Electrochemistry and Medical Devices

Friend or Foe?

by M. E. Gertner and M. Schlesinger

At first glance, it is easy to underappreciate the impact of electrochemistry in medicine. The present article is meant to focus on the topic as it relates to medical devices. We focus on the often overlooked materials science aspects of medical devices rather than the extensively described topic of electrochemical sensors in medical applications. It is hoped and anticipated that this article will give the reader a broader view of the role electrochemistry plays in medical devices, as well as an appreciation of the role electrochemistry can play in devices, particularly in the creation of biomimetic devices.

Medical devices are man-made structures or machines which function inside or outside the body and have a role in human functioning either in sensing a physiologic variable or manipulating the same. If they are implanted in a host, they may be a temporary or permanent device. A well-known medical device is the mechanical heart valve (Fig. 1) and the pacemaker. Although medical devices are generally perceived as macroscopic or permanent ones, many, and in some cases all, of the effects (wanted and unwanted) of the devices are derived from interactions at the surface. When the devices are comprised of metals, many, if not most, of the surface effects are electrochemical in nature. This fact is the subject of this review.

The first goal of this article is to briefly outline the manner in which electrochemistry is crucial to both the mechanical and materials stability of medical devices. In some cases, entirely new industries have been created around advances in our understanding of the electrochemical processes occurring at surfaces. A further goal is to touch upon the ways in which electrochemistry can be used to actively modify surfaces to create a more amicable interaction between the medical device and its host. In at least one example, electrochemistry is used to actually create a medical device.

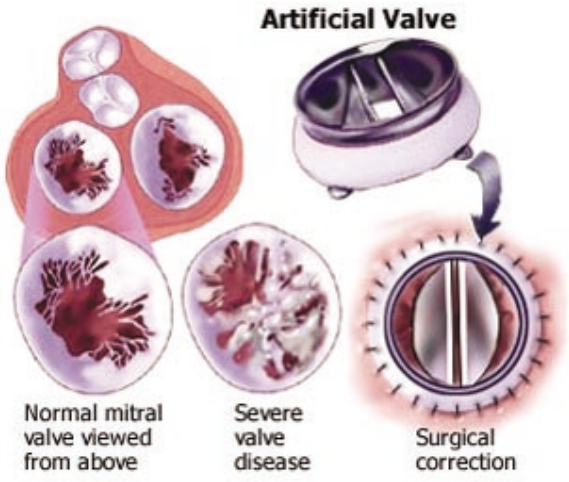

FIG. 1. Mechanical heart valves have been around for decades. Despite many years of research, the surface of the valve (arrow) remains thrombogenic requiring patients to be placed on lifelong anticoagulation medication, which has its own complications. Picture from HeartCenter Online: Artificial Heart Valve; reproduced with permission.

Materials Science

Medical devices comprise a rapidly growing industry where the basic technology changes very quickly; many of these changes come from the ever expanding basic subject of materials science. The major metals and metal alloys used in the device industry today include titanium, nickel-titanium (nitinol), cobalt-chrome, and stainless steel. Tremendous advances have been made over the years in polymer science and in metallurgy, which enable incremental improvements in the devices and sometimes allow for entirely new classes of devices. This is in fact the case for nitinol. However, as will become apparent below, the understanding and consequent exploitation of the chemistry, stability, and durability of nitinol leave a great deal of room for improvement before they can be easily manipulated.

