The Study of the Release Mechanism of TiO_2 Nanotubes-NP Conjugate Using Polymer Encapsulate as a Drug Delivery System

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Abstract

TiO_2 nanotube array was fabricated by anodisation technique of a pure titanium plate. The anodisation process was carried out in ammonium fluoride/ ethylene glycol electrolyte, the applied voltage was 60 volt. The average length and diameter of the nanotubes were 12 µm and 80 nm respectively. After annealing of TiO_2 nanotubes at 500°C for 3h, the amorphous nanotubes walls converted into anatase phase. The TiO_2 nanotubes array material was employed as container for methylene blue (MB) solution. Another layer (container for MB) was created then when TiO_2 coated with nanoparticles (NP) in order to compare the release mechanism with TiO_2 nanotubes. The aim was to develop an additional control of chemical release kinetics polyvinyl alcohol (PVA) which was used to encapsulate the surface of the loaded TiO_2 nanotubes and TiO_2 nanotubes-NP conjugate. The results showed that the release mechanism can be controlled more efficiently by using nanotubes-NP conjugate rather than using single layer of TiO_2 nanotubes only. The morphology of the arrays was characterized by X-ray diffraction (XRD), Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM).

Keywords: Anodisation, polymer encapsulate, drug release and methylene blue.

Introduction

Titanium dioxide nanotubes show good biocompatibility, making them appropriate materials for the use in drug release mechanism. However, their usage as drug carriers is limited by uncontrolled release. The geometry of TiO_2 nanotube as a membrane makes it suitable for investment as an injected capsule or a biomedical implant [1]. Xiao and his workers [2] presented an excellent biocompatibility of both TiO_2 nanotube arrays that prepared by anodisation and annealed in a carbon atmosphere. Employing drug delivery system was achieved by different methods [3]. Different drugs were examined for release mechanism such as ampicillin [4] and ibuprofen[5]. According to Popat and his *et.al* [6] TiO_2 nanotube arrays were exploited for local delivery of antibiotics at the site of implantation. This demonstrated the prevention of bacterial adhesion.

However, precise controlled of the nanotube length and diameter enabled different amounts of drugs to be eluted at diverse rates at the implantation site. However, in their work, only straight, normal circular TiO_2 nanotubes were investigated. Recently Song and coworkers created amphiphilic TiO_2 nanotubes with a hydrophobic monolayer modification after the first step in the anodisation process. These tubes could be invested for biomolecules carriers, in which the outer hydrophobic barrier provides an efficient cap against drug release to the environment. By exploiting the photocatalytic property of TiO_2, a precise controlled removal of the cap with a highly domination release of the hydrophilic drug payload and this was achieved under UV illumination [7]. Wang and his worker used mesoporous Titanium Zirconium Oxide for drug delivery applications [8].

Polymers as biomaterials also used [9-10]. Collagen-templated bioactive titanium dioxide porous networks for drug delivery was also employed [11]. One of the objectives of the work described in this paper was to control the morphology of titanium dioxide nanotubes and nanoparticles in order to develop their applications in the drug delivery release.

Herein, the control of drug release was managed by two methods. Firstly, the release was controlled by TiO_2 nanotubes alone which revealed limited control of release rate, while the second process, TiO_2 nanotubes -NP conjugate, showed an efficient drug release rate.

Experimental details

Titanium foils (99.6% purity) were degreased priory to anodisation by sonicating them in acetone, rinsed with deionised water (DI). The electrochemical set-up was composed of a high-voltage power supply, leaving the electrodes at distance 6 cm and Ti surface at 1 cm^2 open to the electrolyte. The anodisation was carried out in a two-electrode electrochemical system at a constant voltage of 60 V for 120 min. The Ti plates were used as anode and cathode, immersed in ammonium fluoride (NH_4F)/ethylene glycol (EG) electrolyte, (2 vol% H_2O and 0.5 wt% NH_4F and 97.5 wt% EG) at room temperature. After 120 min, nanotubes with lengths of 12 μm and 100 nm in diameter were obtained. SEM and TEM were employed for the morphological characterization of the TiO_2 nanotubular layers. Scanning Electron Microscope study carried out by (Jeol 820 m instrument Uni. of Essex) in UK of TiO_2nanotubular layers .The crystalline structures of the TiO_2 nanotubes wereanalysed by means of X-ray diffraction (XRD). NP an anatase form was taken from sigma-Aldrich. TiO_2 nanotubes were filled with MB using dipping process and then encapsulate the surface using polyvinyl alcohol (PVA) using rotating spinner.

Result and Discussion

Anodisation

Water in the solution reacts with the titanium metal surface leading to the formation of oxide layer under an applied electric field.

$$2H_2O \rightarrow 4H^+ + O_2 + 4e^- \quad \text{.....(1)}$$

$$Ti + O_2 \rightarrow TiO_2 \quad \text{.....(2)}$$

TiO_2 oxide layer is then etched into as it is dissolved with assistance of fluoride ions. Chemical dissolution of the oxide layer is caused by the presence of fluoride ions.

$$TiO_2 + 4H^+ + 6F^- \rightarrow TiF6^{2-} + 2H_2O \quad \text{.....(3)}$$

The directional dissolution originates from the positive bias on the anode. As a result, nanotubes grew onto the Ti plate. Equilibrium was achieved when the oxidation rate at the oxide/metal/ interface equals to the chemical dissolution rate at the oxide/electrolyte interface.

Morphology

The surface morphology of the NP and the nanotubes were characterized as shown in Fig.(1). At which, (a) TEM images shows side view TiO_2 nanotubes (b) SEM image shows the cross-section of TiO_2 nanotubes. SEM images (c and d) show the top and bottom view of TiO_2 nanotubes respectively.

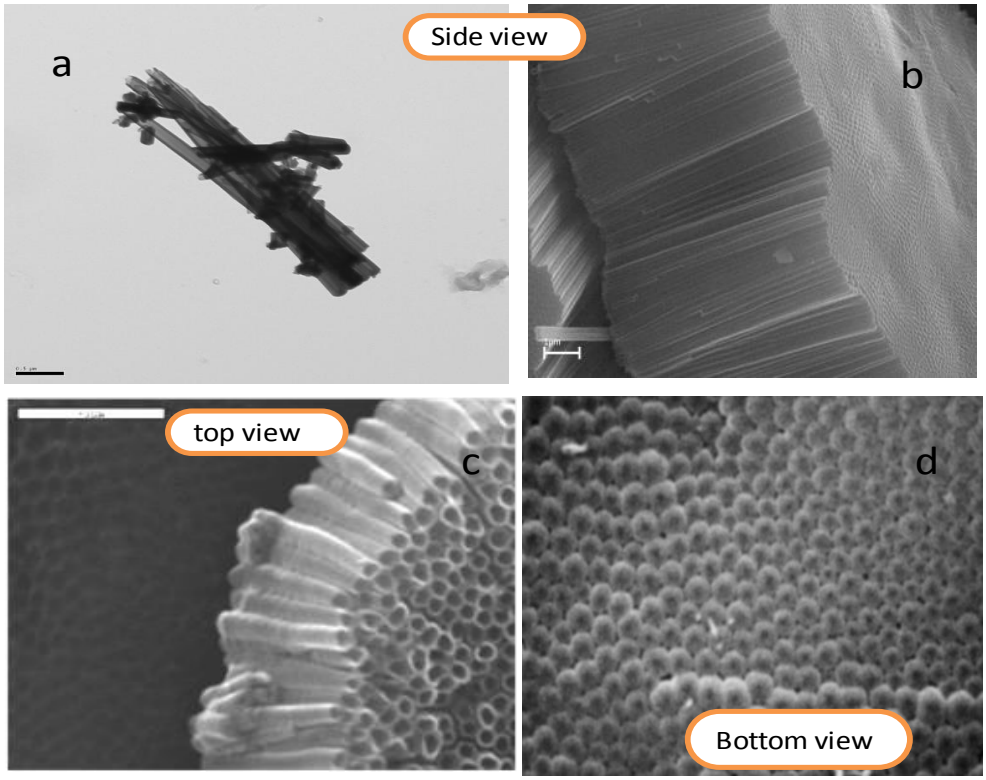

Fig.(1): (a) SEM images show TiO_2 nanotubes, (b) SEM images show the side view of TiO_2 nanotubes, (c) top view and (d) bottom view of TiO_2 nanotubes.

Fig.(2) SEM shows image of TiO_2 nanoparticles. After calcinations at 500°C for 3h, the amorphous nanotubes walls converted into anatase phase without any collapse. Another characterisation was done by using XRD spectra which was occupied on the Ti plate without nanotubes (a) and with (b) nanotubes annealed to 500°C. The spectra showed in Fig.(3).

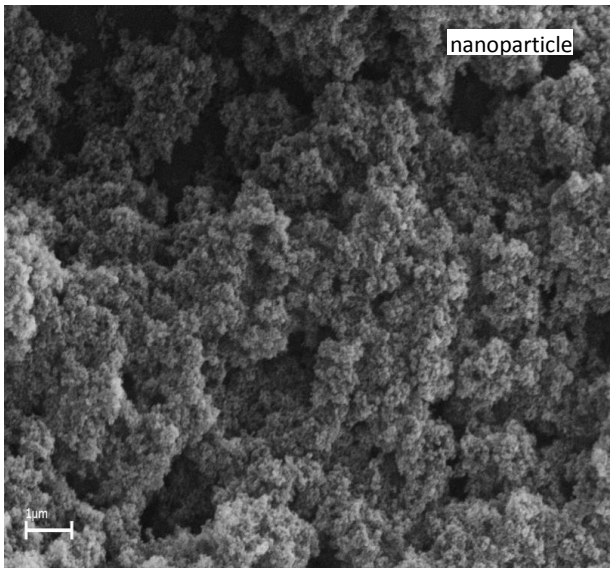

Fig.(2): Shows the SEM image of TiO_2 nanoparticles.

Fig.(3b) shows XRD pattern of TiO_2 nanotubes annealed at 500 °C exist of anatase phase. Anatase phase is important because it is super hydrophilic surface. Thus it improves the release loading by improve the physical absorption.

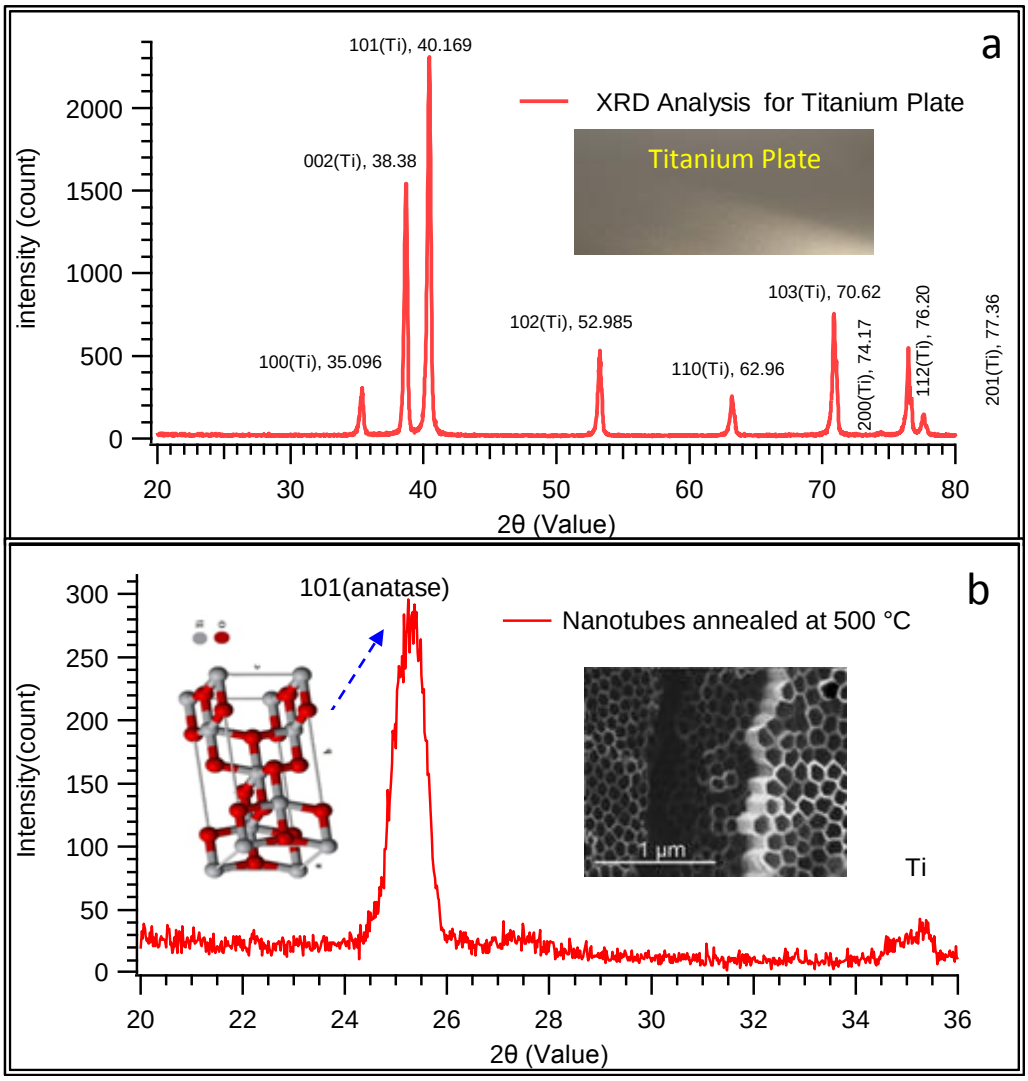

Fig.(3): XRD pattern was occupied on the Ti plate without nanotubes (a) and with nanotubes (b) annealed to 500 °C.

MB Loading

Standard open TiO_2 nanotubes have been considered as possible drug delivery vehicles filled with antibiotics [2]. The purpose of developing nanotubes for drug release is to increase the drug loading and to slow the drug release kinetics. The ability to manage these properties gives significant opportunities for clinical applications. In this study, MB was invested as a convenient drug (MB) because it is a monoamine oxidase inhibitor (MAOI) [12]. The concentration of released MB can be easily monitored by its absorbance at 663 nm with a standard (UV-Vis) spectrometer. Various methods are used for loading chemicals into nanotubes. For example, the drug may be pipetted on to the TiO_2 nanotubes surface in order to cover gently the surface with the drug solution [2]. However, it is important to use careful chemicals on the surface in order not to cause any chemical loss inside the nanotubes. Chemicals can also be introduced by soaking the nanotubes in solution under vacuum condition followed by flushing, under vacuum condition, the gas trapped in the nanotubes that can be released and allowing a more efficient chemical loading achieved [13]. In either methods, the sample has to be completely dried before kinetic measurements.

In our experimental samples of titanium dioxide nanotubes that were immersed for several days in 500 ppm aqueous MB which prepared from 0.02 g of MB in 40 ml distilled water. After filling and rinsing, the TiO_2 nanotubes arrays were left to dry in the air. All operations were carried out at room temperature. Due to the high specific surface area and good surface activity of the TiO_2 nanotubes, MB was loaded on the TiO_2

nanotubes through physical absorption. The released amount of MB was measured by ultraviolet–visible spectroscopy and drug release report was plotted. In order to prepare NP suspension into distilled water the magnetic stirring for 10 min to make NPs uniformly dispersed in water was applied. Then, loading TiO_2 nanotubes, which were immersed in a ceramic container with NP suspension, was done. The samples underwent hydrothermal treatment at 150◦C for 1 hour, coating TiO_2-NPs on the surfaces of loading TiO_2 nanotubes was formed. After rinsing and drying the coated arrays, dipped again in MB solution.

Polyvinyl Alcohol (PVA) encapsulate

As a biocompatible polymer, PVA was used to coat the surface of the loaded TiO_2 nanotubes arrays, in order to develop additional control of the chemical release kinetics. The PVA polymer solution (1% w/v) was made up in a mixture of water and ethanol (1:1) and then stirred for 4 hours. The addition of ethanol accelerates the drying of the PVA coating. After filling the TiO_2 nanotubes arrays with MB, PVA was coated on to the nanotubes surface and TiO_2 nanotubes-NP with a spin coater. An aliquot of PVA solution was applied to the surface and spun for 5 min at 300 rpm. The thickness was controlled by the solution concentration and spin rate. With a fixed solution concentration and spin rate, we could control the thickness by the number of coats [14]. The release kinetics of MB was studied as a function of PVA film thickness.

The Release kinetics of MB

Standard drug release measurements, are usually made in media such as water, or saline or other buffered aqueous solutions [10]. In our experiments, methylene blue release kinetics was measured in 20 ml deionised water at 22 ºC. The concentrations of released MB were measured by UV-Vis spectrometry at 663 nm where the MB has maximum absorbance. Under controlled conditions, MB elution was measured at various times up to 2 weeks, after which the MB concentration reached an area of stability and release finished. Fig.(4) shows the chart for MB release process.

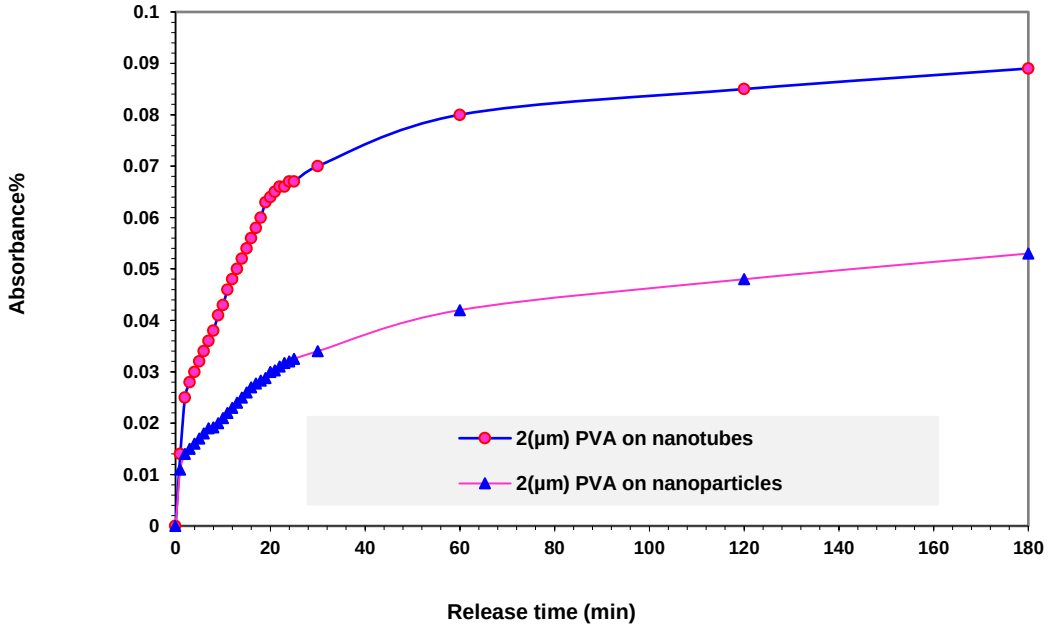

Fig.(4): Shows the chart of MB release process.

The application of nanotubes coated with nanoparticles in drug release confirms that the nanotubes shape effectively delays the drug elution and nanotubes coated with nanoparticles that acquire more times fore releasing of all MB because the loading of MB becomes more efficient when the nanotubes coated with the NP. Additionally, the release

of drugs from nanotubes coated with nanoparticles requires longer time. The release can be controlled efficiently by the use of PVA coatings.

Fig.(5) shows the MB release from both nanotubes and nanotubes coated with nanoparticles. The release time from nanotubes was completed within 30 min in contact with water, However the releasing period from the nanotubes-NP conjugate was completed in 60 min, indicating that the narrow way of the nanotubes-NP controls the drug release because the NP covered nanotubes and lowering the tubes diameter Moreover for lowering the release time the PVA layer prove the release time of nanotubes without NP.

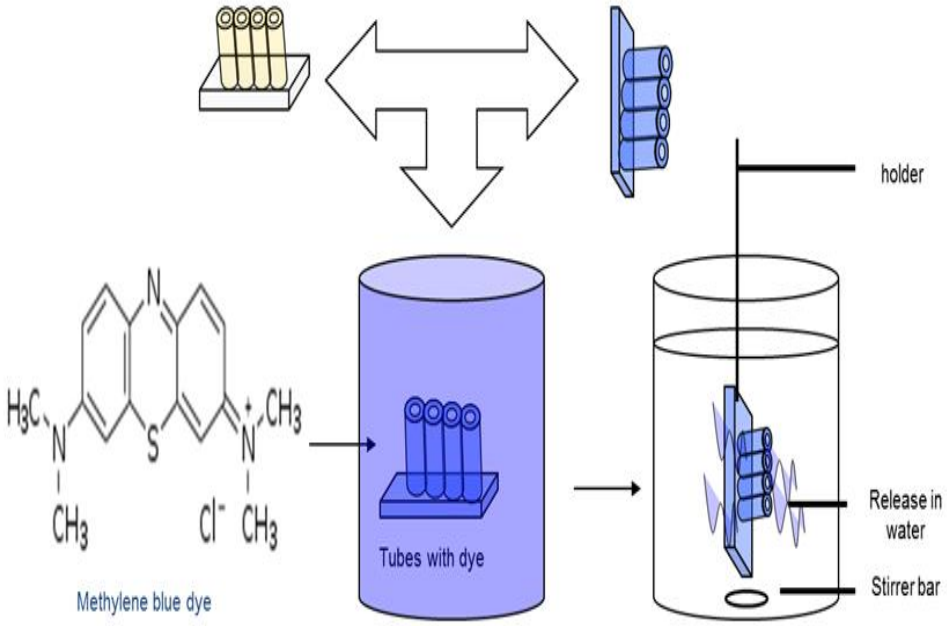

Fig. (5): Shows the MB release from both nanotubes and nanotubes coated with nanoparticles.

Conclusions

A much slower MB release was observed from nanotubes-NP conjugate unique design for highly efficient, time delivery. Delay time is managed by reducing the diameter by covering tubes surface with NP by hydrothermal treatment in addition to the solubility and thickness of polymer coating. Varying diameter vessel, small diameter mouth, large surfaces area was uniformly distributed of NP on Ti surface by hydrothermal treatment that may possibly improve the drug adsorption and reducing the tubes diameter. Therefore this design is very useful for drug delivery target.

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الخلاصة

تضمن البحث تكوين انابيب ثاني أوكسيد التيتانيوم النانوية على معدن التيتانيوم Ti. محلول الانودة الكهروكيميائية مكون من فلوريد الأمونيوم (NH_4F) مع اثيلين كلايكول (ethylene glycol) عند فولطية مسلطة مقدارها . 60 volt حيث كان معدل طول الانبوب 12 µm and 80 nm تقريباً. بعد عملية التلدين الحراري لانابيب ثاني اوكسيد التيتانيوم عند درجة حرارة 500 °C خلال فترة زمنية مقدارها ثلاث ساعات تحولت جدران انابيب ثاني اوكسيد التيتانيوم غير المتبلورة الى طور anatase. في هذا البحث تم استخدام انابيب ثاني اوكسيد التيتانيوم كوعاء حاوي لمحلول methylene blue (MB). تم تكوين طبقات اخرى حاوية لل (MB) متولدة عند طلاء ثاني اوكسيد التيتانيوم بجسيمات نانوية لغرض المقارنة في حالة تحفيزها مع انابيب ثاني اوكسيد التيتانيوم. ان الهدف وضع سيطرة اضافية لحركية تحفيز الكيميائية لبوليمر polyvinyl alcohol (PVA) المستخدم لتغليف سطح انابيب ثاني اوكسيد التيتانيوم المحملة وانابيب ثاني اوكسيد التيتانيوم والجسيمات النانوية. اظهرت النتائج الية التحفيز يمكن السيطرة عليها بكفاءة اعلى في حالة انابيب ثاني اوكسيد التيتانيوم اكثر من حالة استخدام انابيب ثاني اوكسيد التيتانيوم فقط. تم دراسة تركيب من خلال استخدام حيود الاشعة السينية, مجهر المسح الالكتروني ومجهر نفاذية الالكتروني.