# Hydroxyapatite-Reinforced Polymer Biocomposites for Synthetic Bone Substitutes

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*Hydroxyapatite (HA)-reinforced polymer biocomposites offer a robust system to engineer synthetic bone substitutes with tailored mechanical, biological, and surgical functions. The basic design rationale has been to reinforce a tough, biocompatible polymer matrix with a bioactive HA filler. A large number of studies have investigated modifications to the biocomposite structure and composition, aimed at improving the mechanical properties, often through modified or novel processing methods. In this article, the effects of the polymer composition and molecular orientation; the HA/polymer interface; and the HA-reinforcement content, morphology, preferred orientation, and size are reviewed with respect to mechanical properties, drawing frequent comparisons between various HA-reinforced polymer composites and bone tissue.*

## INTRODUCTION

Hydroxyapatite (HA)-reinforced polymer biocomposites were first conceived by W. Bonfield and colleagues[1–6] as a bone analog biomaterial enabling mechanical properties to be tailored to mimic those of bone tissue. Bone tissue exhibits a complex, hierarchical structure over several length scales,[7,8] beginning with a distinction between the more dense cortical bone in the diaphysis and less dense trabecular bone in the epiphyses of long bones, such as a human femur (Figure 1). However, regardless of differences in intermediate levels of structure, the extracellular matrix (ECM) of all bone tissue is essentially constructed by mineralized collagen fibrils, which can be accurately represented as a two-phase composite comprising a collagen matrix reinforced with 40–50 vol.% (50–60 wt.%) apatite crystals (Figure 1). The apatite crystals are nanoscale, plate-like, and elongated with a c-axis preferred orientation in directions of principal stress, such as the longitudinal anatomic axis of long bones.[7–9] Thus, bone tissue exhibits anisotropic and inhomogeneous mechanical properties.[10–12]

Human cortical bone exhibits elastic moduli of 16–23 GPa and 6–13 GPa, tensile strengths of 80–150 MPa and 50–60 MPa, and fracture toughness of 4–6 MPa·m$^{1/2}$ and 2–4 MPa·m$^{1/2}$ for load applied along the longitudinal and transverse axes, respectively.[7,10,13–16] Trabecular bone has an effective elastic modulus and tensile strength in the range of 0.05–0.5 GPa and 1–6 MPa, respectively, depending on the apparent tissue density.[7,14,17] While the apparent properties of trabecular bone (75–95% porosity) are significantly lower than those for cortical bone (5–10% porosity) due to the highly porous structure, the properties of the ECM are relatively similar.[7,14,18] Therefore, cortical bone mechanical properties should be used as the benchmark for the design of new biomaterials prior to the introduction of the porosity requisite for bone ingrowth.

This review will focus on the material design without porosity, recognizing that porosity is ultimately essential for the vascularization and growth of bone into an implant. The justification for this approach is two-fold: first, comparing the mechanical properties of porous materials is complicated by the complexity of the pore architecture, and second, porosity can always be added, though perhaps not easily, by removal of material.

The majority of all commercialized and FDA-approved orthopaedic implants utilize relatively few biomaterials, with mechanical properties that typically deviate from the ECM of bone by an order of magnitude (Figure 2). Metals include stainless steel, cobalt-chrome, and titanium alloys. Ceramics include alumina, zirconia, HA, and other calcium phosphates. Polymers include ultra-high molecular weight polyethylene (UHMWPE), polymethyl methacrylate (PMMA), and polyaryletherketone (PAEK).

Most metals and ceramics are much stiffer than bone tissue, which can result in mechanical mismatch ("stress shielding") between the implant and the

### How would you...

**...describe the overall significance of this paper?**

*Through progress over the last quarter century, hydroxyapatite reinforced polymers have been engineered to mimic important aspects of the structure and properties of human bone tissue.*

**...describe this work to a materials science and engineering professional with no experience in your technical specialty?**

*This review demonstrates how the basic elements of composite materials design—namely, the polymer matrix composition and molecular orientation; the matrix/reinforcement interface; and the reinforcement content, morphology, preferred orientation and size—have been used to engineer synthetic bone substitutes with tailored mechanical, biological, and surgical function.*

**...describe this work to a layperson?**

*Synthetic biomaterials that promote integration with bone tissue are an enabling technology in the development of improved orthopaedic implants, bone grafts, and tissue engineering approaches to treat diseased, malformed, or injured bone tissue.*

adjacent bone tissue, including a loss of integrity at the bone/implant interface due to resorption of bone tissue.[31] On the other hand, most polymers are more compliant than bone tissue and unable to bear physiological levels of load.[32]

Calcium phosphates, while able to incite a favorable biological response from bone tissue ("bioactive"), generally suffer from a low fracture toughness that hinders clinical use in load-bearing implants. In particular, HA $Ca_5(PO_4)_3OH$, is the closest pure synthetic equivalent to human bone mineral, which is a nonstoichiometric, carbonated apatite including a variety of other minor dopants.[24] Numerous studies have consistently shown that HA typically exhibits excellent biocompatibility, bioactivity and, if porous, osteoconduction in vivo.[23,24,33] Therefore, similar to bone, the basic design rationale for HA-reinforced polymer composites has been to reinforce a tough, biocompatible polymer matrix with a bioactive HA filler.