Nitinol is the name given to the alloy consisting of approximately equiatomic nickel and titanium. Thus this alloy is approximately 50% nickel and 50% titanium. It was first created in the 1960s and it was quickly discovered to possess a property called shape memory. This means that it will return to a preferred (preset) shape upon heating above a critical temperature (T_c). The relative percentages of nickel and titanium determine the actual value of T_c. This property has been exploited tremendously in medical devices where T_c is set at body temperature, or 37°C. When the device made from nitinol is inserted into the body, it re-expands to its preformed shape. The advantages of nitinol's shape memory are several fold. For example, a pre-shaped device can be compressed into an "introducer" sheath which is many times smaller than the space the device will ultimately fill, *e.g*, a blood vessel. After implantation, the device expands to its original shape within minutes. A further advantage is that the

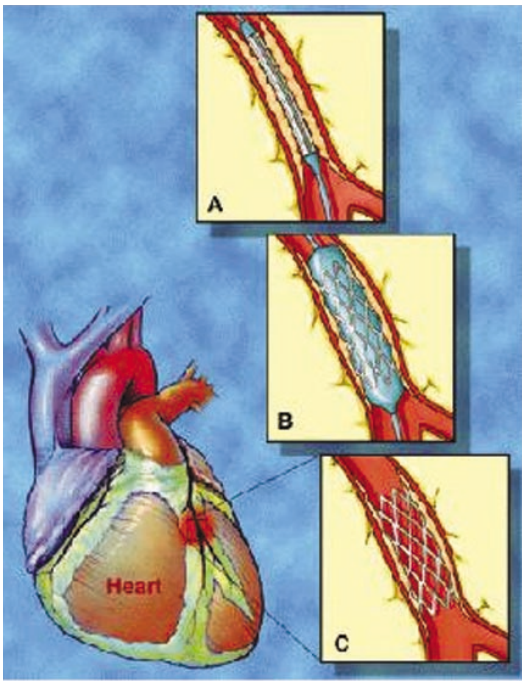

FIG. 2. Stents are used to open arteries of the heart blocked by atherosclerotic plaques: (a) a balloon and stent are placed across the plaque; (b) and then the balloon is expanded, leaving the stent to prop open the artery; (c) restenosis is the process wherein scar tissue builds up around the stent, again causing a flow restriction. A balloon is required for stainless steel whereas a nitinol stent will expand on its own due to the shape memory property of nitinol. Figure from Ref. 1; reproduced with permission.

device tends to exert a continuous positive force on the blood vessel so that if the blood vessel is compressed externally, the stent will return to its original position. This is extremely important when a stent is placed in a peripheral vessel, for example, a carotid artery.

The lag between the time nitinol was first produced and the time it was used commercially in medical devices was due in part to the fear that nickel would leach from the metal and not be tolerable as a human implant. As it turns out, with a correct understanding of the surface electrochemistry and subsequent processing, a passivating surface layer can be induced to form on the nitinol surface, which is comprised of titanium oxide approximately 20 nm thick. This layer actually acts as a barrier to prevent the electrochemical corrosion of the nitinol itself. Without an appreciation for the electrochemistry at its surface, nitinol would not be an FDA approved biocompatible metal and a whole generation of medical devices would not have evolved. This is really a tribute to an understanding of surface electrochemistry within the context of implanted medical devices.

Stents

One of the most commonly used medical devices is the stent (Fig. 2). As seen in the figure, stents are small metallic structures which are expanded in blood vessels, functioning to maintain the patency of the vessel in which it is placed. Although the first use of stents was in vasculature, more recent applications include, for example, implantation between two vertebra to increase the rigidity of the spine. A typical vascular stent is placed in its anatomic location and then either plastically deformed (stainless steel) or allowed to expand to a predetermined size (nitinol).

Recent work in the field of medical devices has focused on creating biomimetic surfaces. Biomimetic surfaces are surfaces created with an understanding of the pathophysiology surrounding the surfaces, typically created with the intention to somehow manipulate the local environment to make it more accommodating for the implant. As an example of a biomimetic surface, one can consider the process of restenosis and its prevention. Restenosis is the process wherein tissue in growth compromises the arterial lumen after angioplasty and stenting. This process typically occurs in 30-50% of patients who receive stents in the coronary (heart) blood vessels. These patients often require subsequent surgery and/or further stenting. Several explanations for restenosis have been put forth, including: a foreign body type reaction to the stent materials; an inflammatory type reaction due to the implantation trauma; and a failure of the normal blood vessel lining (endothelial cells) of the blood vessels to re-normalize after being perturbed by the stent implantation.

