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INTRODUCTION

The field of biomedical materials has grown rapidly over the past 20 years and offers solutions to repair defects, correct deformities, replace damaged tissue and provide therapy. This has contributed to the increase in the average lifetime of individuals in developed countries. The market value for biomaterials is of the order of billions of dollars per annum worldwide and is growing as new products offer improved performance or provide new solutions health problems. Apatites are playing a key role in biomedical implants.

In developing materials used for implantation consideration must be given to both the influence of the implanted material on the body, and how the body affects the integrity of the material. The body will treat implants as inert, bioactive, or resorbable materials. Generally "inert" materials will evoke a physiological response to form a fibrous capsule, thus, isolating the material from the body. Calcium phosphates fall into the categories of bioactive and resorbable materials. A bioactive material will dissolve slightly, but promote the formation of an apatite layer before interfacing directly with the tissue at the atomic level. Such an implant will provide good stabilization for materials that are subject to mechanical loading. A bioresorbable material will, however, dissolve and allow tissue to grow into any surface irregularities but may not necessarily interface directly with the material (Neo et al. 1992).

The first use of calcium phosphate as an implanted biomaterial provided accelerated bone healing in surgically created defects in rabbits (Albee and Morrison 1920). Interest in apatite specifically started in the 1960s and initial studies principally involved the synthesis and analysis of hydroxylapatites in an attempt to better understand biological apatites (Le Geros 1965, McConnell 1965, Nancollas and Mohan 1970, Selvig et al. 1970). Hydroxylapatite is a specific form of apatite with a chemical composition of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. Because of its relationship to bone hydroxylapatites have been synthesized for the purpose of implantation (Aoki 1973, Jarcho et al. 1977, de Groot 1980, Winter et al. 1981, Frame et al. 1981). The early history of calcium phosphate implantation was discussed by Driskell (1994).

Calcium phosphate with an apatitic structure occurs naturally in the human body and can be described as a calcium deficient carbonate-hydroxylapatite. The chemical similarity of hydroxylapatite to the bone mineral suggests an intrinsic biocompatibility. Implantation of solid blocks of hydroxylapatite has revealed direct bonding to soft tissue (Jansen et al. 1985, Aoki et al. 1987), muscle tissue (Negami 1988) and bone tissue. This aspect of being able to create an artificial material, that provokes excellent tissue response, has provided the impetus for development of hydroxylapatite and other apatites for applications in the body.

Biomedical applications of hydroxylapatite are numerous. There are reviews addressing hydroxylapatite (Ben-Nissan et al. 1995, Suchanek 1998), hydroxylapatite coatings (Berndt et al. 1990, Dhert 1994, Thomas 1994, Jaffe and Scott 1996, Heimann et al. 1997, de Groot et al. 1998, Hlavac 1999, Ong and Chan 1999, Willmann 1999, Sun et al. 2001, Geesink 2002), and bioceramics (Le Geros 1993, Hench 1998a, Greenspan 1999, Blokhuis et al. 2000, Kim 2001). Several books also provide extensive discussion on apatite (Le Geros 1991, Elliott 1994, Driessens and Verbeeck 1990, and this volume). Hydroxylapatite is the OH end member of the calcium phosphate apatite group minerals, $\text{Ca}_{10}(\text{PO}_4)_6(\text{F},\text{OH},\text{Cl})_2$. The most common abbreviations of hydroxylapatite are "OHA," "OHAp," "HA" or "Hap." Reference to hydroxylapatite within the present work will be abbreviated as HAp. It is worth noting that hydroxylapatite is often referred to in the literature as *hydroxyapatite*, by the medical community. The International Mineralogical Association, which represents the scientific community in regard to proper use of mineral nomenclature, recommends use of *hydroxylapatite* for consistency (Smith 1994).

This chapter briefly reviews the formation of naturally occurring apatites in the body. For a more in-depth review see Elliott (this volume, p. 427-453). Powder synthesis will be discussed in light of its application for producing an implantable material. The manufacture, performance and applications of various forms of apatite will provide insight into its wide use in biomedical applications.

BIOLOGICAL APATITES

Several minerals are known to be essential by the human body for proper function. These include salts of calcium, magnesium, phosphorus, sodium, chlorine and potassium. The main functions of these minerals are as constituents of the skeleton, as soluble salts to maintain the composition of body fluids and as essential adjuncts to the action of many enzymes and other proteins.

About 20-30% of the calcium intake in a diet is absorbed into the body. The majority of the calcium is incorporated into calcium phosphate, confined to skeletal tissue and teeth. The skeleton provides shape to the body, supports the body weight, protects vital organs, anchors muscles and facilitates locomotion. The skeleton and teeth contain 99% of the total body calcium and 85% of the phosphorus that amounts to a combined mass of about 2 kg in an average person (Matkovic 1991, Power et al. 1999). The remaining 1% of calcium is used for physiological processes in the body. Unlike other nutrients in the body, calcium is stored in excess for short-term needs, but concurrently serves critical structural requirements. An imbalance within the metabolic system will preferentially sacrifice calcium from bones to maintain a balance in the physiological processes. Conversely, a higher serum calcium level may produce crystallization of calcium into kidney stones as calcium oxalate (Pineda et al. 1996). Although the conversion of calcium from the solution to a solid is an important aspect of calcium storage in the body, it may produce undesirable crystallization of apatite in urinary calculi (Konjiki et al. 1980) or on heart valves (Banas and Baier 2000, Deiwick et al. 2001).

Osteoblasts are responsible for the production of bone (a ceramic-polymer composite material filled with living cells). These mononuclear cells deposit an organic matrix that contains collagen, composed of a defined sequence of amino acids in a polypeptide chain. Three polypeptide chains are folded into rod-like triple-helical molecules about 300 nm long and 1.5 nm in diameter (Fig. 1). Collagen chains aggregate so that each molecule is longitudinally displaced by one quarter of the length relative to the nearest neighbor to form a fibril. Small apatite platelets fit into predetermined pockets of the collagen with the *c*-axis aligned with the fibril long axis (Fratzl et al. 1991, Landis et al. 1996). The fibrils are twisted around one another in the opposite direction to form a fiber. The fibers

bundle together to build up the lamellae, 3 to 7 μm thick, located concentrically around a central canal. The numerous levels of order indicate the rich hierarchical structure of bone to assemble the osteon, the building block in bone. Osteons arrange themselves in a dense packing arrangement in compact bone, but take on more random arrangement in porous trabecular bone. Since osteons lie parallel to lines of stress in bone, the apatite crystals then have a set orientation with respect to stresses applied to bone (Martin and Burr 1989).

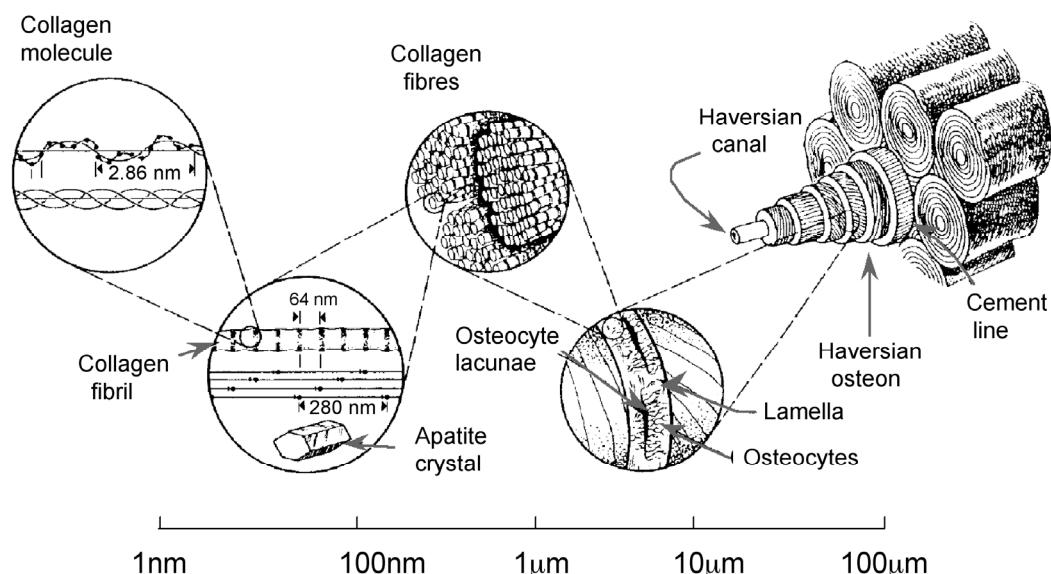


Figure 1. The structural location of hydroxylapatite with collagen in an osteon of bone.

In bone and teeth, apatites are based on a calcium hydroxylapatite composition modified with sodium, potassium, magnesium, zinc, and especially carbonate; see Table 1. Some of these substituent species, particularly carbonate, lead to large lattice strain and higher solubilities (Driessens 1988). Bioapatites with the highest degree of crystallinity and the highest concentration are found in the enamel of teeth. The formation of apatites is preceded by the differentiation of preameloblast cells that secrete enamel matrix proteins (amelogenins and enamelin). The high saturation of calcium and phosphate ions in the protein gel adjacent to the ameloblast causes the precipitation of carbonated apatite. Proteins dissolve or are resorbed to provide space for the growing apatite crystals. Eventually, ameloblasts withdraw, leaving apatite crystals which are stacked as rods or prisms, surrounded by a thin boundary film of enamelin (Ten Cate 1994). Upon completion of the tooth formation, the ameloblast departs and no repair is possible.

Apatite crystals in enamel are aligned perpendicular to the surface of the tooth (Johanssen 1964, Boyde 1997) and in an irregular fashion on the cusp tips and incisal edges, to impart strength in high stress areas. The underlying dentine acts as a support and the inherent flexibility is thought to prevent fracture of the brittle enamel.

Teeth are subjected to a continuous demineralization/mineralization process and, therefore, the apatite in enamel is modified in response to the microenvironment around the teeth. Applications of fluoride through toothpaste and drinking water result in the exchange of F^- for OH^- in hydroxylapatite to form the more stable and acid resistant fluorapatite. Also, development of caries lesions is decelerated as dissolution removes carbonate and magnesium from the outer enamel layer, which further stabilizes the enamel apatite (Le Geros 1999).

Table 1. Chemical and crystallographic characteristics of natural and synthetic apatite (modified from Driessens and Verbeeck 1990 and Le Geros et al. 1995).

	Bone	Enamel	Dentine	Hydroxylapatite
Constituents (wt %)				
Calcium, Ca ²⁺	24.5	36.0	26.9	39.6
Phosphorus, P	11.5	17.7	13.2	18.5
(Ca/P ratio)	1.65	1.62	4.6	1.67
Carbonate, CO ₃ ²⁻	5.80	3.20	0.6	-
Sodium, Na ⁺	0.70	0.50	0.8	-
Magnesium, Mg ²⁺	0.55	0.44	0.06	-
Chloride, Cl ⁻	0.10	0.30	0.02	-
Potassium, K ⁺	0.03	0.08	0.1 (max)	-
Fluoride, F ⁻	0.02	0.01		-
Ash (total inorganic)	65.0	97.0		100
Total inorganic	25.0	1.0		-
Trace elements (max)				
Strontium, Sr ²⁺	0.02	0.14	0.02	
Barium, Ba ²⁺	0.1	0.02	0.005	
Lead, Pb ²⁺	0.08	0.10	0.004	
Iron, Fe ³⁺	0.1	0.08	0.01	
Zinc, Zn ²⁺	0.04	0.12	0.07	
Copper, Cu ²⁺	0.1	0.008	0.005	
Aluminium, Al ³⁺		0.04	0.015	
Silicon, Si ⁴⁺	0.05	0.14	0.01	
Manganese, Mn ²⁺		0.006	present	
Selenium, Se ²⁺		0.002	present	
Tin, Sn ²⁺		0.009	present	
Lithium, Li ⁺		0.001	present	
Nickel, Ni ²⁺		0.001	present	
Silver, Ag ⁺		0.004	0.07	
Sulfur, S		0.005		
Cadmium, Cd ²⁺		0.007		
Lattice parameters				
a-axis	9.419	9.441		9.422
c-axis	6.880	6.882		6.88
Crystallite size, Å	250 x 25-50	1300 x 300		2000
Products after heating at 950°C	HAp + TCP	HAp + CaO		HAp

Because the natural mineral component of bones and teeth is carbonate-hydroxylapatite, the use of synthetic apatites as bone and tooth replacement materials has been extensively investigated. The first step in the manufacture of biomedical devices requires the ability to synthesize pure and reproducible apatite powders.

