OSTEOSET®

Bone Graft Substitute

TECHNICAL MONOGRAPH

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OSTEOSET®

Bone Graft Substitute

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Contents

Proper surgical procedures and techniques are the responsibility of the medical professional. The following guidelines are furnished for information purposes only as techniques used by the design surgeons. Each surgeon must evaluate the appropriateness of the procedures based on his or her personal medical training and experience. Prior to use of the system, the surgeon should refer to the product package insert for complete warnings, precautions, indications, contraindications and adverse effects. Package inserts are also available by contacting Wright Medical Technology, Inc.

Please contact your local Wright representative for product availability.

Medical Grade Calcium Sulfate

Bone Grafts and Bone Graft Substitutes

An estimated 300,000 or more surgeries in the U.S. annually require bone grafting, thus making bone the second most frequently transplanted material after blood.1,2 Bone grafts are needed to fill bone cavities resulting from infections, tumors, surgically created voids and trauma, and to fuse joints or fracture non-unions. Bone grafts are also frequently used in implant revision, dentistry, and plastic surgery.

Autograft (the patient's own bone) is generally considered to be the clinical standard in bone graft surgery because of its great osteogenic capacity and minimal immune response. As the autograft resorbs and is revascularized osteoprogenitor cells differentiate into osteogenic cells.1,2 This osteogenic cell activity results in new bone generation and healing of the bony defect. Issues related to autograft surgeries are:

- A limited quantity of autogenous bone can be harvested.
- The secondary surgery at the harvest site (generally the iliac crest) adds an additional degree of morbidity, results in more blood loss and pain, and increases the potential for infection risks.
- The harvesting surgery increases the anesthesia time and treatment costs.
- The harvest site may present post-operative instability, fatigue fracture or heterotopic bone formation.[3]

Allograft (cadaveric or bank bone) is the second most widely used grafting material.4 The main advantage of allografts are that they are relatively available and come in a wide variety of shapes and forms (cortical, cancellous, and demineralized bone). Allografts are osteoconductive and can have structural strength. Demineralized bone matrix has been shown to have osteoinductive properties promoted by certain non-collagen proteins.1,5 Although allografts result in generally acceptable clinical results, they present the following issues:

- Structural allografts are not readily bioresorbable and serve only as passive scaffolding.6 Poor revascularization and integration of the graft can result in increased incidence of non-union and fatigue fracture.7,8
- Allografts can generate an immunogenic response to the graft recipient.1
- Although allografts have been sterilized, the possibility can still exist for the transmission of viral contamination to the graft recipient.[3]

Wright Medical Technology, Inc., has introduced a calcium sulfate-based bone graft substitute, medical grade OSTEOSET® pellets. This biocompatible product provides surgeons with a bone graft substitute solution free of biological contamination.3,9

The issues related to both autograft and allograft materials have stimulated research for acceptable bone graft substitute alternatives. Some synthetic or animal-based materials can provide appropriate surfaces for osteoblast or osteoblast-like cells to form bones.

Calcium Sulfate and Bone Graft Requirements

One of the first functions of a bone graft substitute is to provide a stable tridimensional structure allowing new bone formation. It is important that this void-filling matrix can be remodeled or replaced by the newly formed bone. The new bone formation should have the same quality, strength and dimension as the original bone it is replacing.

However, mechanical strength is not a prerequisite for a bone graft substitute because the load is supported by the remaining healthy bone or a screw-plate or nail fixation system. High-strength materials can even be problematic because most are not bioresorbable and would not provide proper biomechanical stimuli to new forming bone. Currently, no bone graft substitutes, including human bone, can be used singularly for load-bearing applications without secondary support.

In addition to being biocompatible, the ideal bone graft substitute should stimulate new bone formation. The material can be osteoinductive and/or osteoconductive. Osteoinductive materials support the mitogenesis of mesenchymal cells from the graft site or from revascularization, that leads to the formation of osteoprogenitor cells with the capacity of new bone formation. Osteoconductive materials do not induce new bone formation, but allow the ingrowth of vessels and osteoprogenitor cells from the graft bed into the implant.

