

Signafuse®: Optimal Bone Graft Remodeling

Introduction

The ultimate goal in developing synthetic bone graft materials is to better control implant resorption and bone substitution such that bony fusion can be reliably achieved [1]. Graft materials generally differ in terms of composition and structure, all of which affect resorption, bone bonding potential and remodeling at the defect site. Synthetic bone grafts typically comprise slower resorbing hydroxyapatite (HA) or faster resorbing beta tricalcium phosphate (βTCP) materials despite well documented deficiencies. More recently, biphasic materials comprising a mixture of HA and βTCP have demonstrated desirable properties over the base materials in animal studies as well as clinical success in spine fusion procedures [1-4]. Bioactive glass, a material that bonds to bone through a rapid sequence of surface reactions in the presence of living bone tissue, is commonly used in conjunction with calcium phosphate materials to induce bioactive bone bonding at the graft site [5]. The Signafuse Bioactive Bone Graft Putty has been designed with a proprietary blend of biphasic mineral granulate (1-2 mm) and bioactive glass (212-420 μm) suspended in a resorbable polymer carrier to provide a moldable putty with an unprecedented combination of bone graft technologies optimal for bone remodeling in posterolateral spine fusion procedures.

Bioactivity

The 45S5 bioactive glass component of Signafuse undergoes a unique surface modification within the physiological environment that allows for direct bonding with surrounding bone. Following implantation, an exchange of biologically active ions produces a bioactive hydroxy carbonate apatite (HCA) layer to which bone can readily bond to. These surface reactions are followed by the proliferation and differentiation of bone related cells on the apatite matrix as part of the normal healing process [5,6]. In-vitro testing of Signafuse in simulated body fluid (SBF) has demonstrated apatite layer formation on the bioactive glass surface in as early as 7 days (Figure 1).

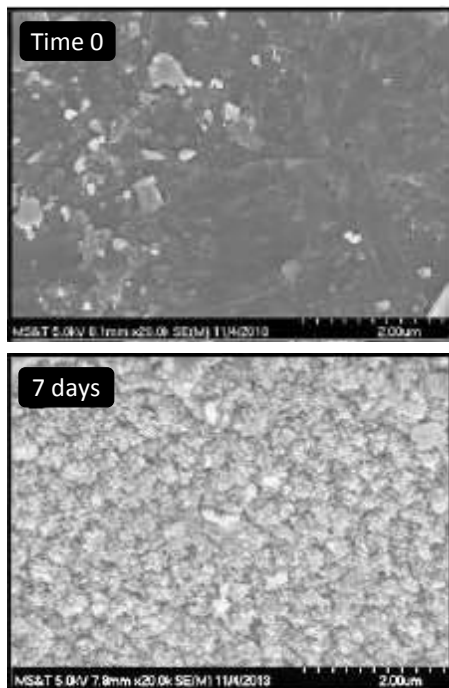


Figure 1: SEM images of Signafuse bioactive glass demonstrating surface apatite layer formation after 7 days in SBF.

Particle size distribution of bioactive glass is a critical factor to bone bonding performance. The patented particle size range of Signafuse bioactive glass (210-420 μm) has demonstrated advantages over the more common 90–710 μm range (Novabone), including higher rates of new bone formation and material remodeling at the defect site [7]. Generally, a narrow particle size distribution will yield a more controlled rate of ion dissolution and surface reactivity, producing a more consistent rate of bone bonding and proliferation throughout the defect site. Smaller particles (< 210 μm) can degrade quickly, causing a transient inflammatory response that may impede the up-regulation of osteoprogenitor cells. Larger particles (> 420 μm) may not fully degrade, leaving unreacted glass particles at the defect site that can delay osteoconduction and remodeling [8].

Biphasic Remodeling

Hydroxyapatite (HA) is similar in composition to human bone. However, the material is largely insoluble with bone bonding limited to the surface. Despite compositional modifications such as “silicate substitution” as with Actifuse ABX (Apatech/Baxter), the potential for limited resorption and remodeling remains, which may leave the defect site susceptible to focused mechanical stress [9,10]. Beta tricalcium phosphate (βTCP) is similar in composition to amorphous bone precursors and readily undergoes remodeling, stimulated by the material’s calcium phosphate-rich surface layers [10,11]. However, βTCP can potentially resorb faster than the rate of new bone formation, resulting in non-mineralized fibrous tissue at the implant site [9-11]. Despite enhancements to βTCP, as with Vitoss Scaffold Foam Pack (Orthovita), resorption of βTCP has been reported to be unpredictable in biological environments [9-12]. To address the limitations of these biomaterials, biphasic calcium phosphate materials combine the long term stability of HA with the solubility of βTCP resulting in an osteoconductive material with a gradual and controlled resorption profile optimal for bone defect remodeling.