The seminal work of Bonfield and colleagues utilized a high-density polyethylene (HDPE) matrix reinforced with variable amounts of micro-scale HA powder particles.[1–6] The formulation containing 40 vol.% HA was commercialized under the trade name HAPEX™ for use in non-load-bearing otologic and maxillofacial implants.[34,35] Over the last quarter century, a large number of studies have investigated design modifications to the biocomposite structure and composition, aimed at improving the mechanical properties, often through modified or novel processing methods.[36] Therefore, this review will consider the following aspects in the design of HA-reinforced polymer biocomposites: the polymer composition and molecular orientation; the HA/polymer interface; and the HA-reinforcement content, morphology, preferred orientation, and size.

Finally, since the introduction of continuous porosity is advantageous for most conceivable orthopaedic applications, such as implant fixation, synthetic bone graft substitutes, and tissue engineering scaffolds, recent developments in porous HA-reinforced polymers will also be introduced.

## THE POLYMER MATRIX

The selection of a biocompatible polymer matrix has primarily served to mitigate the inherent brittleness or low fracture toughness of HA while providing additional function beyond that of HA. Likewise in bone, collagen provides toughness and is also able to be digested via enzymes secreted by osteoclasts during bone remodeling. Thus, biodegradable polymers have received a large amount of interest for designing implant biomaterials to be gradually resorbed and replaced by the formation of new bone tissue.[36–39] Note, however, that this does not diminish the continued utility of non-degradable polymers in many orthopaedic applications, especially when there is a low regenerative capacity. Unlike collagen in native bone tissue, all engineered biomaterials must first be implanted into the body, which raises other important functions for the polymer matrix.

The ductile HDPE matrix of HAPEX™ enabled an implant to be shaped in the operating room using a surgeon's scalpel. Orthopaedic surgical procedures are typically invasive, requiring a large surgical incision (e.g., ≈ 30 cm for the repair of a hip fracture), retraction of muscle and soft tissue to expose the implant site, and removal of damaged or diseased tissue, all prior to the insertion of an implant. Over the last two decades, orthopaedic implants have begun to implement minimally invasive procedures using small incisions (e.g., less than 3 cm), specialized surgical tools similar to those employed in arthroscopic and laparoscopic surgery, and injectable biomaterials which cure or harden in vivo.

The functional aspects of HA-reinforced polymers that are uniquely enabled by the polymer matrix can be summarized by a "matrix of matrices"

