Calcium sulfate bone void filler: Past and Future clinical use/ Dr. Amir Kraitzer

Calcium sulfate use as augmentation material dates back to 1892 reported by Dreesmann to obliterate bone cavities caused by tuberculosis (reviewed by Peltier, 1961; Peltier and Speer, 1981). Since then, researchers and clinicians have continued to explore the effectiveness of the material in various applications. The long clinical history as an augmentation material was reported and published in thousands of scientific articles during 120 years of research in orthopedic, plastic surgery, oncology, revision arthroplasty, spinal arthrodeses (Bucholz, 2002), and maxilo-facial surgery (Coetzee, 1980). It has consistently found highly biocompatible, osteoconductive, and easy to use (Boden, 1999 or more recently by Pietrzak and Ronk, 2000; Ricci et al., 2000; Tay et al., 1999; Thomas et al., 2005; Thomas and Puleo, 2008). In an extensive review of Bhan regarding the use of Calcium Sulfate (Bahn, 1966), he summarized that calcium sulfate is simple, inexpensive substance that offers many advantage as an implant for bone filling.

Calcium sulfate exists in three different forms; calcium sulfate anhydrate, calcium sulfate dehydrate and calcium sulfate hemihydrate (Kim, 2003). The difference between these chemical species is represented by the amount of water molecule reside within a single crystalline unit cell. The crystalline structure defines its physical, mechanical, and dissolution properties. The hemihydrate state of hydration exists in two forms, α and β, which are both found in medical grade calcium sulfate products (Ricci, 2001a; Thomas et al., 2005; Thomas and Puleo, 2008). Gypsum is a common, natural mineral that consists of the dehydrate form. When gypsum is heated to 110 °C, it loses water in a process known as calcination. The resulting product is calcium sulfate hemihydrate, also known as plaster of Paris (Damien and Parsons, 1991; Pietrzak and Ronk, 2000; Ricci et al., 2000; Thomas et al., 2005; Thomas and Puleo, 2008). When the hemihydrate is mixed with water, the dehydrate is formed in a mild exothermic reaction (Thomas and Puleo, 2008).

When calcium sulfate is implanted in the body, it completely dissolves and recedes leaving behind calcium phosphate deposits that stimulate bone growth. Calcium sulfate dissolves into its component elements naturally found in the body; this makes this bone graft material well tolerated and non-immunogenic. No adverse reactions or failure to heal have been reported in the literature. Calcium sulfate bioresorption-studies and clinical experiences have shown consistent osteoconduction and complete resorption, replaced by newly formed bone that ultimately remodeled. When calcium sulfate bone void filler is placed in direct contact with viable host bone, new bone growth occurs in apposition to the calcium of the implant. As the synthetic bone substitute is resorbed, bone grows into the space previously occupied by the scaffold the implant provides. Calcium sulfate is considered a short term space maintainer (STSM). The reports regarding the resorption period of calcium sulfate vary between publications and depend on implant size, vascularity of the grafted site, and resorption model (Stubbs, 2004). For example, calcium sulfate resorbes in about 13 weeks in canine humerus model (Turner, 2003) and resorbes in 6 months in human trials (Kelly, 2001). As material dissolves it promotes bone growth by chemically activating the cycle of new bone formation, reacting with

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platelets to stimulate bone formation and enhance angiogenesis. Its porosity and hygroscopic properties promote absorption and infiltration of platelets. Calcium ions activate platelets to release BMPs and PDGFs that stimulate proliferation and osteogenic differentiation of mesenchymal stem cells (Strocchi, 2002, Intini, 2002, Groeneveld, 2000). After implantation, it can easily be monitored radiologically due to the fact it is radio-opaque.

**Calcium sulfate in dentistry**

In dentistry, calcium sulfate has been used either as solid forms or more preferably as paste or putty that sets during implantation. Numerous publications document both the clinical effectiveness and safety of calcium sulfate used as a bone substitute adjunct to dental implant placement in periodontal defect repair or maxillofacial applications, including sinus augmentation (Ricci, 2001b). Calcium sulfate has also been used as a barrier membrane to prevent ingrowth of soft tissues with great success.

