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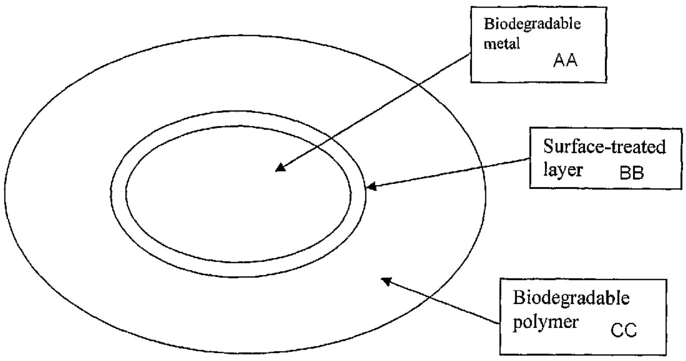

FIG. 1

(57) Abstract: Novel hybrid materials and fabrication methods thereof are provided. The novel hybrid materials can include a biodegradable polymer and a biodegradable metallic material. The hybrid material can also include a coupling agent between the biodegradable metallic material and the biodegradable polymer. A method of fabricating a hybrid material can include performing a surface treatment process on the biodegradable metallic material, and then either performing a solvent formation method or a thermal formation method.

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DESCRIPTION

POLYMERIC BASED AND SURFACE TREATED METALLIC HYBRID MATERIALS AND FABRICATION METHODS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

The subject application claims the benefit of U.S. Provisional Application Serial No. 61/225,279, filed July 14, 2009, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Implants are used very often in surgical, orthopedic, dental, and other related applications, including tissue engineering. One important issue with implants is that due to biomechanical and physiologic requirements, an implant material should have a certain mechanical strength or elasticity to be incorporated into the target tissue and anatomic region. Also, degradability or possibly even incorporating pharmacologically or therapeutically active agents is also desirable.

Several different materials for implants have been used, including metal. Metallic implant materials are usually favorable in terms of toughness, ductility, and fatigue resistance. On the other hand, they are often stiffer than natural bone, resulting in stress shielding. The phenomenon of stress shielding is based on the effect that the implant material bears more of the mechanical load if it is stiffer than the surrounding tissue. This results in a "shielding" of the natural bone tissue from the mechanical load triggering the resorption processes of bone.

Patients with orthopedic fractures or deformities are sometimes treated with surgically implanted metallic materials. The most common metallic materials used in fracture fixation or total joint devices are medical-grade non-degradable metals, such as stainless steel, titanium, and cobalt-chromium-based alloys. Existing permanent metallic implants for fracture fixation and total hip replacement can often cause stress shielding effects due to the mismatch of the mechanical properties between these metallic implants and natural bone. That is, due to a mismatch of the mechanical properties between these metallic implants and natural bone, the major obstacle in using these non-degradable permanent metal implants is that they may cause stress shielding effects, thereby leading to bone loss around the implant. Patients who undergo orthopedic procedures such as fracture fixation, often undergo a second surgery after treatment is done in order to avoid this post-operative complication.

Polymeric implants are sometimes used as an alternative to metallic implants. However, existing polymeric implants often do not have appropriate mechanical strength to withstand load-bearing conditions.

Biodegradable metallic implants such as magnesium alloys have sometimes been used. However, in addition to a mismatch in mechanical properties and poor biocompatibility, magnesium alloys exhibit problems with a rapid degradation rate and hydrogen gas accumulation upon implantation. Rapid corrosion results in the release of a large amount of magnesium ions together with a large volume of hydrogen gas generated. As shown in Reactions (1) – (3) below, if an increase in corrosion rate leads to an increase in magnesium ions. Accordingly, magnesium hydroxide is formed, and hydrogen gas is generated. The human body itself is able to absorb a small amount of hydrogen gas.

An alloying modification method is sometimes applied to attempt to improve the corrosion resistance of magnesium alloys. Although alloying can improve the corrosion resistance of magnesium alloy, this technique may introduce biological toxicity due to the use of rare earth metals, such as cerium and yttrium. Additionally, the compatibility with living cells remains a problem. The mechanical properties of magnesium alloy are closer to human natural bone than those of other metallic materials such as titanium alloys and stainless steel. However, there is still a discrepancy between magnesium alloy and natural bone in terms of bulk mechanical properties.

Reaction (1): $H_2O \rightarrow H^+ + OH^-$
Reaction (2): $2Mg \rightarrow Mg^{2+} + 2e^-$
Reaction (3): $Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$

Each of the existing materials used for orthopedic implants exhibits potentially harmful problems. Thus, there exists a need in the art for an improved material that can be used as an implant in orthopedic and other medical applications, as well as in other non-medical applications where a durable substitute for traditional metals or plastics is desired.

BRIEF SUMMARY OF THE INVENTION

The present invention pertains to novel hybrid materials based on biodegradable polymers and surface-treated biodegradable metallic materials, as well as fabrication methods thereof. These novel hybrid materials are able to tackle the complications of conventional biodegradable materials (including magnesium-based materials), such as mismatched bulk mechanical properties, poor biocompatibility, rapid degradation, and hydrogen gas release upon degradation in orthopedic applications. In addition to the enhancement of biocompatibility, with the materials of the subjection invention, the degradation process can be manipulated by controlling the chemistry of polymeric materials and the surface treatment of metallic materials as well as their ratio when forming the hybrid materials. The novel materials and methods of the subject invention have several applications, including but not limited to orthopedic implantation.

In an embodiment, a hybrid material can comprise: a biodegradable polymer; a surface-treated biodegradable metallic material; and a silane coupling agent chemically bonded to the surface-treated biodegradable metallic material and the biodegradable polymer.

In another embodiment, a method of fabricating a hybrid material comprising a biodegradable polymer and a biodegradable metallic material can comprise: performing a surface treatment process on the biodegradable metallic material; dissolving the biodegradable polymer in an organic solvent to form a solution; adding the biodegradable metallic material, after the surface treatment process has been performed, to the solution; sonicating the solution; drying the solution to obtain a pre-hybrid material; and performing a heat treatment process on the pre-hybrid material.

Yet another embodiment is a method of fabricating a hybrid material comprising biodegradable polymer and a biodegradable metallic material, wherein the method can comprise: performing a surface treatment process on the biodegradable metallic material; melting a biodegradable polymer by a thermal process to obtain a polymer melt; adding the biodegradable metallic material to the polymer melt to form a pre-hybrid material; shearing the pre-hybrid material in a first direction and a second direction; and compressing the pre-hybrid material along a third direction to obtain the hybrid material.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic representation of a unit of hybrid material according to an embodiment of the subject invention.

Figure 2 shows a thermal-mechanical mixing machine that can be used in a fabrication method according to an embodiment of the subject invention.

Figure 3 shows compressive modulus as a function of amount of magnesium in a hybrid material according to an embodiment of the subject invention.