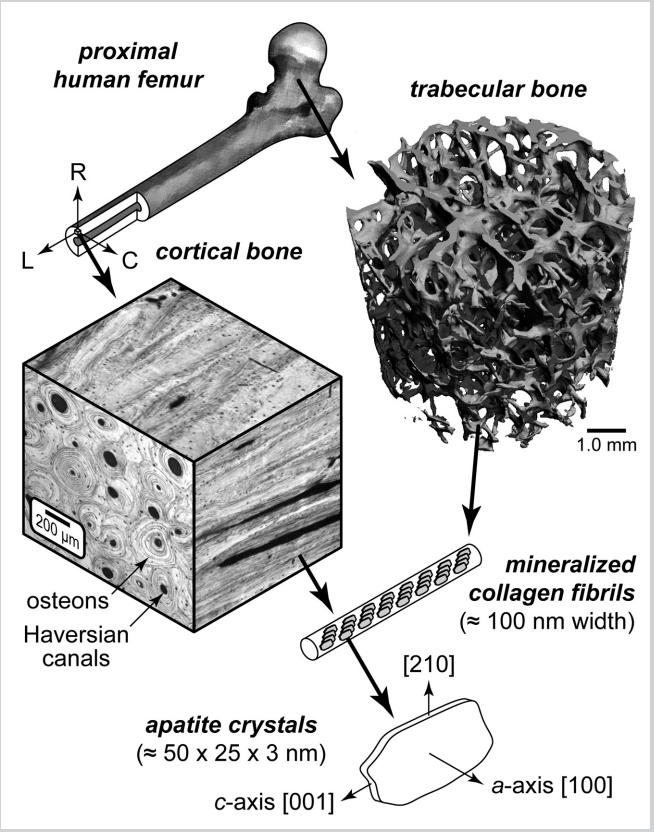



Figure 1. A schematic diagram showing selected levels of the hierarchical structure in human bone tissue. The microstructures of cortical and trabecular bone are shown using reflected light micrographs and a three-dimensional reconstruction from micro-computed tomography, respectively. Note that up to several levels of hierarchical structure, including further differences between cortical and trabecular bone, are not shown due to space constraints and in order to emphasize the commonality of mineralized collagen fibrils at the most fundamental level of structure. The longitudinal (L), radial (R), and circumferential (C) anatomic axes of the femur are shown relative to structural features.

(Figure 3). For example, the polymer matrix may be nonresorbable and non-injectable (e.g., thermoplastics such as PAEK,[40–43] UHMWPE,[44] and HDPE[1–6]), nonresorbable and injectable (e.g., acrylics such as PMMA[45–52] and bis-GMA/TEG-DMA[52–57]), bioresorbable and non-injectable (e.g., collagen[58–61] or poly-α-hydroxy esters such as PLLA and PLGA[62–68]), or bioresorbable and injectable (e.g., collagen, calcium phosphate cements[68–71] and various hydrogels[72–75]). (Collagen may function as either noninjectable or injectable depending on whether it has been cross-linked prior to implantation. In addition, note that calcium phosphate cements were included in this list since those cited were modified with various polymer additives.) Thus, HA-reinforced polymers may be suited for a wide range of potential surgical applications, and polymers from each of the four quadrants in Figure 3 have been reinforced by HA. Note that the polymers and references provided are merely illustrative and introductory. An exhaustive list of all polymers and literature citations is prohibited by space.

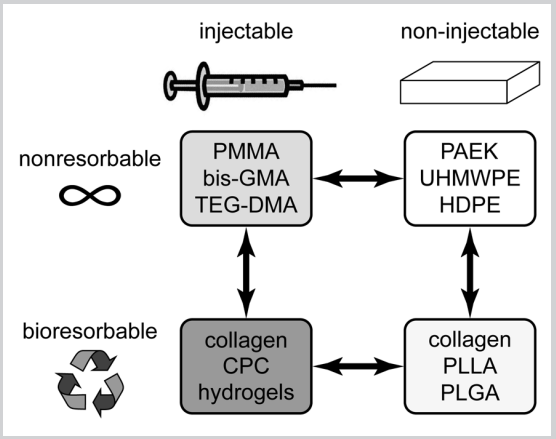



Figure 3. A matrix of polymer matrices that have been reinforced with HA showing the unique function provided by the polymer. (PMMA = polymethyl methacrylate, bis-GMA = bisphenol-*a*-glycidyl methacrylate, TEG-DMA = triethylene glycol dimethacrylate, PAEK = polyaryletherketone, UHMWPE = ultra-high molecular weight polyethylene, HDPE = high density polyethylene, CPC = calcium phosphate cement, PLLA = poly-L-lactide, and PLGA = polylactide-*co*-glycolide).

As in most composites, the mechanical function of the polymer matrix is to transfer load to the reinforcements while providing toughness. Mechanical properties of HA-reinforced polymer composites are summarized in Figure 4. As is evident, the reinforcing effect due to increased HA content is somewhat limited by the properties of the polymer alone. In other words, the order of increased elastic modulus and tensile strength for the polymer alone is generally maintained with HA reinforcement. Exceptions are due to the concomitant effects of other structural features described in subsequent sections. Moreover, the data shown in Figure 4 is influenced, in both magnitude and variability, by the molecular weight, crystallinity, orientation, cross-linking, etc., for the specific polymers used in the cited studies. Finally, note that an Ashby diagram like that shown in Figure 2 could not be plotted for HA-reinforced polymers due to the small number of fracture toughness measurements.[47,51,55,81,82] This paucity of data is somewhat surprising given the importance of fracture toughness to the material performance.

## HA REINFORCEMENT CONTENT

Hydroxyapatite-reinforced polymers offer the ability to tailor the composite's elastic modulus, presumably to meet performance criteria for a particular application or implant, by varying the HA-reinforcement content (Figure 4a). The addition of up to 50 vol.% HA powder reinforcement has resulted in a six- to eight-fold increase in elastic modulus compared to un-reinforced polymer for HDPE,[2–4,76] UHMWPE,[44] and PAEK.[41–43] However, HA-powder-reinforced polymers have not yet been able to mimic the longitudinal elastic modulus of cortical bone, though HA-reinforced PAEK was close (Figure 4a).

