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A Mineralogical View of Apatitic Biomaterials

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Abstract

Biomaterials are synthetic compounds and composites that replace or assist missing or damaged tissue or organs. This review paper addresses calcium phosphate biomaterials that are used as aids to or substitutes for bones and teeth. The viewpoint taken is that of mineralogists and geochemists interested in (carbonated) hydroxylapatite, its range of compositions, the conditions under which it can be synthesized, and how it is used as a biomaterial either alone or in a composite. Somewhat counterintuitively, the goal of most medical or materials science researchers in this field is to emulate the properties of bone and tooth, rather than the hierarchically complex materials themselves. The absence of a directive to mimic biological reality has permitted the development of a remarkable range of approaches to apatite synthesis and post-synthesis processing. Multiple means of synthesis are described from low-temperature aqueous precipitation, sol gel processes, and mechanosynthesis to high-temperature solid-state reactions and sintering up to 1000 °C. The application of multiple analytical techniques to characterize these apatitic, frequently nanocrystalline materials is discussed. An online supplement details the specific physical and chemical forms in which synthetic apatite and related calcium phosphate phases are used in biomaterials. The implications of this overview are the enhanced recognition of the structurally-chemically accommodating nature of the apatite phase, insight into the effects of synthesis techniques on the specific properties of minerals (specifically apatite), and the importance of surface chemistry of apatite nanocrystals. The wide range of synthesis techniques, types of analytical characterization, and applications to human health associated with apatite are a non-geological demonstration of the power of mineralogy.

Key words: apatite, calcium phosphate, biomaterial, synthesis, bone, hydroxylapatite

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On-line Appendix (extensive)

Introduction

The mineral component in bones and teeth is a highly carbonate-substituted, hydroxyl-deficient form of hydroxylapatite, $Ca_{10}(PO_4)_6(OH)_2$. Bone and tooth are referred to biologically, geologically, and medically as biomineralized tissues or biomineralized materials. Intriguingly, however, they are not called "biomaterials." For the past few decades the latter word has been reserved for synthetic materials, including those that contain apatite, that temporarily or permanently replace biological tissues in humans or other animals (Williams 1987). In the words of Donglu Shi, "Biomaterials are artificial materials utilized to repair, assist, or replace damaged or missing tissue or organs...biomaterials can be classified into four different categories: metals, ceramics, polymers, and composites" (Shi 2006, p. 211). By this definition, synthetic forms of apatite and related calcium phosphate phases used to assist diseased or damaged bone or tooth tissue are ceramics or bioceramics.

The increasing need for such synthetic replacements arises not only from an expanding population, but also from the increasing percentage of senior citizens. For example, over 1,200,000 hip and knee surgeries/replacements occurred worldwide in 2013. Although apatitic materials are not strong enough to be used alone in load-bearing situations, such as the hip joint, they are critical as coatings on those stronger biomaterials, enhancers of new bone growth, and implants that do not support heavy loads. As illustrated in Figure 1, modern applications include treatments related to bone fractures, bone defects, cranio-maxillofacial reconstruction, dental implants, and spinal surgery (Hench and Wilson 1993; Dorozhkin 2010; Heimann 2013).

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The types of natural apatite in the body and the biological responses to them are a reflection of apatite's range of mineralogical-geochemical properties. Multiple papers over the years have highlighted apatite's remarkable chemical-structural adaptability (Beevers and McIntyre 1946; Hughes et al. 1989; Elliott 1994; Kohn et al. 2002; White et al. 2005) as revealed, for instance, by its ability to accept in solid solution up to half of the elements in the periodic table (Pan and Fleet 2002; Hughes 2015), to retain or recover its crystallinity even under assault from the decay of structurally incorporated radioactive elements such as uranium (Ewing and Wang 2002; Harrison et al. 2002; Fox and Shuster 2014), to form in large-volume apatite deposits through both low-temperature aqueous precipitation and high-temperature igneous crystallization (Knudsen and Gunter 2002; Ihlen et al. 2014), and to constitute two distinctly different types of biological apatite (Neuman and Neuman 1953; McConnell 1962; Young 1975; LeGeros and LeGeros 1984; Daculsi et al. 1997; Baig et al. 1999; Elliott 2002; Wopenka and Pasteris 2005; Glimcher 2006; Boivin 2007; Rey et al. 2009) in bone (typically with 5-8 wt% CO_3^{2-} substitution) and tooth enamel (2-4 wt% CO_3). All of the above natural geological and biological forms of apatite have been analyzed and interpreted by mineralogists and other geoscientists, as well as by medical researchers and materials scientists. Likewise, medical researchers and materials scientists, but few geoscientists, have described various biomedical applications of apatite (cf. Heimann et al. 1997; Gross and Berndt 2002; short summary in Rakovan and Pasteris 2015). The goal of the current paper is to describe and interpret apatitic biomaterials from a mineralogical viewpoint and to indicate research directions to which geoscientists could contribute.

Criteria for bioapatite substitutes

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The two biological hard tissues that contain apatite, i.e., bones and teeth, exhibit many differences as well as similarities. Specialized apatite biomaterials therefore are required according to the anatomy and function of the original body tissue. Human bone comprises about 55-60 wt% apatite, ~30 wt% of the fibrous protein collagen I, and ~10-15 wt% water (Rogers and Zioupos 1999). Bone is a nanocomposite in which bundles of collagen molecules, each molecule less than 2 nm in diameter, form a scaffold that acts to nucleate and spatially organize plate-like crystallites of carbonated apatite that are on the order of a couple of nanometers thick, about 10-20 nm wide, and 20-50 nm long (Skinner 1987; Weiner and Wagner 1998; Rogers and Zioupos 1999; Glimcher 2006; Alexander et al. 2012; Wagermaier et al. 2015). The mineral and collagen are strongly bound to each other through (bio)chemical affinities that are still under study (Sahai 2005; Landis and Jacquet 2013), but it is well known that this nanocomposite has a strength and flexibility that are not possessed by either of its major constituent phases (Rogers and Zioupos 1999; Currey 2006). Another important aspect of bone is that it undergoes periodic, stress-induced replacement through a process called remodeling, in which specialized cells (osteoclasts) dissolve small controlled volumes of mineral and collagen, which subsequently are replaced (via osteoblasts) by new organized collagen and apatite (Glimcher 2006). Bone apatite therefore must be sufficiently reactive in the acid produced by the osteoclasts to dissolve fully on a relatively short time scale. At the millimeter scale of bone's hierarchical structure, one can distinguish two types of material, i.e., (1) cortical bone – a very compact nanocomposite with little porosity, which forms the external hard tissue in the outer portions of long bones like those in the legs and arms and (2) trabecular bone – a very porous (up to 90 vol.%), spongy-looking material in which the bone forms individual struts oriented in multiple directions, filling the ends

of long bones and the central regions of most bones, adjacent to the marrow cavity (Albright and Skinner 1987; Glimcher 2006).

The anatomy of a tooth exhibits an even greater range of differences between its mineralized sub-regions. The outermost surface of human teeth is covered and protected by a form of bioapatite called enamel. Like bone, enamel is a nanocomposite of bioapatite and organic components, but enamel differs from bone in multiple ways: it is > 95 wt% mineral (apatite), with the remainder as water and proteins other than collagen; its crystallites are about 10 times larger in width and thickness than in bone, but 1000+ times longer. Whereas about 5-8 wt% CO_3^{2-} typically is substituted (mostly for PO_4^{3-}) in the apatite of bone mineral, enamel has only about 2-4 wt% CO_3^{2-} (LeGeros and LeGeros 1984; Elliott 2002; Glimcher 2006). Enamel also is not remodeled or replaced by the body. Beneath and grading into the enamel is the dentin, which is a much more bone-like material in its collagen content and bioapatite mineral chemistry, but dentin does not undergo remodeling (Carlson 1990). Molars are specialized structures that can be placed under very large forces, i.e., up to 1.6 MPa pressure and over 350 N force on portions of human molars during chewing. Such forces are not evenly distributed across the tooth surface, illustrating the high strength and toughness required of enamel and its biomaterial substitutes (Kohyama et al. 2004; Ferrario et al. 2004).

It might appear that, with more detailed information (which does exist) about the biomineralized tissues above, the immediate goal of biomaterials research and the huge biomaterials industry would be to synthesize exact replicas of the natural tissues. Although that may be the ultimate goal, the multi-leveled hierarchical structures of teeth and bones presently elude our synthesis capabilities. The more immediate and attainable goals have been to measure

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and fully characterize the mechanical and chemical properties of natural biomineralized tissues with the aim of simulating the latter's physical (especially mechanical) and chemical capabilities during application, i.e., replicating functionality rather than material chemistry and structure. Thus, we see references in the quotation above to biomaterials constructed from metals, polymers, and ceramics, as well as statements in the literature heralding zirconia as the optimal material for bone repair (Afzal 2014). The broader field of tissue engineering encompasses an even more demanding goal in "the development of biomaterials that can promote regenerative processes...transporting cell populations and therapeutic agents,...providing structural scaffolding..." (Lee et al. 2014, p. 324).

Biological constraints and terminology

To be deemed successful, biomaterials must meet certain criteria and operate within biologically necessary constraints, as illustrated in the terminology applied to these synthetic materials.

Biocompatible: materials that can persist and function appropriately in the biological environment without causing negative reactions in the biological tissue or the biomaterial. Three important attributes of biocompatibility for biomaterials consideration are biochemical compatibility (absence of toxicity, excessive inflammation, or carcinogenicity), biomechanical compatibility (e.g., reasonable match in stiffness) with surrounding tissue, and biological adhesion at the material-tissue contact (LeGeros 1988; Basu and Nath 2009). Some of the more specific attributes of biocompatible materials are described by the following terms.

Bioinert: materials that do not induce bioadhesive bonding between the biomaterial and tissue, e.g., bone. They also do not cause negative reactions, but they may induce non-adherent

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capsules of scar tissue. Examples are alumina, zirconia, titania, and silicon nitride.

Bioactive: materials that can induce direct bio-adhesion at a tissue interface, i.e., through chemical and biological bonding, typically early in the post-implantation period, without intervening fibrous tissue. The phase that does form at the interface is carbonated hydroxylapatite, similar to that in bone.

Bioresorbable: materials that are gradually dissolved and eventually totally replaced by new tissue in vivo; ideally their resorption rate is very similar to the rate of tissue replacement in vivo (Shi 2006; Basu and Nath 2009; Heimann 2013).

The following terms are specifically applicable to biomaterials used for the replacement or reconstruction of bone.

Osteoinduction: ability to promote growth of new bone; stimulation of progenitor cells leading to the formation of ***osteoblasts*** (bone-precipitating cells).

Osteoconduction: supporting the formation of bone on a material's surface, stimulating ingrowth of surrounding bone, acting as a template or scaffold to guide the formation of new bone, which requires interconnectivity of pores at appropriate spatial scales.

Osteointegration: chemical bonding directly with bone, without intervening fibrous tissue; e.g., incorporation of an implant within bone to the extent that the implant is anchored, physically stabilized, integrated into surrounding bone.

Osteogenesis: process of forming a layer of new bone (LeGeros et al. 2003, 2009; Kretlow and Mikos 2007; Stevens 2008; Shepherd and Best 2011).

