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(72) Inventors; and
(71) Applicants : **MALSHE, Ajay, P.** [US/US]; 4105 Georgia St., Springdale, AZ 72762 (US). **JIANG, Wenping** [CN/US]; 1615 N. Rhonda Drive, Fayeteville, AR 72703 (US).

(74) Agent: DOUGHERTY, J., **Charles;** Wright, Lindsey & Jennings LLP, 200 W. Capitol Ave., Ste. 2300, Little Rock, AR 72201 (US).

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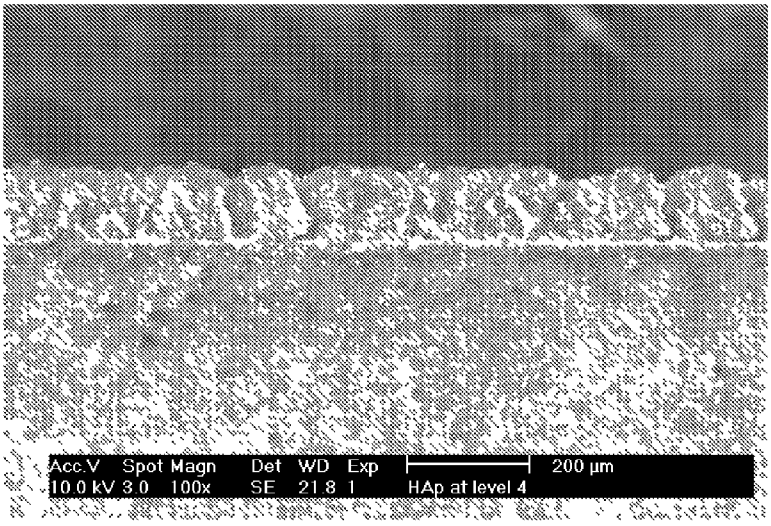

Fig. 3c

(57) Abstract: A high-strength coating for dental and orthopedic implants utilizing hydroxyapatite (HAp) nanoparticles provides for a high level of osseointegration through a range of surface pore sizes in the micro- to nanoscale. Zinc oxide (ZnO) nanoparticles may be incorporated with the HAp nanoparticles to form a composite coating material, with ZnO providing infection resistance due to its inherent antimicrobial properties. A textured surface, consisting of "islands" of roughly square coating structures measuring about 250µm on a side, with spacing of 50-1 OOµm therebetween, may further promote the osseointegration and antimicrobial properties of the implant coating.

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Description

Nanostructured Hydroxyapatite Coating for Dental and Orthopedic Implants

Technical Field

The present invention relates to coatings for dental and orthopedic implants, and in particular to coatings that incorporate nano-scale Hydroxyapatite (HAp) and nano-scale Hydroxyapatite-Zinc Oxide (HAp-ZnO) composites.

Background Art

HAp has been widely used as a coating material for orthopedic and dental applications due to its similar chemical composition to natural bone mineral, and its capability to promote bone regeneration. Unfortunately, however, the failure of HAp-coated implants is commonly seen. It is generally believed that implant failure may be due to multiple reasons, such as poor adhesion between implant and surrounding bone and tissue, and post-implantation infections. Many studies have discussed the issues of poor osseointegration (the bonding of an orthopedic implant to juxtaposed bone) and the inability of implants to match the physical properties of surrounding bones. Currently, there is no effective solution to address the failure issue in a predictable manner, despite the significant research efforts expended in this area.

It has been reported in the literature that HAp with nano-scale crystalline features and controlled porosity and pore size could promote osseointegration. A number of methods have been developed to deposit HAp on metal implants, such as electrophoretic deposition, sputter, dip coating, spin coating, and plasma spray. It has been shown, however, that it is very challenging to produce a crystalline HAp coating with desirable coating functional features, such as surface roughness as well as controlled pore size and porosity that are retained at nanoscale. In addition, it is also necessary for nano-HAp coatings to have good adhesion strength to metallic substrates and sufficient mechanical

properties for load-bearing conditions.

By using novel nano topographies, researchers have shown that nanostructured ceramics, carbon fibers, polymers, metals, and composites enhance cell functions; in particular, nanophase materials (materials with surface features less than 100 nm in at least one direction) promote osteoblast adhesion and calcium/ phosphate mineral deposition. Accordingly, nanophase materials show potential promise in improving orthopedic implant fixation. However, grain growth is one of the major issues for nanoparticle-based HAp coating when synthesized by using thermal techniques such as plasma or thermal spray methods. Additionally, brittleness and cracking are the other major issues associated with HAp coatings, though nanostructured HAp coatings are reported to be less susceptible to cracks. Typically, the cracks are due to residual stress and can cause de-bonding under external loading. As a recent development, it is reported that a textured (grooved surface, organized islands) HAp surface has shown preferentially regulated cell response, and reduced residual stresses and tendency to develop cracks. However, none of the current deposition technologies can be readily applied to achieve a coating that has spatially textured features of this type and a desired combination of passive and bioactive functions.

According to the results of a recent study, almost five times the compressive strength of bone has been achieved in bulk nanostructured HAp (879 MPa vs. 193 MPa for compacted bone), while providing roughly equivalent bending strength of bone (193 MPa vs. 160 MPa for bone), indicating the excellent potential of nanostructured HAp for dental and orthopedic implants. A nanostructured coating of HAp synthesized with an electrophoretic deposition technique showed improved adhesion and corrosion resistance for implants, though the synthesis technique experienced a shrinkage problem due to reduced particle size, leading to increased cracking susceptibility. A solution ripening technique has also been studied for minimizing this susceptibility. To address the HAp nanoparticle delivery in a hypersonic deposition, a mixture of nano-sized HAp particles and micro-sized Ti powder has been used so that the micro-sized powder served as a carrying medium. In addition, sol-gel was used for producing

coatings of nanoparticles of a bioactive glass (CaO.SiO2.P2O5) for increased bioactivity.

Of all these methods for HAp coating, each method has its own advantages over a specific processing window, but each one also has its limitations. Plasma spraying produces amorphous HAp that reduces implant durability. Also, in this process it is difficult to control particle size growth. It has been reported that electrophoretic deposition addresses the formation of amorphous HAp observed in the plasma spray process, but its follow-up consolidation process leads to an increase in cracking susceptibility due to accelerated drying shrinkage from reduced particle sizes. Also, this process is difficult to scale up. The supersonic rectangular jet impingement technique uses micron-sized titanium (Ti) powder as a carrier medium to deliver nanomaterials, which limits its direct application for nanopowders. Therefore, in addition to novel coatings, there is an equally important need for the development of new manufacturer-friendly processes for depositing nanoparticles for bio-implant coatings in general, and nanocomposite HAp coating in particular.

Zinc oxide (ZnO) has also been explored as a coating material for various biomedical applications. ZnO has been reported for its efficacy in producing an antimicrobial effect, with this effect being more pronounced for nanocrystalline ZnO. In addition, experimental results have indicated that nanophase ZnO increases osteoblast functions necessary to promote integration of orthopedic implants. To the inventors knowledge, however, ZnO has not been explored as a component of a multi-material coating for dental or orthopedic implants, or other biomedical applications.

For all the reasons set forth above, a simple and efficient method of producing a durable, high-quality coating for dental and orthopedic implants, which both promotes osseointegration and provides an anti-microbial effect, would be highly desirable.

Disclosure of the Invention

In certain aspects, the present invention is directed to a novel implant coating process, combining electrostatic spray coating (ESC) with a sintering

process to meet mechanical and biological requirements for next-generation dental and orthopedic implants. The coating process offers a high deposition rate, suitability for various composite coatings, compatibility with simple and complex geometries, flexibility, low energy consumption, and low cost. Experiments conducted by the inventors demonstrate that the application of this coating process may reduce or even eliminate the formation of amorphous phase HAp, which is soluble in body fluids and results in subsequent dissolution of the material before natural bone tissue integrates. The HAp nanocoatings fabricated by this coating process have the following benefits: improved adhesion strength prevents coating delamination; biomimetic chemistry to natural bone tissues (Ca/P ratio very close to natural bone); large effective surface areas enhance cell attachment and growth; nano-scale roughness enabled by nanoparticles of HAp promotes implant-tissue integration; nano-to-micron pores provide more anchor sites for inducing enhanced cell activities; a high resistance to scratching; and the highly crystalline HAp coating reduces HAp dissolution in body fluids.