SYNTHESIS OF APATITE

Calcium phosphate apatite formulations that are available commercially from different suppliers exhibit high chemical variability. Thus, manufacturers of apatite for biomedical applications often produce their own powder. Furthermore, synthesis enables a range of chemical substitutions, crystal sizes, shapes and forms (separate crystals or cements, as discussed in the next section). Various reviews cover synthesis methods (Narasaraju and Phebe 1996, Le Geros et al. 1995, Orlovskii and Barinov 2001).

Precipitation from solution is the most common synthesis route and involves simultaneous addition of a calcium salt and a phosphate compound to water, or drop-wise addition of the phosphate into an aqueous solution of the calcium salt. Examples of calcium salts include calcium nitrate, calcium hydroxide, calcium chloride, or calcium acetate. The salts are reacted with a hydrogen phosphate or the phosphate ions are

introduced in solution from di-ammonium hydrogen phosphate or orthophosphoric acid. Two reactions studied in detail involve (i) reaction of calcium nitrate with di-ammonium hydrogen phosphate, and (ii) the addition of orthophosphoric acid to calcium hydroxide (Tagai and Aoki 1980, Osaka et al. 1991).

The precipitation reaction is conducted with pure reactants at a pH greater than 9, with a controlled reactant addition rate, under stirred conditions and a temperature between 25 and 90°C. A yield of 87%, measured on the basis of the initial reactant stoichiometry, is achieved when orthophosphoric acid is reacted with calcium hydroxide at production rates of 50 g/hr. However, when calcium nitrate and diammonium hydrogen phosphate are selected as reactants the yield is 29%, for similar production rates. In reactions where ammonium is part of the precursor, dilute ammonium hydroxide is added continuously to restore the pH after a decrease caused by removal of a hydroxide from the solution to precipitate HAp. The slow incorporation of calcium into the apatitic structure must be accompanied by stirring and aging after the reaction. The Ca/P molar ratio of 1.67 is attained in as little as 5 hours after the completion of the reaction at 90°C (Rodríguez-Lorenzo and Vallet-Regí 2000). Post reaction maturation is an important step for ensuring the production of stoichiometric hydroxylapatite (Honda et al. 1990). During maturation, the crystal shape is modified and slender crystals become more "blocky" as the Ca/P molar ratio approaches 1.67 (Rodríguez-Lorenzo and Vallet-Regí 2000). After maturation, the precipitate is washed several times in double distilled water that may be adjusted for pH with ammonia. High water purity is essential at all times because the apatite lattice readily incorporates foreign elements into the structure. The precipitate is finally dried and calcined.

At lower pH values, a calcium deficient HAp can be formed (Silva et al. 2001, Raynaud et al. 2002a). Reactions conducted at pH ≤ 7.4 are primarily aimed at understanding the crystallization of apatites in the body (Okazaki et al. 1992).

During aqueous precipitation, other species such as NH_4^+ (Vignoles et al. 1987), H_2O (Le Geros et al. 1978, Young and Holcomb 1982), O^{2-} (Young and Holcomb 1982), CO_3^{2-} (Vignoles et al. 1987, Young and Holcomb 1982) and HPO_4^{2-} (Young and Holcomb 1984) may be substituted in the structure or adsorbed onto the surface. Addition of more than one substituent element/group can lead to a combination of an expansion and contraction of the unit cell (Le Geros et al. 1977). For example, carbonate causes a decrease in the a -axis (Le Geros 1965) that could be counteracted by an increase from an acid phosphate group (Young and Holcomb 1984). This reaction sequence is complicated by the ability of carbonate to substitute phosphate or hydroxide, the former being the more common (Shimoda et al. 1990).

The incorporation of foreign ions during the crystallization in solution has inspired researchers to investigate the substitution of chemical groups found naturally in enamel or bone. Application of this knowledge can then be used to adjust properties such as solubility, mechanical behavior and bone bonding ability. Substituent elements and chemical groups can include fluoride (Jha et al. 1997, Rodríguez-Lorenzo et al. 2003), carbonate (Barralet et al. 1998, Nelson and Featherstone 1982), magnesium (Okazaki 1988, Mayer et al. 1997, Ben Abdelkader et al. 2001), zinc (Mayer et al. 1994, Bigi et al. 1995), silicon (Gibson et al. 1999), iron (Okazaki and Takahashi 1997) and strontium (Heijlifers et al. 1979, Leroux and Lacout 2001a, Marie et al. 2001). The addition of many of these chemical groups decreases the growth rate at low concentrations. Full substitution of fluoride for the hydroxyl ion removes lattice distortion, produces a more stable apatite and, thus, is able to drive precipitation to completion more easily (Rodríguez-Lorenzo et al. 2003). Carbonate replaces phosphate in reactions containing fluoride and at high pH (Shimoda et al. 1990).

Chemical elements not found in bone can be substituted for different effects. For example, addition of silver has been used for imparting antimicrobial properties (Kim et al. 1998).

Crystallinity, a term used to describe the crystal perfection and/or crystallite size, can vary depending upon the synthesis conditions. A high crystallinity is typically desired where an apatite is subjected to elevated processing temperatures for consolidation into dense forms (see sections on sintering, porous materials and coatings). However, low crystallinity can impart a higher resorbability in applications such as composites and cements. Synthesis at 90°C produces a more pure apatite with a higher degree of crystallinity, than at room temperature. Crystallinity also increases in the presence of strontium (Leroux and Lacout 2001a) and fluoride. Crystals can be plate-like, acicular or blocky and exhibit a surface area of 30-120 m²/g (Shimoda et al. 1990, Rodríguez-Lorenzo and Vallet-Regí 2000, Senamaud et al. 1997) (Fig. 2). Crystal size in the *c*-axis direction can be as small as 50 nm when produced at 25°C to as large as 700 nm at 90°C. These crystallites agglomerate into clusters upon drying (Fig. 2c). For comparison, the unit cell parameters of biologic and synthetic hydroxylapatites are shown in Table 1. Details of the structure of apatite and the hydroxyl end member are given in Hughes and Rakovan (this volume).

High-temperature synthesis was the first method of apatite production reported and involved passing phosphorus trichloride vapor over red-hot lime (Daubrée 1851). This

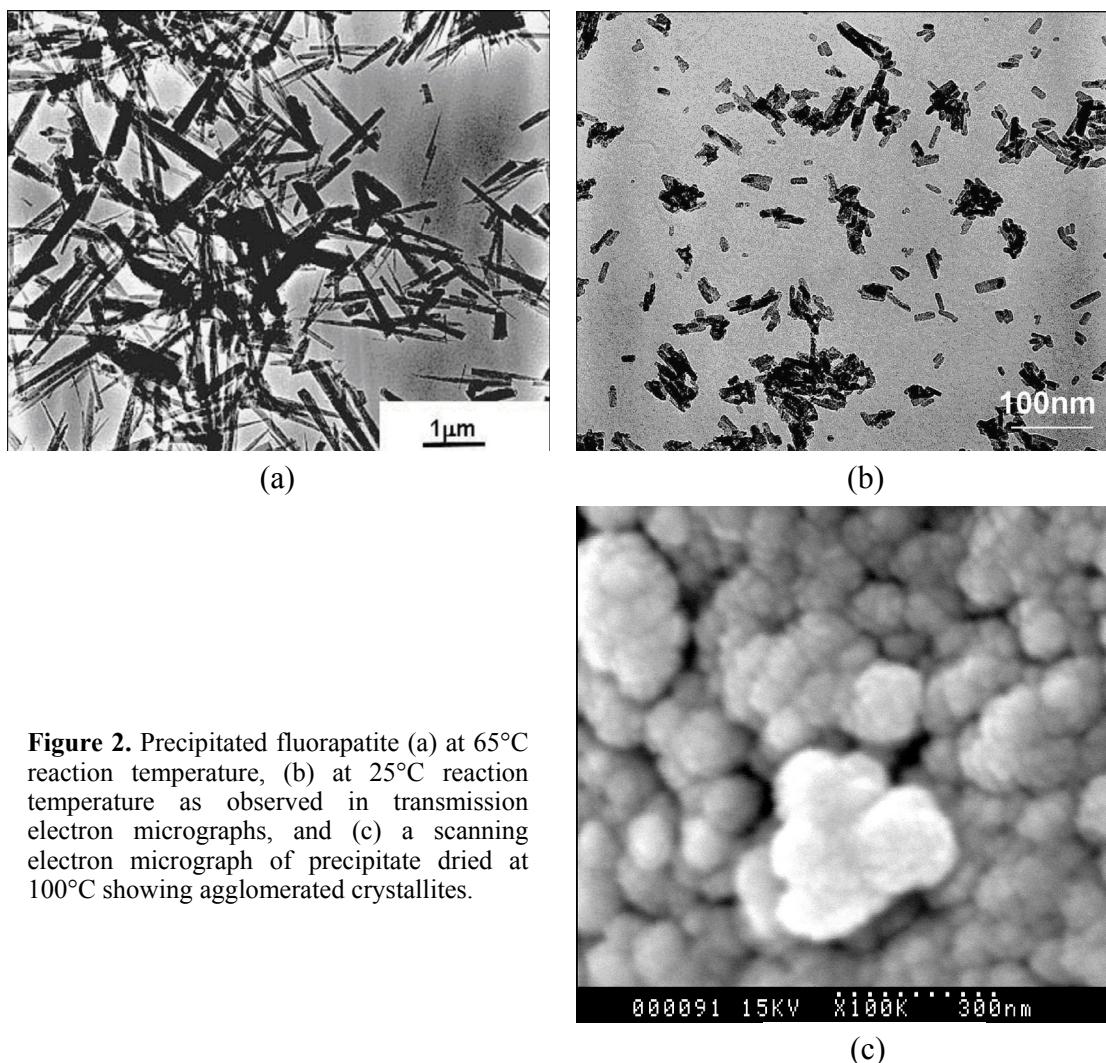


Figure 2. Precipitated fluorapatite (a) at 65°C reaction temperature, (b) at 25°C reaction temperature as observed in transmission electron micrographs, and (c) a scanning electron micrograph of precipitate dried at 100°C showing agglomerated crystallites.

process involved the reaction of a gaseous and solid phase. Diffusion between two solid calcium phosphates also produces hydroxylapatite, at temperatures in excess of 1000°C, however, this method does not produce homogeneous apatites and leads to an increase in grain size through growth and reduction in surface area; two aspects that may be important in the further processing and application of calcium phosphates.