Calcium sulfate is a biocompatible material that resorbs in aqueous media without generating dissolution products that could impede bone formation.[10,11] The medical grade calcium sulfate used to make OSTEOSET® pellets was designed to have a rate of absorption that corresponds with the rate of new bone growth.[9] This material creates an environment for new bone formation that, with time, can provide normal bone structure.[9]

Mechanism of Action

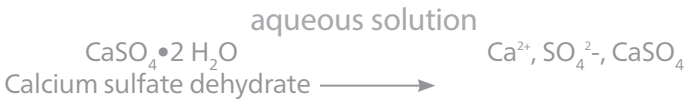
Calcium sulfate has been shown not to stimulate osteoinduction without the presence of bone or periosteum.[9,11,12] Peltier and Speer confirmed that calcium sulfate is an osteoconductive material that allows ingrowth of blood vessels and osteogenic cells.[12] Also, a recent in vitro study has shown that osteoblasts attach to calcium sulfate and that osteoclasts resorb calcium sulfate.[13] This in vitro study delineates a preliminary mechanism for the osteoconductive attributes of calcium sulfate.

Medical grade calcium sulfate acts primarily as a space filler that restores morphological contour and prevents the ingrowth of soft tissue.[11,12,14] The implant provides an osteoconductive matrix for ingrowth of blood vessels and osteogenic cells. Calcium sulfate absorption corresponds with the rate of new bone growth. As the calcium sulfate implant resorbs, new bone restores anatomical features and structural properties of the site.

Mechanism of Calcium Sulfate Dissolution

Calcium sulfate dissolution in aqueous solution generates the ions described in the following diagram:[15]

Ions and undissociated calcium sulfate are metabolized or excreted.[16] The consistent properties of OSTEOSET® medical grade calcium sulfate result in a more reproducible implant dissolution rate.[17] OSTEOSET® pellets



typically dissolve in vivo within weeks to months, depending on the amount implanted and the implant location.[9,18]

Biocompatibility

Wright Medical Technology, Inc. has successfully tested the biocompatibility of OSTEOSET® medical grade calcium sulfate following ISO and ASTM guidelines as shown in the following table:[19,20]

TEST	RESULTS
Cytotoxicity	PASS
Sensitization	PASS
Genotoxicity	PASS
Implantation	PASS
Systemic Toxicity	PASS
Intracutaneous reactivity	PASS

Many published reports by Peltier, Coetzee, Bahn and others also demonstrate the biocompatibility of calcium sulfate in clinical uses.[9,11,14]

Calcium Sulfate Properties

OSTEOSET® Medical Grade Calcium Sulfate

Calcium sulfate can be found in its natural state as gypsum. Wright Medical Technology, Inc. has an exclusive agreement with the world leader in calcium sulfate technology, United States Gypsum Corporation. The medical grade calcium sulfate from United States Gypsum Corporation is processed using proprietary manufacturing methods. These methods produce a consistent, high-quality material with minimal lot-to-lot variation in chemical and material properties. The consistency of this high-quality medical grade calcium sulfate allows for reproducible biological responses in bone graft applications.

Chemical Properties

The high quality of OSTEOSET® medical grade calcium sulfate is controlled through selective sourcing and careful quality analysis. This comparative chemical analysis of OSTEOSET® medical grade calcium sulfate and a regular calcium sulfate material is given in the table below:

Typical Chemical Analysis Grade	OSTEOSET® Medical Calcium Sulfate	Commercial Calcium Sulfate
$CaSO_4 \cdot H_2O$	98%+	80-94%+
$CaCO_3 \cdot MgCO_3$	0.5%	5.1%
$CaCO_3$	0.3%	1.0%
Aggregate	0.3%	4.5%

Mechanical and Physical Properties

The mechanical properties of calcium sulfate material and human bone are given in the table below. These values are for reference only since bone graft substitutes are not typically indicated for load bearing applications. Calcium sulfate implants are designed to bioresorb and be replaced by new bone which will provide mechanical strength for the graft site.

Typical Mechanical Properties	Wet Calcium Sulfate[23]	Dry Calcium Sulfate[23]	Cancellous Bone[24,25]	Cortical Bone[26]
Compressive Strength (psi)	1,500	3,340	800	23,500
Tensile Strength (psi)	300	600	1,000	22,000

Calcium sulfate is also naturally radiopaque which allows X-ray observation of the implant location and its replacement by bone.

Historical use of Calcium Sulfate as Bone Graft Substitute

The history of calcium sulfate use as bone implant material has been reviewed by many authors including Peltier, Bahn, Hulbert, Smith, Mackey and Damien.[3,9,11,25-27] Clinical use of calcium sulfate as a bone substitute for dental and orthopedic applications has been reported in literature for more than a century. In recent years, numerous authors have published reports confirming the safety and efficacy of calcium sulfate in oral and Maxillofacial applications, alone or in association with hydroxylapatite.[28-43] In the 1980's, Coetzee reported clinical results on 100 patients in whom diseased and destructed cranial bones were restored to healthy normal bone using calcium sulfate.[14] He reported an excellent primary procedure success rate (greater than 90%), and no complications were reported for the secondary operations. He stated his opinion: "Calcium sulfate is an outstanding bone substitute, ensuring bone formation and giving results comparable to autogenous bone, if not better."[14]

From 1960 to 1980, Lebourg, Alderman, and Shaffer reported excellent clinical results with the use of calcium sulfate in the treatment of periodontal infrabony defects.[44-46] Bahn also described positive clinical results on 75 patients treated for various oral defects with sterile calcium sulfate pellets.[11]

From 1957 to 1978, Peltier used calcium sulfate clinically as a bone void filler for a variety of cases including traumatic defects of tibia, femur fractures, bone cysts, fibrous dysplasia, enchondromas, aneurismal bone cysts and giant-cell tumors.[9,12,18,47] He observed that bone regeneration occurred in association with the implant resorption. He did not observe any increase in blood calcium level even in patients treated for large defects. He described the calcium sulfate as "a simple, inexpensive, available, stable material for use in filling cavities in bone."[9] A summary of his conclusions based on clinical experience were:

1. Calcium sulfate can be used safely and conveniently in a wide variety of bony defects encountered in patients.
2. The resorption of calcium sulfate and the subsequent regeneration of bone occurs rapidly over a period of weeks or months.
3. The presence of calcium sulfate does not inhibit the normal growth or healing of bone.
4. The use of calcium sulfate in infected cavities does not give rise to hazards or complications.[9]

In 1925, Kofmann, in a review by Bahn, reported the successful use of calcium sulfate to fill many osseous cavities, including one with a tibial abscess seven years post-op.[11] From 1925 to 1945, Oehlecker, Nordmann, Edberg and Nielson reported many successful uses of calcium sulfate to fill bone cavities including resection of benign tumors, aseptic necrosis, dentigerous cysts, giant-cell tumors, ostitis fibroses, and chodroma falangis.[48-51] In 1892, Dreesmann was the he first to report the results of filling osseous defects with this material in eight patients (one patient with two cavities).[9] Four of seven tuberculous cavities healed, and complete bone regeneration was observed in the two remaining cavities. Stachow and Martin reported treated operative defects in sheep and dogs, respectively, which showed complete material absorption and regeneration of normal bone.[11]

Conclusion

Calcium sulfate material has had long and successful clinical experience in a variety of bone defect applications. These successful applications demonstrate the safety and efficacy of this material. As Bahn and Peltier stated: "The material is stable, readily available, and can be easily sterilized."[11] Endochondral and intermembranous refer to bone regeneration pathways as opposed to defect types. A rapid rate of resorption, which corresponds with the rate of new bone growth, makes calcium sulfate especially useful in repairing large defects. Little or no stimulation of foreign-body, giant-cell activity and usefulness for the treatment of infected osseous defects are other attractive characteristics.[11]

OSTEOSET® pellets are made from an exclusive specially formulated and proprietary medical grade calcium sulfate with highly controlled and reproducible properties. OSTEOSET® pellets have a predictable dissolution rate which varies between 30 and 60 days, depending upon the amount implanted and the implant location.

References

1. Urist, M.R.: Bone Transplants and Implants. *In Fundamental and Clinical Bone Physiology* (Urist, M.R., Editor) pp. 331-368 (1980).
2. Cornell, C.N., *et al.*: Multicenter trial of collagraft as bonegraft substitute. *J. Orthop. Trauma* 5:1-8, 1991.
3. Damien, C., *et al.*: Bone graft and bone graft substitutes: A review of current technology and applications. *J. Appl. Biomat.* 2:187-208, 1991.
4. Camper, Y.: Bone grafts and bone substitutes. *Orth. Net. News* 6(4):7-9, 1995.
5. Urist, M., *et al.*: Bone morphogenetic protein. *J. Dent. Res.* 50:1391-1406, 1971.
6. Jasty, M., Mulroy, R.D. and Harris, W.H.; Bone Grafting in Total Hip Replacement and Implant Interface *Bone Grafts and Bone Substitutes* (Habal, M.B. and Reddi, A.R., Eds.) W.B. Saunders Company, 1992, Chapter 26, pp. 276-288.
7. Shenaq, S.M. and Vargo, D.: Vascularized Bone Grafts. *Bone Grafts and Bone Substitutes* (Habal, M.B. and Reddi, A.R., Eds.) W.B. Saunders Company, 1992, Chapter 29, pp. 305-315.
8. Murphy, M.D., Sartoris, D.J. and Bramble, J.M.: Radiographic Assessment of Bone Grafts. *Bone Grafts and Bone Substitutes* (Habal, M.B. and Reddi, A.R., Eds.) W.B. Saunders Company, 1992, Chapter 3, pp.9-36.
9. Peltier, L.F.: The use of Plaster of Paris to fill defects in bone. *Clin. Orthop.* 21:1-31, 1961.
10. Hogset, O. and Bredberg, G.: Plaster of Paris: Thermal properties and biocompatibility. *Acta Otolaryngol* (Stockh) 101:445-452, 1986.
11. Bahn, S., *et al.*: Plaster: A bone substitute. *Oral. Surg. Oral Med. & Oral. Path.*, 21:672-681, 1966.
12. Peltier, L.F. and Speer, D.P.: Calcium sulfate. *Bone Grafts and Bone Substitutes* (Habal, M.B. and Reddi, A.H., eds.) pp. 243-251, 1993.
13. Sidqui, M., *et al.*: Osteoblast adherence and resorption activity of isolated osteoblast on calcium sulphate hemihydrate. *Biomaterials* 16:1327-1332, 1995.
14. Coetzee, A.S.: Regeneration of bone in the presence of calcium sulfate. *Arch. Otolaryngol.* 106:405-409, 1980.
15. Nakayama, F.S., *et al.*: Calcium electrode method for measuring dissociation and solubility of calcium sulfate dehydrate. *An. Chem.* 39:1022-1023, 1967.
16. DeWet, I.S. and Jansen, C.: The use of Plaster of Paris to fill large defects in bone. *South African J Surg.* 11:1-8, 1973.
17. Personal Communication, W. Haggard (Wright Medical Technology) and T. Rosestiel (U.S. Gypsum), July 17, 1996.
18. Peltier, L.F.: The use of Plaster of Paris to fill large defects in bone. *Am. J. Surg.* 97(3):311-315, 1959.
19. EN 30993-1 Biological evaluations of medical devices. Part 1: Guidance on selection of tests. Brussels, CEN/CENELEC, 1994, 1-16.
20. ASTM F981-93, Standard practice for assessment of compatibility of biomaterials for surgical implants with respect to effect of material on muscle and bone. *1995 Annual Book of ASTM Standards.*
21. Earnshaw, R., *et al.*: The tensile and compressive strength of plaster and stone. *Austr. Dent. J.* 11:415-422, 1966.
22. Lee, R., *et al.*: The role of fixation and bone quality on the mechanical stability of tibial knee components. *Clin. Orthop. Rel. Res.* 273:177-183, 1991.
23. Linde, F., Hvid, I. and Pongsoipeetch, B.: Energy absorptive properties of human trabecular bone specimens during axial compression. *J. Orthop. Res.* 7:432-439, 1989.
24. Reilly, D., *et al.*: The mechanical properties of cortical bone. *J. Bone Jt. Surg.* 56A:1001-1022, 1974.
25. Hulbert, S.F., *et al.*: History of bioceramics. *Ceramics Internat.* 8:131-140, 1982.
26. Smith, D.: Implantation of Plaster of Paris of recontouring and regeneration of alveoli. *Dental Students' Magazine*, pp. 121-166, November, 1966.
27. Mackey, D., *et al.*: Antibiotic loaded Plaster of Paris pellets. *Clin. Orthop. Rel. Res.* 167:263-268, 1982.
28. Bissada, N.F., *et al.*: Alveolar bone induction: Alloplasts. *Dental. Clin. Of N. Amer.* 24:739-749, 1980.
29. Frame, J.W.: Porous calcium sulphate dihydrate as a biodegradable implant in bone. *J. Dentistry* 3:177-187, 1975.
30. Bell, W.H.: Resorption characteristics of bone and bone substitutes. *Oral Surg. Oral Med. & Oral Path.* 17:650-657, 1964.
31. Beeson, W.H.: Plaster of Paris as an alloplastic implant in the frontal sinus. *Arch. Otolaryngol.* 107:664-669, 1981.
32. Sasken, H. , *et al.*: A new ceramic for the conduction of bone. *Trans. Soc. Biomater.* 16:98, 1993.

33. Carnevale, R.A., *et al.*: Hydroxylapatite/plaster implantation for treatment of severe periodontal osseous defects. *Proc. Mat. Res. Soc.* 110:247-256, 1989.
34. Frame, J.W., *et al.*: Ridge augmentation using solid and porous hydroxylapatite particles with and without autogenous bone or plaster. *J. Oral Maxillofac. Surg.* 45:171-177, 1987.
35. Hanker, J.S., *et al.*: Plaster of Paris as a scaffold for incorporation of hydroxylapatite. *J. Dental. Res.* 63:325, 1984.
36. Hanker, J.S., *et al.*: Composite plaster/hydroxylapatite implants for jaw bone restoration. *Proc. Mater. Res. Soc.* 55:77-96, 1986.
37. Hanker, J.S., *et al.*: Osteogenesis in cat cranioplasty with composite hydroxylapatite/plaster. *Proc. Mater. Res. Soc.* 110:239-246, 1989.
38. Lewis, R.D., *et al.*: Composite hydroxylapatite/plaster implants for complex endodontic periapical defects and lesions. *Proc. Mater. Res. Soc.* 110:301-310, 1989.
39. Parsons, J.R., *et al.*: Repair of cortical defects with a partially absorbable hydroxylapatite based composite. *Trans. Soc. Biomater.* 10:248, 1987.
40. Ricci, J.L., *et al.*: Filling of fresh tooth root extraction sites with a hydroxylapatite based composite. *Trans. Soc. Biomater.* 10:77, 1987.
41. Ricci, J.L., *et al.*: Simulation of bone ingrowth into an implantable chamber through the use of rapidly resorbing calcium sulfate semihydrate. *Proc. 4th World Biomaterials Congress*, p. 49, 1992.
42. Terry, B.C., *et al.*: Alveolar ridge augmentation with composite implants of hydroxylapatite and plaster for correction of bony defects, deficiencies and related contour abnormalities, *Proc. Mater. Res. Soc.* 110:187-198, 1989.
43. Georgiade, N.G., *et al.*: The use of the particulate hydroxylapatite and Plaster of Paris in aesthetic and reconstructive surgery. *Aesth. Plast. Surg*. 17:85-92, 1993.
44. Lebourg, L. and Biou, C.: The embedding of Plaster of Paris in surgical cavities of the jaws. *Semaine des Hopitaux*. 37:1195-1197, 1961.
45. Alderman, N.E.: Sterile Plaster of Paris as an implant in infrabony environment: A preliminary study. *J. Periodontol.* 40:11-12, 1969.
46. Shaffer, C.D., et al.: The use of plaster of Paris in treating infrabony periodontal defects in humans. *J. Periodontol.* 42:685-690, 1971.
47. Peltier, L.F. and Jones, R.H.: Treatment of unicameral bone cysts by curettage and packing with Plaster of Paris pellets. *J. Bone Jt. Surg.* 60A:820-823, 1978.
48. Oehlecker, F.: Ueber knochenplombe. Zentralbl. *Chir.* 52:993, 1925.
49. Nordmann, O.: Die behandlung der lunatumnekrose und ahnlicher erkankugen mit der gipsplombe. Zentralbl. *Chir.* 66:824-839, 1939.
50. Edberg, E.: Some experiences of filling osseous cavities with plaster. *Acta Chir. Scandinav*. 67:313-319, 1931.
51. Nielson, A.: Filling of infected or sterile bone cavities by means of Plaster of Paris. *Acta Chir Scandinav*. 91:17-24, 1944.

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