Ion Leaching from Implantable Medical Devices

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Abstract.   Implantable medical devices must be able to withstand the corrosive environment of the human body for 10 or more years without adverse consequences. Most reported research and development has been on developing materials and devices that are biocompatible and resistant to corrosion-fatigue, pitting, and crevice corrosion. However, little has been directly reported regarding implantable materials with respect to the rate at which they generate soluble ions *in-vivo*. Most of the biocompatibility studies have been done by examining animal implants and cell cultures rather than examining the rate at which these materials leach ions into the body. This paper will discuss what is currently known about the rate at which common implant materials (such as stainless steels, cobalt-chromium alloys, and nitinol) elute ions under *in vitro* conditions, what the limitations are of such data, and how this data can be used in medical device development.

Introduction

Implantable medical devices are expected to operate trouble-free in a corrosive aqueous environment for, in some cases, over 30 years or more. Although the *in-vivo* environment is well controlled by homeostasis, keeping the pH, chemistry and temperature relatively constant compared with many consumer products, it is however, a corrosive environment. The corrosivity of the *in-vivo* environment is primarily affected by the dissolved oxygen and salt content of the body, i.e., an oxygenated 0.9 wt% NaCl solution.

Ratner has succinctly summarized many of the issues regarding the testing of materials for biocompatibility [1]. He notes that animal experiments are expensive and of somewhat questionable value for predicting human response, that human clinical trials are very expensive, and that there is currently no physical or chemical measurements that can reliably predict the *in-vivo* biocompatibility of biomaterials. Currently, with respect to metallic implants, one of the test standards is to evaluate the material's resistance to localized corrosion through the use of electrochemical polarization testing [2]-[4]. Obviously, if a passive metal implant pits *in-vivo*, there is likely to be an adverse biological response to the high rate of metal ion release. This type of testing, however, does not look at the rate at which metal ions leach from the implant's surface while undergoing uniform corrosion. Even though these uniform corrosion rates will provide a much lower metal ion release rate, there could still be adverse tissue reaction [5]. Currently there is no generally accepted practice to determine the rate of metal or other ions from biomaterials. In the article we well briefly review some of this data.

***In-Vitro* Corrosion Metals.**   Stainless steels, cobalt-chromium, and nitinol alloys are commonly used in implantable medical devices. Herting et al., has investigated the effect of various simulate physiological solutions (Gamble's solution and ALF artificial lysosomal fluid) on the rate of metal ion leaching from various stainless steels [6]. They found metal dissolution decreases with exposure time and for stainless steels the metal

ion leaching rate is faster at pH 4.5 than at 7.4. For instance, Herting et al., observed the average metal ion release rate on the first day of exposure of 316L stainless steel in the "as-received" surface condition to ALF solution (pH 4.5) to be 5.3 (Fe), 0.40 (Cr), and 0.33 (Ni) μg cm^{-2} per week, respectively. The release rate averaged over the first week had dropped to 1.2 (Fe), 0.1(Cr), and 0.08 (Ni) μg cm^{-2} per week, respectively. The average metal ion release rates in pH 7.4 Gamble's solution was at least one order of magnitude lower, with the one week average values being 0.075 (Fe), 0.002 (Cr), and 0.006 (Ni) μg cm^{-2} per week, respectively. Pre-exposure to Gamble's solution for 8 to 24 hours reduces the total metal ion leaching rate during one week's exposures to the higher pH ALF solutions. This suggests that calcium and phosphate deposit during the pre-exposure to Gamble's solution at pH 7.5 and act to limit further metal ion leaching [6], [7].

Ornberg et al., has reported the metal ion release rate of passivated Ni-Co-Cr alloy 35N LT (36Ni33Co20Cr10Mo), exposed to phosphate buffered saline (pH 7.4) to which 100mM H_2O_2 was added to simulate immunological response, to be 0.55 (Ni), 0.175 (Cr), and 0.125 (Co) μg cm^{-2} per week, respectively [8] after 3 hours of exposure. These leaching values are probably higher than what is observed for the stainless steel due to the short exposure time and the oxidizing effect of the peroxide. From this research we observe that the dissolution rate of metal ion from medical implants is a function of both *in-vitro* chemistry and exposure time. Very little, if any, data exists for *in-vivo* metal leaching rates.

Difference between In-Vivo and *In-Vitro* Leaching of Silica from an Active Implantable Electronic Device (AIMD). Active implantable medical devices have a promising future but key safety issues must be resolved [9]. An implantable medical device (AIMD) is any medical device that relies on any source of power (e.g., electrical) other than that generated by the human body or gravity to perform its function. Examples of AIMDs include: pacemakers, implantable defibrillators, auditory brainstem implants, neuro-stimulators for nerves, diaphragm, and bladder, cochlear devices, implantable active drug administration, artificial retinal implants, deep brain stimulation (DBS), etc. Operating electronics in salt laden environments, such as the human body has always been challenging. Currently there are many methods used to protect such active electronic devices such as hermetically sealing them in packages or coating them with various materials to prevent exposure to the environment. However, a number of these devices cannot be easily protected by hermetically sealing them in a package, such as retinal implants. In other cases, the designer desires the product to be resistant to the environment in the event that the coating or sealing system leaks or otherwise fails to enhance *in-vivo* device reliability.

For instance, new advanced designs require the use of conformal coatings such as parylene or polyimide and inorganic films such as silica or silicon nitride to replace the hermetically sealed metal cans previously used, which separate the electronics from the *in-vivo* environment [10]. These thin coatings must not leach toxic elements or compounds into the body and prevent the saline environment from affecting the electrical performance over decades of service life. As an example of where there are unanticipated differences between *in-vivo* and *in-vitro* testing, test data indicates silica coatings (frequently used as passivation materials on consumer electronics) are more rapidly dissolved *in-vivo* than *in-vitro* in 0.9 wt% saline compared with material that had been implanted in an animal [11]-[13].

***In-Vivo* Compared to *In-Vitro* Dissolution of Silica.** Hämmerle et al., has demonstrated that silica deposited by low pressure chemical vapor deposition (LP-CVD) of tetra-ethyl-

ortho-silicate (TEOS)[1] has an *in-vivo* dissolution rate of 600 to 1000 nm per year; whereas no significant damage (<90 nm/yr)[2] was found on *in-vitro*[3] exposed chips that had been immersed in saline for up to 21 months. The silica layer had dissolved *in-vivo*[4] within 6 to 12 months, damaging the underlying silicon layer [11]. Rojahn et al., also comments on the work of Hämmerle et al., and cites Fromherz as further evidence of rapid dissolution of silica when exposed to brain tissue [13].

Maloney et al., have measured *in-vivo*[5] dissolution rates of silica as 3.5 nm per day (1,277 nm per year) for plasma enhanced chemical vapor deposition (PECVD)[6] silicon oxide [12]. Maloney et al., have plotted the film thinning over time and the rate of silica dissolution appears to be linear with time.

Brady and Walther show that the dissolution rate of pure silica is relatively constant at a rate of 0.86 nm per year when exposed to solutions with pH's that range from 2.0 to pH 7.5 [14]-[15]. This pH range is significantly broader than the range expected *in-vivo* (accounting for the immunological response). Icenhower and Dove also report amorphous silica dissolution rates of 0.86 to 2.7 nm per year in distilled water at 25°C and 40°C, respectively. They report that the addition of 0.05 m NaCl at 40°C increased the rate by about a factor of 10x to 27 nm per year [16]. These rates are significantly slower (by a factor of 1000) than what has been observed *in-vivo*, keeping in mind that the *in-vivo* rates are measured on silica, incorporating some hydrogen since it is grown from TEOS and may dissolve faster than quartz or amorphous silica.

In addition there have been many studies on the dissolution rate of silica containing mineral fibers stimulated by human health concerns since such mineral fibers can be detrimental to health if they do not dissolve sufficiently rapid *in-vivo* [17]-[22]. The majority of this data is not directly comparable to TEOS silica dissolution since these fibers are not pure silica but generally contain an appreciable of alkaline earth oxides and other oxides. For instance, the dissolution rate of pure silica (0.86 nm per year) in water is significantly lower than the dissolution rate of high silica (62 wt% silica) containing mineral fibers (330 or 3,400 nm per year at pH 4.5 or 7.7, respectively, in Gamble's solution[7]). How much this effect is due to the alkaline/alkali oxidation and how much to the organic components of the Gamble's solution is unknown [18].

In summary there appears to be biological processes going on *in-vivo* that has not been duplicated *in-vitro*.

Factors Affecting Dissolution of Silica. The dissolution rate of silica as a function of pH, salinity, and other conditions are discussed in a number of references [14]-[16], [23]-

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[1] The first layer was a 15nm deposit of high-quality low pinhole density thermally grown oxide (30 min. at 900°C in oxygen. The thermally grown oxide grows to slow to achieve the desired 500 nm thickness and therefore LP-CVD at 395°C for 60 seconds using TEOS to grow the outer layer [Hämmerle, 2002].

[2] Hämmerle does not give an estimate of their minimum detectable dissolution rate. We estimate this rate to be approximately less than 90 nm per year (0.24 nm per day) based on interference color change over 21 months.

[3] For *in-vitro* testing Hämmerle's chips were exposed to phosphate buffered saline containing 0.2% sodium azide to prevent the growth of bacterial (PBS) in order to assess the biostability of the implants.

[4] *In-vivo* exposure was performed by implanting the chips in the subretinal space in either rabbit or mini-pig eyes. The retina was reattached with the conventional surgical means, e.g., infusion of SF_6 gas [Hämmerle, 2002].

[5] *In-vivo* testing was done by implanting the chips in the back of rats for up to 300 days.

[6] Deposition temperature was 350°C and 1,060 nm thickness of silica was deposited. The precursors for the silicon oxide film were SiH_4, N_2O, He, and N_2, and the deposition rate [Maloney, 2005].

[7] Citrate is used in Gamble's solution to replace proteins and acetate to represent organic acids [Herting, 2007].

[28]. All these studies seem to give much lower rates of dissolution compared to these *in-vivo* results. Generally, the corrosion or dissolution mechanism for silica is the formation of a hydrated surface that dissolves to form aqueous $Si(OH)_4$, although the specific mechanism is thought to include several coupled mechanisms: hydration, hydrolysis of covalent network, and exchange between alkali ions and protons in solution involving protonation-deprotonation reactions [12], [14], [23], [24], [29]. For instance, the buildup of silica in the test solution can ultimately saturate the solution with silica, and slow dissolution process by up to a factor of 1000. Correspondingly, the effect of surface area to solution volume ratio on dissolution rate has been known for over 30 years [17]. Recently, however, Cilleteau et al., have reported that in some cases this sharp drop in glass corrosion may not be associated with the solution saturation effect but instead a result of densification of the outer layers of the surface film [29]. In addition, there is recent research that indicates the presence of certain cations and organic compounds will also affect the dissolution rates [24], [25]. For instance, Bennett has reported the multifunctional organic acids such as citrate and oxalate accelerate quartz dissolution by decreasing the activation energy by approximately 20% while increasing silica by 100% [25].

In-Vivo **Dissolution Silica.** The biochemical process responsible for the rapid rate of dissolution of silica *in-vivo* but not *in-vitro* is currently unknown [13]. The differences in *in-vivo* and *in-vitro* solution chemistry from pH and chemically reactive species generated from the immunological responses have been mentioned but there are other factors that could provide clues to the difference in dissolution rates. The linear rate of dissolution is interesting particularly when compared to the typical immunological response *in-vivo* which shows various cell responses to the implant that increase and then decrease over time [30]. The measured *in-vivo* linear dissolution rate may indicate that what is responsible for the rapid dissolution rate *in-vivo* may not be a result of the immunological response (decreased pH, peroxide, hypochlorite, free radicals, etc.) but rather some other constituent in the body that is more constant over time. This may or may not be the case since the foreign body reaction, consisting primarily of macrophages or foreign body giant cells, may persist at the tissue/implant interface for the lifetime of the implant [30], [31].

Exponent has demonstrated that significant increases in silica dissolution can be achieved in simulated *in-vitro* environments through the use of Fenton's reaction to generate free radicals in the presence of peroxide in PBS type solutions; however these rates are still about a factor of 4 to 6 lower than what is observed *in-vivo*.

Such differences between *in-vitro* and *in-vivo* testing are troubling since there are chemical or electrochemical processes that are occurring *in-vivo* that are not being duplicated *in-vitro*.

Conclusions

1. Ion dissolution *in-vivo* can affect biocompatibility and the corrosion of medical devices.
2. There are no known comparisons of *in-vivo* and *in-vitro* metal leaching rates.
3. There are examples of *in-vivo* dissolution (silica dissolution) that cannot currently be duplicated *in-vitro*.
4. Such discrepancies between *in-vitro* and *in-vivo* dissolution or leaching of ions make it difficult to evaluate the long-term reliability of implantable medical devices from *in-vitro* testing.

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