Figure 4 shows compressive modulus as a function of amount of magnesium in a hybrid material according to an embodiment of the subject invention.

Figures 5 and **6** show fluorescent photos using enhanced Green Fluorescent Protein Osteoblasts (eGFPOB) culture.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains to novel hybrid materials including biodegradable polymers and surface-treated biodegradable metallic materials, as well as fabrication methods thereof. These novel hybrid materials are able to overcome the problems of conventional biodegradable materials (including magnesium-based materials), such as mismatched bulk mechanical properties, poor biocompatibility, rapid degradation, and hydrogen gas release upon degradation in orthopedic applications. In addition to the enhancement of biocompatibility, with the materials of the subjection invention, the degradation process can be manipulated by controlling the chemistry of polymeric materials and the surface treatment of metallic materials as well as their ratio when forming the hybrid materials. The novel materials and methods of the subject invention have several applications, including but not limited to orthopedic implantation. For example, the novel materials of the subject invention can be used for other medical applications, as well as for non-medical applications such as a substitute for metal and/or plastic in consumer goods.

The hybrid materials of the subject invention, which can be used as biodegradable implants, can include polymeric and metallic materials. Referring to Figure 1, the hybrid material can include a biodegradable metal with a surface treatment and a biodegradable polymer.

Biodegradable metallic implants can have an advantage over biodegradable polymeric implants since metal has better mechanical properties than polymers; this can be particularly advantageous in instances where the implants are used in a high load-bearing situation. Biodegradable metallic materials, such as magnesium alloys, are able to withstand higher mechanical loading than biodegradable polymeric materials. In an embodiment of the present invention, the biodegradable metallic material can include magnesium and/or a magnesium alloy. In another embodiment, the biodegradable metallic material can include iron and/or an iron alloy. In certain embodiments of the subject invention, the biodegradable metallic materials can be beads, rods, tubes, or any combination thereof.

With the hybrid materials of the subject invention, the mechanical properties of the materials can be modified so as to obtain the approximate mechanical properties of natural bones without inducing biological toxicity.

In addition, the subject invention provides novel methods of fabricating hybrid materials incorporating biodegradable polymers and surface-treated biodegradable metallic materials. The hybrid materials of the subject invention can achieve controllable degradation, controllable bulk mechanical properties similar to human bone, and superior biocompatibility to cells.

The hybrid materials of the subject invention can impart many advantageous benefits, including for patients undergoing orthopedic procedures. The subject invention can help eliminate the risks of having a metallic implant left inside the body, as well as the need for additional surgery for implant removal.

The biodegradable hybrid materials of the subject invention have many applications, including but not limited to, orthopedic implants for bone fracture fixation. For example, the hybrid materials can be used as different orthopedic implants including bone screws and bone plates. The hybrid materials can also be used in cardiovascular, dental, and/or renal procedures; and in innumerable non-medical applications where a durable substitute for metal or plastic is desired.

This subject invention involves new hybrid materials, and fabrication methods thereof, for a wide range of applications, including orthopedic, dental, and cardiovascular procedures. The novel fabrication methods can help control the material degradation process and provide bulk mechanical properties similar to natural bone. In addition, these new materials are highly compatible with cells, whereas related art degradable metallic materials are not.

The novel hybrid materials can be formed by biodegradable polymers and surface-treated biodegradable metallic materials. In a particular embodiment, the biodegradable metallic materials can include magnesium and/or magnesium alloys. In an embodiment, the biodegradable polymer can be derived from ε-caprolactone, either used alone or combined with other lactone monomers. The other lactone monomers, can include, for example, γ-butyrolactone (γ-BL), δ-valerolactone (δ-VL), γ-valerolactone (γ-VL), and γ-caprolactone (γ-CL). In further embodiments, other monomers can be used, for example, xylitol can be used to form a biodegradable xylitol-based polymer.

The biodegradable metallic materials can be surface-treated. In certain embodiments, the biodegradable metallic materials can be surface-treated by heat treatment, magnetron sputtering, plasma immersion ion implantation, or plasma immersion ion implantation and deposition before mixing with the polymer component.

In an embodiment of the present invention, the biodegradable polymer of the novel hybrid material can be a polymer or copolymer derived from ε-caprolactone. The polymer derived from ε-caprolactone (ε-CL) alone forms a biodegradable polymeric material referred to as polycaprolactone (PCL). Other biodegradable polymers can be formed by the copolymerization process using other lactone monomers such as γ-butyrolactone (γ-BL), δ-valerolactone (δ-VL), γ-valerolactone (γ-VL), and γ-caprolactone (γ-CL). The biodegradable polymer can be a polymer or copolymer of any of these monomers or any combination thereof. The formation process of the polymer can be either with or without catalysts. In an alternative embodiment, instead of chemically synthesizing the polymer from monomers, the polymer may be obtained by purchasing a commercially available sample. For example, granules of PCL with different molecular weights (for example 80,000 g/mol) are commercially available.

In a further exemplary embodiment, xylitol can be used to form a biodegradable xylitol-based polymer. For example, a biodegradable xylitol-based polymer can be formed by polycondensation of xylitol with water-soluble citric acid. In yet a further embodiment, other monomers can be used to form a biodegradable polymer.

In certain embodiments, the polymer used can be PCL, a biodegradable xylitol-based polymer, or a copolymer of ε-CL with one or more of γ-BL, δ-VL, γ-VL, and γ-CL.

In an embodiment of a fabrication process, after preparing the biodegradable polymer, the biodegradable metallic material can be surface-treated. There can be more than one biodegradable metallic material, and these materials can be in different forms. The biodegradable metallic material or materials is/are subjected to a surface modification process to change the surface chemistry for hybrid material formation. The modification method can be, for example, plasma immersion ion implantation or thermal treatment.

In certain embodiments, the modification method can be plasma immersion ion implantation with different sources such as aluminum, iron, silicon, strontium, calcium, zirconium, carbon, nitrogen, ammonia, and/or oxygen. In a further embodiment, the modification method can be thermal treatment. Depending on the biodegradable metallic material(s) used, the thermal treatment can allow formation of an oxide layer on the metallic surface. In yet a further embodiment, both plasma immersion ion implantation and thermal treatment can be performed. A change in surface chemistry can enhance the bonding or adhesion between the biodegradable metallic material(s) and a biodegradable polymeric substrate.

In an embodiment, coupling agents can be applied to help form chemical bonds between the polymer(s) and the metal(s). The coupling agent can be chemically bonded to a polymer and a metallic material of the hybrid material. The coupling agent can be, for example, a silane coupling agent. In certain embodiments, the coupling agent can be 3-(trimethoxysilyl)propylmethacrylate or 3-aminopropyltrimethoxysilane. A coupling agent treatment can be performed, optionally including a solvent and a catalyst. A catalyst can be, for example, propylamine or triethylamine; and a solvent can be, for example, cyclohexane or toluene.

