

IN SITU CALCIUM PHOSPHATE MINERALS—METHOD AND COMPOSITION

INTRODUCTION

1. Technical Field

The field concerns the preparation of calcium phosphate minerals and their applications.

2. Background

A number of calcium phosphate minerals, such as hydroxyapatite, fluorapatite, octacalcium phosphate (OCP), whitlockite (TCP), brushite and monetite, do, or may, find application as biocompatible minerals. The various crystalline forms have different properties which in particular applications may be more or less desirable. For example, OCT ($k_{sp} \approx 10^{-27}$), TCP (α or β form) or $\text{Ca}_3 - x\text{Mg}_x(\text{PO}_4)_2$ ($k_{sp} \approx 10^{-27}$) are resorbable, while brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) ($k_{sp} \approx 10^{-7}$) and monetite (CaHP_4) ($k_{sp} \approx 10^{-7}$) are very resorbable. (Brown and Chow, *Ann. Rev. of Materials Science* (1976) 6:213-236). By forming the different minerals with their varying crystalline structures, compositions and chemical and physical properties, mineral products may be obtained having different properties for particular applications.

Apatite is a general term for a wide range of compounds represented by the general formula $\text{M}^{2+}_{10}(\text{ZO}_4^{3-})_6\text{Y}_{-2}$, wherein M is a metal atom, particularly alkali or alkaline earth metal atom, and ZO_4 is an acid radical, where Z may be phosphorus, arsenic, vanadium, uranium or silicon, or may be substituted in whole or in part with carbonate (CO_3^{2-}). Y is an anion, usually halide, hydroxy, or carbonate.

Hydroxyapatite, as well as modified forms thereof, assumes substantial interest and importance by virtue of the fact that it is a major naturally occurring building block in bone, teeth, and some invertebrate skeletons. There are many situations where bone has been broken, destroyed, degraded, become too brittle, or been subject to other deteriorating effects. In many of these situations it would be desirable to be able to replace the bone structure or strengthen the bone structure. In providing materials to substitute for natural bone, there are a number of restraints on the nature and composition of the material.

The material should be physiologically acceptable, so as to avoid the initiation of clots, inflammatory response, and the like. Two different product forms are desirable: one being an hydroxy- or fluorapatite which is non-resorbable in vivo; the other including substantial amounts of OCP, TCP, brushite, and monetite, which are resorbable in vivo. In addition, the material must be strong and not friable. Furthermore, there should be strong adhesion between the material and any remaining bone. Also, desirably, the material should be subject to assuming some of the natural role of bone, such as accommodating stem cells, allowing remodelling by osteoclasts followed by new bone ingrowth, and normal metabolic calcium exchange of native bone.

Besides the biological and physiological considerations, there are the additional considerations of how the material is made and the ease with which it may be formed to a desired shape. Specifically, a material which could be injected as a liquid to fill voids and completely fill in areas deficient of hard bone is very desirable. Where the material is to be placed in situ, a variety of considerations come to the fore. For example,

the rate at which the reaction occurs for formation of hydroxyapatite, as well as the change in enthalpy of the reaction, are important. Where the reaction is highly exothermic, it may not be tolerated by the patient. The form in which it is introduced must be stable in the environment in which it is introduced, so that not only must the final product be stable, but also the intermediate products as the reaction occurs.

It has therefore been found difficult to provide physiologically useful forms of hydroxyapatite and/or other calcium phosphate minerals. For the most part, the hydroxyapatites and other calcium phosphate bone grafting particulates which have been available have lacked one or more of the properties necessary for a useful implant, and, therefore, have failed to obtain general acceptance.

Relevant Literature

Patents of interest include U.S. Pat. Nos. 3,787,900; 3,913,229; 3,679,360; 4,097,935; 4,481,175; 4,503,157; 4,612,053; 4,659,617; and 4,693,986. See also, Arends and Jongebloed, *Rec. Trav. Chim. Pays-Bas* (1981) 100:3-9. Use of calcium phosphate as a sealer-filler material is described in Chohayeb et al., *J. Endodontics* (1987) 13:384-387. See also, Ohwaki et al., 13th *Ann. Mtg. of the Soc. for Biomaterials*, June 2-6, 1987, New York, NY, p. 209.

SUMMARY OF THE INVENTION

Calcium phosphate minerals are prepared using highly concentrated phosphoric acid as a liquid or solid, a source of an alkaline earth metal, particularly calcium, usually at least in part basic, usually a base source, water, and optimally hydroxyapatite crystals. The components are thoroughly mixed to provide a substantially uniform mixture, at which time the product may be shaped, followed by annealing and hardening to a final stable form. Ceramic fibers, proteins and/or organic polymers may be added to this product during mixing to give the final product specific material properties.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Methods and compositions are provided for producing bone-like materials comprising structures analogous to the naturally occurring calcium phosphate minerals, particularly fluoro- and hydroxyapatite. The products are readily formed by combining the reactants to provide a substantially uniform mixture, shaping the mixture as appropriate, and allowing the mixture to anneal and harden. The reactants are for the most part a phosphoric acid source, substantially free of unbound water, an alkaline earth metal source, optimally crystalline nuclei, particularly calcium phosphate crystals, more particularly hydroxyapatite crystals, a source of base, particularly hydroxide and/or carbonate, and water. The dry ingredients may be preprepared as a mixture and combined with the liquid ingredients, under conditions where substantially uniform mixing occurs. Where gases evolve, the mixture is agitated, so as to provide for the release of any large pockets of gas. After a short mixing time period, the mixture is allowed to anneal while remaining quiescent, followed by an extended period of time of hardening.