International Journal of Pharmaceutics 518 (2017) 119–129

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Physicochemical characterisation and investigation of the bonding mechanisms of API-titanate nanotube composites as new drug carrier systems

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 20 December 2016
Accepted 22 December 2016
Available online 24 December 2016

Keywords:
Titanate nanotube
Diltiazem hydrochloride
Diclofenac sodium
Atenolol
Hhydrochlorothiazide
Composite
Interaction

ABSTRACT

Titanate nanotube (TNT) has recently been explored as a new carrier material for active pharmaceutical ingredients (API). The aim of the present work was to reveal the physicochemical properties of API-TNT composites, focusing on the interactions between the TNTs and the incorporated APIs. Drugs belonging to different Biopharmaceutical Classification System (BCS) classes were loaded into TNTs: diltiazem hydrochloride (BCS I.), diclofenac sodium (BCS II.), atenolol (BCS III.) and hydrochlorothiazide (BCS IV.).

Experimental results demonstrated that it is feasible for spiral cross-sectioned titanate nanotubes to carry drugs and maintain their bioactivity. The structural properties of the composites were characterized by a range of analytical techniques, including FT-IR, DSC, TG–MS, etc. The interactions between APIs and TNTs were identified as electrostatic attractions, mainly dominated by hydrogen bonds. Based on the results, it can be stated that the strength of the association depends on the hydrogen donor strength of the API. The drug release of incorporated APIs was evaluated from compressed tablets and compared to that of pure APIs. Differences noticed in the dissolution profiles due to incorporation showed a correlation with the strength of interactions between the APIs and the TNTs observed in the above analytical studies.

1. Introduction

The rapidly developing nanotechnology shows an increasing interest in various organic and inorganic nanotubes. These nanomaterials shortly fulfilled the expectations in several fields (physics, chemistry and electronics), which aroused curiosity to discover their possible application in the medical field as well. The adaptation of nanotubes to medical use is limited by strict safety requirements (Wacker et al., 2016; Dobrovolskaia, 2015) that many types of nanotubes, e.g. carbon nanotubes do not meet (Ema et al., 2015). At the same time, others such as titanate nanotubes (TNTs) show perfect suitability for therapeutic use, thus getting into focus and deserving special attention (Kulkarni et al., 2015).

Titanate nanotubes are made of titania, a versatile material used in diverse applications (food, biomedicine, cosmetics, paints, photocatalysis, etc.). The first TNTs were synthesized in 1996 by Hoyer, but the most widespread synthesis method, the alkali hydrothermal treatment was reported by Kasuga et al. in 1998 (Camposeco et al., 2015; Liu et al., 2014). The TNTs prepared in this way have many advantageous properties, making them worthwhile for pharmaceutical industry. Most importantly, they are biocompatible and do not show any toxicity (Fenyvesi et al., 2014; Wadhwa et al., 2011). Moreover, their special tubular structure make them ideal for being filled with active pharmaceutical ingredients (APIs) and thereby to be used as carrier materials. Due to their ability to take in and stabilize nanonized APIs, the TNTs can offer a solution to one of the biggest challenges of pharmaceutical

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http://dx.doi.org/10.1016/j.ijpharm.2016.12.053
0378-5173/

industry, the improvement of processing, solubility and bioavailability of active substances (Hodos, 2007).

A considerable part of medical research focuses on the application of the TNTs in orthopaedic and dental implant therapy, where TNTs act as local drug delivery and controllable drug release systems. According to the results, TNT coatings on implants have high osteogenetic ability and thus can promote osteointegration, while as a drug delivery platform they can provide local release of drugs, e.g. growth factors, anti-bacterial or anti-inflammatory agents (Chennell et al., 2013; Kumeria et al., 2015; Roguska et al., 2016; Yu et al., 2015; Wang et al., 2015; Zhang et al., 2016). Another important segment of medical research attempts to characterize the TNTs themselves, including their preparation, structure and physicochemical properties as well as their capacity of being loaded with different drugs and their functioning as carriers (Doadrio et al., 2015; Brunatova et al., 2014; Cho et al., 2010; Khan et al., 2015; Mandal et al., 2014; Preda et al., 2015). Nevertheless, this segment is underrepresented for the present, which results in incomplete knowledge in this field.

In order to expand this insufficient knowledge and to explore the possible medical application of TNTs as carriers, the objective of the present study was to thoroughly characterize four different API-TNT composites by revealing their morphological properties, discovering the interactions between the APIs and the TNTs (if there are any) and determining their effect on the dissolution of the drugs from solid dosage form. A quasi-similar research topic has been reported by Dodario et al., who investigated ibuprofen loaded nanotubular titanium surface and attempted to identify the interactions between the drug and the nanotubes. However, the results of Dodario et al. cannot be translated to the free TNTs as despite the common nomenclature, the free and surface attached TNTs differ in many aspects, including the formation mechanism, the tubular structure and the physicochemical properties. Hence, the present work is unique to focus on the characterisation of free TNTs as potential carrier materials. Through displaying the capacity of the TNTs to be loaded with different APIs (diltiazem hydrochloride, diclofenac sodium, atenolol, hydrochlorothiazide), identifying the interactions between the APIs and the TNTs and the impact of the bonds on pharmaceutical use, the present study aims to reveal the potential pharmaceutical benefits of the use of TNTs as carriers, e.g. the improvement of the solubility and bioavailability of the incorporated APIs and the realisation of modified drug release from solid dosage form.

