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Nanostructured Titanium and CH-HA as Drug Carrier Systems

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Abstract:

In this study, we report two drug delivery systems based on titanium nanostructures and polymer-inorganic network. Firstly, titanium nanotubes were fabricated by electrochemical method. Hydroxyapatite was then deposited on the nanotubular structure to form a coating layer. Effect of anodization, nanotube formation and hydroxyapatite deposition on sorption and release of the model drug; Paracetamol were investigated. Results showed that HA electrode can hold greater amounts of Paracetamol for longer times than the anodized sample. Titanium nanostructures were also characterized by scanning electron micrographs. Secondly, we prepared a cubic gel like carrier based on chitosan and hydroxyapatite. It was observed that this structure has a potential in absorption of high amount of drug in short amount of time followed by a sudden burst release property. The titanium nanotubes and natural polymers with drug release properties have a potential application in implantology and other therapeutic devices.

Introduction:

Drug delivery is an area dealing with health care. In recent years, the requirement for the development of innovative technologies to improve the delivery of pharmaceutics has gained much attention. Various drug carriers have been considered as a drug delivery systems including nanostructured titanium (nanotubes, nanoparticles, nanorods, nanowires) [1-15], gold nanoparticles [16] and etc. Here in this study we aimed to work on two carrier systems including polymer carrier system and metallic carrier system.

Methods:

Preparation of CH/HA

CH powder was dissolved in 3% v/v acetic acid on magnetic stirrer for 45 minutes to achieve a homogenous polymer solution. The HA powder was then added to prepared CH solution on the magnetic stirrer at room temperature in order to make paste of polymer/HA. 0.5% w/v surfactant solution was prepared by dissolving TPP in deionized water. The HA/CH were syringed into the TPP solution. TPP cross linking was allowed over 24h. Then the final solution was freeze dried for 3 days and rinsed with water.

Drug Loading

CubGl was placed in a tube containing 5ml of model drug; Paracetamol solution. The absorbance of the solution through time interval of 30 min, 60 min, 90 min, 105 min was measured by UV-Visible spectrophotometer.

Drug Release

Drug loaded CubGl was taken out from the drug solution and placed in a tube containing phosphate buffered saline (PBS) which was selected as a release media in this study. The release behavior of drug from CubGl was analyzed through time intervals of 15min, 30min, 45min, 60min, 75min, 90min, 105min.

Formation of titanium nanotubes (TNT) and deposition of HA layer (HATNT)

Anodic oxidation process was performed in a two electrode electrochemical cell where titanium alloy (Ti-6-4) sheet was used as anode and ST316 was used as cathode. The electrodes were kept parallel position with about 4cm distance from each other and 1M Ammonium sulfate (NH□)□SO4 and 5wt% Ammonium fluoride NH_4F solution was used as electrolyte. Constant potential of 25V and a temperature of 25°C were applied. The time duration of the anodization was 60 minutes. Calcium Phosphate coatings were deposited onto titanium alloy substrates via electro-deposition method in an electrolyte containing 0.04M Ca $(NO_3)_2$, 0.1M $NaNO_3$ and 0.027 mol/L $(NH_4)_2HPO_4$ and water. The electrolyte was thermostated at 60-80°C and stirred.

Drug loading

To adsorb analgesic drug on TNT and HATNT, the samples were plunged into Paracetamol aqueous solution in the test tube closed by a tight polyethylene cap with no atmosphere.

Drug release

By placing each drug loaded samples into 10ml of phosphate buffered saline (PBS) in a test tube, drug release was investigated by picking 1ul of the solution. The absorbance was read by NanoDrop 1000 spectrophotometer.

Results:

CH/HA formation

Chitosan has a cationic nature in acidic medium [22]. Cations present when it dissolved in acetic acid. Anions created when Sodium Tripolyphosphate (TPP ($Na_5P_3O_{10}$)) dissolves in water. Thus, crosslinking of CH occurs by adding these two solutions together. In fact, when CH solution syringed into the TPP solution, the tripolyphosphoric ions and OH^- diffuses into the CH droplets and reacts with $-NH3^+$ functionalities of chitosan [23] This is where ionic crosslinking happens. Addition of HA created a structure with desirable mechanical strength. As a result of this process, we obtained a cubic gel like structure (CubGl).