Calcium sulfate is well tolerated by the tissues when used for the treatment of bone defects, guided tissue regeneration, and sinus augmentation in animals and humans, and the material was rapidly resorbed (Thomas et al., 2005; Thomas and Puleo, 2008). In the 1960s, sterile plaster of Paris pellets were tested in a preliminary clinical study as an implant in infrabony periodontal lesions in 35 humans. Seventy-nine percent of defects treated in this manner demonstrated regeneration of osseous tissue. There was no evidence of inflammation, edema, foreign body reaction, rejection of implant, or infection noted in any of the test sites in all 35 patients (Peltier, 1957). The results paralleled the report of Juillet (1976) who noted that calcium sulfate was beneficial to osseous regeneration and that the material was well tolerated by hard and soft tissue in dental implant placement. Kim and Cho (2007) reported that calcium sulfate Osteoset® pellets found very active on early consolidation in distraction osteogenesis versus control. In the calcium sulfate group, the percentage of bone mineral density in the distracted area, compared with the normal mandible, was significantly higher than in the control group (p<0.05). The authors concluded that calcium sulfate is a biocompatible osteoconductive material.

Sbordone and colleagues (2005) reported the successful treatment of a post-extraction maxillary buccal dehiscence in a patient. Calcium sulfate mixed with sterile 0.9 % NaCl to a putty-like consistency was packed into the defect, and 4 dental implants were placed in the edentulous ridge. Histologically, complete filling of the defect with mature, newly formed bone and complete resorption of the grafted material was noted five months later. The implants appeared to be successfully osseointegrated. Calcium sulfate root form implants for ridge preservation following tooth extraction produced significantly greater preservation of bone height and width than the ungrafted controls. Compared to a bovine-derived xenograft, allograft combined with putty induced significantly more vital bone in the experimental putty group (61 % versus 26 %) in humans. When used as a guided tissue regeneration barrier, together with demineralised freeze-dried bone allograft and calcium sulfate composite graft, calcium sulfate slowed epithelial and connective tissue ingrowth; furthermore, calcium sulfate was successfully applied in periodontal defects, other osseous defects, and post-extraction maintenance (Sottosanti, 1992a; Sottosanti, 1992b).
Sinus augmentation

Calcium sulfate cement was used to regenerate bone around endosseous dental implants in humans during maxillary sinus augmentation. Pecora and colleagues (1998) performed a series of studies and wrote a case report on calcium sulfate as a graft material for the maxillary sinus. The clinical and radiographic evaluation showed that it was possible to achieve the formation of new tissue that was quantitatively and qualitatively suitable for endosseous implant placement. Initially, the authors described the successful integration of 4 implants in 2 patients 9 months after calcium sulfate hemihydrate (SurgiPlasterTM) had been used as a graft material. Following this successful case report, De Leonardsis and Pecora (1999) performed a prospective, longitudinal trial consisting of a pilot group of 15 sinuses in 12 healthy patients requiring maxillary sinus augmentation for implant placement and a test group of 50 sinuses in 45 patients. The groups differed only in the technique of calcium sulfate application (SurgiPlasterTM), as described below. Implants were then placed and followed for at least 1 year. The overall success rate for the 130 placed implants 1 year post implantation was high (98.5 %). Histological analysis indicated type II or III bone in all specimens. In a subsequent publication, De Leonardsis and Pecora (2000) compared the histological differences in the pilot and test groups. In the test groups, the authors placed preformed calcium sulfate with a putty-like consistency in a stratified manner (N = 65 sinuses), which allowed each layer to harden as the next layer was placed. They stated that this allowed a denser fill and slowed the resorption of the material after sinus augmentation. As a result, the test group showed a mean bone concentration of 55.54 % (±19.82), while the control group showed a mean histomorphometric bone density of 34.25 % (±10.02). The authors further noted that both of these measurements compared favorably with other studies on bone concentration in grafted maxillary sinuses.

Guarnieri and co-workers (2007) used SurgiPlasterTM in sinus augmentation. The study evaluated the radiographic and histological results using granular medical-grade calcium sulfate hemihydrate (SurgiPlasterTM) as a grafting material in sinuses. Forty tooth implants were implanted along with grafting material in 10 patients, representing 15 sinuses. Radiographs were taken prior to sinus augmentation, monthly until 6 months postoperatively, 9 and 12 months after implant placement, and annually thereafter. Bone biopsies were harvested from all patients for histological and histomorphometric evaluation. The author concluded that SurgiPlasterTM Calcium Sulfate when used as grafting material in sinus lift procedures may lead to appropriate Osteointegration of dental implants and can be used to create adequate bone volume before implant placement.