Recently, Johnson and Johnson Corporation began marketing a stent with a polymer based coating containing a drug which inhibits the restenosis process. The drug is released from the polymer slowly over time while the polymer remains on the stent permanently. Early results have been dramatic with a reduction in the restenosis rate from 40% to 10%.[1] This is one of the most dramatic examples of a biomimetic coating in clinical use. Whether polymer coated metal is the best coating, however, remains to be seen.

There has been extensive research into the biomimetic effects of surface morphology on the attachment, spreading, and even second messenger systems of cells. For example, in the field of orthopedic surgery, implants used to replace joints or fix fractures can have a sintered surface, or a surface roughened by fixing 1mm size metallic beads to it. With the roughened, porous surface, the activity of osteoblasts, or bone synthesizing cells, is dramatically upregulated, so much so, in fact, that bone cement is not required to maintain fixation of some implants. Recent work has begun to evaluate the potential for nitinol as an orthopedic material.[2] The advantages cited for a nitinol based implant include its damping properties as well as its shape memory. The surface processing used in this study was simple mechanical abrasion, the one which the supply company provided. Adequate bone ingrowth was obtained. However, if prior surface electrochemistry research were to be considered, the bony ingrowth could be greatly enhanced.

More recent work has utilized advanced electrochemical methods to create coatings which can provide drug to the local environment as well as provide for more biocompatible and corrosion resistant surfaces.[3] In this study, the final processing of the device surface included an electrochemical method to create voids on the surface. Pharmaceuticals were loaded into the voids which were released over a long period of time. The coating also enhanced corrosion resistance. There is no doubt that an understanding of surface electrochemistry specifically at the metal-blood interface will allow for further biomimetic enhancement.

Electrochemistry and Its Importance in the Processing of Biomaterials

As discussed, the success of nitinol as a medical biomaterial can be attributed to an understanding of the electrochemistry at its surface. Although previously unexploited, electrochemical methods can accomplish many of

the desirable biomimetic effects described above. Electrochemistry has the potential to alter surface morphology, release drugs, enhance radio-opacity, and prevent corrosion, all with the same coating. Electrochemical methods are also highly economical with low capital costs. In this context, electrochemistry can be considered a nanotechnology in terms of its efficiency, size scale, and self-assembly properties. Electrochemical coatings can be applied at scales of ten to hundreds of nanometers, allowing for the manufacture of nanocomposite coatings. As an example of a composite, the first one-hundred nanometer span increases radio-opacity while the next one-hundred nanometer span release the drug, and the third hides the first two from the physiologic environment. Because electrochemical deposition is an evenly applied process that can quickly be turned on and off, such composite coatings can be created on the order of one μm in thickness, a property not amenable to other methods for providing the same effects. Furthermore, and importantly, such a composite will not greatly affect the bulk material properties.

Extensive research regarding electrochemical processes at the surface of metallic implants has been performed in the past. This research has almost exclusively focused on the corrosive processes occurring at the surface of the device and its prevention. "Bare" metals have been intensely scrutinized with regard to corrosion. Surprisingly, specific devices such as stents have not been systematically studied and certainly have not been studied under conditions of mechanical stress and strain. The first stents were implanted in the early 1990s and were made from stainless steel, 316L grade. As would be expected, these stents show excellent resistance to corrosion under physiologic conditions but under conditions of static stress. However, corrosion processes are highly sensitive to shape and surface defects. Interestingly, to date, there have not been any studies on the effects of the polymer coating on corrosion at the stent surfaces. Polymer coatings can potentially be both a detriment to corrosion protection or may enhance corrosion protection.