While certain aspects of the present invention are directed to a coating incorporating HAp, other aspects incorporate a combination of nanocrystalline HAp and ZnO in an implant coating. Due to their compatibility and stability in composite form even at relatively high temperature, and their complementary properties in increasing osteoblast functions and antimicrobial activities, the result is a multi-functional coating for dental and orthopedic implants and other biomedical applications. The resulting coating is micro-patterned and has inter-connected nanopores, and is believed to offer osseointegration, antimicrobial activities, and a reduced tendency to form cracks.

In certain aspects, the coating incorporates antimicrobial nanostructured ZnO, with particle sizes of about 50 nm, and bioactive HAp, with particles sizes of about 100nm. The combination material is deposited in a textured form by use of an ESC process on, for example, a titanium implant surface. The multifunctional coating that results from the combination of textured nanostructured HAp and ZnO by use of ESC and a transient microwave sintering process facilitates nanoparticle deposition while retaining the nanostructured

features.

In one aspect, the invention is directed to an implant comprising a substrate and a coating material, wherein the coating material comprises HAp particles and ZnO particles, and wherein the coating material comprises a plurality of pores ranging from nano-scale pores to micro-scale pores.

In another aspect, the invention is directed to a coated implant for biomedical applications comprising a substrate and a coating, wherein the coating consists essentially of nano-sized HAp particles and nano-sized ZnO particles.

In another aspect, the invention is directed to an article comprising a coating and a substrate, wherein the coating comprises HAp particles arranged in a plurality of islands with a plurality of spaces dispersed therebetween.

In another aspect, the invention is directed to a method for manufacturing an implant comprising a substrate and a coating, wherein the coating comprises nano-sized HAp particles, the method comprising the steps of de-agglomerating the HAp particles, electrostatically spraying the HAp particles from a spray gun onto the substrate to form the coating, and sintering the implant whereby the coating is bound to the substrate, wherein the resulting coating comprises a plurality of pores with diameters in the range of nano-size to micro-size.

In another aspect, the invention is directed to a method for manufacturing an article comprising a substrate and a coating, the coating comprising nano-sized HAp particles and nano-sized ZnO particles, the method comprising the steps of de-agglomerating the particles, electrostatically spraying the particles from a spray gun onto the substrate to form the coating, and sintering the article.

These and other features, objects and advantages of the present invention will become better understood from a consideration of the following detailed description of the best mode for carrying out the invention, and the appended claims, in conjunction with the drawings as described following:

Brief Description Of Drawings

Fig. 1 is a functional schematic for the ESC system for deposition of

nanoparticles according to a preferred embodiment of the present invention.

Fig. 2a is a scanning electron microscope (SEM) micrograph depicting an HAp coating preform (before microwave sintering) on Ti substrates, shown at low magnification, according to a preferred embodiment of the present invention.

Fig. 2b is an SEM micrograph depicting an HAp coating preform (before microwave sintering) on Ti substrates, shown at medium magnification, according to a preferred embodiment of the present invention.

Fig. 2c is an SEM micrograph depicting an HAp coating preform (before microwave sintering) on Ti substrates, shown at high magnification, according to a preferred embodiment of the present invention.

Fig. 2d is a graph depicting energy-dispersive X-ray spectroscopy (EDX) results of HAp particles before the coating process according to a preferred embodiment of the present invention.

Fig. 2e is a graph depicting EDX results of HAp particles after deposition onto a Ti substrate according to a preferred embodiment of the present invention.

Fig. 2f is an SEM micrograph depicting an HAp nanocoating on a Ti substrate in cross-section according to a preferred embodiment of the present invention.

Fig. 3a is an SEM micrograph depicting an HAp coating after microwave sintering, shown at low magnification, according to a preferred embodiment of the present invention.

Fig. 3b is an SEM micrograph depicting an HAp coating after microwave sintering, shown at high magnification, according to a preferred embodiment of the present invention.

Fig. 3c is an SEM micrograph depicting an HAp coating after microwave sintering in cross-section according to a preferred embodiment of the present invention.

Fig. 3d is a graph depicting EDX results of an HAp nanocoating after microwave sintering according to a preferred embodiment of the present invention.

Fig. 3e is a graph depicting X-ray diffraction (XRD) results of an HAp nanocoating after microwave sintering according to a preferred embodiment of the present invention.

Fig. 4a is a bar graph depicting experimental results of human palatal mesenchymal cell attachment on HApTiP, TiP, HApTiM, and a control TCP surface according to a preferred embodiment of the present invention.

Fig. 4b is an SEM micrograph depicting cell morphology and cell interaction with an HAp-coated surface according to a preferred embodiment of the present invention.

Best Mode for Carrying Out the Invention

Two preferred embodiments of the invention will be discussed below, one involving an HAp coating and the other a composite HAp-ZnO coating, but the pre-deposition and deposition processes that will be described following are generally common to both. The techniques described herein allow (1) homogeneous mixing, (2) deagglomeration, and (3) deposition and texturing followed by sintering without significant grain growth. These processes are scalable and relatively low-cost.

In the preferred embodiments, the pre-deposition process begins with ball milling. In ball milling, two main collisions are involved, one between two interacting balls, and the second between a colliding ball and the wall of the container vial. Various parametric considerations are essential, including types of balls and vials to minimize cross contamination, milling time, and charge ratio. In the preferred embodiments, ceramic vials and balls are employed to avoid cross contamination, and an inert gas medium is introduced for the ball milling. Variable parameters will be the charge ratio of nanoparticulate powders, time of milling, and rotations per minute (RPM) of milling.

After milling, the nanoparticulates may be exposed to supersonic jet milling. A jet mill employs compressed air to produce powder particles or de-agglomerate particle clusters into sizes less than a few microns. In the jet milling process, a mixing of air and particles takes place in a high velocity,

turbulent flow and is characterized by significantly non-equilibrium phase velocity. This mixing process creates particle-to-particle, cluster-to-cluster impact, which refines the powder particles and partially helps to de-agglomerate large clusters of particles held mainly by adhesion forces (Van der Waals forces including dipole/dipole, dipole/non-polar, and non-polar/non-polar). Further, pulverization occurs in the engineered central chamber as the mixture is driven at near sonic velocity around the perimeter of the chamber by multiple air jets, leading to additional reduction of particle or cluster size. The process allows recirculation of over-sized particles or clusters, enhancing the incidence and the effect of collisions between particles of the process material itself, and between particles and the chamber. As particles or clusters are reduced in size and progressively lose mass, they move toward the central discharge port. Typically, in addition to air or gas quality and the physical properties (density and hardness) of the process material itself, pressure for the pushing nozzle and grinding nozzles, and mass feed rate of powder, are the major parameters affecting the resulting powders.

After the material is ball milled and then supersonic jet milled, it can be used as a feed material to the ESC unit. ESC is a process involving physical spray of nano and/or micro particulates in powder or in suspension forms. It various forms, it is widely used in the paint industry to coat materials with pigments. As shown schematically in Fig. 1, the powder particles or suspension will be charged with the same electrical polarity as they are ejected out of the spray gun and are exposed to an electrostatic field. The field is generated by a point electrode with applied voltage of typically a few tens of kilovolts (e.g., - 60 ~ -80 kV). The charged particles follow the electrostatic field lines in 3D and deposit on the grounded 3D substrates conformally. In addition, this design may offer the capability to align the nanoparticles and pattern them in a specific direction based on templates for desired properties with the assistance of an electrostatic field and shadow mask. A pre-designed shadow mask made of steel pre-form is typically aligned conformally with the Ti implant substrate. This mask is

introduced in the path of trajectory of the charged nanoparticles on the way to the electrically grounded Ti implant substrate. Typically, one can deposit lines and pads as small as 100 μm in width. Optionally, an array of lines and circular pads as the starting templates can be used. This patterning will allow a further increase in the surface area while at the same time arriving at a solution to achieve intimate mechanical integrity and reliability of the coating. Further, this may provide an interconnected network of x-y axes microchannels and enhanced "mobility" of ions in the vicinity of the implant.

Another important point of ESC deposition is process control for a given material. The resulting coating thickness and uniformity are determined by material (powder or liquid suspension) feeding mass, the electrical voltage applied to the electrode, the electrode-to-substrate distance, and the main air pressure. As a combination of physical properties of the particles and parameters of the process, the charge-to-mass (q/m) ratio is an important indication of how well the particles are charged and the resulting coating efficiency. Normally, optimization is required for the process to achieve uniform deposition. Feeding mass, electrical voltage of the point electrode, mask pattern, and substrate to mask to point-electrode distance are variable parameters to achieve uniform coating thickness up to 50 μm.

Other types of coating processes may be used in alternative embodiments either in lieu of or in addition to the ESC process. For example, ultrasonic spray coating may be employed, either in place of ESC or as a post-deposition second coating technique. ESC hybrids and ESC spin-offs may be employed. In addition, multiple ESC processes may be used to achieve multiple coatings in various embodiments.