Drug Release

The use of a drug loaded plaster in the treatment of infected bony defects have been supported by various studies without any evidence of a local or systemic adverse effect. The property of resorbability endows calcium sulfate the ability to be used as implant device loaded with various materials, e.g. antibiotics, pharmacological agents and growth factors (Damien and Parsons, 1991; Pietrzak and Ronk, 2000; Thomas et al., 2005; Thomas and Puleo, 2008). Absorbable calcium sulfate pellets impregnated with antibiotics are currently widely used, e.g., for the management of diabetic foot infections (Armstrong et al., 2001). Historically, using calcium sulfate as a carrier material for antiseptics and antibiotics (review of Tay et al., 1999) began as early as 1928 (Nyström, 1928; Petrova, 1928). The local delivery of antibiotics was initiated in the 1930s with the introduction of sulphonamide. Kovacevic (1953) implanted...
calcium sulfate cylinders containing penicillin and sulphonamide powder into patients suffering from haematogenic osteomyelitis. The author reported primary healing of the operative wounds, slow absorption and disappearance of the plaster and, finally, bony regeneration through the area of the defect. The introduction of antibiotic-impregnated cement in the 1970s increased the concentration of antimicrobial compounds in a local area, augmenting the use of systemic-parental antibiotics for bone infection therapy (Klemm, 1980). Finally, bone graft substitute materials containing growth factors in their composition, including recombinant human bone morphogenetic protein-2 (BMP-2) and rhBMP-7 (OP-1), demonstrate osteoinduction in clinical application (Tay et al., 1999).

**Bi-Phasic Calcium sulfate (Bond Bone®, 3D Bond™)**

Along the history of using calcium sulfate there was one major obstacle connected to the use of the cement form of calcium sulfate (calcium sulfate hemihydrate). Its suboptimal setting under blood, proteins, saliva, and other biological macromolecules retarded its conversion from paste to a rigid matrix. This obstruction has led to fast and unpredictable resorption of the material in some clinical cases. Optimal setting required a modification that would enable an increase of the structure's crystallinity, to allow a higher stability of the graft and equalize its degradation to be synchronized with bone formation rate. Over the year, numerous efforts were made in order to overcome the inability of the material to set and harden in the presence of blood or saliva (e.g using additives, accelerators) with partial success.

**Bi-phasic calcium sulfate (Bond bone®, 3D Bond™)** is a novel, self-reinforced graft binder cement composed of highly pure calcium sulfate. The cement incorporates both phases of calcium sulfate (hemihydrate and dehydrate) in a defined granular formulation. The dehydrate fraction forms nucleation zones thereby accelerating the setting process while the hemihydrate fraction contributes cementing and moldability characteristics. This formulation reduces the time of setting from about 20 minutes into three minutes making the material less susceptible to fast washout and fast resorption maintaining a low exothermic reaction during setting (up to 30°C). Making use of bi-phasic calcium sulfate addresses the previous setting issues by providing highly crystalline material that benefits a higher strength and a longer degradation duration. From a practical point of view, its most advantageous property is the material's ability to set and crystallize even in the presence of blood and saliva. These two main characteristics, combined with the material's high biocompatibility enable excellent STSM scaffolding formation. Figure 1 presents the unique structure of bi-phasic calcium sulfate seed particles, composed of both hemi and dehydrate phases of calcium sulfate at a particular dispersion and proportion. Mixing the granulated powder with sterile saline activates an accelerated setting mechanism. BondBone®, 3D Bond™ sets effectively under body fluids, resulting in a rigid scaffold post-setting; the scanning electron microscope images demonstrate needle-like crystalline structures (Figure 2) with an overall 46% porosity volume. The micro-pores allow growth factors infiltration, and macro-pores allow osteoblasts infiltration and angiogenesis..
Figure 1 – Bi Phasic calcium sulfate consists of particles of different sizes and phases

Figure 2: Post-setting structure, composed of needle like crystals, SEM

When used by itself Bi Phasic calcium sulfate is indicated for relatively small defects (up to 10 mm in width) supported by 3-4 bony walls. Horowitz et al, have shown impressive clinical, radiological and histological vital bone results in 4 months case series (n=40) treating extraction sockets with Bi Phasic Calcium Sulfate leading to 100% success in implant placement and loading. Yet, for indications of large defects, where a longer term space maintainer is required, Bi Phasic Calcium Sulfate should be used as a composite graft combined with a long term space maintaining bone graft substitute (e.g. Hydroxyapatite or beta TCP granules). In these cases it serves as cementable matrix, preventing particle migration of the granules, reducing working time and healing time thereby increasing the percentage of the vital bone formed.

