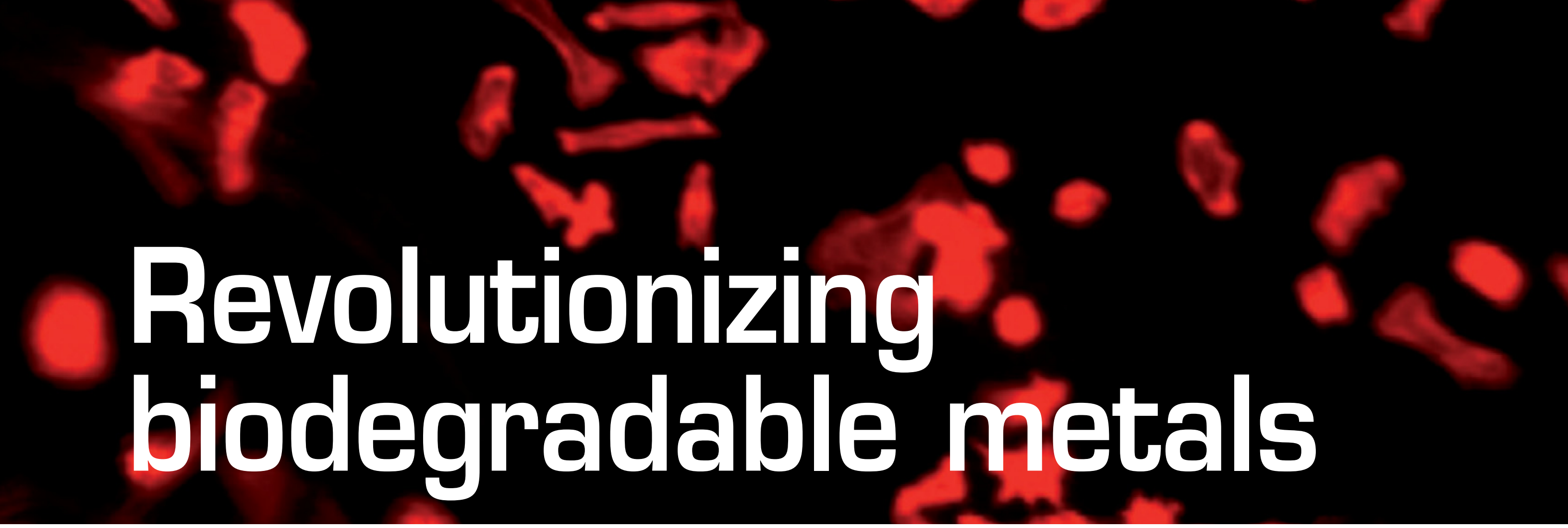

Revolutionizing biodegradable metals

Development of biodegradable metal implants is a complex problem because it combines engineering and medical requirements for a material. This article discusses the development of sensing and corrosion control techniques that can help in the design of biodegradable metallic implants. Biodegradable metallic implants dissolve as new tissue is formed. One of the most important factors in the design of biodegradable implants is to study the active interface, which should be monitored and controlled to address the medical concern of biocompatibility. Thus miniaturized and nanotechnology-based sensors that measure the activities of the degradation process and the formation of tissue are discussed for use with *in vitro* and *in vivo* experiments. These sensors can monitor chemical components and also cell activity and can provide new knowledge about biodegradable interfaces and how to actively control the interface to provide the best bioactivity to regenerate new tissue in a short time. Development of new alloys, nano-materials, miniature sensors, corrosion control coatings, and auxiliary applications such as biodegradable drug delivery capsules is expected to open up a new era in the engineering of materials for medicine.

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Importance of biodegradable metallic implants

Market research indicators put the total US biomedical implant market at about US$27bn, the biocompatible materials market at about US$11bn, the microelectronics medical implant market at about US$12bn, and these markets are increasing at about nine percent per year. Writers and inventors like Robert Freitas, Justin Rattner, and Ray Kurzweil are describing the interfacing of men and machines. The national institutes of health roadmap plan and national science foundation programs are producing phenomenal progress in biomedical research. These are examples of the increasing spotlight on developing engineered systems that can interface with the human body and that promise to improve our quality of life and reduce our costs for health care. Biodegradable systems in particular offer large advantages in specific applications over implants used today. The promise is that new kinds of implants based on biodegradable metals such as magnesium and iron can adapt to the human body in which they are implanted and eventually dissolve when no longer needed. That would spare patients such as children suffering from cleft palate or with fractures, angular deformities of long bones, or limb length discrepancies the pain and expense of multiple procedures used to implant, then later remove, refit and re-implant the current generation of devices. As another example, metallic wire mesh stents are currently used for millions of people to treat blockages in the coronary artery or at other locations in the circulatory system. In a small percentage of cases the stent may elicit an immune response that leads to the growth of scar tissue and the formation of blood clots. If blockages form again, these stents are difficult to remove and additional stents must be inserted. Using biodegradable stents could avert this cycle and minimize the number of invasive procedures. Biodegradable stents as well as most proposed biodegradable implants will have their own target and market as in this case of younger patients having congenital heart disease or adult patients that are prone to restenosis. This article surveys the literature and covers a wide area to describe activities that are underway to make biodegradable metals practical. Included are new techniques to produce tunable degradable metallic implants, innovative coating technologies to yield special surface functionalities, new materials, and methods to develop nanodevices for monitoring implants.

Corrosion monitoring of implants

Corrosion mechanism

The standard electrode potential of magnesium (Mg) is -2.37 V measured against a standard hydrogen electrode (SHE), which is given a standard electrode potential of zero volts. This standard potential is so negative that Mg is widely used for sacrificial anodes for cathodic metal protection. The corrosion rate of Mg is very low in air, but is high in chlorides and sulphate solutions. As shown in the Pourbaix (Potential-pH) diagram in Fig. 1a, Mg corrosion can be controlled by changing the local pH or potential. The degradation processes of biodegradable Mg implants are complex[1-10]. Mg is dissociated by a corrosion reaction with water to produce a crystalline film of magnesium hydroxide and hydrogen, and Mg particles are also mechanically detached by hydrogen stress cracking. Fig. 1b shows a schematic of Mg corrosion. The important reaction products to look at