Other synthesis reactions include hydrothermal techniques, hydrolysis of other calcium phosphates (Monma and Kayima 1987) and sol-gel methods (Masuda et al. 1990). Hydrothermal synthesis is the second most common method and, in comparison to the wet chemical method, is able to produce well-crystallized, compositionally homogeneous apatite (Yoshimura and Suda 1994). In this process, a mixture of calcium carbonate and di-ammonium hydrogen phosphate is subjected to 12,000 psi and heated to 275°C (Roy and Linnehan 1974). A high crystallinity, carbonate substituted HAp is produced by this method. Calcium phosphates that have been hydrolysed to HAp include octacalcium phosphate (Graham and Brown 1996), tricalcium phosphate (Nakahira et al. 1999), and brushite (Monma and Kayima 1987, Fulmer and Brown 1998, Manjubala et al. 2001). The chemical formulas of these and other inorganic compounds are provided in Appendix 1.

APATITE CEMENTS

Traditionally, particles or blocks were used for reconstruction of defects in bone, but particles easily migrate or disperse into the surrounding tissue after implantation (Wittkampf 1988). In periodontal defects, calcium sulphate dental cement was used to prevent migration. Larger volumes (greater than about 5 ml) are more difficult to seal. Calcium phosphate cements take a special place in implantable ceramics. They are easily formed into bony defects of any geometry. Upon mixing of the reactants, they can be plastically formed into an osseous cavity to precisely fit the defect geometry.

Production of apatite cements

The initial work on calcium phosphate cements involved an equimolar mixture of tetracalcium phosphate and calcium hydrogen phosphate (Brown and Chow 1983). Finely ground and homogenized powders are mixed with water to form a paste. Initially, dicalcium phosphate dihydrate is formed with a plate-like morphology. Dissolution of this phase governs the initial reaction rate. The pH initially climbs to 10.6 where HAp crystallizes on the tetracalcium phosphate and then a decrease in pH yields a calcium deficient HAp (Walsh et al. 2001). The pH fluctuation can be minimized with a smaller particle size, presence of HAp seeds and a less than stoichiometric amount of tetracalcium phosphate (Liu et al. 1997, Matsuya et al. 2000). As HAp growth occurs according to Equation (1), the rate-limiting step is dictated by diffusion of ions through the acicular HAp layer to the tetracalcium phosphate. Unlike methacrylate bone cement, the reaction is isothermal and avoids cell and tissue damage that would normally occur from the heat of reaction.



Hardening of the cement occurs mostly within the first six hours, yielding an 80% conversion to HAp and a compressive strength of 50-60 MPa (Liu et al. 1997, Otsuka et al. 1995). Hardening can be accelerated with phosphate solution (Chow et al. 1999), sodium fluoride (Brown and Fulmer 1996), sodium hydrogen phosphate (Miyamoto et al 1995), and sodium alginate (Ishikawa et al. 1995). Alternatively, the use of alpha-tricalcium phosphate based bone cements has provided a means for fast curing times (Kon et al. 1998, Takagi et al. 1998, Fernandez et al. 1999). Thus, the setting time can be controlled to suit different sites within the body.

Inclusion of porosity, with the aim to improve the osteoconductivity, can be introduced by the addition of soluble inclusions such as sucrose, sodium hydrogen carbonate, sodium hydrogen phosphate (Takagi and Chow 2001), or calcium carbonate that reacts to evolve carbon dioxide (Walsh et al. 2001). These reactants produce ionic substitutions in the structure and further improve the resorbability. Another example is that of strontium, which has been shown to be incorporated at low concentrations, while higher concentrations require a heat treatment (Leroux and Lacout 2001b). Since the cement is designed to harden in the body, the composition is modified *in situ* by reaction with the physiological solutions.

The low temperature of formation and inherent porosity also permits the addition of antibiotics (Bohner et al. 1997, Takechi et al. 1998) or growth factors that stimulate the differentiation of preosteoblastic cells (Blom et al. 2000). However, the enhanced capability of the cement is somewhat offset by a longer hardening time (Ginebra et al. 2001).

Animal studies

Takagi et al. (2001) showed that a carbonate is not needed to seed the initial reaction. *In vivo* studies revealed that apatite incorporates 1 wt % carbonate from the available physiological fluids in as early as 12 hours.

In situ hardening in the body can result in particle release and a change in alkalinity in the surrounding environment. Implantation of a cement that is hardened prior to insertion in the body has revealed a less pronounced foreign body response (Frayssinet et al. 2000). This result may be attributed to the early particle release (Pioletti et al. 2000) or the increase in pH that has been known to trigger an inflammatory response and cell death (Silver et al. 2001).

Normal bone remodeling processes occur around calcium phosphate cement with osteoclastic resorption removing bone followed by deposition of new bone directly on the resorption line (Yuan et al. 2000). Bone growth on pre-hardened cement situated in muscle tissue suggests that bone cement is osteoinductive.

Clinical studies

The treatment for osteoporotic compression fracture of the vertebrae has been investigated on human cadaver vertebrae with calcium phosphate cement (Ikeuchi et al. 2001) and results indicate that cement provides an increased compressive strength where cancellous bone is replaced with cement.

An amorphous calcium phosphate cement retrieved from human biopsies, has indicated an absence of fibrous tissue and partial replacement by new bone. The surface of the cement was surrounded by cells indicative of a bone remodeling process leading to new bone with regular trabecular and osteonal patterns (Sarkar 2001). Patients with complex calcaneal fractures treated with calcium phosphate cement have indicated full weight-bearing as early as three weeks postoperatively (Schildhauer et al. 2000).

Other applications include reconstruction of an alveolar bone defect (Yoshikawa and Toda 2000), craniofacial reconstruction (Friedman et al. 1998), closure of cranial base and temporal bone defects following surgery (Kamerer et al. 1994), spinal surgery (Bohner 2001), filling of periodontal osseous defects (Brown et al. 1998), sealing of root canals (Macdonald et al 1994, Cherng et al. 2001) and, possibly, dental pulp-capping (Chaung et al. 1996). While filling of larger defects employs the use of a plastic mass, smaller voids can be filled by injecting a more fluid mass through a needle (Lim et al. 2002). This technique of injection may be adapted as a minimally invasive approach.

COMPOSITES

Matching the stiffness of the implant material to bone allows stress transfer from the implant to the surrounding bone in loading conditions. Known as Wolff's law (Wolff et al. 1986), this effect stimulates the surrounding bone for continued bone remodelling, a part of which includes bone deposition onto the biomaterial surface. The high elastic modulus (100 GPa for HAp) can be lowered to that of cortical bone (20 GPa) by blending with a polymer. In so doing, the low fracture toughness of HAp is also improved. Figure 3 shows a comparison of the component materials for elastic modulus vs. density (Gross and Ezerietis 2002).

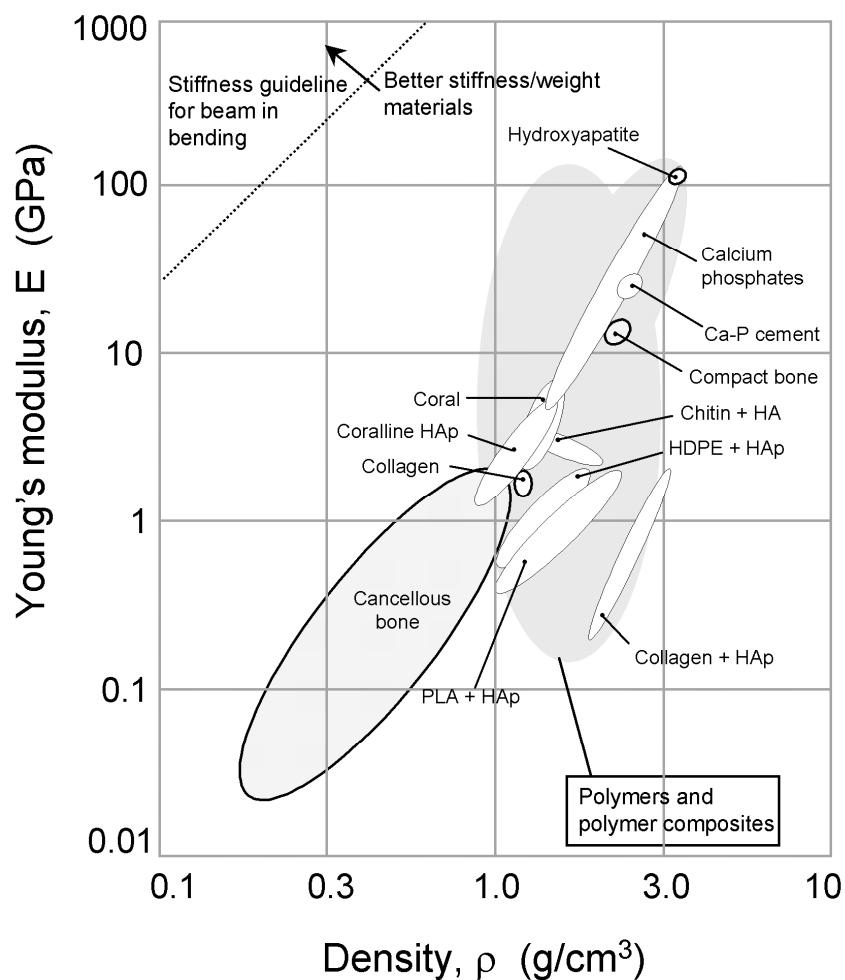


Figure 3. An Ashby diagram with the modulus of sintered hydroxylapatite, porous hydroxylapatite and polymer-apatite composites.

The first polymeric composite designed for implantation into bone was reported in 1981 (Bonfield et al. 1981). The limit of blending is dictated by the ductile/brittle transition at about 40 vol % HAp. At compositions lower than 40 vol %, the fracture toughness is higher than bone, but the elastic modulus is comparable to bone. Hydroxylapatite particles are blended in a twin screw extruder to promote mechanical bonding between the rough particle surface and high density polyethylene (Suwanprateeb et al. 1995, Wang et al. 1998). This bonding can be improved by chemically coupling the particles to the polymer (Deb et al. 1996). Use of fiber processing and compaction or compression molding together with extrusion has been shown to improve the ductility and tensile strength, respectively (Wang et al. 2000, Ladizesky et al. 1997). Other non-resorbable polymer composites that have been manufactured include polyetherketone

(Abu Bakar et al. 1999), polyhydroxybutyrate (Luklinska and Bonfield 1997) and polysulfone (Wang et al. 2001). These composites are easily formed and are used in maxillofacial augmentation. More specific uses include nasal reconstruction (Lovice et al. 1999), middle ear reconstruction (Geyer 1999, Meijer et al. 2002) and repair of orbital fractures (Tanner et al. 1994). Recently, a pilot study has been conducted to examine the feasibility of thin sheets for the outer ear canal (Zanetti et al. 2001). The bone grows up to the composite and establishes a bond with the low resorbable HAp particles.

The low elastic modulus of composites has been used to lower the stress level around implants. Such polymer-hydroxylapatite coatings have been successfully manufactured by thermal spraying (Sun et al. 2002). Finite element analysis has illustrated that a coating at the neck of a dental implant lowers the stress gradient at the coating-bone interface and the stress level in the surrounding bone (Abu-Hammad et al. 2000).

Resorbable polymer composites can be used when bone health is sufficient for remodeling to rebuild the bone. Bone can reclaim the empty space and adapt to the new loading conditions as the material resorbs. The polymer systems used for this approach include polylactic acid (Ignatovic et al. 2001), collagen (John et al. 2001), starch (Mano et al. 1999), chitosan (Ito et al. 1999), and polyglycolic acid (Durucan and Brown 2000). A polylactic acid-hydroxylapatite composite has been successfully used for repair of the rib cage in a child (Watanabe et al. 1989). Alternatively, porous apatite containing bodies may be used for drug delivery (Yamashita et al. 1998).

Resorbable polymers are also used in the construction of porous scaffolds for tissue engineering (Laurencin et al. 1996). Stem cells are seeded onto the scaffold, which multiply and fill the pore volume as the material resorbs. The porous network serves to transport nutrients and remove the degradation products from the degrading scaffold. Inclusion of HAp as a filler in these resorbable polymers has provided a means of conducting tissue growth inside the pore system (Ma et al. 2001, Laurencin et al. 1999, Thomson et al. 1998, Devin et al. 1996). Furthermore, the dissolution of HAp minimizes the fall in pH associated with degradation of the polylactic/glycolic acid composites (Agrawal and Athanasiou 1997, Ignatius and Claes 1996). Porous scaffolds for stem cell growth are presently receiving immense interest from the commercial and scientific communities.

SINTERING OF DENSE CERAMICS

The sintering process involves calcination, and compaction at room temperature followed by heating at high temperatures. Calcination is performed at 600–900°C for apatites intended for high temperature processing. Adsorbed moisture, carbonates and chemicals remaining from the synthesis stage, such as ammonia and nitrates in some specific reactions, are removed as gaseous products. The removal of these gases facilitates the production of dense materials during sintering. These chemical changes are accompanied by a concurrent increase in crystal size and a decrease in the specific surface area. Apatites with a Ca/P molar ratio less than 1.67 will form beta tricalcium phosphate (as opposed to alpha tricalcium phosphate stable at high temperatures), but calcium rich compositions, with a Ca/P molar ratio greater than 1.67, will form calcium oxide. Thus, phase identification by X-ray diffraction after heating can be used to determine if the Ca/P ratio was above or below 1.67.

Apatite ceramics are consolidated by uniaxial or biaxial pressing (Rodríguez-Lorenzo et al. 2001a), cold isostatic pressing for a more homogeneous green density (Akimov et al. 1994), slip casting for complex shapes (Nordström and Karlsson 1990, Shareef et al. 1993, Toriyama et al. 1995, Rodríguez-Lorenzo et al. 2001b), or injection moulding (Cihlar and Trunec 1996). Some press-sintered ceramics are shown in Figure 4.



Figure 4. Sintered hydroxylapatite as powder, granules, pellets and other forms for implantation into bone and soft tissue.

Sintering of un-calcined powders produces lower shrinkage upon heating. The high surface area of the submicron crystallites leads to a lower fluidity and powder compaction is not very effective, but densification is greater on heating (Juang and Hon 1996, Landi et al. 2000). Densification occurs at the nanoscale between the individual crystallites within the particles and between the individual particles.

Chemically substituted apatites

Substituent elements and chemical groups play an important role in producing phase pure apatite ceramics. Sintering of HAp requires high temperature stability of the source powder and must avoid additions that decrease the stability at high temperatures. A desired powder will retain the apatite structure and not decompose to tricalcium phosphate and tetracalcium phosphate. The apatite structure can be destabilized by magnesium (Baravelli et al. 1984), carbonate (Ellies et al. 1988, Merry et al. 1998), and partial substitution with fluorine ions (Zhang et al. 2001). Manganese as a trace element, readily detected by a color change to blue by oxidation upon heating, is often present (Li et al. 1993b). The black color in teeth recovered from archeological sites suggests that manganese may also lead to black apatite (Stermer et al. 1996). The presence of silicon, replacing calcium ions, does not alter the thermal stability. Full substitution of hydroxyl groups by fluorine ions improves the thermal stability. More on the location of these substituent elements is available in Pan and Fleet (this volume).

A partial vapor pressure of water is needed to retain the structural OH⁻ at temperatures greater than 900°C (Riboud 1973); however this has also been noted to decrease the densification rate. Dehydroxylation in HAp produces an oxy-hydroxylapatite (Kijima and Tsutsumi 1979). The inclusion of peroxide ions (Zhao et al. 2000) is expected to decrease the diffusion and, hence, also slow densification at high temperatures.

Stoichiometry, described by the Ca/P molar ratio, has a major influence on the physical properties of the apatite and, hence, its application. For calcium-deficient hydroxylapatite, a decrease in surface area starting at 700°C leads to a lower shrinkage (8% less for a powder with Ca/P of 1.64 relative to stoichiometric HAp at 1200°C) (Raynaud et al. 2002b). Low shrinkage in the final sintered product is usually accom-

panied by porosity that leads to low mechanical strength. Tricalcium phosphate formed from the decomposition of the calcium deficient apatite decreases the sinterability. In Ca-rich hydroxylapatites, densification is again lower in comparison to stoichiometric hydroxyl-apatite (Słosarczyk et al. 1996).

Sintering additives

Densification is promoted by incorporating given chemical groups into the crystal lattice. Carbonate, when substituted for phosphate, promotes sintering to a higher density at lower temperatures (Ellies et al. 1988, Doi et al. 1993, Merry et al. 1998) achieving full density in an atmosphere of wet carbon dioxide (Barralet et al. 2000). No change in sintering is observed when carbonate substitutes for the hydroxyl group. Densification increases with sodium (Correia et al. 1996), lithium (Fanovich and Lopez 1998), fluoride (Senamaud et al. 1997), but is lowered with potassium and magnesium (Fanovich and Lopez 1998). These individual influences may be compounded. Use of sodium hydrogen carbonate in the synthesis of HAp has been shown to further accelerate the sintering process (Suchanek et al. 1997).

Chemical additives such as MnO_2 (Muralithran and Ramesh 2000a), lithium phosphate (Vaz et al. 1999) and sodium phosphate (Suchanek et al. 1997) may be used solely to improve densification and remain either at grain boundaries or included in the crystal structure. Particulate additives including zirconia, alumina, silicon nitride, silicon carbide (Ruys et al. 1993, Suchanek et al. 1997), stainless steel and titanium (Knepper et al. 1998) may be included to improve the mechanical strength. Suchanek et al. (1997) reviews processing aspects of HAp with an emphasis of improving strength. The affect of sintering additives, both chemical and particulate, after dissolution in the human body and the effect on normal cell function is presently unknown (Ballestri et al. 2001).

Another approach to enhance the sintering kinetics is to take advantage of the high surface area of ultrafine powders. Higher surface area powders can be sintered at 150°C lower than powders with a low surface area (Gibson et al. 2001). These particles can be incorporated into an emulsion to enable ease of movement between the crystallites in the particles and produce a high compacted and sintered density (Murray et al. 1995).

Sintering temperatures

Sintering of HAp is usually conducted at an average temperature of $1200 \pm 100^\circ\text{C}$ for periods up to three hours (Jarcho et al. 1976, Peelen et al. 1978, Akao et al. 1981, de With et al. 1981, Kondo et al. 1984, Wang and Chaki 1993, Puajindener et al. 1994, van Landuyt et al. 1995, Lu et al. 1998, Muralithran and Ramesh 2000b). The development of microstructure, as observed from the decrease in porosity in fractured ceramics, shows an increase in density upon sintering at high temperatures (Fig. 5). The densification rate depends on the atmosphere, decreasing as the environment is changed from vacuum to air to moist air for hydroxylapatite (Wang and Chaki 1993). Grain growth requires an activation energy of 235 kJ/K mol (Jarcho et al. 1976). Grain growth can be minimized with other techniques such as microwave sintering (Fang et al. 1994), hot pressing (Halouani et al. 1994), or gel casting (Varma and Sivakumar 1996). At higher temperatures the decomposition to tetracalcium phosphate and tricalcium phosphate degrades the properties of the sintered body, the exact temperature depending on the synthesis technique employed and the impurities present.

The bending strength of HAp in three point bending is between 40 and 200 MPa (Jarcho et al. 1976, Akao et al. 1981) depending upon the surface finish and composition. It can be further noted that the three-point bend test intrinsically demonstrates a wide variability in results. Fracture strength reaches a maximum at a Ca/P ratio of 1.60-1.65 and decreases outside of this Ca/P range (Royer et al. 1993, Słosarczyk et al. 1996,

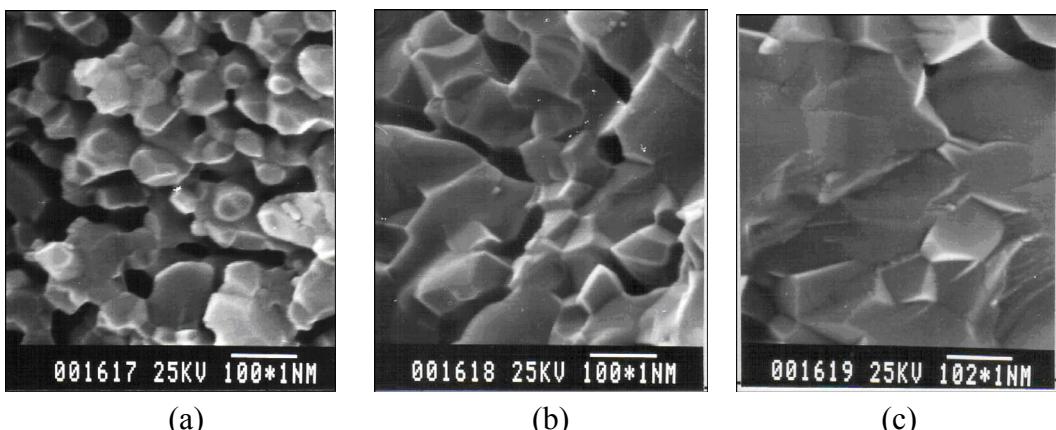


Figure 5. Fracture surface of hydroxylapatite sintered for one hour at:
 (a) 1150°C, (b) 1200°C, (c) 1250°C.

Raynaud et al. 2002c). Mechanical mixtures of tricalcium phosphate and HAp suggest that tricalcium phosphate is beneficial up to 30 mol % in increasing the composite strength (Toriyama et al. 1987). This may be attributed to the higher bending strength of tricalcium phosphate sintered at the same temperatures (Akao et al. 1984). At high sintering temperatures tricalcium phosphate assists densification by liquid phase sintering. Tricalcium phosphate can also be included as a submicron powder by the decomposition of a calcium deficient apatite into hydroxylapatite and tricalcium phosphate. This approach leads to a larger decrease in surface area of the powder at temperatures below 800°C and a resulting lower sinterability at higher temperatures (Asada et al. 1988). The reader is directed to Suchanek et al. (1997) for more information on mechanical properties.

In vitro and animal studies of sintered apatites

Materials implanted into bone are modified by degradation and the action of different cell types. Degradation occurs by dissolution and the action of osteoclasts. Osteoclasts are very effective in material removal and provide a material resorption mechanism at the surface of the ceramic and particulate removal by phagacytosis (Heymann et al. 2001). Degradation of calcium phosphates as obtained from *in vitro* studies employing cells or animal studies has been discussed in several reviews (Frayssinet et al. 1993, Le Geros 1993, Heymann et al. 1999).

Hydroxylapatite in the sintered form is less soluble than biologically formed HAp in bone and teeth, attributable to the fine crystal size and substituent elements. The solubility of sintered hydroxylapatite is increased with additions of strontium (Christoffersen et al. 1997, Okayama et al. 1991) and carbonate (Nelson 1981, Doi et al. 1998), but lowered with zinc (Mayer and Featherstone 2000) and fluorine. A discussion of dissolution mechanisms is available in a review by Dorozhkin (Dorozhkin 2002). The higher solubility of apatites may be linked to increased osteoclastic resorption, as found with carbonated apatite (Doi et al. 1999).

Bioactivity is determined by the ability of a material to invoke a crystallized carbonated apatite layer from a physiological fluid. Silica incorporation in HAp promotes early crystallization and a higher rate of osteoblastic cell proliferation on sintered materials. This response has not been isolated from the effects of different Ca/P ratio, surface area, and presence of other calcium phosphate phases (Best et al. 1997). Such comparative information on the influence of different substituent elements on the bioactivity still remains to be developed. In assessing the cell growth on apatites, it is

important to separate the effects of the topology from the composition. Bodies fired at 1200°C to create a low surface porosity, have exhibited a higher cell growth (Frayssinet et al. 1997).