A special coated-part handling fixture may be used as the patterned nanopowder is held together on the Ti implant by electrostatic forces and needs careful handling before sintering. Microwave sintering can be performed using microwave radiation (about 2.45 GHz). In microwave sintering, heating of an isothermal disc of silicon carbide is achieved by internal absorption on which the coated representative implant substrate is

placed. One can achieve high temperatures (up to 1000-1 500^{0}C) and variable rapid heating rates and fast sintering time (as little as 5-1 0 minutes) for HAp coating as compared to traditional thermal heating. Use of traditional thermal heating or infrared (IR) heating poses a challenge in nanomanufacturing due to the extended time and temperature spectra allowing extended diffusion and grain growth. Nevertheless, in alternative embodiments other sintering methods, such as but not limited to pulsed infrared (IR) and laser sintering, may be employed. These sintering processes may be employed globally or selectively on the coated article. For example, local sintering could be employed if the coating is desired on only a portion of the article; after sintering, the unsintered portion of the coating could be easily removed, resulting in an article that is only partially coated.

In a first preferred embodiment for preparing a coating for a dental or orthopedic implant using the deposition techniques described above, HAp nanoparticles were used as the sole coating material, without the addition of other agents. The HAp nanoparticles are generally electrically insulating in nature and can carry the static surface charge over a distance of a few tens of centimeters. The HAp particles were charged when they exit the powder spray gun, and follow the electric field lines toward the grounded objects (Ti substrates in this example) and formed a uniform and conformal coating preform. The coating preform can be consolidated with desired chemistry and surface morphology, and reasonable adhesion achieved, by the use of a variety of processes, such as laser. The HAp coating preform is then sintered in a microwave furnace. The sintering of HA-coated Ti implants is performed in an air environment in order to achieve desirable nano-HA chemistry (Ca/P ratio of 1.60 ± 0.06 to mimic natural bone mineral). In one set of examples, the parameters for the sintering were set at a temperature of 1000-1 300 ^{0}C for 5-20 minutes.

The deposited HAp coating was characterized for grain size and pore size using an environmental scanning electron microscope (ESEM), the chemical composition and Ca/P ratio using EDX analysis, and crystalline

phases using XRD analysis. Such HAp coating was further characterized for its mechanical properties, such as adhesion strength (scratch resistance), hardness, and toughness. The microscratch test method is commonly used to measure the critical load of a coating, which is directly correlated to the coating adhesion. Microscratch testing according to ASTM C1624 was carried out for HA-coated samples produced as stated above. The diamond stylus was drawn on top of each sample by using an increasing load, between 0.03N to 30 N, at constant velocity of 0.75 mm/min, until a well-defined failure occurred. The normal load under which the de-lamination of the coating from the Ti implants occurred is defined as critical load, which is typically determined by optical observation in combination with acoustic emission technique.

Human palatal mesenchymal cells were cultured in MEM Eagle Medium (EMEM) with 10% fetal bovine serum (FBS). The specimens of four different surfaces—textured titanium (TiP), HAp coating on textured titanium (HApTiP), HA coating on machined titanium (HApTiM), and a control surface (TCP) were ultraviolet (UV) sterilized for 10 minutes on each side. SEM was utilized for the study of cell morphology and its interaction with the coating surfaces after 72 hours of culture. Early matrix expression was measured using a key transcription factor for bone differentiation, cbfa-1 , an early marker for the capacity for organic mineral formation, alkaline phosphatase, and a late differentiation matrix-related protein, osteocalcin.

Figure 2 shows the results of HAp nanocoatings deposited by the ESC system described above before the microwave sintering. The HAp coating surface morphology was characterized using SEM, with different magnifications of the resulting surface shown in Figs. 2a-2c. The chemical composition of the HAp coating before microwave sintering was characterized using EDX technology. As shown in Figure 2e in comparison with the original HAp particles as shown in Fig. 2d, the chemical composition of the deposited HAp coating preform is consistent with that of the as-received HAp particles. The coating thickness variation was characterized using cross sections, and statistical results showed the thickness to be

about 60 ± 2.1 μm. A representative cross section of the deposited HAp nanocoating is shown in Fig. 2f.

Due to the high surface area (and thus large number of grain boundaries) of nanoparticles, size growth and chemistry control are two major challenges in sintering of the deposited HAp nanoparticles. Typically, the size growth rate is inversely proportional to grain diameter, thus, the grain growth of a sintered product from loose powder strongly depends on the initial particle average size (at time zero), and the duration of the sintering process. In addition, the onset of sintering of nanoparticles occurs at a much lower temperature partially because of high surface area, leading to better heat conduction and absorption. Therefore, a transient heating process is needed. To address this issue, sintering in a microwave furnace (3kW, 2.45 GHz) was performed on deposited HAp nanoparticles. The sintered HAp not only retains particle size with good adhesion, but also keeps the chemistry (ratio of Ca/P) desired for implant applications.

After the microwave sintering, the results demonstrated that a nanocrystalline HAp coating with a grain size from 50 to 300 nm and a gradient of nano-to-micron pore sizes was fabricated successfully using this novel coating process, as shown in Figs. 3a-3c. The controlled nano-scale grain size and a gradient of pore sizes are believed to promote bone cell functions and to facilitate bone healing. EDX results shown in Fig. 3d demonstrate that the nano-HAp coating had a Ca/P ratio of about 1.6, very close to natural bone, and thus favorable for bone cell growth. XRD results confirmed that the nano-HAp coating was highly crystalline after sintering, as shown in Fig. 3e.

Optical examination at the end of the microscratch test coupled with both acoustic emission response and fhctional properties variation during the test provided insight into the coating adhesion. Microscratch test results showed that the critical load of coating de-lamination reached as high as 10 N.

Human palatal mesenchymal cell attachment on HAp nanocoatings were very high, with an average of 88.20 ± 2.03 % for the HATiP and 86.5 ±

1.35 % for HATiM, as shown in Fig. 4a, which suggests nano crystalline and quasi-stoichiometric HAp surfaces were capable of high degrees of cell attachment, and did not result in early cytotoxic cellular necrosis. Cell differentiation assays indicated that HAp nanocoatings were capable of high levels of cell adhesion, which, in turn, led to high level of early osteoblast (bone forming cells) gene expression. Initial in vitro results suggested positive effects of HAp nanocoatings on cell functions. Fig. 4b depicts cell morphology and cell interaction with the HAp-coated surface.

In a second preferred embodiment of the present invention, a homogenous mixture of HAp and ZnO nanoparticles are applied as a composite to a surface for implants and other biomedical applications. In overview, the process involves the following steps: (1) create the mixture of ZnO and HAp nanoparticles, (2) fluidization and deagglomeration of the nanoparticle mixture, (3) deposition of multifunctional nanoparticles and texturing of the coating, and (4) binding of the nanoparticulate coating while keeping phase, structure and texture intact.

A number of antimicrobial materials choices could be used in alternative embodiments. Silver (Ag), for example, is well known as an anti-microbial agent. ZnO is, however, used in the preferred embodiment for the following reasons: (1) zinc is well demonstrated to work in the human body to enhance the immune response; (2) ZnO in a host titanium dioxide (TiO_2) ceramic matrix is an effective antimicrobial agent; (3) ZnO has been found to perform in an HAp matrix to enhance densification of the HAp composite ceramic, and it will allow better mechanical strength and integrity through intra-granular bonding, and (4) the low melting temperature of silver (about 960^0C) puts serious limitations on the recommended sintering of the host HAp matrix, where sintering temperature is much higher (about 1250^0C). This melting temperature mismatch may result in serious restrictions, and force a sacrifice of the quality of the bonding due to a lack of intra-granular bonding.

Texturing refers to a porous network in the coating as well as an intentionally deposited x-y pattern. Such texturing is commonly seen in

nature. For example, microbial symbiosis and air breathing in soil is accomplished in a porous network of soil particles in a fertile ground, and the surface pattern on a lotus leaf along with nano hair offers superhydrophobicity. A microscale pattern with a nanoscale porous network of channels in the coating, such as texturing, coupled with the ZnO on HAp coated orthopedic materials, enhances osseointegration, significantly reduces bacteria count, and allow excellent mechanical adhesion between implant and bone. An embodiment of the present invention includes the HAp-ZnO nanocomposite coating formed into small and organized islands such that residual stresses and cracking due to shrinkage and thermal mismatch may be reduced. The patterned HAp-ZnO nanocomposite can also promote cell organization through contact guidance, topology, and its unique cell interactions.

