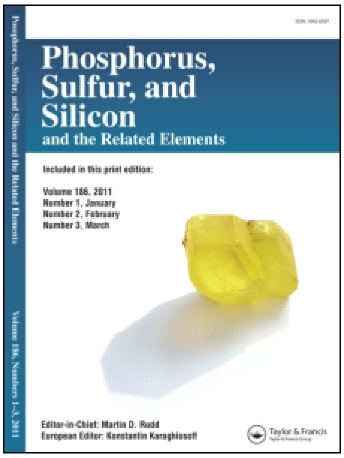

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Hydroxyapatite-Polymer Composites

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An hydroxyapatite (HAp)/collagen composite can be regarded as an example of an inorganic/organic composite which forms in mineralizing systems. The principles governing the *in vivo* formation of HAp-based composites can be mimicked. This is desirable because composites self-assemble at low temperature and at net shape. Thus, it is possible to form synthetic analogs of hard tissues by chemical processes which occur *in vivo*. Accordingly, model matrix and mineralizing materials which form inorganic composites by processes and emulate the formation of composites of biological origin have been identified and investigated. A variety of HAp/polymer composites can be prepared under conditions compatible with their formation *in vivo*. These include HAp-gelatin, HAp-collagen, HAp-polyacrylics, and HAp-polyphosphazenes. The factors governing the formation of composites will be reviewed with consideration being given to the relationships between polymer chemistry, the chemistry driving the reactions to form HAp, and the materials properties attained.

Keywords: hydroxyapatite; polymers; composites

INTRODUCTION

Potential attributes of organic-inorganic composites as biomaterials are high toughness and minimal geometric constraint. In contrast to "filled" polymer composites there are a number of systems which consist of combinations of organic polymers and inorganic materials. In these types of composites the mutual presence of each constituent substantially influences composite behavior through synergistic chemical effects. Accordingly, properties are developed which are unique to these composites. One system is "macro-defect free (MDF) cements." A typical MDF cement is a combination of a calcium aluminate capable of hydrolysis and polyvinyl alcohol (PVA)[1]. Property development in this composite occurs as the result of the solubilization of aluminum ion or aluminate species which form crosslinks with the PVA[2,3].

A second class organic-inorganic composites is glass-ionomer cements[4]. These materials are combinations of polyacidic polymers, such as polyacrylic acid (PAA), and basic ion-leachable glasses. The polymers used are water soluble. Polymers in particulate form or in aqueous solution are mixed with a finely ground calcium aluminosilicate or calcium fluoroaluminosilicate glasses. Property development occurs as calcium or aluminate ions, leach from the glass and facilitate deprotonation of the acidic polymer. As with MDF cements, crosslinks form and composites having rather high strengths develop.

Glass-ionomer cements and MDF cements share a characteristic in common. Both rely on the crosslinking by an aluminate species. Property development occurs by two, distinct mechanisms. One involves the crosslinking of the ionomer and the other involves the formation of inorganic hydrates. Using the reaction between a calcium aluminosilicate glass and PAA as an example, hydrolysis of the glass increases the basicity of the solution.

This causes a conformational change in the polymer as the carboxyl groups become ionized. The ionized groups then become initially cross-linked by divalent calcium. However, eventually the calcium ions become displaced by aluminum ions.

A third class of composite materials are made when acid catalyzed sol-gel reactions are carried out in the presence of polyacidic polymer. This can be done under anhydrous conditions or under aqueous conditions. An example of an anhydrous reaction is that of carboxy-telechelic polybutadiene in non-aqueous solutions containing metal alkoxides. An example of an aqueous phase reaction involves that in the tetraethoxysilane (TEOS)-poly(tetramethyl oxide) PTMO system. Significantly, the morphology of the inorganic, silicate phase is strongly mediated by the presence of the organic matrix[5].

Common among these composites is the ability of the inorganic constituent to hydrolyze in water with an inorganic matrix forming by dissolution-precipitation reaction and the ability of the polymeric constituent to participate in this process by incorporating hydrolyzed cations, by influencing the crystallization of the inorganic constituent, or both. The present paper discusses the formation of composites in which the inorganic constituent is HAp. Depending on the manner by which HAp interacts with the polymeric constituent, composite formation may be accelerated or retarded and property development will be strongly affected.