A challenge apparent in Figure 4 has been the ability to reach a bone-mimetic reinforcement level of 40–50 vol.%, which is not only important for mechanical properties but also biological behavior. Cellular activity has been shown to be enhanced with increased levels of HA.[6,56] Hydroxyapatite powders have been most commonly mixed with thermoplastic polymers (HDPE, UHMWPE, PLLA, and PAEK) using compounding or other melt-mixing techniques. However, the viscosity of the polymer melt becomes prohibitively high for reliable and uniform mixing at greater than 40 vol.% HA using melt-mixing processes. An alternative powder processing approach enabled mixing up to 60 vol.%, although HA-powder-reinforced HDPE composites became extremely brittle at greater than 50 vol.% HA.[76] For injectable, self-setting acrylics, HA powders have been typically mixed directly into either the curing cement of powder/liquid formations (e.g., conventional PMMA bone cement) or the polymer resins of liquid/liquid formulations (e.g., bisphenol-a-glycidyl methacrylate [bis-GMA] / tri-

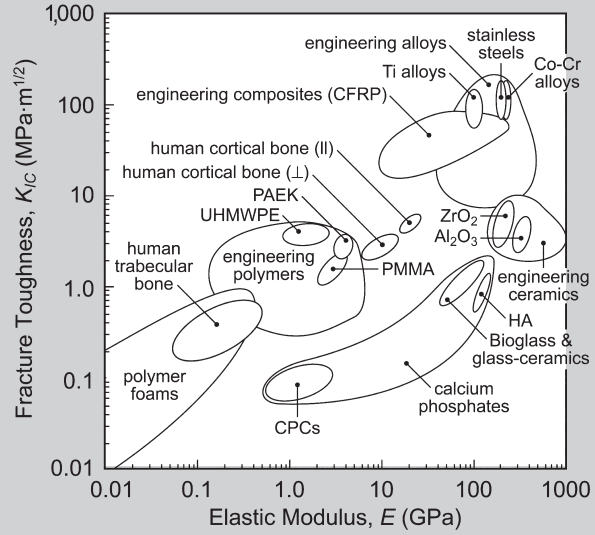



Figure 2. An Ashby diagram showing the elastic modulus and fracture toughness of bone tissue compared to biomaterials commonly utilized in orthopaedic implants. The mechanical properties of cortical bone are shown for loading parallel (II) and perpendicular (⊥) to the longitudinal anatomic axis. Note that the diagram was constructed using data adapted from References 7, 10, and 13–30.

ethylene glycol dimethacrylate [TEG-DMA]).[52] The viscosity of the PMMA cement quickly becomes limiting for greater than 20 vol.% HA, while liquid/liquid bis-GMA/TEG-DMA formulations have readily incorporated up to 60 vol.% HA (Figure 4b).

The ultimate tensile strength of HA-reinforced bis-GMA/TEG-DMA reached that of cortical bone at similar levels of reinforcement (Figure 4b), but the ultimate tensile strength of other HA-reinforced polymers has often posed limitations. Hydroxyapatite-reinforced PAEK and PLLA were able to mimic the strength of cortical bone, but at lower levels of HA. High-density polyethylene and UHMWPE exhibited a maximum tensile strength at 20–40 vol.%, but were much lower than other HA-reinforced polymers and bone tissue at all levels of reinforcement.

Most HA-reinforced polymers have exhibited decreased ultimate tensile strength with increased HA content (Figure 4b). Hydroxyapatite powder particles act as "flaws" in the continuous polymer matrix, particularly in less compliant polymers, due to limited interfacial bonding with the polymer matrix and a limited effect on toughening mechanisms (e.g., crack deflection, pullout, bridging, etc.). The net effect on design is that PAEK, for example, is alone of similar strength to human cortical bone and suited for load-bearing orthopaedic implants,[83] but biologically inactive (bioinert). Therefore, the addition of bioactive HA is potentially advantageous for forming a stable bone/implant interface, but could be prohibited by the concomitant decrease in strength (Figure 4b).

## MOLECULAR ORIENTATION

The mechanical properties of HA-powder-reinforced HDPE were substantially improved with molecular orientation in the polymer matrix resulting from the addition of oriented high modulus polyethylene fibers,[77] hydrostatic extrusion,[78,79] and high-shear injection molding.[80] The processing variations used in each of the above studies resulted in anisotropic mechanical properties, though only properties in the direction of molecular orientation are shown by the "HA-anisotropic HDPE" regions in Figure 4. Similarly, molecular orientation was added to HA-reinforced PLLA by the addition of PLLA fibers[67] and a forging process,[65] which explains the high tensile strength reported by Y. Shikinami and M. Okuno[65] compared to other studies of HA-reinforced PLLA (Figure 4b).

