Available online at www.sciencedirect.com
ScienceDirect
Acta Biomaterialia 4 (2008) 2037–2044
Acta BIOMATERIALIA
www.elsevier.com/locate/actabiomat

Pt/TiO_2 brain biocompatible nanoparticles: GBM treatment using the C6 model in Wistar rats ☆

T. López [a,b], S. Recillas [a,b], P. Guevara [b], J. Sotelo [b], M. Alvarez [a,b], J.A. Odriozola [c,*]

[a] Universidad Autónoma Metropolitana-Xochimilco, Health Department, Calzada del Hueso 1100, México DF 04960, México
[b] Nanotechnology Laboratory, National Institute of Neurology and Neurosurgery, Insurgentes 3877, México DF 14279, México
[c] Department of Inorganic Chemistry and Materials Science Institute, Universidad de Sevilla – CSIC, Av. Américo Vespucio 49, 41092 Sevilla, Spain

Received 24 October 2007; received in revised form 8 May 2008; accepted 14 May 2008
Available online 8 June 2008

Abstract

In the present work we synthesized inorganic oxide nanoparticle carriers of platinum compounds and tested their therapeutic effect on animal models in which C6 glioma cells have been inoculated. TiO_2-containing $Pt(NH_3)_4Cl_2$ complexes were synthesized using sol–gel methods. The platinum species are chemically bonded to the TiO_2 carrier, as shown by Fourier transform infrared spectroscopy of probe molecules. Treatment with TiO_2–Pt nanoparticles reduces tumour growth rate by up to 56%, showing that a synergistic effect exists between the TiO_2 carrier and the platinum drug.
© 2008 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.

Keywords: Nanotherapy; Cancer; Platinum; TiO_2; Nanoparticles

1. Introduction

The medical applications of nanotechnology, a multidisciplinary field that implies materials and devices designed with very high-therapeutic selectivity, are usually collectively referred to as nanomedicine [1–3]. Because cancer is one of the leading causes of death all over the world and less than half of diagnosed patients have a survival period of 5 years, much research and development of novel therapeutic methodologies has been carried out [2]. As an example, conventional therapy for glioblastoma consists primarily of a surgical procedure followed by radiation therapy. The survival after surgical intervention alone is around 6 months, and if radiation therapy is added to the surgical treatment the survival extends to 9 months [4]. However, clinical state-of-the-art cancer chemotherapies are toxic to both healthy and tumourous cells, and therefore the efficacy of chemotherapy is often limited by the undesirable side effects of the drug [5].

The development of new methodologies that have higher drug selectivity for cancer while simultaneously reducing the toxicity of healthy tissues is a major challenge in cancer treatment. The size of the blood capillaries in a tumour (ca. 400–800 nm) allows extravasation of colloid particles to the cancerous tissue; on the other hand, as cancerous tissues have fewer lymphatic capillaries, drainage from these capillaries to healthy tissues is reduced. This causes colloidal particles to become entrapped in the cancerous tissues, referred to as an "enhanced permeability and retention effect" [6,7].

Nanoparticles fabricated by the self-assembly of amphiphilic copolymers have been used as carriers for cisplatin [8,9].

The development of nanoscale delivery carriers, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic nanoparticles and cross-linked liposomes, can be targeted to cancer cells. This increase in selectivity of drugs towards cancer cells will reduce the toxicity to normal tissue [5,10,11].

☆ This research was presented at the Materials Today Asia 2007 Conference.

* Corresponding author. Tel.: +34 954489544.
E-mail address: odrio@us.es (J.A. Odriozola).

1742-7061/$ - see front matter © 2008 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.actbio.2008.05.027

The use of inorganic oxide nanoparticles offers a suitable method of delivering drugs to tissue or cells [12,13]. Their submicrometric size favours the take-up by cells via endocytosis/phagocytosis. The hydrophilic character of their surfaces allows recognition by the reticuloendothelial systems to be avoided, and their intrinsic stability prevents degradation in the bloodstream. In addition, they may have large surface areas, a controlled pore size distribution and, if required, the acid–base properties of the surface can be tailored in order to adapt them to site specificity. This will radically change the way in which the diagnosis, treatment and prevention of cancer is done nowadays. Gliomas – brain tumours that develop from glioma cells – are the most common primary tumour of the brain. Glioblastoma multiforme (GBM) is the most common and most aggressive of the malignant primary brain tumours, having a mean survival time of 1 year [13,14].

A common model for experimental studies in oncology consists of transplanting tumours to susceptible animals [15]. In the present work we synthesize inorganic oxide nanoparticle carriers of platinum compounds and test their therapeutic effect on animal models in which C6 glioma cells have been inoculated. This will provide clues for the development of inorganic carrier–drug nanodevices with high-selectivity for cancer treatment and minimum side effects.

2. Materials and methods

TiO_2 nanoparticles were synthesized by the sol–gel method. To a mixture of 190 ml of ethanol and 29 ml of deionized water 69 ml of the TiO_2 precursor titanium *n*-butoxide was added dropwise over a 4 h period under constant stirring at 343 K. The resulting sols were maintained under constant stirring until gelation occurred. The total molar water:alkoxide:alcohol ratio was 8:1:16. After an aging period of 72 h at room temperature, xerogel samples were obtained by oven drying the obtained solids at 343 K.

A similar procedure was followed for incorporating the Pt drug to the TiO_2 carrier. To obtain 1 wt.% platinum metal on TiO_2, 320 mg of $Pt(NH_3)_4Cl_2{\cdot}xH_2O$ was incorporated into a mixture containing 190 ml of ethanol and 29 ml of deionized water, under constant stirring at 343 K. This mixture was refluxed for 10 min at 343 K prior to the addition of the titanium alcoxide. Then 69 ml of titanium *n*-butoxide was added dropwise over a 4 h period. The resulting sols were maintained under constant stirring until gelation occurred. The total molar water:alkoxide:alcohol ratio was 8:1:16. After an aging period of 72 h at room temperature, xerogel samples were obtained by oven drying the obtained solids at 343 K.

Scanning electron microscopy studies were carried out in a JSM-5400 JEOL instrument. Transmission electron microscopy (TEM) observations were carried out in a Philips CM200 microscope operating at 200 kV. In both cases, the samples were dispersed in ethanol by sonication and dropped onto a copper grid with a carbon film.

Laser Raman spectra were carried out in a HORIBA Jobin Yvon HR800 UV spectrometer using a 514.5 nm excitation line and a 600 g mm^{-1} grating. All the spectra were taken with a 1 s exposure time, fie scans and a pinhole of 100 mm.

Thermogravimetric analysis (TGA)–differential thermal analysis (DTA) experiments were carried out in a Setaram DTA-TG 92 instrument. The sample was placed in a Pt crucible and heated from room temperature to 1573 K, in flowing air, at a rate of 10 K min^{-1}.

X-ray diffraction (XRD) was recorded using a ẊPert Pro Philips diffractometer working with Cu K_α radiation ($\lambda = 1.5404$ Å) in continuous scan mode from 20 to 80° of 2θ using a 0.05°/1.0 s sampling interval.

The surface acid–base properties were characterized by Fourier transform infrared (FTIR) spectra of probe molecules: pyridine and CO. IR spectra were taken in transmission mode using a Nicolet 710 FTIR spectrometer with a resolution of 4 cm^{-1} and 150 scans. The TiO_2–Pt nanoparticles were pressed into thin (300 mm thick) self-supported wafers and placed in a Pyrex glass cell equipped with CaF_2 windows and coupled to a vacuum line. The samples were outgassed at 323 K for 2 h prior to the adsorption experiments in order to allow the elimination of any excess water. This treatment does not allow the complete removal of weakly adsorbed water but prevents decomposition of the platinum drug, and in any case may allow a realistic environment since the material will be placed in liquid medium. Probe molecule adsorption was carried out at room temperature by either breaking a sealed capillary tube inside the IR cell (pyridine) or allowing gas phase CO to enter via the manifold attached to the vacuum line. After adsorption, the samples were submitted to the study temperatures of 298 and 100 K, for pyridine and CO, respectively, and outgassed until the final pressure remained constant.

The C6 glioma cells, obtained from the American Tissue Culture Collection (Rockville, MD), were cultured in a Petri dish before being inoculated. The cells were cultured under sterile conditions at 310 K in a humid environment with 5% of CO_2 in Dulbecco's modified Eagle's medium supplemented with bovine foetal serum (10%). Then 1×10^7 cultured C6 cells were inoculated intraperitoneally into a 12-week-old Wistar rats. After the cultures became confluent, the cells were washed with saline solution, harvested and counted, and 1×10^7 C6 cells were intraperitoneally inoculated into 12-week-old male Wistar rats. Fifteen days later, a large, multilobed peritoneal tumour developed. This procedure was used since in this way tumours are easier to dissect, the tumour growth is simpler to follow, the injection of Pt/TiO_2 nanoparticles into the tumour is easier and, finally, resection of the tumour in this area presents less difficulties.

The rats developed a tumour with a diameter of approximately 2 cm, after which they were randomly allocated into four groups: group A ($n = 21$) was followed as the control; animals from group B ($n = 22$) were injected with 1×10^{-4} g of $Pt(NH_3)_4Cl_2$ dissolved in 10 ml of 0.154 mM

ID	Title	Pages
1777	Pt/TiO2 brain biocompatible nanoparticles: GBM treatment using the C6 model in Wistar rats ☆	8

Download Full-Text Now

http://fulltext.study/article/1777

fullText.study

Categorized Journals
Thousands of scientific journals broken down into different categories to simplify your search

Full-Text Access
The full-text version of all the articles are available for you to purchase at the lowest price

Free Downloadable Articles
In each journal some of the articles are available to download for free

Free PDF Preview
A preview of the first 2 pages of each article is available for you to download for free

http://FullText.Study