HAp FORMATION

Monolithic HAp can be formed by a variety of reactions which involve the direct hydrolysis of particulate calcium phosphate precursor solids. Two reactions for the formation of stoichiometric and calcium-deficient HAp, respectively, at physiologic temperature are as follows [6,7]:

$$2\mathrm{CaHPO_4(\cdot 2H_2O)} + 2\mathrm{Ca_4(PO_4)_2O} \Rightarrow \mathrm{Ca_{10}(PO_4)_6(OH)_2}\ (+\ 4\mathrm{H_2O}) \qquad \text{EQ. 1}$$

$$6\mathrm{CaHPO_4(\cdot 2H_2O)} + 3\mathrm{Ca_4(PO_4)_2O} \Rightarrow 2\mathrm{Ca_9(HPO_4)(PO_4)_5OH}\ (+\ n\mathrm{H_2O}) \qquad \text{EQ. 2}$$

with $n = 1$ or 13. The preparation of precursors and the factors controlling reaction kinetics have been discussed elsewhere[6,7] but typically involves the formation of particulate $\mathrm{Ca_4(PO_4)_2O}$ by pyroprocessing and comminution. $\mathrm{CaHPO_4(\cdot 2H_2O)}$ is produced by acid-base reaction and drying. However, the clinical relevance of HAp formed by EQ. 1 and EQ. 2 depends on a variety of factors. Among them are the rates of reaction, the conditions in solution during reaction, the composition of the HAp which forms, and its physical characteristics. Although it has been demonstrated that HAp exhibiting a compressive strength as high as 170 MPa can be formed[8], the applications for such preparations will be limited by the tendency of inorganic, nonmetallic solids to fail catastrophically. Additionally, because the reactions shown in EQ. 1 and 2 occur through solution, residual porosity will be present after they have reached completion. From the standpoint of physical property development, the presence of porosity is detrimental. For these reasons, it is desirable to incorporate a polymer.

COMPOSITE FORMATION

Composites comprised of acrylics and various inorganic constituents (ZnO, glasses, etc.) are familiar in dental applications[9]. Recent work has demonstrated that composites can be formed using acrylic-based polyelectrolytes and basic calcium phosphates e.g.[10,11]:

$$\mathrm{Ca_4(PO_4)_2O} + \text{Polyacrylic acid (PAA)} \Rightarrow \text{HAp} + \text{Ca-polyacrylate} \qquad \text{EQ. 3}$$

Particulate $Ca_4(PO_4)_2O$ is mixed with particulate PAA or with PAA solution. The former requires the application of heat and pressure to drive composite formation[11] which occurs by simultaneous acid-base and dissolution-precipitation reactions; Ca and hydroxyl ions are liberated as $Ca_4(PO_4)_2O$ dissolves. These neutralize and cross-link with carboxyl acid sites on the PAA; both the Ca salt of PAA and HAp precipitate. Composites formed in this way can exhibit significant physical properties. The PAA solution contributes to property development as its Ca salt forms and a commensurate reduction in porosity is achieved. However, because the composite is comprised of a salt-bridged polymer and a ceramic, it will still tend to exhibit a low strain capacity and fail catastrophically.

Controlling the nature of the interaction between composite constituents has been shown to affect the failure mechanism. For example, composites have been constituted by forming calcium-deficient HAp according to EQ. 2 in the presence of poly[bis(carboxylatophenoxy)phosphazene[12]. While the opportunity exists for the formation of salt bridges similar to those formed according to EQ. 3, two factors limit salt bridge formation in these composites. The polyphosphazene is less acidic than PAA[13] and the bulky phenoxy groups limit the extent of salt bridge formation due to steric hindrance. Thus, compared to HAp-PAA composites, control of polymer conformation can be used to influence properties. In this circumstance, composite properties can also be influenced by the proportions of the organic and inorganic constituents. This is shown in Figure 1[after 12] which plots stress-strain curves for HAp produced according to EQ. 2 along with those for composites constituted at calcium phosphate precursor-to-polymer weight ratios of 20-to-1, 10-to-1 and 5-to-1. The figure illustrates the mode of failure changes from catastrophic in the absence of polymer (curve a) to ductile when the inorganic-to-organic ratio is approximately 5-to-1 (curve d).

