Biometals
https://doi.org/10.1007/s10534-018-0078-6

TiO_2 and its composites as promising biomaterials: a review

Naveen Kumar · Nar Singh Chauhan · Anuj Mittal · Shankar Sharma

Received: 15 January 2018 / Accepted: 26 January 2018

Abstract TiO_2 is a well-known material and has remarkable physical, chemical and biocompatible properties which have made it a suitable material in the biological world. The development of new TiO_2-based materials is strongly required to achieve desired properties and applications. A large number of TiO_2 composites have been synthesized and applied in various fields. The present review reports the utility of TiO_2 and its composites in biosensing, in Photodynamic Therapy, as an antimicrobial agent and as a nanodrug carrier. The aim of this review is to discuss the biological application of the TiO_2 based materials and some recent advancement in TiO_2 to enhance its application in the biological world.

Keywords Biocompatibility · Composites · Biosensing · Antimicrobial · Nanodrug carrier

N. Kumar (✉) · A. Mittal · S. Sharma
Department of Chemistry, Maharshi Dayanand University, Rohtak, India
e-mail: naveenkumar.chem@mdurohtak.ac.in

N. S. Chauhan
Department of Biochemistry, Maharshi Dayanand University, Rohtak, India

Introduction

Biomaterials are biocompatible substances used in biological world for analysis, treatment and support to the living beings. They may be originated naturally or synthesized in laboratory. Among synthesized materials, TiO_2 is one of the well-known semiconductor material used in the biological world. Utilization of TiO_2, in water splitting (Fujishima and Honda 1972) and in photokilling of various microorganisms (Matsunaga et al. 1985) revolutionized the chemical and biological world respectively to a great extent. In the present scenario TiO_2 is widely used in cosmetics, paints, ceramics, photocatalysis, solar cell, food coloring etc.

TiO_2 and TiO_2 based conjugates exhibit antimicrobial activity and are also being applied in various biological applications like biosensing, blood clotting, drug delivery and photodynamic therapy due to their stability, sensitivity, selectivity, biocompatibility and non-toxic nature to the living beings. Titanium and its alloys have good mechanical properties, low density and excellent biocompatibility (Hunt and Shoichet 1985; Olmedo' et al. 2008) which make these compounds highly applicable in the field of implants such as osteointegrated dental and orthopedic implants (Sahar et al. 1988).

TiO_2 exists in three forms i.e. anatase (tetragonal), rutile (tetragonal) and brookite (orthorhombic). TiO_2 when synthesized is found in amorphous state and becomes crystalline on calcination. Its anatase phase is formed in the temperature range 400–500 °C (Cordero-García et al. 2016; Mattle and Thampi 2013). Further increase in the temperature pushes it into rutile phase that completes in the temperature range of 800–900 °C (Zheng et al. 2008). It is a general perception that the key property of semiconductor functioning is their electronic properties, especially the band gap. The band gap of anatase and rutile are 3.2 and 3.0 eV respectively, (Dette et al. 2014; Scanlon et al. 2013) which is responsible for the antimicrobial activity and biosensing property. To achieve desired properties and applications, band gap of TiO_2 can be altered by incorporation of various elements (metals and nonmetals) in TiO_2 (Chenga and Sunb 2012; Yu et al. 2014; Souza et al. 2014; Sotelo-Vazquez et al. 2015; Wang et al. 2011; Li et al. 2009). Absorption shift to visible region is highly appreciable regarding efficiency and cost effective purposes i.e. for the fabrication of self sterilizing materials and biosensors. Recently improved properties of TiO_2, like low band gap and charge separation have been achieved by making their composites with carbon. Carbon materials are highly environment friendly and cheaper as compared to inorganic materials because carbon is one of the major elements present in the earth crust (Jo et al. 2014).

TiO_2 on irradiation with the light of appropriate energy leads to the production of electron hole which further generates the highly oxidizing species like hydroxyl free radical, superoxide free radical etc. which have the power to oxidize various organic pollutants and to kill microorganisms like algae, bacteria, viruses, fungi etc. Photokilling of various microorganisms using TiO_2 has opened the door to use it in making self-sterilizing equipments and remove the biofouling caused by the microorganisms.

In this review we focus on the various biological application of the TiO_2 (Fig. 1), and various modifications made to improve the properties of TiO_2 for its utilization on the globular scale.

Biosensing

An analytical device which converts a biological response into an electrical or any other readable form is known as biosensor. The working of an electrochemical biosensor is based upon the electrical current, potential or the charge accumulation induced as a result of biochemical reaction on the surface. A biosensing process mainly consists of four steps: (a) binding of receptor to analyte (b) a specific biochemical reaction taking place on interface and giving rise to a signal received by transducer (c) signal being converted to electronic signal and amplified by detector circuit using appropriate reference and (d) signal being sent to computers for data processing and resulting quantity presented through an interface to operator.

Biosensors are the fantastic tools in the field of chemical and biological analysis, healthcare, environmental monitoring, process industries, drug development and pharmaceuticals. Efficient biosensing depends upon sensitivity, selectivity and response time. In the view of these factors electrochemical biosensing (Iwamoto et al. 1994; Wang et al. 2009) was found as a better analytical technique over the other analysis techniques like luminescence analysis (Li and Liu 2011; Deng et al. 2011), fluorometry (Niu et al. 2012), colorimetry (Park et al. 2005; Durocher et al. 2009). Each biosensing unit uses a semiconductor material (Fig. 2), followed by the biological agent or biomaterial to either specifically bind or catabolize