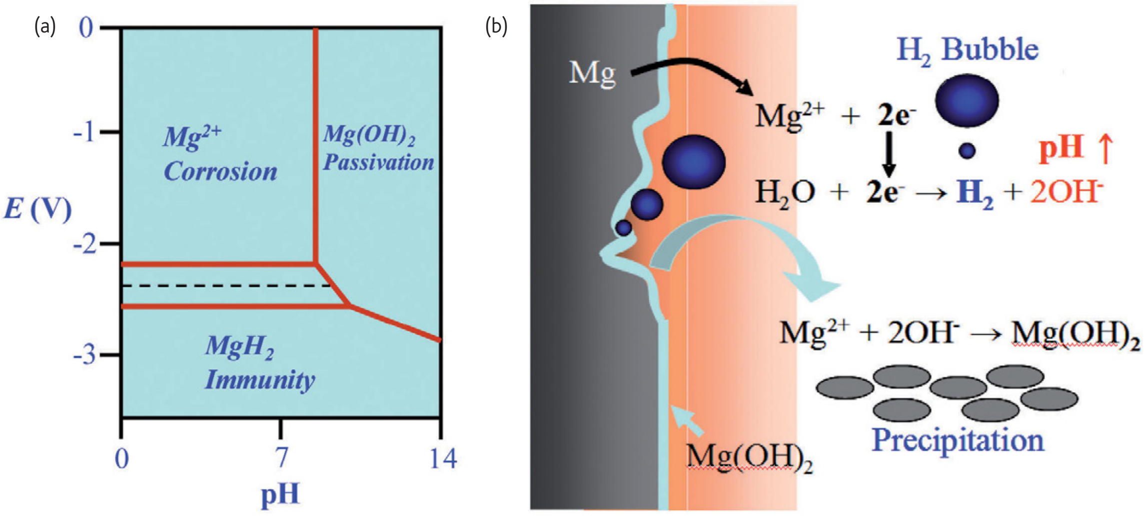

Fig. 1 Corrosion characteristics of Mg: (a) Equilibrium of Mg-H_2O systems in the presence of H_2 at 25 °C (modified from[7]); (b) Schematic representation of Mg degradation, Mg dissolves as Mg^{2+} which reacts with water, generates hydrogen bubbles, creates hydroxyl groups, and increases pH. Micro-bubbles that get larger and float in the air are generated from pitting or active corrosion sites. Dissolved divalent Mg^{2+} ions react with hydroxyl groups (OH^{--}) and precipitate as Mg hydroxide. Also, a passive interlayer of Mg hydroxide or Mg oxide is formed on the degradation surface.

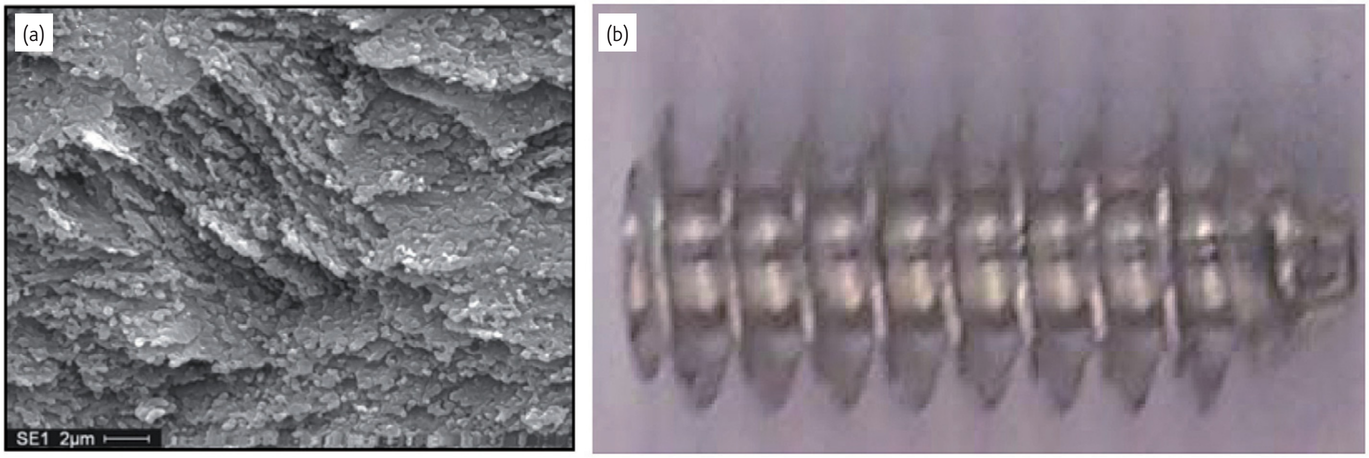

Fig. 2. Corrosion of components: (a) environmental scanning electron microscope (ESEM) image of Mg (99.9% purity) after 24 hour immersion in 0.15 M NaCl; (b) a Mg-4% wt Yitrium alloy screw. After a severe injury of the anterior cruciate ligament (ACL), repair screws may be used as part of reconstruction surgery. Biodegradable screws may return the joint closer to its original condition.

for biological applications are hydrogen evolution (H_2), hydroxyl groups (OH^{--}), and magnesium hydroxide ($Mg(OH)_2$).

Compared to conventional metals such as aluminum and iron and their alloys, Mg and Mg alloys have an unusual corrosion behavior. For example, Song *et al.* suggested a different corrosion mechanism of Mg and its alloys called the negative difference effect (NDE) which describes the phenomenon that the rate of hydrogen evolution increases with increasing anodic polarization of magnesium. Besides typical electrochemical corrosion, it is well known that Mg also exhibits physical detachment of metal portions from the anodic metal called the chunk effect[1]. Jian Chen *et al.*[2] suggested that Mg hydride could fail by brittle fracture. Stress caused by hydrogen pressure called hydrogen embrittlement (HE)[3-4] occurs along grain boundaries and dislocations and can cause brittle fracture. Our group also confirmed the embrittlement behavior of pure Mg during corrosion as shown in Fig. 2a. Design of hardware such as the Mg screw shown in Fig. 2b therefore must include evaluating the strength of the part as it corrodes and developing coatings and alloys that produce the desired corrosion rate and reduction in strength with time.