In producing composites to serve as synthetic analogs of bone (a collagen-HAp composite) it is desirable to permit their formation *in vivo* while retaining the porosity which facilitates boney ingrowth. However, it is also highly desirable to avoid catastrophic failure. The presence of porosity and the ability to tolerate the presence of cracks are conflicting requirements. These conflicting requirements are resolved in bone architecture by controlling the interaction between the individual polypeptide chains which form collagen and those between the collagen fibrils and bone mineral (HAp). Thus, natural hard tissue composites offer attributes desirable in synthetic analogs. In addition to these functional requirements, *in vivo* formation requires the reactions leading to composite formation proceed to a sufficient extent to permit timely surgical closure.

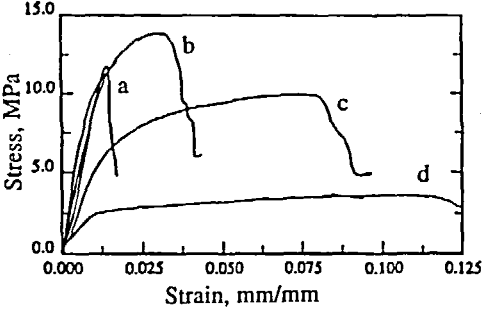

Figure 1. Stress-stain curves for HAp-polyphosphazene composites.

Gelatin and collagen are compositionally similar; both are polypeptides whose chains contain the same sequences of amino acid groups. Gelatin is denatured collagen and the tripeptide assembly associated with collagen is destroyed. Figures 2 and 3 compare the rates of formation of gelatin-HAp and collagen-HAp formation when calcium-deficient HAp is formed by EQ. 2. Figure 2 [after 14] compares the rates of HAp formation depending on the presence of gelatin. Figure 2 shows rate curves for HAp formation in D.I. water when composites are constituted to produce HAp-to-gelatin volume ratios of 10-to-1, 5-to-1 and 2-to-1 at 38°C. This figure illustrates that HAp formation is indifferent to the presence of gelatin, reaching completion in about 5.5 hours regardless of the presence of gelatin. Figure 3 [after 15] shows the effect of the presence of Type I collagen on HAp formation at 38°C. Sigma collagen was processed by chemical and thermal means to develop a tennis net-like structure which contained interstices of approximately 5 µm[15]. Although Figures 2 and 3 both illustrate the rate of calcium-deficient HAp formation by EQ. 2, the kinetics differ because of variations in the particle size distributions in the calcium phosphate precursors. Figure 3 shows HAp formation in the absence of collagen reaches completion in about 4.5 hours. When calcium phosphate precursors and collagen are constituted at weight ratios of 22-to-1, 11-to-1 and 4.5-to-1, the rates of HAp formation increase with an increasing proportion of collagen. HAp formation is complete after about 2.5 hours at the highest proportion of collagen. The data in Figures 2 and 3 again illustrate the importance polymer conformation in directing composite formation.

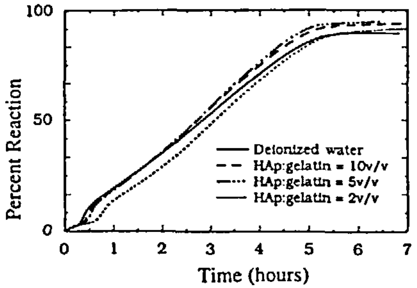

Figure 2. Rates of HAp formation in HAp-gelatin composites.

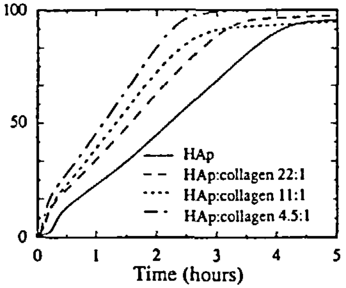

Figure 3. Rates of HAp formation in HAp-collagen composites.

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