Sintered HAp particles are remodeled by the host tissue when implanted into bone. Implantation into the cortical bone of the femur of sheep has revealed that stoichiometrically pure HAp resorbs by several microns after 18 months with dissolution occurring mainly at the grain boundaries (Benhayoune et al. 2000). The tensile strength of bone from the tibia of a rabbit onto a HAp cylinder is 0.85 MPa after 3 months (Edwards et al. 1997).

Clinical studies

The ability of hydroxylapatite to accept foreign ions into its structure and onto the surface has been used to incorporate radionuclides. Radioactive samarium and rhenium have been incorporated into hydroxylapatite microspheres sized at 20-40 µm and injected into knee joints to treat rheumatoid joint synovitis (Chinol et al. 1993). Clinical studies have shown that hydroxylapatite particles are easily labeled with radionuclides, exhibit low leakage of radioactive species, and provide a reduced inflammation of the synovium and restored joint motion to the patient (Clunie et al. 1996).

Where hydroxylapatite is used in the powder form for orthopaedic or dental applications, the particles are normally immobilized by mixing with collagen (Sugaya et al. 1989), gelatin (Nagase et al. 1989), or fibrin glue (Wittkampf 1988). This limits the application to bone graft onlay applications. The mixture of collagen and HAp, known as Collagraft® (Collagen Corporation, Palo Alto, California, USA) has been shown to be an effective aid in fracture healing (Cornell 1992).

Fully densified bodies of hydroxylapatite have been employed for reconstruction of the middle ear (Shinohara et al. 2000), dental root implants (Ogiso 1998) and skull reconstruction (Koyama et al. 2000).

Large complex shapes require computer aided design and computer-aided manufacturing to fit the anatomical constraints. Mechanical strength has been optimized in terms of curvature, thickness, width, and porosity (Ono et al. 1998) and further employed for large complex cranial bone defects (Ono et al. 1999). The porosity serves the purpose for bone ingrowth, as explained in the next section.

Bioresorbable β-tricalcium phosphate is occasionally used in conjunction with hydroxylapatite to improve solubility (Klein et al. 1984, Yamada et al. 1997) and hence the osteoconductivity. Applications include nose reconstruction (Abe et al. 2001), fusion of the backbone (Ueda et al. 2001), and use as a bone graft (Fujibayashi et al. 2001).

POROUS APATITE BODIES

Implantation of "inert" ceramics with non-connecting cylindrical channels has shown that bone is capable of growing into pores larger than 100 µm. Bone growth occurs at 20 µm/week in a 100 µm pore and 70 µm/week in a 200 micrometer pore (Ravaglioli and Krajewski 1992). A porous surface provides mechanical fixation in addition to providing sites on the surface that allow chemical bonding between HAp and bone. The inclusion of pores increases the solubility at the expense of mechanical properties. Various types of pore geometries have been introduced into HAp, e.g., pore morphologies, which are both closed and open. An interconnecting pore network offers circulation of nutrients and facilitates deeper bone penetration. As bone grows into the porous network, the solubility of the filled pores decreases and the strength of the implant is improved by a mechanism of natural reinforcement.

Artificial porous structures

Pores can be created by a variety of techniques. In keeping with the sintering methodology, pores can be created by control of crystallite morphology (Nakahira et al. 2000) or sintering parameters (Liu 1996) to obtain a different degree of particle coalescence. These pores are small and cannot accommodate bone ingrowth. The process can be modified by including a foaming agent prior to heating (Dong et al. 2001), or by the evolution of gases from hydrogen peroxide (Peelen et al. 1978) or organic compounds such as naphthalene (Monroe et al. 1971), polyvinylacrylate (Vaz et al. 1999) or starch (Rodríguez-Lorenzo et al. 2002b) during the heating cycle. Pore size and content can be further increased by adding the foaming step prior to removal of organics during the heating stage (Engin and Tas 1999). Gel-casting of HAp produces bodies with sufficient strength for shaping of porous bodies before the firing process (Sepulveda et al. 2000). Porosity leads to a decrease in elastic modulus and fracture toughness, i.e., to 100 GPa compared to 160 GPa and $1.1 \text{ MPa} \cdot \text{m}^{1/2}$ compared to $1.8 \text{ MPa} \cdot \text{m}^{1/2}$ for 100% dense materials (Rodríguez-Lorenzo et al. 2002).

Biologically architectured porous materials

The pore architecture of naturally occurring porous networks have been adapted for implantation. The exoskeleton of coral is a material with small crystallites of aragonite and pore connectivity (Fig. 6). *Porites* and *Goniopora* are coral species with a pore size range of 140 to 160 and 200 to 1000 μm , respectively. Coral skeletal material can be converted to carbonate-hydroxylapatite by hydrothermal exchange with di-ammonium hydrogen phosphate at 275°C and 82.7 MPa (Roy and Linnehan 1974). The pseudo-hexagonal structure of aragonite facilitates ease of conversion to the hexagonal unit cell of HAp. Conversion of calcite, another polymorph of calcium carbonate, under the same conditions produces tricalcium phosphate (Zaremba et al. 1998). This process preserves the interconnecting porosity and produces a carbonated, strontium enriched HAp along with magnesium substituted β -tricalcium phosphate (Le Geros et al. 1995). The carbonate and beta-tricalcium phosphate increases the material derived solubility in addition to the increase in surface area from the pores. The stimulation of bone growth by strontium shown in other studies improves the integration of converted corals in bone. Recent work has revealed that hydrothermal processing in the presence of a potassium dihydrogen phosphate can cause a complete transformation to an apatite (Xu et al. 2001).

Trabecular bone from a bovine source already possesses the desired interconnected porosity (Hing et al. 1999) and can be used as a suitable porous body after removal of the organic fraction by heating (Joschek et al. 2000). Large pores allow bone remodeling and trabecular bone formation within the pores (Chang et al. 2000).

Clinical applications of porous apatites

Porous HAp is used in a broad range of applications including filling bone defects (Yamamoto et al. 2000), facial reconstruction (Hobar et al. 2000), orbital implants in eyes (Jordan and Bawazeer 2001), hand surgery (Baer et al. 2002), correction of scoliosis (Delecrin et al. 2000) and drug delivery (Jain and Panchagnula 2000, Netz et al. 2001). The pore size and solubility are important aspects to promote osteoconduction (Kurioka et al. 1999). These porous bodies may be modified with tricalcium phosphate to enhance the solubility or may be enriched by the addition of biological species. The addition of a human osteogenic protein that adsorbs onto the surface of the porous body has been a key element in providing more complete bone growth inside a porous hydroxylapatite (Ripamonti et al. 2001).

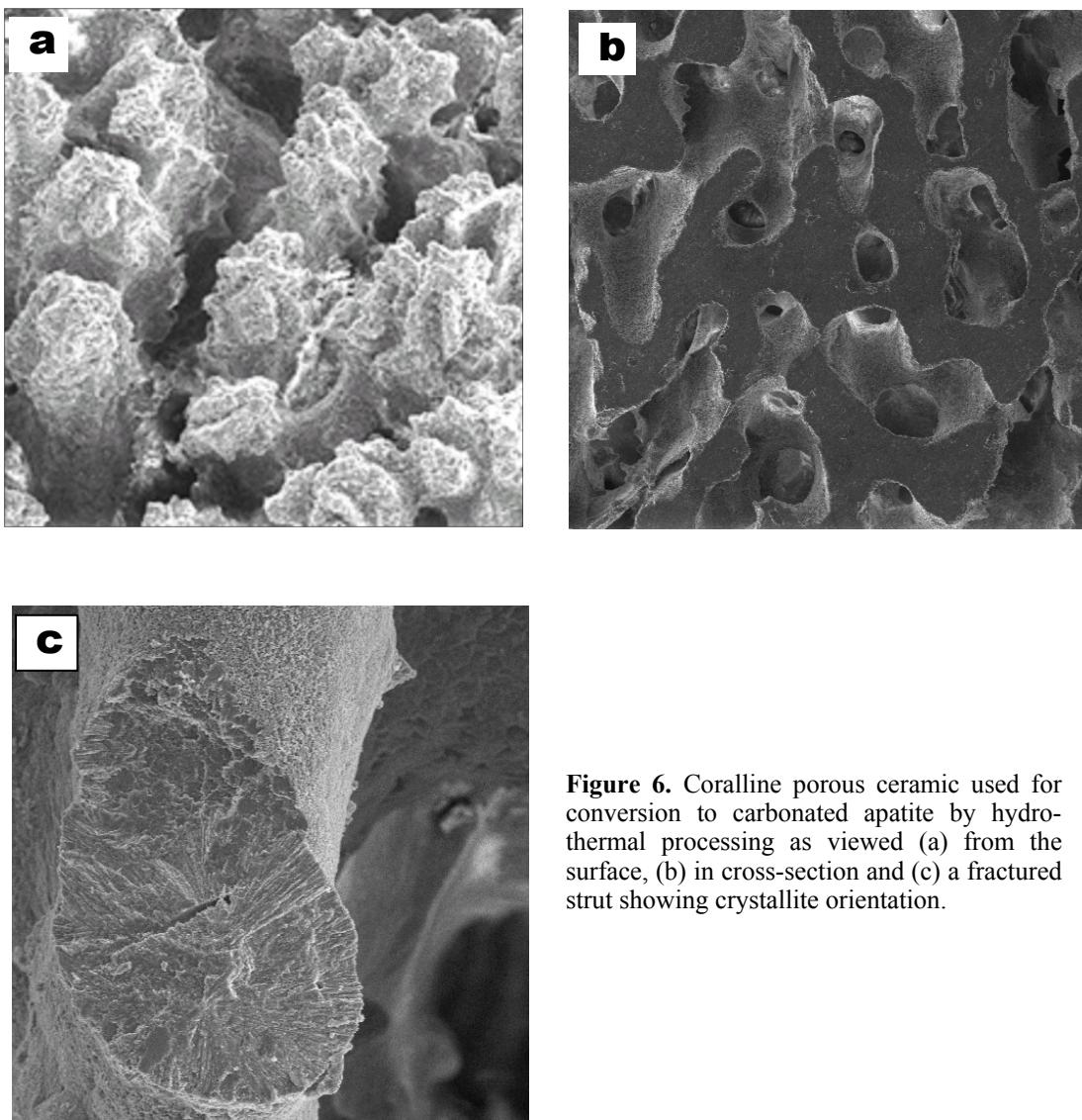


Figure 6. Coralline porous ceramic used for conversion to carbonated apatite by hydrothermal processing as viewed (a) from the surface, (b) in cross-section and (c) a fractured strut showing crystallite orientation.

COATINGS

The mechanical properties of sintered apatites has limited their application to low stress areas in the body. To overcome this difficulty, apatites are applied as coatings on the surface of metallic implants where high loads on the implant are expected. Various coating options are available including thermal spraying, sputter deposition, pulsed laser deposition, sol-gel deposition, electrophoretic coating, electrodeposition, and biomimetic deposition. These are discussed in turn.

Thermal spraying

Thermal spraying is the most widely used technology to manufacture a coating on implants (Fig. 7). Thermal spray was chosen as a candidate technology due to its high deposition rate. While conventional ceramics are delivered to the thermal heating zone at a rate of 5-10 kg/hr, hydroxylapatite powder is transported at 1kg/hr. The first clinical studies in the early 1980s revealed the greatly improved prosthetic bone performance of plasma sprayed coatings. Application of a coating minimizes the release of metallic ions from the underlying metal substrate (Sousa and Barbosa 1996, Browne and Gregson 2000, Finet et al. 2000, Ektessabi et al. 2001), provides a stimulus for bone growth, and a

surface for bone to establish a strong bond. Thermal spraying involves concurrent heating and propulsion of feedstock though a thermokinetic medium to produce a melted particle traveling at high speeds. Hydroxylapatite has been sprayed with plasma spraying, vacuum plasma spraying (Chang et al. 1998, Heimann and Vu 1997, Ha et al. 1998, Cabrini et al. 1997, Bellemans 1999), high velocity oxy-fuel spraying (Oguchi et al. 1992, Wolke et al. 1992, Matsui et al. 1994, Haman et al. 1995, Li et al. 2000, Knowles et al. 1996, Brown et al. 1994), and the detonation gun process (Erkmen 1999, Gledhill et al. 1999). These processes all use powder as a feedstock material, sized between 10 and 150 μm , and subject the powder to different thermal and kinetic environments. Suspension plasma spraying is a unique technique in that an atomized suspension of HAp is fed into a radio-frequency plasma (Bouyer et al. 1997). The slow velocity allows the liquid to be vaporized and the remaining solid then melts. This technique avoids the high processing costs normally associated with drying, calcining, spheroidising, and particle sizing before injection into a plasma or a flame. Plasma spraying, also known as air plasma spraying, is the main method of choice, followed by vacuum plasma spraying.



Figure 7. Hydroxylapatite plasma sprayed on various femoral stems (top) and a femoral component of the knee prosthesis showing hydroxylapatite on the internal surface (bottom).

Plasma spraying. The plasma spray process is controlled by a multitude of processing parameters, all of which influence the quality of the sprayed coating. The heat available for melting of the powder can be controlled by a selection of plasma gases. Plasma gas combinations used for depositing apatite coatings include Ar/H₂, N₂/H₂, Ar/N₂ and Ar/He. Powder injected into the heat source is rapidly heated over the melting temperature. Overheating can lead to decomposition into tetracalcium phosphate, tricalcium phosphate and calcium oxide (Lugscheider et al. 1991a, Radin and Ducheyne 1992, Palka et al. 1993, Yang et al. 1995, McPherson et al. 1995, Vogel et al. 1999, Tufekci et al. 1999). The particle characteristics such as particle morphology, particle size, inherent porosity, and crystallite size all influence the heat conduction and, hence,

the thermal chemistry and particle melting at high temperatures.

Crystallinity of coatings. The molten droplets are impacted onto roughened substrates. The heat from the droplet is rapidly removed providing a quench rate of about 10^5 °C/sec (Gross et al. 1998d). The brief time at which the chemical species are mobile within the droplet during cooling is insufficient for crystallization. Crystallization of melted regions is further impeded due to the loss of structural water in the shell of the particles. Plasma spraying is thus programmed by a choice of spray conditions (Weng et al. 1995) to produce melting of the outer shell that upon deposition will predominantly form an amorphous calcium phosphate. The crystallinity of coatings is adjusted by controlling the amount of heat input into the powder. This is conducted by changing the spray conditions or the particle size; smaller size produces lower crystallinity (Klein et al. 1994, Tong et al. 1996, Gross et al. 1998d).

The relative location of the amorphous phase has been shown in coatings (Chen et al. 1994, Gross et al. 1997), and the location of the possible decomposition phases proposed in a model (Gross et al. 1998b). Crystalline areas within a coating can be viewed in terms of thermal changes within a droplet during particle traverse within the plasma, heat conduction within the coating as successive molten droplets release their heat to the already deposited material, and post-deposition heating operations. A typical microstructure of a coating showing crystalline regions is shown in Figure 8.

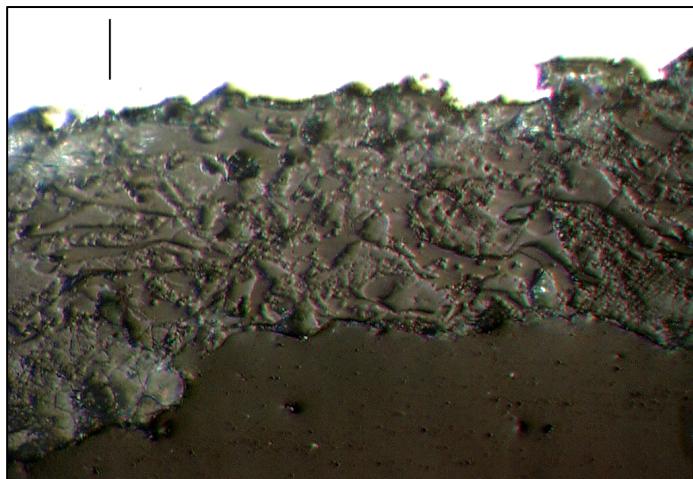


Figure 8. Cross-section of hydroxylapatite plasma-sprayed coating exhibiting small crystalline islands. The vertical bar represents 20 microns.

There may be three distinct regions identified within a HAp droplet. These arise from (1) dehydroxylated amorphous calcium phosphate on the outer periphery of a particle that may transform into oxyapatite (Gross et al. 1998c), (2) hydroxylated amorphous calcium phosphate inside the droplet that forms HAp where sufficient heat is conducted to promote crystallization (Zyman et al. 1994, Gross et al. 1998e), and (3) regions in the particle core which are insufficiently heated and remain in their original crystalline state. Crystalline regions can form during droplet deposition as successive droplets release their heat and crystallize underlying amorphous regions. Finally, crystallinity can be further increased after thermal spraying with an appropriate heat treatment between 500 and 700°C (Filiaggi et al. 1993, Ji and Marquis 1993, Brossa et al. 1994, Wang et al. 1995, Gross et al. 1998e, Burgess et al. 1999) but, as will be discussed in a latter section, post depositional processing influences the coating adhesion because the residual stresses of the material system are altered.

Powders for spraying. A range of powder compositions have been examined for use in plasma spraying. Amorphous calcium phosphate (Liu et al. 1994), biologically derived

(Joshi et al. 1993) and calcium deficient (Ellies et al. 1992) HAp's have been shown to be unsuitable for plasma spray processing since they decompose. A biphasic calcium phosphate has been chosen as one coating preference for the improved dissolution characteristics imparted by the addition of tricalcium phosphate (Burr et al. 1993, Tissel et al. 1994, Lee et al. 2001). Fluorapatite is more thermally stable than hydroxylapatite and accordingly produces higher crystallinity coatings when comparable plasma spray conditions are selected (Lugscheider et al. 1991b, Rocca et al. 1998, Overgaard et al. 1998). Regulatory bodies have proposed standards to limit the range in decomposition and loss in crystallinity, structural factors that can in part be linked to the purity of the spray material.

Powder agglomeration techniques such as spray drying (Lugscheider et al. 1992; Luo and Nieh 1996, Kweh et al. 1999), freeze drying (Hattori et al. 1987, Lu et al. 1998, Itatani et al. 2000), spray pyrolysis (Aizawa et al. 1996, Osaka et al. 1997, Vallet-Regi et al. 1994, Inoue and Ono 1987), or sintering and crushing can be used for developing a desired particle size range for thermal spray operations. Of these, spray drying is the most commonly used agglomeration process.

Implant materials for coating. Prosthetic materials coated with HAp include titanium, Ti-6Al-4V, stainless steel, Co-Cr-Mo, and alumina (Jiang and Shi 1998). These materials are roughened by grit blasting for a mechanical interlock between the melted component of the particle and the substrate. The Ti-6Al-4V and Cr-Co-Mo alloys are the most common. Ideally, the elastic modulus and co-efficient of thermal expansion of the substrate and the coating material will be matched to minimize any residual stresses at the interface. Hydroxylapatite ($E = 100 \text{ GPa}$ and $\alpha = 12 \times 10^{-6} \text{ }^{\circ}\text{C}^{-1}$ (Perdok et al. 1987)) is well matched to the titanium alloy ($E = 110 \text{ GPa}$ and $\alpha = 10 \times 10^{-6} \text{ }^{\circ}\text{C}^{-1}$) and is coated directly onto the prepared surface.

Cr-Co alloys are known for their high strength and wear resistance. Despite these benefits, there is a concern about the adverse biocompatibility of chromium and cobalt ions, whereas other studies have indicated that chromium promotes the crystallization of HAp (Wakamura et al. 1997) and, therefore, might be an important contributing factor leading to good fixation in bone.

A bond coat, used to promote adhesion between the coating and the substrate, has been employed for a variety of purposes in biomedical applications. A rough titanium bond coat provides a porous surface for bone attachment after the calcium phosphate coating has dissolved. A titania (TiO_2) ceramic bond coat can decrease the quenching rate of deposited molten droplets and, thus, produce a crystalline coating (Heimann et al. 1999). An alumina (Al_2O_3) base layer between the Ti-6Al-4V substrate and the calcium phosphate coating has also been used (Labat et al. 1999). Ceramic bond coats have not been used commercially for apatite coatings.

Surface preparation and bonding. Diffusion has been proposed to occur between titanium and HAp to produce a calcium titanate (de Groot 1987). Sintering studies between titanium and HAp have confirmed this diffusion (Lacout et al. 1984, Chai et al. 1993, Knepper et al. 1998) with another study suggesting incorporation of titanium into the HAp structure (Weng et al. 1994). Titanium oxide (TiO_2) is an essential component of this diffusion reaction, and improved bond strength on oxidized substrates has been reported (Ueda et al. 2000).

The surface of the implant or prosthesis is grit blasted not only to establish a mechanical bond between the substrate and the coating, but also to establish a stronger mechanical bond with bone once the HAp has been resorbed. A surface roughness, R_a , as little as 1 μm can lead to a twofold increase in the removal torque of an implant from

bone (Carlsson et al. 1988). The roughness for bonding of thermally sprayed HAp to the substrate is usually two to five fold higher (Yankee et al. 1991). Various types of macrotexturing or porosity have been designed to further improve bone attachment (Kienapfel et al. 1999). An implant surface may contain vacuum plasma sprayed porous titanium (Nakashima et al. 1997), sintered mesh (Wilke et al. 1993), or sintered beads (Moroni et al. 1994). A coating placed on top of the porous surface provides high bone to implant interfacial contact (Bloebaum et al. 1993). Grooves may also be placed on the surface of an implant to provide mechanical resistance against torsion of the hip prosthesis. Grooves 1 mm deep provide improved biological fixation and earlier fixation compared to porous coated implants (Hayashi et al. 1999). A comparison of the shear strength between the different macrostructured surfaces with bone, using the same implant site, is not available.

Coating thickness and residual stress. A coating thickness of 50 μm has been determined to provide good fatigue resistance with good resorption and bone attachment characteristics in orthopedic applications (Geesink et al. 1987). In comparison, a 200- μm thick coating produced a 50% decrease in bonding strength (Wang et al. 1993a). Animal studies have shown that fracture occurs at the coating-bone interface for 50 μm thick coatings but within the coating for the 200- μm thick coatings (Wang et al. 1993b). The fracture mode can be described as "cohesive" in the latter case. At a low residual stress, failure occurs within the coating, but at higher values is shifted toward the coating-Ti alloy substrate (Yang et al. 2001). The lower bond strength can be related to the residual stress that reaches a maximum at the interface and exhibits larger values for thicker coatings (Yong et al. 2001). Real-time residual stress measurement during spraying reveals that the stress is tensile in nature and increases in value upon cooling (Tsui et al. 1998). Yang et al. (2000) has shown a higher residual stress with well-melted particles.

It can be assumed that coatings formed from lower crystallinity particles exhibit low residual stress because feedstock also has inherent porosity that would tend to relieve process-induced stresses. A comparison of the high velocity oxy-fuel and plasma spray processes has revealed that the residual stress is lower in the former process (Knowles et al. 1996). Heat treatment at temperatures of 800°C can minimize these process-induced stresses (Brown et al. 1994). Despite the large influence of thickness on coating strength, no difference in bone apposition has been found for 50 μm and 100 μm coatings.

Strength of coatings. Plasma sprayed coatings contain process-induced porosity, partially molten particles, and a range of grain sizes. The pancake structure of the flattened particles produces a higher population of pores parallel to the surface of the implant. Fracture toughness of these coatings is low and is attributed to the pore content in these coatings. Mancini et al (2001) have indicated that this pore level can vary between 2 and 10%. Attempts at improving the fracture mechanical properties of these coatings have involved incorporation of a second phase. Examples of the second phase include titanium (Zheng et al. 2000), titanium alloy (Khor et al. 2000), titania (Ramires et al. 2001), alumina (Morimoto et al. 1988), and zirconia (Chou and Chang 1999). The faster resorption time of plasma sprayed coatings in comparison to sintered apatites can potentially lead to the release of the non-resorbable particulate and possibly lead to implant loosening from an overload of particulate in bone. The inclusion of crack healing additives, such as glass, may improve the fracture toughness. Some initial work with calcium phosphate glass has indicated that other aspects such as the wetting, surface charge, and resorbability need to be considered to produce a coating that would integrate easily with bone (Ferraz et al. 2001). The mechanical performance of coatings is available in a review by Sun et al. (2001).

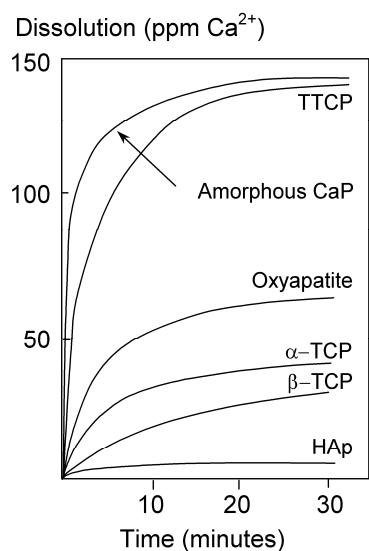


Figure 9. Solubility of hydroxylapatite compared to oxyapatite, amorphous calcium phosphate, tetracalcium phosphate (TTCP), α -tricalcium phosphate and β -tricalcium phosphate determined in 0.1M potassium acetate at pH 6 (modified from Le Geros et al. 1995).

Bioactivity of coatings. Immersion of HAp plasma sprayed coating into a buffered solution or a simulated body fluid leads to partial coating dissolution, the extent of which depends upon the phase composition, surface area and residual stress. The solubility of the calcium phosphate phases increases in the order HAp, tricalcium phosphate, oxyapatite, tetracalcium phosphate and amorphous calcium phosphate (Ducheyne et al. 1990, Le Geros et al. 1995) (Fig. 9). Dissolution of plasma sprayed coatings depends primarily on the coating crystallinity (Leali Tranquilli et al. 1994, Klein et al. 1994, Fazan and Marquis 2000). Coating loss occurs by (1) dissolution which is dominated by the amorphous calcium phosphate, and (2) particle release (Gross et al. 1997, Ogiso et al. 1998b). The loss of amorphous calcium phosphate is very clearly identified by a change in the surface morphology (Fig. 10). Despite the importance of crystallinity, other factors can contribute to a five-fold change in dissolution rate (Paschalis et al. 1995). The presence of protein in the testing solution can lead to faster initial calcium ion release (Bender et al. 2000). After the surrounding solution is saturated with respect to calcium and phosphate ions, reprecipitation occurs on the surface of the coating (Fig. 11). Fine crystallites form preferentially in recessed areas such as pores and cracks (Gross 1991, Weng et al. 1997). Low crystallinity coatings produce a higher concentration of dissolved ions in solution (Chou et al. 1999) and, hence, have a shorter induction time before precipitation of the carbonated apatite (Anselme et al. 1997). Cell proliferation on these surfaces has been difficult to compare, since cells are more sensitive to topographical variation preferentially depositing on smooth areas (Lumbikanonda and Sammons 2001).

A comparison in bone bonding to sintered HAp and HAp plasma sprayed coatings has revealed higher attachment strength of bone to the coating (Ogiso et al. 1998a). The higher bioactivity of the plasma sprayed coatings provides earlier fixation. The propensity for bone bonding is highlighted by the bonding that occurs during early loading of coated hip prostheses (Overgaard et al. 1998).

Clinical performance. The lifetime of these coatings extends up to several years depending upon the coating characteristics, prosthesis design, and the implantation site. Hydroxylapatite coatings placed in trabecular bone maintain bone contact and, thus, prevent high dissolution that could occur from the physiological fluids (Caulier et al. 1995, Lind et al. 1999). The design of the implant plays an important role. Areas of the implant receiving the most loading from the bone, such as the tip of dental root implants (Finet et al. 2000), the apical edges of blade implants (Baltag et al. 2000) and the thread tips of a collar on a femoral stem (Gross et al. 1998a) have been observed to produce the most coating resorption.

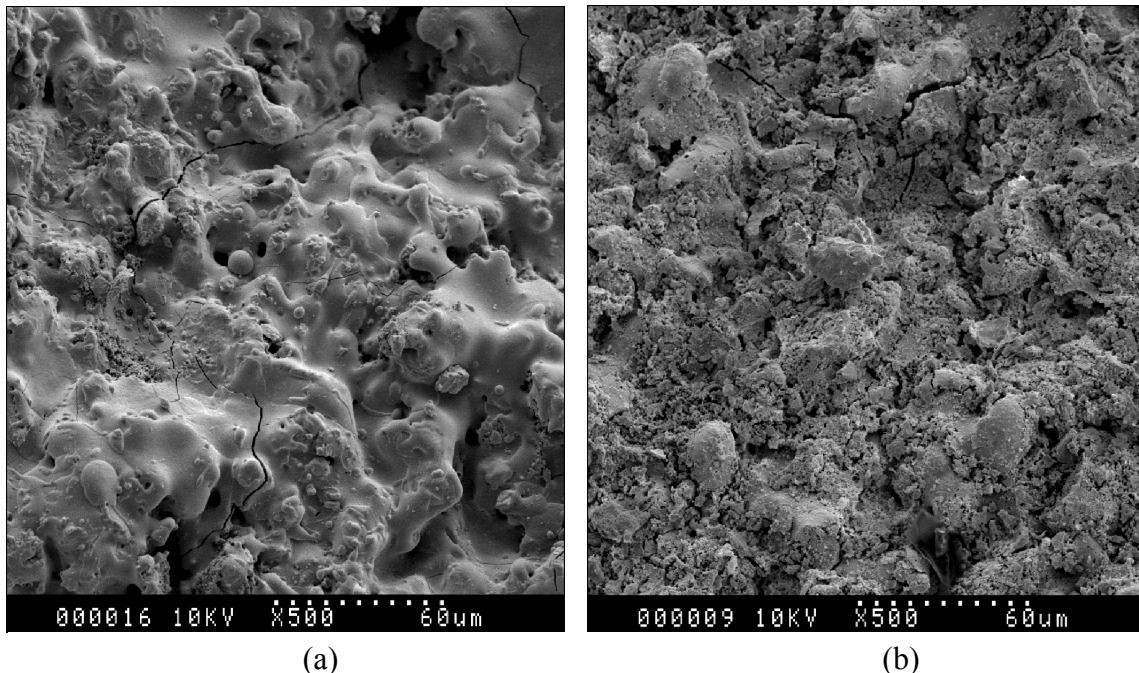


Figure 10. A surface view of a hydroxylapatite plasma sprayed coating revealing (a) smooth areas more commonly associated with the amorphous calcium phosphate and (b) a change in surface topography due to the loss of the amorphous phase after immersion in 0.1M potassium acetate at pH 6 for 2 days.

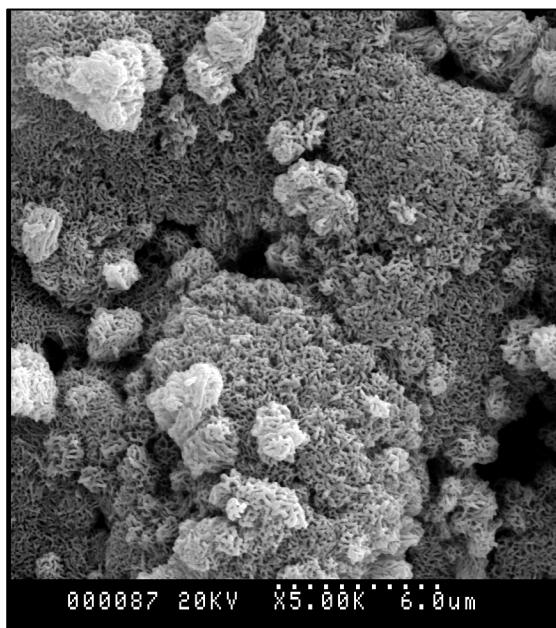


Figure 11. Precipitate formed on a plasma-sprayed coating exhibiting the small crystallite size associated with the newly deposited apatite layer.

The rate of coating loss is further dictated by the physical activity of the implant recipient. Higher loading on the prosthesis has been found to produce more active bone remodeling and result in more rapid coating loss (Tonino et al. 1999). Loading on the coating can, in part, be influenced by the amount of coating coverage on a femoral stem. Examination of radiographs has revealed that a coating shifts the load transfer distally for uncoated prostheses to the proximal region in a fully coated prosthesis (Abrahams and Crothers 1992). A coating placed on the upper half of the stem may further shift the loading to the surrounding bone in the proximal region and, thus, alter the applied stress distribution on the coating.

Hydroxylapatite plasma sprayed coatings have been used in total hip arthroplasties (Jaffe and Scott 1996), dental implants (Ong and Chan 1999), knee replacements, ankle arthroplasties (Zerahn et al. 2000), orthopaedic screws (Magyar et al. 1997), and spinal implants. The most widely used application is the femoral stem where 11 year clinical results show slightly better performance than cemented prostheses (Havelin et al. 2000).

Biomimetic processing

The biological response to metals can be improved by modifications to the surface composition of an implantable metal alloy. This follows from the work on bioactive glasses which, when implanted into the body, produce a modified surface that facilitates apatite precipitation (Hench 1998a). Various chemical enrichment treatments have been proposed to aid the precipitation of a carbonate apatite.

The most commonly used approach involves transforming the oxide layer of a metal surface that is rich in hydroxyl ions. Titanium soaked in sodium hydroxide and then heat-treated produces an amorphous sodium titanate layer. The minimum concentration found to create a layer of sodium titanate hydrogel is 0.5 M at 60°C for 24 hours (Kim et al. 1997). After immersion in simulated body fluid, sodium ions released from the layer are exchanged with hydronium ions (H_3O^+) to form a hydrated titanium layer. Formation of a hydrated layer incorporates calcium and phosphate ions from the fluid to form an amorphous calcium phosphate. It is thought that the gel takes on a positive charge that attracts phosphate ions into the structure resulting in a Ca/P ratio of 1.40. The release of sodium increases the pH and ionic activity in the solution, thus creating a supersaturated environment for apatite precipitation (Jonasova et al. 2002). Crystallization of the layer incorporates more calcium from solution to increase the Ca/P ratio to 1.65, similar to the value of bone mineral (Takadama et al. 2001a,b). The layer grows at 0.5 to 7 μm per day (Hata et al. 1995).