Typical characteristics of Mg corrosion are described next. Mg hydroxide called Milk of Magnesia or brucite which has low solubility in water can be formed after particles physically detach from a Mg metal surface. Also, hydrogen bubbles start to grow on the corrosion sites. This is a problem because in the body hydrogen gas is difficult to release to the atmosphere (a needle might be used), and hydrogen gas causes a toxic effect to tissue. During corrosion, for pure Mg, 1 ml of H_2 is evolved for every 1 mg of Mg that is dissolved[5]. Another concern is that the local pH increases at the implant due to the hydroxyl groups. High pH inhibits cell proliferation and tissue formation. In a static solution, pH can increase up to ten[5]. These problems may be more severe in a laboratory bench top experiment than in the body. What is really happening *in vivo* in a cardiovascular situation can be more accurately simulated *in vitro* by using an electrolyte having appropriate chloride, phosphate, and protein concentrations, by applying a mechanical stimulus, and using a flow-cell environment with convection and diffusion[6]. The increase of pH on the corroding surface can be neutralized in the body's buffered solutions and through shear flow systemically. But increasing the flow rate increases the corrosion rate of biodegradable implants and the mechanical stimulus creates stress-corrosion cracking, pit-growth, and fatigue corrosion. Thus, careful optimization is needed to design biodegradable implants. As an example of Mg alloy design, the use of lithium in Mg increased the pH which stabilized the Mg hydroxide film on the corroding surface[9]. Weight loss measurement after immersing a metal in a specific solution provides a general idea of the corrosion rate. The corrosion rate can be controlled by injecting current into the implant or coating the implant with apatite[10], phosphate, silane, or other coatings. Surface treatments such as electro or electro-less plating, anodization, inhibitors, or organic coatings are used for corrosion protection.

Corrosion simulation

Multi-physics software[11] is very useful to analyze fluidics, corrosion behavior, loss of mechanical properties, chemical reaction by diffusion, and tissue regeneration. Data generated might be be integrated with intracellular signaling and network models to predict an implant's biocompatibility and find hidden relationships that help explain toxicity. Fig. 3a shows a corrosion model, which consists of an intermetallic particle (IMP), a Mg anodic metal, and insulation. The IMP plays the role of a cathode in micro-galvanic Mg corrosion which is represented by a 20 µm radius disk surrounded by the Mg bulk material. In the real world, this situation represents an intermetallic particle

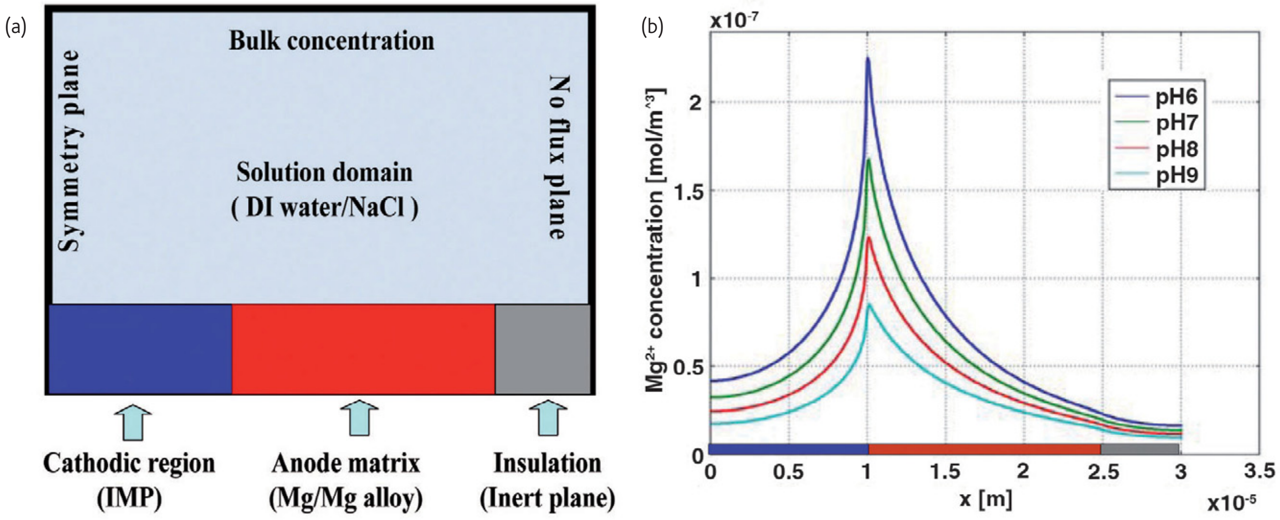

Fig. 3 COMSOL[11] simulation model: (a) Schematic geometry and boundary conditions; and (b) spatial distribution of Mg^{2+} ion concentration with different pH.

embedded in a large Mg matrix which may occur due to impurities or alloying elements in the base material. As shown in Fig. 3b, Mg ion concentration sharply increases on the boundary between the anodic and cathodic region as the pH in the solution decreases. This shows that Mg tends to corrode rapidly in an acid solution as compared to a neutral or alkaline solution. Miniature sensors will be used to measure the concentrations of chemicals spatially and temporally to verify results of the modeling.

Corrosion sensors

A miniaturized potentiostat to measure electrochemical polarization, corrosion current, and open circuit potential can be developed as a corrosion sensor. The working electrode can be embedded into a biodegradable metal, which can measure current, open circuit potential, surface resistance, and surface capacitance[13-26]. Electrochemical methods can be simply applied to measure specific cases of corrosion such as the corrosion rate with time, the initiation of crevice corrosion, and stress corrosion cracking. Also, evaluation of coating layers and breakdown of the coating layers on biodegradable implants can be detected. Optical-based corrosion sensors were developed by depositing specific materials such as a nickel-phosphorus layer[27] or a Fe–C alloy layer[28] on the unclad area of an optical fiber. Optical transmission power dropped with the loss of this coating layer. Optical interferometry[28] was also used to measure corrosion. Depositing