Absorption

From Fig. 1, it can be observed that the drug is encapuslating into the structure of polymer/HA structure. The continuous and fast adsorption was viewed. This growing encapsulation is indicative of the formed cubic structure's ability to take paracetamol into itself easily. This improving loading can also be attributed to the good interaction of paracetamol with polymer/HA mixture.

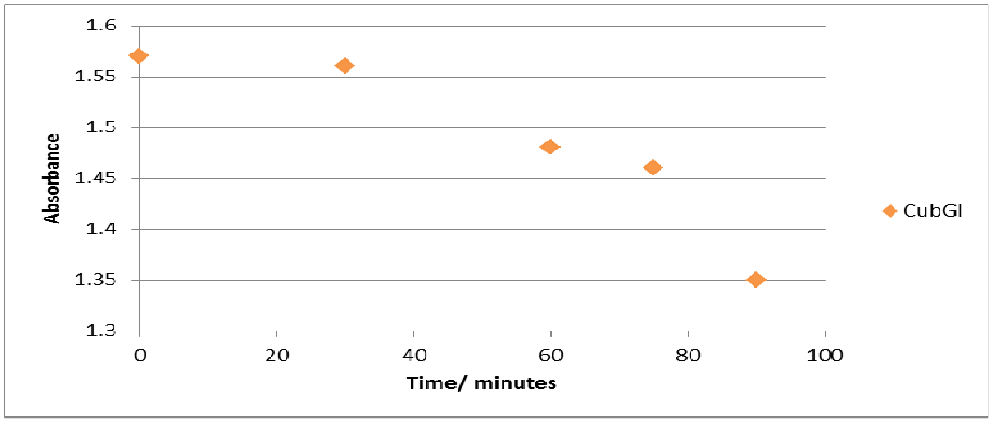

Fig. 1 Drug adsorption in CubGl; the absorption of drug solution is decreasing when drug is diffusing into CubGl

Desorption

The release profile of Paracetamol from the CubGl is shown in Fig. 2. In contrast with previous literature, we first observed a sustained release and then a sudden burst release. It seems encapsulated drug molecules disconnected the polymer networks during the 105-125min of the experiment and caused the diffusion of PBS into the networks causing the sudden increased drug release in 105-120min. It can be concluded that diffusion of Paracetamol through CubGl is really fast as well as its release, including sustained release followed by a sudden fast release. Its structure is prone to absorption and burst release behavior. Therefore, this carrier system is appropriate for the applications in which fast release of the pharmaceutics is needed.

We assume two reasons for the burst drug release in this experiment

A) Poor interaction between CH/HA

This poor interaction can be improved by increasing the amount of crooslinker. Increasing number of functional groups results in the stronger interaction and higher density of the matrix.

B) Large pore sizes

Another solution can be adding more HA to the polymer solution. The pore size can be decreased by increasing HA% [24]. Consequently, the CubGl can entrap the drug molecules for longer time.

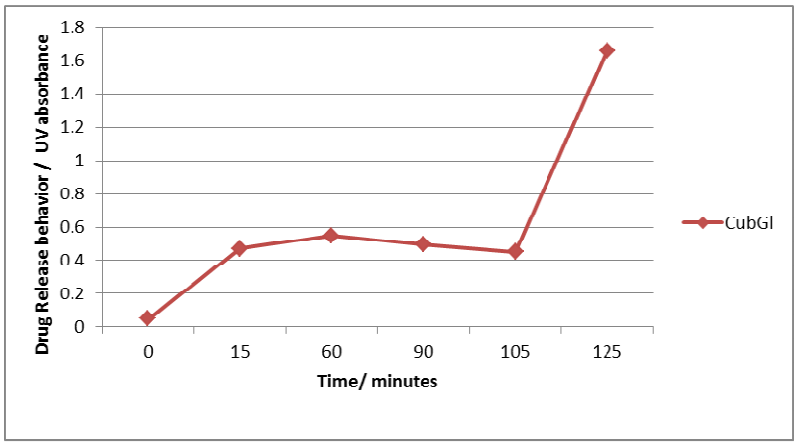

Fig. 2 Drug release behavior of CubGl

Titanium nanotubes and HA coating formation

The nanoarchitecture of titania nanotube arrays was examined for uniformity and repeatability using scanning electron microscope (Fig. 3A). HA flakes are also can be observed in Fig.3B