**Use of calcium sulfate with in conjunction with other bone grafts (composite graft)**

Another concern regarding calcium sulfate is related to its fast resorption as reported in the review written by Thomas and Puleo (2008). The review mentioned two animal trials having unfavourable outcomes using calcium sulfate implants. The authors of these reports described the results, in part, to a lack of stable osteoconductive scaffold, presumably due to rapid dissolution of the calcium sulfate thus losing its mechanical properties. In some indications it may be required to prolong scaffolding properties beyond those available by calcium sulfate. In order to improve the scaffolding properties of calcium sulfate, and due to its excellent binding characteristics, it has been used with other bone grafts. Various authors have reported using calcium sulfate combined with
other bone grafts in a number of techniques; examples include repair of furcation perforations, grafting residual defects from root amputations, treatment of periodontal defects associated with developmental grooves, as a graft extender/binder for various bone grafts and growth factors, or as delivery vehicle for pharmacological agents (Thomas et al., 2005; Thomas and Puleo, 2008).

One example is the use of calcium sulfate in conjunction with Hydroxyapatite (HA). The setting properties of calcium sulfate allow it to be applied in a slurry form making it easier to handle and applied (Stubbs, 2004). HA is a calcium phosphate mineral and is the primary constituent of human bones and teeth (Manley 1993); it occurs in bone as major component between 60 and 70% (Frame, 1987, Venkatesan 2010) and up to 98% in enamel (Rodella 2011). HA used in clinical service is similar the chemical structure of the inorganic composition of human bone and thus has excellent biocompatibility in human studies (Manley 1993, Weiss, 2003). HA bone substitutes have been developed synthetically, derived from corals or algae, or naturally derived from bone mineral. The use of synthetic grafts in therapies for bone defects and bone related diseases is gaining popularity, as the synthesized materials are readily available and do not possess the health risks associated with the biological grafts, e.g. risk of disease transmission (Rodella 2011).

HA was used in alveolar ridge augmentation, periodontal lesion filling blocks and coatings in restorative dental and orthopaedic implants. HA has been shown to be an osteoconductive material, acting as a mineral scaffold into which new bone can grow; this is due to its properties that facilitate cell proliferation, migration and new bone apposition (Rodella 2011). HA demonstrated excellent biocompatibility as the material was found to be nontoxic, non-allergenic, and non-inflammatory after implantation in humans (Frame 1987, Manley 1993, Venkatesan 2010). In particular, HA is generally well tolerated by the hard and soft tissues of the mouth and jaws (Frame 1987). In vivo, HA undergoes some slight degradation after implantation, probably by gradual dissolution in tissue fluid as well as phagocytosis (Frame 1987). HA is poorly reabsorbed in the body (Manley 1993, Rodella 2011, El Deeb Me, 1988) with good bone augmentation properties (Kent 1983, Rothstein, 1984, Yamamichi, 2008, Scarano 2006). HA can be used alone as bone graft substitute as well as in combination with calcium sulfate (Murali 1994, Stubbs, 2004), chitosan (Venkatesan, 2010), and other materials.