Figure 3 is a high magnification scanning electron micrograph (SEM) of a commercially available nitinol stent. Notable are μm size crevices on the surface. Note that this picture is taken prior to expansion and prior to any stresses placed upon it. Although the titanium oxide layer at the surface of the nitinol is highly biocompatible and protects the underlying substrate from electrochemical corrosion, the titanium oxide layer itself is mechanically very brittle. Under mechanical stress, such as the shear of blood flow in the aorta or under the bending moments of aortic pulsations, the titanium oxide surface layer can fracture, exposing the underlying metal to corrosion. Not only is corrosion undesirable as far as biocompatibility (*i.e.* leaching of nickel and its oxides), but corrosion can lead to deterioration of the mechanical properties at the location where the corrosion occurs.

To summarize, surface defects are inherent in the processing of nitinol; the surface defects cause stress discontinuities in the surface of the titanium oxide film; the stress discontinuities lead to film breakdown and localized pitting corrosion; the pitting corrosion in turn leads to bulk mechanical breakdown at the site as well.

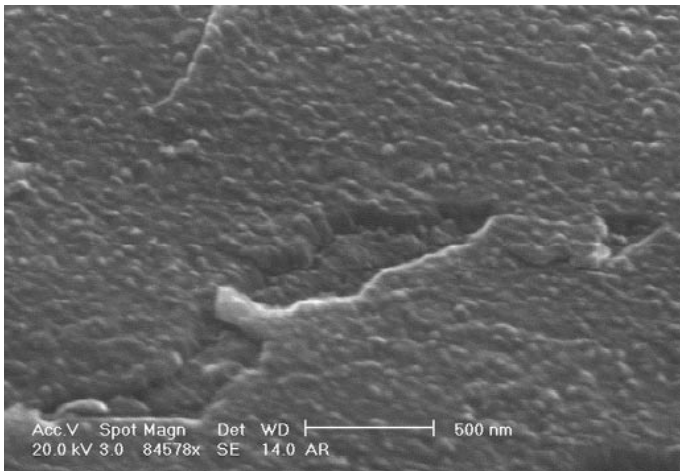

FIG. 3. High magnification SEM of the surface of a nitinol stent, the Smart stent. The μm scale crevices create stress concentrations when they are subjected to bending moments. Despite the biocompatibility of the titanium oxide layer, the stress concentrations at these surface defects leads to microcracks, which lead to localized corrosion and further widening of the crevices. Picture courtesy of Nanomedical Technologies, Inc.

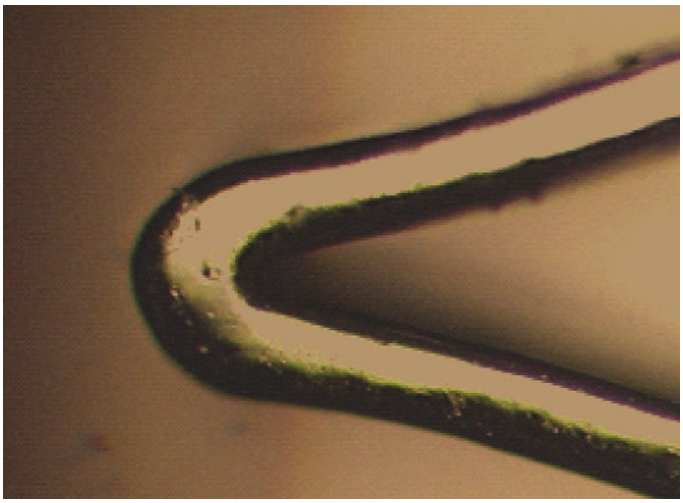

FIG. 4. An optical micrograph of a commercially available nitinol stent, Smart tm stent. Picture courtesy of Nanomedical Technologies, Inc.

Figure 4 is an optical micrograph of a commercial nitinol stent surface seen prior to implantation. Even pre-implantation, surface craters can readily be discerned. These large surface defects are on the order of 1-10 μm and are most likely formed secondary to surface heating during laser cutting. As mentioned above, these defects link the macro and micro scales because crevices promote electrochemical corrosion as well as mechanical instability, each of which is linked to one another.