In the case that the coupling agent is used, the surface treated biodegradable metallic material is added into the coupling agents solution, and then the coupling agent solution mixture is heated under reflux with nitrogen, for example, at a temperature of from about 80 °C or about 110 °C for a period of time of about 3 hours. The coupling agent treated biodegradable metallic material might undergo a heat-treating in low –vacuum oven. For example, the coupling agent treated biodegradable metallic material might be heat-treated at a temperature of about 80 °C to about 100 °C for a period of time of about 5 hours to about 8 hours at a pressure of about 100 mBar.

Solvent formation and/or thermal formation can be performed to fabricate the hybrid materials. In an embodiment with solvent formation, the polymer(s) can be dissolved in a solvent. The solvent can be, for example, an organic solvent, such as a solvent wherein a ratio of weight of PCL / volume of dichloromethane (DCM) is about 1 g/ml, a solvent wherein a ratio of weight of PCL / volume of chloroform is about 1 g/ml, or a combination thereof. Note that, even though 1 g/ml DCM and 1 g/ml chloroform have been listed by way of example, embodiments of the subject invention are not limited thereto. Any reasonable concentration of organic solvent can be used. For example, an organic solvent wherein a ratio of weight of polymer/volume of solvent can be from about 0.05 g/ml to about 2.0g/ml, or even greater, being limited only by the solubility of a chosen polymer in a chosen solvent as would be readily recognized by one of ordinary skill in the art.

In an embodiment, the biodegradable metallic material(s) can be thermally treated. Depending on the material(s), the thermal treatment can help establish an oxide layer on the metallic surface. Varying the proportions of thermally treated metallic material(s) to be mixed with the polymer solution can result in hybrid materials of varying concentrations. The metallic materials are preferable nano-sized or micro-sized units, such as beads, cones, rods, etc. The solution mixture can then be sonicated so that the metallic material(s) can be aligned or dispersed evenly within the polymer substrate. The sonication could be performed for a period of time of from about 30 minutes to about 1 hour. Next, the mixture can undergo a drying process. The drying process can be carried out for a period of time of from about 12 hours to about 24 hours. In certain embodiments, a second thermal treatment process can be performed on the hybrid materials to enhance the mechanical properties of the materials. This second thermal treatment process can be performed at a temperature of about 80 °C for a period of time of from about 30 minutes to about 1 hour.

In certain embodiments, the biodegradable metallic material can be magnesium beads. The beads can have sizes of from about 100nm to about 150μm, for example, about 100 nm, about 45 μm, or about 150 μm, and can be thermally treated to help establish an oxide layer on the surface. In a specific embodiment, the thermal treatment can be performed at a temperature of about 100 °C for a period of time of about 60 minutes. Varying the proportions of thermally treated magnesium beads to be mixed with the polymer solution can result in hybrid materials of varying concentrations. The solution mixture can then be sonicated so that the beads can be aligned or dispersed evenly within the polymer substrate. The sonication could be performed for a period of time of from about 30 minutes to about 1 hour. Next, the mixture can undergo a drying process. The drying process can be carried out for a period of time of from about 12 hours to about 24 hours. In certain embodiments, a second thermal treatment process can be performed on the hybrid materials to enhance the mechanical properties of the materials. This second thermal treatment process can be performed at a temperature of about 80 °C for a period of time of from about 30 minutes to about 1 hour

The degradation rates and mechanical properties of the hybrid materials of the subject invention can be determined by the concentrations and reaction parameters during a fabrication method of the present invention.

The novel hybrid materials of the subject invention provide a stable degradation rate for the whole material since the polymer and metallic material are distributed approximately evenly. Additionally, strong bonds (e.g., chemical bonds) can form between the metallic material and the polymer. For example, a coupling agent can be used to modify the metallic material so that chemical bond can be formed with the polymer, thereby improving the mechanical properties of the hybrid material.

EXAMPLES

Example 1: Plasma Immersion Ion Implantation (PIII)

One of the surface modification methods can be PIII, and the implantation sources that can be used include nitrogen (N_2), oxygen (O_2), carbon (C), ammonia (NH_3), aluminum (Al), zirconium (Zr), iron (Fe), silicon (Si), strontium (Sr), calcium (Ca), and water. Table 1 shows implantation conditions for the implantation sources of nitrogen, water, and strontium. All values listed will work with slight variations, such that each value should be interpreted as having the word "about" in front of it.

Table 1: Implantation conditions for PIII for selected implantation sources

Sources / Parameters	Nitrogen (N_2)	Water (H_2O)	Strontium (Sr)

Base Pressure	7.0×10^{-6} Torr	7.0×10^{-6} Torr	7.0×10^{-6} Torr
Working Voltage	40kV	40kV	15kV
Pulse Width	30μs	30μs	30μs
Implantation Time	4hrs	4hrs	3hrs
Frequency	200Hz	200Hz	200Hz
Working Pressure	5.0×10^{-4} Torr	6.0×10^{-4} Torr	6.4×10^{-4} Torr

Example 2: Plasma Immersion Ion Implantation and Deposition (PIII & D)

Apart from PIII, PIII together with deposition can be used as another surface treatment technique. Similar to PIII, different sources such as nitrogen (N_2), oxygen (O_2), carbon (C), ammonia (NH_3), aluminum (Al), zirconium (Zr), iron (Fe), silicon (Si), strontium (Sr), calcium (Ca), and/or water can be used for PIII & D. Table 2 shows the working parameters for implanting and depositing Al and O_2 at the same time. All values listed will work with slight variations, such that each value could be interpreted as having the word "about" in front of it.

Table 2 Implantation and deposition conditions for implanting and depositing Al and O_2 to form Al_2O_3

Negative High Voltage Power Supply	
NH Current	1.0 mA
NH Voltage	15 kV
Pulse Duration	300 μs
Frequency	10 Hz

Pulsed Filtered Cathodic Arc Source	
Arc Current	0.1 A
Arc Voltage	92 V
Triggering Voltage	12.6 kV
Coil Current	2.3 A
Pulse Duration	250 μs

Frequency	10 Hz
Oxygen Flow	10sccm

Example 3: Magnetron Sputtering

Magnetron sputtering can be used for a surface treatment process according to an embodiment of the subject invention. The sputtering source can be, for example, aluminum oxide (Al_2O_3). Tables 3 shows the process conditions during the magnetron sputtering process. All values listed will work with slight variations, such that each value could be interpreted as having the word “about” in front of it.

Table 3: Process conditions of magnetron sputtering

Frequency	40 kHz – 60 kHz
Voltage	100 – 1000 V
Current	0.1 – 1 A

Example 4: Thermal Treatment

Thermal treatment can be used for a surface modification method to induce an oxide layer formation. Table 4 shows an example of process conditions during thermal treatment. All values listed will work with slight variations, such that each value should be interpreted as having the word “about” in front of it.

Table 4: Thermal treatment process conditions

Temperature	60 °C – 100 °C
Pressure	100 mBar
Humidity	10% - 20%
Treatment Time	8 – 24 hrs

Example 5: Coupling Agent Treatment

A coupling agent treatment can be applied to the biodegradable metallic materials directly or after a surface treatment such as discussed and exemplified in any of Examples 1-3. Coupling agents can be silane coupling agents, such as 3-(trimethoxysilyl)propylmethacrylate and 3-aminopropyltrimethoxysilane ("ASCA"). The coupling agents can modify the surface of the biodegradable metallic materials. The coupling agent can be added to a solvent together with a catalyst. The treated or untreated biodegradable metallic materials can be added to the solution mixture which is then heated under reflux with nitrogen for a period of time at a given temperature. After the silane treatment, the metallic materials can be heat treated again in a low vacuum oven at a given temperature. Tables 5 and 6 show examples of coupling agent treatment process conditions using 3-(trimethoxysilyl)propylmethacrylate and 3-aminopropyltrimethoxysilane as the coupling agent, respectively. All values listed will work with slight variations, such that each value should be interpreted as having the word "about" in front of it.

Table 5: Process conditions with 3-(trimethoxysilyl)propylmethacrylate

Silane Treatment	
Silane coupling agent	3-(Trimethoxysilyl)propylmethacrylate (Weight of Mg / Volume of ASCA : 1 g/ml – 20 g/ml)
Solvent	Cyclohexane
Catalyst	Propylamine
Treatment Temperature	60 °C - 80 °C
Treatment Time	1 - 5 hrs
Post Heat Treatment	
Temperature	80 °C - 100 °C
Duration	5 – 8 hrs
Pressure	100 mBar

Table 6: Process conditions with 3-aminopropyltrimethoxysilane

Silane Treatment

Silane coupling agent	3-Aminoproyltrimethylsilane (Weight of Mg / Volume of ASCA : 1 g/ml – 20 g/ml)
Solvent	Cyclohexane / Toluene
Catalyst	Triethylamine
Treatment Temperature	60 °C - 80 °C / 80 °C - 110 °C
Treatment Time	1 - 5 hrs
Post Heat Treatment	
Temperature	80 °C - 100 °C
Duration	5 – 8 hrs
Pressure	100 mBar

Example 6: Solvent Formation Method

After surface treatment of the biodegradable metallic materials, the hybrid material can be fabricated by, for example, the solvent formation method. A solvent, e.g. an organic solvent such as DCM or trichloromethane (TCM; also known as chloroform) is used to dissolve the organic polymer (e.g., PCL). When the polymer is dissolved, the surface-treated biodegradable metallic materials (e.g., magnesium beads) are then added to the polymer solution. The mixture is then sonicated to let the metallic materials align or distribute evenly in the solution within the polymer substrate. After the process of sonication, the mixture is then dried. A heat treatment process is finally conducted to enhance the bonding and adhesion between the biodegradable metallic materials and the biodegradable polymer. The ratio of the polymer to the metallic materials can be varied. For example, 50%-99.9% polymer can be used, and 50%-0.1% metallic materials can be used. Table 7 shows an example of process conditions for solvent formation using PCL and magnesium beads. All values listed will work with slight variations, such that each value should be interpreted as having the word “about” in front of it.

Table 7: Process conditions for solvent formation

Solvents used	Dichloromethane (Weight of PCL / Volume of DCM: 0.05 g/ml – 1 g/ml) /

	Trichloromethane (Weight of PCL / Volume of TCM: 0.05 g/ml – 1 g/ml)
Polymer added	1 g of PCL
Metallic materials added	0.1 g to 1 g magnesium beads
Sonication time	30 mins to 1 hr
Drying duration	12 -24 hrs
Heat treatment temperature	60 °C - 80 °C
Heat treatment time	30 mins to 3 hrs

Note: The ratio of the polymer to the metallic materials can be varied (e.g., 99.9% PCL / 0.1% Mg to 50% PCL / 50% Mg)

Example 7: Thermal Formation Method

The biodegradable polymer together with the surface-treated biodegradable metallic materials can undergo a thermal treatment in a thermal-mechanical mixing machine, as seen in Figure 2. The biodegradable polymer(s) are mixed with surface-treated biodegradable metallic material(s) through a thermal-mechanical process. The thermal-mechanical process includes five main steps: melt polymer by thermal process; add metallic powder into melt polymer to form pre-hybrid material; shear pre-hybrid material in x and y axis; compress pre-hybrid material along the direction of z axis; and the shearing and compression steps are repeated until a hybrid material with evenly distributed components is achieved. The thermal-mechanical mixing device of Figure 2 has been designed to carry out the thermal-mechanical process. The mixing device can be programmed to make a specific environment for fabricating different compositions of hybrid by adjusting a set of parameters.

The set of parameters includes: temperature; magnitude of applied mechanical force; direction of applied mechanical force; sequence of raw materials feed; timing of raw materials feed; and duration of each action. The parts of the mixing device of Figure 2 are as follows: a) raw materials trays; b) raw materials transfer pipe; c) valve; d) vertical compressor; e) mixing chamber; f) heat element; g) support rollers; h) horizontal rolling plate; i) user input interface; j) controller; and k) outer most shell. Raw materials are stored in raw materials trays (**a**) and are ready to be fed into the mixing chamber (**e**). The raw materials trays (**a**) are connected to the mixing chamber (**e**) via the raw materials transfer pipes (**b**). The amount of raw materials to be fed is controlled by the valves (**c**) situated at the chamber side end of the raw materials transfer pipes (**b**). All surfaces (except that of the roller plates) which are in contact with raw/hybrid materials are coated with polytetrafluoroethylene (TEFLON) which is to avoid the sticky hybrid blocking the pipes, trays, and chamber. Surfaces of the horizontal rolling plates (**h**) are coated with reinforced glass that provides sufficient friction to shear the hybrid materials during rolling. The temperature of the mixing chamber is controlled by a heating system at the outer wall of the mixing chamber. The controller (**j**) controls all action according to the user pre-set program.

Example 8: 150 μm Magnesium Beads

Magnesium beads with a size of about 150 μm were used to fabricate an embodiment of the hybrid material of the subject invention. The polymer used was PCL. Tables 8 and 9 show the process conditions used. Table 8 is with no pre-heat treatment, and Table 9 is with pre-heat treatment. All values listed will work with slight variations, such that each value should be interpreted as having the word “about” in front of it. Additionally, Figure 3 shows the compressive modulus for the resulting hybrid materials (“_ASCA” indicates no pre-heat treatment, and “_pre&ASCA” indicates pre-heat treatment; the amount of Mg is in grams. Figure 5 shows fluorescent photos after 1 day and after 3 days using enhanced Green Fluorescent Protein Osteoblasts (eGFPOB) culture by incorporating 0.1g ASCA-treated 150 μm magnesium beads as an example. The photos suggest that the hybrid material of the subject invention is compatible with the growth of osteoblasts.