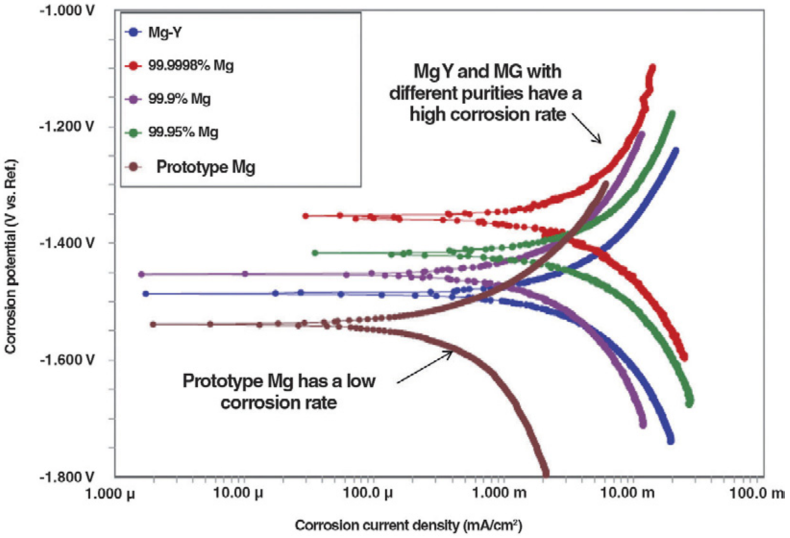

Fig. 4 DC polarization testing to evaluate the corrosion properties of different Mg materials after 48 hrs immersion in simulated body fluid. The corrosion potential in volts relative to a reference electrode is plotted versus the corrosion current density. Corrosion rate is proportional to corrosion current density.

fluorescent dyes on the corroding metal is another way to visualize the corrosion process[29-31] and the change in the local pH[32]. Portable UV lamps can be used to visualize the loss of a coating layer. Julie Levesque *et al.*[33] developed a test bed to reproduce the physiological conditions in which stents are subjected when implanted in coronary arteries. DC polarization testing is useful to evaluate the corrosion properties of different metals. Comparison of the corrosion of different Mg materials after 48 hrs immersion in simulated body fluid (SBF) is shown in Fig. 4. A prototype Mg has a lower initial corrosion rate than other materials tested. Further testing and scale up of the material processing approach is needed to determine if the prototype is a candidate implant material. A potentiostat used as a sensor can monitor the corrosion of an implant with time.

Wireless corrosion monitoring

Monitoring a biomedical implant while it is corroding in the body can help to understand the corrosion process for a specific application and also verify that the implant is not degrading too quickly or too slowly for a particular person. Ideally, the implant should follow an optimal dissolution response. During the initial stages, the implant must carry load and allow the injury to heal slowly. As the injury heals, the implant should gradually degrade and transfer increasing load to the body until the body fully recovers or heals. Additionally, the corrosion rate should be slow enough so that the implant does not fracture under load and the concentration of the corrosion by-products does not exceed the limit the body can tolerate[34]. A wireless eddy current technique for monitoring the corrosion of a Mg implant is being developed. This approach is safe, simple, and low cost as compared to X-ray or magnetic resonance imaging techniques. The eddy current method works on the principle of applying an AC current to a primary coil which generates a magnetic field in and around it. When an electrical conductor comes in close proximity to this magnetic field, electrical currents called 'eddy currents' are induced in the conductor[35]. The eddy currents create a magnetic field that opposes the field that created the eddy current. The effect of the eddy current can be measured by winding a secondary coil (output) within the primary coil (input). Coupling between the two coils is reduced when a conductor comes within the magnetic field. Typically eddy current is used to find cracks in aluminum aircraft or corrosion in steel pipelines.

An experiment was performed to simulate monitoring the corrosion of an implant in the human body. A Mg-Y 4% plate 25.4 x 15.8 x 3.2 mm was weighed then immersed in a beaker containing a high (10x) concentration phosphate buffered saline (PBS) solution to accelerate the corrosion process and shorten the test time. The beaker wall represents skin while the PBS solution represents the body environment. The flexible coil was wrapped around the outside of the beaker to generate a magnetic field that couples to the Mg implant. The distance between the coil and the implant was 10 mm. When the Mg plate is first put into the electrolyte, the maximum electrical conductivity and eddy currents occur in the plate and the output voltage of the secondary coil is the smallest. As the implant corrodes, the voltage of the output coil gradually increases because the size of the implant is decreasing and hence producing smaller eddy currents. The maximum output voltage occurs when the implant is completely dissolved. The excitation voltage was turned off when the measurement was not being made because eddy currents may affect the corrosion rate of the implant. A schematic of the experimental setup is shown in Fig. 5a. The voltage change versus reduction in weight of the implant is graphed in Fig. 5b. The weight of the implant increases slightly at the beginning of the test due to build-up of an oxide or hydroxide layer on the Mg surface. After 2 days the weight of the Mg plate began decreasing. As the weight loss of the Mg plate increases, the voltage of the output coil also increases. The change in voltage (ΔV) was obtained by subtracting the output voltage at

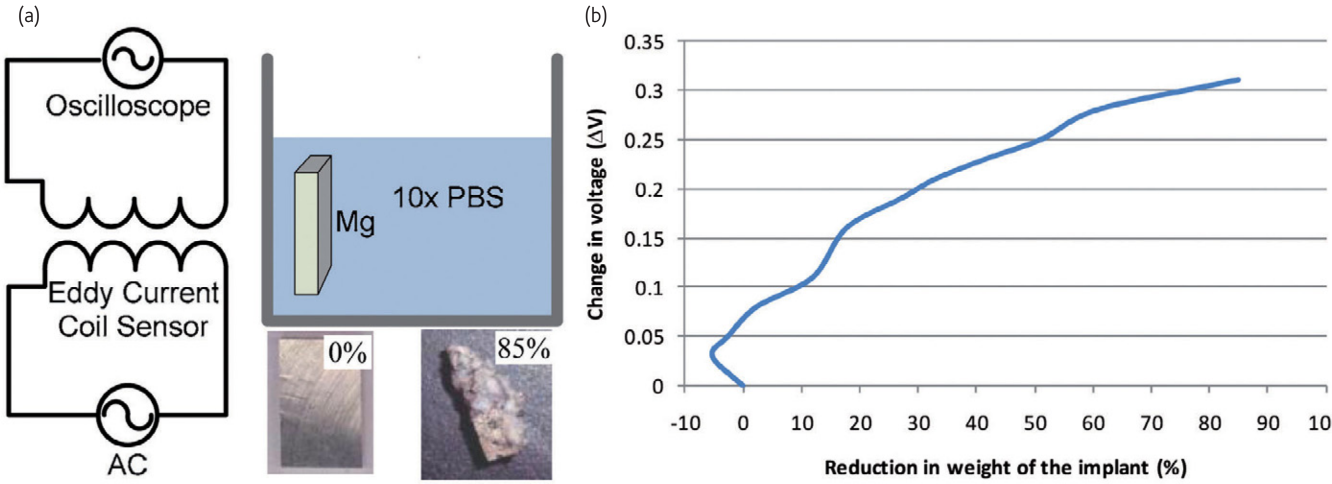

Fig. 5 Corrosion monitoring of a Mg-Y 4% alloy in a concentrated 10x PBS solution: (a) schematic of the experimental setup and photos of the Mg implant at the beginning with 0% corrosion and when the implant is 85% dissolved after 12 days; (b) change in voltage versus reduction in weight of the implant.

the beginning of the experiment from the output voltage measured each day during the test. Once this experiment is run for a specific condition, the implant can be used in the human body and voltage data recorded. Then the percent corrosion of the implant can be determined using a curve like Fig. 5b. Also, any abnormality like fast or slow corrosion or fracture of the implant might be detected. The remaining life of the implant can also be predicted based on the corrosion profile. The accuracy of this approach depends on how well the *in vitro* simulation matches the environment in the body. A next step is to put the implant in an animal model and measure the voltage versus time as the implant corrodes. X-ray imaging could be used to indicate the percent corrosion of the implant in the animal. Further research in the area of corrosion measurement will focus on optimizing the eddy current coil geometry, e.g. using a larger coil, potentially using CNT thread to replace copper as the coil material, and increasing the current to improve the sensitivity of corrosion measurement. Also needed is to perform the measurement when the implant is placed deep in the body. Evaluating the corrosion monitoring technique for different Mg alloys, porous implants, and different coatings on implants is also planned.

Chemical sensors to characterize the interface at the implant

The biodegradation of metal implants such as Mg alloys releases chemicals into the adjacent biological fluid and tissue. Since larger size sensors already exist for some of these chemicals such as hydrogen ion (H^+), ionized Mg (Mg^{2+}), and dissolved hydrogen, the species in the bulk solution could be monitored by sensors during the biodegradation process. Although such information could be very useful in developing appropriate biomaterials, little use of sensors has been made thus far. As described in this section, sensors have already been demonstrated in other biological studies, which provide encouragement that they could also be effective for use in developing biodegradable metal implants.

pH sensor

Local pH is an important parameter in the corrosion of biodegradable metallic implants, since the pH at or near the metal/tissue interface affects the rate of the corrosion reaction and provides information about the process itself. A reliable and implantable pH sensor is therefore required for the metallic implant. Hydrogen ions are involved in most life processes, and different ways have been developed to measure the pH in single cells and plasma. Here we discuss several kinds of pH sensor and the possibility for sensing at the implant.

Glass pH electrodes have been studied for more than 70 years and because of their excellent selectivity have become the standard pH sensor for the bulk solution[36,37]. However, glass electrodes are fragile, difficult to shrink, and prone to bio-fouling, which limits their use *in vivo*, and so glass pH electrodes are mostly used *in vitro*[38]. Since the 1960s, the oxide electrode systems known as solid state ion selective electrodes have been studied for measuring pH[39]. Cammilli *et al.*[40] described a pH electrode based on iridium/iridium oxide and implanted it in the right ventricle of rats. A stable pH response could be maintained for a 40-day period of implantation. However, metal/metal oxide electrodes are subject to severe interference from other electroactive species in blood, such as ascorbic acid and uric acid[41]. Since 1970, ion sensitive field-effect transistors (ISFETs) have evolved into a new type of chemical-sensing electrode. The ISFET is a modified metal oxide semiconductor FET in which the metal oxide gate is replaced by an ion-sensitive membrane. Instead of measuring the potential difference, ISFET uses the potential to control the current flow between the source and the drain regions. Thus, the current is used to monitor the analyte activity. ISFET's can be easily miniaturized and mass produced as multiple sensing elements incorporated into one chip. Currently, most implantable ISEFTs are used to monitor electrolytes (K^+, Ca^{2+} and Na^+) in blood. Commercializing implantable ISEFT sensors poses problems that may require considerable effort to fix such as specialized packaging, burn-in periods, or compensation to correct for drift during continuous *in vivo* monitoring[41].

Optical and fiber-optic pH sensors have advantages over glass electrodes in that they are immune from electrical interference, can be miniaturized, and may be used for remote sensing and *in vivo* tests[42]. Most optical pH sensors are based on pH indicators immobilized on/in solid substrates, and fabricated in the form of membranes or thin films coated on transparent solid supports. However, most fiber-optic pH sensors are fabricated by attaching the sensing elements to the end of an optical fiber, or by direct coating. This kind of optical pH sensor has been used to measure intracellular pH inside individual biological cells and in blood for clinical tests[43]. Commercial implantable optical pH microsensors have been developed by the PreSens Precision Sensing Company based on a glass-fiber tip. This kind of sensor has a long cable connected with the tip, and is not convenient.

The development of carbon nanotubes (CNTs) since 1991[44] has provoked their use in a wide variety of applications including nanoelectronics and various types of sensors[44-47]. CNTs functionalized with the carboxyl group (-COOH) on a glassy carbon electrode were used to detect pH by Weber[48]. Kwon made a sprayed CNT sensor that shows an amperometric response in buffer solutions at different pHs[49]. In 2007, a layer-by-layer CNT-polyelectrolyte thin film to sense corrosion that can stand extreme loading was developed by Loh[50]. The pH-dependent conductance properties of CNT multilayer thin-film sensors were reported by Lee[51]. Other pH sensing based on CNTs includes attaching pH sensitive molecules to CNTs[52,53] and decorating them with fluorescent molecules[54,55]. Graphene, an allotrope of carbon, has stimulated intense interest recently because of its potential applications in ultrafast electronics[56,57]. The sensitivity response of graphene to surface charge or ion density makes it possible to make a pH sensor[58].

Sensing the evolution of hydrogen gas from Mg implants

During the corrosion of Mg in an aqueous and chloride containing environment such as the human body, electrons released by the corroding Mg reduce water, and cathodic hydrogen gas is evolved. It would be desirable to measure the amount of hydrogen gas in the body to determine if toxic levels are being formed[59,60]. While many methods for detecting hydrogen gas are recently established for transportation, petrochemical, aerospace, and energy[61], they are not suitable for making measurements in biological samples. However, since the late 1950s hydrogen gas has been used as an indicator substance for *in vivo* measurement of local blood flow in the body[61,62]. Hyman[63] established a technique to measure and quantify hydrogen gas in the blood stream. On this background a sensor to measure the hydrogen evolution next to an implant could be developed.

Mg^{2+} sensors

Mg ion selective electrodes are an effective way to monitor Mg^{2+} in biological matrices allowing the degradation of candidate implant materials to be monitored in real time. It is equally important to monitor localized Mg^{2+} concentrations near, or adjacent to, the implant for *in vivo* and cell culturing experiments. In this situation, very small implantable sensors can be used. This requires electrodes for use near living tissue. The majority of Mg ion selective electrode (ISE) technologies use a liquid type membrane impregnated with an ionophore that has selectivity towards Mg^{2+}. Intracellular measurements of Mg^{2+} are the focus for much of the research associated with micro ISEs. Micro ion selective electrodes made from glass capillaries with a liquid type membrane that respond to Mg^{2+} have existed since the late 1960s and a significant amount of research has concentrated on their usefulness in biological applications[64-66]. Larger liquid membrane ISEs are used routinely in clinical chemical analyzers that monitor a variety of biologically relevant ions in blood[67,68]. While progress has been made since the inception of the ISE, there are still some problems associated with the traditional liquid membrane ISEs. The lifetimes of liquid membrane electrodes are short (days) compared to glass membrane electrodes (pH), which can last for years[69]. Typically, Mg ISEs suffer from interference from alkali and alkali earth metal ions, with the divalent cations causing the most interference. As an alternative to liquid membrane electrodes, solid state ISEs are being developed that mitigate some of the problems associated with the liquid membrane electrodes[70]. Solid state electrodes are easier to maintain and have a longer useful lifespan than traditional capillary electrodes[71]. Additionally, solid-state ISEs are easier to miniaturize than traditional capillary electrodes[72]. Making use of CNT seems likely to revolutionize the solid state ISE design as electrode sizes are pushed to the limits of miniaturization.

Sensors used in scanning electrochemical microscopy

Scanning electrochemical microscopy (SECM) is an electrochemical technique that is analogous to atomic force microscopy (AFM), but uses miniature sensors to map out localized concentrations of ions adjacent to a surface. Miniature sensors for Mg^{2+} and pH enable SECM to be used to study ion gradients and the degradation of implants on the micrometer scale. Lamaka et al. demonstrated the use of Mg^{2+} and pH ISEs to map ion concentrations above a degrading Mg sample[73]. The technique gives a detailed picture of the dissolution of Mg implant candidate materials on the microscale. Studying the initiation of micro pitting of metals is an area where SECM is shown to be useful[74]. Biocoatings that release drugs or retard implant degradation are thought to be integral to degradable implants. The effects of biodegradable coatings on the implant and adhering cells, and mineralization on the localized dissolution rates of Mg should be observable using SECM. Using SECM as a tool to study thin films and their interaction with metal substrates is reported[75]. The resolution of SECM is limited by electrode size. Thus the

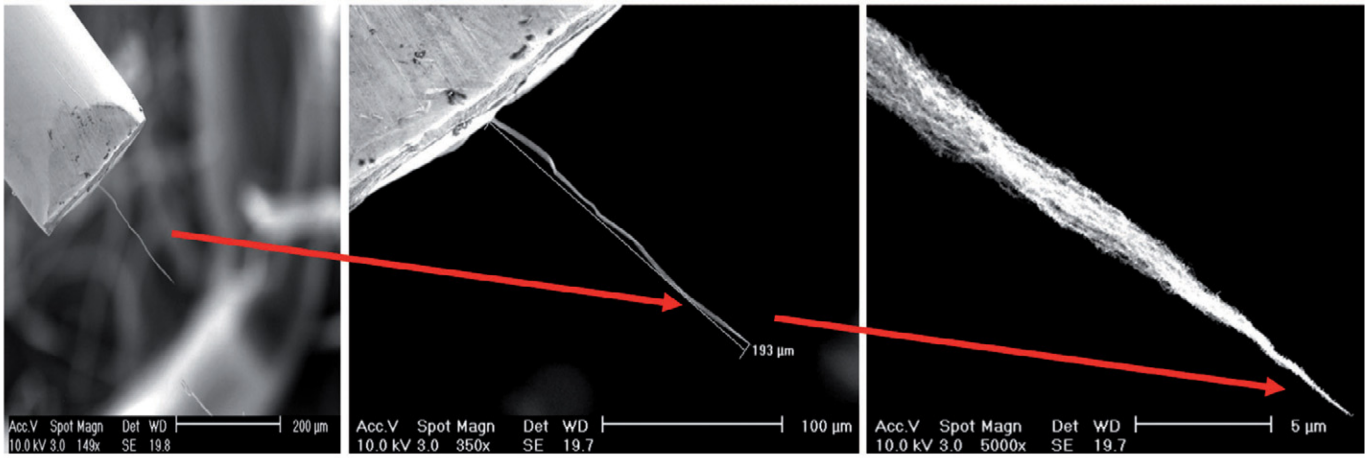

Fig. 6 Nanotube electrode with small size and large surface area for high sensitivity (magnification increases L to R). This electrode was formed in an ESEM using a Kleindiek nanomanipulator.

advances in sensor miniaturization described are important to allow the resolution of SECM to further push the limits of ISE microscopy towards increasingly detailed data. For all the sensor types described above, development of CNT electrodes as shown in Fig. 6 may provide advantages of inert behavior, good strength, small size, and large surface area to volume.

Cell based sensors to study toxicity

Once a biodegradable metallic implant is designed, *in vitro* experimentation is necessary to determine whether cells will attach to the implant's surface or not. If cells do not like a biodegradable implant, the cell will either migrate away from the site or even worse, the cell will die either by apoptosis (programmed cell death) or necrosis. In the case of necrosis, the cell loses membrane integrity and dies rapidly as a result of cell lysis. In the case of apoptosis, the cell stops actively growing and activates a specific gene network for controlled cell death. Apoptosis and necrosis assays are commercially available. Also initial cell proliferation and cytotoxicity screening can be done using commercial assay techniques. Total internal reflection fluorescence, two photon microscopy, a microplate reader, and confocal microscopes are widely used. Flow cytometry for cell separation, fluorescence resonance energy transfer (FRET), photobleaching, and ratiometric dyes for intracellular membrane potential, pH, Ca^{2+}, and Mg^{2+} are available. These methods are based on colorimetric and fluorescence, which need washing steps and are in general impossible to use for real-time monitoring. Biodegradable metals will dissolve during PBS washing and antibody incubation, which causes cells to wash away from the implant surface. In fact, the corrosion rate is much higher in PBS than in cell culture medium. Another point is the biodegradable metal is not transparent which limits the use of optical microscopes. Thus, new engineering tools for noninvasive diagnostic and nondestructive structural analysis are needed to identify and investigate tissue and cell response such as cell migration, proliferation, and attachment on the biodegradable metal surface. New instruments should be tuned to specific orthopedic, neural, and cardiovascular applications. Engineering methods such as surface plasmon resonance (SPR), surface enhanced Raman spectroscopy (SERS), imprint-lithography, and electrode-cell impedance sensing (ECIS) are being actively studied coupled with nanotechnology. Cell activity measurement is illustrated using ECIS in a Mg conditioned medium. If we assume that biodegradable Mg implants mainly dissolve as divalent Mg ions (Mg^{2+}), the effect of Mg ions on cell behavior is important. As shown in Fig. 7a, a real time monitoring technique based on ECIS was used for measuring cell proliferation, migration, adhesion, and cytotoxicity in Mg conditioned media. Fig. 7b shows that as the concentration of Mg increases the impedance decreases due to cell death. Fewer cells on the ECIS electrode reduces the electrical impedance.

Real time monitoring for biodegradable implant corrosion, breakdown of the corrosion inhibition coating, behavior of the extracellular matrix coating, new tissue formation, and the effect of drugs are important. Further incorporation of ECIS with bioreactors coupled with microfluidic channels and mechanical stimulators can mimic a more realistic environment for the implant. Complex metallic materials which are porous, have nano-roughness, or 3-dimensional structure are in demand for specific applications. To study these materials, a more quantitative way to monitor cell interaction with pH and hydrogen will be important. Hydrogen gas in a small amount can be used as an antioxidant agent which can effectively neutralize OH in a living cell[76]. Thus slow degradation of a biodegradable implant is critical for biocompatibility. Fig. 8 shows osteoblast U2-OS cell behavior on a Mg substrate patterned by photo-lithography. U2-OS cells interestingly migrated to and spread on the Mg surface.

Coating implants with bioactive materials such as hydroxyapatite can improve cell adhesion. The transmembrane protein integrin is a cell-adhesion molecule which senses a signal from the environment

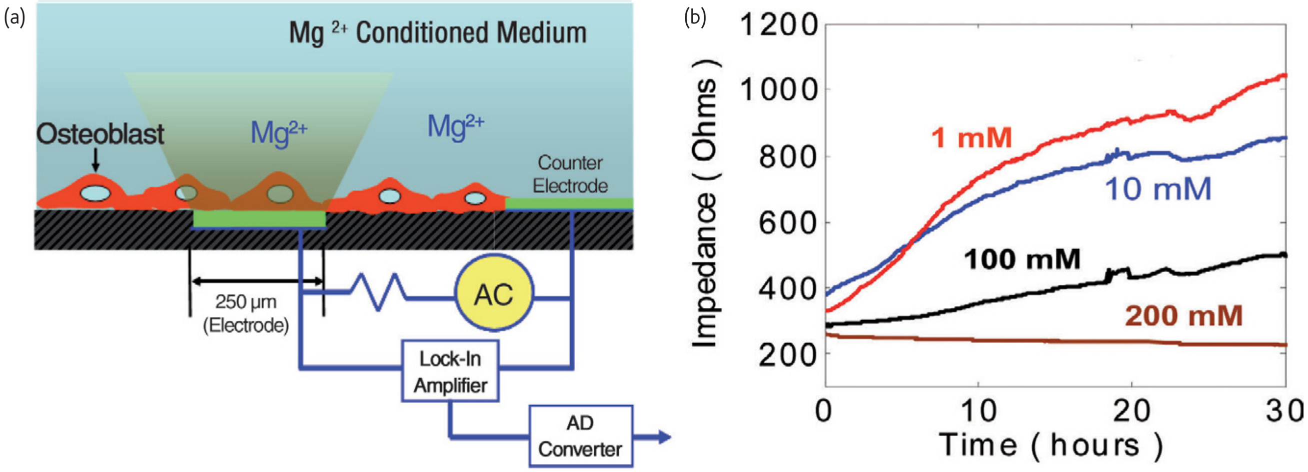

Fig. 7 Electrode-cell impedance sensing system; (a) schematic of the ECIS principle for osteoblast cell reaction in a Mg conditioned medium; (b) impedance response for different Mg concentrations.

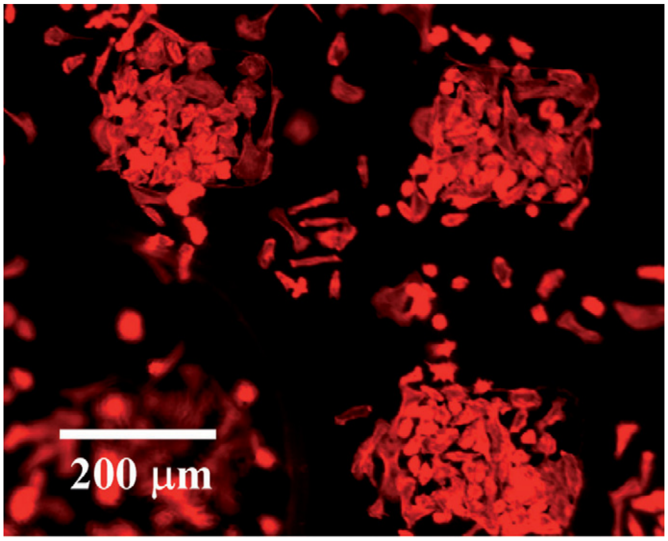

Fig. 8 Osteoblast (U2-OS) behavior on the surface of Mg squares surrounded by polymer. The cells were incubated for 4 hours and F-actin was used for staining.