Li et al. (1993a) indicated that a silica gel induced an apatite layer on the surface. The precipitated crystal shape changed from a plate-like morphology to flakes by increasing the pH from 7.2 to 7.4. Crystals formed as rods in the presence of magnesium, and needles where fluorine ions were present. Studies on titania and alumina gels indicated that apatite precipitation can be induced on the surface of other gel compositions (Li et al. 1994). Noble metals such as tantalum and niobium have illustrated this capacity through an alkali treatment. Zirconia, alumina and silica can also be transformed to possess a bioactive surface. Hydroxylation of metals, zirconia (Uchida et al. 2001), tantalum (Miyazaki et al. 2001), zirconium (Uchida et al. 2002), and niobium (Kokubo et al. 2000), provides faster apatite formation on the surface. Such a treatment lowers the contact angle and facilitates spreading of neutrophils and osteoblasts (Lim et al. 2001). At four weeks, alkali modified titanium implanted into the femur of a rabbit exhibits a bond with bone that is eight times stronger (2.4 to 4.5 MPa) compared to untreated titanium (0.3 to 0.6 MPa). At 12 weeks, the superior bond strength is maintained, while the bonding between bone with titanium improves two-fold (Nishiguchi et al. 2001).

Precipitation has also been shown to occur on modified polymeric surfaces. An example of this includes Ca(II) containing hybrids of gelatin and 3-(glycidoxypropyl)trimethoxysilane (Ren et al. 2001). Silanol groups on silicone (Oyane et al. 1999), poly (ethylene terephthalate), polyether sulfone and polyethylene (Kokubo 1998), polymethylmethacrylate (PMMA), polyamide 6, and polyethersulfone (PESF) (Tanahashi et al. 1994) can also provide sites for apatite formation.

An alternative method lies in ion implantation of the alkali ion into the metal surface (Pham et al. 2000). Fluorine (Ellingsen 1995) and calcium ion (Feng et al. 2002)

enrichment of titanium alloys have also shown to promote apatite precipitation.

Sol-gel deposition

Sol-gel technology offers a chemically homogeneous and pure product and has been used for HAp production since 1988 (Masuda et al. 1990). A calcium alkoxide mixed with an organic phosphate undergoes various intermediate states before a stoichiometric composition is obtained. This chemical process requires an aging time (Chai et al. 1998). Use of an intermediate phosphate composition eliminates the aging step (Ben-Nissan et al. 2001). A coating can be applied by dipping or by spinning followed by a heat treatment to remove the organics (Weng and Baptista 1998). The small grain size permits sintering of dense apatite compositions at temperatures less than 900°C to avoid the phase transformation in the parent titanium alloy (Gross et al. 1998f, Lopatin et al. 1998, Cheng et al. 2001). Furthermore, this coating can be solidified during a rapid thermal processing schedule of 100°C/min (Russell et al. 1996).

Electro-deposition

Electrophoretic deposition involves movement of synthesized particles under the influence of an electrical field. The implant is placed as an electrode upon which the particles collect. Particle shape, composition, electric field and stirring conditions influence the deposit characteristics (Zhitomirsky and Galor 1997). After coating by this method the implant needs to be dried and sintered. Sintering requires temperatures greater than 1000°C to produce a dense coating layer. Cracking may evolve during the cooling stage due to the difference in thermal expansion substrate and the newly formed interlayer. This process has been useful in coating porous surfaces (Ducheyne et al. 1990). Electrococrystallization represents a low temperature process whereby calcium and phosphate in an electrolyte migrate to an electrode where crystals are formed. A heat treatment at 125°C followed by calcination at 425°C can densify an apatite. Carbonated and fluoridated apatites with a thickness of 50 µm have been produced in one hour (Shirkhanzadeh 1995).

Vacuum deposition

Sputtering was introduced as a possible coating technique alongside thermal spray processes in the late 1980s. This technique involves displacing atoms from a target material with high-energy ions and transfer to a flat substrate under vacuum conditions. Addition of another gas such as carbon dioxide to the plasma forming gas can modify the composition to a carbonated calcium phosphate (Yamashita et al. 1996). Use of a magnetron produces a deposition rate of 1 micrometer/hour. Such films produce an amorphous phase when deposited on a cold substrate and an oriented columnar HAp at higher temperatures. An increase in discharge power leads to a crystalline coating (van Dijk et al. 1995). The dense layer formed during magnetron sputtering creates a residual stress that, along with crystallinity (Wolke et al. 1998), influences the dissolution behavior due to the residual stress (Burke et al. 2001).

Pulsed laser deposition ablates a target material that results in transfer of a droplet onto the substrate to be coated. This process occurs under vacuum and like sputtering produces an amorphous phase at low substrate temperatures, and a crystalline phase at higher temperatures (Cotell et al. 1992).

In vitro cell culture studies on HAp coatings produced by plasma spraying, sol-gel and sputtering revealed that the sol-gel coating exhibited the highest cell growth (Massaro et al. 2001). The difference in purity, density, grain size, surface roughness, and contaminant phases of the various coatings makes it difficult to isolate the characteristic that enables a better *in vitro* response.

FUTURE WORK

While calcium phosphates are currently widely used as implants in the body, more detailed work on the role of chemically enriched apatites on the biological response, characterization of apatites and microstructural control will reveal the optimal characteristics of an apatite for clinical application.

The rich elemental substitution (Pan and Fleet this volume) of apatites can lead to a wide variety of biomaterials with differences in processing, resulting microstructure and tissue bonding behavior. This is an area of active research and the outcome can produce tissue-bonding maps similar to those established for bioactive calcium phosphate glasses developed by Hench (1998b). Such maps can indicate how substituent elements enhance the tissue bonding response and can serve as useful guides for selecting the appropriate apatite composition for implantation into different types of bone.

An important chemical aspect of apatites for biomedical use is the Ca/P molar ratio. Synthesized apatites may be calcium deficient or rich and yet display an X-ray diffraction pattern typical of apatite. Those apatites that are subjected to low temperature processing such as cements and biomimetically processed coatings require a wet chemical analysis for determination of the Ca/P molar ratio. With the new interest in chemically modified apatites, the Ca/P molar ratio, the impurity elements according to present standards (ASTM 1998) and the major substituent elements will need to be reported to provide a better understanding of the apatites being investigated for biomedical applications.

Hydroxylapatite is typically subjected to heating during processing. Heat treatment creates a stoichiometric apatite along with a secondary phase for non-stoichiometric compositions. For example, a calcium deficient apatite will lead to the formation of tricalcium phosphate upon heating, and quantitative phase analysis can be used to determine the Ca/P molar ratio (Toth et al. 1991; Ishikawa et al. 1993). Recently, Rietveld analysis has been proposed as a useful and fast alternative to time consuming solution techniques for the determination of Ca/P ratios (Raynaud et al. 2001). The X-ray diffraction can also provide information such as contaminant phase identification, crystallite size, and crystal orientation, which are very useful when dealing with complex material systems such as coatings produced by plasma spray techniques (Keller 1995; Keller et al. 2000). Further work will need to develop methods for ascertaining the location of substitutional elements within the apatite lattice.

The detection of different phases and their chemistry is presently limited. This, in part, is attributed to the small size, low concentration or the presence of numerous phases. X-ray diffraction is limited, since the very small grain size produces significant peak broadening, and the small quantity of phases is at the limit of detection. The best technique would provide viewing of the microstructure while an analysis is conducted. Raman microprobe data exhibit peak overlapping and, therefore, distinction between a tricalcium phosphate and an amorphous calcium phosphate is difficult (Tudor et al. 1993), however useful data can be obtained from interface studies with bone (Walters et al. 1991). Cathodoluminescence microscopy has been developed to distinguish between the amorphous calcium phosphate and HAp (Gross et al. 1998g). Transmission electron microscopy remains the only reliable technique for detection of chemical phases in very small quantities. For complicated microstructures, such as those produced in thermal spraying, the preparation of large areas will be necessary to view the location of the different chemical phases.

Recent studies reveal that microstructural surface features possibly influence the cell response to implanted synthetic apatites. The roughness is an important aspect of cell

adhesion, but can influence the spreading of cells. A comparison of sputtered, sol-gel and plasma sprayed coatings has indicated that sol-gel coatings provide the best surface for cell multiplication and proliferation (Massaro et al. 2001). It is not clear, whether, this behavior can be attributed to the high chemical purity or low surface roughness of sol-gel coatings. Another study has shown that cells prefer to spread over smooth areas of plasma sprayed coatings that represent well melted areas (Lumbikanonda and Sammons 2001). HAp powder is not completely melted during the plasma spray process and thus rough areas on the coating surface are expected from unmolten particle segments. To improve the smoothness of plasma sprayed coatings, it would be necessary to increase the melting of the particle, that would produce a lower crystallinity, or improve the thermal stability of HAp powders, and thus retain a high crystallinity within the coating. Such modifications would provide good cell spreading in addition to retaining the osteoconductivity and good bone bonding achievable with present coatings.

The charge state of apatites has recently been found to be important in the integration into bone. Sintered apatite poled at high temperature to produce a negative charge has been shown to (i) induce earlier precipitation (Ohgaki et al. 2000), (ii) promote the formation of osteoblast-like cells (Ohgaki et al. 2001), and (iii) enhance bone bonding (Kobayashi et al. 2001). The long-term bone bonding ability remains to be assessed.

Apatites presently used in clinical applications are utilized solely for their ability to either bond to tissue or promote bone growth. The next stage of development will involve the optimization of the microstructure to allow incorporation of biological or chemical species that can be released for stimulation or therapy. Such work presently is being focused on microspheres (Paul et al. 2002; Sivakumar and Rao 2002).

The solubility of apatites is becoming more important as emphasis is being placed on biomaterials for regeneration of tissues (Hench 1998b). Where apatites are incorporated with resorbable polymers for tissue engineering applications, it will become necessary to match the solubility rate of the inorganic and organic components within the composite.

APPENDIX 1

CHEMICAL FORMULAS FOR INORGANIC COMPOUNDS

Alumina	Al_2O_3
Calcium acetate	$\text{CH}_3(\text{COOCa})_2\text{H}_2\text{O}$
Calcium carbonate	CaCO_3
Calcium chloride	CaCl_2
Calcium deficient hydroxylapatite	$\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ where $0 \leq x \leq 2$
Calcium hydrogen phosphate	CaHPO_4 (also known as monetite)
Calcium hydroxide	$\text{Ca}(\text{OH})_2$
Calcium sulphate	$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$
Calcium nitrate	$\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$
Carbonated hydroxylapatite	$\text{Ca}_{10-x}\text{Na}_x(\text{PO}_4)_{6-x}(\text{CO}_3)_x(\text{OH})_2$ (B-type) $\text{Ca}_{10}(\text{PO}_4)_6(\text{CO}_3)_x(\text{OH})_{2-2x}$ (A-type)
Diammonium hydrogen phosphate	$(\text{NH}_4)_2\text{HPO}_4$
Dicalcium phosphate dihydrate	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (also known as brushite)
Fluorapatite	$\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$
Hydrogen peroxide	H_2O_2
Hydroxylapatite	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$

Lime	CaO
Lithium phosphate	Li ₃ PO ₄
Manganese oxide	MnO ₂
Octacalcium phosphate	Ca ₈ H ₂ (PO ₄) ₆ ·5H ₂ O
Orthophosphoric acid	H ₃ PO ₄
Oxyapatite	Ca ₁₀ (PO ₄) ₆ O
Phosphorous trichloride	PCl ₃
Potassium dihydrogen phosphate	KH ₂ PO ₄
Silica	SiO ₂
Silicon carbide	SiC
Silicon nitride	Si ₃ N ₄
Silica	SiO ₂
Sodium fluoride	NaF
Sodium hydroxide	NaOH
Sodium hydrogen carbonate	NaHCO ₃
Sodium hydrogen phosphate	Na ₂ HPO ₄
Sodium phosphate	Na ₃ PO ₄
Tetracalcium phosphate	Ca ₄ P ₂ O ₉
Titania	TiO ₂
Tricalcium phosphate	Ca ₃ (PO ₄) ₂
Zirconia	ZrO ₂

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