The role and properties of biological apatite

Apatite plays more than one role in vertebrate tissue. Not only is it the functionally

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222 necessary hard phase in natural bone and tooth nanocomposites, but it also is the major chemical
223 reservoir of both calcium and phosphorus in the body. In case the biological/medical need arises
224 for more Ca or P to be available in body fluid, bone can be resorbed by osteoclasts to release
225 those elements (Glimcher 2006; Boskey 2007). Moreover, the specific composition of the
226 bioapatite, namely the carbonate:phosphate ratio, is both a monitor of and a buffer for the pH of
227 body fluid (Bushinsky et al. 2002). The fact that osteoclast and osteoblast cells are already
228 biologically programmed (Kanayama et al. 2011; Nakamura et al. 2016), respectively, to resorb
229 non-optimal calcium phosphate stores (e.g., old bone) and replace them with new, fully
230 functional bone also ensures apatite's enduring appearance among the constituents of
231 biomaterials.

232 There are multiple instances in which substitutes for natural bone and tooth materials are
233 required. The example of missing whole or partial teeth is the most straightforward to
234 understand. There is no biological mechanism for large-scale repair or replacement of the tooth,
235 in contrast to bone. The ability of bone to heal itself, however, is more limited than typically is
236 recognized. If a defect in the bone, for instance due to removal of a tumor, exceeds a critical size
237 (depending upon the animal in question), the body will not span the breach with woven bone as it
238 does for a simple fracture. Some bones with relatively small breaches also do not heal fully (i.e.,
239 nonunion bone defects), for instance, due to infection or insufficient blood flow to transport
240 needed ions and cells. Biomaterials are required to fill the breach and enable the bone to
241 recover. Although both the collagen and mineral component of the bone are required for optimal
242 regeneration, this review only addresses the mineral component.

243 One of the persistent misconceptions in the medical literature on bone is that

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hydroxylapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$, is the mineral constituent in bones and teeth. This oversimplification has made its way into the biomaterials literature, essentially ensuring that stoichiometric HA is often selected for the mineral component in biomaterials. The actual composition of bone mineral, however, is more like those shown in Skinner's (2005) compilation or the formula $(Ca_{8.61-y}Mg_{0.2}Na_{0.42})[(PO_4)_{5.02-y}(CO_3)_{0.98}(HPO_4)_y](OH)_{1.02-y} \bullet 1.5H_2O$, which is a composition based on electron microprobe analyses of a hypermineralized (>95 wt% apatite) bone (Li and Pasteris 2014). The subscripted "y" indicates an unknown but significant concentration of $(HPO_4)^{2-}$ that will cause even greater depletion in OH and some additional charge-balancing in the Ca-site. Note also the approximately 3 wt% of lattice-incorporated molecular H_2O that, together with anions such as OH^-, resides in the channel sites (Yoder et al. 2012a; Pasteris et al. 2014). In any event, the strongly carbonated and hydrated phase that comprises bone apatite is significantly different in composition from HA, which accounts for bone apatite's higher solubility, smaller crystallite size, plate-like (rather than prismatic) morphology, and incorporation of large amounts of both adsorbed and structural water in distinction to stoichiometric HA. Its ability to accommodate variations in composition accounts for much of apatite's biocompatibility and osteoconductivity (Heimann 2013).

Some guiding principles for bioapatite-substituting materials

The above comments on the currently dominant trends in the biomaterials industry should not be interpreted to mean there is a dearth of research on how to simulate the true composition of bioapatite or how to mimic the hierarchically organized nanocomposite of actual bone. For multiple decades there have been research groups that experimentally have explored pathways to creating carbonated apatites with all the pertinent properties of bone apatite (e.g., Neuman and

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Neuman 1958; LeGeros et al. 1969, 1978; Termine 1972; Posner 1985; Rey et al. 1994, 1995, 2009; Daculsi et al. 1997; LeGeros 2008; Eichert et al. 2009; Tas 2014) and that have analyzed in detail the structural and chemical properties of bone (e.g., Robinson 1955; Biltz and Pellegrino 1969; Zipkin 1970; Driessens and Verbeeck 1990; Veis 1993; Weiner and Wagner 1998; Elliott 2002; Glimcher 2006; Boskey 2007; Grynpas 2007; Xie and Nancollas 2010; Chen et al. 2011; Landis and Jacquet 2013; Reznikov et al. 2014; Tao et al. 2015). There are also multiple laboratories that are synthetically producing apatite-mineralized collagen (and other polymer) constructs in an attempt to mimic the nano- to micro-meter scale hierarchy of bone (e.g., He et al. 2003; Olszta et al. 2007; Deshpande and Beniash 2008; Nudelman et al. 2010, 2013; Liu et al. 2011, 2014; Habraken et al. 2016).

There is a clear need for bone and tooth substitutes. Bone material is second only to blood as the most often transplanted tissue (Jones 2013). The first documented application of a calcium phosphate (Ca-P) component to stimulate bone growth/regeneration is a 1920 article describing experiments in which 1-ml aqueous aliquots of 5 wt% $Ca_3(PO_4)_2$ were injected into surgically induced 6.3-mm gaps in dogs' legs. X-ray images of the affected legs showed remarkably faster healing in the presence of just one such injection compared to untreated controls (Albee and Morrison 1920). Almost one hundred years later, however, why do we still focus on calcium phosphate/apatite? Why do we not exclusively choose stronger, lighter substances with enhanced biomechanical functionality? Certainly, the inherent biocompatibility of apatite is difficult to surpass, but Shepherd and Best (2011) identify apatite's prize characteristic as its bioresorbability. The use of an appropriate composition of apatite for bone replacement or reconstruction assures that the body does not have to permanently host a foreign

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material, but rather that the original bone defect eventually becomes totally filled with and strengthened by new, natural bone that has replaced a temporary, apatitic biomaterial. Habraken et al. (2016) predict a bright future for Ca-P biomaterials as they continue to evolve.

The properties of apatite that must be emulated (either by the implanted materials or the new bone that replaces the implants) are those imparted by nanometer-scale crystallite size, ability to accommodate variations in composition, calcium deficiency compared to HA, appreciable carbonate substitution in the structure, and atomic disorder that varies with the concentration of carbonate. Experimental and clinical observations should guide the selection of what compositions of apatite to use as bone substitutes and how to produce them. For instance, in a comparison of responses to implant materials, carbonated HA was associated with increased bone production over stoichiometric HA (Ellies et al. 1988; Rupani et al. 2012). In both in vitro (Kanayama et al. 2011) and in vivo tests, carbonated apatite is more readily resorbed by osteoclasts and replaced by new bone than is HA (Bang et al. 2014; Nakamura et al. 2016).

Whatever the calcium phosphate implant material, if its resorption rate is too slow, growth of new bone is hindered. On the other hand, if the resorption rate is too fast, gaps develop between the implant and the newly forming bone, possibly leading to mechanical failure (Nilsson et al. 2013). For example, the stoichiometric HA phase does not dissolve passively over time in the body; it must be biologically resorbed via osteoclast activity, i.e., through addition of acid. Moreover, HA that is synthesized at or subsequently processed at elevated temperature is highly crystalline and therefore remarkably un-bonelike. Such material can persist unresorbed in the body for tens of years. Thus, the degree of crystallinity, which strongly affects solubility, is a property of great significance in the formulation of apatite used as a biomaterial.

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Much of the biocompatibility, bioactivity, and bioconductivity of bone arises from the surface properties of its crystallites. The surfaces contain not only ions of the dominant elements in the crystal lattice, but also minor ions such as Na^+, K^+, Mg^{2+}, and HPO_4^{2-}, that affect the charge as well as chemical properties of the surface.

Calcium-phosphate-based phases used in biomaterials and desired properties

In the system CaO-P_2O_5-H_2O are several calcium phosphate phases that are relevant medically as biomaterials (see Table 1) and, to some extent, biologically in the formation of bone and tooth (Skinner 1973; Brown 1992). These materials differ from each other chemically, e.g., in their Ca:P atomic ratios, the pH-sensitivity of their stabilities, and their solubilities, which are of great importance. The solubility of Ca-P phases in water (see Figure 2) and in body fluid (Johnsson and Nancollas 1992) is inversely proportional to their Ca:P ratio. Phases with a Ca:P ratio less than 1 may not be implanted alone in the body, because they are either too soluble or too acidic (Dorozhkin 2010). Ca-P phases also differ in the method by which they are synthesized, either (1) by precipitation from an aqueous solution below 90 °C or (2) by chemical synthesis or post-synthesis processing at high (400-1200 °C) temperature (Oliveira and Reis 2005). Many materials scientists still insist on high-temperature sintering of their biomimetically produced materials, e.g., Na-substituted HA (Rupani et al. 2012: 700°C; Cho et al. 2013: 1100 °C). This sequence of materials handling seems counterintuitive. Although high-temperature processing enhances the strength of such materials, as well as their crystallinity, it reduces their bioactivity and bioresorption, thereby strongly decreasing the initial biomimetic character of the product.

The crystalline Ca-P phases used most frequently in biomaterials are hydroxylapatite

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(HA) and tricalcium phosphate (TCP), which exists in two polymorphic forms, α-TCP and β-TCP (see Figure 3), where α-TCP (labeled on diagrams as α-C_3P) is the higher-temperature form (see Table 1 for both sets of abbreviations). Only two Ca-P phases are stable in the presence of body fluid or water at body temperature, and their stabilities are pH dependent (Fig. 2): dicalcium phosphate dihydrate (DCPD), i.e., brushite ($CaHPO_4•2H_2O$; Ca:P = 1.0), stable at pH < 4.2, and HA (Ca:P = 1.67), stable at pH > 4.2 (Riboud 1973; Kreidler and Hummel 1967; Oliveira and Reis 2005; Shi 2006).

As documented in detail in Brown's (1992) study on the ternary system CaO-P_2O_5-H_2O at 25 °C (see Figure 4), the phase relations in the compositional region of Ca:P = 1.0-1.67 are more complex than typically has been acknowledged. For instance, there is a significant solid solution field for "hydroxylapatite," extending from stoichiometric $Ca_{10}(PO_4)_6(OH)_2$ [Ca:P = 1.67] to so-called calcium-deficient apatite $Ca_9(PO_4)_5(HPO_4)(OH)$ [Ca:P = 1.5]. Moreover, HA dissolves congruently, whereas $CaHPO_4$ and $CaHPO_4•2H_2O$ dissolve incongruently. Phase relations in the ternary system at just about ten degrees higher than shown in Figure 4b are directly applicable to the reaction(s) that produce natural bioapatite and those by which some biomaterials are aqueously precipitated. The ternary system at 200 °C, as shown in Figure 4a, represents phase relations at the low end of the sintering temperature range.

Although HA typically (however misguidedly) is recognized as the phase most similar to bone mineral and has demonstrated itself to be strongly biocompatible and bioactive, stoichiometric well crystalline HA both dissolves and precipitates at the slowest rate among all the Ca-P bioceramic phases, making it bioactive, but essentially non-resorbable by passive means in the body. In contrast, the much more soluble TCP (Fig. 2) has a dissolution rate so

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high that it exceeds that of the regeneration of bone tissue. Application of TCP therefore is typically in the form of a mixture of TCP and HA (LeGeros et al. 2003; Shi 2006).

Apatite has lackluster mechanical properties (see Table 2). For this reason, monolithic constructs of pure HA and other HA bioceramics are not used as load-bearing biomaterials, but rather as micro- and nano-particulate powders, coatings, and porous scaffolds (Shi 2006). HA, however, works effectively in composites with other crystalline materials (e.g., Al_2O_3 or ZrO_2), with natural (e.g., collagen) and synthetic (e.g., polyethylene, polylactic acid) polymers, and -- most importantly -- as a coating on implants such as hip and knee replacements (Nath and Basu 2009; LeGeros et al. 2009; Heimann 2013, 2016).