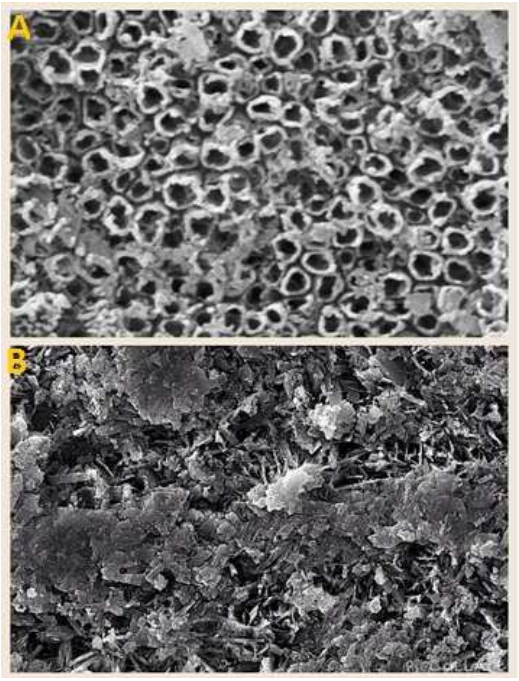

Fig. 3 Scanning electron micrographs of A) TNT B) HATNT

Sorption

Drug sorption behavior depicted in Fig. 4 indicates the diffusion of paracetamol. Comparing the sorption profiles of HATNT and TNT, one can conclude that larger pores along with small pores are loaded with higher amount of drug. In fact, HATNT due to the higher and larger amount of porous structure is loaded with higher drug. Moreover, it is observed that saturation time of Paracetamol on the anodized sample was 30% shorter than the hydroxyapatite coated sample.

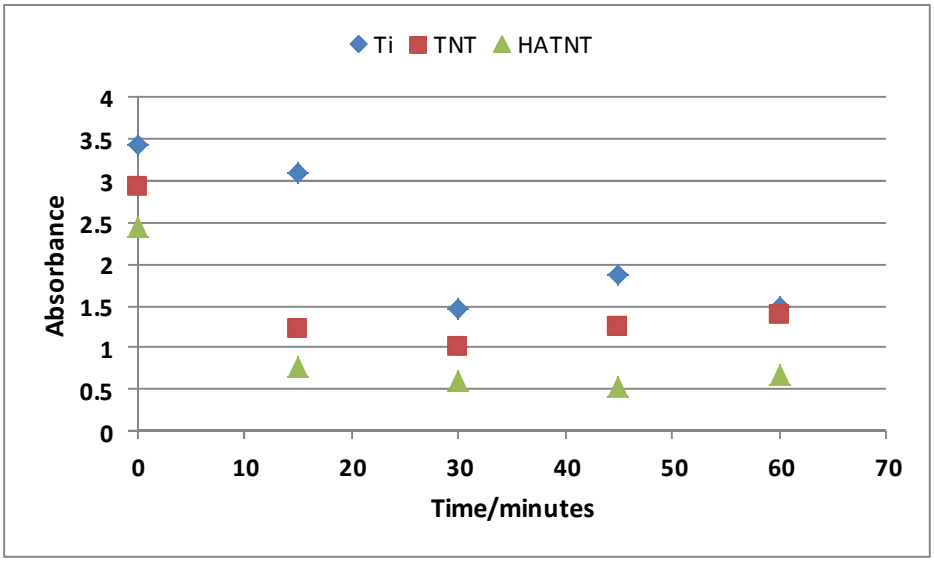

Fig. 4 Drug sorption behavior

Desorption

As a result of nanostrucuring the titanium alloy surface along with deposition of a bioceramic layer, significant changes in the drug release profile was observed (Fig. 5). From this decrease, it can be said that nanotubular structures carry the drug and HA layer is acting as a barrier not letting the drug to release fast.