As may be seen from the discussion above, texturing relates to two important surface features, namely (1) an interconnected network of nano- and micro-sized pores (channels) in x-y-z axes formed during the spray deposition and microwave sintering of the HAp-ZnO nanoparticles composite, and (2) an array of microstructures (e.g., a pattern of square shaped microstructures, about 250x250 μm^2 with 50-100 μm spacing between square structures) of HAp-ZnO nanocomposite particulate matrix intentionally deposited using ESC and a shadow mask. It is believed that this structure will result in a multifunctional interface, where bone tissues can see nanostructure, with further enhancement due to texturing surface-to-volume ratio along with HAp-ZnO nanochemistries to obtain enhanced osseointegration and antimicrobial responses, and at the same time discontinuous deposition of ceramic brittle coating, particularly on large area and/or intricate implant parts. In addition, it is believed that this textured coating may allow integration of other desired compounds, such as drugs, in particular peptide drugs, whereby the textured surface acts as a sacrificial or permanent drug delivery system. While the pattern in the texture may create microchannels for drug delivery, both the porous structure and the texture may contribute to the drug delivery aspect of the various embodiments.

In alternative embodiments, various combinations of materials and coatings may be used, in single or multiple coatings of an implant or other article. Materials employed may include, for example, HAp, ZnO, Ag, gold (Au), and titanium dioxide (TiO_2). These materials may be used in initial coatings or subsequent coatings, either pre- or post-sintering. For example, in a few illustrative alternative embodiments, a first HAp-based coating may be coating with a second HAp coating, or with an overcoating of Ag. Other post-sintering applications could include therapeutic drugs, particularly peptide drugs, for purposes of drug delivery. The drugs may be applied in various manners, including ESC, vapor deposition, and dipping.

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13. Zhang, Zongtao, Dunn, Mattew F., Xiao, T.D., Tomsia, Atoni P., and Siaz, E., *Materials Research Society Proceedings,* 703, pp. 291-296 (2002).

As used herein, "comprising" is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As used herein, "consisting of" excludes any element, step, or ingredients not specified in the claim element. As used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim. Any recitation herein of the term "comprising", particularly in a description of components of a composition or in a description of elements of a device, is understood to encompass those compositions and methods consisting essentially of and consisting of the recited components or elements. The invention illustratively described herein suitably may be practiced in the absence of any element or elements,

limitation or limitations which is not specifically disclosed herein.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims. Thus, additional embodiments are within the scope of the invention and within the following claims.

In general the terms and phrases used herein have their art-recognized meaning, which can be found by reference to standard texts, journal references and contexts known to those skilled in the art. The preceding definitions are provided to clarify their specific use in the context of the invention.

All references cited herein are hereby incorporated by reference to the extent that there is no inconsistency with the disclosure of this specification.

The present invention has been described with reference to certain preferred and alternative embodiments that are intended to be exemplary only, and not limiting to the full scope of the present invention as set forth in the appended claims.

Claims

1. An implant comprising a substrate and a coating material, wherein the coating material comprises HAp particles and ZnO particles, and wherein the coating material comprises a plurality of pores ranging from nano-scale pores to micro-scale pores.

2. The implant of claim 1, wherein the HAp particles have a diameter in the range of about 50 nm to about 300 nm.

3. The implant of claim 2, further comprising a second coating material.

4. The implant of claim 3, wherein the second coating material comprises a material selected from the group consisting of HAp, ZnO, Ag, Au, and TiO_2.

5. The implant of claim 1, further comprising a therapeutic drug applied to the coating.

6. The implant of claim 1, wherein the coating material comprises a surface texture.

7. The implant of claim 1, wherein the coating material comprises a pattern of islands comprising HAp particles and ZnO particles, with spaces therebetween.

8. The implant of claim 7, wherein the islands comprise a side length of about 250 μm.

9. The implant of claim 6, wherein the spaces comprise have a length in the range of about 50 μm to about 100 μm.

10. The implant of claim 1, wherein the coating material comprises a critical load of delamination of at least 10 N.

11. The implant of claim 1, wherein the coating material comprising a surface area configured to bond to a plurality of cell tissues along at least 85% of the surface area.

12. A coated implant for biomedical applications comprising a substrate and a coating, wherein the coating consists essentially of nano-sized HAp particles and nano-sized ZnO particles.

13. The coated implant of claim 12, further comprising a second coating.

14. The coated implant of claim 13, wherein the second coating comprises a material selected from the group consisting of HAp, ZnO, Ag, Au, and TiO_2.

15. The coated implant of claim 12, wherein the coating has a critical load of delamination of at least 10 N.

16. The coated implant of claim 12, wherein the coating comprises a textured surface.

17. The coated implant of claim 12, wherein the coating comprises a plurality of islands comprising nano-sized particles.

18. The coated implant of claim 17, wherein the islands have a side length of about 250 μm.

19. The coated implant of claim 17, wherein a distance between the islands is in the range of about 50 μm to about 100 μm.

20. The coated implant of claim 17, further comprising a therapeutic drug integrated with the textured surface.

21. The coated implant of claim 12, wherein the coating comprises a plurality of pores.

22. The coated implant of claim 21, wherein the pores comprise a range of sizes.

23. The coated implant of claim 22, wherein the pore sizes range from nano-scale sizes to micro-scale sizes.

24. The coated implant of claim 22, wherein the pore sizes range from less than 100 nm to more than 1 μm.

25. An article comprising a coating and a substrate, wherein the coating comprises HAp particles arranged in a pattern of islands with spaces dispersed therebetween.

26. The article of claim 25, wherein the HAp particles comprise a diameter in the range of about 50 nm to about 300 nm.

27. The article of claim 25, further comprising a therapeutic drug integrated with at least a subset of the plurality of islands.

28. The article of claim 25, wherein the coating has a critical load of delamination from the substrate of at least 10 N.

29. The article of claim 25, wherein the islands comprise a side length of about 250 μm.

30. The article of claim 29, wherein the spaces between the islands have a

length in the range of about 50 μm to about 100 μm.

31. The article of claim 25, wherein the coating comprises a plurality of pores.

32. The coated implant of claim 31, wherein the pore sizes range from nano-scale sizes to micro-scale sizes.

33. The coated implant of claim 32, wherein the pore sizes range from less than 100 nm to more than 1 μm.

34. The coated implant of claim 25, further comprising a drug applied to the coating.

35. A method for manufacturing an implant comprising a substrate and a coating, wherein the coating comprises nano-sized HAp particles, the method comprising the steps of de-agglomerating the HAp particles; spraying the HAp particles from a spray gun onto the substrate to form the coating; and sintering the implant whereby the coating is bound to the substrate, wherein the resulting coating comprises a plurality of pores with diameters in the range of nano-size to micro-size.

36. The method of claim 35, wherein the sintering step comprises microwave sintering.

37. The method of claim 35, wherein the de-agglomerating step comprises the step of ball milling.

38. The method of claim 35, wherein the de-agglomerating step comprises the step of jet milling.

39. The method of claim 38, wherein the de-agglomerating step further comprises the step of ball milling.

40. The method of claim 35, wherein a mask is introduced between the spray gun and the substrate before the electrostatically spraying step.

41. The method of claim 35, wherein the HAp particles comprise a diameter in the range of about 50 nm to about 300 nm.

42. The method of claim 35, wherein the resulting coating comprises a textured surface.

43. The method of claim 35, wherein the coating comprises a plurality of islands of nano-sized particles.

44. The method of claim 43, wherein the islands comprise a side length of about

250 μm.

45. The method of claim 44, wherein a distance between the islands is in the range of about 50 μm to about 100 μm.

46. The method of claim 35, wherein the pores range in diameter from less than 100 nm to more than 1 μm.

47. The method of claim 35, further comprising the step of infiltrating the coating with a compound operable to provide a compound when the implant is implanted into a living organism.

48. The method of claim 35, wherein said spraying step is performed by means of a spraying method selected from the group consisting of ESC, an ESC hybrid method, and an ESC spin-off method.

49. A method for manufacturing an article comprising a substrate and a coating, the coating comprising nano-sized HAp particles and nano-sized ZnO particles, the method comprising the steps of de-agglomerating the particles; spraying the particles from a spray gun onto the substrate to form the coating; and sintering the article.

50. The method of claim 49, further comprising the step of introducing a drug to the coating.

51. The method of claim 50, wherein the coating comprises pores, and the introducing step comprises the step of introducing the drug into the pores.

