

Enhancement of Biocompatibility and Degradation Properties in a Poly-L-Lactide/ Hydroxyapatite Blend

Introduction

Hydroxyapatite (HA) is a particular crystal form and composition of a larger family of calcium phosphates. Calcium phosphate ceramics are perhaps the most biocompatible synthetic substances for use in hard tissue repair and have some 15 years of clinical history. The first successful repair of a bony defect using these materials was described by Albee in 1920.¹ Major academic groups then progressed this technology toward commercialization in the 1970s,² leading to the large number of calcium phosphate-based products currently on the market. Hydroxyapatite is the preferred calcium phosphate as it has over a decade of clinical use and is a natural bone mineral. Tricalcium phosphate (TCP) is another calcium phosphate that has been investigated, but it is not a natural bone mineral⁹ and is less stable than hydroxyapatite and therefore has limited applications.

The high degree of biocompatibility is a feature of HA and is largely attributable to its presence in natural calcified tissue. Bone is a natural composite of small hydroxyapatite crystals (Figure 1) and oriented collagen fibers.

When hydroxyapatite is implanted into a bony site it has been shown to have a high biocompatibility and good bioaffinity. It is slowly replaced by host bone after implantation.³ Implanted hydroxyapatite is slowly resorbed by the body, providing calcium and phosphate that is then available for the process of biomineralization and new bone formation.

Hydroxyapatite has been used in skeletal repair in the form of porous granules,⁴ porous blocks,⁵ and as a coating on metal implants.⁶ It has also been used as granules incorporated in polymeric matrices.⁷⁻⁸ The HA granules and porous blocks are used as bone void fillers where the integrity and stability of the bone is not reliant on the implant.

The use of porous blocks is limited, however, because hydroxyapatite has only modest tensile strength and a low fracture toughness, leaving it susceptible to fracture or fragmentation if subjected to mechanical loading. Incorporating hydroxyapatite granules into a biocompatible polymeric matrix produces a more robust material. Judicious selection of the loading level of the HA allows for a highly biocompatible device with mechanical properties appropriate to the clinical need.

This study describes the evaluation of a PLLA/HA composite material.

Materials and Methods

Medical grade poly-L-lactic acid was obtained with an intrinsic viscosity (IV) of between 3.5–3.8 and blended with a uniform particle size medical grade hydroxyapatite to give a homogeneous distribution of HA particles within the PLLA matrix. The material was injection-molded into interference screws using standard processing conditions. The screws were ethylene oxide sterilized and implanted into an ovine ACL model using a bone-tendon-bone autograft technique. Samples were evaluated at regular time points.

Results and Discussion

Polarized light microscopy clearly demonstrates the uniform distribution of the HA within the PLLA matrix (Figure 2). It can also clearly be seen that the HA particles are a regular size and shape.

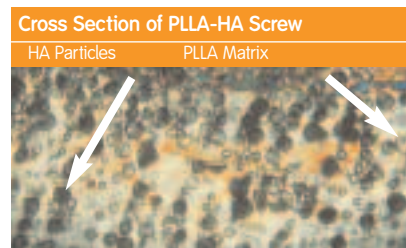


Figure 2. Homogeneous distribution of HA throughout the screw

After only four weeks in the ovine model new bone has infiltrated the ACL tunnel and integrated totally with the screw (Figure 3).

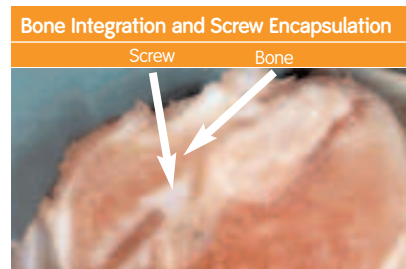


Figure 3. Sectioned ovine tibia at four weeks after ACL surgery illustrating bone integration

Bone can be seen attaching to the screw and has even grown within the driver slot. At six weeks the histology section shown in Figure 4 clearly demonstrates bone growth up to the screw and within the screw threads and driver slot. However at this point in time no osteoconduction is observed, probably due to the lack of degradation and mass loss of the polymer component. There is no evidence of any inflammatory response. At this point the screw is completely encapsulated by new bone.

The PLLA-HA blend has excellent biocompatibility properties which can be explained by the addition of HA. HA has been shown to functionally integrate with bone, forming direct intimate bonds with the surrounding bone.⁹ Protein absorption

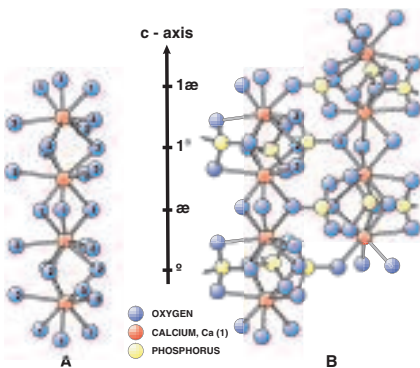


Figure 1. Structure of Hydroxyapatite
(Adapted from Beevers and McIntyre,⁷ published in "Structure and Chemistry of the Apatites and Other Calcium Orthophosphates," Studies in Inorganic Chemistry¹⁸, J.C. Elliott, Elsevier).