Molecular transport of the drug in the layer is dependent on the permeability of the coating for drug molecule [5]. This permeability is dependent on the coating's chemical composition, structure, charge and interfacial properties (hydrophobicity/hydrophicility) [5]. Popat and coworkers [25] confessed that vicinity of terminal hydroxyl groups on the surface of TNTs results in formation of negative charge which in turn leads to retarded release of positively charged drugs. In this study, the model drug, Paracetamol, is neutral with low molecular weight of 151.163 Da. Therefore, it is assumed that encapsulation of drug and its rate of release for TNT is not affected by its electrostatic charge whereas the small size of drug molecules (molecular weight lower than 900 Dalton (Da) are counted as small molecules) can be a reason of the slower release of TNT comparing with Ti spotted in our study. TNTs have the smaller pore sizes than Ti, so drugs cannot release in a fast rate.

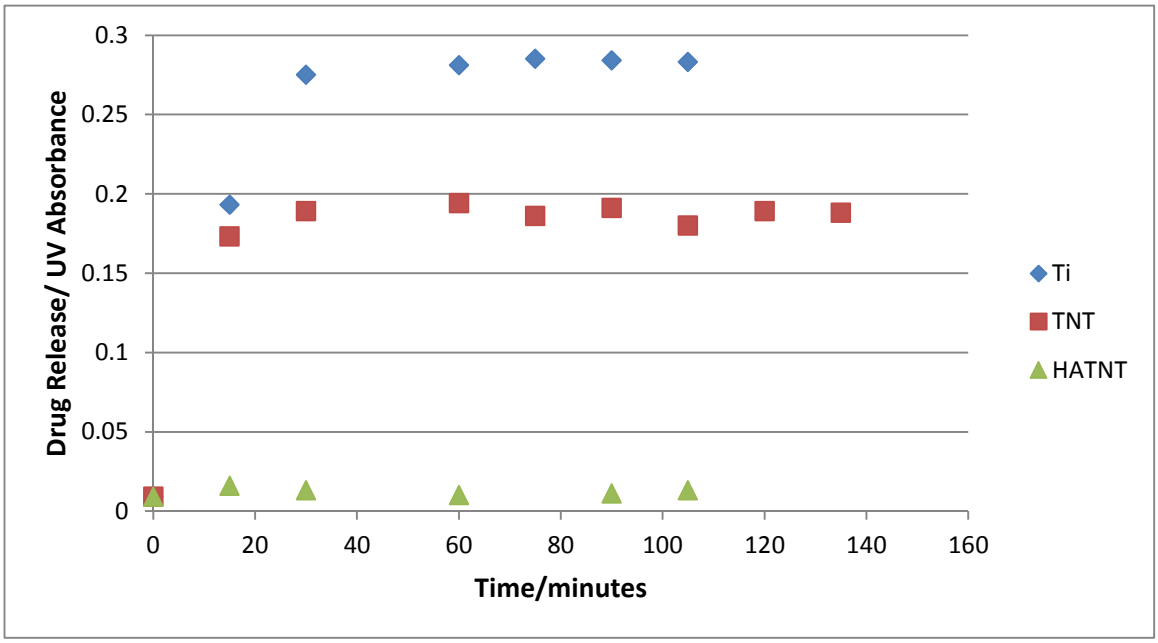

Fig. 5 Drug release behavior

Discussions:

In conclusion, we report on the preparation of two drug delivery systems. First, drug carrier based on chitosan and hydroxyapatite was gained. Prepared CubGl exhibited a good drug absorption and a release behavior including a sudden burst release. The reasons for this phenomon was implied. Second, titanium nanotubes and HA coated titanium nanotubes were achieved by electrochemical method. We tested Paracetamol sorption and desorption behavior for this metallic carrier. Results showed that nanopores and micropores are involved in encapsulating of the model drug. These delivery systems can be used for various biomedical applications such as in implantology and vaccine delivery using different types of drug i.e antibacterials, anticancer. Such medical device with drug loading ability can reduce the number of repeated administrations and results in a more efficient course of treatment.

Keywords: Nanostructured titanium, Nanotube, Carrier, Drug delivery