52. The method of claim 49, wherein the coating has a critical load of delamination from the substrate of at least 10 N.

53. The method of claim 49, wherein the coating comprises a textured surface.

54. The method of claim 49, wherein the coating comprises a plurality of islands comprised of HAp particles and ZnO particles.

55. The method of claim 54, wherein the islands comprise a side length of about 250 μm.

56. The method of claim 54, wherein a distance between the islands is in the range of about 50 μm to about 100 μm.

57. The method of claim 49, wherein the coating comprises a plurality of pores with diameters ranging from nano-scale sizes to micro-scale sizes.

58. The method of claim 57, wherein the pore diameters range from less than

100 nm to more than 1 μm.

59. The method of claim 49, wherein said spraying step is performed by means of a spraying method selected from the group consisting of ESC, an ESC hybrid method, and an ESC spin-off method.

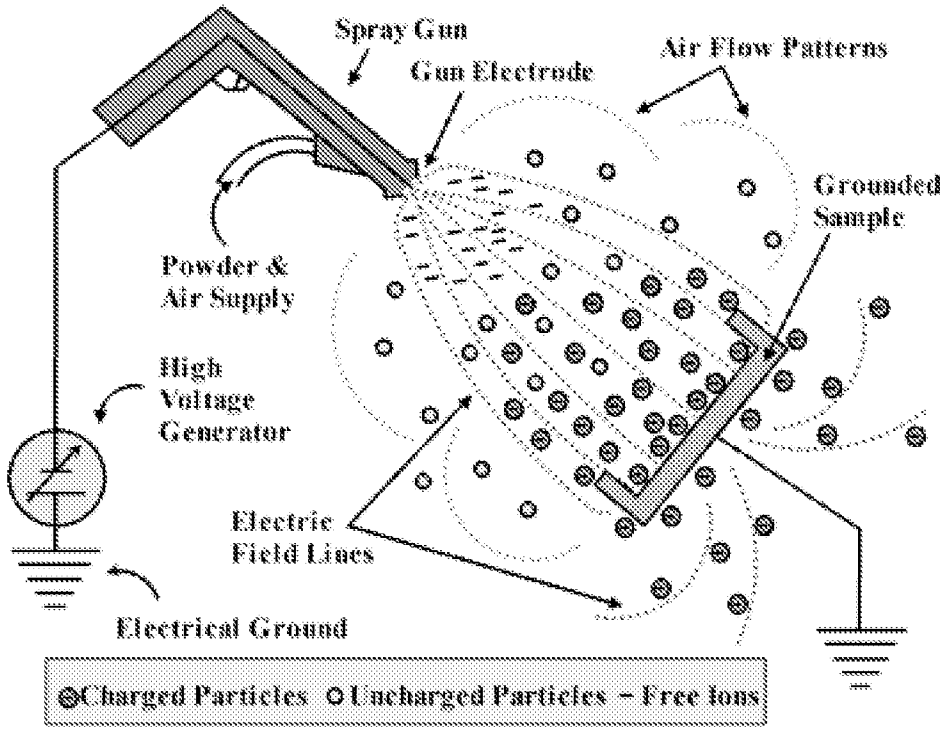

Spray Gun
Gun Electrode
Air Flow Patterns
Grounded Sample
Powder & Air Supply
High Voltage Generator
Electric Field Lines
Electrical Ground
Charged Particles
Uncharged Particles
Free Ions

Fig. 1

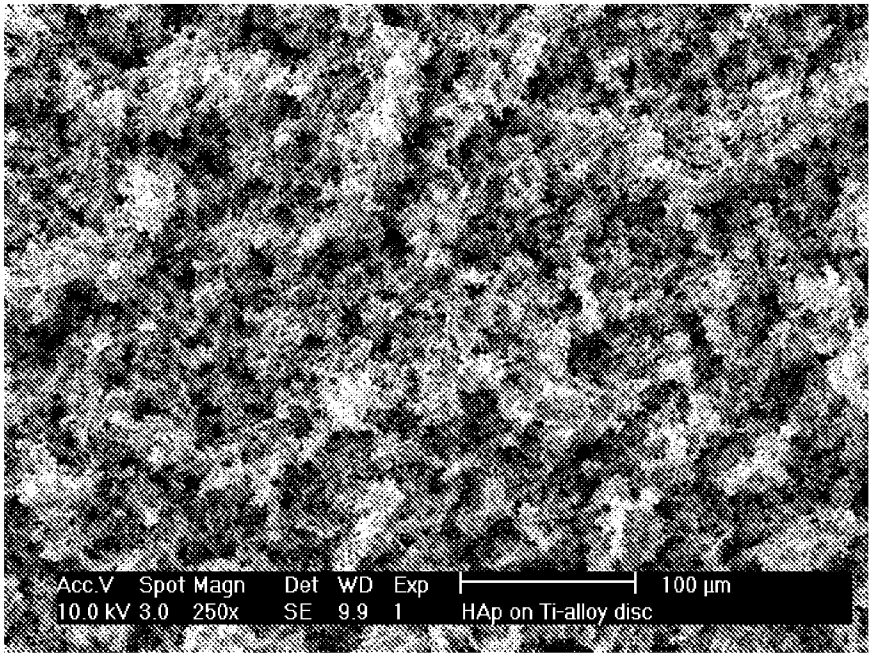

Acc.V Spot Magn Det WD Exp 100 µm
10.0 kV 3.0 250x SE 9.9 1 HAp on Ti-alloy disc

Fig. 2a

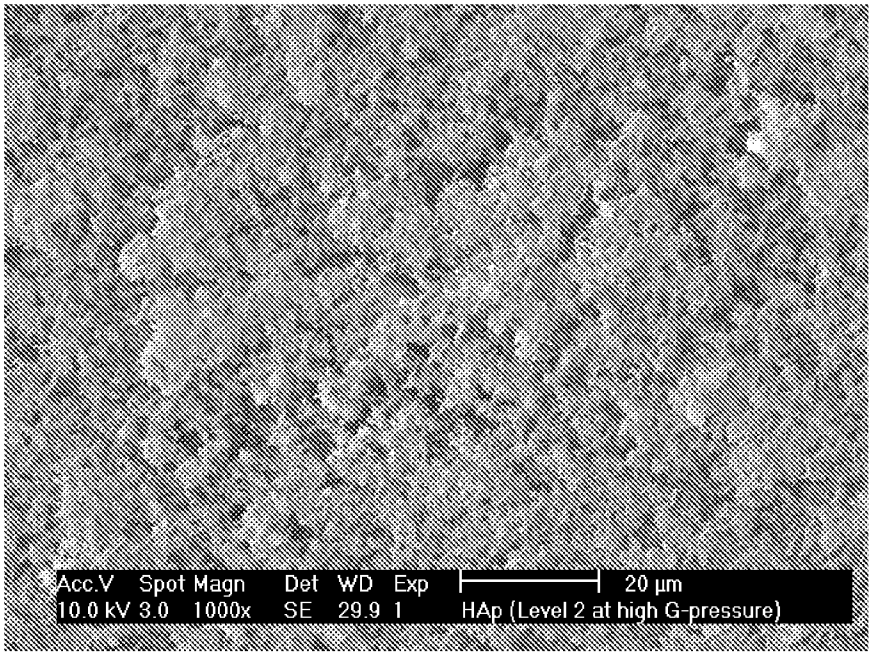

Acc.V Spot Magn Det WD Exp 20 µm
10.0 kV 3.0 1000x SE 29.9 1 HAp (Level 2 at high G-pressure)

