PREPARATION OF SELF-SETTING CEMENT-BASED MICRO- AND MACROPOROUS GRANULES OF CARBONATED APATITIC CALCIUM PHOSPHATE

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ABSTRACT

A method of preparing spherical, micro- and macroporous (50 to 550 μm pores), carbonated apatitic calcium phosphate granules (2 to 4 mm in size) has been developed by using the NaCl porogen technique. A calcium phosphate self-setting cement powder (comprising a specially designed cement powder mixture of α-$Ca_3(PO_4)_2$, $CaHPO_4$, $CaCO_3$ and precipitated $Ca_{10}(PO_4)_6(OH)_2$) was mixed with 65 wt% NaCl crystals ranging in size from 1 mm down to 400 μm, followed by kneading with a dilute Na_2HPO_4 initiator solution and then sieving the setting paste to the desired sizes. Embedded NaCl crystals were leached out from the formed granules by soaking in deionized water at room temperature. The calcium phosphate granules comprised macro- and micropores substantially communicating with one another throughout the body with a porosity of 45-50% or more. Produced granules were only composed of carbonated, calcium-deficient, poorly-crystallized, apatitic calcium phosphate as the mineral phase, which is quite similar to that of human bones. Granules are used (marketed in Europe under the trade name of "Calcibon® Granules") as a substitute or a repair material for bone, carrier material for drug delivery and controlled release system. These granules have been the first calcium phosphate granules directly produced from a self-setting calcium phosphate orthopedic cement powder at room temperature, and they are also suitable for augmentation with autologous bone graft, bone marrow aspirate, blood or platelet-rich plasma.

INTRODUCTION

Calcium phosphate (CaP) bioceramics are used for bone reconstruction because of their close resemblance to the bone mineral phase, i.e., biological apatite. Stoichiometric calcium hydroxyapatite (HA: $Ca_{10}(PO_4)_6(OH)_2$) is far from mimicking the bone mineral. "Biological" or "bone-like" apatites, which constitute the mineralized portion of bones, are carbonated (4 to 6 wt%, and this fact alone makes them somewhat closer to the mineral dahllite rather than hydroxyapatite), poorly-crystallized, alkali (i.e., Na and K) and alkaline earth (Mg) element-doped, non-stoichiometric, calcium-deficient (about 10%) apatitic phosphates with a Ca/P molar ratio variable over the range of 1.55 to 1.70 [1-6]. In addition to possessing a chemical make-up closer to that of natural bone, orthopedic implants should have particularly designed structural characteristics, in order to better serve as desired. Orthopedic implants developed for bone repair should be porous, so as to invite ingrowth of newly formed bone into the implant, leading to a more securely fixed and integrated repair. Porous structures are particularly favorable when utilized in conjunction with natural cancellous bone, as they can closely mirror the structure of the host bone.

Bioactive and biocompatible CaP ceramics exhibit excellent osteoconductive properties. CaP-based bone substitutes are typically used for bone replacement or augmentation in a wide spectrum of clinical applications [7-9]. CaP ceramics used as bone substitutes are commercially

available as single-phase powders, self-setting cements [10-19], granules [20-23] or macroporous blocks [24-27]. Synthetic CaP bone substitutes with interconnected macropores will facilitate the penetration of cells and biologic growth factors into the implant allowing the osteogenic process to occur within the inner surfaces of pores. Macropores (from 100 to 600 μm), as well as micropores (i.e., pores ranging from 3 to 30 μm), are shown to be necessary for bone ingrowth to take place in synthetic bone substitute materials [28, 29].

Bone substitutes in the shape of granules of well-defined geometry, preferably in the shape of spheres in different sizes, provide the surgeon with an unmatched ease in filling the bone defects of irregular shape, in comparison to pre-shaped prismatic blocks. Granules, impregnated with, for instance, platelet-rich plasma, will be easily packed together by the orthopedic surgeon to fill and reconstruct the bone voids that may have been caused by trauma or other genesis, such as a benign tumor, from surgery or congenital defects.