2. Materials and methods

2.1. Materials

Hydrothermally synthesized titanate nanotubes (TNTs) were produced by the University of Szeged, Department of Applied and Environmental Chemistry. Diltiazem hydrochloride (DiltHCl), diclofenac sodium (DicNa), atenolol (ATN) and hydrochlorothiazide (HCT) were kindly supported by Sanofi-Aventis PLC, Egis Pharmaceuticals PLC, TEVA Pharmaceuticals PLC and Gedeon Richter PLC, respectively, and were chosen to be incorporated into titanate nanotubes. Avicel PH 112 (FMC Biopolymer), Tablettose 70 (Meggle Pharma), talc and magnesium stearate were used as tableting excipients.

In order to incorporate the API into TNTs and to achieve a 1:1 ratio of API:titanate nanotube composites, 1:1 ratio of API: 70% alcohol dissolution and the same 1:1 ratio of TNT:70% alcohol dispersion were prepared. After reaching a smooth dispersion of TNTs by 30 min of magnetic stirring, the 2 compositions were mixed and subjected to an hour-long ultrasonic treatment. Finally, the solvent was eliminated from the system in a vacuum dryer. The powder retained in this way contained the wanted API-titanate nanotube composites, which were the following in the study: diltiazem hydrochloride-TNT (DiltTi), diclofenac sodium-TNT (DicTi), atenolol-TNT (ATNTi), hydrochlorothiazide-TNT (HCTTi).

2.2. Morphology

The texture of the TNTs was analysed with a HITACHI S-4700 scanning electron microscope (Hitachi, Tokyo, Japan) and a FEI Tecnai G2 20 X-TWIN transmission electron microscope (FEI, Hillsboro, OR, USA). The scanning electron microscopy (SEM) pictures were taken at a magnification of 2.0–25 k, the electron energy was set to 10.0 kV for the APIs and the composites and to 25.0 kV for the TNTs. A sputter coating unit (Polaron E5100, VG Microtech, UK) was used to charge the surfaces for the SEM measurements. The air pressure during the analyses was 1.3–13 mPa. The transmission electron microscopy (TEM) images that were taken at 100 kV of electron energy also served to analyse the particle size of TNTs by using Image J 1.47 t (National Institute of Health, Bethesda, MD, USA) software.

2.3. Thermal properties

Thermoanalytical measurements were performed to reveal the behaviour of TNTs, APIs and composites under rising temperature. TGA and DSC tests were accomplished by a Mettler Toledo TGA/DSC1 simultaneous analyser (Mettler-Toledo Ltd, Budapest, Hungary) in the range of 25–500 °C with a heating rate of 10 K/min, using nitrogen as purge gas. 10 ± 1 mg of sample was measured and closed into an aluminium pan (100 μL). The results were evaluated with STARe Thermal Analysis Software. With the objective of comparing the curves, the results were normalized to sample weight and to the temperature of the reference pan.

To complete the analysis with the identification of gases, TGA/DSC was coupled to a ThermostarTM GSD 320 quadrupole MS (Pfeiffer Vacuum GmbH, Asslar, Germany) operated under N_2 atmosphere (purity = 99.999%, 70 mL min^{-1} flow rate). The connection between the TG and the mass spectrometer was made by means of a silica capillary, which was maintained at 120 °C. The evolved gases were first scanned in the range of 1–300 m/z to identify the characteristic peaks of the raw materials. Afterwards, the measurements were performed on these selected m/z masses. The results of MS were evaluated with Quadera software.

2.4. Surface free energy

The surface free energy of the materials was determined with a DataPhysics OCA 20 (DataPhysics Instruments GmbH, Filderstadt, Germany) optical contact angle tester, by using the sessile drop method. The polar and apolar test liquids (water and diiodomethane) were dropped onto the surface of 13-mm-diameter tablets prepared with a Specac hydraulic press (Specac Ltd., Orpington, UK) at a pressure of 4 tons. The disperse and polar components of the materials were calculated with Wu equations (Eq. (1) and (2)) in the knowledge of the surface tensions of the test liquids:

$$(1 + cos\theta_1)\gamma_1 = \frac{4\gamma_1^{Disp}\gamma_S^{Disp}}{\gamma_1^{Disp} + \gamma_S^{Disp}} + \frac{4\gamma_1^{Pol}\gamma_S^{Pol}}{\gamma_1^{Pol} + \gamma_S^{Pol}} \quad (1)$$

$$(1 + cos\theta_2)\gamma_2 = \frac{4\gamma_2^{Disp}\gamma_S^{Disp}}{\gamma_2^{Disp} + \gamma_S^{Disp}} + \frac{4\gamma_2^{Pol}\gamma_S^{Pol}}{\gamma_2^{Pol} + \gamma_S^{Pol}} \quad (2)$$

where θ_1 is the contact angle between the first test liquid and the solid phase and θ_2 is the contact angle between the second test