Fig. 2b

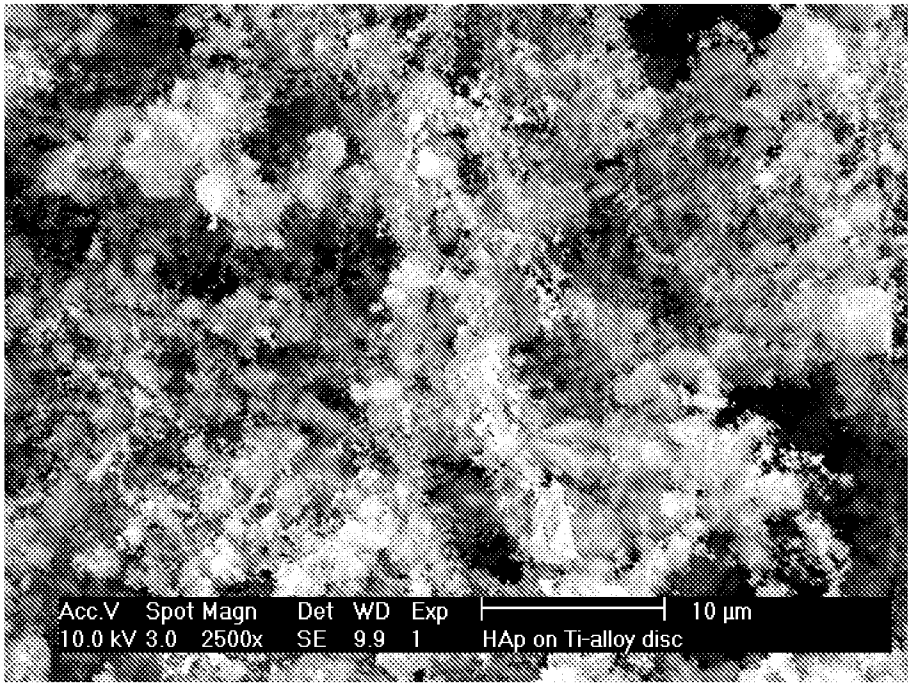
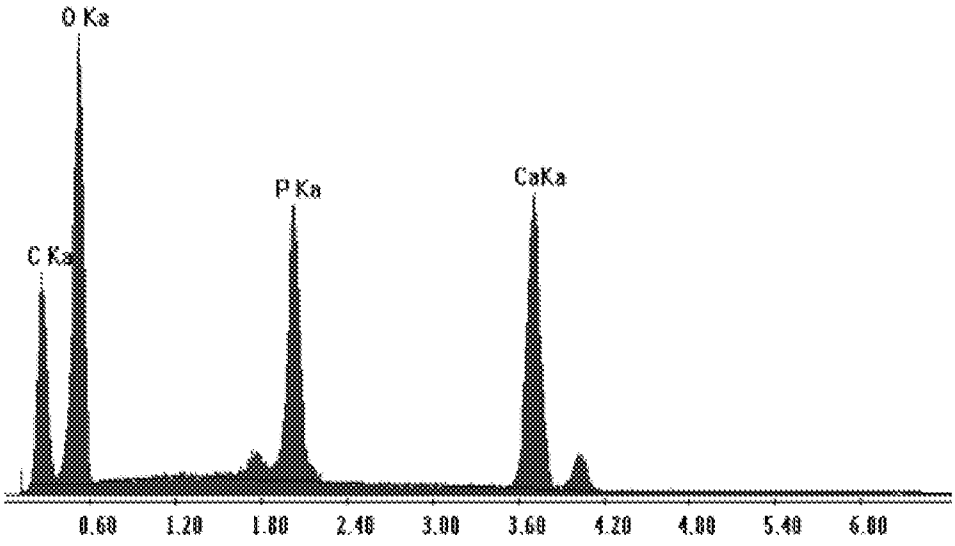

Acc.V Spot Magn Det WD Exp 10 µm
10.0 kV 3.0 2500x SE 9.9 1 HAp on Ti-alloy disc

Fig. 2c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C Ka
P Ka
CaKa
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1.80
2.40
3.00
3.60
4.20
4.80
5.40
6.00

Fig. 2d

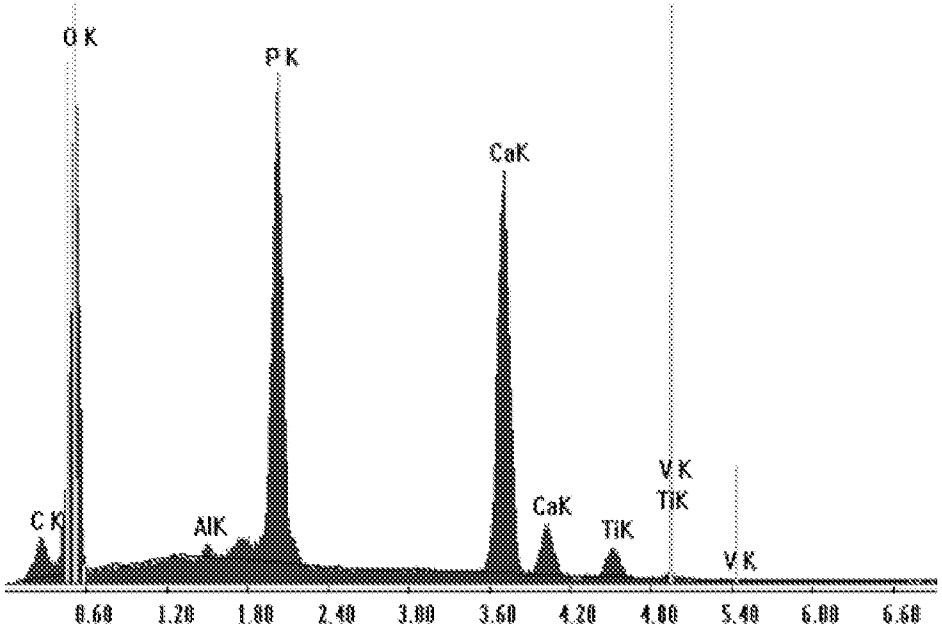

O K
P K
CaK
V K
Ti K
C K
Al K
CaK
Ti K
V K
0.60
1.20
1.80
2.40
3.00
3.60
4.20
4.80
5.40
6.00
6.60

Fig. 2e

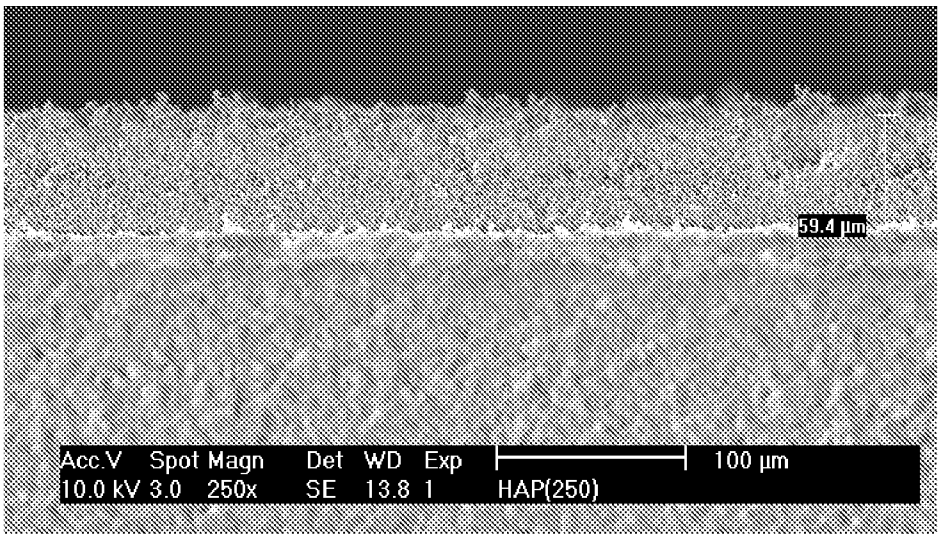

59.4 µm
Acc.V Spot Magn Det WD Exp
10.0 kV 3.0 250x SE 13.8 1
100 µm
HAP(250)

Fig. 2f

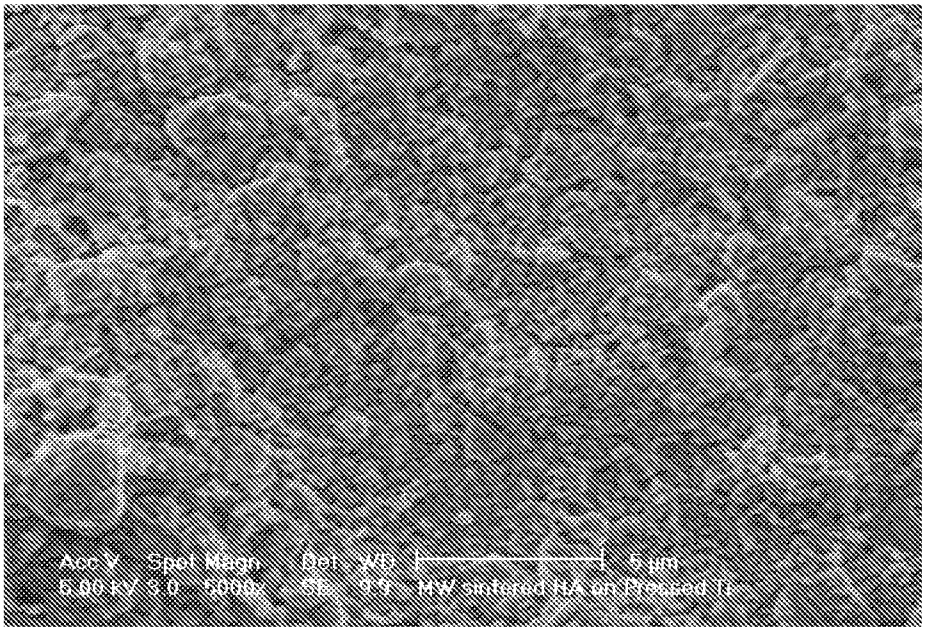

Acc.V Spot Magn Det WD 9 µm
6.00 kV 3.0 5000x SE 9.1 MW sintered HA on pressed Ti