Figure 5 depicts an explanted stent, or a stent removed from a patient.[4] This particular stent was placed in the patient's aorta to exclude an aneurysm from the blood flow in the aorta. These stents are originally made from a combination of nitinol and a polyester material (nitinol metal supporting a polyester

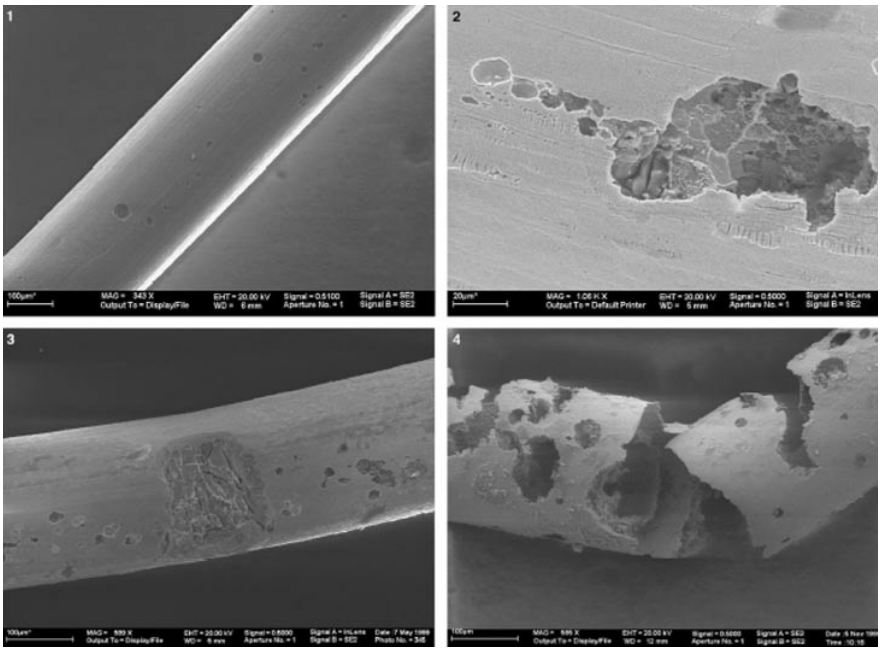

FIG. 5. Explanted nitinol struts from failed aortic stent grafts.[4] The arrow represents approximately a 100 µm scale. The large surface pits seen in the top right and bottom left are likely responsible for the failures seen in the bottom right. The surface pits are likely expansions of the defects seen in Figs. 3 and 4. Figure from Ref. 4; reproduced with permission.

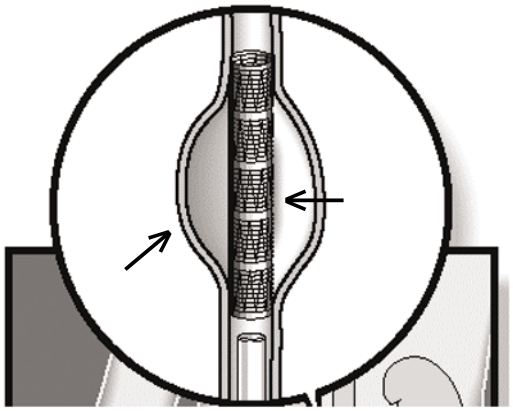

FIG. 6. An aortic stent graft is depicted in the figure. The polyester weave around the stent (short arrow) creates a barrier to blood flow from entering the aneurysm sac (long arrow). Failure of the metallic struts will lead to weakness in the stent and leakage back into the aneurysm.

skin); Figure 6 depicts the configuration of a stent graft once implanted into the aorta. The explanted stent represents a catastrophic failure in this patient; that is, leakage through the stent wall secondary to failure of the struts and resulting in blood filling into the aneurysm with ultimate rupture and likely death of the patient. Large crevices can be seen on the surface of the nitinol metal in Figure 5. These crevices are large discontinuities in the surface contour, which are presumably expansions of the smaller surface defects in Figures 3 and 4. Nonetheless as the nitinol is stressed and bent, the region around the pits experiences tremendous and disproportionate strain. It is here that the titanium oxide layer can fracture and expose the underlying surface to corrosion.