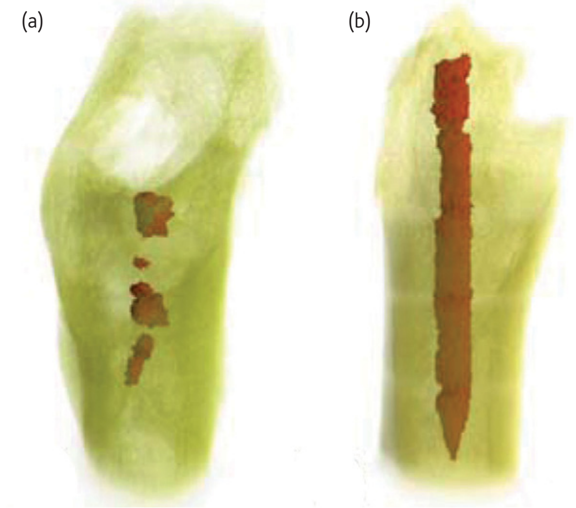

Fig. 9 A 3-D reconstruction of corroding Mg alloy implants (red) segmented from the bone matrix (yellow) by region[91]. (a) shows a corroding Mg alloy AZ91 after 18 weeks of implantation; (b) shows a Mg alloy LAE442 after 18 weeks of implantation, Bar = 1.5 mm.

such as from the extracellular matrix to the inside of the cell through the cytoskeleton and results in the expression of growth factors and cytokines. Coating the surface of implants using integrin-stimulating agents helps cell adhesion to the implant. Arginine-glycine-aspartic acid (RGD) is well known for the affinity for integrins. Also an extracellular matrix coating such as collagen is another way to improve biocompatibility.

In vivo imaging of implants

Non-invasive *in vivo* visualization of Mg and its alloys is important to measure implant stability and osteointegration. X-ray microtomography (micro-CT) has the spatial resolution from mm to μm which is useful for small animal testing. Now X-ray CT or magnetic resonance imaging (MRI) systems are combined with positron emission tomography (PET) or single photon emission computed tomography (SPECT) scanners which monitor the functional processes of biologically active molecules in the body by injecting a short-lived radioactive tracer isotope into the body[76]. Non-irradiation techniques such as micro MRI and functional magnetic resonance imaging (fMRI) are widely used, and have resolution that can be less than the trabecular bone thickness[77]. Mg isotope use was also reported[78]. Synchrotron radiation computed micro-tomography (SRμCT) offers a more powerful way to distinguish between Mg implants and mineralized bone[79]. Mechanical property changes with the degradation of Mg alloys can be monitored as in Fig. 9. Adhesion of cells, sensing, and X-ray imaging are discussed[80-91].

Advanced techniques for corrosion control

There are several advanced techniques that might be used to control Mg corrosion[92]. Biodegradable Mg coils may be put inside the body to provide sensing and power into the body wirelessly. Also, we can make the implant smart where it can sense and control its own degradation. Controlling the corrosion rate of the implant can be done using a cathodic protection technique wherein an external current is applied using a reference electrode so that the external current polarizes the cathodic elements to the open circuit potential of the anodes. In this condition, the potential across the anode and cathode become equal and the corrosion current becomes very small[93]. Electronic corrosion control would improve the biocompatibility of implants and not require the development of exotic alloys to slow corrosion. The authors speculate that implanting engineering materials and medical devices in the body including biodegradable implants, sensors, and electromechanical systems is going to become an area of extreme engineering where highly sophisticated devices will be used to transcend biology and to repair the body and cure diseases that have plagued mankind for millennia. Expandable implants such as auxetic self-expanding biodegradable plates and stents can provide adaptability of the implant for pediatric orthopedic applications and for other applications where the implant must change shape for installation purposes or to allow for growth of the body, or expansion of blood vessels, or for use in possible other applications such as muscle. Materials development may be the most important aspect in developing biodegradable implants. Hence, a new physical vapor deposition system was designed and manufactured to develop nanostructured Mg materials that have increased corrosion resistance such as those shown in Fig. 10. The nanostructured materials would be used as a coating to slow the initial corrosion of the implant. A recent advance in controlling the by-products of degradation is development of a MgZnCa glass material that greatly reduces hydrogen evolution[94] as compared to crystalline materials.

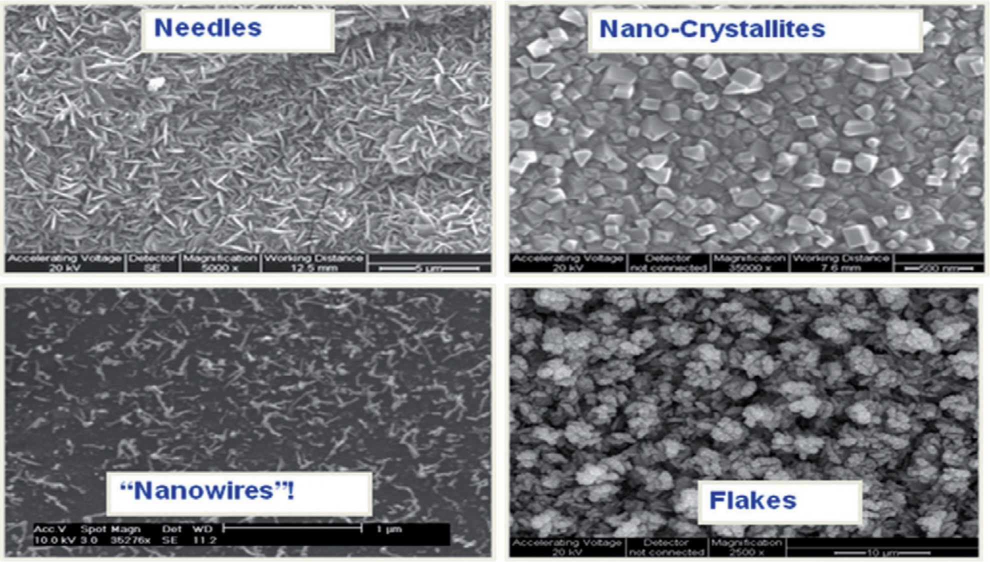

Fig. 10 Different MgO nanostructures can be synthesized for biodegradable implant coatings. The growth conditions control formation of MgO nanostructures with different morphology.

Auxiliary applications

Many other applications[95-103] of biodegradable metals may be possible. These include developing drug delivery nanosystems, biodegradable nanorobots, sensors, multi-functional particles, biogalvanic batteries, and electronic components that dissolve and disappear. Other devices can be imagined. Development of components, surface treatments, metallic nanotubes, and miniature sensors that work inside the body and that can be left in the body or removed by minor surgery are under development[104-112].

Conclusions

Biodegradable implants and devices have been shown or predicted to provide improved regeneration of tissue and have other advantages for different biomedical applications. The biomedical implants market needs these new types of medical devices and within this market the development of biodegradable implants is an area that is wide open for innovation. Thus the materials world is responding with research in the areas of metallic, glass, and nano materials and sensors that is revolutionizing the field of biomaterials. mt

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