Synthesis Methods of Apatite for Use in Biomaterials

The synthesis technique determines not only which Ca-P phase is produced, but also the properties of that phase, such as solubility, morphology, porosity, surface activity, and crystallite size. Somewhat counterintuitively, most apatite in biomaterials either has been synthesized at or subsequently processed (i.e., sintered) at high temperature (400-1200 °C), presumably to produce a more stiff, easily handled material. The most common Ca-P phase in biomaterials is stoichiometric HA. The first Ca-P phases used as biomaterials were HA and β-TCP, both synthesized at high temperature. As mentioned above, they often are used together as what is called biphasic calcium phosphates, BCP (LeGeros et al. 2003; Daculsi et al. 2009, 2010), due to their different rates of resorption (Eichert et al. 2009). Hench (1998) provides detailed discussions of clinical applications of individual biomaterials. The current state of knowledge about the structure and composition of high-temperature, high-pressure carbonated

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hydroxylapatite is documented and discussed in Fleet (2015). Additional, more specific information on the physical forms in which Ca-P materials are manufactured for biomedical use and some of the biological responses to their use appears in the online supplement.[1]

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[1] Deposit item AM-....., Supplementary Material. Deposit items are free to all readers and found on the MSA web site, via the specific issue's Table of Contents (go to http://www.minsocam.org/MSA/AmMin/TOC/).

There is, however, increasing interest in low-temperature (room temperature to about 400 °C) synthesis techniques that can be tailored to produce a range of chemical compositions (e.g., carbonate concentration), lead to a more biomimetic product, and save energy (Eichert et al. 2009). Such low-temperature materials tend not to be HA but rather non-stoichiometric and Ca-deficient apatite, as are bone crystallites. Their Ca-deficiency can be controlled by the temperature and pH of precipitation, mainly through the equilibrium concentration of HPO_4^{2-} in the solution.

The above interest in more biomimetic synthesis techniques is consonant with current emphasis on the bioactivity and osteostimulation properties of apatitic biomaterials. There is increasing recognition of the importance of detailed physical and compositional features of the materials synthesized. Physically, those mesenchymal stem cells (from bone marrow) that differentiate into bioapatite-precipitating osteoblasts are sensitive to micrometer- and nanometer-scale topography on biomaterials. Their cell differentiation occurs more rapidly on a surface of randomly distributed pits than on one with a highly ordered array of such pits (Stevens 2008).

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This response suggests that an atomically disordered apatite might be biologically favored. Compositionally, recognition that Mg^{2+} (up to about 0.75 wt%) and $(CO_3)^{2-}$ (up to ~7 wt%) are significant components in bone apatite has provided pathways to increased tailoring of the properties of apatite synthesized for biomaterials (Suchanek et al. 2004; Nakamura et al. 2016). As briefly described below, the solid-state and wet-chemical techniques used to synthesize apatite strongly affect the mineral's internal and surface properties.

Solid-state reactions

Stoichiometric HA can be formed at elevated temperatures by reacting $Ca(OH)_2$ with either $CaHPO_4$ or $Ca_3(PO_4)_2$ accompanied by release of excess H_2O. The raw materials typically are ground, mixed, compressed, and then sintered at > 950 °C to enhance ion diffusion. Substituted apatites, such as with Sr for Ca and F for OH substitutions, can be created with the addition of other reagents to the above. Ion diffusion in the solid state leads to well crystalline HA. Varying the ratio of the reactants can lead to biphasic products such as TCP + HA, which are desired end-products for certain uses (LeGeros and LeGeros 1993; Shi 2006; Shepherd and Best 2011).

Plasma-sprayed hydroxylapatite coatings

Biomaterials must fulfill the demands of both biocompatibility and appropriate mechanical properties. To meet the demands for strength, as in the replacement of the total hip joint or tooth socket, a metal (e.,g., steel, titanium) implant may be called for. Metals, however, are not osteoinductive or osteoconductive. A transitional phase is needed to stably bond with the metallic implant, as well as to induce bonding with the existing adjacent and newly forming bone. Apatitic coatings are ideal for this purpose, as shown by the 2- to 7-fold increase in

interfacial bond strength of porous Ti when plasma-sprayed with apatite (Hench 1998). Plasma-sprayed HA coatings, as have been so effective for hip replacements and other metal implants, constitute the most widespread application of hydroxylapatite in biomaterials.

Apatitic coatings can be deposited at low (<40 °C) or high (many hundred degrees Celsius) temperatures. For plasma-spraying, the most common high-temperature process, HA particles (feedstock) are melted and projected at high velocity by a plasma (e.g., of argon) at 5000-20,000 °C. The molten droplets are flash quenched as they splat onto the surface of the target metal (Carayon and Lacout 2003; Shi 2006; Dorozhkin 2012b; Heimann 2013, 2016).

Among the challenges to the functionality of plasma-sprayed HA are its possible non-uniformity in thickness and coverage, and its crystallinity. The high temperature imparted by the plasma to the surface of an implant also can produce problems (Oliveira and Reis 2005). More details on the plasma-spraying techniques are available in the appendix.

Mechanosynthesis

Mechanosynthesis (also called mechanochemical synthesis) is typically a solvent-free technique for the synthesis of nanoparticulate compounds. For the purpose of combining metals or oxides to form compounds, mechanosynthesis appears to have become an accepted technique early in the 1990s (Sepelak et al. 2012). Only in about the past 15 years (Boudeville et al. 2001) has it been applied to Ca-P compounds, especially for production of biomaterials. The technique involves placing a few compositionally simple, solid components (e.g., oxides, salts) into a high-energy ball mill, as of the planetary ball mill type, and operating the system for periods of a few minutes to hours. This process produces a homogeneous, nanocrystalline new compound whose stoichiometry exactly reflects the ratios of the reactants (Chaikina et al. 2004; Mochales et al.

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2011).

Activation of the reaction at room temperature occurs mechanically when the dry components are impacted between two metal/ceramic balls or between one ball and the walls of the mill. Among the common reactants to produce Ca-P phases are acid phosphates (as discussed in the next section), whose reactions generate water. This internally produced water is important to the mechanochemical synthesis and to the generation of more ductile particles compared to the original brittle constituents (Chaikina et al. 2004; Fahami et al. 2015). Ca-P samples produced this way have broader XRD peaks (indicative of smaller grain size) than compositionally similar phases produced by thermal synthesis, which is attributed both to their low synthesis temperature and mechanically induced defects. Mechanochemically synthesized Ca-P materials have a particle size on the order of 15-20 nm, but the particles typically aggregate into granules up to 100 nm. The degree of (non-)stoichiometry and chemical substitution (as by CO_3, Na, K, Zn) in various apatitic products is controlled by the choice and ratio of the reactants (Chaikina et al. 2004; Suchanek et al. 2004; Mochales et al. 2011). Variations on the dry mechanochemical synthesis method include the preparation of powder-water slurries of the reactants, which are then mixed and processed in a ball mill, a technique referred to as mechanochemical-hydrothermal synthesis. Although instantaneous temperatures may be elevated at the point of impact in the ball mills, thermocouple measurements during a mechanochemical-hydrothermal experiment were close to room temperature (Suchanek et al. 2004). The most significant concern is possible contamination of the product by particles abraded from the ball mill materials.

Low-temperature, wet-chemical synthesis techniques

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Water is the solvent/reactant either for (1) chemical precipitation induced by mixing of Ca- and P-bearing solutions or for (2) hydrolysis of a single starting phase. Precipitation reactions at 25-95 °C and 1 atm can involve any of several pairs of soluble salts of calcium and phosphorus, such as $CaCl_2 + (NH_4)_2HPO_4$ or $Ca(NO_3)_2 + (NH_4)_2HPO_4$. One of the earliest procedures was to create an aqueous suspension of $Ca(OH)_2$ into which H_3PO_4 was added dropwise: $10Ca(OH)_2 + 3H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + X$. Ammonium hydroxide was added to the solution to retain a strongly basic pH, helping to assure that the HA precipitate was stoichiometric (LeGeros and LeGeros 1993). An alternative method was reaction of calcium nitrate and ammonium hydrogen phosphate, with ammonium hydroxide again added to assure high pH: $10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 2NH_4OH \rightarrow Ca_{10}(PO_4)_6(OH)_2 + Y$. Calcium acetate often was preferred over calcium chloride or nitrate, to avoid incorporation of the latter two anions in the apatite structure (LeGeros and LeGeros 1993). For the same reason, ammonium, rather than sodium, hydrogen phosphate was preferred. A soluble carbonate such as $NaHCO_3$ can be added, and the CO_3:PO_4 ratio of the solution can be used to control the degree of carbonate substitution in the apatite. Likewise, substituents for Ca (e.g., Mg, Sr), OH (e.g., F, Cl, Br), and non-carbonate substituents for PO_4 (e.g., VO_4, BO_3) can be introduced during synthesis (e.g., LeGeros and LeGeros 1993; Yoder et al. 2012b; Goldenberg et al. 2015).

If HA is the desired product, the disadvantages of the above synthesis route are its typical formation of non-stoichiometric apatite and its contamination with CO_3, HPO_4, and other ions (e.g., K, Na, NO_3, Cl) that were present in the reactants (Wilson et al. 2006b; Shi 2006; Shepherd and Best 2011). An alternative to mixing two solutions is to use a single solution of chemically simulated body fluid, SBF, in some cases at concentrations higher than physiological (such as

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1.5xSBF or 2xSBF) in order to stimulate precipitation (e.g., Tas 2014). Apatite precipitation from 1.0xSBF solutions is a reminder that body fluid actually is supersaturated with respect to bioapatite, which is prevented from precipitating by the presence of biomolecular nucleation inhibitors, except where desired (Menanteau et al. 1982; Pasteris et al. 2008; Talmage and Mobley 2009; Drouet 2013; Landis and Jacquet 2013).

Synthesis solutions must be pH-buffered to assure that apatite, e.g., not brushite, is the equilibrium product. Ion concentrations of the two reacting solutions typically are chosen to cause high degrees of supersaturation with respect to an apatite phase upon mixing. The coupling of supersaturation with the low temperature (<100 °C) of the solutions does not encourage equilibration in the system. There is evidence that an intermediate phase, such as octacalcium phosphate, often forms before and may affect the stoichiometry of the final apatite product (Brown et al. 1991; Borkiewicz et al. 2010).

The second type of low-temperature aqueous reaction that will produce an apatitic product involves hydrolysis of acid Ca-P phases that are not stable in water. Among the possible starting phases are DCPD, DCP, TCP, and OCP (see Table 1), which can produce Ca-deficient apatite powders (Shi 2006). Depending on the desired composition of the apatitic product, aqueous solutions of chloride, fluoride, carbonate, or hydroxides of sodium, potassium, or ammonium can be used. Hydrolysis of TTCP, α-TCP, β-TCP, or amorphous calcium phosphate (ACP) also yields calcium-deficient apatite. To create a less Ca-deficient apatite and thereby decrease the amount of TCP produced during sintering, appropriate amounts of $Ca(OH)_2$ can be added to the synthesis solutions (LeGeros and LeGeros 1993).

In contrast to high-temperature dry reactions, aqueous methods involving either reaction-

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precipitation or hydrolysis save energy and produce non-stoichiometric apatite, whose advantage is higher solubility and more biomimetic character than HA. By decreasing the solution temperature and by increasing the degree of carbonation, the size of the precipitate grains can be decreased, while also producing a higher surface-area-to-volume ratio. The effects of substituting other ions are detailed in LeGeros et al. (2009). Another important example of low-temperature aqueous formation of apatite is in the self-setting pastes (when mixed with water) known as bone cements. These are discussed in the online supplement.