Sun *et al.*[5] in an excellent study and review revealed the heterogeneity of nitinol under various temperature conditions even in a simple lactated Ringer's solution. Lactated Ringer's solution is a mixture of salts and water meant to simulate the tonicity of blood. In this set of experiments, the surfaces were obtained from commercial sources and each sample had undergone similar surface processing prior to experimentation. When a nitinol sample was simply placed in the solution at a given temperature, current transients were seen, which represent breakdown and repassivation of the oxide film. Incredibly, such a study has yet to be done under dynamic (or conditions of bending) of the nitinol. Such dynamic stress would undoubtedly increase the number of passivation and repassivation events. Each event has the potential to release nickel into the surroundings and further the pit formation.

Nitinol achieves its shape memory properties after a series of heat treatment steps, which leaves a thick oxide residue on the surface. The oxide layer is removed by etching, mechanical abrasion, or electropolishing. After the heat induced oxide layer is removed, a fine layer of titanium oxide (a ceramic) remains on the surface. The titanium oxide layer is extremely important for the biocompatibility of nitinol, as the passivation layer prevents corrosion of the nitinol alloy.

Electrochemical processes are involved in several ways at the surface of the nitinol. The electropolishing step, a preparation step, is an electrochemical process wherein the substrate is made the cathode and the surface is evened out on a microscopic scale. Once the device is implanted, electrochemical corrosion occurs along the device surface. Pits such as the one seen in Fig. 5, when covered by a titanium oxide layer, do not undergo corrosion. However, the titanium oxide layer covering the pits is highly susceptible to mechanical stress and cracking when bending moments are applied.

Electrodeposition Methods and Materials in Medical Devices

Aside from discussion of the processing of nitinol discussed above, not much has been done to enhance medical device surfaces using electrochemical methods, in particular, with the aim of accomplishing a medically relevant goal. Gold, and more recently iridium, have been considered "ideal" biomaterials for stents. They are highly radio-opaque and are considered inert in that corrosion should not be expected from the surface due to their "noble"characteristics.

Indeed, a gold plated stainless steel stent made it through clinical trials and was actually approved for clinical use.[6] It was a failure because its rate of restenosis was higher than stents already on the market. When the production process for the stent was reviewed, it turned out that proper heat treating of the plated surface was not performed. Early animal data[7] show that changing this one variable reduces the restenosis rate to that of historical data for restenosis. This is another example where failure to appreciate surface electrochemistry caused clinical failure of a device.

More recently, work has been done to couple organic surfaces to electroplated surfaces. It has been well known for many years that organic molecules containing a thiol group at one end will strongly adhere to gold surfaces and form molecular monolayers. Recent work has expanded this knowledge by first electroplating a gold layer on the device surface and then applying an organic layer to the electroplated surface.[8] In this case, the device was a pacemaker lead. The organic layer was utilized to prevent scarring around the lead and to decrease the resistance that traditionally develops after electrode implantation.

As is well known in the field of electrochemistry, deposition can be accomplished by electroless and/or electrodeposition. With regard to medical devices, which often are not planar and often have sub-millimeter features, electroless deposition offers many advantages. Electroless deposition is a wet electrochemical method in which deposition occurs evenly along the surface of the device including sub-millimeter features and non-planar surfaces. Electroless deposition can be used to evenly coat nanoparticles and to fill submicrometer holes. Electroplating, on the other hand, is very sensitive to the electric field lines between the anode and the cathode. As a result, the coating derived from an electroplating process can be highly irregular.[9] As such, electroless deposition may meet the biocompatability goals.