Specifically, biphasic mineral formulated in a 60:40 (HA:βTCP) ratio, as featured with Signafuse, has demonstrated advantageous bone remodeling properties in both bench testing and in clinical relevant animal studies [1,2,13]. Following implantation, dissolution of biphasic mineral produces a direct bonding interface with host bone through the release of calcium and phosphate ions and subsequent formation of a surface apatite layer similar to bone mineral [13]. In addition, the structural microporosity and macroporosity of Signafuse biphasic granules (1-2 mm) are in the optimal ranges needed to allow penetration of biological fluids (>10 μm) and to support osteoconductivity (>100 μm), providing a more sustained remodeling response at the defect site. Clinical studies have shown efficacy of microporous and macroporous biphasic calcium phosphate in the reconstruction of large bony defects, including in posterior spinal fusion procedures, and suggest biphasic mineral is a safe and predictable alternative to autografts and allografts [3,4,12].

Signafuse biphasic mineral granulate provides distinct advantages over HA-based materials such as Actifuse ABX in terms implant resorption and remodeling. Figure 2 visually demonstrates the gradual resorption of the Signafuse biphasic mineral compared to Actifuse ABX in a rabbit posterolateral spine fusion (PLF) study at 6 weeks [14]. The gradual resorption rate, porosity and microstructure of the Signafuse biphasic mineral result in a stable scaffold that allows sustained osteoconductivity during the healing process.

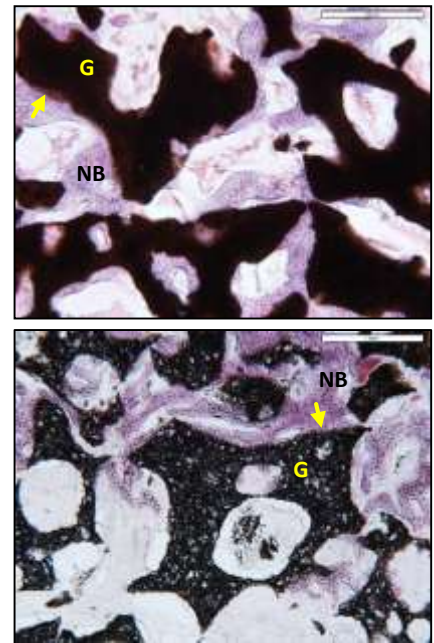


Figure 2: Surface resorption of the Signafuse biphasic mineral (top) is observed histologically by the loss of distinction at the new bone interface (arrows), which is less evident with the HA-based Actifuse ABX granules (bottom).
NB=new bone; G=granule

Synergistic Fusion Effect

The proprietary combination of 45S5 bioactive glass and 60:40 biphasic mineral provide a synergistic composite bone graft optimized for sustained bioactivity and remodeling in posterolateral spine fusion procedures. Figure 3 demonstrates the representative performance of Signafuse in a rabbit PLF model, where bridging bone was consistently observed spanning transverse processes by 12 weeks in-vivo, with new bone in direct apposition to and dispersed between the biphasic granules [14].

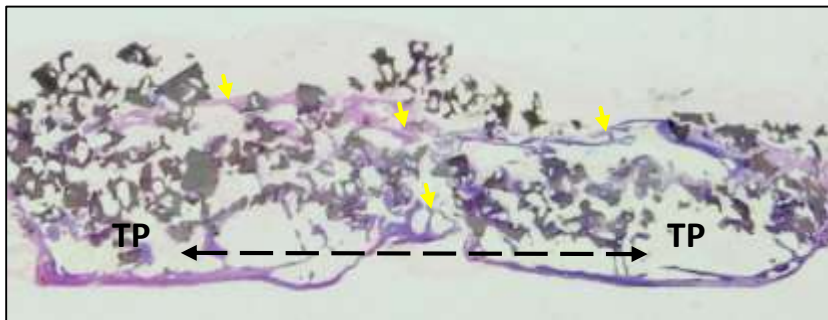


Figure 3: Representative histology of Signafuse in a rabbit PLF model showing new bone (arrows) spanning the transverse processes at 12 weeks.

applications. The Signafuse 45S5 bioactive glass composition and particle size range are advantageous over other bioactive glass materials. The Signafuse biphasic mineral features a controlled resorption profile compared to HA-based and βTCP graft materials, and microstructure optimal for bone remodeling. Signafuse provides a bioactive and osteoconductive scaffold optimal for sustained bone defect remodeling throughout the healing process.

Conclusion

The Signafuse Bioactive Bone Graft Putty combines a proprietary and synergistic combination of bone graft technologies optimal for sustained bioactivity and remodeling in bone graft

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