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Biocompatible titania microtubes formed by nanoparticles and its application in the drug delivery of valproic acid

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Abstract

In this study we have successfully implanted an inorganic device consisting of titania microtubes in the brain of a wistar rat. Biocompatibility was established as shown by the fact that there were no perturbations on the surrounding tissue over a period of six months. An immunohistochemical study also showed that there were no alterations in the neighboring neurons over the six-month duration of the study.

Keywords: Microtubes; Sol–gel; Titania; Brain biocompatibility; Electronic microscopy

1. Introduction

Nanostructured materials in general, tend to have properties, which may differ substantially from those observed in bulk materials [1]. Much attention has recently been focussed on the synthesis of nanoparticles, nanorods, nanowires and microtubes due to their potential in many applications [2]. Following the discovery of carbon nanotubes Iijima [3], inorganic nanostructured materials such as wires, rods and tubes have attracted increased attention due to their electronic, structural and textural properties and potential applications. Nanotube structures include TiO_2 [4], MnO_4 [5], and V_2O_5 [6]. The synthesis of TiO_2 microtubes has become an area of intense research during recent years [7–11]. Applications of TiO_2 nanotubes include catalysis, gas sensing, and corrosion resistant materials. It is also gaining interest because of its desirable properties in areas such as electronics, photochemical and biological applications [12,13]. In particular, titania nanotubes, due to their large surface area, make them useful in catalysis [14], semiconductor devices [15] and photovoltaic cells [16]. These titania microtubes are generally characterized by having large diameters and walls composed primarily of nanoparticles.

Titania nanotubes can be synthesized by several methods, including replication processes [17], hydrothermal processes [18] and template techniques [16]. When the sol–gel synthesis method is used, organic templates are selected such that the microstructures or nanostructures can be made to fit the application of interest. The templates employed usually involve surfactants or natural templates such as sugar. Sol–gel matrices may, through templating or process design, be constructed in such a way that the pores may be designed to encapsulate host molecules, which will allow free access through flow processes [19,20]. During gel formation, templates are trapped in the gel matrix. Because the templates are organic, it is easy

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to burn them off through combustion processes. This leaves a gel matrix cavity with dimensions, which are similar to those of the template molecule [21]. Using this method, porous materials with a wide variety of shapes and pore size distributions are synthesized and used in different applications.

The accepted definition of biocompatibility of a material is '*the ability of a material to perform with appropriate host response in a specific application*' [22–24]. Ti and Ti alloys are corrosion resistant, light, yet sufficiently strong for use as a load-bearing and machinable orthopedic implant material. They are one of the biocompatible metals which oseo-integrate (direct chemical or physical bonding with adjacent bone surfaces without forming a fibrous tissue interface layer). For this reason, they have been used successfully as orthopedic and dental implants [25,26]. To enhance the bioactivity of Ti and enhance bone growth, surface treatments such as surface roughening by sand blasting, the formation of the TiO_2 anatase phase, hydroxyapatite, (HAP) coating, or chemical treatment have been utilized [27–29].

Controlled release devices have grown from a research curiosity in the late 1960s to an important component of clinical medicine and a successful industry. However, long-term, implant controlled release devices are relatively rare, and where there have been in vivo applications, there have also been problems associated with performance. Criteria for a successful, long-term controlled release implant device should include, release rate, drug delivery to the body paralleling the release rate from the device, stability (of the device itself and the drug inside) and, reasonable size with respect to the anatomy, sterilizability and biocompatibility [23]. Due to the porous structure of TiO_2 microtubes it is possible to store drugs as hosts on a titania surface. These drugs can be stored for relatively long periods of time on titania making them ideal for long time drug release applications. Drug efficiency and the reduction of drug toxicity due to the alteration of tissue may also be achieved.

2. Experimental

2.1. TiO_2-microtubes

The support used as a template was an activated carbon cloth (RS 1301, from Acrtitex). The BET surface area of this material was found to be around 70 m^2/g using N_2 adsorption at 77 K. The mean pore diameter was found to be 0.6–0.8 nm and the ash content was 0.48%. It was subjected to a soft oxidation treatment using a solution consisting of 12N H_2O_2 for a period of 65 h at room temperature. It was washed using deionized water and dried at 110 °C for 24 h. The carbonaceous material was then contacted with a tetrahydrofuran (THF) solution of Ti(IV) isopropoxide (Aldrich, 97%). This was adjusted to obtain a weight loading consisting of 50 wt.% TiO_2. The titanium precursor was hydrolyzed to TiO_2 by keeping the impregnating cloth in a climatic chamber at 65% humidity at room temperature over a period of 24 h. The sample was subsequently dried at 110 °C in air followed by heating in static air at 250 °C for 2 h. Finally the samples were calcined at 500 or 900 °C for 12 h.

3. Characterization

3.1. SEM

Physicochemical techniques were used to complete the characterization of each tissue sample. A JEOL 5600 LV scanning electron microscope equipped with an EDS attachment for chemical analysis was used to perform both the morphological and the chemical composition of each sample.

3.2. Adsorption studies

Specific surface areas were calculated from nitrogen adsorption isotherms at 77 K. A Quantasorb-3B adsorption was used for these studies.

3.3. Biological tests

For the biological study, adult male wistar rats (180–250 g, $n = 10$) were used. They were maintained under a 12:12 light:dark cycle with food and water available ad libitum. One 1×1.5 mm titania cylinder (1.1 mg weight) was surgically implanted in all rats under ketamine–xilazine (80 and 30 mg/kg, i.p. respectively) anesthesia through a stainless-steel guide canula (18-gauge) into the basolateral amygdala (BLA) (AP:-2.3, L:4.8, V:8.5) [30]. Following surgery, the animals were allowed to recover in their home cage with food and water ad libitum, in a 12:12 light dark cycle with lights on at 07:00 h. In order to observe the behavior of the animals, they were placed in a plexiglas cubicle ($30 \times 30 \times 30$ cm) for the duration of the experiment. The canula was maintained in the implantation site for 10 min following implantation. At the end of the experiment, the animals were injected with an overdose of sodium pentobarbital and transcardially perfused with saline and 3.7% formalin. The brains were removed and post-fixed in 3.7% formalin. The implantation sites were verified in coronal slices stained with hematoxin eosin. Each animal was used only once, and the experiments were performed under the guidelines of the Mexican Law of Animal Protection.

3.4. Histological study

The brains were removed and set in a 4% paraformaldehyde solution for a period of 15 days. The tissue was embedded in paraffin and 10 μm sections were obtained. The sections were stained with Hematoxin–Eosin, Bielchovsky and were studied using a Leica light microscope.