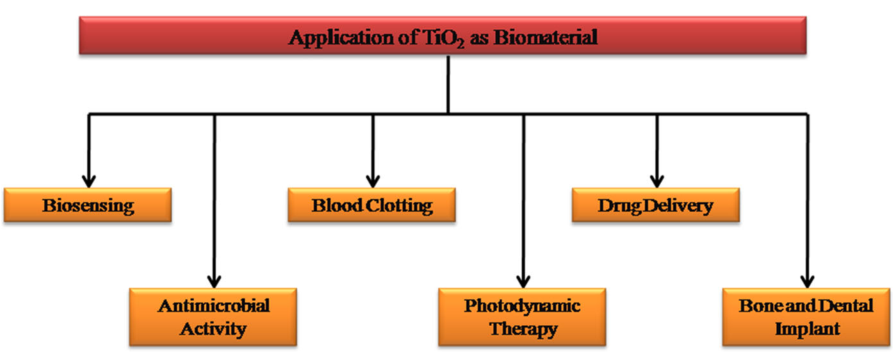

Fig. 1 Flow chart of biological applications of TiO_2

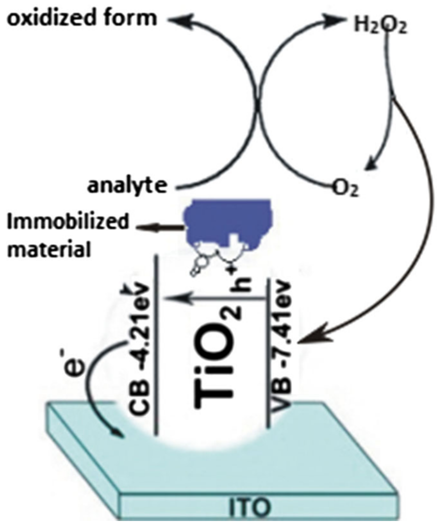

Fig. 2 Layout of the semiconductor assisted biosensor

an analyte. Natural biomaterials like antibodies and enzymes are not widely used as sensing materials due to high cost and environmental influence. So, there is a great need for the stable and low cost artificial biosensor. In this context nontoxicity, biocompatibility, low cost, high specific surface area, chemical and photochemical stability, optical transparency, electrochemical activities make nano structured TiO_2 a suitable semiconductor material to be used as biosensor (Mun et al. 2010; Mathurab et al. 2009; Topoglidis et al. 1998). It was supposed that large internal surface area, negative surface charge and high effective refractive index of TiO_2 nanotube arrays could allow convenient incorporation of biomolecules and show high analyte sensitivity. Generally, hydroxyl (OH) functional group formed on the surface of a metal oxide (TiO_2) binds the biomolecules by either chemical or physical method for their future application as a biosensor (Sakata et al. 2004). TiO_2 synthesized with different methods has modified surface structure and covalently binds the analyte recognizing biomolecules such as proteins, enzymes, DNA, and RNA by interacting with the terminal functional groups such as carboxylic (–COOH), aldehyde (–CHO), amine (NH_2) etc. present in the biomolecules (Mondal et al. 2014; Rios and Smirnov 2009; O'Brien et al. 2000; Kim et al. 2009) and enhance the biosensing property by promoting electron transfer (Zang et al. 2007).

TiO_2 nanocomposites with other semiconductor materials like NiO, SiO_2, CeO_2, IrO_2 etc. exhibit enhanced electron transportation and show an excellent capability to immobilize enzyme (Tang et al. 2013; Cui et al. 2014; Zhao et al. 2015; Liu et al. 2006). IrO_2–hemin–TiO_2 nanowire arrays with enhanced selectivity, sensitivity and stability were used in the detection of the glutathione (Tang et al. 2013). Heterostructures containing p-type NiO and n-type TiO_2 nanobelts exhibit enhanced electrocatalytic activities in the oxidation of 6-Phosphate aminopurine (^{6}PA) due to the formation of p–n junction heterostructure which improves the charge transport and exhibited higher surface accumulation ability (Cui et al. 2014).

Various doped and composites like Mn/TiO_2, TiO_2/CeO_2 have been tried for urea detection that showed good response time and sensitivity (Pandey et al. 2010; Ansari et al. 2009) (Table 1). PbO_2/TiO_2/Ti electrode modified with acetylcholinesterase enzyme (AChE) was also used as photoelectrochemical biosensor for organophosphates (OPs) having a linearity range of 0.01–20 μM with a detection limit of 0.1 nM (Wei et al. 2009).

Biomolecules such as DNA, antibodies, polymer, cellulose, enzyme or protein enhanced biosensing response of TiO_2 (Li et al. 2012; Zhuo et al. 2011). TiO_2/cellulose composite fibers are easy to synthesize, stable over high range of pH and can be easily stored and used for the enzyme immobilization (Kafi and Chen 2009). TiO_2/polymer composites are also used for enzyme immobilization because the presence of polymer reduces the risk of cracking of TiO_2 structure (Zhu et al. 2015). Luo et al. (Luo et al. 2009) found that cytochrome c (cyt c) is stably immobilized onto the TiO_2 nanoneedles film and cyt c-TiO_2 nanocomposite shows high selectivity for the detection of H_2O_2, with a lower detection limit and without any interference by cathodic and anodic current. Porphyrin-functionalized TiO_2 nanostructures were used for the sensing of glutathione (GSH) through the dentate binding of TiO_2 (Tu et al. 2010). Glucose is one of the important analytes and a large number of biosensing materials have been tried to detect glucose (Table 2). The detection mechanism of glucose comprises of two steps i.e. oxidation of glucose to gluconic acid and H_2O_2 in the presence of dissolved oxygen and the GO_x followed by oxidation of H_2O_2 at anode which produces the anodic current indicating the presence of the glucose.

Table 1 List of the TiO_2 based materials for the Urea sensing

Sr. No.	Electrode material	Sensitivity	Detection limit	Reference
1.	Mn doped TiO_2	2.3 μA mM^{-1} cm^{-2}	0–6.5 mg/ml	Pandey et al. (2010)
2.	ITO coated with TiO_2–CeO_2 NPs prepared via sol–gel method	0.9165 μA mM^{-1} cm^{-2}	10–700 mg/dl	Ansari et al. (2009)
3.	TiO_2 nanoparticle via sol–gel method	–	0.008–3 mM	Chen et al. (2009)
4.	ITO coated with TiO_2/ZrO_2	–	5–100 mg/dl	Srivastava et al. (2013)

Table 2 List of the modified TiO_2 materials for sensing of glucose

Sr. No.	Electrode material	Sensitivity	Detection limit	Reference
1.	Au/TiO_2 nanospheres	–	10.0–500 pg/ml	Zhuo et al. (2011)
2.	Etched titanium nano tube with grapheme oxide synthesized by anodization method	0.954 μA mM^{-1} cm^{-2}	0.1–6 mM	Wang et al. (2015)
3.	TiO_2 nanowires synthesized by hydrothermal method	–	0.09 nM	Tang et al. (2014)
4.	Titania sol–gel film synthesized by vapour phase deposition	7.2 mA mM^{-1} cm^{-2}	0.07–15 mM	Yu et al. (2003)
5.	TiO_2/graphene (GR) synthesized by aerosol assisted self-assembly	6.2 mA mM^{-1} cm^{-2}	0–8 mM	Janga et al. (2012)
6.	Titanium nanotubes	45.5 mA mM^{-1} cm^{-2}	0.01–1 mM	Xie et al. (2007)
7.	Modified TiO_2 nanotube/carbon nanotube	0.24 mA mM^{-1} cm^{-2}	0.006–1.5 mM	Pang et al. (2009)
8.	Platinum electrode/TiO_2 nanofibers synthesized by electrospinning	9.25 μA mM^{-1} cm^{-2}	0.01–6.98 mM	Tang et al. (2010)
9.	TiO_2 NTs/Prussian blue (PB)/Au synthesized by anodization	36 μA mM^{-1} cm^{-2}	0.015–4.00 mM	Benvenuto et al. (2009)
10.	TiO_2 NPs/Prussian blue synthesized by sol–gel method	12.74 μA mM^{-1} cm^{-2}	0.02–15 mM	Liang et al. (2008)
11.	TiO_2 NPs/graphene/NiO synthesized by hydrothermal method	4.129 μA mM^{-1} cm^{-2}	1.0–12.0 mM	Pan and Lin (2009)
12.	TiO_2 NPs/Nafion synthesized by sol–gel method	240 μA mM^{-1} cm^{-2}	0.1–0.6 mM	Yao et al. (2011)

$$C_6H_{12}O_6 + O_2 + GO_x \rightarrow C_6H_{12}O_7 + H_2O_2$$

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$$

Yang et al. (2016) synthesized copper and carbon loaded TiO_2 composite nanofibers and fabricated it with the copper containing enzyme laccase and a polymer nafion for the detection of hydroquinone. TiO_2-GR nanocomposite modified electrode is also used for the sensing of the compounds having crucial role in the biological system which include nucleobases such as adenine and guanine (Fan et al. 2011a) and amino acids like L-tryptophan and L-tyrosine (Fan et al. 2011b) and also tried for PCR product from transgenic soybean gene (Gao et al. 2012). The presence of the graphene helps in the adsorption of analyte and also facilitates the transfer of electrons whose synergetic effect improves the electrochemical response for the sensing. Due to high adsorptivity and conductivity, TiO_2-GR nanocomposite has potential applications in designing low cost and high performance electrochemical sensors/biosensor.