Fig. 3a

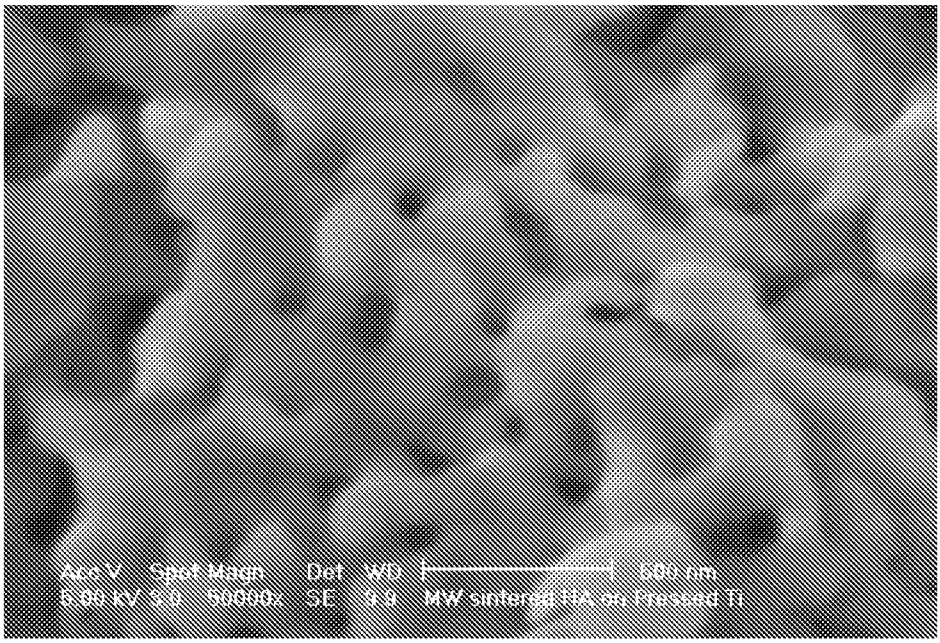

Acc.V Spot Magn Det WD 60 µm
6.00 kV 3.0 500x SE 9.1 MW sintered HA on pressed Ti

Fig. 3b

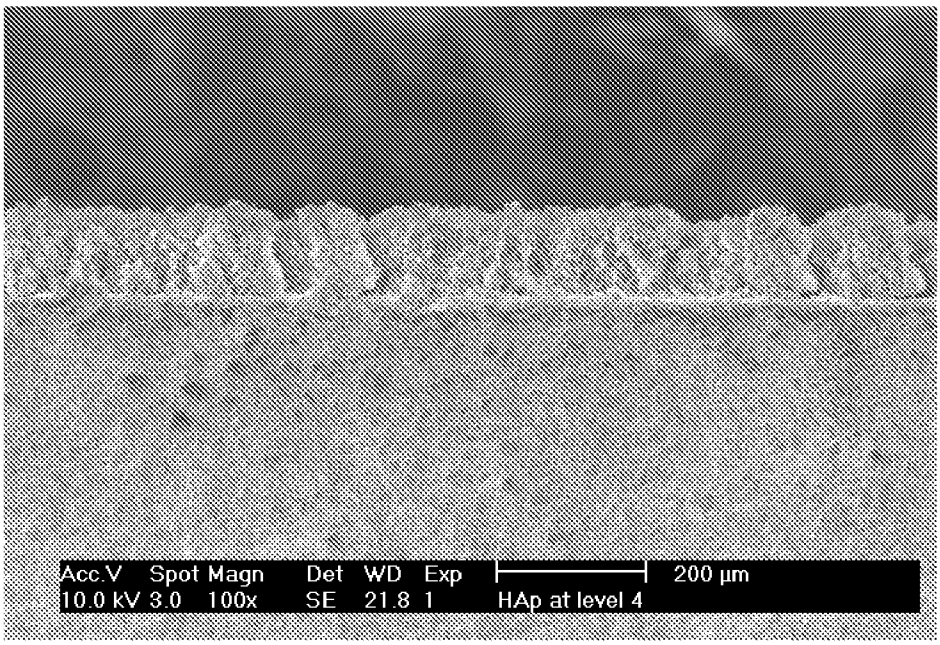
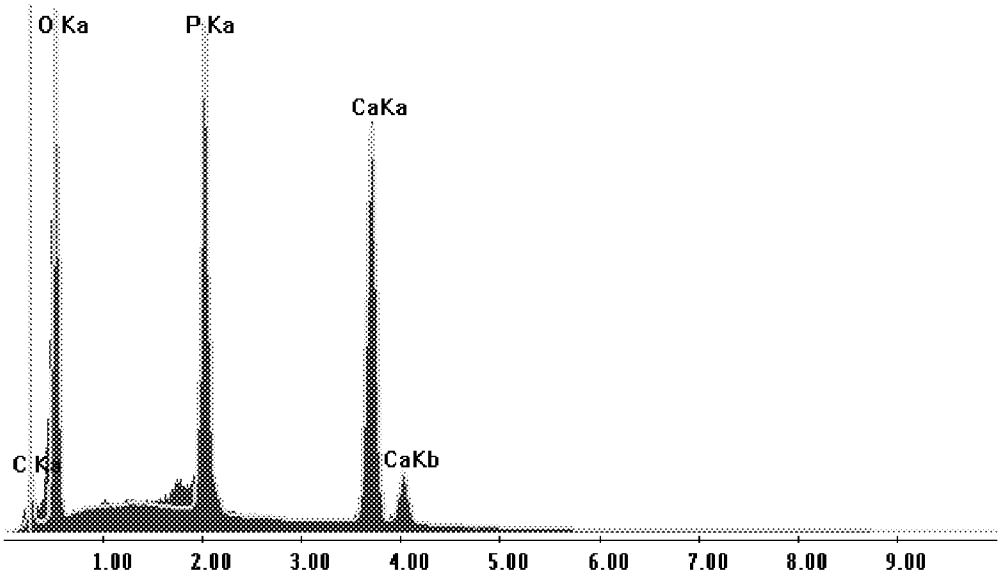

Acc.V Spot Magn Det WD Exp
10.0 kV 3.0 100x SE 21.8 1
200 µm
HAp at level 4

Fig. 3c


O Ka
P Ka
CaKa
C Ka
CaKb
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2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00

Fig. 3d

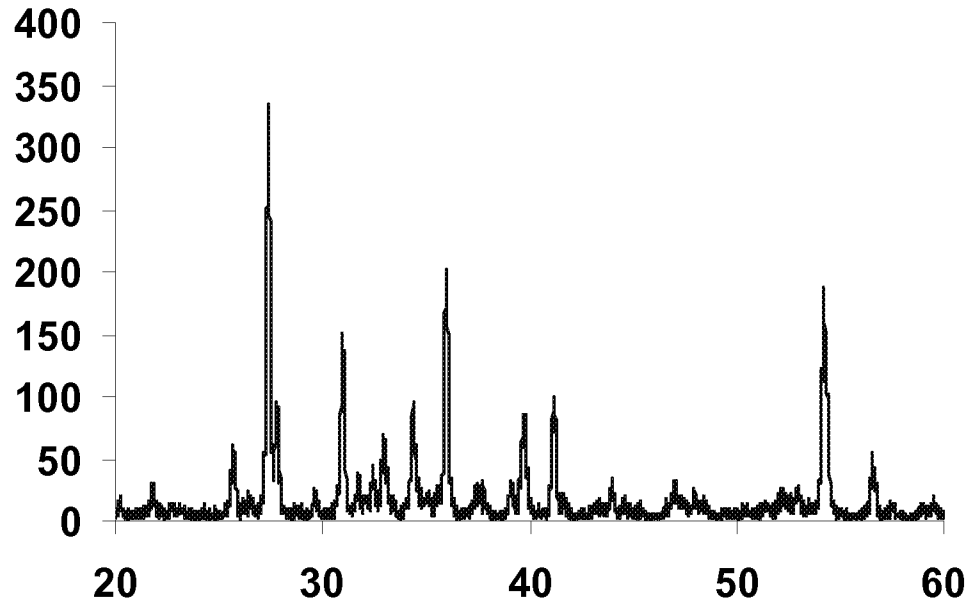
400
350
300
250
200
150
100
50
0
20
30
40
50
60