Overall, despite substantial improvements in the mechanical properties, composites with molecular orientation in the polymer matrix were not able to mimic the longitudinal elastic modulus of cortical bone but were able to mimic the ultimate tensile strength of cortical bone at lower reinforcement levels (Figure 4). The collagen matrix, or collagen fibrils (Figure 1), of cortical bone tissue also exhibits molecular orientation along directions of principal stress,

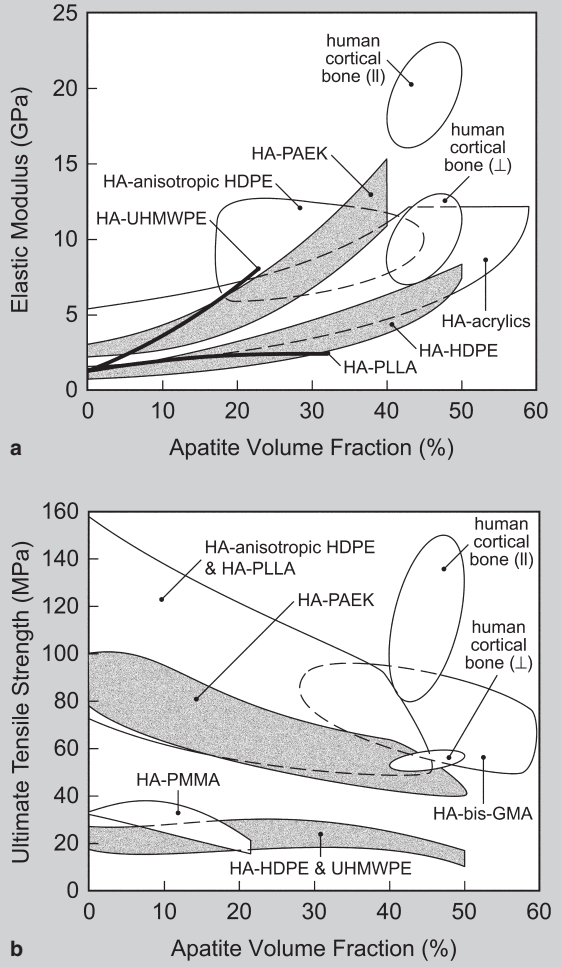
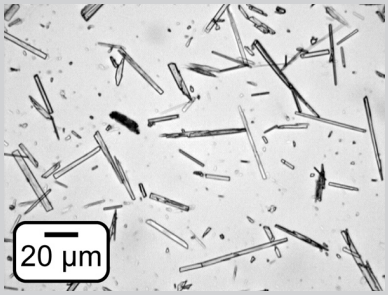



Figure 4. The (a) elastic modulus and (b) ultimate tensile strength of human cortical bone tissue compared to polymers reinforced with varying amounts of HA powder. The mechanical properties of cortical bone are shown for loading parallel (II) and perpendicular (⊥) to the longitudinal anatomic axis. Note that the regions are shown to simplify and be inclusive of a large number of data points from the literature for HDPE,[1–4,76] PAEK,[41–43] UHMWPE,[44] acrylics (including PMMA[49–52] and bis-GMA/TEG-DMA[52–57]), PLLA,[65,66] and anisotropic (oriented) HDPE.[77–80] The data set was limited to uniaxial tensile tests in order to be free from ambiguity due to variations in testing methods (e.g., bending tests).

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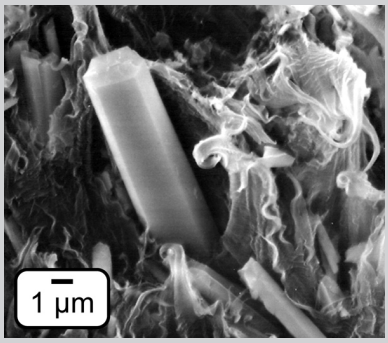


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Figure 5. (a) A transmitted-light micrograph of as-synthesized HA whiskers prepared by the chelate decomposition method[89] showing the size and morphology. Note that the apparent optical transparency indicates that the whiskers are single crystals. (b) A scanning-electron micrograph of a whisker exposed on the tensile failure surface of HDPE reinforced with 20 vol.% HA whiskers.[76]

such as the longitudinal anatomic axis of long bones, and strongly influences the strength and toughness of bone tissue.[13,15,84] However, the elastic anisotropy of cortical bone is derived from the preferred orientation of the much more rigid apatite crystals, not the more compliant collagen molecules.[11,13,15]

## HA/POLYMER INTERFACE

Collagen and bone mineral are coupled by non-collagenous proteins which bind to apatite via carboxy ligands.[84] Hydroxyapatite and thermoplastics (HDPE, UHMWPE, PLLA, and PAEK) have little or no chemical bonding at the interface and are limited to mechanical interlock due to friction and residual stresses. Efforts to chemically couple HDPE and HA did not produce the sizeable results required to significantly improve the tensile strength.[85,86] In contrast, acrylics, in particular bis-GMA/TEG-DMA, have benefited from silane coupling to HA.[48,52–57] In non-degradable biocomposites, chemical bonding seems necessary in order to maintain a stable interface during chemical attack and fatigue loading in vivo, which has historically been problematic in many biocomposites.[52,87] On the other hand, any new chemical agent introduced to enhance interfacial strength may pose biocompatibility concerns and will certainly invite added scrutiny from the U.S. Food and Drug Administration. Silanated bis-GMA/TEG-DMA composites are used in extracorporeal dental implants (e.g., fillings), but orthopaedic implants remain in clinical trials. Therefore, for these and other reasons, investigators have also examined the effects of increasing load transfer at the interface through roughened reinforcement surfaces[88] and/or anisometric reinforcements.

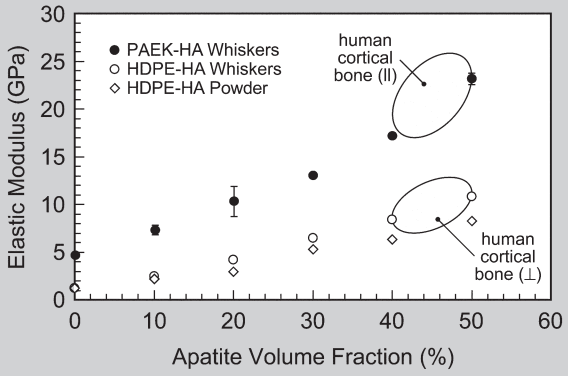


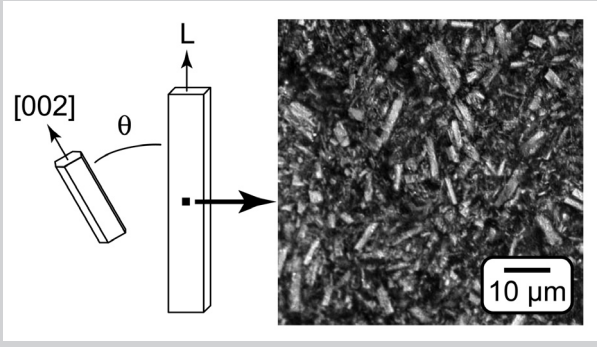

Figure 7. The elastic modulus of HA powder and whisker reinforced HDPE[76] and PAEK[93] in the longitudinal specimen direction with varying amounts of HA reinforcement. The elastic modulus of cortical bone loaded parallel (II) and perpendicular (⊥) to the longitudinal anatomic axis is shown for comparison. Error bars span the first standard deviation. Error bars not shown lie within the data point.

## HA-REINFORCEMENT MORPHOLOGY AND PREFERRED ORIENTATION

The vast majority of work, including all data used to construct Figure 4, has utilized HA powder reinforcements; however, HA generally prefers to form elongated crystals (whiskers or plates) with a hexagonal habit during precipitation both in vivo (Figure 1) and in vitro (Figure 5). Hydroxyapatite whiskers of controlled size and aspect ratio have been synthesized by a number of low-temperature (25–200°C), hydrothermal methods.[89] The viability and proliferation of osteoblasts was similar, and cell spreading was enhanced, on HA whiskers versus a powder of similar composition.[90] Therefore, HA whisker-reinforced polymers were recently introduced as a means to overcome some of the aforementioned limitations of HA powder reinforcements and to more closely mimic the structure of bone tissue.

High-density polyethylene [76,91,92] PAEK,[93] PMMA,[94–96] bis-GMA/TEG-DMA,[94] collagen,[97] and CPC[98] have been reinforced with HA whiskers. A powder processing approach was implemented to mix HA whiskers with HDPE and PAEK powders in order to attain high volume fractions and minimize whisker degradation (fracture) during processing.[76,91–93] A subsequent compression molding step densified the powder compact and induced a c-axis preferred orientation of HA whiskers dispersed within the polymer matrix (Figure 6), which was similar to that measured for human cortical bone.[76,93] Hydroxyapatite whisker-reinforced acrylics, collagen, and CPC simply implemented the same methods used for HA powders.

Hydroxyapatite whisker-reinforced HDPE and PAEK have resulted in improved mechanical properties that more closely mimic those of human cortical bone as compared to conventional HA powder reinforcement. The combined

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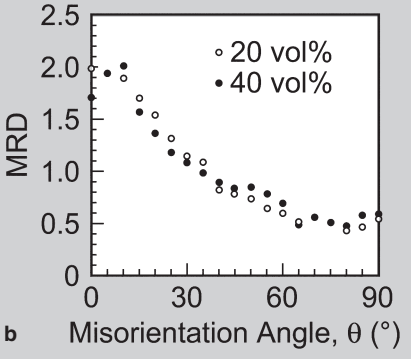


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Figure 6. The c-axis (002) preferred orientation of HA whiskers in the longitudinal specimen direction of HA whisker reinforced PAEK tensile bars showing (a) an optical micrograph of a polished specimen surface and (b) axisymmetric orientation distributions measured for composites containing 20 vol.% and 40 vol.% HA whiskers. Note that the degree of preferred orientation is shown in multiples of a random distribution (MRD).

effects of the whisker morphology and preferred orientation resulted in orthotropic composites with increased elastic modulus (Figure 7), ultimate tensile strength and work-to-failure compared to HA powder reinforcement.[76] Increased HA whisker content resulted in increased elastic modulus, but decreased ultimate tensile strength and work-to-failure.[76,93] Hydroxyapatite whisker-reinforced PAEK was able to mimic the elastic modulus (Figure 7) and elastic anisotropy of human cortical bone at the same level of reinforcement, and the ultimate tensile strength at lower levels of reinforcement.[93]

A micromechanical model was developed to predict the elastic moduli of HA-whisker-reinforced polymers based upon the reinforcement volume fraction, morphology, and preferred orientation.[91] Furthermore, HDPE reinforced with HA whiskers exhibited a four- to five-fold increase in fatigue life compared to an equiaxed powder for either a 20 vol.% or 40 vol.% reinforcement level.[92] Hydroxyapatite-whisker-reinforced HDPE was more tolerant of fatigue damage and exhibited less permanent deformation (creep) at a given number of cycles compared to HA powder. Fatigue cracks and microcracks showed evidence of toughening by uncracked ligaments, polymer fibril bridging, and HA whisker pullout (Figure 8), similar to observations in human cortical bone.[16]

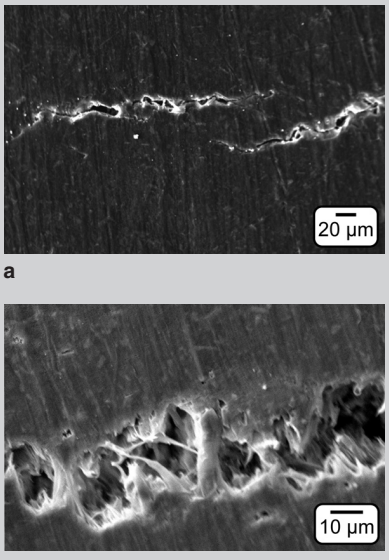


Figure 8. Scanning-electron micrographs of fatigue cracks and microcracks on the tensile surface of a specimen for HDPE reinforced with 20 vol.% HA whiskers, showing crack bridging by (a) uncracked ligaments, (b) HDPE fibrils and HA whiskers.[92] The specimen shown was loaded in four-point bending fatigue at 15 MPa to approximately two-thirds of the expected fatigue life (500,000 cycles). The applied tensile stress was normal to the direction of crack propagation.

## HA REINFORCEMENT SIZE

Small changes in the particle size of microscale HA powders (e.g., 3–4 µm vs. 7–8 µm), have resulted in small or insignificant changes in mechanical properties.[4,57] Despite recent excitement in polymer nanocomposites for improved mechanical behavior and cellular activity,[99] as well as the fact that apatite crystals in bone are nanoscale, there has been no effort to systematically examine the effects of the HA reinforcement size, particularly nano- vs. micro-scale, while holding other factors constant. This is most likely due to the limited commercial supply of HA powders, as well as the difficulty of uniformly dispersing nanoscale powders in a viscous polymer matrix using the methods described above.

## POROUS HA-REINFORCED POLYMER SCAFFOLDS

A synthetic bone substitute must not only be able to bear physiological levels of load, but also promote osteointegration. While bioactive HA reinforcements exposed on the surface of a biocomposite promote a stable bone-implant interface, osteointegration requires the vascularization and growth of bone into an implant via interconnected porosity, preferably 70–90% and 200–500 µm in size.[100] Research in porous HA-reinforced polymer scaffolds has primarily focused on poly-α-hydroxy esters such as PLLA and PLGA, as well as various processing routes such as particle leaching, solvent casting, thermally induced phase separation, solid free-form fabrication, and

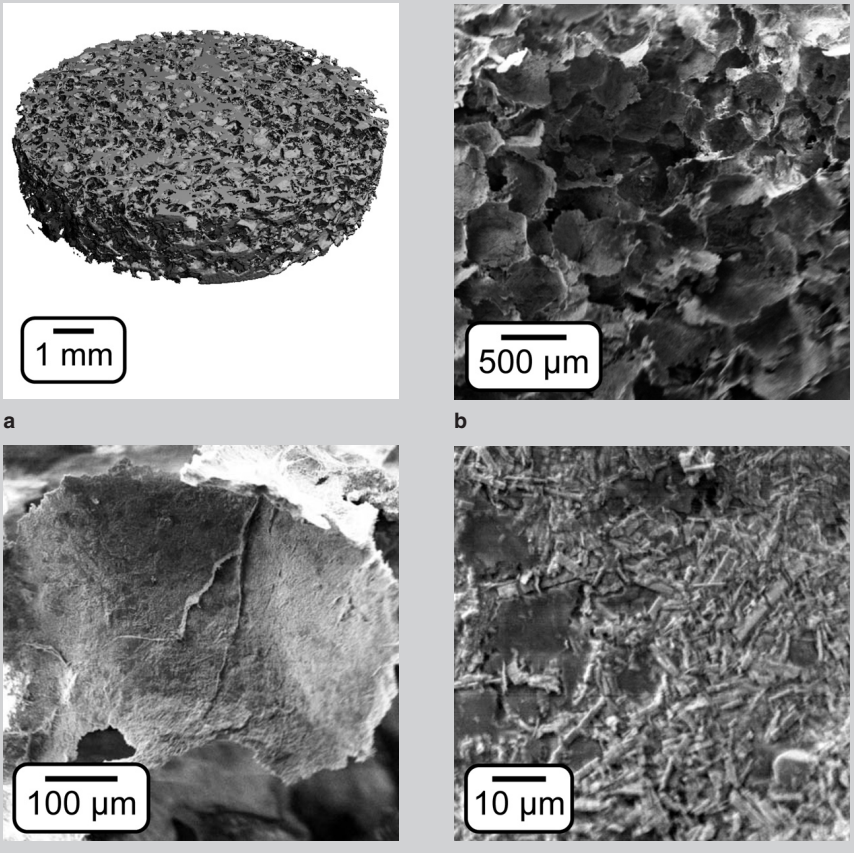


Figure 9. Porous HA whisker-reinforced PAEK scaffolds were prepared with 75 vol.% porosity and 40 vol.% HA whiskers within the scaffold struts: (a) three-dimensional reconstruction from micro-computed tomography showing the scaffold architecture, and scanning-electron micrographs showing (b) the scaffold architecture, (c) a single strut, and (d) HA whiskers aligned in a sheet texture and exposed on the surface of a strut.

microsphere sintering.[39] A recent review noted that the mechanical properties reported for porous biocomposite scaffolds are typically at least an order of magnitude lower than trabecular bone.[39] Due to a number of factors, HA is often limited to a surface coating or poorly integrated within the polymer scaffold struts.

Recent work for porous HA-whisker-reinforced PAEK scaffolds has shown that HA whiskers can be incorporated within and exposed on the surface of the scaffold struts (Figure 9) using a sequence of powder processing, compression molding, and particle leaching steps. Micro-computed tomography of the scaffold in Figure 9 revealed an interconnected porosity with a mean pore size of 265 μm. The mechanical properties of these scaffolds are expected to be improved similar to the results for dense HA-whisker-reinforced polymers.

## CONCLUSIONS

Hydroxyapatite-reinforced polymer biocomposites offer a robust system to engineer synthetic bone substitutes for orthopaedic implant fixation, synthetic bone graft substitutes, and tissue engineering scaffolds. Many aspects of the composite structure can be tailored in order to design for specific mechanical, biological, and surgical functions: the polymer composition and molecular orientation; the HA/polymer interface; and the HA reinforcement content, morphology, preferred orientation, and size. Research to date has led to many improvements, but several gaps remain in the understanding of key structure-property relationships and in translation from laboratory to clinical practice. Thus, HA-reinforced polymers will remain a fruitful and active area of biomaterials research for the foreseeable future.

## ACKNOWLEDGEMENTS

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