Sol-gel processes

Sol-gel processes at room temperature can be used to create either bioactive glass or crystalline HA. In the making of a glass, a silica-rich solution (such as tetraethyl orthosilicate) with the desired precursor components (typically Ca, P, and Si, but P can be absent) is reacted with water under either acidic or basic conditions. Polymerization occurs through hydrolysis, and a sol of spherical nanoparticles forms. Specific solution conditions cause the nanoparticles to coalesce and bond together to form a gel. This aqueous network of covalently bonded silica tetrahedra undergoes drying and subsequent heating to > 600 °C, which forms a nanoporous glass (Jones 2013). The sol-gel process of forming bioactive glass permits a wider range in SiO_2 concentrations and higher chemical purity than would melting. The pH of the original solution is very important to the degree of crystallinity of the product after heating, e.g., pH = 9 may yield an amorphous phase (Dorozhkin 2012a), whereas an initial pH of 11.5 can yield crystalline products (Luz and Mano 2011).

Synthesis of crystalline HA via a sol-gel process begins with the mixing of calcium nitrate and a phosphate compound (in the exact molar ratio of Ca:P = 1.67), dissolved in ethanol

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at temperatures < 100 °C, to produce an amorphous Ca-P precipitate. Subsequent sintering at several hundred degrees Celsius produces a single-phase powder of stoichiometric HA that does not break down until temperatures above 1200 °C, indicating high purity and exact stoichiometry. Particle sizes of the phase-pure HA range down to less than 10 nm (Kuriakose et al. 2004; Kim and Kumta 2004). Compared to other techniques to synthesize HA, e.g., aqueous precipitation, hydrothermal formation, and electrodeposition, the sol-gel method offers the benefits of low temperatures, high purity, and the ability to produce nanoparticles without grinding. Allowing the precipitate to age for a sufficient time (48 hrs. in one study) is necessary in order to assure phase purity, e.g., no detectable TCP (Bakan et al. 2013).

Hydrothermal methods

Aqueous solutions in pressure vessels are taken above 100 °C at elevated pressures in various types of chemical systems. For instance, TCP or TTCP in the presence of $Ca(OH)_2$ can be converted readily to HA by hydrothermal reaction at 275 °C and steam pressure of about 80 MPa (LeGeros and LeGeros 1993). Continuous hydrothermal flow synthesis works well to create HA nanoparticles, as well as HA with controlled degrees of carbonate or silica substitution. Chaudhry et al. (2012) produced the latter two types of substituted apatites at 400 °C and 24 MPa, both of which are more bioactive than pure HA.

Hydrothermal techniques also can be used to transform calcium carbonate to (carbonated) HA, especially to make use of the inherent porosity of carbonate-biomineralized coral and cuttlebones in the production of porous scaffolds for new bone growth. The typical conversion reaction used is $CaCO_3 + CaHPO_4$ or $(NH_4)_2HPO_4$ to produce $Ca_{10}(PO_4)_6(OH)_2$.

Calcium carbonate-biomineralized materials are selected for their pore sizes, 3-D

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552 microstructure, and surface nanomorphology. Hydrothermal solutions at temperatures of about
553 270 °C and pressures of about 85 MPa are used to transform corals into HA with an
554 interconnected porosity of about 65 vol%, exactly mimicking that of the coral (Gross and Berndt
555 2002; Shi 2006). In another example, cuttlebone, the internal aragonite skeleton of the cuttlefish,
556 has a microstructure much like that of trabecular/spongy bone. The organic material of the
557 cuttlebone is chemically removed through bleaching, which also eliminates health concerns. The
558 above reaction is then carried out at 180 °C in a Teflon-lined, stainless steel reactor. The
559 resultant porous apatite scaffold has a high protein-adsorption rate; it can induce bone formation
560 on its surfaces even without the addition of bone growth factors and living cells, which otherwise
561 could cause medical problems (Hongmin et al. 2015). Such phosphate-pseudomorphed
562 constructs are almost as successful as autografts in inducing new bone growth, but they eliminate
563 the worries of permanent damage to the patient at the site from which bone material would have
564 been removed for autografting.
565 Hydrothermal conversion of carbonate-biomineralized materials also enables facile
566 production of the more (cf. HA) biomimetic carbonated apatite. Low-porosity blocks of
567 carbonated hydroxylapatite (CHA) also can be produced from blocks of gypsum ($CaSO_4 \cdot 2H_2O$)
568 or calcite by hydrothermal conversion using $(NH_4)_2HPO_4$ or Na_2HPO_4 (LeGeros et al. 2009).
569 Combined "mechanochemical-hydrothermal" synthesis (see "mechanosynthesis" section
570 above) can be used to produce Mg- and CO_3-bearing HA (Suchanek et al. 2004). The
571 component powders of $Ca(OH)_2$, $MgCO_3$, and $(NH_4)_2HPO_4$ are placed in a small amount of
572 water and ground in a multi-ring media mill. The as-formed Ca-P material is X-ray amorphous
573 and relatively homogeneous. Heat treatment can follow at several hundred degrees Celsius to

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574 produce Mg-CO_3-bearing apatites of compositions controlled by the initial bulk chemistry, the
575 temperature of subsequent heating, and the (low) solubility of Mg in HA (Suchanek et al. 2004).

576 **Fabrication of porous, apatitic biomaterials**

577 For high-temperature processing that produces porous material, powders of bioceramic
578 particles can be mixed with organic components, such as starch or polymethylmethacrylate. The
579 mixture is compressed into the desired shape and then heated to burn out the polymer
580 component. Higher-temperature sintering of the bioceramic often follows, producing a material
581 with up to 70% porosity (Shi 2006). Alternatively, a slurry of bioceramic particles <100 μm
582 diameter, a water-soluble compound of high molecular weight (e.g., a cellulose derivative), and a
583 fatty acid that acts as a non-ionic surface-active agent are all vigorously stirred at a temperature <
584 20 °C. The slurry is frothed by addition of a non-reactive gas. The material forms a gel, which
585 is dried at < 100 °C, degreased at much higher temperatures, and then sintered at ≥1000 °C.
586 Higher temperatures yield higher-strength materials. The products can have up to 80% porosity
587 with pore sizes of 5 to 1500 μm (Naqshbandi et al. 2013). Numerous procedures to form porous
588 biomaterials have been patented, including freeze casting and use of polymer sponges, as
589 described by Naqshbandi et al. (2013) and compared via extensive illustrations and tables.

590 Lower-temperature processes include adding soluble particles such as salt or sugar to
591 mixtures of Ca-P phases that react to form HA in the presence of water (e.g., TTCP + $CaHPO_4$
592 → HA). The soluble particles dissolve leaving a porous solid behind. Most such porous
593 bioceramics have very weak biomechanical properties, but these increase markedly with
594 ingrowth of new bone into the pores (Shi 2006).

595 **Compacting and sintering of nanocrystalline apatites**

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The level of biocompatibility of Ca-P bioceramic materials is highest when the material is nanocrystalline and carbonated, i.e., biomimetic, but these attributes also create the least favorable mechanical properties. To counter the latter problem, Ca-P ceramics typically are sintered at 1000-1200 °C. Particle coalescence begins below 1000 °C, but actual densification increases with temperature above 1000 °C. Hydroxylapatite, however, becomes unstable above 1250-1300 °C depending on its exact composition (Dorozhkin 2010) and on the water pressure of the system (cf. Fig. 3). Sintering causes the following chemical changes in the bioceramic: release, as gases, of molecular water (adsorbed and structurally incorporated) and carbonate, as well as volatiles remaining from the synthesis reactions; increase in crystal size and decrease in surface area; transformation of any HPO_4^{2-} component of the apatite into $P_2O_7^{4-}$ accompanied by the release of H_2O; the apatite becomes more stoichiometric in composition, including filling of OH-vacancies in the channel sites by OH^- ions derived from the released H_2O; and the apatite gains toughness and mechanical strength (Dorozhkin 2010; Pasteris et al. 2014). In the many ways listed above, Ca-P bioceramics that are constructed ex situ and inserted into the body, differ from natural biological hard tissue.

Low-temperature consolidation processes are a compromise, in which the inherent properties of the hydration layer of HA nanoparticles are better preserved. Uniaxial compression below 200 °C causes crystal-crystal interactions that, in conjunction with ion mobility in the hydrated surface layers, produce a more compact and ceramic-like material with enhanced mechanical properties that can approach the values for materials sintered at much higher temperature (Drouet et al. 2009).

Dorozhkin (2010) documents the values of specific mechanical properties in HA

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bioceramics (cf. Table 2), comparing them to those of bone and tooth enamel. Fracture toughness of Ca-P bioceramics is less than half of that for human bone, whereas mechanical strength increases with the Ca:P ratio of the material up to a maximum at a Ca:P ratio of 1.67 (HA). The Young's modulus of dense HA bioceramics is 35-120 GPa compared to ~18-22 GPa for cortical bone. It is this brittleness of HA bioceramics that precludes their use as load-bearing implants (Dorozhkin 2010).

Synthesis of substituted apatites, particularly by SiO_4^{4-}

Atomic substitutions in the apatite structure, such as Sr^{2+} for Ca^{2+}, F^- for OH^-, and CO_3^{2-} for PO_4^{3-}, can be produced via modest changes to the composition of the reactants in the synthesis. In biomaterials, such ions typically are incorporated to better mimic the composition of natural bone (e.g., CO_3^{2-}) or for therapeutic applications (e.g., Sr^{2+} to address osteoporosis). Because modern calcium phosphate bioceramics typically are designed to be resorbed, their formulation also provides the opportunity to include elements such as Sr^{2+}, Zn^{2+}, or Si^{4+} that can assist in bone healing when they are released during dissolution (Salinas et al. 2013). In aqueous syntheses, for instance, soluble metal nitrates could be used to introduce cations, whereas soluble metal halides could be used to introduce anions for the channel site (see citations in Goldenberg et al. (2015) for methods of specific ion substitutions).

In addition to the carbonated apatites discussed in several sections of this paper, only one other substitution of significance to biomaterials will be described, i.e., that of silicate. Silicon is known to be a trace component in bone mineral (Quelch et al. 1983) and collagen and to be important to the healthy formation of both (Jugdaohsingh 2007; Mostafa et al. 2011). The formulation and proposed application of silicate-substituted apatites as biomaterials follows from

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640 the above observations as well as from the widely recognized success of silicate-based bioactive
641 glasses (see online supplement) and the documented substitution in geological apatites of SiO_4^{4-}
642 for PO_4^{3-} (McConnell 1937; Pan and Fleet 2002). It is also possible to substitute small
643 concentrations of silicon in TCP, reported as $Ca_3(P_{0.9}Si_{0.1}O_{3.95})_2$ (Reid et al. 2005). Si-substituted
644 apatites typically are precipitated from aqueous solutions, in which silicon tetra-acetate
645 $[Si(COOCH_3)_4]$ or silicon tetra-ethyl orthosilicate $[Si(OCH_2CH_3)_4$, TEOS] is a reactant
646 (Chaudhry et al. 2012; Bang et al. 2014) or to which sodium silicate has been added (Mostafa et
647 al. 2011). One alternative method is to precipitate a Ca-P phase aqueously, mix it with fumed
648 silica particles, and subsequently sinter the mixture at about 1000 °C (Reid et al. 2005).
649 Many groups have worked on the formulation and characterization of silicate-substituted
650 hydroxylapatite (Si-HA), but some of the mineralogically most interesting work has been done
651 on multi-substituted HA, e.g., by CO_3^{2-} and SiO_4^{4-} (Bang et al. 2014) and by Na^+, CO_3^{2-}, and
652 SiO_4^{4-} (Mostafa et al. 2011). The latter two studies also made excellent use of analytical
653 techniques (see next section) that were well selected to characterize the resultant apatitic
654 materials. Their results on Si-HA confirmed those of other researchers, namely that SiO_4^{4-}
655 substitution causes a decrease in crystallite size and degree of crystallinity in the apatite.
656 Mostafa et al. (2011) and Bang et al. (2014) both determined from experiments that
657 doubly substituted Si-CO_3-HA powders had an even smaller particle size and crystallite size than
658 their CO_3-HA counterparts. Compositional analyses (especially for Ca:P atomic ratio) strongly
659 indicated that CO_3^{2-} and SiO_4^{4-} both substitute primarily for PO_4^{3-}, that is, they compete for the
660 PO_4^{3-} site. Although the two research groups observed different upper bounds on the
661 concentration of SiO_4^{4-} that was structurally incorporated (which appears to depend on the

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662 concentration of incorporated CO_3^{2-} -- different in the two studies), both groups detected the
663 eventual formation of an apparently amorphous and incipiently polymerized siliceous coating on
664 the samples. Bang et al. (2014) additionally tested the response of mechanical properties to the
665 substitutions. When SiO_4^{4-} was added to CO_3^{2-} as a substituent, the sintered apatites were denser
666 and also stronger under tension than CO_3-HA. Moreover, the incorporation of SiO_4^{4-} increased
667 solubility over that of CO_3-HA alone (Bang et al. 2014). Mostafa et al. (2011) provided details
668 on the mechanisms of charge balance due to substitution of PO_4^{3-} by CO_3^{2-} and/or SiO_4^{4-}. The
669 mechanisms changed according to the concentration of SiO_4^{4+}, which reached at least 2.23 wt%
670 Si incorporation in the lattice; the CO_3^{2-} concentration rose as SiO_4^{4-} did (Mostafa et al. 2011).
671 In their Si-HA samples, Chaudhry et al. (2012) reported an upper bound of 1.1 wt% Si.

672 In recognition of the known importance of Mg in the development of healthy bone and its
673 recorded concentration of 0.12-1.07 wt% MgO in natural bone (Skinner 2005; Li and Pasteris
674 2014), Sprio et al. (2008) studied the effects on HA of substitution by Mg^{2+}, CO_3^{2-}, and SiO_4^{4-}.
675 They interpreted from their solubility experiments that the apparent incongruent dissolution of
676 multi-substituted apatite probably reflects the non-stoichiometric composition and concentration
677 of ions in the hydration layer on the individual crystallites. As above, Sprio et al. (2008) also
678 found evidence that CO_3^{2-} and SiO_4^{4-} competed for occupation of the PO_4^{3-} site, but unlike in
679 later studies (Mostafa et al. 2011; Chaudhry et al. 2012; Bang et al. 2014), they reported a
680 combined CO_3^{2-} + SiO_4^{4-} concentration beyond which the Ca-P product was X-ray amorphous.
681 Concentrations of up to 2.4 wt% Si were stably incorporated in carbonated (2.4 wt% CO_3) HA.
682 Incorporation of approximately biological concentrations of all three substituents were attained
683 in some of the experiments (Sprio et al. 2008).

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Si-HA has been tested in vivo against other biomaterials, including TCP and calcium sulfate. Si-HA showed itself to be strongly bioactive, e.g., resorbed biologically by osteoclasts rather than undergoing passive dissolution. Its resorption rate, analogously to that of CO_3-HA, is well synchronized with the rate of new bone deposition, allowing Si-HA scaffolds to retain their ability to support the bone structures surrounding them (Hing et al. 2007).

Characterization of Apatite for Use in Biomaterials

"Although apatites are among the most stable and most easily formed calcium phosphates, their composition, and crystal structure are still the object of intense research" (Rey et al. 2007b, p. 198). Not all "apatites" are the same, and not every phase comprising calcium and phosphate is an apatite. Quality control on every Ca-P bioceramic requires phase identification and determination of basic physical-chemical properties (e.g., particle size, porosity, density, chemistry). More detailed compositional and structural data than the above would be needed to provide insights into a specific Ca-P's level of bioactivity, the mechanism(s) of its interaction with tissues, and its ability to stimulate osteogenesis at the cellular level. Data continue to be compiled on the physical-chemical characteristics of these bioceramics in conjunction with their responses in vitro and in vivo to simulated or actual physiological conditions (both chemical and cellular), as exemplified below.

There are two main reasons behind the need for multi-instrument, detailed analyses of synthetic Ca-P biomaterials. Firstly, there are so many different synthesis pathways and recipes for the fabrication of Ca-P biomaterials that one should not assume all products with the same name, e.g., "hydroxyapatite," have the same properties. For instance, there are concerns about

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incorporation of impurities – not externally derived contaminants, but rather retention of the additional ions that were introduced into the synthesis solution from reactant compounds, e.g., Na^+, Cl^-, and NH_4^+ (Koutsopoulos 2002). Secondly, apatite's lattice is so accommodating that even small differences in temperature of formation, time for maturation in the precipitating solution, post-precipitation storage environment, etc. could induce chemical and/or physical differences among aliquots of "the same" kind of apatite (Vandecandelaere et al. 2012).

Mineralogists and materials scientists are well aware of the many tools available for bulk and point analysis of the chemistry and structure of crystalline and non-crystalline materials. This section therefore is limited to highlighting the analysis of some properties of nanocrystalline apatite and its end-products (e.g., after heat-treatment) that are important to their functionality as biomaterials, e.g., phase identity, degree of crystallinity, crystallite and particle size, particle shape, chemical composition, solubility, and reaction with biological tissue and fluids (Shi 2006).

The nanometer scale, low degree of crystallinity, and reactive-metastable nature of biomimetic apatite (often the raw or "green" product of reaction) make it difficult to characterize reproducibly. For instance, one of the most important controls on the bioactivity of nanocrystalline apatite is its surficial hydration layer, yet this is one of the most challenging features to document. This ion-rich coating on apatite nanoparticles enhances the mobility of its entrained ions as well as their transfer from the coating to the underlying crystal lattice (Neuman and Neuman 1958; Rey et al. 2007a; Bertinetti et al. 2009; Eichert et al. 2009). The presence of a surficial, hydrated, ion-rich layer also makes it difficult to distinguish how much carbonate is within the apatite lattice compared to how much is in the hydration layer – a parameter that

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affects bioactivity and therefore should be documented, but is extremely difficult to measure. Another analytical challenge is determining how much HPO_4^{2-} (which, together with CO_3^{2-}, substitutes in the PO_4^{3-} sites) is present, because it is difficult to distinguish PO_4^{3-} from HPO_4^{2-} using standard colorimetric techniques. Instead, carefully calibrated IR techniques must be used (Eichert et al. 2009).

An essential distinction to recognize in Ca-P materials is the difference between stoichiometric HA and "calcium-deficient apatite" (CDA). The long-used term CDA unfortunately can create misunderstandings between the mineralogical and materials communities, since all biological carbonated apatite is calcium deficient compared to HA, i.e., $Ca_{10-x}(PO_4)_{6-x}(CO_3)_x(OH)_{2-x}$ cf. $Ca_{10}(PO_4)_6(OH)_2$. The medical and, by extension, the materials science communities apply the term CDA with reference to the molar ratio of Ca:P rather than to how many moles of Ca are in the unit cell. Whereas the Ca:P atomic ratio is 1.67 for stoichiometric HA, the medically defined CDA has a ratio of 1.4-1.6. The distinction between the mineralogical and materials science views of Ca deficiency arises because of a difference in the dominant ion recognized to substitute for PO_4. In the bioapatite formula above, the dominant substitution is recognized as CO_3^{2-} for PO_4^{3-}. According to the above formula, CO_3^{2-} substitution causes a decrease in the [Ca] of the apatite, but an increase in the Ca:P ratio to values exceeding 1.67 as a function of (10-x)/(6-x), where x = the number of moles of CO_3^{2-}. The medical and biomaterials communities, however, often exclude CO_3 physically as well as conceptually in their formulations. For them the pertinent substitution is often recognized as HPO_4^{2-} for PO_4^{3-}, i.e., $Ca_{10-x}(PO_4)_{6-x}(HPO_4)_x(OH)_{2-x}$. The resultant Ca:P ratio is (10-x)/6 rather than (10-x)/(6-x), where x = the number of moles of HPO_4^{2-}. The difference in the effect on the Ca:P ratio of

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apatite by CO_3^{2-} vs. HPO_4^{2-} substitution is that the substituent HPO_4^{2-} contains P. Increasing substitution for PO_4^{3-} by HPO_4^{2-} therefore leads to a decrease in Ca:P, thus, formation of calcium-deficient apatite, CDA. LeGeros et al. (2003) more broadly defined CDA as $Ca_{10-x}M_x(PO_4)_{6-y}(HPO_4)_y(OH)_2$, where M is a Ca-substituting cation such as Mg^{2+} or Na^+, the incorporation of which would further decrease Ca concentration.

The materials-community-defined CDA shows lower degrees of crystallinity than does HA, as documented by CDA's broader (as well as weaker) X-ray diffraction peaks (reflecting smaller crystallite sizes) and broader Raman and IR peaks (reflecting greater atomic disorder). The *a*-axis dimension of the unit cell of CDA is larger than that for HA (9.438-9.461 Å for CDA compared to 9.422 Å for HA) likely due to substitution of $(HPO_4)^{2-}$ for $(PO_4)^{3-}$, as indicated by an IR absorption peak at about 864 cm^{-1} (LeGeros et al. 2009). One of the most straightforward ways to evaluate the Ca:P ratio of an apatite is to sinter it above 800 °C, which will yield only HA if the sample's bulk Ca:P = 1.67, but a mixture of HA + CaO if Ca:P > 1.67 or HA + β-TCP if Ca:P < 1.67 (LeGeros 1981; LeGeros et al. 2003).

X-ray powder diffraction is very useful for phase identification, e.g., of HA. However, the broad peaks associated with nanocrystalline apatite, indicative of small crystallite size, make it difficult to infer compositional attributes and to detect the presence of additional phases simply by XRD (see Figure 5). In addition, octacalcium phosphate, $Ca_8H_2(PO_4)_6 \cdot 5H_2O$, OCP, has an XRD pattern very similar to that of HA, and amorphous calcium phosphate produces only a broad featureless hump at 27-40° and a much weaker feature at 50-60° 2Θ using Cu-K_α radiation (Eichert et al. 2009). In X-ray powder diffraction, one can assess the peak profile for line-broadening indicative of crystallite size (via the Scherrer equation), as distinguished from

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772 "microstrain" in the crystallites (Danilchenko et al. 2002). Baig et al. (1999) used Rietveld
773 analysis of XRD data to infer microstrain, which they believed exerted the major control on the
774 solubility of nanocrystalline apatite. In contrast, Eichert et al. (2009) concluded that the XRD
775 features attributed to microstrain actually might more strongly reflect compositional
776 heterogeneity within the sample. Our own research in applying Raman microprobe spectroscopy
777 to carbonated HA samples aqueously precipitated at 60-80 °C confirms such heterogeneity with
778 respect to carbonate concentration (Pasteris and Yoder, unpublished). TEM images of synthetic
779 apatite precipitates often indicate larger dimensions than XRD-derived size values for the same
780 samples (Alix Deymier, pers. comm.). This consistent mismatch appears to reflect the difference
781 between crystallites (length-scales of lattice continuity defined by XRD) and particles (TEM-
782 imaged objects, which in some cases may be aggregates of crystallites).
783 IR and Raman spectral band positions can be used to distinguish among the various Ca-P
784 phases (Wopenka and Pasteris 2005; Eichert et al. 2009), as well as to document the presence of
785 OH and H_2O (Fig. 5b) and, to some degree, to indicate chemical substitutions (e.g., F for OH).
786 IR is especially effective in distinguishing between A-type and B-type carbonate substitution for
787 OH or PO_4, respectively (Penel et al. 1998; Rey et al. 2007a; Wopenka and Pasteris 2005;
788 Eichert et al. 2009). Deconvolution of the observed IR peaks into recognized underlying bands
789 (see Figure 6) reveals the important distinction between the phosphate and carbonate groups that
790 are structurally incorporated in the lattice ("apatitic") and those groups adsorbed in the hydration
791 layer, i.e., "non-apatitic" (Rey et al. 2007a). Band widths in Raman and IR spectra (Fig. 5b)
792 reflect the degree of atomic order in the apatite, where narrower bands indicate a higher degree
793 of order (Penel et al. 1998; McElderry et al. 2013). With the application of a laboratory-specific

