understand the difference between these materials which would prevent a proper conversion to beta phase tricalcium phosphate. The investigation of this unusual phenomena was frustrated by the fact that the manufacturers were not willing to divulge sufficient information to indicate what differences starting material methods of manufacture might have accounted for these unusual differences in the ability to produce tricalcium phosphate. Both of the successful materials were produced by Fischer, we suggest that the method of calcium carbonate manufacturers is the key element. Most probably, Fischer utilizes a precipitation method for production of their calcium carbonate. Fischer C64 material will be used for further production of tricalcium phosphate.

Characterization of Tricalcium Phosphate Powder for Chemical Composition and Physical Properties

X-ray diffraction analysis of the above powder revealed it to be hydroxyl-apatite with a trace of monolite. To crush the large, hard agglomerates, formed during drying, the precipitate powder was dry ball milled for 2 hours in a polyethylene container with aluminum oxide balls. To convert

the hydroxyl-apatite to whitlockite, the powder was calcined for 3-1/2 hours at 1500°F followed by an X-ray diffraction analysis. The powder was 100 percent converted to whitlockite. To break up sintered agglomerates, the calcined powder was ball milled with hexane for 12 hours in a polyethylene jar with aluminum oxide balls.

Since the characteristics of this powder are similar to those of the powder produced in 1981, a sintering study of this powder was not undertaken. Within its usual sintering range, tricalcium phosphate has a destructive transformation from β to α form with the alpha form having a lower density. This conversion begins approximately at 2050°F and limits the sintering temperature of the tricalcium phosphate matrix to 2000°F.

Conduct Study of Ceramic-Organic Mix Formulation for Hot Extrusion Forming

In formulating mixes for hot extrusion, a modification of the ASTM D-281-31 oil adsorption test was performed to indicate the optimum binder concentration. This method was previously utilized in our last year's effort. An identical formulations which produced the successful result in last year's effort was employed.

Produce Fluted Sheets to Form Tricalcium Phosphate Continuous Porosity Structures

To obtain sheets of correct thickness, a die previously purchased from Brabender Plastograph Company having the capability of extruding sheets ranging in thickness from 1.5 to 3.0 mm with a predetermined width of 25 mm. Using the mix formulated, flat sheets 25 mm wide and 1.5 mm thick were formed by hot extrusion. An embossing tool was machined from a Teflon rod with circular grooves of the dimension required. After extrusion, the sheets are heated and embossed. Single embossed sheets are quickly laser drilled by a Neodymium glass pulse laser. After sintering, a 0.5 mm hole is produced without cracking the ceramic. Laser drilling is now a practical, commercial machining technique.

Build the Matrix Structure

Methods as outlined in our last annual report were employed to stack the sintered layers to produce the desired unidirectional matrix structures. In previous successful patches the extruded sheets had been cut and glued together utilizing a coating of camphorated cottonseed oil. The oil slightly solubilized the surface of the hot extruded material and allowed the laminates to stick together before sintering. However, with the present materials a poor quality product was obtained following burnout and sintering. An intense analysis was undertaken why such poor quality material was obtained. Even though the sheets had been pressed together to obtain an intimate contact, the laminated sheets did not sinter into a homogenous mass. This result was totally unexpected since we had previously obtained high quality material with this laminating and sintering technology. In an attempt to solve this problem we performed numerous experiments including different binder agents, additives, and methods of sintering. A matrix of approximately 50 variables were attempted and none to-date have solved the problem. The matrix of variables was an extension of that originally utilized in previous studies to develop the previously successful technique. There were marginal improvements but none provided a totally successful product.

Metallographic sections of the failed material were prepared so that the sintered interface could be observed microscopically. The analysis revealed that the tricalcium phosphate mass of the two sheets to be laminated together were not coming in intimate contact during the burnout or subsequent sintering step. It appears that binder material had migrated during the burnout phase to the surface of the specimens thus preventing proper bonding of the layers. Since chemical analyses indicated that the starting materials and the finished materials are chemically correct but a physical space exists between the remaining material it is our hypothesis that binder matrix ratio or formulation is incorrect. The hypothesis was further strengthened by an experiment where surfaces of the extruded pieces were extremely abraided approximately .01 inches of the material was removed. These pieces were coated with camphorated cottonseed oil and processed through burnout and sintering. A successful bond was obtained. This experiment indicated that

organic material probably migrated to the surface and prevented normal bonding. The binder concentration and formulation needs to be re-evaluated.

CONCLUSIONS AND DISCUSSIONS

Research progress was extremely hampered during this year's effort due to our inability to successfully reproduce material that had previously been produced in our laboratory. Two totally distinct difficulties with the process were discovered. First a true tricalcium phosphate material could not be obtained due to slight differences still undetermined in the stock calcium carbonate utilized as the starting material. A calcium carbonate which produced an acceptable end product was eventually identified. However, the exact chemical reason why calcium carbonate from several manufacturers would not produce a satisfactory yield of tricalcium phosphate was never thoroughly determined. It appears that the method of manufacture, which is proprietary to the manufacturer, determines ability to obtain reasonable yields of tricalcium phosphate. This problem was precipitated because the product originally used in our previous studies is no longer manufactured.

The second problem arose in that the extruded sheets of tricalcium phosphate that had been successfully laminated and sintered together in the past would no longer properly fuse. An intense investigation of the technology and chemistry ensued. It appeared that binder material necessary for the processing was disproportionately migrating to the edges of the extruded material. The excess of binder material at the edges prevented sintering together of the specimens following burnout. It is recommended that the ratio of binder to calcium phosphate powder be investigated to determine the sensitivity of this parameter to producing successful material. It appears that this ratio must be critical since the mixtures utilized were similar to those which had previously provided satisfactory results. The critical powder volume concentration test based upon ASTM D-281-31 oil adsorption test will be run on each lot of material to determine whether we are maintaining the optimum ceramic to plastic binder ratio with each individual batch of material produced.

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