TiO_2 is used not only for the sensing of organic compounds, but also for the sensing of viruses (Vitera et al. 2012; Viter et al. 2017) by immobilizing antibodies or antigens of that particular virus on TiO_2 and such biosensors are known as *immune biosensors or immunosensors*. Tereshchenko et al. (2015) immobilized the biorecognition agents (antibodies and antigen for *Salmonella* spp. and *Bovine leucosis* respectively) onto TiO_2 for the diagnosis of the *Bovine leucosis* and *Salmonella* spp. viruses. According to a report, the TiO_2 coated on glass substrate and immobilized with the antibodies (anti-S-

Ab) was used for the detection of virus *Salmonella typhimurium* (Viter et al. 2017). The interaction of antibody with the virus results in the change in photoluminescence (PL) wavelength and intensity, which become the basis of the biosensing activity of TiO_2 against the viruses. The biosensing property of TiO_2 against the viruses is due to change in the optical response, hence it is also known as the *optical biosensor*. Similarly, the leucosis virus which is responsible for leukemia-like malignant viral disease in cattle was detected by the application of antigens of Leucosis on TiO_2 surface (Vitera et al. 2012) and change in optical response showed the presence of the virus.

Antimicrobial activity

Biological air pollutants are one of the major components of air pollution. The biological air pollutants include the micro-organisms which cause the degradation of indoor air quality and contribute to Sick Building Syndrome (Cooley et al. 1998). Microorganisms may produce contaminants, i.e., aerial particles, such as toxins, spores, allergens and other metabolites that can be serious health hazards to the residents and frequent exposure to these contaminants may lead to various health problems such as allergies, irritations, infections and other respiratory diseases (Santucci et al. 2007; Nielsen et al. 2004; Spengler and Chen 2000; Dillon et al. 1999; Samson et al. 1994; Williamson et al. 1997).

In the treatment of polluted water, membrane choking due to attachment and growth of microorganisms like algae and bacteria is a dominating problem during membrane filtration processes. It also reduces membrane efficiency and enhances the cost and energy consumption. Biofouling also affects the water quality and is responsible for water borne diseases like Cholera or Diarrhea etc. Traditional methods are not much efficient for the removing of biofouling, however TiO_2 under sunlight irradiation is an appropriate microbial photokilling agent. Usage of TiO_2 as bactericidal agents has many advantages like; being a heterogeneous catalyst it provides an easy separation; is not easily photo bleached during light irradiation and shows activity even under sunlight (Suzuki et al. 2017). The photokilling activity of TiO_2 has opened the new door to make inexpensive, non-toxic and self-sterilizing equipments for the health care applications.

Matsunaga et al. (1985) were the first to discover the antibacterial activity of TiO_2 and since then TiO_2 has widely been used for the synthesis of antibacterial materials (Markowska-Szczupak et al. 2015; Kim et al. 2003; Rincón and Pulgarin 2004; Aysin et al. 2013). Due to high oxidative power, high surface area and suitable band gap, it is widely used for photo-killing of a wide range of microorganisms like algae, fungi, viruses and bacteria (Wu et al. 2016; Vatansever et al. 2013). Modified TiO_2 with enhanced surface area and high visible light activity is a potential material for controlling the growth of microorganisms (Wanga et al. 2016; Lee et al. 2013). The formation of new energy levels between the valance band (VB) and conduction band (CB) was responsible for visible light activity of doped TiO_2 (Ashkarran et al. 2014). Doping involves the introduction of either nonmetals like boron, carbon, fluorine, nitrogen, phosphorous etc., or metals like silver, iron, copper, yttrium etc. The same characteristics were also observed by the formation of nanocomposites such as TiO_2/CeO_2, TiO_2/ZnO, TiO_2/CdS etc. (Li et al. 2009; Zhao et al. 2015; Ansari et al. 2009). Metal and Nonmetal co-doped TiO_2 were with enhanced selectivity and activity than the mono doped materials. Wanga et al. (2016) reported that singly doped TiO_2 with boron (B) and yttrium (Y) has higher antibacterial activity for *E.coli* as compared to *S. aureus,* while the B and Y co-doped TiO_2 have higher activity for *S. aureus* than *E. coli*. It was found that the silver acts as an electron trapper and helps in the separation of charge carriers to enhance bactericidal activity (Baifu et al. 2005).

The proposed photo killing mechanism initiates with photocatalysis by generating electron hole pairs. These electron hole pairs react with surface adsorbed water or oxygen and generate highly reactive superoxide radical $O_2^{\cdot-}$, $HO^{\cdot}$ and H_2O_2 that induce antibacterial activity by oxidative damage (Aysin et al. 2013). These oxidizing agents affect the integrity of outer membrane and release cytoplasmic fluid in surrounding followed by cell death. The reactive oxygen species are highly selective and different species play different roles in the deactivation of the microorganisms. Verdier et al. (2014) found that hydroxyl radicals were responsible for the photokilling of the *E. coli*, whereas Suzuki et al. (2017) reported that the high anti-fungal effect of TiO_2 was due to the H_2O_2 and remain unaffected by the production of superoxide radical. Imase et al. (2013) found that hydrogen peroxide made holes in the cell wall of algae and entered in the cell. This intracellular H_2O_2 destroy viability of the cells by oxidizing the DNA and proteins.

Efficient photokilling activity of doped TiO_2 as compared to bare TiO_2 was attributed to the small particle size and high surface area. It provides more active sites or anatase phase which help in charge separation and reduction in the band gap due to formation of new energy level between the valance band and conduction band (Wanga et al. 2016). Carbon and fluorine doping not only enhances the optical response of TiO_2 but is also responsible for the formation of surface oxygen vacancies and enhancement of Ti^{3+} ions which are important for the high rate of photo-deactivation of microorganisms (Sangari et al. 2015).

Blood clotting

Blood coagulation is based on the formation of a high strength barrier to resist the flow of blood (Fries et al. 2005). Various substances like anti-fibrinolytic agents (Fries et al. 2005), fresh frozen plasma (FFP), activated coagulation factor VII (rFVIIa) (Rizoli et al. 2006), platelet concentrators, drugs of Liquemin family (Wirz et al. 2003) are adopted to stimulate the clotting process. However, the synthesis and storage of these susbstances is expensive and quite difficult. The biocompatibility of TiO_2 opens the door for the scientists to use it as a cost effective blood clotter (Carr et al. 2007; Maitz et al. 2003; Liu et al. 2003; Albrektsson et al. 1981). TiO_2 nanotubes due to their high surface to volume ratio and variation in pore size, length and thickness allow it to be used as blood clotter and are found better in blood clotting (higher clot strength and reduced clotting time) than TiO_2 nanoparticles (Roy et al. 2007). The high clot strength of nanotubes containing blood was due to its high fibrin matrix density and good heme affinity as compared to anatase phase of nanoparticles. The heme affinity of TiO_2 could be improved by the doping of metal or nonmetals, change in the surface energy and the introduction of the complex functional groups (Spijker et al. 2002; Lee et al. 1998; Vienken et al. 1995). The adsorption of protein on the surface also increases the heme affinity and decrease platelet activation (Lyman 1991). The electrostatic interactions between protein and surface adsorbed calcium ions were responsible for adsorption of proteins on the surface. The adsorption of protein increases with thickness of oxide layer (Sunny and Sharma 1991). It was found that the TiO_2 enhances blood clotting not only when mixed with blood but also when it is applied on gauze bandages. The blood-clotting property of the Ti surface is also an important factor for bone and dental implant applications (Thor et al. 2007).