Fig. 3e

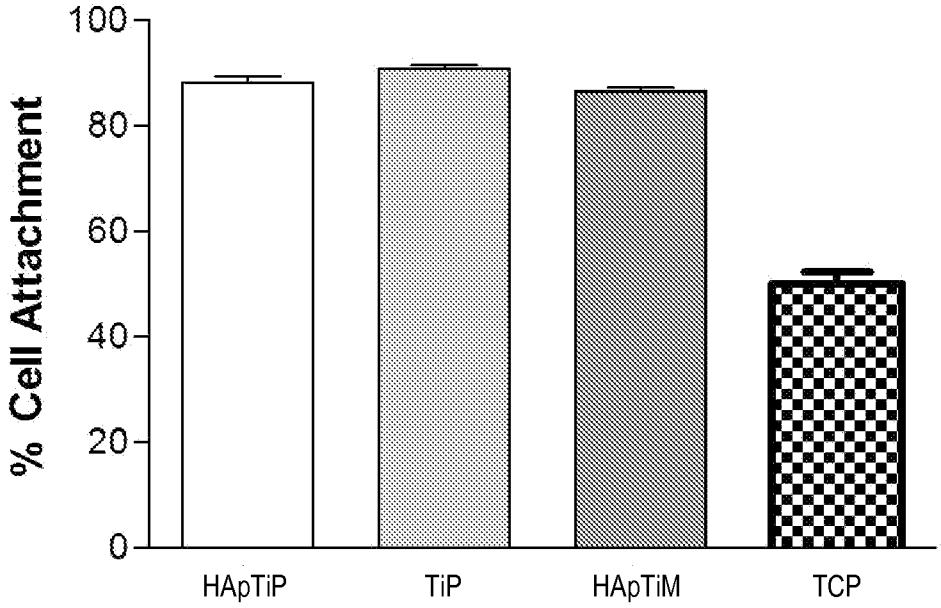
% Cell Attachment
100
80
60
40
20
0
HApTiP
TiP
HApTiM
TCP

Fig. 4a

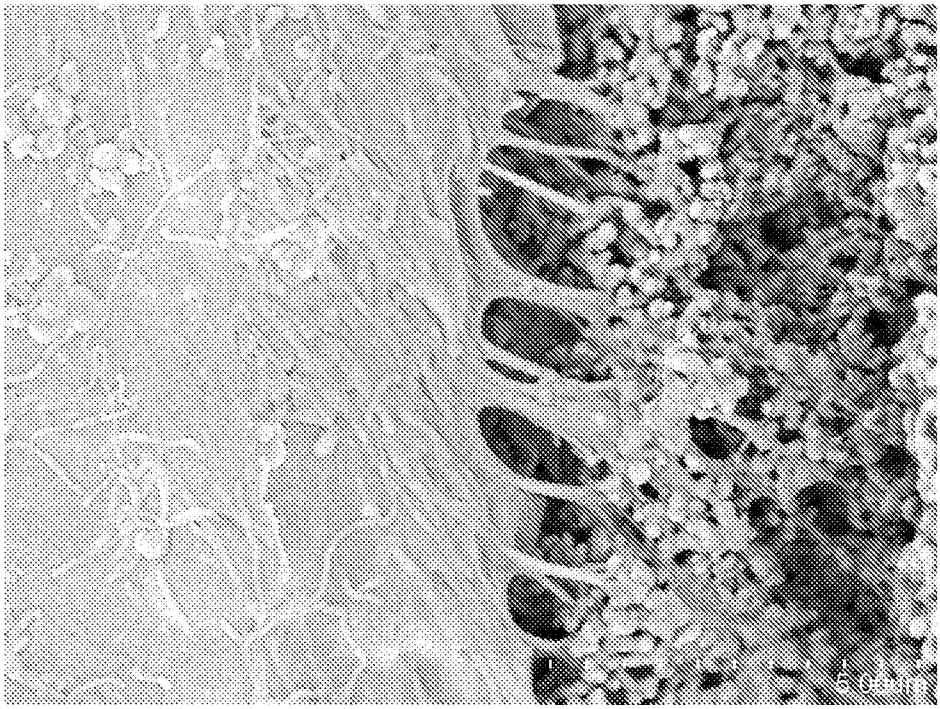

Fig. 4b

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 10/46158

A CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61 L 27/32 (201 0.01)
USPC - 427/2 27
According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8) - A61L 27/32 (2010 01)
USPC - 427/2 27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST (PGPB, USPT,USOC, EPAB.JPAB) Terms - Zinc ZnO hydroxyapatit β nano nanoparticle nanosphere nanorod nanometer implant bone pores porous porosity electrostatic spray gun mill milling Malshe
Google - nanostructured hydroxyapatite ZnO coating implants (pores OR porous) spray-gun

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X --- Y	US 2008/0243231 A1 (FLANAGAN, ET AL) 02 October 2008 (02 10 2008), para [001 1], [0060]-[0061], [0070]-[0075], [01 12], [01 15]	1-6, 10 --- 7-9, 11, 40-41
Y	US 2006/0159916 A1 (DUBROW, ET AL) 20 July 2006 (20 07 2006), para [0183], [0193]	7-9, 43-45
Y	US 2007/0142916 A1 (OLSON, JR , ET AL) 21 June 2007 (21 06 2007), para [0032]	11
Y	US 2006/0122706 A1 (LO) 08 June 2006 (08 06 2006), paras [001 1], [0018]-[0019], [0026]-[0028], [0037], [0040]	35-48
Y	US 6,607,782 B1 (MALSHE, ET AL) 19 August 2003 (19 08 2003), col 11, ln 35-43	35-48
Y	US 2005/0084608 A1 (YADAV, ET AL) 21 Apπl 2005 (21 04 2005), para [0059]	37-39

[ ] I Further documents are listed in the continuation of Box C

*	Special categories of cited documents	"T"	later document published after the international filing date or pno πty date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"x"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent but published on or after the international filing date		
' L"	document which may throw doubts on pno πty claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	uγ .,	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	•<£••	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2010 (16 11 2010)	**06 DFC 7Mf)**
Name and mailing address of the ISA/US Mail Stop PCT, Attn ISA/US, Commissioner for Patents P O Box 1450, Alexand πa, Virginia 22313-1450 Facsimile No 571-273-3201	Authorized officer Lee W Young PCT Helpdθsk 571 272-4300 PCT OSP 571-272 7774

Form PCT/ISA/2 10 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 10/46158

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 ☐ **Claims Nos**
because they relate to subject matter not required to be searched by this Authority, namely

2 **D** Claims Nos
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3 **D** Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authoπty found multiple inventions in this international application, as follows
Group I claims 1-1 1 and 35-48

Group II claims 12-24 and 49-59

Group III claims 25-34

see extra sheet for details

1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2 ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees

3 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos

4 ☒ No required additional search fees were timely paid by the applicant Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos
1-1 1 and 35-48

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation

☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No

PCT/US 10/46158

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13 1

Group I claims 1-11 and 35-48 directed to an implant comprising a substrate and a coating material wherein the coating material comprises HAp and ZnO particles, with nano to micro-scale pores, and a method of making the implant

Group II claims 12-24 and 49-59 directed to a coated implant comprising a substrate and a coating wherein the coating consists essentially of nano-sized HAp and ZnO particles, and a method of making the implant

Group III claims 25-34 directed to an article compnsing a coating and a substrate wherein the coating comprises HAp particles arranged in a pattern of islands

The inventions listed as Groups I ? III do not relate to a single general inventive concept under PCT Rule 13 1 because, under PCT Rule 13 2, they lack the same or corresponding special technical features for the following reasons

Groups II and III do not include the inventive concept of nano to micro-scale pores, as required by Group I

Groups I and III do not include the inventive concept of nano-sized HAp and ZnO particles, as required by Group II

Groups I and II do not include the inventive concept of HAp particles arranged in a pattern of islands, as required by Group III

The groups share the technical features of an implant comprising a substrate and a coating material wherein the coating material comprises nano-sized HAp and ZnO particles However, this shared technical feature does not represent a contribution over the prior art of US 2007/0259181 A1 to Furuzono et al (8 November 2007), which teaches an implant (para [0002]), compnsing a substrate and a coating (para [0003]) wherein the coating comprises HAp (Abstract) and ZnO particles (para [0136], [0137]) As the HAp / ZnO coated implant was known, as evidenced by the teaching of Furuzono, this cannot be considered a special technical feature that would otherwise unify the groups

Groups I - III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature