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(54) **Title:** SYSTEMS AND METHODS FOR SELECTIVE COATING REMOVAL FOR RESORBABLE METAL MEDICAL DEVICES

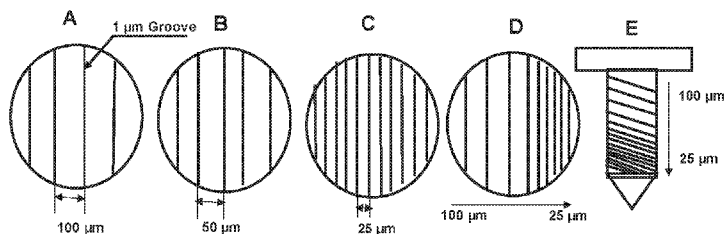


Figure 1

(57) **Abstract:** The invention relates to self-assembled organosilane coatings for resorbable medical implant devices. The coatings can be prepared from coating compositions containing organosilane and can be applied to metal or metal alloy substrates. Prior to applying the coatings, the surfaces of the substrates can be pretreated. The coatings can be functionalized with a binding compound that is coupled with an active component. The coatings can be selectively removed, e.g., patterned, to expose portions of the uncoated substrate. Selecting different patterns can provide the ability to regulate or control various properties, such as, corrosion and hydrogen generation.

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**SYSTEMS AND METHODS FOR SELECTIVE COATING REMOVAL
FOR RESORBABLE METAL MEDICAL DEVICES**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) from U.S. provisional patent application no. 62/290,555, entitled "SYSTEMS AND METHODS FOR SELECTIVE COATING REMOVAL FOR RESORBABLE METAL MEDICAL DEVICES", filed on February 3, 2016, the contents of which are incorporated herein by reference.

GOVERNMENT SUPPORT

This invention was made with government support under Grant No. EEC08 12348 awarded by the National Science Foundation (NSF). The government has certain rights in the invention.

Field of the Invention

[0001] The present invention relates to self-assembled organosilane-containing compositions, methods of preparing the compositions, systems and methods of depositing/applying the compositions on substrates to form coatings and selectively removing a portion of the coatings, e.g., patterning, to control or tune properties, including but not limited to, corrosion. The invention also relates to uses for the partially coated substrates as medical implant devices.

Background of the Invention

[0002] Every year millions of orthopedic and craniofacial surgical procedures are performed in the United States, which require placement of metal, e.g., stainless steel or titanium, hardware in a patient body. After bone healing is complete, these metal implant devices are no longer needed. The devices can be left *in situ* or, alternatively, they can be removed. Each of these alternatives has disadvantages or problems associated therewith. For example, leaving the hardware *in situ* increases the chances of infection and rejection, and removal of the hardware requires a second surgery and causes a risk of infection, pain and discomfort to the patient, as well as it being an additional expense. To overcome

these disadvantages or problems, there has been developed a number of resorbable polymeric devices that are effective to degrade over a period of time. Thus, the device does not remain in-situ and there is no need to surgically remove the device because when the device is no longer needed, the polymeric material degrades or dissolves within the patient body. However, there are also disadvantages associated with the resorbable polymer devices. For instance, it has been found that the resorbable polymeric materials, which are used for the construction of biodegradable medical implant devices, can lack mechanical strength as compared to that exhibited by metal implants and have a limited set of applications. As a result, there is an interest in the art to identify materials that degrade over time while demonstrating sufficient mechanical strength prior to degradation.

[0003] It has been found that the development of new technologies for implantable devices based on resorbable magnesium and magnesium alloys has the potential to make a significant clinical impact. Magnesium and magnesium alloys are suitable materials for the construction of resorbable devices because they have mechanical properties compatible to bone and can be resorbed over a period of time. However, there are other properties of magnesium and magnesium alloys that are problematic for their use as medical implant devices. For example, magnesium is not typically used in the fabrication of medical implant devices primarily because the corrosion of magnesium results in the production of hydrogen. Medical implant devices constructed of magnesium can cause the accumulation of hydrogen in areas surrounding the device and thus, result in the formation of gas cavities in the patient body. In order for magnesium and magnesium alloys to be considered as suitable materials for use in constructing medical implant devices, the rate of corrosion of these materials needs to be closely monitored and controlled to prevent formation of gas cavities. Thus, there are a number of important characteristics that have to be controlled in order to achieve the best clinical outcomes including, for example, rate of resorption, control of corrosion products, tissue integration and osteoconduction properties of the device.

[0004] It is known to deposit a coating composition on the surface of metal implant devices to modify the properties, e.g., corrosion, of the devices. Coatings for metal-based implants have been classified as conversion or deposition coatings. Conversion coatings are generally formed *in situ* through a reaction between the substrate and its environment, and are typically inorganic. For application to magnesium or

magnesium alloys, these coatings are often composed of oxides, phosphates or fluorides. Conversion coatings typically advantageously exhibit good adhesion to the substrate, however, there are disadvantages associated with mechanical durability and biocompatibility of these coatings. Deposition coatings are typically organic or ceramic and are applied through physical interactions with the surface of a metal substrate. For application to magnesium or magnesium alloy substrates, deposition coatings often require a conversion coating pre-treatment to improve adhesion to the alloy substrates. In the absence of a conversion coating pre-treatment, e.g., one-step coatings, it is likely that the coated substrate will demonstrate poor adhesion and corrosion protection.

[0005] There is a desire in the art to develop a mechanism for controlling the rates of corrosion of magnesium and magnesium alloy in order to reduce or minimize the production and accumulation of hydrogen resulting therefrom, and to construct medical implant devices from materials that demonstrate sufficient mechanical strength when needed and degradation over time when no longer needed. Further, there is a desire to develop a coating that is effective to control rates of corrosion of magnesium and magnesium alloy and to reduce or minimize the production and accumulation of hydrogen resulting therefrom, and demonstrates good adherence or adhesion to the magnesium and magnesium alloy. Moreover, it would be advantageous for the coatings to be capable of being customized or modified to allow properties, such as, corrosion and hydrogen generation, to be tuned or regulated.

SUMMARY OF THE INVENTION

[0006] An object of the present invention is to develop novel coating compositions for application to magnesium and magnesium alloy substrates for use as medical implant devices. In particular, an object of the present invention is to develop hybrid bio-inspired anticorrosive coatings based on self-assembled multilayer organosilane. The surface of these coatings can be modified via covalent bonding with an active component, including bioactive molecules, such as proteins and peptides. These surface chemistry modifications can provide the ability to control different physical chemical properties of the coatings, including but not limited to, hydrophobicity and charge, as well as bioactivity. These coatings can effectively control the degradation rate of magnesium and magnesium alloy resorbable devices to insure safety and efficiency.

and to induce desirable tissue responses. Further, these coatings can be functionalized to regulate the rate of corrosion and insure the device integration into target tissues.

Furthermore, these coatings can be selectively removed, e.g., patterned, to expose portions of uncoated substrate, which can be effective to regulate pre-selected properties, such as, but not limited to corrosion rate.

[0007] In one aspect, the invention provides a medical implant device including a magnesium or magnesium alloy substrate, having a first surface and an opposing second surface; a self-assembled organosilane-containing coating applied to at least one of the first and second surface; and a pattern applied to the coating on at least one of the first and second surfaces. The pattern includes one or more areas of selective removal of the coating from the substrate. Further, a binding compound can be combined with the coating and furthermore, an active component can be coupled to the binding compound.

[0008] In certain embodiments, a binding compound is combined with the coating. Furthermore, an active component can be coupled to the binding compound.

[0009] The device can also include a pretreatment applied to the at least one of the first and second surfaces, and the coating applied to the pretreatment.

[0010] In certain embodiments, a first portion of the pattern has a first configuration and a second portion of the pattern has a different, second configuration.

[0011] The one or more areas of selective removal of the coating is effective to increase the corrosion rate of the substrate.

[0012] In another aspect, the invention provides a method of forming a patterned coating on a medical implant device. The method includes obtaining a uncoated substrate having a top surface and an opposing bottom surface; preparing a coating composition including organosilane; applying the coating composition to at least one of the top and bottom surfaces of the uncoated substrate to form a coating thereon; and selectively removing a portion of the coating to expose the uncoated substrate.

[0013] The method can further include functionalizing the coating with a binding compound, and coupling an active component to the binding compound.

[0014] The step of selectively removing can include a process selected from the group consisting of laser ablation, ion etching, electron beam etching and combinations thereof. The selective removal of a portion of the coating forms a pattern exposing one or more areas of the uncoated substrate. Furthermore, one or more of the size, density and

spatial distribution of the one or more areas of the uncoated substrate is controlled to regulate a pre-selected property, such as, corrosion rate.

[0015] In certain embodiments, a portion of the coating is selectively removed to expose the uncoated substrate on both of the top and bottom surfaces.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 is a schematic that shows various patterns formed by selectively removing a coating deposited on a magnesium or magnesium alloy substrate to expose portions of uncoated substrate for use in regulating corrosion rate, in accordance with certain embodiments of the invention;

[0017] Figure 2 shows SEM micrographs A, B and C of laser ablated substrate samples at various magnifications, i.e., A is low magnification, B is intermediate magnification and C is high magnification, wherein the coating is completely removed in the ablated areas and the underlying metal remains intact, in accordance with certain embodiments of the invention;

[0018] Figure 3 is a plot of hydrogen evolution verses time (i.e., days) for patterned Mg-OH-AS coated substrate samples, in accordance with certain embodiments of the invention; and

[0019] Figure 4 is a SEM micrograph that shows a patterned magnesium disk exposed to simulated body fluid (SBF) for a period of seven days with a bare Mg side on the left and AS coated on the right, and wherein insets show an EDS spectra from the respective areas, in accordance with certain embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The invention generally relates to self-assembled organosilane-containing coating compositions applied to, or deposited on, substrates to form patterned coatings; and methods of applying/depositing the coating compositions onto the substrates, and subsequently selectively removing a portion or part of the coatings to expose the uncoated substrates (e.g., underneath the coatings). The invention also relates to the use of the patterned coated substrates in constructing and fabricating medical implant devices for use in various surgical applications, such as, but not limited to, dental, orthopedic, craniofacial, and cardiovascular.

[0021] The substrates, e.g., medical implant devices, can be composed of a wide variety of materials that are known in the art for such purposes. In accordance with the objectives of controlling the rates of corrosion of the substrates in order to reduce or minimize the production and accumulation of hydrogen resulting therefrom, and to construct medical implant devices from materials that demonstrate sufficient mechanical strength when needed and degradation over time when no longer needed, it is preferred that the substrates, e.g., medical implant devices, be composed of magnesium or magnesium alloy.

[0022] In certain embodiments, the coating composition is directly applied to, or deposited on, the surface of the substrate, e.g., medical implant device, in the absence of any pretreatment or pre-coating of the surface, to form a coating thereon. However, in other embodiments, for the purpose of improving the adherence and/or adhesion of the coating to the surface of the substrate, a pretreatment or pre-coating is applied to the surface of the substrate prior to applying the coating composition. Suitable pretreatments or pre-coatings include those known in the art for use with magnesium or magnesium alloy substrates to improve adherence and/or adhesion of a coating to the surface of the substrates.

[0023] Following the application of the coating composition and formation of the resultant coating on the surface of the substrate, the coating is partially removed. The partial removal of the coating from the surface of the substrates can be selectively conducted by forming various patterns of coated and uncoated substrate. In certain areas of the pattern, the uncoated surface of the substrate is exposed and in other areas, the surface has the coating applied thereto. The selective removal, e.g., pattern, can be effective to regulate or control certain properties of the substrate, such as, corrosion rate and hydrogen generation.

[0024] Without intending to be bound by any particular theory, it is believed that the patterned coatings are effective to modify various properties and characteristics of the underlying magnesium/magnesium-containing substrate of the a medical implant device. For example, a patterned coating can be effective to control one or more of the following properties of the magnesium/magnesium-containing substrate: corrosion rate, production/accumulation of hydrogen, rate of resorption, tissue integration and osteoconduction. In certain embodiments, the patterned coating can be effective to reduce or preclude the corrosion rate and, in turn, the production-accumulation of

hydrogen. Further, the surface of the coated portions of the substrate can include covalent bonding with different molecules, including bioactive molecules, such as proteins and peptides.

[0025] Surface chemistry modifications can provide the ability to control different physical chemical properties of the coating, including but not limited to, hydrophobicity and charge, as well as bioactivity. Furthermore, the patterned, substrate surface including coated and uncoated portions or parts can be used to control or regulate pre-selected or desired properties.

[0026] Conventional apparatus and techniques are generally known for preparing and applying/depositing a silane coating composition onto a substrate, modifying or functionalizing the surface of the formed silane coating, and selectively removing a portion of the coating formed. For example, various amphiphilic organosilanes are used to form nanostructured films for glass coating applications, and the application of organosilanes for corrosion control are known. However, there is a need in the art to develop organosilane-containing compositions for use in coating resorbable metallic, e.g., magnesium and magnesium alloy, substrates, such as medical implant devices. In particular, the coatings for medical implant devices require special properties, including the ability to adapt to the intrinsically unstable physical and chemical environment of a corroding metal substrate, as well as the ability to be functionalized with bioactive molecules.

[0027] In general, self-assembled coatings, e.g., monolayers, are thin films produced by deposition of materials, such as, organosilanes. The coatings are formed, e.g., spontaneously, on a surface of a substrate by adsorption and include a head group, tail and functional end groups. The head group can be in a vapor phase or a liquid phase. The head group assembles onto the substrate surface, while the tail group organizes and assembles farther from the surface of the substrate. The substrate and head group are selected to react with each other. In certain embodiments, a hydrophilic end (e.g., head group) may bond with the substrate surface while a hydrophobic end may be opposite the hydrophilic end.

[0028] In accordance with the invention, the self-assembled coating compositions include organosilane, such as, hybrid organosilanes. In certain embodiments, the coating compositions include amphiphilic organosilanes having an aliphatic tail containing a backbone of 4 to 20 carbon atoms (i.e., C₄ to C₂₀) and a silane head. A non-limiting

example of suitable organosilanes include alkylsilanes, such as, alkylalkoxysilanes including, but not limited to, decyltriethoxysilane. In certain embodiments, the alkylalkoxysilanes, such as, but not limited to, decyltriethoxysilane, are co-polymerized with another polymer component, such as, but not limited to, tetramethoxysilane (TMOS). Further, in certain embodiments, the alkyltrialkoxysilanes are combined with a crosslinking material, such as, but not limited to, a UV crosslinking agent.

[0029] The self-assembled coating compositions are applied or deposited onto the magnesium or magnesium alloy surface, e.g., of the medical implant device. The magnesium alloy may be selected from a wide variety of magnesium alloys known in the art for constructing medical implant devices. Non limiting examples of suitable magnesium alloys include those magnesium-containing compositions described in PCT Application having International Application No. PCT/US2012/058939 entitled "Biodegradable Metal Alloys" filed on October 5, 2012, published as US20140248288 on September 4, 2014, and issued as US Patent 9,510,932 on December 6, 2016, and based on United States Provisional Patent Application 61/544,127 entitled "Biodegradable Metal Alloys" filed on October 6, 2011, which are incorporated in their entirety herein by reference.

[0030] In certain embodiments, the magnesium alloys include elemental magnesium and one or more other elemental components, such as, but not limited to, iron, zirconium, manganese, calcium, yttrium and zinc. The amount of each of the components can vary and, in general, the amounts are selected such that the resulting magnesium alloys are within acceptable non-toxic limits, sufficiently biocompatible and degradable over a period of time.

[0031] In general, the self-assembled organosilane coatings can be formed using known apparatus and conventional coating techniques, including, but not limited to, physical vapor deposition, electro-deposition or electro-less deposition. For example, a self-assembled coating can be formed on a magnesium or magnesium alloy substrate at ambient conditions by spinning, dipping or spraying techniques, which are known in the art. In certain embodiments, a coating is formed by employing a deep-coating process at ambient conditions. This process includes combining organosilane and solvent, e.g., water, to form a solution and applying the solution to a magnesium or magnesium alloy substrate by dipping-immersing the substrate into a bath of the solution. The immersion can be for a time period ranging from minutes to hours and, typically includes sufficient

time to allow the organosilane to bond to the substrate. As previously described, the solution can be applied directly to the substrate (in the absence of pretreating or pre-coating) or the solution can be applied to a pretreated or pre-coated substrate. Subsequent evaporation of the solvent, by conventional methods, induces the organosilane to self-assemble into micro- or nano-structures and thin film. The resulting coating, e.g., thin film, is rigid, uniform and has a thickness that can vary from about 100 nanometers to tens of micrometers

[0032] The coating thickness can depend on various factors including the organosilane composition components, the process conditions and the intended use of the coated substrate. In one embodiment, the coating has a thickness of about 1 μm . Further, the coating, e.g., laminar structure, can include multiple layers. In certain embodiments, the coating may be composed of about 30 nm thick layers. Furthermore, the coating can be hydrophobic which may be particularly beneficial for cardiovascular applications.

[0033] The coating process in accordance with the invention can optionally include pre-treating or pre-coating the surface of the substrate prior to applying/depositing the organosilane coating composition thereto. The pre-treatment or pre-coating is applied to, or deposited on, the bare, e.g., uncoated, surface of the magnesium or magnesium alloy substrate. The pre-treatment/pre-coating step can vary and may be selected from known pretreatment compounds/compositions, techniques and processes that are employed to improve adherence or adhesion of a coating to the surface of a substrate. In certain embodiments, the pretreatment includes polishing and/or etching the uncoated substrate with nitric acid, and/or passivating with sodium hydroxide. Without intending to be bound by any particular theory, it is believed that pretreating the substrate prior to applying the coating composition, e.g., solution, results in a more uniform coating having improved adhesion or adherence properties, as compared to coatings that are formed in the absence of pretreating the substrate.

[0034] The coating in accordance with the invention has numerous advantages as compared to conventional coatings, including, but not limited to, for example, tunability and controllability. The thickness of the coating and its mechanical properties can be tuned or controlled. For example, using organosilanes with UV crosslinkable groups provides the ability to increase stiffness simply by exposure to a UV source. Further, copolymerizing organosilanes with tetramethoxysilane produces liquid-like coatings

having increased flexibility, which may be particularly useful for cardiovascular applications.

[0035] Furthermore, the surface of the coatings can be modified or functionalized to attach or bind an active component. A binding compound, such as, but not limited to amine, carboxyl, thiol, hydroxyl and mixtures thereof, is used to bind one or more active components to the coatings. In certain embodiments, the binding compound is attached to the surface of the coating. For example, a plurality of molecules containing silane groups, e.g., aminosilanes, such as, but not limited to aminopropyl-trimethoxysilane, can be covalently attached to the surface of the coating to provide chemistry for attachment of the active component, such as, but not limited to alkaline phosphatase, or for modifying hydrophobicity of the surface. In certain other embodiments, the binding compound can be permeated or encapsulated within the composition that is applied to the substrate to form the coating.

[0036] As used herein, the term "active component" and related terms refer to at least one molecule, compound, complex, adduct and/or composite that exhibits one or more beneficial activities, such as, therapeutic activity, diagnostic activity, biocompatibility, corrosion-resistance, and the like. Active components that exhibit a therapeutic activity can include bioactive agents, pharmaceutically active agents, drugs and the like. Non-limiting examples of bioactive agents include, but are not limited to, bone growth promoting agents, such as growth factors, drugs, proteins, antibiotics, antibodies, ligands, DNA, RNA, peptides, enzymes, vitamins, cells and the like, and combinations thereof.

[0037] With the binding of one or more active components, the coatings and coated magnesium or magnesium alloy substrates, can be effective to combine anti-corrosion properties with bioactive surface modifications, which can facilitate improved tissue integration and induce desired biological responses in resulting medical implant devices.

[0038] Moreover, the coatings, e.g., thin films, formed as a result of the self-assembled coating compositions applied or deposited onto the magnesium or magnesium alloy surface, e.g., of the medical implant device, can be partially, e.g., selectively, removed to regulate or control various properties, such as, corrosion. The selective removal of the coating to expose portions or parts underneath, e.g., uncoated substrate, can be performed by employing various conventional techniques and apparatus known in

the art. For example, selective removal of a coating can be conducted using one or more of laser ablation, ion etching and electron beam etching. In certain embodiments, the selective removal can include forming various patterns in the coating. The patterns can include a plurality of lines or grooves. The number, width and configuration of the lines or grooves can vary, and may correspond to, or depend on, a pre-determined amount of exposed uncoated surface necessary to achieve pre-selected or desired properties.

Further, the pattern can be formed on one or more surfaces of the substrate. For example, wherein the substrate has upper and lower surfaces, the pattern can be formed on one or both of these surfaces.

[0039] Without intending to be bound by any particular theory, it is believed that selective removal of the coating eliminates inhibition of the corrosion in the exposed areas of the substrate and increases the rate of corrosion. By changing size, density and spatial distribution of exposed areas of the substrate, the corrosion rate of the entire substrate, e.g., medical implant device, or portions or parts thereof can be controlled or tuned.

[0040] FIG. 1 is a schematic showing a plurality of coated substrates A, B, C, D and E, having a given surface area and various removal patterns formed by lines, e.g., grooves, applied to the surface. As shown in FIG. 1, substrate B has a greater density of grooves, e.g., a higher number of grooves or less spacing between the grooves, in the pattern as compared to substrate A. Substrate C has a greater density of grooves in the pattern as compared to both substrates A and B. In substrate A, there are four, 1- μ m wide grooves spaced apart by a distance of 100 μ m. Substrate B has five grooves and shows a spacing of 50 μ m, and substrate C has 11 grooves with a spacing of 25 μ m. An increase in the density, e.g., higher number of grooves or less spacing between the grooves, results in an increase in the exposed area of the uncoated substrate and therefore, an increase in the rate of corrosion. A similar effect may be achieved by varying the width of the exposed areas, e.g., grooves, without changing their density. In FIG. 1, substrates D and E show that the rate of corrosion can be spatially regulated in different portions or parts, e.g., of a medical implant device, by having the density of the grooves be different for certain portions or parts. That is, the pattern for substrate D has a lesser density of grooves on the left-side portion of the disk and a greater density of grooves toward the right side portion of the disk. From left to right, the spacing is shown to decrease from 100 μ m to 25 μ m. Similarly, the pattern for the screw E has a lesser density of grooves at

the top portion of the shaft and a greater density of grooves toward the lower portion of the shaft. From top to bottom, the spacing is shown to decrease from 100 um to 25 um.

[0041] Patterned, organosilane-coated, magnesium or magnesium-containing substrates, in accordance with the invention, are generally effective for tissue regeneration and, in particular, bone regeneration, within a body of a patient. These substrates can be employed as materials of construction for various medical implant devices. Non-limiting examples of suitable medical devices include, but are not limited to, scaffolds, plates, meshes, staples, screws, pins, tacks, rods, suture anchors, tubular mesh, coils, x-ray markers, catheters, endoprotheses, pipes, shields, bolts, clips or plugs, dental implants or devices, such as but not limited to occlusive barrier membranes, graft devices, bone-fracture healing devices, bone replacement devices, joint replacement devices, tissue regeneration devices, cardiovascular stents, nerve guides, surgical implants and wires.

[0042] It will be appreciated by those skilled in the art that changes can be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed and the following examples conducted, but it is intended to cover modifications that are within the spirit and scope of the invention.

EXAMPLES

Example 1 - Patterning of Coated Mg Samples

[0043] A plurality of Mg-OH-AS (wherein AS represents alkylsilane) coated substrate samples were patterned with the use of laser ablation. Several 0.2 mm-wide lines were etched on each of the top and bottom surfaces of AS-coated disks by laser ablation (as shown in views A, B and C of Figure 2). The laser ablation was conducted using a low energy setting such that the treatment removed only the AS coating and the underlying substrate remained intact.

Example 2 - Hydrogen Evolution

[0044] Four experimental groups of three samples each were assembled, including: (a) bare Mg-OH disks (absent of a coating), (b) Mg-OH-AS coated disks with 6-line patterns, (c) Mg-OH-AS coated disks with 4-line patterns, and (d) fully-coated Mg-

OH-AS disks (absent of a pattern). Hydrogen evolution experiments were conducted over a seven-day period. As shown in Figure 3, the results of these experiments demonstrated that the presence of patterning increased the corrosion rate of the Mg-OH-AS samples (i.e., (b) and (c)) as compared to the Mg-OH-AS sample absent of patterning (i.e., (d)). However, the rate of corrosion was significantly lower for the patterned substrates (i.e., (b) and (c)) as compared to the bare Mg-OH substrate (i.e., (a)). The differences among the four groups were highly statistically significant ($p < 0.0001$). Furthermore, the initial corrosion burst was prevented in the patterned Mg-OH-AS samples (i.e., (b) and (c)). These results demonstrate that the corrosion rate of the substrate, e.g., medical implant device, can be fine-tuned by partial removal of the coating from the substrate.

Example 3 - Prevention of calcium phosphate deposition

[0045] It was determined that local pH increase in an area around the corroding Mg devices led to spontaneous calcium phosphate precipitation. This is a highly undesirable outcome, especially in cardiovascular applications (e.g., stents and other devices). The present data indicated that the AS coatings effectively prevented calcium phosphate precipitation and therefore, may be effective to reduce calcium phosphate formation in the area of a medical implant device constructed of the substrate in accordance with the invention.

Example 4 - Elemental Analysis

[0046] Elemental analysis of the patterned Mg samples containing AS coated and non-coated areas was conducted and revealed the presence of calcium and phosphate on exposed areas while these elements were not detected on the coated areas (see Figure 4). The results of the elemental composition are shown in Table 1 below.

Table 1. The elemental composition of the AS coated and uncoated areas of a Mg sample

Element K edge	Corroded Area		Coated Area	
	Weight%	Atomic%	Weight%	Atomic%
O	48.79	62.24	25.81	35.57
Mg	29.69	24.93	50.88	46.14
P	<u>8.76</u>	<u>5.77</u>	-	-
Cl	8.57	4.93	-	-
Ca	<u>4.19</u>	<u>2.13</u>	-	-
Si	-	-	23.31	18.30

We claim:

1. A medical implant device, comprising:
 - a substrate selected from the group consisting of magnesium and magnesium alloy, having a first surface and an opposing second surface;
 - a self-assembled organosilane-containing coating applied to at least one of the first and second surfaces; and
 - a pattern applied to the coating on at least one of the first and second surfaces, the pattern comprising:
 - one or more areas of selective removal of the coating from the substrate.
2. The device of claim 1, further comprising a binding compound combined with the coating.
3. The device of claim 2, further comprising an active component coupled to the binding compound.
4. The device of claim 1, further comprising a pretreatment applied to at least one of the first and second surfaces, and the coating applied to the pretreatment.
5. The device of claim 1, wherein a first portion of the pattern has a first configuration and a second portion of the pattern has a different, second configuration.
6. The device of claim 1, wherein the one or more areas of selective removal is effective to increase the corrosion rate of the substrate.
7. A method of forming a patterned coating on a medical implant device, comprising:
 - obtaining an uncoated substrate having a top surface and an opposing bottom surface;
 - preparing a coating composition comprising organosilane;

applying the coating composition to at least one of the top and bottom surfaces of the uncoated substrate to form a coating thereon; and

selectively removing a portion of the coating to expose the uncoated substrate.

8. The method of claim 7, further comprising functionalizing the coating with a binding compound.

9. The method of claim 8, further comprising coupling an active component to the binding compound.

10. The method of claim 7, wherein the selectively removing includes a process selected from the group consisting of laser ablation, ion etching, electron beam etching and combinations thereof.

11. The method of claim 7, wherein the selectively removing a portion of the coating forms a pattern exposing one or more areas of the uncoated substrate.

12. The method of claim 11, wherein one or more of the size, density and spatial distribution of the one or more areas of the uncoated substrate is controlled to regulate a pre-selected property.

13. The method of claim 12, wherein the property is corrosion rate.

14. The method of claim 7, wherein the selectively removing a portion of the coating to expose the uncoated substrate is performed on both of the top and bottom surfaces.

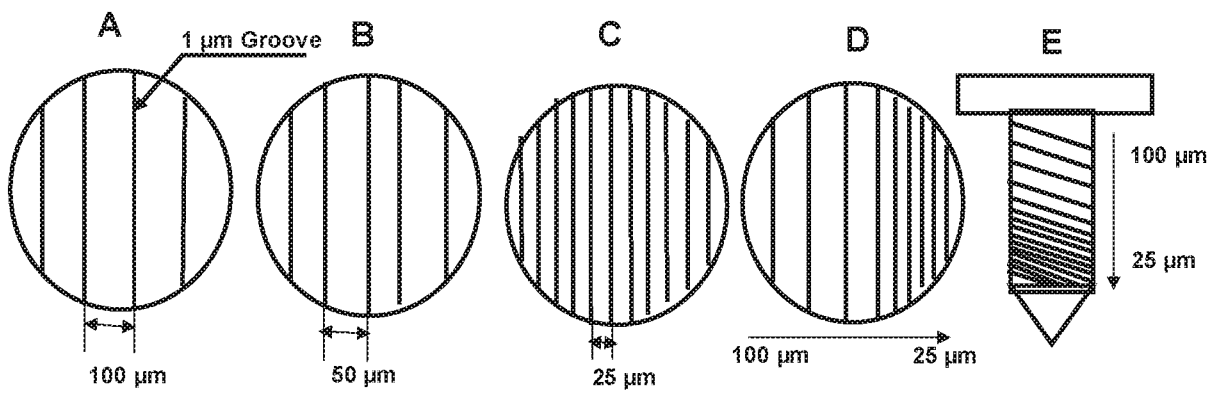


Figure 1

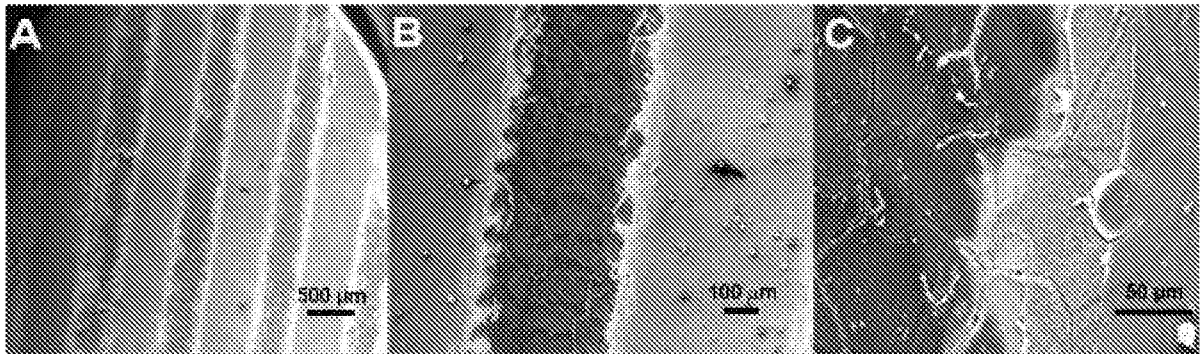


Figure 2

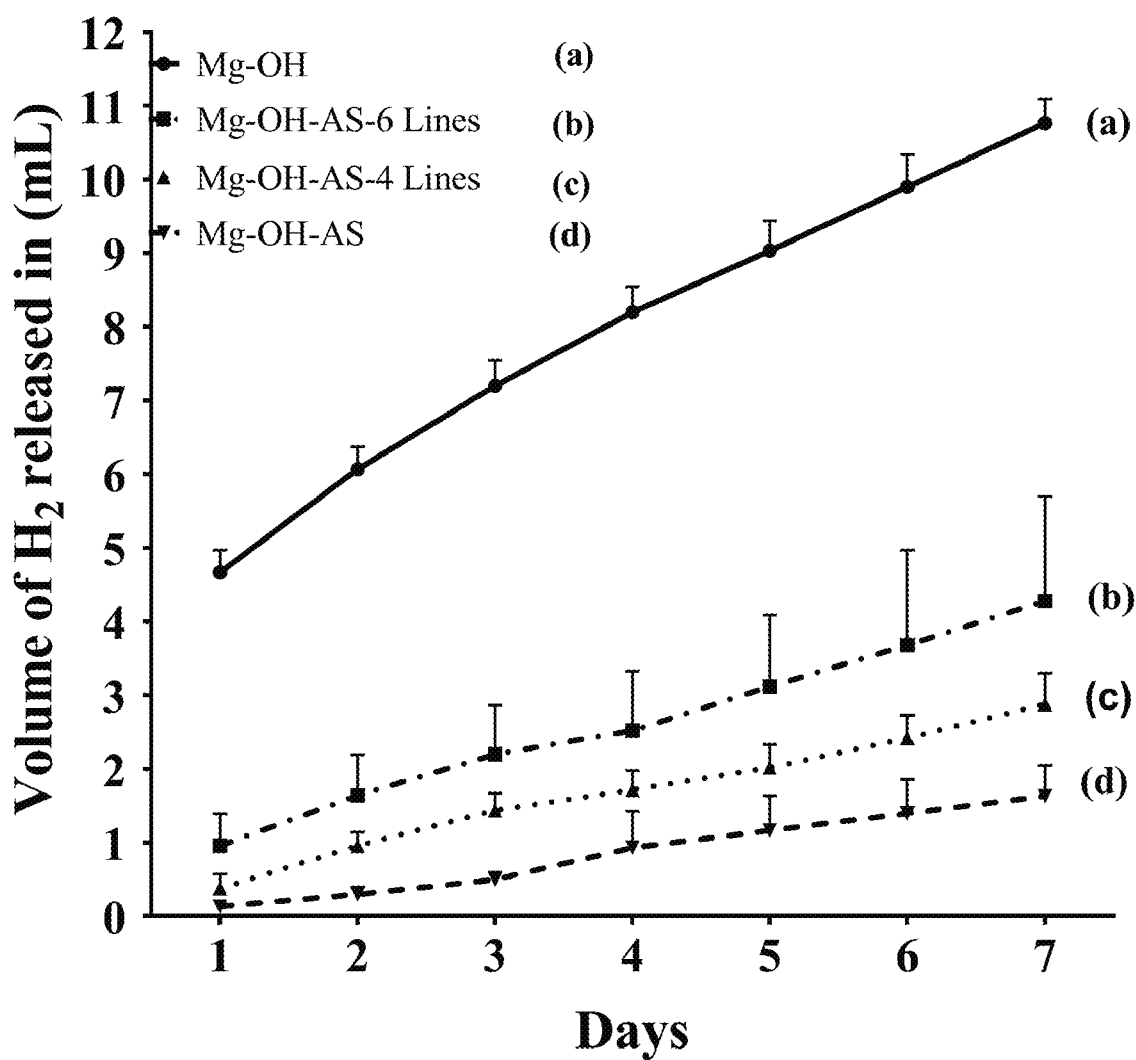


Figure 3

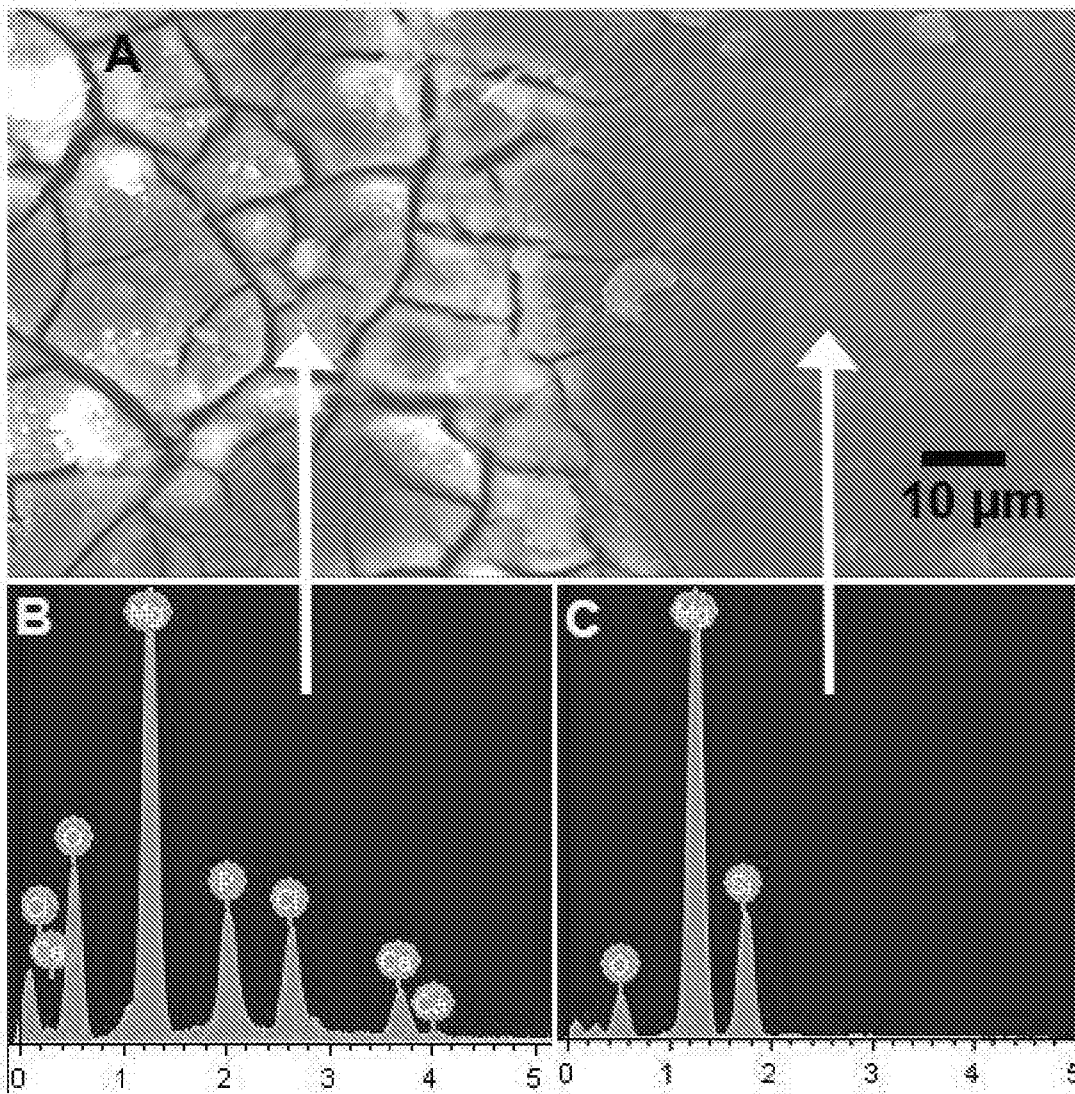


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/016347**A. CLASSIFICATION OF SUBJECT MATTER**

A61L 27/04(2006.01)i, A61L 27/28(2006.01)i, A61L 27/54(2006.01)i

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)

A61L 27/04; A61F 2/02; A61F 2/06; A61F 2/82; A61L 27/28; A61L 27/54

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: metal, alloy, degradation, oragno, silane, coating, pattern, selectively, remove, magnesium, corrosion, spinal, implant, medical, device

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category [*]	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	W0 2006-108065 A2 (ELIXIR MEDICAL CORPORATION et al.) 12 October 2006 See paragraphs [0058], [0059]; claims 38, 145, 150, 160, 163.	1-14
Y	US 2009-0123516 A1 (AGRAWAL et al.) 14 May 2009 See claims 1, 13, 122.	1-14
A	LIU, X. et al., Biofunctionalized anti-corrosive silane coatings for magnesium alloys, Acta Biomaterialia, 2013, Vol. 9, pages 8671-8677 See the whole document.	1-14
A	WO 2015-069919 A1 (WICHITA STATE UNIVERSITY et al.) 14 May 2015 See the whole document.	1-14
A	ZUCCHI, F. et al., Organo-silane coatings for AZ31 magnesium alloy corrosion protection, Materials Chemistry and Physics, 2008, Vol. 110, pages 263-268 See the whole document.	1-14

I 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

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"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

12 May 2017 (12.05.2017)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/016347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006-108065 A2	12/10/2006	AU 2006-231652 AI	12/10/2006
		CA 2604419 AI	12/10/2006
		CA 2604419 C	24/03/2015
		CA 2885981 AI	12/10/2006
		CN 101257860 A	03/09/2008
		CN 101257860 B	21/10/2015
		CN 104146795 A	19/11/2014
		CN 105030390 A	11/11/2015
		EP 1865882 A2	19/12/2007
		EP 2796112 AI	29/10/2014
		EP 2796112 BI	16/11/2016
		JP 2008-534232 A	28/08/2008
		JP 2013-063319 A	11/04/2013
		JP 2014-176740 A	25/09/2014
		JP 2016-052602 A	14/04/2016
		JP 5312018 B2	09/10/2013
		JP 5572686 B2	13/08/2014
		US 2006-0229711 AI	12/10/2006
		us 2016-0128849 AI	12/05/2016
		wo 2006-108065 A3	28/06/2007
US 2009-0123516 AI	14/05/2009	wo 2007-019478 A2	15/02/2007
		wo 2007-019478 A3	24/05/2007
WO 2015-069919 AI	14/05/2015	us 2016-0271301 AI	22/09/2016