Table 8: 150 µm Magnesium beads with no pre-heat treatment

Metallic material	150µm Magnesium beads (5g)
Silane Treatment	
Silane coupling agent	3-Aminoproyltrimethylsilane (Weight of Mg / Volume of ASCA: 2g/ml)
Solvent	Cyclohexane (250 ml)
Catalyst	Triethylamine (0.75 ml)
Treatment Temperature	80 °C
Treatment Time	3 hrs
Post Heat Treatment	
Temperature	80 °C
Duration	5 hrs
Pressure	100 mBar
Hybrid fabrication	
Amount of Mg beads added	0.1g; 0.4g; 0.6g; 0.8g
Amount of PCL added	1g
Method of fabrication	Thermal formation method

Table 9: 150 µm Magnesium beads with pre-heat treatment

Metallic material	150µm Magnesium beads (5g)
Pre-treatment	
Temperature Duration	80 °C 24 hrs
Silane Treatment	
Silane coupling agent	3-Aminoproyltrimethylsilane (Weight of Mg / Volume of ASCA: 2g/ml)
Solvent	Cyclohexane (250 ml)
Catalyst	Triethylamine (0.75 ml)
Treatment Temperature	80 °C
Treatment Time	3 hrs
Post Heat Treatment	
Temperature	80 °C
Duration	5 hrs
Pressure	100 mBar
Hybrid fabrication	
Amount of Mg beads added	0.1g; 0.4g; 0.6g; 0.8g
Amount of PCL added	1g
Method of fabrication	Thermal formation method

Example 9: 45 µm Magnesium Beads

Magnesium beads with a size of about 45 µm were used to fabricate another embodiment of the hybrid material of the subject invention. The polymer used was PCL. Tables 10 and 11 show the process conditions used. Table 10 is with no pre-heat treatment, and Table 11 is with pre-heat treatment. All values listed will work with slight variations, such that each value should be interpreted as having the word "about" in front of it. Additionally, Figure 4 shows the compressive modulus for the resulting hybrid materials ("_ASCA" indicates no pre-heat treatment, and "_pre&ASCA" indicates pre-heat treatment; the amount of Mg is in grams) Figure

6 shows fluorescent photos after 1 day and after 3 days using enhanced eGFPOB culture by incorporating 0.1g ASCA-treated 45 μm magnesium beads as an example. The photos suggest that the hybrid material of the subject invention is compatible with the growth of osteoblasts.

Table 10: 45 μm Magnesium beads with no pre-heat treatment

Metallic material	45μm Magnesium beads (5g)
Silane Treatment	
Silane coupling agent	3-Aminoproyltrimethylsilane (Weight of Mg / Volume of ASCA: 2g/ml)
Solvent	Cyclohexane (250 ml)
Catalyst	Triethylamine (0.75 ml)
Treatment Temperature	80 °C
Treatment Time	3 hrs
Post Heat Treatment	
Temperature	80 °C
Duration	5 hrs
Pressure	100 mBar
Hybrid fabrication	
Amount of Mg beads added	0.1g; 0.4g; 0.6g; 0.8g
Amount of PCL added	1g
Method of fabrication	Thermal formation method

In Figures 3 and 4, the compressive modului of both 150 μm and 45 μm magnesium beads increased when the amount of magnesium beads increased. The result suggested that with different magnesium beads to PCL ratio, the mechanical properties would than be altered. Moreover, different size of the magnesium beads would also change the mechanical properties. Hence, by choosing the suitable particle size and ratio, hybrid with different mechanical properties can be fabricated. In addition, since the magnesium beads and PCL have different degradation rate, by altering the ratio, different mechanical properties and degradation rate can be obtained. Therefore, the properties of the hybrid can be tailor made according to different applications. Apart from the metallic materials to polymer ratio, the mechanical properties and the degradation rate of the hybrid can be varied with different types of materials use while the degradation rate can even be controlled by applying different types of surface treatment to the metallic materials. To conclude, with the combination of different metallic materials and polymer that is having different properties, different properties of the hybrid can be fabricated. Therefore, the hybrid is able to tailor made and to fit with different applications.

Table 11: 45 μm Magnesium beads with pre-heat treatment

Metallic material	45μm Magnesium beads (5g)
Pre-treatment	
Temperature Duration	80 °C 24 hrs
Silane Treatment	
Silane coupling agent	3-Aminoproyltrimethylsilane (Weight of Mg / Volume of ASCA: 2g/ml)
Solvent	Cyclohexane (250 ml)
Catalyst	Triethylamine (0.75 ml)
Treatment Temperature	80 °C
Treatment Time	3 hrs
Post Heat Treatment	
Temperature	80 °C
Duration	5 hrs
Pressure	100 mBar
Hybrid fabrication	
Amount of Mg beads added	0.1g; 0.4g; 0.6g; 0.8g
Amount of PCL added	1g
Method of fabrication	Thermal formation method

All patents, patent applications, provisional applications, and publications referred to or cited herein, *supra* or *infra*, are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

CLAIMS

What is claimed is:

1. A hybrid material, comprising:

a biodegradable polymer;

a surface-treated biodegradable metallic material; and

a silane coupling agent chemically bonded to the surface-treated biodegradable metallic material and the biodegradable polymer.

2. The hybrid material according to claim 1, wherein the biodegradable polymer is polycaprolactone, or a copolymer of ε-caprolactone (ε-CL) and γ-butyrolactone (γ-BL), δ-valerolactone (δ-VL), γ-valerolactone (γ-VL), γ-caprolactone (γ-CL), or any combination thereof.

3. The hybrid material according to any one of claims 1 to 2, wherein the surface-treated biodegradable metallic material comprises magnesium, magnesium alloy, or both.

4. The hybrid material according to any one of claims 1 to 3, wherein the surface-treated biodegradable metallic material comprises magnesium beads with a size of from about 100 nm to about 150 μm.

5. The hybrid material according to any one of claims 1 to 4, wherein the silane coupling agent is 3-(trimethoxysilyl)propylmethacrylate or 3-aminopropyltrimethoxysilane.

6. A method of fabricating a hybrid material comprising a biodegradable polymer and a biodegradable metallic material, wherein the method comprises:

performing a surface treatment process on the biodegradable metallic material;

dissolving the biodegradable polymer in an organic solvent to form a solution;

adding the biodegradable metallic material, after the surface treatment process has been performed, to the solution;

sonicating the solution;

drying the solution to obtain a pre-hybrid material; and

performing a heat treatment process on the pre-hybrid material.

7. The method according to claim 6, further comprising performing a coupling agent treatment on the biodegradable metallic material before adding the biodegradable metallic material to the solution; wherein performing the coupling agent treatment comprises:

adding a silane coupling agent and a catalyst to a second solvent to form a coupling agent solution;

adding the biodegradable metallic material to the coupling agent solution to form a coupling agent solution mixture;

heating the coupling agent solution mixture under reflux with nitrogen; and

heat-treating the biodegradable metallic material in a low-vacuum oven.

8. The method according to claim 7, wherein the silane coupling agent is 3-(trimethoxysilyl)propylmethacrylate or 3-aminopropyltrimethoxysilane.

9. The method according to any one of claims 7 to 8, wherein heating the coupling agent solution mixture comprises heating the coupling agent solution mixture at a temperature of from about 80 °C or about 110 °C for a period of time of about 3 hours; and wherein heat-treating the biodegradable metallic material comprises heat-treating the biodegradable metallic material at a temperature of about 80 °C to about 100 °C for a period of time of about 5 hours to about 8 hours at a pressure of about 100 mBar; and wherein the second solvent is cyclohexane or toluene; and wherein the catalyst is propylamine or triethylamine.

10. The method according to any one of claims 6 to 9, wherein the organic solvent is dichloromethane or trichloromethane; and wherein sonicating the solution

comprises sonicating the solution for a period of time of from about 30 minutes to about 1 hour; and wherein drying the solution comprises drying the solution for a period of time of from about 12 hours to about 24 hours; and wherein performing a heat treatment process on the pre-hybrid material comprises performing a heat treatment process on the pre-hybrid material at a temperature of about 80 °C for a period of time of from about 30 minutes to about 1 hour.

11. The method according to any one of claims 6 to 10, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation process, a plasma immersion ion implantation and deposition process, a magnetron sputtering process, or a thermal treatment process on the biodegradable metallic material.

12. The method according to claim 11, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation process with a base pressure of about 7.0×10^{-6} Torr, a working voltage of from about 15 kV to about 40 kV, a pulse width of about 30 μs, an implantation time of about 3 hours to about 4 hours, a frequency of about 200 Hz, and a working pressure of from about 5.0×10^{-4} Torr to about 6.4×10^{-4} Torr.

13. The method according to claim 11, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a thermal treatment process on the biodegradable metallic material at a temperature of about 60 °C to about 100 °C, a pressure of about 100 mBar, a humidity of from about 10% to about 20%, and a treatment time of from about 8 hours to about 24 hours.

14. The method according to claim 11, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation and deposition process utilizing:

a negative high voltage power supply with current of about 1.0mA, a voltage with a magnitude of about 15kV, a pulse duration of about 300 μs, and a frequency of about 10 Hz;

and a pulsed filtered cathodic arc source with an arc current of about 0.1A, an arc voltage with a magnitude of about 92V, a triggering voltage with a magnitude of about 12.6kV, a coil current of about 2.3A, a pulse duration of about 250 μs, and a frequency of about 10 Hz.

15. A method of fabricating a hybrid material comprising a biodegradable polymer and a biodegradable metallic material, wherein the method comprises:

performing a surface treatment process on the biodegradable metallic material;

melting the biodegradable polymer by a thermal process to obtain a polymer melt;

adding the biodegradable metallic material to the polymer melt to form a pre-hybrid material;

shearing the pre-hybrid material in a first direction and a second direction; and

compressing the pre-hybrid material along a third direction to obtain the hybrid material.

16. The method according to claim 15, further comprising performing a coupling agent treatment on the biodegradable metallic material before adding the biodegradable metallic material to the solution; wherein performing the coupling agent treatment comprises:

adding a silane coupling agent and a catalyst to a second solvent to form a coupling agent solution;

adding the biodegradable metallic material to the coupling agent solution to form a coupling agent solution mixture;

heating the coupling agent solution mixture under reflux with nitrogen; and

heat-treating the biodegradable metallic material in a low-vacuum oven.

17. The method according to claim 16, wherein the silane coupling agent is 3-(trimethoxysilyl)propylmethacrylate or 3-aminopropyltrimethoxysilane; and wherein heating the coupling agent solution mixture comprises heating the coupling agent solution mixture at a temperature of from about 80 °C or about 110 °C for a period of time of about 3 hours; and wherein heat-treating the biodegradable metallic material comprises heat-treating the

biodegradable metallic material at a temperature of about 80 °C to about 100 °C for a period of time of about 5 hours to about 8 hours at a pressure of about 100 mBar; and wherein the second solvent is cyclohexane or toluene; and wherein the catalyst is propylamine or triethylamine.

18. The method according to any one of claims 15 to 17, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation process, a plasma immersion ion implantation and deposition process, a magnetron sputtering process, or a thermal treatment process on the biodegradable metallic material.

19. The method according to claim 18, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation and deposition process utilizing:

a negative high voltage power supply with current of about 1.0mA, a voltage with a magnitude of about 15kV, a pulse duration of about 300 μs, and a frequency of about 10 Hz;

and a pulsed filtered cathodic arc source with an arc current of about 0.1A, an arc voltage with a magnitude of about 92V, a triggering voltage with a magnitude of about 12.6kV, a coil current of about 2.3A, a pulse duration of about 250 μs, and a frequency of about 10 Hz.

20. The method according to claim 18, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a plasma immersion ion implantation process with a base pressure of about 7.0×10^{-6} Torr, a working voltage of from about 15 kV to about 40 kV, a pulse width of about 30 μs, an implantation time of about 3 hours to about 4 hours, a frequency of about 200 Hz, and a working pressure of from about 5.0×10^{-4} Torr to about 6.4×10^{-4} Torr.

21. The method according to claim 18, wherein performing a surface treatment process on the biodegradable metallic material comprises performing a thermal treatment

process on the biodegradable metallic material at a temperature of about 60 °C to about 100 °C, a pressure of about 100 mBar, a humidity of from about 10% to about 20%, and a treatment time of from about 8 hours to about 24 hours.

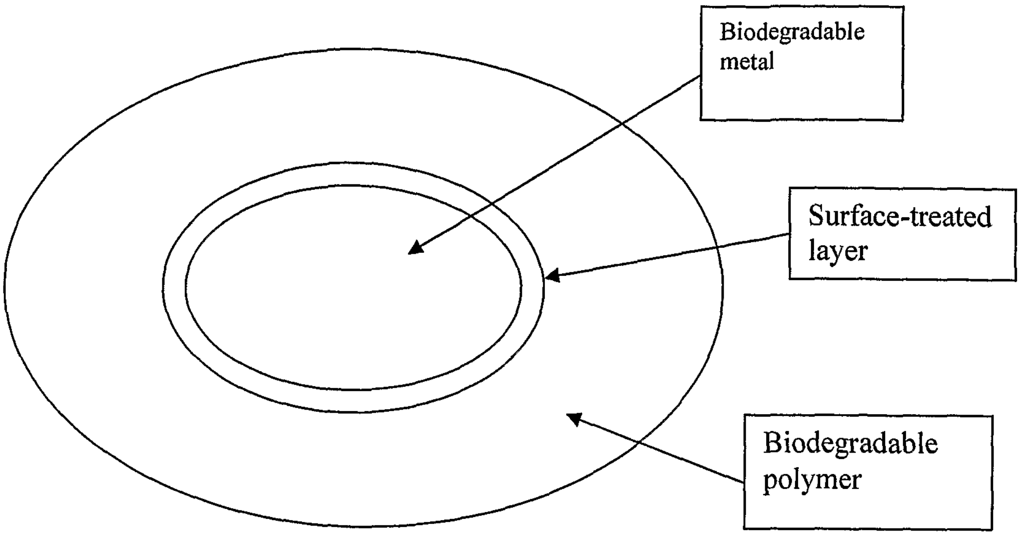
Biodegradable metal
Surface-treated layer
Biodegradable polymer

FIG. 1

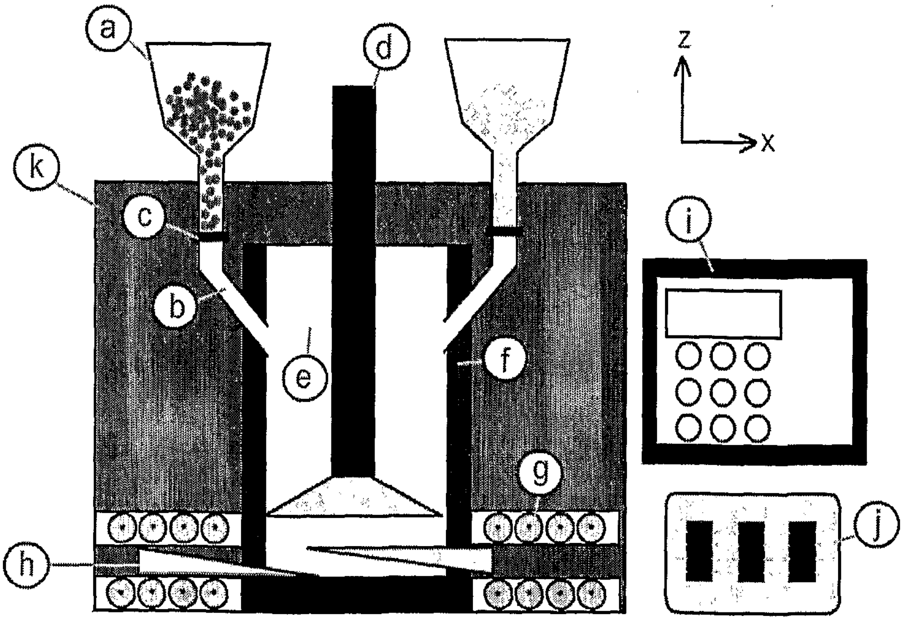
a
d
z
x
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FIG. 2

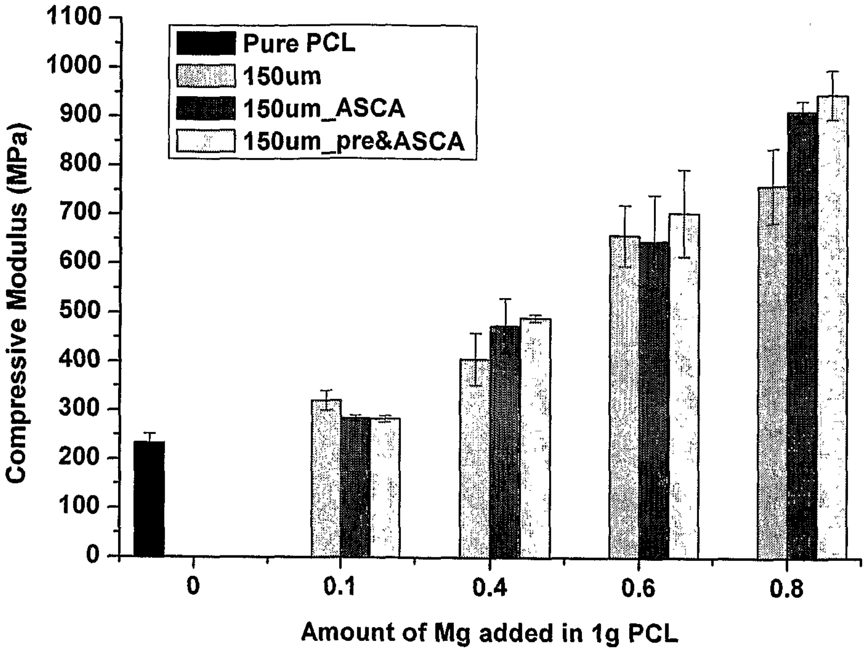
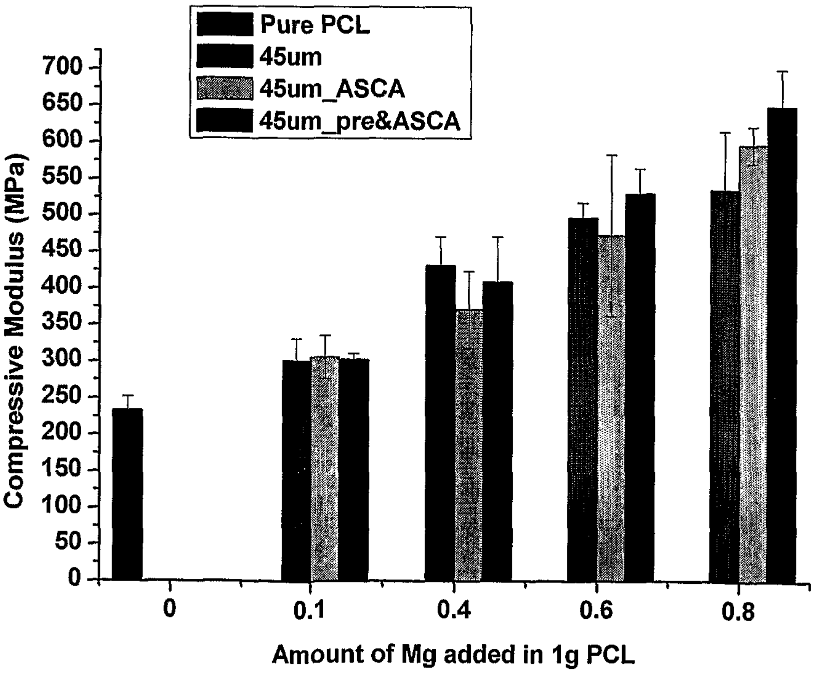

Pure PCL
150um
150um_ASCA
150um_pre&ASCA
Compressive Modulus (MPa)
1100
1000
900
800
700
600
500
400
300
200
100
0
0
0.1
0.4
0.6
0.8
Amount of Mg added in 1g PCL

FIG. 3


Pure PCL
45um
45um_ASCA
45um_pre&ASCA
Compressive Modulus (MPa)
700
650
600
550
500
450
400
350
300
250
200
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100
50
0
0
0.1
0.4
0.6
0.8
Amount of Mg added in 1g PCL

FIG. 4

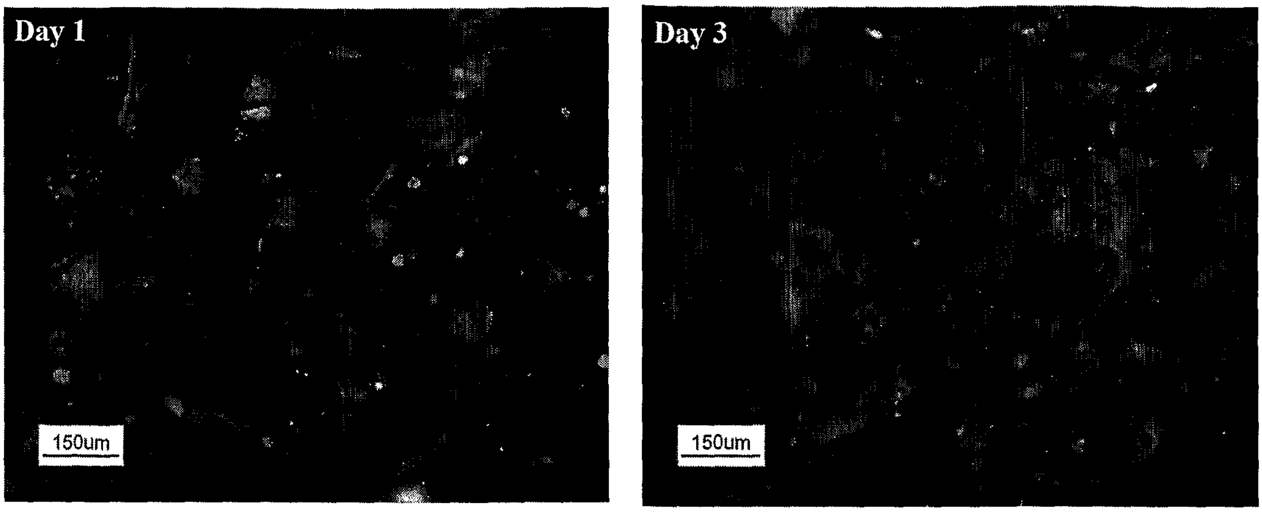

FIG. 5

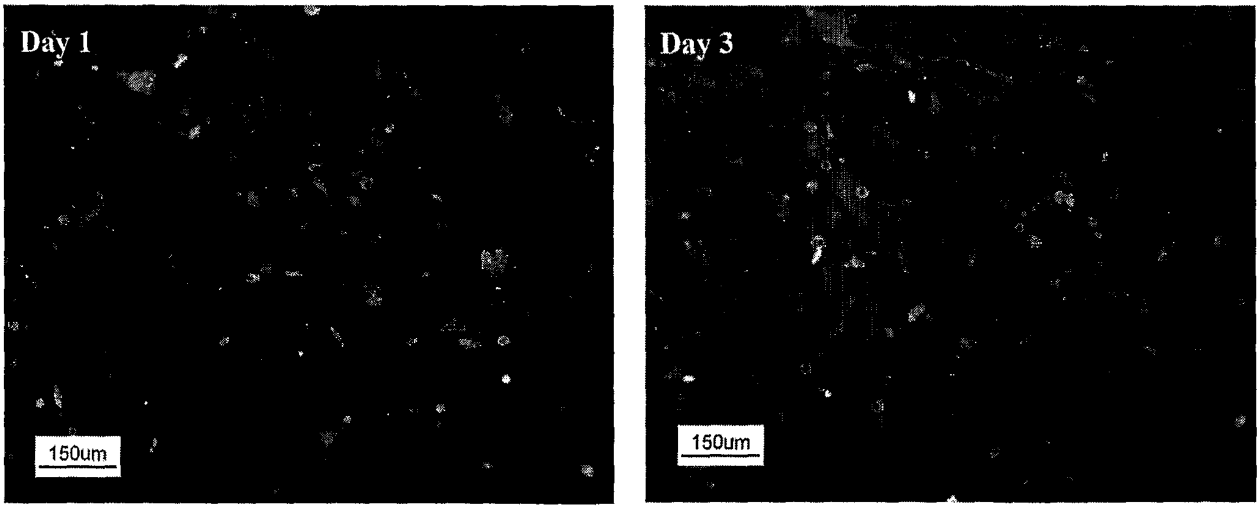

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2010/001053

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: A61L 27, A61L31

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)
CPRS,CNKI,EPODPC,WPI: polymer, biodegradable, metal+, silane, coupl+, +rolactone, magnesium, alloy, Mg, surface w treated

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2007/041972A1(CV THERAPEUTICS INC) 19 Apr. 2007(19.04.2007)	
	claim 1, description paragraph 0033, example 1	1-14,16-21
	CN101032632A (CHINESE ACAD SCI METALS INST) 12 Sep. 2007 (12.09.2007)	
X	claims 6 and 7	15,18-21
Y	claims 6 and 7	1-14,16-21
Y	CN1633313A (CV THERAPEUTICS INC) 29 Jun. 2005 (29.06.2005)	
	claim 1, description paragraph 0033, example 1	1-14,16-21

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" 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

"&"document member of the same patent family

Date of the actual completion of the international search 20 Aug. 2010 (20.08.2010)	Date of mailing of the international search report **28 Oct. 2010 (28.10.2010)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer ZHAO Jie Telephone No. (86-10)62084695

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/001053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN1628863A(UNIV DALIAN TECHNOLOGY) 14 Oct. 2004 (14.10.2004) whole document	1-21

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001053

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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		CA2625904A1	19.04.2007
		EP1937328B1	26.08.2009
		DE602006008814E	08.10.2009
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		EP1492581A1	05.01.2005
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		NZ534682A	27.10.2006
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		CN1279984C	18.10.2006
		DE60310540E	01.02.2007
		EP1764118A2	21.03.2007

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/001053

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		US2007071879A1	29.03.2007
		US2007071926 A1	29.03.2007
		CN1911460A	14.02.2007
		ES2276084T	16.06.2007
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		AU2003215495B	14.08.2008
		AU2008243209A1	04.12.2008
		MX262554B	26.11.2008
CN1628863A	14.10.2004	None	

Continuation of: second sheet, A. CLASSIFICATION OF SUBJECT MATTER

A61L 27/36 (2006.01) i
A61L 27/24 (2006.01) i
A61L 27/20 (2006.01) i
A61L 27/18 (2006.01) n
A61L 27/34 (2006.01) n
A61L 27/60 (2006.01) n