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794 calibration curve, one can determine the weight% carbonate substituted in an apatite sample
795 based on the Raman spectrum (Awonusi et al. 2007; Li et al. 2013) or IR spectrum.
796 Several other analyses provide direct characterization information or data that can aid
797 prediction of the apatite's biological response. For instance, the wettability of the
798 nanocrystalline apatite (actually, of its surface) helps control cell adhesion (Lim and Donahue
799 2004). Hydration-layer-controlled surface reactivity helps define the setting reaction(s) in a Ca-
800 P cement and how strongly an apatite coating adheres to its substrate (Rey et al. 2007a).
801 Several papers are extremely useful references because they either examine the relation
802 between experimental synthesis methods (including post-synthesis treatment) and the physico-
803 chemical properties of the apatites produced (e.g., Koutsopoulos 2002), or they effectively
804 document how to apply multiple analytical techniques to a suite of synthesized Ca-P materials.
805 For example, Sprio et al. (2008) synthesized multi-substituted (Si, Mg, CO_3) apatites and
806 characterized them by XRD (phase analysis, crystallinity), FTIR (multiple spectral regions; B-
807 type vs. A-type CO_3 substitution, effect of CO_3 substitution on [OH], H_2O adsorption), ICP bulk
808 chemical analysis, BET (specific surface area, reflecting particle size), thermal analysis by TGA
809 and DTA (temperature of CO_2 release, wt% CO_3 in apatite; thermal stability), and solubility tests
810 (distinguishing effects of Si, Mg, and CO_3). Bang et al. (2014) also synthesized and analyzed
811 CO_3- and Si-CO_3-substituted hydroxylapatites. In addition to XRD (lattice parameters and
812 crystallite size), FTIR, solubility measurement, and ICP (for Si and Ca) analysis, Bang et al.
813 (2014) added XRF (for Ca:P analysis) and mechanical properties tests for tensile strength.
814 LeGeros and LeGeros (1993), Eichert et al. (2009), and Drouet (2013) summarized the
815 application of a number of techniques to synthetic nanocrystalline apatites, relating properties to

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synthesis conditions in many cases. Rey et al. (2007a,b) summarized their earlier work in IR spectroscopy to tease apart information on apatitic (i.e., crystallographically incorporated) vs. non-apatitic (i.e., adsorbed) PO_4, HPO_4, CO_3, and H_2O in nanocrystalline biological and synthetic apatite.

Various types of NMR spectroscopy have been applied to bone and synthetic apatite in the past several decades (Jäger et al. 2006; Kolmas and Kolodziejski 2007), typically to identify the presence of specific ions involving the elements H, P, and C and their abundance, as in the case of hydroxyl (Cho et al. 2003; Kolmas et al. 2012). NMR data also helped to clarify the siting of molecular and ionic species in the apatite structure, for instance, that of molecular H_2O (Wilson et al. 2006a), as summarized in Pasteris (2012). NMR has been used to distinguish compositional components within the core of apatite crystals from those in the hydration shell (Jäger et al. 2006; Drouet 2013). It also has been applied to interpret plasma-sprayed hydroxylapatite coatings (Heimann 2012). Additional information on the fabricated forms and fabrication processes of specific types of biomaterials (e.g., apatite cements, apatitic coatings, and bioactive glass) can be found in the online supplement.

Factors that Control the Success of Apatitic Biomaterials

As described above, there are widely varying functions for which apatitic materials have been formulated. In some cases, the apatite enables better functionality of another biomaterial (e.g., a metal), whereas in other cases, the apatite IS the biomaterial (e.g., porous HA blocks). Some of the characteristics of greatest significance to apatitic biomaterials are their surface properties (smooth, rough, with or without asperities), particle size, specific composition (e.g.,

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838 Ca:P ratio and concentration of Mg and CO_3), porosity (pore size and percent of bulk material),
839 ability to incorporate and be biocompatible with cells and bioactive molecules, mechanical
840 properties (e.g., hardness, stiffness, wear resistance), and solubility in body fluid (Kretlow and
841 Mikos 2007). Even if osteogenic responses can be measured, however, the mechanisms behind
842 them are not always clear. For instance, less crystalline or amorphous apatite is more readily
843 resorbable, but better crystalline (especially carbonated) apatite encourages more cell adsorption
844 and proliferation (Surmenev et al. 2014; Nakamura et al. 2016).
845 Drouet et al. (2009) summarized very clearly the results of their many types of
846 experiments in low-temperature aqueous precipitation of apatite, as well as their chosen mineral
847 characterization techniques. They described how changes to the temperature and pH of the
848 synthesis solution, as well as the maturation time during which the precipitates remained in the
849 solution, can be used to tailor such characteristics of apatite nanoparticles as the crystallite size,
850 bioresorbability, degree of crystallinity, degree of non-stoichiometry, physical extent of
851 hydration layer, ion concentration in non-apatitic sites (i.e., in the hydration layer rather than in
852 the crystal lattice), and the bulk chemical composition (including Ca:P, $[HPO_4^{2-}]$).
853 LeGeros et al. (2003) described the history of the development of biphasic calcium
854 phosphate, BCP (i.e., HA + β-TCP), including how the HA:TCP ratio is controlled. BCP
855 formation begins with precipitation of a Ca-deficient HA, which is then sintered at 700 °C. The
856 more Ca-deficient the original material, the greater the proportion of TCP after sintering.
857 Additional substituting ions in the precursor material also affect the HA:TCP ratio. For instance,
858 structural incorporation of CO_3^{2-} and Mg^{2+} in the unsintered material causes an increase in the
859 HA:TCP of the sintered product. If the initial aqueous synthesis step is done at "high"

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860 temperature (80 - 100 °C) but low pH (4-6), a CDA phase of relatively high crystallinity and
861 large crystal size develops, in contrast to the much less crystalline CDA formed at the same
862 temperature but at a pH of 9 (LeGeros et al. 2003).

863 Pore size in bone cement can be controlled by the grain size of the reactant compounds
864 and the relative solubility of the compounds (as in Ca-S + HA mixtures). The pore dimensions
865 control both the bioactivity of the material (vascularization, cell incorporation) and its drug-
866 delivery capability. The degree of crystallinity (a function of thermal processing and ion
867 substitution) strongly affects solubility and therefore resorption rate of the cement, as does the
868 crystallite size (Ginebra et al. 2012).

869 The materials science community has recently begun to explore the effects of carbonate
870 concentration in synthetic apatite on the body's cellular response. Adams et al. (2014) reported
871 that elevation of carbonate concentration in apatite increased the number of osteoblast-like (i.e.,
872 bone-forming) cells attracted to the surface of synthetic apatite discs. However, such increases
873 in carbonate also decreased the degree of differentiation of the osteoblasts, suggesting that they
874 would be less able and likely to induce mineralization. In analogous types of experiments,
875 Nakamura et al. (2016) determined more recently that higher carbonate concentration in
876 synthetic apatite favored the differentiation of bone marrow cells into osteoclasts (bone-
877 resorbing cells), thereby inducing more resorption of bone. Such experiments indicate that the
878 carbonate concentration in apatitic biomaterials could be tailored for specific purposes, such as
879 temporary scaffolding that subsequently would be removed/resorbed within a controlled time-
880 frame (Adams et al. 2014; Nakamura et al. 2016).
881

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Implications

Research into the development of biomaterials offers mineralogists and geochemists a novel view of the adaptability of the apatite structure and its implications for human health. Biomaterials research highlights (1) the important effects of synthesis techniques on the properties developed in a chemically and structurally accommodating phase such as apatite, (2) the applicability of cutting-edge analytical techniques in the characterization of mineral properties, especially those of nanocrystalline phases, (3) the importance of a mineral's surface chemistry, including the presence of water and adsorbed ions, and (4) how this calcium-phosphate mineral remains "apatite" throughout such a wide range of compositional substitutions and consequent structural perturbations. The key to the latter is a kind of chemical-structural choreography that assures the nature of the ions and their spatial positioning remain appropriately synchronized. The formulation, synthesis procedures, and analytical characterization of apatitic biomaterials before, during, and after implantation in a living creature (typically a human) provide unique non-geological examples of the power of mineralogy. Biomaterials research clearly is not one of the new subfields, such as geobiology or biomineralization, that have become important in the geosciences. However, we geoscientists should consider viewing biomaterials as a major subfield of materials research that offers opportunities for both observation and participation by the broader mineralogical-geochemical community.

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Figure Captions

Figure 1. List of many of the most commonly used biomaterials for replacement or enhancement of skeletal and other elements of the human body. Adapted and used by permission of World Scientific, from Hench and Wilson (1993), *An Introduction to Bioceramics*, Fig. 1, p. 2.

Figure 2. Solubility of Ca-P phases at 37 °C in a solution containing equal total molar concentrations of Ca and P (i.e., T_{Ca} and T_P, respectively) and with an ionic strength of 0.1 mol l^{-1}. At pH values above 4, HA is the least soluble, i.e., most stable, Ca-P phase. Modified and used by permission of Sage Publications, from Johnsson and Nancollas (1992), Critical Reviews in Oral Biology and Medicine, vol. 3, Fig. 1, p. 65.

Figure 3. Two different representations of the CaO-P_2O_5 binary system, showing that the partial pressure of water is key to hydroxylapatite stability. The C_xP_y notation indicates the CaO:P_2O_5 molar ratio in the phase; see Table 1 for abbreviations. (**a**) Essentially anhydrous CaO-P_2O_5 binary, on which there is no stability field for HA. Shading indicates the HA-pertinent compositional region. Adapted and used by permission of the American Chemical Society, from Kreidler and Hummel (1967), Inorganic Chemistry, vol. 6, no. 5, Fig. 3, p. 891. (**b**) Quasi-binary of the CaO-P_2O_5-(H_2O) system at H_2O partial pressure of 65.5kPa. Adapted and used by permission of Elsevier, from Riboud (1973), Annales de Chimie (Paris), vol. 8, no. 6, Fig. 3a, p. 384. Shading indicates fields in which HA is stable. Note that the values of phase transition temperatures T_1 and T_2 depend on the specific water pressure (cf. White et al. 2010). Figures

modified from Heimann and Lehmann (2015, p. 264).

Figure 4. (**a**) The system CaO-P_2O_5-H_2O at 200 °C and 1700 kPa. Adapted and used by permission of John Wiley and Sons, from Feng and Rockett (1979), Journal of the American Ceramic Society, vol. 62, Fig. 1, p. 620. The C_xP_y notation indicates the CaO:P_2O_5 molar ratio in the phase; see Table 1 for abbreviations. Under these conditions, only three solid phases coexist with aqueous solution, i.e., HA, monetite (DCP, C_2P), and MCPM (CP). In the central 3-phase field of HA + $CaHPO_4$ (DCP) + LIQ, two solid phosphate phases coexist together with aqueous solution. Experiments at lower temperature show brushite (DCPD, C_2P dihydrate) in equilibrium with solution (Elmore and Farr 1940). Note the narrow width of the HA + LIQ field. (**b**) Schematic representation of the system CaO-H_3PO_4-H_2O at 25 °C. Adapted and used by permission of John Wiley and Sons, from Brown (1992), Journal of the American Ceramic Society, vol. 75, Fig. 3b, p. 19.

Figure 5. Analyses of (1) hydroxylapatite standard from the National Institute of Standards and Technology and (2) cow bone that has been soaked in bleach to remove much of the collagen. (**a**) X-ray diffractograms. Extreme peak-broadening in (2) indicates a low degree of crystallinity. Note that all peaks exhibited by the bone apatite can be referenced to those in the (1) HA standard. (**b**) Infrared spectra. The spectrum of bone apatite (2) displays vibrational bands for carbonate (C-O) and water (H-O-H), whereas the HA standard (1) shows no incorporated carbonate, but more hydroxyl (H-O). Adapted and used by permission of John Wiley and Sons, from LeGeros et al. (2009), Advanced Biomaterials: Fundamentals, Processing,

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and Applications, Fig. 2.11, p. 41.

Figure 6. FTIR analysis of a synthetic carbonated apatite in the ν_4PO_4 portion of the spectrum. The recorded peaks (coarsely dotted traces, in blue on-line, showing the highest absorbance values) have been deconvolved into their underlying bands, which are shown in narrower vs. bolder line width for distinction. As labeled, some of the bands reflect features of the apatite lattice ("apatitic") and others reflect features of ions adsorbed on the crystallites ("non- apatitic"). Adapted and used by permission of Nova Science Publishers, from Eichert et al. (2009), Nanocrystalline Apatite-Based Biomaterials, Fig. 5, p. 23.

Table 1. Calcium-phosphate (Ca-P) phases of interest in biomaterials

Name(s) and abbreviation(s)	Formula	Xl syst, pH stabil.*	Ca/P	Form, Use, Comments
Monocalcium phosph. monohydrate, MCPM or CP	$Ca(H_2PO_4)_2•H_2O$	tricl., 0.0-2.0	0.5	very acidic
Dicalcium phosphate dihydrate, ***brushite***, DCPD or C_2P	$CaHPO_4•2H_2O$	mono., 2.0-6.0	1.0	powder
Dicalcium phosphate anhydrous, ***monetite***, DCP or C_2P	$CaHPO_4$	tricl., Stable > 100°C	1.0	powder
Amorphous calcium phosphate, ACP	$(Ca,X)_x(PO_4,Y)_y•nH_2O$ $X=Mg^{2+},Zn^{2+},Sn^{2+},Al^{3+}$; $Y=CO_3^{2-}$, $P_2O_7^{4-}$	amorph., ~ 5-12	1.3-2.5	powder; always metastable
Octacalcium phosphate, OCP, C_8P_3	$Ca_8H_2(PO_4)_6•5H_2O$	tricl., 5.5-7.0	1.33	powder
Tricalcium phosphate, α-TCP, β-TCP = ***whitlockite*** or C_3P	$Ca_3(PO_4)_2$	hex., Not from aq. soln.	1.50	sintered body or powder; bone graft substitute, spinal fusion, orthopedic, dental
Calcium-deficient hydroxylapatite, CDHA or CDA	$Ca_{10-x}(HPO_4)_x$-$(PO_4)_{6-x}(OH)_{2-x}$, $0<x<1$	6.5-9.5	1.5-1.67	Ca/P depends on pH of precipitating solution
Carbonated hydroxylapatite, CAP	$Ca_{10-x}(CO_3)_x(PO_4)_{6-x}$-$(OH)_{2-x}$, where $0< x< 2$	pH variable	1.67-2.0	powder, sintered body, bone graft substitute; natural bone
Hydroxylapatite, HA or $C_{10}P_3$	$Ca_{10}(PO_4)_6(OH)_2$	hex., 9.5-12	1.67	sintered body (dense or porous), powder, coating, fiber, composite; bone graft subst., see Fig. 1 for uses.
Fluorapatite, FA	$Ca_{10}(PO_4)_6F_2$	hex., 7-12	1.67	powder; dental
Oxyapatite, OA	$Ca_{10}(PO_4)_6O$	hex., NA	1.67	Not stable in aqueous solution.
Tetracalcium phosph. ***hilgenstockite***,TTCP or C_4P	$Ca_4(PO_4)_2O$	mono., NA	2.0	powder; + H_2O, rapidly converts to HA; too basic to be implanted alone in body
Biphasic calcium phosphate, BCP	$Ca_{10}(PO_4)_6(OH)_2$ + $CaSO_4•2H_2O$	mixed		powder; spinal fusion, bone graft subst., trauma surgery, scaffold, ophthalmic implant

Note: Solubility at 25°C: ACP > DCPD > OCP > β-TCP > CDHA >> HA > FA (LeGeros et al. 2009; Dorozhkin 2012b).
* pH stability range in aqueous solutions at 25 °C. Data from LeGeros et al. (2009), Dorozhkin (2012a,b), and Bayazit et al. (2010).

Table 2. Biomechanical properties of Ca-P and related biomaterials

Material	Young's modulus (GPa)	Compressive strength (MPa)	Fracture toughness (MPa $m^{1/2}$)
alumina bioceramic	365-400[b,i] (Al_2O_3 98-99.8%)	1800-4500[b,i]	5-6[b,i]
full sintered zirconia	220[i]		7.4[i]
sintered hydroxylapatite	35-120[c,h,i]	16-145[h]	1.0[i]
Ca-P cement	30[c]		
calcium phosphate phases	8-130[c]		
silicate 13-93 bioglass scaffolds	13 ± 2[j]	86 ± 9[j]	
human tooth enamel	9-90[d,i,k]		0.52-1.3
human tooth dentin	11-20[i], 32.4[d]		2.8-3.1[i]
cortical bone	7-30[a,b,d,e,h,i,k]	100-250[b]	2-12[b,k]
trabecular bone	0.05-2.0[b,d,e]	2-12[b]	
deer and elk antler	wet 6-8[f,g,,i]; dry 7.6[f], 17.5[g]		10.3[f] [wet, transverse]
collagen	0.6-2[e,k]		

Notes: Data from Bonfield et al. (1981)[a], Hench and Wilson (1993)[b], Gross and Berndt (2002)[c], Nath and Basu (2009)[d], Pasteris et al. (2008)[e], Chen et al. (2009)[f], Currey et al. (2009)[g], Dorozhkin (2010)[h], Bayazit et al. (2010)[i], Liu et al. (2013)[j], Wegst et al. (2015)[k].

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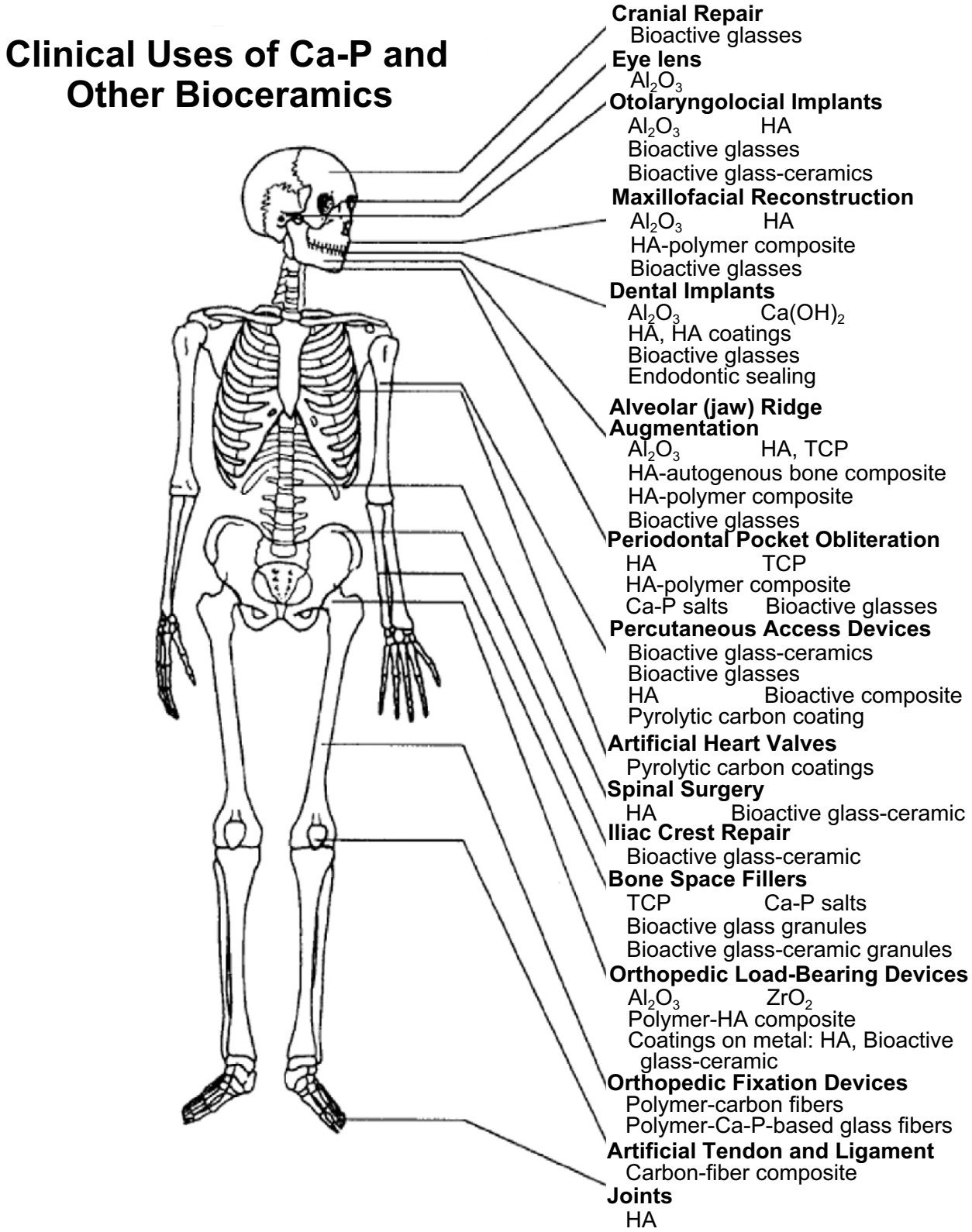
Figure 1



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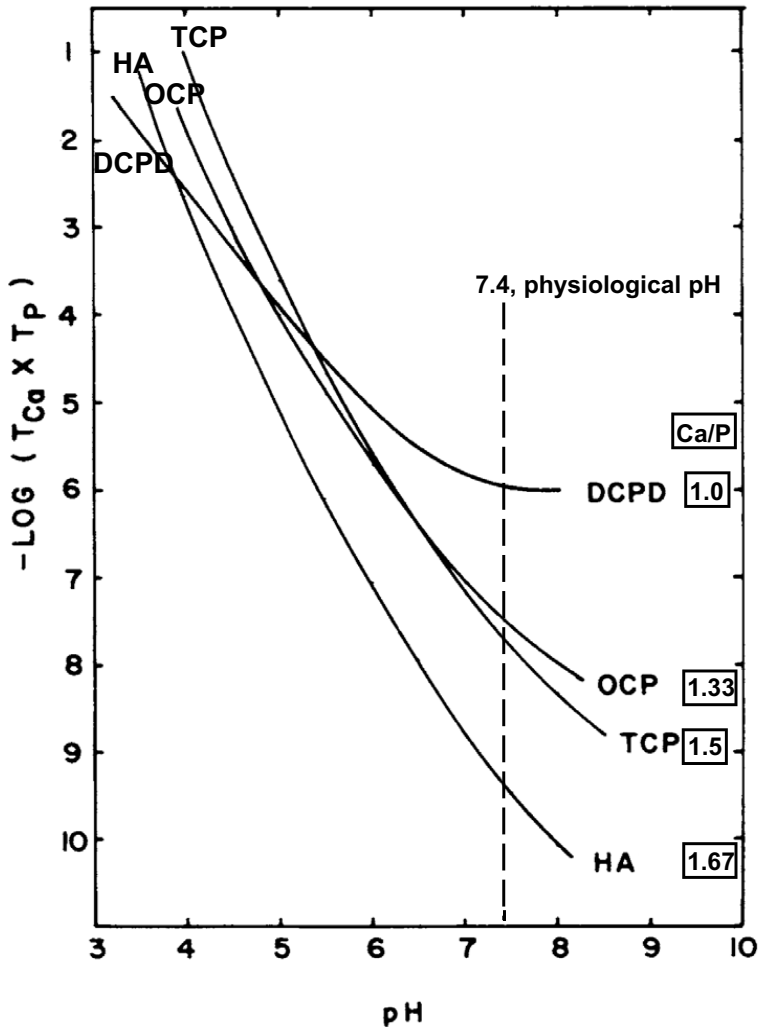

Figure 2

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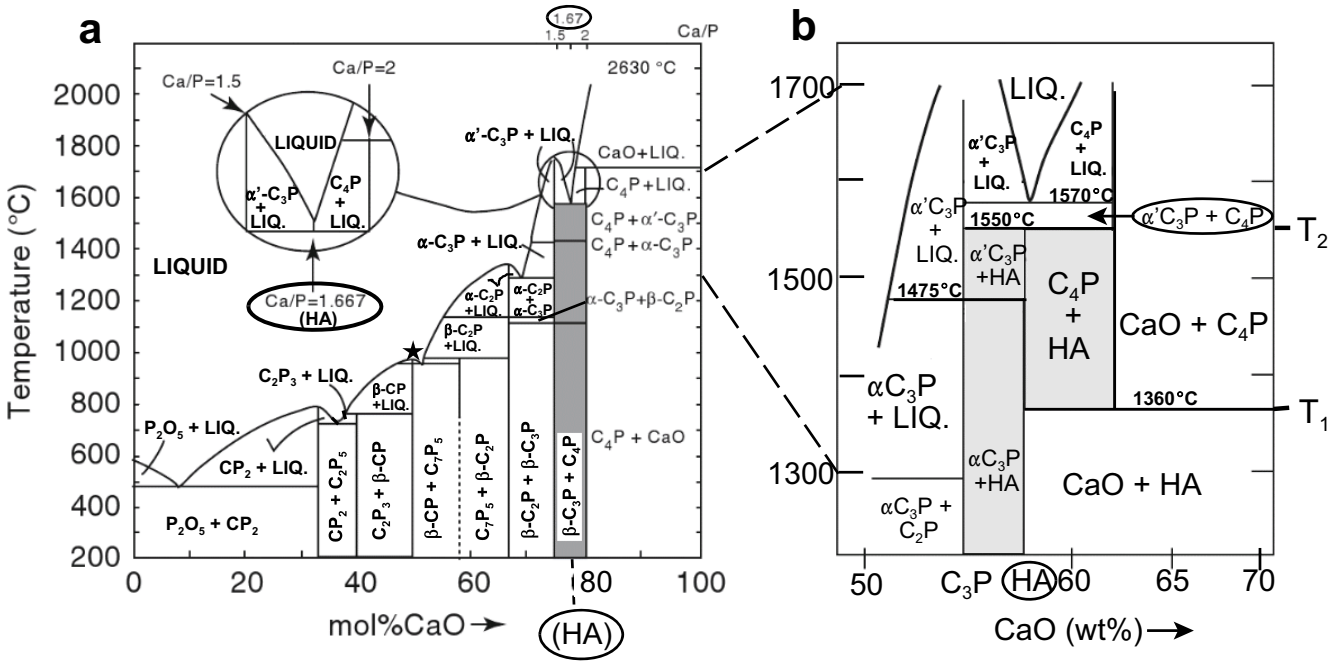
Figure 3



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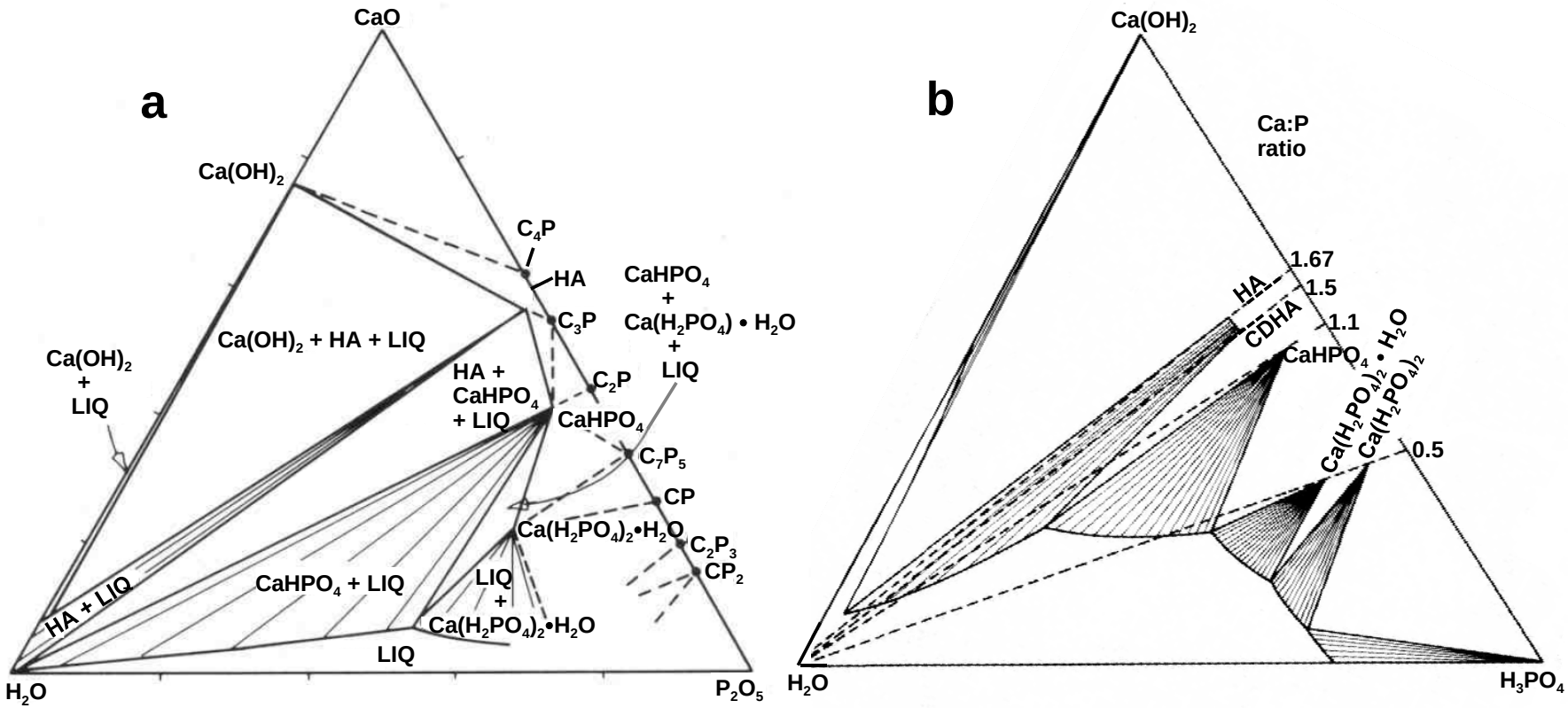

Figure 4

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Figure 5

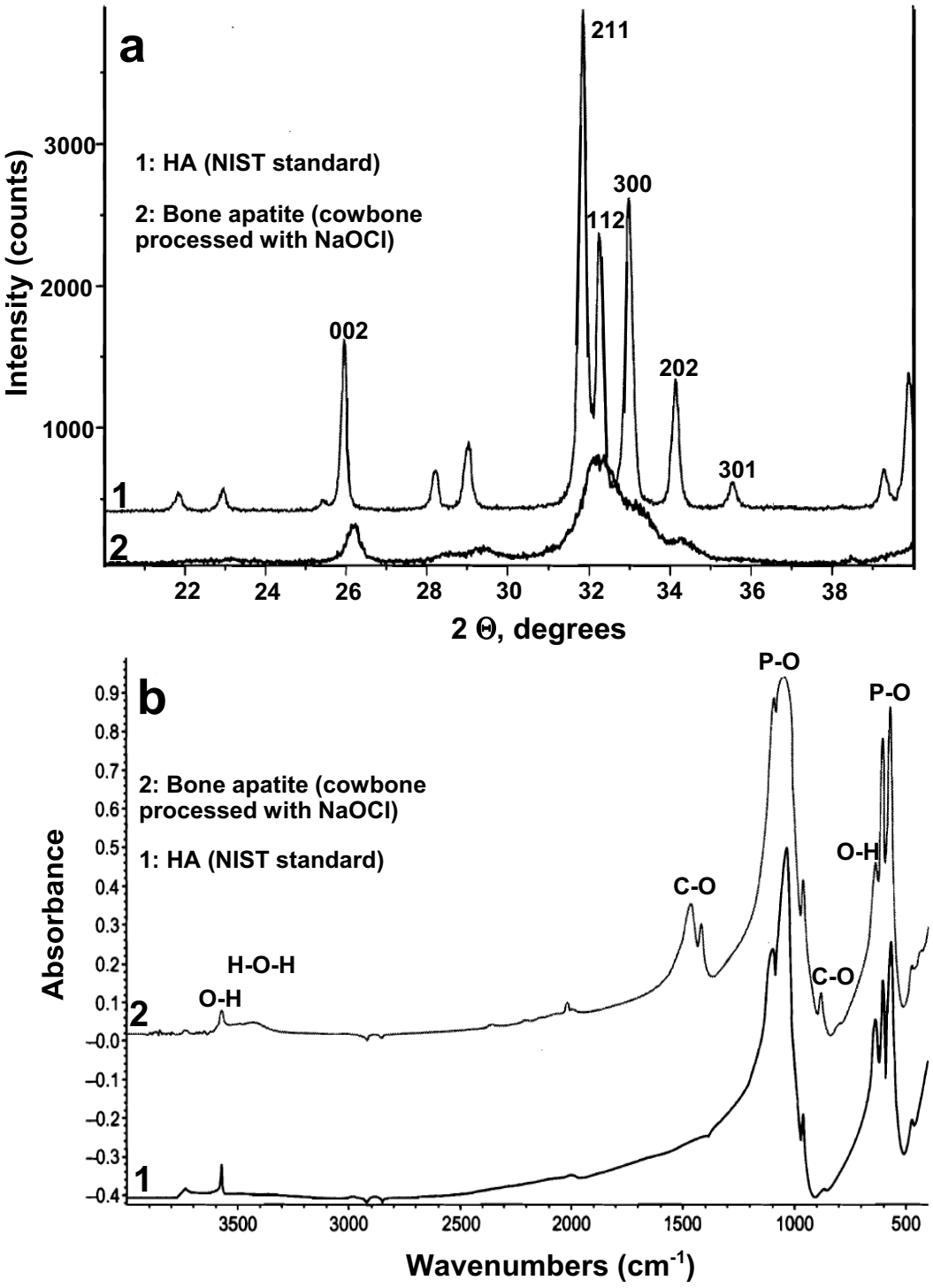

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Figure 6