Over the last two decades, hydroxyapatite-based granules have received quite a significant attention from both the orthopedic surgeons and the materials scientists, and consequently, numerous reports were encountered in the open literature [30-72]. Highlights of the previous research on CaP granule production will be briefly summarized in the following. Fabbri *et al.* [39] formed millimeter-sized HA granules by dripping a ceramic suspension into liquid nitrogen, followed by sintering. Granules of coralline-origin materials were prepared and tested *in vivo* by Holtgrave [41] and Baran *et al* [71]. Spray granulation process has also been tested for the micron-sized CaP granule production [42, 47]. However, this technique also necessitated a follow-up sintering step. Liu *et al.* [44] modified the dripping procedure originally developed by Fabbri *et al* [39], and added polyvinylbutyrale (PVB) into the ceramic suspensions. Granules were then sintered at 1200°C. The use of PVB, as the porogen, was also tested by Zyman *et al.* [72] in forming porous granules. Complete burn off of PVB always necessitated high temperatures (<1150°C). Maruyama *et al.* [46] formed a paste consisting of HA powders, CaO, ZnO, chitosan and malic acid, wet granules were first formed out of this paste, followed by sintering at 1150°C. Gauthier *et al.* [50] used the technique of wet granulation on chemically synthesized CaP powders to obtain 200 to 500 microns granules. Oonishi *et al.* [22, 56] tested the *in vivo* response of granules made from poorly-crystallized CaP powder mixtures. Merkx *et al.* [51] examined the *in vivo* behavior of porous, bovine-origin granules in a goat model. Paul *et al.* [54] first prepared the HA powders by starting with $Ca(OH)_2$ and H_3PO_4, then formed viscous suspensions by using chitosan and paraffin, and obtained granules upon stirring in those thick suspensions. Formed granules were fired at 1100°C to achieve the strength required for handling. Patel *et al.* [66] used a similar procedure to produce CaP granules with that used by Paul *et al* [54]. Preparation of apatite-wollastonite (A-W) glass-ceramic granules were reported by Ikeda *et al.* [53]. Schwartz *et al.* [55] studied the preparation of porous biphasic (HA-$Ca_3(PO_4)_2$) granules after sintering the wet, organic substance-containing granulates at 1200°C. A similar procedure for granule manufacture was recently reported by Tanaka *et al* [69]. Barinov *et al.* [63-65] first prepared a CaP suspension, and then dissolved gelatin in it. Upon stirring this suspension in a bath of oil, spherical granules of micron size were formed. Wet granules were collected and then sintered. Rodriguez-Lorenzo *et al.* [67] prepared HA suspensions containing soluble starch, and utilized the swelling of starch to form pores, followed by sintering at 1100°C and granulation. Takagi *et al.* [61] blended CaP powders with sucrose and $NaHCO_3$, followed by granulation, to obtain porous granules with sizes ranging from 125 to 250 microns.

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Calcibon® Granules) as bone substitute
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EXPERIMENTAL PROCEDURE

Granule preparation

Powders of Calcibon® (Biomet
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phosphate (α-TCP), 26.8 wt% dical
carbonate ($CaCO_3$) and 1.8 wt% hydro
Merck, Darmstadt, 3 wt% solution p
(99.9%, Merck, Darmstadt) was used a

Granule preparation method c
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f.) checking the efficiency of leaching
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the obtained granules at 37°C, follo
geometry, with sizes varying from 2
method on an industrial scale.

However, none of the CaP granules used or manufactured in these previous studies [30-72] was able to simultaneously meet the following crucial criteria for a successful porous bone substitute:

(1) to be produced without being heated at temperature higher than the physiologic temperature, and without sintering,
(2) to be comprised of carbonated, calcium-deficient, apatitic CaP just as the human bones, not just of stoichiometric HA or TCP ($Ca_3(PO_4)_2$) ceramic,
(3) to possess an interconnected network of micro- and macropores,
(4) to have the ability of being impregnated (i.e., wicking ability) with the patient's own blood or bone marrow aspirate prior to the implantation,
(5) to contain nanocrystals of carbonated, calcium-deficient apatitic CaP on its surface.

This study [73] reported a simple, industrial method of preparing micro- and macroporous, Ca-deficient, carbonated, apatitic calcium phosphate granules over the size range of 2 to 4 mm, starting with a high-strength, self-setting synthetic calcium phosphate cement (*Calcibon*®, Biomet-Merck Biomaterials GmbH, Darmstadt, Germany) [10-13, 74] powder. This robust method uses NaCl crystals as the porogen. Granule preparation was achieved within minutes on an automatic sieve shaker, with desired sizes of sieves stacked on top of one another, under clean room conditions. Upon setting of the cement matrix, porogen crystals were leached out of the granules in water to form pores. These granules are already in clinical use (i.e., Calcibon® Granules) as bone substitute materials for repair and reconstruction of bone defects, in combination with bone marrow aspirate, blood or platelet-rich plasma of the patient.

EXPERIMENTAL PROCEDURE

Granule preparation

Powders of Calcibon® (Biomet-Merck Biomaterials GmbH, Darmstadt) were used as the self-setting CaP cement. The cement powder [75] consisted of a mixture of 62.5 wt% tricalcium phosphate (α-TCP), 26.8 wt% dicalcium phosphate anhydrous (DCPA), 8.9 wt% calcium carbonate ($CaCO_3$) and 1.8 wt% hydroxyapatite (HA). An aqueous solution of Na_2HPO_4 (99.9%, Merck, Darmstadt, 3 wt% solution prepared in water) was used as the initiator liquid. NaCl (99.9%, Merck, Darmstadt) was used as the porogen.

Granule preparation method comprised the steps of a) mixing the Calcibon® cement powder (40.0 g) and NaCl (70.0 g) in a Turbula mixer for 90 minutes, b) wetting the powder with an appropriate volume of a mixture of high-purity ethanol (99.9%, Merck, Darmstadt), and 3.5 wt% Na_2HPO_4 aqueous solution (i.e., 6.7 mL ethanol mixed with a 12 mL aliquot of Na_2HPO_4, c) kneading the wet powder body for 4 minutes to form a cake with a special mixer, d) immediately sieving that wet body over the following 2 minutes in an automatic sieve shaker, with multiple sieves, to *in situ* form granules of desired sizes, e) leaching out the NaCl porogen by soaking the granules in a special sterile bath with circulating water at room temperature from 24 to 48 hours, f.) checking the efficiency of leaching (of NaCl) by measuring the conductivity of the washing water, g) optionally, soaking the granules in a 1 wt% Na_2HPO_4 solution for curing, and h) drying the obtained granules at 37°C, followed by gamma-ray sterilization. Granules of spherical geometry, with sizes varying from 2 to 4 mm, were produced by using the above-outlined method on an industrial scale.

Granule characterization

Granules were characterized by scanning electron microscopy (SEM, JEOL630, Jeol Corp., Tokyo, Japan), energy-dispersive X-ray spectroscopy (EDXS, Thermo-Kevex, San Jose, CA), powder X-ray diffraction (XRD, Cu K_α radiation, D5000, Siemens GmbH, Karlsruhe, Germany), Fourier-transformed infrared spectroscopy (FTIR, Nicolet 550, Thermo-Nicolet, Woburn, MA), water absorption [76], density (Pycnometer, AccuPyc 1330, Micromeritics, Norcross, GA), and compressive strength measurements (Model 4500, Instron Deutschland GmbH, Germany).

Samples were coated with a 50 to 70 nm-thick layer of carbon prior to SEM imaging. EDXS analyses were also performed on such carbon-coated samples. XRD data were gathered over the 2θ range of 10 to 60°, with a step scan rate of 0.02 per minute and preset time of 1 second. 35 mA and 40 kV were the respective power and voltage settings of the X-ray diffractometer during operation. FTIR analyses, on the other hand, were performed after diluting the pulverized (into a fine powder) granule samples in KBr at the sample-to-KBr weight ratio of 1:100, followed by pelletizing in a 1 cm steel die at 25 MPa. Granule densities were measured with a standard gas pycnometer. Compressive strength measurements were performed after filling a 2.1 cm diameter stainless steel die cavity with approximately 0.85 g of granules, followed by gentle tapping of the die to facilitate the even packing of granules. An automated Instron universal testing machine was used to push the upper punch into the die cavity at the crosshead speed of 1 mm/min.

RESULTS AND DISCUSSION

The size distribution of granules obtained in one typical setting-sieving batch (i.e., wet cement paste was set *in situ* during sieving) is given in Table 1. The weight percentages given in Table 1 were the average values obtained from ten separate sieving runs. Size distribution could be altered simply by varying or adjusting the L/P (liquid-to-powder) ratio of the cement body placed onto the sieve shaker.

Table I. Granule size distribution

Granule size (mm)	Weight % (± 3%)
2.8 to 4	15
2 to 2.8	35
1.25 to 2	36
1 to 1.25	4
< 1	10

Figure 1a exhibit the low-magnification SEM image of the obtained granules, and the cubic imprints of the embedded NaCl porogen crystals are shown, which were totally leached out upon washing. In other words, NaCl crystals left behind their footprints. Those square nests formed (after dissolution of these NaCl crystals) in the calcium phosphate cement matrix were like the "replicas" of those crystals, and thus the product could be identified according to its manufacturing process. Macropores, being simply dependent on the crystal size of NaCl used in processing, could be readily varied over the range of 50 to 800 μm. However, for the sample shown in Fig. 1a, pore sizes were from 50 to 500 μm. High-magnification SEM micrograph of

the granules given in Figure 1b shows t
Fig. 1a). Interconnected micropores ra
study, i.e., *Calcibon*®, is an α-TCP-bas
$CaCO_3$, upon setting within 7 to 8 r
nanosize platelets (as shown in Fig. 1b
1.52±0.1. Granulation process used did

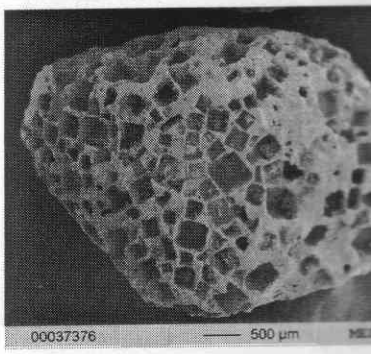

Fig. 1 SEM images of granules; (*left*) r

"Biological" or "bone-like" apa
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element-doped, non-stoichiometric, cal
variable over the range of 1.50 to 1.70
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XRD analysis of these granules
spectra, as shown in Fig. 2a. The s
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the major component of this cement, i.
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deficient apatitic CaP. $CaCO_3$ preser
hydrolysis process facilitating the form
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precipitated HA present in the cement
processes, which continued at the body
XRD data given in Fig. 2a belonged to
the NaCl porogen crystals in deionized
granule production by using this cemen

The carbonated nature of the po
CO_3^{2-} bands seen at 873 and 1450 cm^{-1}
cm^{-1} belonged to the OH stretching
characteristic positions [83].

the granules given in Figure 1b shows their microporous matrices (i.e., the dense looking areas of Fig. 1a). Interconnected micropores ranged in size from 1 to 4 μm. Since the cement of this study, i.e., *Calcibon*®, is an α-TCP-based cement [11], with the major additives of $CaHPO_4$ and $CaCO_3$, upon setting within 7 to 8 minutes, it formed a web of interlocked, intermingling nanosize platelets (as shown in Fig. 1b) of Ca-deficient apatitic CaP with a Ca/P molar ratio of 1.52±0.1. Granulation process used did not alter or destroy this stoichiometry.

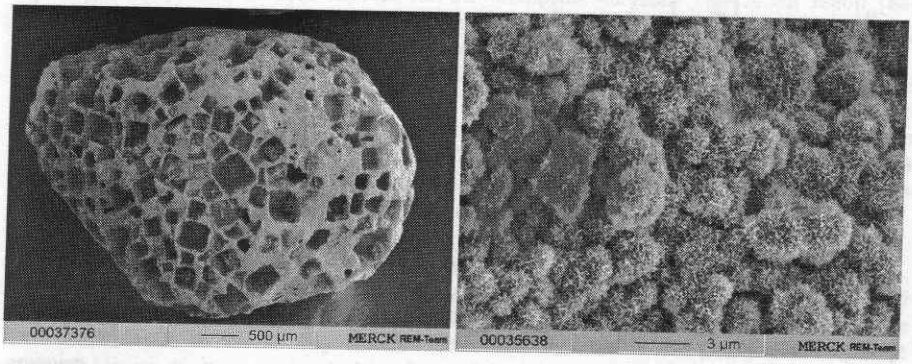

Fig. 1 SEM images of granules; (*left*) macroview, (*right*) microstructure of dense-looking areas

"Biological" or "bone-like" apatite, which constitutes the bone mineral, is known to be a carbonated (4 to 10 wt%), poorly crystallized, alkali (i.e., Na and K) and alkaline earth (Mg) element-doped, non-stoichiometric, calcium-deficient apatitic phosphate with a Ca/P molar ratio variable over the range of 1.50 to 1.70 [1, 77-79]. The CaP cement used in the production of the porous granules of this study was shown [16] to yield a fast deposition of new bone at the cement surface and is considered to be biocompatible [80, 81].

XRD analysis of these granules yielded the characteristic poorly-crystallized apatitic CaP spectra, as shown in Fig. 2a. The setting reaction for this high strength (>55 MPa under compression) cement has been described elsewhere in detail [11]. However, to mention briefly, the major component of this cement, i.e., α-$Ca_3(PO_4)_2$, went through a hydrolysis reaction upon its contact with the setting solution of pH 9. The end product of the hydrolysis reaction was Ca-deficient apatitic CaP. $CaCO_3$ present in the cement powder rapidly participated in this hydrolysis process facilitating the formation of carbonated apatitic CaP [82]. $CaHPO_4$ itself also underwent a similar hydrolysis procedure to the apatitic CaP, and the small amount of precipitated HA present in the cement formulation acted as an accelerator for those hydrolysis processes, which continued at the body temperature till the completion of the cement setting. The XRD data given in Fig. 2a belonged to the freshly produced porous granules after washing off of the NaCl porogen crystals in deionized water at 37°C for 72 hours. Presence of NaCl crystals in granule production by using this cement did not affect the cement setting process.

The carbonated nature of the porous granules was strongly indicated by the characteristic CO_3^{2-} bands seen at 873 and 1450 cm^{-1} in the FTIR data of Fig. 2b. The weak band seen at 3571 cm^{-1} belonged to the OH stretching. Orthophosphate bands were also observed at their characteristic positions [83].

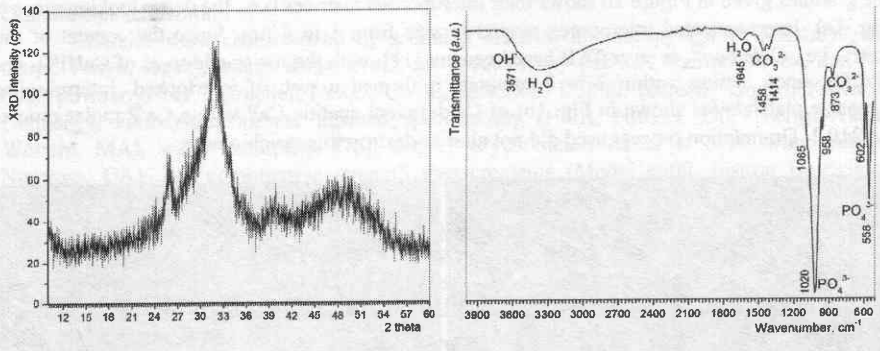

Fig. 2 XRD trace of granules (*left*), FTIR spectrum of granules (*right*)

EDXS analyses performed on the final granules showed that they did not contain any Na^+ or Cl^- ions originating from the use of NaCl as the porogen. EDXS results (accurate to ±0.5 wt%, data not shown), only exhibited the extraneous C peaks due to the carbon coating of granules prior to the analysis.

The formed granules (between 2 to 4 mm sizes) had a pycnometer-measured density of 1.60 ± 0.15 g/cm^3, which corresponded to about 50% total porosity, considering the fact that the density of the fully set, dense *Calcibon*® cement was around 3.2 g/cm^3 [11]. Porous granules also possessed a water absorption percentage of 150, measured according to the aforementioned ASTM standard [76]. This property itself imparted the granules a significant wicking ability. Compressive strengths of the granules were measured to be 10 ± 1 MPa (average of 5 measurements). Porous nature of the granules caused this reduction in compressive strength.

The cement liquid (3.5 wt% Na_2HPO_4 solution), when mixed with the cement powder of this study, resulted in a smooth and malleable calcium phosphate paste. This paste showed the ability of seamlessly embracing and surrounding the cubic NaCl crystals. The use of ethanol in the granule manufacturing was only for the purpose of retarding the setting reaction for a few more minutes to allow successful sieving. Ethanol used was either evaporated or washed away with water during the later, washing and drying stages of the granule manufacturing process. During leaching out of the embedded NaCl crystals, the effluent solutions were monitored with respect to their resistivity on a real time basis. It is known that even ppm levels of dissolved NaCl in water would cause a decrease in the resistivity values of such solutions. Washing operation was terminated when the resistivity of the effluent solutions reached the level of that of pure, distilled water (i.e., 18 MΩ).

The wet, freshly formed granules hardened at the ambient temperature by an endothermic reaction. The chemical composition and crystalline structure of the cured material did mimic the mineral part of natural bone, as depicted in Figures 2(a) and 2(b).