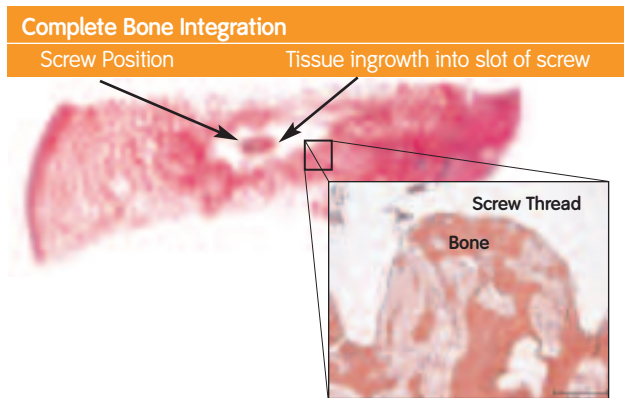


Figure 4. Ovine femoral bone tunnel fixation with PLLA-HA screw six weeks after ACL surgery

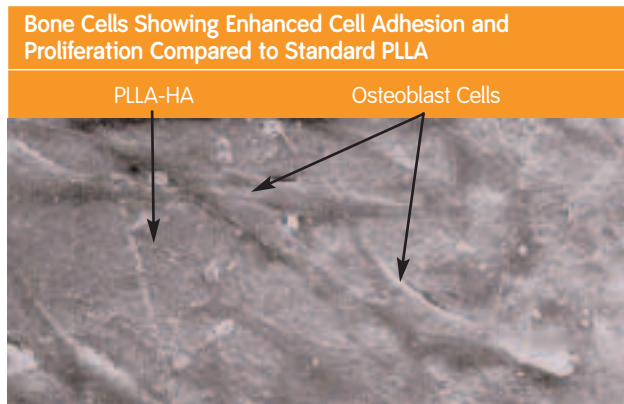


Figure 5. SEM micrograph of osteoblast growth on PLLA-HA¹⁴

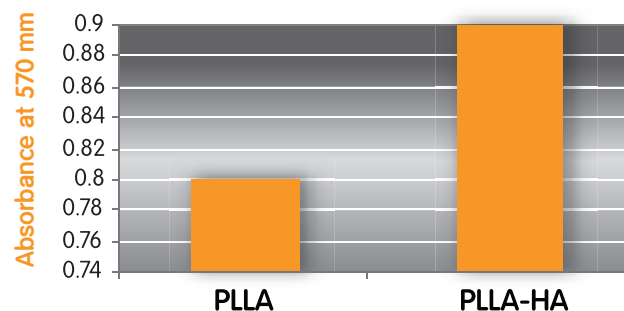


Figure 6. Cell vitality and proliferation assay (MIT). Osteoblasts cultured on PLLA and PLLA-HA. Adapted from 14.

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and bonding osteogenic properties have both been demonstrated for HA, giving the material its excellent osteoconductive properties.² Candrelli et al.¹⁴ screened a number of bioresorbable materials. Cells were cultured and analyzed for morphology, proliferation, and viability. They found that the addition of hydroxyapatite always resulted in an enhancement of performance with respect to plain polymer. Figure 5 shows osteoblastic growth on a PLLA-HA polymer, and the authors found an increase in cell attachment/adhesion and proliferation compared to cells grown on a PLLA plain polymer.

Figure 6 also shows a significant increase in cell vitality with cells grown on a PLLA-HA polymer. The authors attributed this enhancement to the hydrophilic nature of HA.

The addition of HA to a degradable polymer will not only improve the biological properties of the polymer due to HA's intrinsic biocompatibility properties, but it also has potentially another mode of action – pH control. Maintenance of physiological pH close to a degrading surface is important when enhancing the biocompatibility of a device. The addition of HA has a dual action:

- buffering pH changes
- decreasing the number of potential acid groups within the implant

It has been shown that HA can buffer the pH of media in the vicinity of degrading PLA-PGA specimens¹⁰ and when placed in an acidic solution will rapidly raise the pH.¹¹

The addition of HA will also proportionally decrease the mass of polymer which will significantly decrease the number of potential acidic groups.

The addition of HA to PLLA can also result in improved mechanical properties. Both the initial properties and the degradation properties can be significantly enhanced. The decrease in autocatalytic degradation has been shown to lead to an increased strength retention¹⁰ in the material. Also, the incorporation of HA granules to a polymeric matrix, such as polyethylene, has been shown to have a positive reinforcing effect on the mechanical performance of the matrix.^{8,12} This can be explained by the higher modulus of elasticity of HA (80 to 110 GPa) and the high compressive strength (500 to 1000 MPa) which is 3 to 6 times that of cortical bone.¹³

Conclusions

At this early point in time the addition of HA to PLLA has not resulted in osteoconduction, but the resulting material has been shown to be exceptionally biocompatible. It is expected that at later points in time the composite material should show improved biocompatibility over the pure polymer due to its natural biocompatibility with bone and also by decreasing acidity within the implant.

References

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Figure 5 Calandrelli L, Immirzi B, Malinconico M, Orsello B, Volpe MG, Della Ragione F, Zappia V, Oliva A. Biocompatibility studies on biodegradable polyester-based composites of human osteoblasts: A preliminary screening. *J Biomed Mater Res* 2002; 59: 611–617. Reprinted by permission of John Wiley & Sons, Inc. ©2001 John Wiley & Sons, Inc.