Photo dynamic treatment (PDT)

In this therapeutic technique, a photosensitizer (PS) that could be a macromolecule or nanosized inorganic or organic particle is used in the treatment process. This technique is used as an alternative to surgery for the treatment of cancer and of many such diseases. PDT is useful for the treatment of superficial tumors and many dermatological problems. The light used in PDT could not penetrated deep, thus making it ineffective for the treatment of internal organs or deep cavities (Hou et al. 2015).

The PSs are important component for the PDT. TiO_2 as PS, on irradiation with the appropriate photon produces the reactive oxygen species (ROS) which have the ability for the production of singlet oxygen (Yan et al. 2010; Marchal et al. 2015). The hydrophilic nature of PSs and their delivery process are two most important factors for the PDT (Marchal et al. 2015; Synatschke et al. 2014; Cheng et al. 2011). Due to hydrophilic nature and formation of hierarchical structures of TiO_2, it is highly suitable inorganic material for the photodynamic treatment of skin diseases, microbial infection and tumor like cancer (Townley et al. 2012; Montazer et al. 2011).

Despite of these features, the photoactivation of the TiO_2 in UV region constrained its large scale use for the PDT, because UV light has less penetrating power and cause destruction to the proteins, DNA and other enzymes (Scholkmann et al. 2014). Hence to make TiO_2 suitable for PDT, it is associated with some converting material which could absorb light in the region above 600 nm and convert radiation internally to highly energetic UV for absorption by TiO_2 to produce ROS. Hou et al. (2015) synthesized up conversion nano particles (UPCNPs)/TiO_2 nano structures using UPCNPs as core shell to coat TiO_2. These newly synthesized nanoparticles have absorption in NIR region which enables the application of TiO_2 in full spectrum of solar light without affecting the essential biomolecules. Tokuoka et al. (2006) investigated in vitro treatment of the murine thymic lymphoma cancer cell line (EL-4) using visible light activated chlorine e6@TiO_2 nanoparticles and obtained better results as compared to the results obtained by their individual treatment. It was reported that the in vitro activity of the TiO_2 was far better than the in vivo which was the result of the weak electrostatic adsorption force of nano-TiO_2 during in vivo.

Drug delivery

Transmission of drug or medicine to the target tissue or organ in an appropriate amount is necessary for better treatment of diseases. In the early days, silver and gold nanoparticles were used for the drug transmission and for the therapeutic purposes (Heikal 2016; Dreaden et al. 2012). Recently, titanium oxide is found as an efficient phonondynamic therapeutic and drug delivery agent for the treatment of the various diseases (Ninomiya et al. 2012). The application of the TiO_2 in the drug delivery is based on its porous nature and ability to load different amount of therapeutic drugs.

Electrochemical anodization is one of the best methods to synthesize porous TiO_2 for a better drug carrier (Moon et al. 2014; Ge et al. 2016; Zhang et al. 2015). TiO_2 is combined with the other materials to enhance its efficacy and the specificity. A good drug carrier should also exhibit persistent and controlled drug release. The rapid release of drug may cause adverse effect hence the rate of drug release is a matter of great concern. In this regard, Yin et al. (2014) reported that when TiO_2 is synthesized using hyaluronic acid, hyaluronic acid act as controller for the release of doxorubicin, a chemotherapeutic agent. Mani (2012) used mesoporous TiO_2 for the delivery of Duloxetine and found that pore size distribution in TiO_2 affect the release of drug. In this report it was found that burst release occurs in two stages i.e. between 0 and 5 h and the other one between 7 and 12 h, after 12 h there is slow release of drug for more than 40 h.

TiO_2 act a smart drug carrier because the release of the drug can be triggered by making change in pH (Liu et al. 2015), temperature (Cai et al. 2010), light, magnetic field (Aw et al. 2012), sound frequency (Aw and Losic 2013) and radiofrequency (Aw et al. 2014) etc. Hydrogel coated Titanium nanotubes (TNTs) release the drug slowly as compared to simple TNTs at 25 °C (Cai et al. 2010). Rate of drug release of TNTs composites increases beyond the lower critical solution temperature of composite. Liu et al. (2015) synthesize the TNTs with poly(lactic-co-glycolic acid) (PLGA) for the drug transmission and found that PLGA enhance the transmission ability of TiO_2. The extent of PLGA/TNTs swelling varies with pH which indicates that its drug releasing power is associated with pH. In the magnetic field sensitive drug carrier, magnetic nanoparticles are associated with the drug carrier which responses on change in the magnetic field (Aw et al. 2012; Aw and Losic 2013; Shrestha et al. 2009). For this purpose TNTs are loaded with magnetic nanoparticles in the bottom and drug to be delivered loaded above the magnetic nanoparticles. When these systems come in contact with the magnetic field the process of drug release starts. Oscillating pressure waves in solution stimulate the release of drug from the drug carrier in ultrasound sensitive drug carrier (Aw and Losic 2013). Amphiphilic TNTs were used as light sensitive drug carrier in which the hydrophobic cap is light sensitive and removed by the ultra violet light (Chen et al. 2013). The stimulation of drug release using the sound waves was found to be more controlled as compared to using magnetic field.

Bone and dental implantation

Primary aim of implant is to provide the mechanical stabilization for the maintenance of bones during physiologic loading of bones. The implants facilitate the normal use of injured part of body. Titanium and its alloys have good mechanical properties, low density and excellent biocompatibility (Hunt and Shoichet 1985; Olmedo' et al. 2008). Due to superior mechanical property, titanium and its alloys are highly applicable in the field of implant such as osteointegrated dental and orthopedic implant (Sahar et al.

1988). The greatest challenge in dental and bone implant is improving the structural connection between living bone and implant. The bone consists of cell, protein and mineral. The inorganic phase of bone is mainly composed of carbonated hydroxyapatite (HA). Hydroxyapatite (HA; Ca_{10} $(PO_4)_6(OH)_2$) found in bone is considered for orthopedic and dental applications. The new bone formation on the implant surface is improved by the coating of surface with HA which prevents the formation of fibrous tissue (Søballe 1993; Søballe et al. 1993). The introduction of small amount of Zn^{2+} into hydroxyapatite, significantly increase the bioactive property of hydroxyapatite (Ishikawa et al. 2002). The zinc doped hydroxyapatite can be prepared by a sol gel technique. The particle size of zinc doped hydroxyapatite powder increased with increasing the calcination temperature and decreasing the concentration of zinc doping. The implant surface coated with biomolecule also enhances the osteoinduction. To achieve the effective osteointegeration, the loading of biomolecule on the implant surface must be in a proper manner with the help of suitable method such as hydrogel coatings, layer-by-layer coatings, and immobilization.

Titanium is very reactive towards oxygen and form chemically stable oxide film layer. The native oxide layer of titanium can't directly bond with bone due to its amorphous nature, poor mechanical and low bio compatibility. To improve the property of TiO_2, the alloys of titanium are used for surface modification. The implant tissue interaction is dependent on the surface chemistry of biomaterial. This oxide layer grows spontaneously in contact with air and prevents the diffusion of oxygen from the environment providing corrosion resistance.

The surface modifications of titanium dental implants are very important before the clinical use. To improve the properties of Ti dental implants, the modification of surface was done by surface treatments, inorganic coatings and organic coatings. The surface can be modified by using physical and chemical agent. The laser treatments are also used to improve the property of Ti surface. The introduction of chemical element such as strontium (Sr) on the surface of titanium implant accelerates the bioactivity and osteointegeration process. Anodization is a simple technique for surface modification. The anodized titanium nanotubes (TNTs) possess the potential for biomedical applications and increase osteoblast cell adhesion and desirable functions (Webster and Ejiofor 2004). The high surface area of anodized TNTs increases the growth of hydroxyapatite and influence cellular behavior to enhance the tissue integration. The titanium implants with TiO_2 nanotube increase the bone bonding strength (Bjursten et al. 2010).

The Si doped on the titanium surface also improved their osteogenic activity. The introduction of small amount of silicon into α-tri-calcium phosphate (α-TCP) significantly enhanced the osteoblastic activities and bone integration compared to pure to α-TCP (Camire et al. 2005).The Si doped TiO_2 can be prepared by some suitable method such as cathodic arc deposition or micro-arc oxidation (Wang et al. 2012; Zhang et al. 2011).

The surface area and the surface roughness of a material are properties of major concern for a material to be effective for the implanting. It was reported that titanium nanotubes array are better than conventional titanium in implanting and found that nanotubes perform 300–400% better than the conventional titanium in proliferation of osteoblasts (Oh et al. 2005) which was attributed to the generation of well defined, reproducible and reliable roughness of titanium nanotubes array with enhanced bone cell function using nano-topography. The surface roughness was independent of size of nanotube, while the depth of nanotubes was directly proportional to the diameter of the tube. The diameter of nanotubes is important for cell shape and adhesion of the osteoblast on the surface of the nanotubes. It was reported that there was uniform distribution of protein on tubes with diameter 30 nm, while the proteins were present only near the top wall of the tubes with diameter 100 nm (Grimes and Mor 2009). Suh et al. (2003) reported that osteoblasts on the hydrothermally treated samples were uniformly distributed than on the only anodized samples.

Highly ordered and the crystalline phase of titanium is more effective for the osteoblast than the amorphous because "Hydroxyapatite" a major inorganic component of bone has similar lattice structure of crystalline phases of titanium (Oh et al. 2006). The ordered nanotubes also have great potential for loading and releasing of bioactive molecules that can further activate osteoblast attachment, function and growth. The phase of titanium is also influenced by the anodization parameters. Due to increase in voltage from 140 to 300 V, changes occur in thickness of TiO_2 layer and surface topographic as a result of which the osteoblast adhesion also increases. It was reported that the heat treatment enhances the crystallinity and reduce the surface fluorine concentration. It was also found that the tubes with larger diameter possess only crystalline phase while that of smaller diameter possess only rutile phase (Ercan et al. 2011). The larger tube (80 nm) after heat treatment produced the greater antibacterial activities against both *S. aureus* and *S. epidermidis* as compared to the smaller tubes.

Anodized Ti surfaces were loaded with rhBMP-2 showing a dispersed pattern over the surface. The rhBMP-2 release profile showed a linear release pattern over 21 days with a 91% initial release after 4 days, and an additional 7% release after 7 days (Bae et al. 2010). The rhBMP-2 released from the anodized nanotubular Ti surface stimulated osteoblast differentiation, which was confirmed by higher ALP activity and increased levels of calcium deposition after 21 days of culture.

Conclusion

TiO_2 and its composites exhibit the high stability, biocompatible properties and suitable band gap, hence widely used as biomaterial. Introduction of metal, nonmetal and other metal oxide with TiO_2 further improves its application in the biological world by enhancing its stability and reducing the band gap. Fast response towards the sensing of the biological compounds and good antimicrobial activity was highly thanks to its band gap and charge separation ability. Anatase phase plays major role in the antimicrobial activity while rutile phase helps in the implantation. High surface area and porous structure makes it as effective drug carrier and its compounds with the upconversion materials promote for its use as photodynamic therapeutic agent.

References

Albrektsson T, Brånemark PI, Hansson HA et al (1981) Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 52:155–170

Ansari AA, Sumana G, Pandey MK et al (2009) Sol–gel derived titanium oxide–cerium oxide biocompatible nanocomposite film for urea sensor. J Mater Res 24:1667–1673

Ashkarran AA, Hamidinezhad H, Haddadic H et al (2014) Double-doped TiO_2 nanoparticles as an efficient visible-light-active photocatalyst and antibacterial agent under solar simulated light. Appl Surf Sci 301:338–345

Aw MS, Losic D (2013) Ultrasound enhanced release of therapeutics from drug-releasing implants based on titaniananotube arrays. Int J Pharm 443:154–162

Aw MS, Addai-Mensah J, Losic D (2012) Magnetic-responsive delivery of drug-carriers using titania nanotube arrays. J Mater Chem 22:6561–6563

Aw MS, Kurian M, Losic D (2014) Non-eroding drug-releasing implants with ordered nanoporous and nanotubular structures: concepts for controlling drug release. Biomater Sci 2:10–34

Aysin B, Ozturk A, Par J (2013) Silver-loaded TiO_2 powders prepared through mechanical ball milling. Ceram Int 39:7119–7126

Bae IH, Yun KD, Kim HS et al (2010) Anodic oxidized nanotubular titanium implants enhance bone morphogenetic protein-2 delivery. J Biomed Mater Res B 93:484–491

Baifu X, Zhiyu R, Haiyuan H et al (2005) Photocatalytic activity and interfacial carrier transfer of Ag–TiO_2 nanoparticle films. Appl Surf Sci 252:2050–2055

Benvenuto P, Kafi AKM, Chen A (2009) High performance glucose biosensor based on the immobilization of glucose oxidase onto modified titania nanotube arrays. J Electroanal Chem 627:76–81

Bjursten LM, Rasmusson L, Oh S et al (2010) Titanium dioxide nanotubes enhance bone bonding in vivo. J Biomed Mater Res A 92:1218–1224

Cai K, Jiang F, Luo Z et al (2010) Temperature-responsive controlled drug delivery system based on titanium nanotubes. Adv Eng Mater 12:B565–B570

Camire CL, Saint-Jean SJ, Mochales C et al (2005) Material characterization and in vivo behavior of silicon substituted α-tricalcium phosphate cement. J Biomed Mater Res B 76:424–431

Carr ME, Krischnaswami A, Martin E (2007) Method of using platelet contractile force and whole blood clot elastic modulus as clinical markers. US patent no 7:192,726

Chen X, Yang Z, Si S (2009) Potentiometric urea biosensor based on immobilization of urease onto molecularly imprinted TiO_2 film. J Electroanal Chem 635:1

Chen R, Wang X, Yao X et al (2013) Near-IR-triggered photothermal/photodynamic dual-modality therapy system via chitosan hybrid nanospheres. Biomaterials 34:8314–8322

Cheng Y, Meyers JD, Broome AM et al (2011) Deep penetration of a PDT drug into tumors by noncovalent drug-gold nanoparticle conjugates. J Am Chem Soc 133:2583–2591

Chenga C, Sunb Y (2012) Carbon doped TiO_2 nanowire arrays with improved photoelectrochemical water splitting performance. Appl Surf Sci 263:273–276

Cooley JD, Wong WC, Jumper CA et al (1998) Correlation between the prevalence of certain fungi and sick building syndrome. Occup Environ Med 55:579–584

Cordero-García A, Guzmán-Mar JL, Hinojosa-Reyes L et al (2016) Effect of carbon doping on WO_3/TiO_2 coupled oxide and its photocatalytic activity on diclofenac degradation. Ceram Int 42:9796–9803

Cui J, Chen S, Liu H et al (2014) Nano-p–n junction heterostructures enhanced TiO_2 nanobelts biosensing electrode. J Solid State Electrochem 18:2693–2699

Deng R, Xie X, Vendrell M et al (2011) Intracellular glutathione detection using MnO_2-nanosheet-modified upconversion nanoparticles. J Am Chem Soc 133:20168–20171

Dette C, Pérez-Osorio MA, Kley CS et al (2014) TiO_2 anatase with a bandgap in the visible region. Nano Lett 14:6533–6538

Dillon HK, Miller JD, Sorenson WG et al (1999) Review of methods applicable to the assessment of mold exposure to children. Environ Health Perspect 107:473–480

Dreaden EC, Austin LA, Mackey MA et al (2012) Size matters: gold nanoparticles in targeted cancer drug delivery. Ther Deliv 3:457–478

Durocher S, Rezaee A, Hamm C et al (2009) Disulfide-linked, gold nanoparticle based reagent for detecting small molecular weight thiols. J Am Chem Soc 131:2475–2477

Ercan B, Taylor E, Alpaslan E et al (2011) Diameter of titanium nanotubes influences anti-bacterial efficacy. Nanotechnology 22:295102–295112

Fan Y, Huang KJ, Niu DJ et al (2011a) TiO_2-graphene nanocomposite for electrochemical sensing of adenine and guanine. Electrochim Acta 56:4685

Fan Y, Liu JH, Lu HT et al (2011b) Electrochemistry and voltammetric determination of L-tryptophan and L-tyrosine using a glassy carbon electrode modified with a Nafion/TiO_2-graphene composite film. Microchim Acta 173:241

Fries D, Haas T, Salchner V et al (2005) Gerinnungsmanagementbeim Polytrauma. Anaesthesist 54:137–154

Fujishima A, Honda K (1972) Electrochemical photolysis of water at a semiconductor electrode. Nature 238:37–38

Gao H, Sun M, Lin C et al (2012) Electrochemical DNA biosensor based on graphene and TiO_2 nanorods composite film for the detection of transgenic soybean gene sequence of MON89788. Electroanalysis 24:2283–2290

Ge M, Cao C, Huang J et al (2016) A review of one-dimensional TiO_2 nanostructured materials for environmental and energy applications. J Mater Chem A 4:6772–6801

Grimes CA, Mor GK (2009) TiO_2 nanotube arrays. Use of TiO_2 nanotube arrays for biological applications. Springer, New York, pp 285–314

Heikal T (2016) Fundamentals of analytical toxicology. J Environ Anal Toxicol 6:4

Hou Z, Zhang Y, Deng K et al (2015) UV-emitting upconversion-based TiO_2 photosensitizing nanoplatform: near-infrared light mediated in vivo photodynamic therapy via mitochondria-involved apoptosis pathway. ACS Nano 9:2584–2599

Hunt JA, Shoichet M (1985) Biomaterials: surface interactions. Solid State Mater Sci 5:161–162

Imase M, Ohko Y, Takeuchi M et al (2013) Estimating the viability of Chlorella exposed to oxidative stresses based around photocatalysis. Int Biodeterior Biodegrad 78:1–6

Ishikawa K, Miyamoto Y, Yuasa T et al (2002) Fabrication of Zn containing apatite cement and its initial evaluation using human osteoblastic cells. Biomaterials 23:423–428

Iwamoto M, Mukundan S, Marzilli LG (1994) DNA adduct formation by platinum anticancer drugs. Insight into an unusual GpGIntrastrand cross-link in a hairpin-like DNA oligonucleotide using NMR and distance geometry methods. J Am Chem Soc 116:6238–6244

Janga HD, Kimab SK, Changa H et al (2012) A glucose biosensor based on TiO_2–Graphene composite. Biosens Bioelectron 38:184–188

Jo WK, Won Y, Hwang I et al (2014) Enhanced photocatalytic degradation of aqueous nitrobenzene using graphitic carbon–TiO_2 composites. Ind Eng Chem Res 53:3455–3461

Kafi AKM, Chen A (2009) A novel amperometric biosensor for the detection of nitrophenol. Talanta 79:97–102

Kim B, Kim D, Cho D et al (2003) Bactericidal effect of TiO_2 photocatalyst on selected food-borne pathogenic bacteria. Chemosphere 52:277–281

Kim WJ, Kim S, Lee BS et al (2009) Enhanced protein immobilization efficiency on a TiO_2 surface modified with a hydroxyl functional group. Langmuir 25:11692–11697

Lee JH, Khang G, Lee JW et al (1998) Platelet adhesion onto chargeable functional group gradient surfaces. J Biomed Mater Res 40:180–186

Lee HU, Lee SC, Choi SH et al (2013) Highly visible-light active nanoporous TiO_2 photocatalysts for efficient solar photocatalytic applications. Appl Catal B 129:106–113

Li P, Liu S (2011) A sensitive sensor for anthraquinone anticancer drugs and hsDNA based on CdTe/CdS quantum dots fluorescence reversible control. Coll Surf A 392:7–15

Li GS, Zhang DQ, Yu JC (2009) A new visible-light photocatalyst: CdS quantum dots embedded mesoporous TiO_2. Environ Sci Tech 43:7079–7085

Li YJ, Ma MJ, Zhu JJ (2012) Dual-signal amplification strategy for ultrasensitive photoelectrochemical immunosensing of α-fetoprotein. J Anal Chem 84:10492

Liang R, Jiang J, Qiu J (2008) An amperometric glucose biosensor based on titania Sol–gel/Prussian blue composite film. Anal Sci 24:1425

Liu JX, Yang DZ, Shi F et al (2003) Sol–gel deposited TiO_2 film on NiTi surgical alloy for biocompatibility improvement. Thin Solid Films 429:225–230

Liu YG, Feng P, Xue XY et al (2006) Room-temperature oxygen sensitivity of ZnS nanobelts. Appl Phys Lett 88:102904

Liu G, Zhou L, Wu Y et al (2015) The fabrication of full color P(St-MAA) photonic crystal structure on polyester fabrics by vertical deposition self-assembly. J Appl Polym Sci 132:41750

Luo Y, Liu H, Rui Q et al (2009) Detection of extracellular H_2O_2 released from human liver cancer cells based on TiO_2 nanoneedles with enhanced electron transfer of cytochrome c. Anal Chem 81:3035–3041

Lyman DJ (1991) Bulk and Surface Effects on Blood Compatibility. J Bioact Compat Polym 6:283–295

Maitz MF, Pham MT, Wieser E et al (2003) Blood compatibility of titanium oxides with various crystal structure and element doping. J Biomater Appl 17:303–319

Mani G (2012) Drug release evaluation of mesoporous TiO_2: a nano carrier for duloxetine. Computer Applications for Modeling, Simulation, and Automobile. Springer, Berlin, pp 237–243

Marchal S, Dolivet G, Lassalle HP et al (2015) Targeted photodynamic therapy in head and neck squamous cell carcinoma: heading into the future. Lasers Med Sci 30:2381–2387. https://doi.org/10.1007/s10103-014-1703-4

Markowska-Szczupak A, Wang K, Rokicka P et al (2015) The effect of anatase and rutile crystallites isolated from titania

P25 photocatalyst on growth of selected mould fungi. J Photochem Photobiol B 151:54–62
Mathurab S, Erdemc A, Caveliusa C et al (2009) Amplified electrochemical DNA-sensing of nanostructured metal oxide films deposited on disposable graphite electrodes functionalized by chemical vapor deposition. J Sens Actuators B 136:432
Matsunaga T, Tomoda R, Nakajima T et al (1985) Photoelectrochemical sterilization of microbial cells by semiconductor powders. FEMS Microbiol Lett 29:211
Mattle MJ, Thampi KR (2013) Photocatalytic degradation of remazol brilliant blue® by sol–gel derived carbon-doped TiO_2. Appl Catal B 140–140:348–355
Mondal K, Ali MA, Agrawal VV et al (2014) Highly sensitive biofunctionalized mesoporous electrospun TiO_2 nanofiber based interface for biosensing. ACS Appl Mater Interfaces 6:2516–2527
Montazer M, Behzadni A, Pakdel E et al (2011) Photo induced silver on nano titanium dioxide as an enhanced antimicrobial agent for wool. J Photochem Photobiol B 103:207–214
Moon KS, Bae JM, Jin S et al (2014) Infrared-mediated drug elution activity of gold nanorod-grafted TiO_2 nanotubes. J Nanometer 4:750813
Mun KS, Alvarez SD, Choi WY et al (2010) A stable, label-free optical interferometric biosensor based on TiO_2 nanotube arrays. ACS Nano 4:2070–2076
Nielsen KF, Holm G, Uttrup LP et al (2004) Mould growth on building materials under low water activities. Influence of humidity and temperature on fungal growth and secondary metabolism. Int Biodeterior Biodegrad 54:325–336
Ninomiya K, Ogino C, Oshima S et al (2012) Targeted sonodynamic therapy using protein-modified TiO_2 nanoparticles. Ultrason Sonochem 19:607–614
Niu LY, Guan YS, Chen YZ et al (2012) BODIPY-based ratiometric fluorescent sensor for highly selective detection of glutathione over cysteine and homocysteine. J Am Chem Soc 134:18928–18931
O'Brien JC, Stickney JT, Porter MD (2000) Self-assembled double-stranded DNA (dsDNA) microarrays for protein:dsDNA screening using atomic force microscopy. J Am Chem Soc 122:5004
Oh SH, Finõnes RR, Daraio C et al (2005) Growth of nano-scale hydroxyapatite using chemically treated titanium oxide nanotubes. Biomaterials 26:4938–4943
Oh S, Daraio C, Chen LH et al (2006) Significantly accelerated osteoblast cell growth on aligned TiO_2 nanotubes. J Biomed Mater Res A 78:97–103
Olmedo' DG, Duffó G, Cabrini RL et al (2008) Local effect of titanium implant corrosion: an experimental study in rats. Int J Oral Maxillofacial Surg 37:1032–1038
Pan TM, Lin JC (2009) A TiO_2/Er_2O_3 stacked electrolyte/insulator/semiconductor film pH-sensor for the detection of urea. Sens Actuators B 138:474
Pandey RR, Saini KK, Dhayal M (2010) Using nano-arrayed structures in sol–gel derived Mn^{2+} Doped TiO_2 for high sensitivity urea biosensor. J Biosens Bioelectron 1:1–4
Pang X, He D, Luo S et al (2009) An amperometric glucose biosensor fabricated with Pt nanoparticle-decorated carbon nanotubes/TiO_2 nanotube arrays composite. Sens Actuators B 137:134–138
Park EK, Lee SB, Lee YM (2005) Preparation and characterization of methoxy poly(ethylene glycol)/poly(epsilon-caprolactone) amphiphilic block copolymericnanospheres for tumor-specific folate-mediated targeting of anticancer drugs. Biomaterials 26:1053–1061
Rincón AG, Pulgarin C (2004) Bactericidal action of illuminated TiO_2 on pure *Escherichia coli* and natural bacterial consortia: post-irradiation events in the dark and assessment of the effecttive disinfection time. Appl Catal B 49:99–112
Rios F, Smirnov S (2009) Biochemically Responsive Smart Surface. ACS Appl Mater Interfaces 1:768
Rizoli SB, Nascimento BJ, Osman F et al (2006) Recombinant activated coagulation factor VII and bleeding trauma patients. J Trauma-Inj Infect Crit Care 61:1419–1425
Roy SC, Paulose M, Grimes CA (2007) The effect of TiO_2 nanotubes in the enhancement of blood clotting for the control of hemorrhage. Biomaterials 28:4667–4672
Sahar A, Allah F, Quahtany M et al (1988) Surface modification of titanium plate with anodic oxidation and its application in bone growth. J Prosthet Dent 60:75–84
Sakata T, Kamahori M, Miyahara Y (2004) Immobilization of oligonucleotide probes on Si_3N_4 surface and its application to genetic field effect transistor. Mater Sci Eng C 24:827
Samson RA, Flannigan B, Flannigan ME et al (1994) Health implications of fungi in indoor environments. Elsevier Science Ltd., Kidlington
Sangari M, Umadevi M, Mayandi J et al (2015) Photocatalytic and antimicrobial activities of fluorine doped TiO_2-carbon nano cones and disc composites. Mater Sci Semicond Process 31:543–550
Santucci R, Meuniera O, Ottb M et al (2007) Fungic contamination of residence: 10 years assessment of analyses. Rev Fr Allergol Immunol Clin 47:402–408
Scanlon DO, Dunnill CW, Buckeridge J et al (2013) Band alignment of rutile and anatase TiO_2. Nature Mater 12:798–801
Scholkmann F, Kleiser S, Metz AJ et al (2014) A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. Neuro Image 85:6–27
Shrestha NK, Macak JM, Schmidt-Stein F et al (2009) Magnetically guided titania nanotubes for site-selective photocatalysis and drug release. Angew Chem Int Ed 48:969–972
Søballe K (1993) Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs. Acta Orthop Scand Suppl 255:1–58
Søballe K, Hansen ES, Brockstedt-Rasmussen H et al (1993) Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. J Bone Joint Surg Br 75:270–278
Sotelo-Vazquez C, Noor N, Kafizas A et al (2015) Multifunctional P-doped TiO_2 Films: a new approach to self-cleaning, transparent conducting oxide materials. Chem Mater 27:3234–3242
Souza JS, Krambrock K, Pinheiro MVB et al (2014) Visible-light photocatalytic activity of NH_4NO_3 ion-exchanged nitrogen-doped titanate and TiO_2 nanotubes. J Mol Catal A 394:48–56
Spengler JD, Chen Q (2000) Indoor air quality factors in designing a healthy building. Annu Rev Energy Environ 25:567–601

Spijker HT, Bos R, Busscher HJ et al (2002) Platelet adhesion and activation on a shielded plasma gradient prepared on polyethylene. Biomaterials 23:757–766

Srivastava S, Ali MA, Solanki PR et al (2013) Mediator-free microfluidics biosensor based on titania–zirconianananocomposite for urea detection. RSC Adv 3:228

Suh JY, Jang BC, Zhu X et al (2003) Effect of hydrothermally treated anodic oxide films on osteoblast attachment and proliferation. Biomaterials 24:347

Sunny MC, Sharma CP (1991) Titanium-protein interaction: changes with oxide layer thickness. J Biomater Appl 5:89–98

Suzuki N, Sanada T, Terashima C et al (2017) Systematic studies of TiO_2-based photocatalysts anti-algal effects on *Chlorella vulgaris*. J Appl Electrochem 47:197–203

Synatschke CV, Nomoto T, Cabral H et al (2014) Multicompartment micelles with adjustable poly(ethylene glycol) shell for efficient in vivo photodynamic therapy. ACS Nano 8:1161–1172

Tang H, Yan F, Tai Q et al (2010) The improvement of glucose bioelectrocatalytic properties of platinum electrodes modified with electrospun TiO_2 nanofibers. Biosen. Bioelectron 25:1646–1651

Tang J, Kong B, Wang Y et al (2013) Photoelectrochemical detection of glutathione by IrO_2–hemin–TiO_2 nanowire arrays. Nano Lett 13:5350–5354

Tang J, Wang Y, Li J et al (2014) Sensitive enzymatic glucose detection by TiO_2 nanowire photoelectrochemical biosensors. J Mater Chem A 2:6153–6157

Tereshchenko A, Viter R, Smyntyna V et al (2015) Euro Nano Forum, 2015, Conference paper

Thor A, Rasmusson L, Wennerberg A et al (2007) The role of whole blood in thrombin generation in contact with various titanium surfaces. Biomaterials 28:966–974

Tokuoka Y, Yamada M, Kawashima N et al (2006) Anticancer effect of dye-sensitized TiO_2 nanocrystals by polychromatic visible light irradiation. Chem Lett 35:496–497

Topoglidis E, Cass AEG, Gilardi G et al (1998) Protein adsorption on nanocrystalline TiO_2 films: an immobilization strategy for bioanalytical devices. Anal Chem 70:5111

Townley HE, Kim J, Dobson PJ (2012) In vivo demonstration of enhanced radiotherapy using rare earth doped titania nanoparticles. Nanoscale 4:5043–5050

Tu W, Dong Y, Lei J et al (2010) Low-potential photoelectrochemical biosensing using porphyrin-functionalized TiO_2 nanoparticles. Anal Chem 82:8711

Vatansever F, Melo WC, Avci P et al (2013) Antimicrobial strategies centered around reactive oxygen species—bactericidal antibiotics, photodynamic therapy and beyond. FEMS Microbiol Rev 37:955–989

Verdier T, Coutand M, Bertron A et al (2014) Antibacterial activity of TiO_2 photocatalyst alone or in coatings on *E. coli*: the influence of methodological aspects. Coatings 4:670–686

Vienken J, Diamantoglou M, Hahn C et al (1995) Considerations on developmental aspects of biocompatible dialysis membranes. Artif Organs 19:398–406

Viter R, Tereshchenko A, Smyntyna V et al (2017) Toward development of optical biosensors based on photoluminescence of TiO_2 nanoparticles for the detection of Salmonella. Sens Actuators B 252:95–102

Vitera R, Smyntyna V, Starodub N et al (2012) Novel immune TiO_2 photoluminescence biosensors for leucosis detection. Proc Eng 47:338–341

Wang Y, Lu J, Tang L et al (2009) Graphene oxide amplified electrogenerated chemiluminescence of quantum dots and its selective sensing for glutathione from thiol-containing compounds. J Anal Chem 81:9710–9715

Wang Q, Xu S, Shen F (2011) Preparation and characterization of TiO_2 photocatalysts co-doped with iron(III) and lanthanum for the degradation of organic pollutants. Appl Surf Sci 257:7671–7677

Wang B, Sun J, Qian S et al (2012) Proliferation and differentiation of osteoblastic cells on silicon-doped TiO_2 film deposited by cathodic arc. Biomed Pharmacother 66: 633–641

Wang J, Xu G, Zhang X et al (2015) Electrochemical performance and biosensor application of TiO_2 nanotube arrays with mesoporous structures constructed by chemical etching. Dalton Trans 44:7662–7672

Wanga Y, Wua Y, Yangb H et al (2016) Co-doping TiO_2 with boron and/or yttrium elements: effects on antimicrobial activity. Mater Sci Eng B 211:149–155

Webster TJ, Ejiofor JU (2004) Increased osteoblast adhesion on nanophase metals: Ti, Ti6Al4V, and CoCrMo. Biomaterials 25:4731–4739

Wei Y, Li L, Qu Y et al (2009) A novel biosensor based on photoelectro-synergistic catalysis for flow-injection analysis system/amperometric detection of organophosphorous pesticides. Anal Chim Acta 643:13

Williamson IJ, Martin CJ, McGill G et al (1997) Damp housing and asthma: a case–control study. Thorax 52:229–234

Wirz S, Knuefermann P, Baumgarten G et al (2003) Head trauma and blood coagulation disorders. AnaesthaseolIntensiv 44:478–490

Wu X, Huang YY, Kushida Y et al (2016) Broad-spectrum antimicrobial photocatalysis mediated by titanium dioxide and UVA is potentiated by addition of bromide ion via formation of hypobromite. Free Radical Bio Med 95:74–81

Xie Y, Zhou L, Huang H (2007) Bioelectrocatalytic application of titania nanotube array for molecule detection. Biosens Bioelectron 22:2812–2818

Yan YJ, Zheng MZ, Chen ZL et al (2010) Studies on preparation and photodynamic mechanism of chlorin P6-13,15-*N*-(cyclohexyl)cycloimide (Chlorin-H) and its antitumor effect for photodynamic therapy in vitro and in vivo. Bioorg Med Chem 18:6282–6291

Yang J, Li D, Fu J et al (2016) TiO_2–CuCNFs based laccase biosensor for enhanced electrocatalysis in hydroquinone detection. J Electroanal Chem 766:16–23

Yao H, Shum AJ, Cowan M et al (2011) A contact lens with embedded sensor for monitoring tear glucose level. Biosens Bioelectron 26:3290

Yin M, Ju E, Chen Z et al (2014) Upconverting nanoparticles with a mesoporous TiO_2 shell for near-infrared-triggered drug delivery and synergistic targeted cancer therapy. Chem Eur J 20:14012–14017

Yu J, Liu S, Ju H (2003) Glucose sensor for flow injection analysis of serum glucose based on immobilization of glucose oxidase in titania sol–gel membrane. Biosens Bioelectron 19:401–409

Yu S, Yun HJ, Kim YH et al (2014) Carbon-doped TiO_2 nanoparticles wrapped with nanographene as a high performance photocatalyst for phenol degradation under visible light irradiation. Appl Catal B 144:893–899

Zang J, Li CM, Cui X et al (2007) Tailoring zinc oxide nanowires for high performance amperometric glucose sensor. Electroanalysis 19:1008

Zhang Z, Sun J, Hu H et al (2011) Osteoblast-like cell adhesion on porous silicon-incorporated TiO_2 coating prepared by micro-arc oxidation. J Biomed Mater Res B 97:224–234

Zhang Y, Jiang Z, Huang J et al (2015) Titanate and titaniananostructured materials for environmental and energy applications: a review. RSC Adv 5:79479–79795

Zhao H, Dong Y, Jiang P et al (2015) Highly dispersed CeO_2 on TiO_2 nanotube: a synergistic nanocomposite with superior peroxidase-like activity. ACS Appl Mater Interfaces 7:6451–6461

Zheng R, Lin L, Xie J et al (2008) State of doped phosphorus and its influence on the physicochemical and photocatalytic properties of P-doped titania. J Phys Chem C 112: 15502–15509

Zhu J, Liu X, Wang X et al (2015) Preparation of polyaniline–TiO_2 nanotube composite for the development of electrochemical biosensors. Sens Actuators B 1:450–457

Zhuo Y, Chai YQ, Yuan R et al (2011) Glucose oxidase and ferrocene labels immobilized at Au/TiO_2 nanocomposites with high load amount and activity for sensitive immune electrochemical measurement of ProGRP biomarker. Biosens Bioelectron 26:3838–3844