More than a year after the completion of our study on the production of porous CaP granules by the technique described here [73], Tadic *et al.* [84] independently published an article on the manufacture of porous HA objects that avoided sintering. Tadic *et al.* study [84] used a NaCl porogen technique similar to ours to produce macropores with pore diameters in the range of 250 to 400 μm in their 3D objects. Nevertheless, their starting material was just a

precipitated hydroxyapatite in powde
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received. Tadic *et al.* [84] unfortunat
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CONCLUSIONS

Micro- and macroporous carb
by using the NaCl porogen technique
CaP cement used as the starting m
granules.

(1) The robust process used in
specification of the final gran
(2) Pore sizes over the range of 5
(3) Granules had about 50% poro
(4) Granules were produced from
$Ca_3(PO_4)_2$, $CaHPO_4$, $CaCO_3$ a
(5) Granules comprised carbonat
(6) Granules had a high wicking
(7) Granule production was perfo
ambient and 37°C,
(8) Good manufacturing practice
production.

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A. C. Tas was formerly a staff scientist in GmbH" in Darmstadt, Germany, from S

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precipitated hydroxyapatite in powder form, which was far from being a self-setting cement. In order not to cause any undesired grain growth and a decrease in the surface reactivity of their powders, they apparently did not calcine their precipitated powders, and used such powders as received. Tadic *et al.* [84] unfortunately needed to compact their NaCl-embedded hydroxyapatite powder blocks by using cold isostatic pressing. Since they didn't sinter their 3D objects, after porogen removal and consequent pore formation, it was not possible to mention any handling strength to be present in such devices for the orthopedic surgeon. This recent report [84] constituted a vivid example on the significance of using strong self-setting cements in forming porous CaP-based medical devices by the porogen technique.

The granules of the present study regarded to be one-time bone implants staying in place until biodegradation by the body. The *in vivo* resorption rate of porous granules can be theoretically predicted to be much faster in comparison to the dense blocks or prismatic objects made out of the same material [85]. Such granules can be used in every aseptic bone bed, except the area of open epiphyseal discs. Depending on the indication, fixation or stabilization should be performed as if using an autologous bone graft.

CONCLUSIONS

Micro- and macroporous carbonated, apatitic calcium phosphate granules were produced by using the NaCl porogen technique with a self-setting cement powder. The high strength of the CaP cement used as the starting material here facilitated the robust production of porous granules.

(1) The robust process used in granule manufacturing allowed the precise selection and specification of the final granule sizes over the range of 1 to 5 mm,
(2) Pore sizes over the range of 50 to 550 μm were easily achieved,
(3) Granules had about 50% porosity,
(4) Granules were produced from totally synthetic and biocompatible materials, such as α-$Ca_3(PO_4)_2$, $CaHPO_4$, $CaCO_3$ and $Ca_{10}(PO_4)_6(OH)_2$,
(5) Granules comprised carbonated, calcium-deficient, poorly-crystallized apatitic CaP,
(6) Granules had a high wicking ability (*ca.* 150%),
(7) Granule production was performed, from the start to its end, at temperatures between the ambient and 37°C,
(8) Good manufacturing practices (GMP) were implemented at all stages of the granule production.

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A SELF-SETTING, MONETITE (Cal

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Clemson, SC 29634

ABSTRACT

A low compressive strength (
$CaHPO_4$ cement was developed by us
starting powder component. The setti
(H_3PO_4) solution, with a small amoun
Calcium was provided by the powder
solution. The setting solution was acid
of forming the phase of dicalcium pho
(liquid-to-powder) ratio of 1.54 and
time of 19±2 minutes. Set cements co
solubility than octacalcium phosphat
aqueous solutions at the physiological
vivo resorbability in comparison to th
XRD, FTIR and SEM. Compressive
Gillmore needles) of the cement sampl

INTRODUCTION

Beyond the autologous bone g
of choice for skeletal repair, mainly d
and even bioresorbability (i.e., osteo
first commercialized about two decad
supplied CaP-based powder compone
provided the orthopedic surgeon with
within minutes in the surgical theater
were needed to be chiseled and hamm
accordance with the defect peculiarity.

Most CaP-based orthopedic co
hydroxyapatite [HA, $Ca_{10}(PO_4)_6(OH)_2$
similarity of HA with the mineral p
solubility among all the calcium pho
tests,[3,4] such cements based on HA w
lacking full participation in the bone
HA-based cements typically used α-tr
phosphate [TTCP, $Ca_4(PO_4)_2O$] as t
undergo hydrolysis, into apatitic calci
solutions. Nevertheless, α-TCP (or TT
and both are fully stable only at high