

TiO₂ and its composites as promising biomaterials: a review

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Received: 15 January 2018 / Accepted: 26 January 2018 / Published online: 1 February 2018
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Abstract TiO₂ 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 TiO₂-based materials is strongly required to achieve desired properties and applications. A large number of TiO₂ composites have been synthesized and applied in various fields. The present review reports the utility of TiO₂ 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 TiO₂ based materials and some recent advancement in TiO₂ to enhance its application in the biological world.

Keywords Biocompatibility · Composites · Biosensing · Antimicrobial · Nanodrug carrier

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, TiO₂ is one of the well-known semiconductor material used in the biological world. Utilization of TiO₂, 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 TiO₂ is widely used in cosmetics, paints, ceramics, photocatalysis, solar cell, food coloring etc.

TiO₂ and TiO₂ 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).

TiO₂ exists in three forms i.e. anatase (tetragonal), rutile (tetragonal) and brookite (orthorhombic). TiO₂ when synthesized is found in amorphous state and becomes crystalline on calcination. Its anatase phase is

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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 TiO₂ can be altered by incorporation of various elements (metals and nonmetals) in TiO₂ (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 TiO₂, 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).

TiO₂ 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 TiO₂ has opened the door to use it in making self-sterilizing equipments and remove the biofouling caused by the microorganisms.

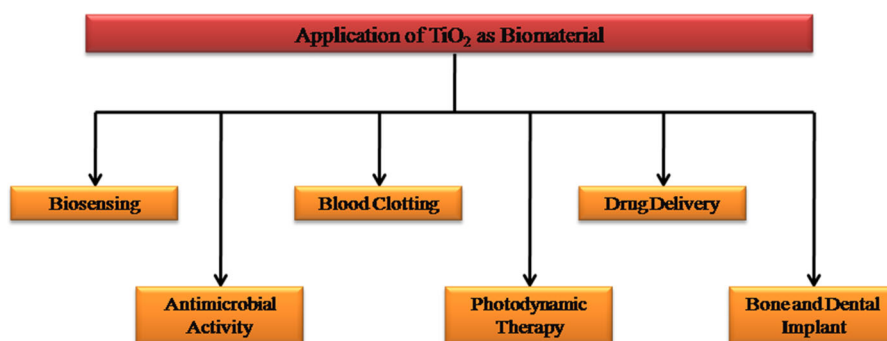
In this review we focus on the various biological application of the TiO₂ (Fig. 1), and various modifications made to improve the properties of TiO₂ for its utilization on the globular scale.

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 TiO₂



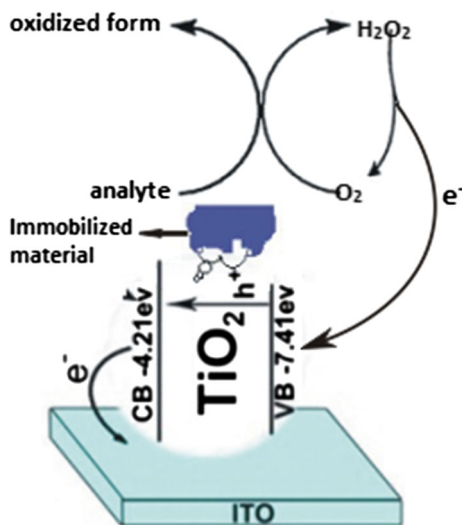


Fig. 2 Layout of the semiconductor assisted biosensor

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 ($-\text{COOH}$), aldehyde ($-\text{CHO}$), 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 (^6PA) 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 , $\text{TiO}_2/\text{CeO}_2$ have been tried for urea detection that showed good response time and sensitivity (Pandey et al. 2010; Ansari et al. 2009) (Table 1). $\text{PbO}_2/\text{TiO}_2/\text{Ti}$ 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).

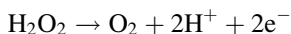
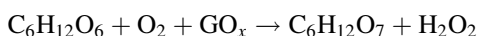
Biomolecules such as DNA, antibodies, polymer, cellulose, enzyme or protein enhanced biosensing response of TiO_2 (Li et al. 2012; Zhuo et al. 2011). $\text{TiO}_2/\text{cellulose}$ composite fibers are easy to synthesize, stable over high range of pH and can be easily stored and used for the enzyme immobilization (Kafi and Chen 2009). $\text{TiO}_2/\text{polymer}$ 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 TiO₂ based materials for the Urea sensing

Sr. No.	Electrode material	Sensitivity	Detection limit	Reference
1.	Mn doped TiO ₂	2.3 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	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 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	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 TiO₂ 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 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	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 $\text{mM}^{-1} \text{cm}^{-2}$	0.07–15 mM	Yu et al. (2003)
5.	TiO ₂ /graphene (GR) synthesized by aerosol assisted self-assembly	6.2 mA $\text{mM}^{-1} \text{cm}^{-2}$	0–8 mM	Janga et al. (2012)
6.	Titanium nanotubes	45.5 mA $\text{mM}^{-1} \text{cm}^{-2}$	0.01–1 mM	Xie et al. (2007)
7.	Modified TiO ₂ nanotube/carbon nanotube	0.24 mA $\text{mM}^{-1} \text{cm}^{-2}$	0.006–1.5 mM	Pang et al. (2009)
8.	Platinum electrode/TiO ₂ nanofibers synthesized by electrospinning	9.25 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	0.01–6.98 mM	Tang et al. (2010)
9.	TiO ₂ NTs/Prussian blue (PB)/Au synthesized by anodization	36 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	0.015–4.00 mM	Benvenuto et al. (2009)
10.	TiO ₂ NPs/Prussian blue synthesized by sol–gel method	12.74 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	0.02–15 mM	Liang et al. (2008)
11.	TiO ₂ NPs/graphene/NiO synthesized by hydrothermal method	4.129 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	1.0–12.0 mM	Pan and Lin (2009)
12.	TiO ₂ NPs/Nafion synthesized by sol–gel method	240 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	0.1–0.6 mM	Yao et al. (2011)



Yang et al. (2016) synthesized copper and carbon loaded TiO₂ composite nanofibers and fabricated it with the copper containing enzyme laccase and a polymer nafion for the detection of hydroquinone. TiO₂-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, TiO₂-GR nanocomposite has potential applications in designing low cost and high performance electrochemical sensors/biosensor.

TiO₂ 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 TiO₂ 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 TiO₂ for the diagnosis of the *Bovine leucosis* and *Salmonella* spp. viruses. According to a report, the TiO₂ 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 TiO₂ against the viruses. The biosensing property of TiO₂ 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 TiO₂ 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 TiO₂ under sunlight irradiation is an appropriate microbial photokilling agent. Usage of TiO₂ 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 TiO₂ 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 TiO₂ and since then TiO₂ 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 photokilling of a wide range of microorganisms like algae, fungi, viruses and bacteria (Wu et al. 2016; Vatansever et al. 2013). Modified TiO₂ 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 TiO₂ (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 TiO₂/CeO₂, TiO₂/ZnO, TiO₂/CdS etc. (Li et al. 2009; Zhao et al. 2015; Ansari et al. 2009). Metal and Nonmetal co-doped TiO₂ were with enhanced selectivity and activity than the mono doped materials. Wanga et al. (2016) reported that singly doped TiO₂ 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 TiO₂ 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 O₂⁻, HO[·] and H₂O₂ 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 TiO₂ was due to the H₂O₂ 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 H₂O₂ destroy viability of the cells by oxidizing the DNA and proteins.

Efficient photokilling activity of doped TiO₂ as compared to bare TiO₂ 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 TiO₂ but is also responsible for the formation of surface oxygen vacancies and enhancement of Ti³⁺ 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 substances is expensive and quite difficult. The biocompatibility of TiO₂ 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). TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ 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. TiO₂ 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 TiO₂, 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 TiO₂ 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 TiO₂ 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 TiO₂ to produce ROS. Hou et al. (2015) synthesized up

conversion nano particles (UPCNPs)/TiO₂ nano structures using UPCNPs as core shell to coat TiO₂. These newly synthesized nanoparticles have absorption in NIR region which enables the application of TiO₂ 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@TiO₂ 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 TiO₂ was far better than the in vivo which was the result of the weak electrostatic adsorption force of nano-TiO₂ 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 phonodynamic therapeutic and drug delivery agent for the treatment of the various diseases (Ninomiya et al. 2012). The application of the TiO₂ 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 TiO₂ for a better drug carrier (Moon et al. 2014; Ge et al. 2016; Zhang et al. 2015). TiO₂ 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 TiO₂ is synthesized using hyaluronic acid, hyaluronic acid act as controller for the release of doxorubicin, a chemotherapeutic agent. Mani (2012) used mesoporous TiO₂ for the delivery of Duloxetine and found that pore size distribution in TiO₂ 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.

TiO₂ 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 TiO₂. 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; $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) 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 osteointegration, 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 osteointegration 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 Ejiófor 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

TiO₂ 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 TiO₂ 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.

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