A bibliographic review of Biphasic Calcium Phosphate technology and veterinary clinical studies

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Graftys was created in September 2005 in order to harness the potential of academic research to a proactive and dynamic commercial organization in the field of bone tissue engineering. We design, manufacture and market calcium phosphate-based synthetic bone substitutes to address the global orthopaedic and dental surgery markets. Through its unique portfolio of proprietary technology, Graftys provides innovative solutions to major unmet market needs. Our research and development projects include the latest generation of injectable and resorbable synthetic bone substitutes, biological repair of cartilage and of the spine, as well as bone substitutes combined with pharmaceutical agents.

Graftys® BCP is a safe and effective synthetic biomaterial. It is a biphasic phosphocalcic micro/macro porous ceramic where chemical composition has been balanced to provide a physiologic optimal resorption/substitution process. The porosity structure has been fine-tuned by using a proprietary transitional porogenic process which improves interconnectivity and optimizes fluid percolation and cell invasion. Graftys® BCP is available in a wide variety of shapes to address many clinical requirements.

Figure 1: Bioactys® Granules
Introduction:

Bone loss is still a major problem in orthopedic, maxillofacial and dental surgery. Currently the gold standard technique of filling remains the autologous bone graft, which consists of harvesting cancellous bone, most often from the iliac crest in order to replace lost bone [1]. However the amount is often insufficient and this technique creates donor site complications such as chronic pain, hematoma, infection or fracture for about 30% of the patients [2, 3, 4]. To overcome these drawbacks and propose an alternative solution, many bone substitutes have been developed, including calcium phosphate ceramics, which emerged during the 1980s.

These calcium phosphate ceramics may include tricalcium phosphate (β-TCP), hydroxyapatite (HA), or biphasic calcium phosphate (BCP).

Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ is able to promote apatite precipitation at its surface immediately after implantation which gives it bone bonding properties. However HA presents a low resorption rate so it has to be mixed with tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ that is characterized by higher solubility and rapid degradation rate.

The BCP consists of a mixture of β-TCP and HA whose ratio HA / β-TCP may vary their resorption rate and mechanical strength properties. The ratio of 60% HA and 40% β-TCP is the most used. They are prepared by chemical synthesis involving sintering which allows controlling two very important parameters of BCP characteristics, the porosity and the interconnectivity of pores. There are two main types of porosity: Microporosity (pore diameter less than 10 microns) due to spaces remaining between crystals after sintering and macroporosity (pore diameter between 100 and 500 microns) which encourage penetration of cells into the BCP ceramic [5].
Graftys® BCP is an osteoconductive macroporous biodegradable biomaterial with a composition of 60% HA and 40% β-TCP. In contact with biological fluids, β-TCP is partially dissolved before precipitating as apatite crystals on the HA structure. These apatite crystals, similar to native bone crystals, promote cellular adhesion to start the natural resorption cycle; this is the concept of dissolution/precipitation [6]. The low dissolution rate of HA offers a stable scaffold needed for cells to form bone. Bone formation occurs throughout the material and occurs simultaneously with resorption of the implant. The porosity structure of Graftys® BCP can be fully penetrated by biological fluids and cells. Its global porosity is 70%, distributed as follows: 45% microporosity (<10 µm); 20% mesoporosity (10 - 100 µm); 35% macroporosity (100 - 600 µm).

Graftys® BCP is intended for use as a bone void filler for voids or gaps of the skeletal system caused by trauma or surgery, that are not intrinsic to the stability of the bony structure. Its mechanical compressive strength exceeds 10 MPa. Graftys® BCP can be used with autograft as a bone graft extender.

Veterinary case report:

Numerous studies have demonstrated the bioactivity of BCP (the capacity to bond with the bone tissue without fibrous interposition) and the osteoconduction property of BCP (the capacity to be invaded by osteoprogenitor cells and blood vessels and to serve as a framework within which the new bone can grow) [5-7].

In 1989, Daculsi et al. have demonstrated posterior spine arthrodesis in dogs using 3 types of calcium phosphate biomaterials namely hydroxyapatite (HA), tricalcium phosphate (TCP) and macroporous biphasic calcium phosphate (BCP) composed of 10% HA and 90% TCP. Using histopathological analysis, classical histological and transmission electron microscopy analysis, they showed that BCP and TCP allowed creation of
bone formation between vertebrae and into the ceramics after 3 months of implantation when immediate mechanical stability was ensured. TCP implants were almost completely degraded after 4 months of implantation. With HA biomaterial, a fibrous encapsulation was present preventing osseointegration of implants [8].

The same year using the same model of arthrodesis, these authors have compared bone formation kinetics of a macroporous BCP composed of 60% HA and 40% TCP and autologous bone. Their results, obtained by histological analysis, showed that bone formation kinetics in both conditions were similar. After 3 months of implantation, osseointegration of implants were present on at least one bone-implant interface [9].

Macroporous BCP (60% HA / 40% TCP) have also been used to fill an large segmental femoral shaft defects. In a 1997 study, the authors have compared three different bone substitutes [BCP, allograft and methyl methacrylate loaded with HA (PMH)], implanted in dogs with interlocking intramedullary nailing over 6 to 12 months [10]. Although in all cases the result of functional recovery of animals was considered very satisfactory, radiological monitoring showed that with PMH no consolidation has been achieved. With allograft or BCP, consolidations of bone-biomaterial junctions have been obtained after 3 months (Fig. 2).

![Figure 2: Radiographic pictures of BCP implant after 24 (A) or 41 weeks (B) of implantation in a dog [10].](image)

Moreover, histological analysis showed that the consolidations were the results of periosteal callus consisting of woven bone with allograft and periosteal and endosteal callus accompanied of lamellar bone with BCP. This lamellar bone extended from the cortical to macropores of BCP [10].

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The influence of macropore diameter on bone ingrowth was also studied. Gauthier et al. have implanted macroporous BCP with two different pore sizes (300 and 565 µm) and two different proportion of porosity (40 and 50%) into a distal femoral site in rabbits. After 8 weeks, histological evaluation showed that implants with 565 µm pore size provided more abundant newly formed bone than those with 300 µm pore size (Fig. 3). No significant differences were found between implants with 40 and 50% of porosity [11].

![Figure 3: Macroporous BCP after 8 weeks of implantation in rabbit.](image)

Solochrome-cyanine staining showing a haversian structure into macropore of BCP (A). Backscattered electron pictures of BCP with 565 µm pore size (B, C, D) [11]. Magnification of the center (C) and periphery (D).

BCP can be also used for dental surgery in animals. Gauthier et al. have reported in 2000 the treatment of a young female dog suffering from odontoma needing surgery. Given the size of bone loss caused by tumor removal, the authors used macroporous BCP granules to fill the bone cavity. Radiological monitoring of the animal showed that 2 months after
Implantation, bone reconstruction was complete even if the biomaterial was not yet fully resorbed (Fig. 4). After 18 months, no recurrence of tumor was observed [12].

**Figure 4:** Radiographic pictures of BCP implant after 0 (A) or 8 weeks (B) of implantation in dog [12].

**Conclusion:**

Macroporous biphasic calcium phosphate ceramics are bioactive and appear well adapted to fill small bone defects such as in dental surgery, for bone defects with large contact with bone, or in spine surgery. Their dissolution/precipitation properties and their low dissolution rate offer a stable scaffold to bone ingrowth. Finally, the osteoconductive properties created by macroporosity allows perfect osseointegration and bone formation into the BCP.
References:


