3. Titanium Dioxide Coatings in Medical Device Applications

3.1 Introduction

Titanium dioxide (TiO_2, titania) is a widely abundant and inexpensive material. In bulk form it is produced as a white powder and it is the most widely used white pigment because of its brightness and very high refractive index (n=2.4). Applications include filler pigment in paints, cosmetics, pharmaceuticals, food products (such as E171, e.g., white lettering on M&Ms) and toothpaste. When deposited as a thin film, its refractive index and color make it an excellent reflective optical coating for dielectric mirrors. It is also widely used in sun block creams due to its photostability, high refractive index and UV absorption properties. TiO_2 is chemically and photo-chemically stable, non-toxic and insoluble under normal pH conditions. The corrosion resistance of titanium metal is due to the formation of a native oxide passivation layer.

TiO_2 occurs in three crystalline forms; brookite, anatase and rutile, the latter two being the more common. Rutile is the thermodynamically stable form. In the crystal lattice of TiO_2 each Ti atom is bonded to six O atoms and each O atom is bonded to three Ti atoms to form a tetragonal crystal lattice. Anatase differs from rutile by the number of common edges of the TiO_6 octahedra i.e., 4 for anatase and 2 for rutile. TiO_2 is effectively an insulator at normal temperatures, however, the band gap (3.0 eV for rutile and 3.2 eV for anatase) is such that it will absorb ultra violet light at wavelengths just under 400 nm and it is referred to as a wide band gap semiconductor.

TiO_2 powder is prepared on an industrial scale either by the sulphate process or by the vapour phase oxidation of titanium tetrachloride ($TiCl_4$). In the sulphate process the ilmenite ore ($FeTiO_2$) is dissolved in sulphuric acid, iron is removed and the solution is hydrolysed. The hydrated TiO_2 is calcined to remove water. Anatase is the main crystal form produced from this process because sulphate ions,

inherently present in the product, stabilise this phase. In vapour phase oxidation (also know as flame hydrolysis) titanium tetrachloride is sprayed into a high temperature flame to produce nanometer-sized particles. The main contaminant is chloride and the phase purity is not good. Powder preparations can be used to make coatings by methods including plasma spray, dip coating, and electrophoretic coating. This chapter reports on advances made in this important field of medical research [1-25].

Other methods may be used to produce coatings by the formation of TiO_2 from precursors directly on a substrate surface. If the substrate is Ti metal or alloy, the simplest method of producing a thin film of TiO_2 is to oxidise the surface. This may be achieved by simply leaving the titanium sample in the open atmosphere where a natural oxide layer will form with time. Alternatively one may increase the rate of oxidation and control the oxide film thickness by simple thermal treatment in an oxygen atmosphere, exposure to an oxidising solution or atmosphere, or by electrochemical oxidation (anodisation). Methods of producing thin films of TiO_2 on other supporting substrates have been developed including physical, chemical and physicochemical routes. These methods may also be used to coat Ti metal and it's alloys.

The main physical route to TiO_2 films is sputter deposition. This involves the formation of a plasma e.g., argon in a vacuum system. A high electric field is produced between the TiO_2 target and the substrate to be coated. The plasma contains positively charged argon ions, which are accelerated towards the TiO_2. The argon ions impact with a billiard ball effect, dislodging titanium and oxygen atoms, or clusters of TiO_x, with high kinetic energy. These species move out into the plasma and upon collision with the substrate adhere to the surface and form a film of TiO_2. Under optimal conditions one can achieve a uniform coating of TiO_2 with the desired crystal structure and film thickness. The sputter deposition route lends itself to the coating of a wide range of substrate materials, including polymers, and to different substrate conformations. A disadvantage is the requirement for a vacuum plasma system that can be expensive.

An alternative wet chemical route to TiO_2 thin films is sol gel processing, which has been used in the production of ceramic and glass coatings for many years. For TiO_2 sol gels the most common

precursors are alkoxides, e.g., titanium (IV) propoxide and titanium (IV) butoxide, although inorganic compounds may also be used. Alkoxides are metal organic compounds where the metal is bonded to a hydrocarbon via a bridging oxygen i.e., the titanium atom replaces the proton in the alcohol. The metal alkoxides are liquid at room temperature and can be produced with high purity. Alkoxides are very reactive with water and the controlled hydrolysis of the alkoxide is followed by a condensation and polymerisation step whereby the titanium hydroxide sol gives up water to form a polymeric TiO_x gel. The sol gel can be coated onto a wide range of substrates using techniques such as dip coating, spin coating, roll coating, etc. In the case of TiO_2 sol gel processing, a high temperature thermal treatment stage is normally required to yield a crystalline film. High temperature treatment is obviously not applicable for thermolabile materials such as polymers. However, other methods such as hydrothermal annealing have been used to produce crystalline films at much lower temperatures (100–150^{o}C).

Another commonly employed route to TiO_2 films is chemical vapour deposition (CVD). In this technique the substrate to be coated is heated and exposed to a volatile metal organic precursor in a carrier gas. Upon contact with the surface the reactive precursor decomposes to yield an oxide film. Other physicochemical approaches may involve a mixture of techniques e.g., reactive sputter deposition or plasma enhanced CVD.

Titanium metal and its alloys are important as biomedical and dental implant materials because of their relatively high corrosion resistance and good biocompatibility. The passivating oxide layer is responsible for these properties. However, despite widely reported low rates of corrosion for titanium *in vitro*, there is evidence to suggest that corrosion rates may be enhanced *in vivo*, leading to the release of titanium and accumulation in adjacent tissues or transport to other areas of the body [22]. Indeed, the biological environment may be aggressive towards titanium or the native oxide film. Furthermore, oxide film growth and ion incorporation into the film have been noted following implant into humans. Different methods of surface modification have been attempted in order to improve the corrosion resistance and biocompatibility of titanium, titanium alloys and stainless steel. It was reported [23] on the corrosion resistance for

biomaterial applications of TiO_2 films deposited on titanium and stainless steel by ion-beam-assisted sputter deposition (IBASD). In that approach, a pure titanium target is sputtered by an argon ion beam, and the sputtered atoms are deposited onto the substrate while a flow of neutral oxygen gas is introduced on the substrate (normal reactive sputter deposition). An additional oxygen ion beam is used as the assisting beam. They reported a two-layer model of the oxide film deposited using this method and that the IBASD films exhibited improved corrosion resistance as compared to a native oxide layer on titanium or stainless steel.

Hemocompatability is an important parameter for implant materials that come into contact with blood. Almost any medical device introduced into the human body will initially come into contact with blood. Furthermore, thrombogenicity of artificial implant devices such as artificial heart valves is a serious problem as the implant induces blood clotting and patients with such implant devices must be given anticoagulant drugs as ongoing therapy. Surface modification of implant devices is therefore an important approach to improving hemocompatability. Different materials have been investigated for coating implant devices e.g., diamond like carbon, silicon carbide, titanium nitride, and aluminium oxide, and low temperature isotropic pyrolytic carbon (LTIC). LTIC is widely regarded as the best hemocompatible coating. It has been reported that albumin can passivate a surface, that complement activation can result in the neutrophil recruitment to surfaces, and that fibrinogen initiates the acute inflammatory response. Platelets and inflammatory cells are likely to respond to the layer of adsorbed proteins, not to the material surface itself. However, the composition of the layer of adsorbed proteins is dependent on the properties of the material. Therefore, the initial reactions that take place on the material surface upon exposure to blood will determine the conditions for subsequent reactions. Nygrean, Tengvall and Lundstrom [20] investigated the initial reactions that take place on exposure of TiO_2 surfaces to blood. They compared Ti metal that was passivated in nitric acid to Ti metal which had been passivated by annealing in air at 700^{o}C. In order to study the initial interactions they used capillary blood from human donors (without addition of anticoagulants), which was exposed to the surface for only 5 seconds. Fluorescent immunoassay was used to determine the presence of platelet cells, fibrinogen,

$C1_q$, and prothrombin/thrombin. They reported that the serine proteases of the coagulation and complement systems were initiated within 5 seconds of the blood exposure to the TiO_2 surface. They also found that platelets were adhered to the surface in the initial 5 seconds' exposure. Both plasma proteins and cells were found at the blood-surface interface after only 5 seconds and this implied that a complex "biofilm" was formed within a very short contact time. The interaction of plasma proteins will differ for hydrophilic and hydrophobic surfaces. Both annealed and acid treated samples were macroscopically hydrophilic and there was no significant difference in contact angle, however, there was a significant difference between the levels of prothrombin/thrombin and platelets adhered to the different surfaces. The authors suggest that this may be due to different levels of carbon impurity in the two films. Platelet adhesion to a surface, although probably a pre-requisite to activation, does not in itself mean activation.

Huang et al. [13] reported on the hemocompatibility of titanium oxide and tantalum doped titanium oxide films prepared by plasma immersion ion implantation and deposition (PIIID) and sputtering. The first event to occur following implant's surface contact with blood is the adsorption of a protein layer. If the surface characteristics of the material result in a change in the configuration of the adsorbed protein e.g., fibrinogen or globulin, it may enhance coagulation and/or platelet activation. Alternatively, adsorption of albumin on the surface with maintenance of the native configuration discourages coagulation. Therefore, a reduction in protein adsorption and denaturation is a key strategy to enhancing anticoagulation properties of surfaces. The anticoagulation nature of a surface depends on multiple characteristics of the material including surface energy, surface charge and surface topography and on the surface effects imposed at different stages of the blood-surface interaction process. Huang et al. [13] reported that their TiO_2 films exhibited lower interface energy compared to LTIC, leading to less fibrinogen adsorption on the TiO_2. Furthermore, changing the structure of the TiO_2 film from amorphous to crystalline, and doping of the films with tantalum also can affect the anticoagulation properties. They postulated that the semiconducting nature of the TiO_2 films is an important contributing factor where n-type semiconductor properties helps to prevent protein denaturation on the surface by inhibiting charge transfer from the protein into the

TiO_2. Indeed they found improved behaviour of platelet adhesion on crystalline rutile as compared to amorphous TiO_2 films.

The surfaces of implants used for dental and orthopaedic applications also become coated with a proteinacious film. The nature of this protein layer depends on the surface of the implant and may affect the biological response to the implant, including cell attachment. Fibronectin is one of the first extracellular matrix proteins produced by odontoblasts and osteoblasts, and therefore, is a useful model to investigate protein surface interactions *in vitro*. Fibronection is composed of two similar polypeptide chains whose subunits are linked by disulphide bonds and this protein is reported to play a major role in interaction of the implant material and the body. Yang et al. [25] investigated fibronectin adsorption on titanium surfaces and its effect on osteoblast precursor cell attachment. They used Ti metal that was pretreated by wet grinding followed by passivation in 40% v/v nitric acid (HNO_3) for 30 minutes. Each sample was sterilised by UV irradiation for at least 24 hours, a step that may have had other consequences. X-ray photoelectron spectroscopy analysis confirmed an amorphous oxide layer on the surface of the Ti following the treatment stages. The researchers observed a significant difference in the fibronectin adsorbed after 15 and 180 minutes exposure to protein containing solution. The amphoteric charactistics of TiO_2 mean that the surface charge changes with pH. The isoelectric point of TiO_2 has been reported to be between pH 4.0 and 6.2, and therefore, at a pH 7.4, the oxide will be mainly anionic (net –ve charge) in character and will electrostatically bind proteins that are cationic (net +ve charge) at pH 7.4. Binding of proteins to surfaces may also involve hydrophobic bonding the extent of which will be affected by the wettability of the implant surface. TiO_2 surfaces have been reported to have both hydrophilic and hydrophobic components. Therefore the extent of specific protein attachment to TiO_2 surfaces will be dependent on a complex interplay between hydrophobicity/hydrophillicity and electrostatic interaction. Yang et al. [25] also reported that the pre-adsorption of fibronectin to the TiO_2 surface enhanced the attachment of osteoblast cells as compared to control Ti samples without pre-adsorption of fibronectin. It has been suggested that the presence of fibronectin promotes cell attachment by binding through cell surface receptors and mediating adhesive interactions. Furthermore, adsorption

of low concentrations of fibronectin on surfaces causes unfolding of the protein into an inactive conformation, but a high adsorption concentrations unfolding is prevented by steric hindrance due to molecule packing.

More recently it has been reported that nanostructure control of TiO_2 films can not only improve biocompatibility, but can improve the bioactivity of the surfaces for bone adhesion. It is hypothesised that tissue-biomaterial interactions occur within 1 nm of the material surface, and therefore the ability to engineer surfaces on the nanometre scale will have major impact on the production of materials with improved biocompatibility and bioactivity.

Due to the increased life expectancy of the population there has been an enormous increase in the incidence of bone fracture and the need for bone implant surgery. The improvement of implant-bone interface is a real problem. Titanium and its alloys are the most commonly employed metals used in the manufacture of orthopaedic prostheses on account of their excellent mechanical properties, corrosion resistance and biocompatibility. Even so, osseointegration results have not always been satisfactory under altered metabolic bone conditions. Research and development into improvements in osseointegration have focussed on implant surface properties such as morphology, roughness and chemical composition. All of these factors may affect cell and biochemical responses of host bone and the ability to control these may allow one to promote bone apposition through the acceleration of the chemical bonding between the new bone and the implant surface. For titanium implants, the oxide layer grows slowly on the surface following implant and contributes to the formation of apatite and bone-like tissue. Current passivation methods used in the pretreatment of titanium prosthesis (machining, ultrasonic cleaning, sterilisation, and anodisation) still present limits. For example, low-level contamination with impurities may have a deleterious effect on the osseointegration process, the TiO_2 film thickness is linearly dependent on the anodic potential employed in electrochemical oxidation and the anodically grown oxide may present significant porosity. Giavaresi et al. [10] reported on the osseointegration of a nanostructured titanium oxide coating produced by chemical vapour deposition (CVD). The aim of the study was to compare the *in vivo* (implanted in rabbits) osseointegration of Ti implants coated with TiO_2 CVD thin films

with that of Ti machined implants. They reported that the affinity index (AI: the interface contact between bone and implant as calculated as the length of the bone profile directly opposed to the implant divided by the total length of the bone-implant interface) of the Ti/CVD implants were significantly higher than that of the machined implants. SEM analysis confirmed a high level of osteintegration for the Ti/CVD implants in cortical bone and enhanced osseointegration in cancellous bone, as compared to that observed for the machined implants. They concluded that their histomorphometric, ultra-structural and microhardness findings demonstrated that the nanostructured TiO_2 coating positively affected the osseointegration rate of commercially pure Ti implants in terms of bone mineralization in both cortical and cancellous bone. Further studies were planned on mechanical bonding with bone and bone remodelling around implants.

In 2001 Ramires et al. [23] reported on the influence of titania-hydroxyapatite (TiO_2-HA) composite coatings, obtained via a sol gel route, on *in vitro* osteoblast behaviour. They found that these materials have no toxic effects (at least *in vitro*). Cell growth and morphology were similar on TiO_2-HA coatings and TiO_2 coatings. However, alkaline-phosphatase-specific activity and collagen production of osteoblasts cultured on TiO_2-HA coatings were significantly higher than uncoated titanium or polystyrene culture plates. They concluded that the TiO_2-HA coatings were bioactive owing to the presence of hydroxyl groups on the surface that promote calcium and phosphate precipitation and improve interactions with osteoblastic cells.

Other workers have also investigated bone cell proliferation on hybrid TiO_2-HA coatings on Ti implants. For example, Lee et al. [15] produced TiO_2 films by a method known as micro-arc oxidation (MAO) in which a DC pulsed potential is applied to the Ti substrate in an electrochemical cell. In this case the Ti metal was pre-coated with HA (using e-beam evaporation). The logic behind this approach was to introduce Ca and P into the TiO_2 films to improve osseointegration and cellular activity. The rough, porous TiO_2 films produced by MAO should enhance mechanical interlocking of tissue and implant. A CaP layer is thought to enhance the initial cellular response, due to high osteoconductivity and bioactivity. When the MAO treatment was carried out at 230 V the coating surface was observed by SEM to become rough and porous (only isolated areas were affected at

lower potentials) and caused the dissolution of the HA layer, however, a large amount of Ca and P were incorporated into the TiO_2 layer and some of the CaP layer remained after MAO treatment. The proliferation of the human osteosarcoma cells was decreased only slightly on the HA surface treated by MAO, similar to Ti surface treated by MAO, and was attributed to the increase in surface roughness. However, there was a marked increase in the alkaline phosphatase activity of the cells on the MAO treated TiO_2-HA compared to the MAO treated Ti. They concluded that the use of hybrid coatings obtained by pre-coating of HA on Ti followed by MAO treatment is a possible route to enhanced cell responses for bone implant materials.

Secondary infections are a cause of implant failure, particularly with percutaneous (skin penetrating) implants. However, infections at skin-penetrating titanium implants anchored in the temporal bone can often be cured by local treatment. As mentioned previously, host protein adsorption to the implant material occurs within seconds of implant. Protein adsorption to the surface depends on a number of parameters. Furthermore, microbial adhesion will depend on the nature of the surface and indeed on the nature of the surface bound proteins. Fibronectin has been proposed to mediate adhesion of staphylococci to implant materials in blood. Staphylococcus epidermidis is a common etiological agent with infections involving polymeric implants whereas Staphylococcus aureus is the most common etiological agent with infections involving metal implants. Understanding the mechanism of bacterial attachment to surfaces is crucial for enabling the engineering of surfaces for reduced biofilm recruitment and implant failure due to secondary infection. Holgers and Ljungh [12] reported a study into the cell surface characteristics of microbial isolates from human percutaneous titanium implants. They found that no isolates expressed a hydrophobic cell surface, however, isolates from infected implants were less hydrophilic than those from non-inflamed tissue. The degree of hydrophillicity of an implant surface will influence the recruitment of biofilm. This leads to the possible exploitation of other, perhaps more exciting, properties of TiO_2.

The important biocompatible and bioactive properties of TiO_2 have been addressed above. TiO_2, has additional properties which bring added value as a material for use in biomedical applications. In 1972 Japanese researchers, Honda and Fujishima [8], published a

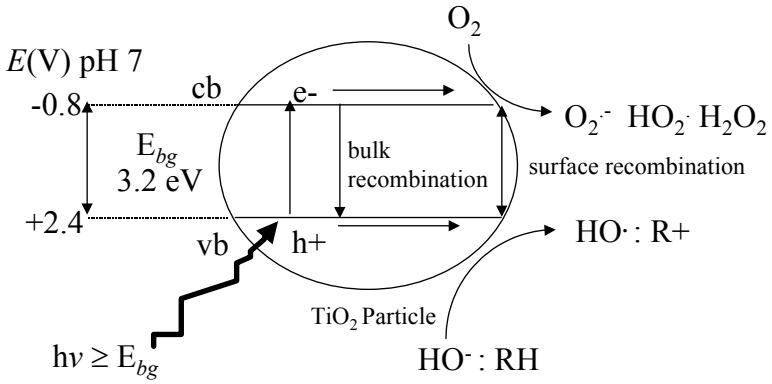

Fig. 3.1. Mechanism of TiO photocatalysis (potentials vs SCE)

paper in Nature reporting the photo-splitting of water using a single crystal of rutile TiO_2 under ultra violet irradiation (Honda and Fujishima, [8]). If one could achieve efficient water splitting into hydrogen and oxygen with solar energy then the world's energy problems might be solved.

Since then, the ability of TiO_2 to absorb UV electromagnetic irradiation and use that energy to drive electrochemical reactions on it's surface, has been investigated for a wide variety of applications, including water and air treatment and purification [1,2,5,11,17-19,24] and "self-cleaning" surfaces [9]. Indeed, Pilkington's are now selling "self cleaning" glass called *Activ*, with a 15 nm layer of TiO_2 on the surface which, under the action of solar UV, can destroy and remove organic contamination. The process has been aptly named photocatalysis, meaning the use of a catalyst to speed up a photochemical reaction. The mechanism of photocatalysis is shown in Figure 3.1.

TiO_2 is a wide band gap semiconductor material. The valence band is filled with electrons and is separated from an empty conduction band by band gap energy (E_{bg}). If illuminated with UV light ($E = h\nu$ where E_{bg} of 3.2 eV is equivalent to 387 nm) a photon is absorbed and an electron is promoted from the valence band to the conduction band, leaving a hole in the valence band. These charge carriers can recombine in the bulk, or they can move to the surface of the particle. An electron in the conduction band has a negative electrochemical reduction potential and can reduce an electron acceptor species at

the interface, e.g., molecular oxygen producing superoxide radical anion, perhydroxyl radical, and hydrogen peroxide. The hole has a very positive electrochemical reduction potential, positive enough to oxidise water or hydroxyl ions to yield hydroxyl radicals. Hydroxyl radicals are powerful and indiscriminate oxidising species. The redox reactions at the surface of the particle lead to the generation of active oxygen species which can attack organic and inorganic species at or near the surface. There are literally thousands of papers in the literature reporting photocatalysis for the destruction of a wide range of organic pollutants, including microorganisms such as viruses, bacteria, and fungi, and even tumour cells [1,7,9,14].

The potential for this "self sterilising" property has been identified for use in medical devices. Ohko et al. [21] reported on self-sterilising and self-cleaning of silicone catheters coated with TiO_2 photocatalyst thin films. They described a sol gel method for coating silicone catheters with TiO_2 to produce a photoactive film. The self-cleaning effect was demonstrated using the bleaching of methylene blue dye and the self-sterilising effect was demonstrated by the killing of *E. coli*. The application proposed was that the catheter could be irradiated prior to insertion thus helping to prevent catheter related bacterial infection. The authors suggested practical use as an intermittent self-sterilising catheter for neurogenic bladder patients and or for self-sterilising suction tubes for frequent draining of sputa and oral fluid. They also suggested that a dark bactericidal action could be incorporated by surface doping of the TiO_2 with silver.

Another property of TiO_2 that has created a great deal of excitement is the phenomenon of photo-induced superhydrophilicity. UV excitation of the TiO_2 generates electrons and holes. The electrons tend to reduce the Ti(IV) cations to the Ti(III) state, and the holes oxidize the O_2^- anions. This results in the ejection of oxygen atoms creating oxygen vacancies. Water molecules can then occupy these oxygen vacancies, producing adsorbed OH groups, which tend to make the surface more polar or hydrophilic. After about 30 minutes or so under a moderate intensity UV source, the contact angle for water approaches zero. It is a combination of this superhydrophilic effect and the photocatalytic effect that is responsible for the 'self-cleaning' nature of these coatings. Even more interesting is that TiO_2 surfaces have been reported to be amphiphilic in nature i.e., displays

both hydrophilic and hydrophobic properties. Fujishima, Rao and Tryk [9] reported light induced reduction in contact angle for water approaching zero and light induced reduction in contact angle for glycerol trioleate (a component of vegetable oils) approaching zero.

The wettability of a surface will have an effect on the interactions of the surface with proteins. Therefore the ability to induce changes in contact angle of the surface would have important implications for implant materials. Liu et al. [16] reported that UV irradiation of TiO_2 coatings prior to immersion in simulated body fluid enhanced the formation of bonelike apatite. They used plasma sprayed nano-particle TiO_2 to form coatings on the surface of Ti metal. Following coating, one set of samples was irradiated for 24 h using a 125 W medium pressure Hg lamp (main output 365 nm) and a non-irradiated sample set was used as the control. Following four weeks immersion in simulated body fluid they used energy dispersive x-ray spectroscopy, XRD and FTIR to analyse the surfaces. They found that the samples that had been irradiated with UV prior to immersion had a newly formed layer on the surface that was carbonate containing hydroxyapatite (bonelike apatite). Without UV irradiation prior to immersion no new surface precipitates were detected. They reasoned that oxygen vacancies were created and that Ti^{3+} sites were more favourable for the dissociation of water to form an abundance of surface Ti-OH groups. OH groups on ceramic surfaces are suggested to be effective for inducing the formation of an apatite layer. The mechanism is thought to involve the Ti-OH surface groups reacting with hydroxyl ion in the simulated body fluid to produce negatively charged $Ti\text{-}O^{-}$.

$$Ti\text{-}OH + OH^{-} \rightarrow Ti\text{-}O^{-} + H_2O \qquad (3.1)$$

The Ca^{2+} ions in the solution are electrostatically attracted to the negatively charged surface, followed by reaction with HPO_4^{2-} to form calcium hydrogen phosphate. The CaP continues to grow, also incorporating carbonate anions from solution, and crystallises to form carbonate-containing hydroxyapatite (bonelike apatite). Liu et al. [16] reported that the photo-induced bioactive surface remained for at least one week following UV irradiation.

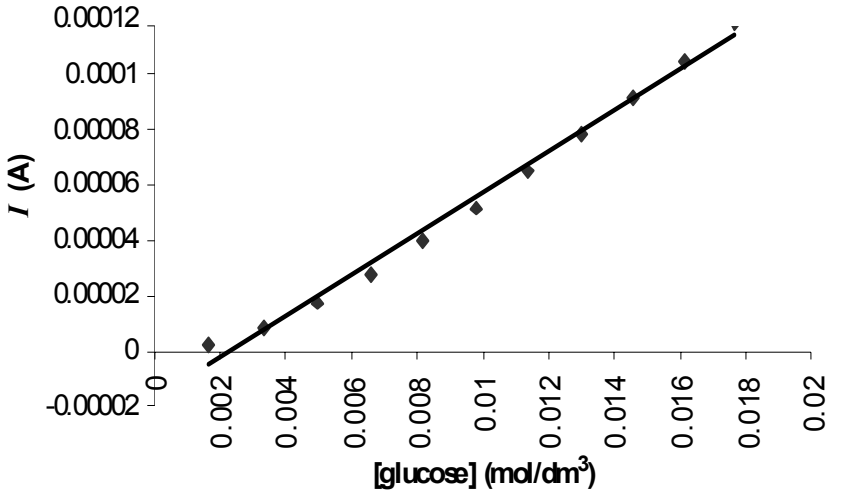

Fig. 3.2. Nanocrystalline TiO_2 electrode's amperometric response to standard additions of glucose. 10 mg GOD was present as free enzyme in 30 cm^3 pH 6 phosphate buffer. The TiO_2 electrode was held at a fixed potential of –0.4 V (SCE) [4].

Cosnier et al. [6] reported the use of nanocrystalline TiO_2 films for use in biomedical sensor applications i.e. an electrochemical transducer material for the detection of hydrogen peroxide in the presence of oxygen. There is a wide range of oxidase enzymes which play different roles in the body. The best known is glucose oxidase (GOD), which acts to oxidise glucose to gluconic acid and in the process, reduces molecular oxygen to hydrogen peroxide. GOD is commonly employed in commercial glucose biosensors in which the electron transfer to the electrode is mediated by a free redox couple. However, the Holy Grail of glucose sensing is to develop an implantable sensor for feedback control of an insulin delivery system (artificial pancreas) and remove the need for routine blood sampling.

Mediated biosensors are not suitable for implant as free mediators will simply diffuse away into the blood stream and immobilised mediators are not as efficient or the mediator may be toxic. An alternative is to use non-mediated electrochemical sensing. TiO_2 has a lower overpotential for the electrochemical reduction of hydrogen peroxide than for the reduction of dissolved oxygen. Therefore, as hydrogen peroxide is a by product of the action of GOD, a TiO_2

sensor incorporating GOD could be used to detect glucose by the electrochemical reduction of hydrogen peroxide without interference from oxygen reduction. Therefore, there is no requirement for a mediator and TiO_2 is biocompatible. Figure 3.2 shows electrochemical reduction current measured for nanocrystalline TiO_2 electrode as a function of glucose concentration in a solution containing free GOD. The response is linear in the concentration range for glucose found in physiological blood.

In conclusion, TiO_2 coatings are important for improving the biocompatibility and bioactivity of implant materials. The additional properties of photocataltyic sterilisation and photo-induced superhydrophilicity may bring added value. This remains a vibrant field of research.

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