Calcium sulfate was used in conjunction with synthetic HA, coralline HA and presented good bone healing properties. Murali and co-workers (1994) presented new bone formation in an osteoporotic patient treated with calcium sulfate, HA and a growth hormone in the proximal femur. Abundant new bone formation seen by SEM with a fine network of new bone between the HA particles. X-ray microanalysis revealed that the newly formed bridges between HA particles were mineralized, having a similar chemical composition to bone. There were no morphological signs of an intolerance of calcium sulfate + HA. The results from this report suggest that a mixture of HA, CS and GH is a potent stimulus to new bone formation. Schindler (2007) used a composite graft containing 35% calcium sulfate hemihydrate and 65% HA granules (mixed with autologous venous bone) to fill osteolytic defects in peri-articular areas of the knee (N=10). They showed that this composite graft can provide results equal to those achieved with autologous bone. The composite was well tolerated by all patients and no deformities were observed during the follow up period (average of 4.5 years). Bone integrity and joint stability were re-established. Similar results were obtained by the same group in (Schindler, 2008). They treated 13 patients with benign bone tumors in the lower limbs with a composite ceramic bone graft substitute containing 65% HA granules and 35% calcium sulfate hemihydrate (mixed with autologous venous bone). The composite did not disturb the proliferation of bone marrow or alter the normal
growth pattern of bone in locally aggressive benign bone tumor. Bone integrity and joint stability were regained in 11 out of the 13 patient. They concluded that composite ceramic bone graft substitutes containing a mixture of calcium sulfate and HA can provide clinical results similar to those achieved through autologous bone grafting. Stubbs et al (2004) examined the in vivo response of calcium sulfate alone and as a carrier for a coralline hydroxyapatite in an established bilateral corticocancellous defect model in rabbits. Defects were filled flush to the anterior cortex with a resorbable porous HA alone and in combination with calcium sulfate slurry and examined at time points up to 52 weeks. Calcium sulfate improved the surgical handling of Pro Osteon 200 R, and played an important role in the ultimate closure of the cortical windows. Pro Osteon 200 R supported new bone ingrowth into its porous domains even at the early time points while calcium sulfate resorption was nearly complete by 6 weeks. Overall, clinical experience with HA alone or combined with calcium sulfate provides additional information on the safety and clinical efficacy in use as a bone graft in humans.
**Bond Apatite™**

Bond Apatite™ is composed bi-phasic calcium sulfate and synthetic hydroxyapatite granules. Bond Apatite™ goes through setting as it encounters saline in about three minutes and results in a cemented material. The implanted material is actually Hydroxyapatite granules embedded in calcium sulfate cement. Bond Apatite™ presents porosity of 41%. The micro and macro structure of Bond Apatite™ is composed of needle-shaped crystallites of calcium sulfate that coat the Hydroxyapatite grains. The narrow gaps between Hydroxyapatite and calcium sulfate suggest that there is a strong interaction between Hydroxyapatite grains and calcium sulfate in Bond Apatite™. The structure has pore size having two populations: micropores (0-10µm) and macropores (50-500µm).

![Images showing micro and macro structure in different magnifications](image)

**Figure 3:** Bond Apatite™ micro and macro structure in different magnifications

**Conclusion**

Through its 120 year-long published clinical history of calcium sulfate it has consistently found highly biocompatible, osteoconductive, and easy to use as a bone graft in orthopedic, spine, and maxillofacial procedures. However, its sub optimal setting under blood, proteins, saliva retarded its hardening. Another concern regarding calcium sulfate is related to its fast resorption. Optimal setting under blood and saliva may be obtained by bi-phasic calcium sulfate. Calcium sulfate used in conjunction with synthetic hydroxyapatite, beta-TCP, coralline bone grafts and other granular bone grafts presented good bone healing properties including defects that require longer space maintaining time periods. Biphasic calcium sulfate improved the handling and the setting properties of calcium sulfate and provided clinicians with the ability to confront more augmentation challenges.
References


Edberg, E., Some experiences of filling osseous cavities with plaster. Acta Chir. Scand., 313-319,


Morikuni, T., A fundamental study on plaster implants applied to infrabony pockets. The histologic response of periodontal tissue to granulated Plaster of Paris implants. Shika Igaku [Dental medicine], 50(3):441-465, 1987


Sottosanti, J., Calcium sulfate: An aid to periodontal, implant and restorative therapy. CDA J., 4:45-62, 1992b


TOXNET, Toxicology Data Network, calcium sulfate CAS-RN 7778-18-9, 2008


Uhlmann, R., Bond-Bone™ (Batch No. 0011) - Test for in vitro cytotoxicity: Evaluation of materials and medical devices (MTT test). Harlan Biotech Israel Ltd., 2009


Horowitz RA., Rohrer MD.,Prasad HS.,Tovar N, Mazor Z, Enhancing Extraction Socket Therapy with a BiPhasic Calcium sulfate, Compendium, Volume 33, Number 6, 2012