Recent work[3] ultilized the inherent porosity of electrolessly deposited metals to incorporate drugs and provide for their storage and release, thereby opening new doors in device design and surface chemistry. Figure 7 depicts such a porous surface with pore size estimated to be on the 10-50 nm scale, depending on the depth of examination.

Electroforming is a process in which electroplating is performed on a mandrel in a given pattern. When the desired thickness is achieved, the mandrel is etched away from the electroformed stent, leaving a free standing structure, in this case a fully functional stent . In such a process, an entire stent including structure and surface can now be formed by a low energy, low capital electrochemical process. Indeed, Hines[10] has developed a process to electroform stents from a gold electroplating solution. Such a process raises the intriguing possibility of having only a monolithic process to both form the stent and to modify its surface for optimal biocompatability.

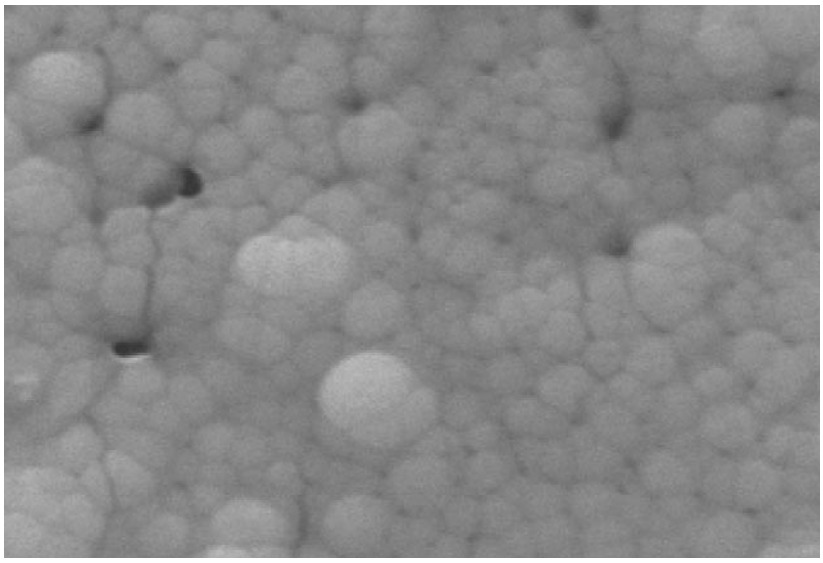

Fig. 7. The surface of a medical device coated with a nickel-phosphorous alloy deposited via electroless deposition. The white calibration bar represents 500 nm. Bioactive materials can be incorporated in between the grains. Courtesy of Nanomedical Technologies, Inc.

Conclusion

In conclusion, electrochemistry in fact manifests in biomaterial-host interactions and is an integral component in medical device design. Electrochemistry should be viewed as a tool that can work for or against the medical device engineer and biochemist. Electrochemical methods, including electro- and electroless plating methods, can be used to create micrometer scale surface morphologies to induce specific types of cellular differentiation or attract and/or repel a specific type of cells: they can be used to increase the radio-opacity of the device; to produce nano-composite coatings on a device; to enhance or control drug delivery from a device; or to accommodate a non-metallic coating. They can even be used to create a complete medical device. The above merits have to be balanced with the fact that electrochemical corrosive processes tend to destabilize surfaces and can undermine the mechanical stability of a device.

There is no doubt that the field of electrochemistry and its continual progress can and will have a substantial impact on the future of medical devices. Devices continue to be scaled down in size, which will necessitate a greater understanding of corrosion processes. As analytical tools for the study of surface chemistry improve and become more widespread, and as nanoarchitectured control permeates into the medical world, electrochemistry will be viewed as an economical, simple, yet powerful technique to modify and create biomimetic surfaces and medical devices. ■

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