International Journal of Pharmaceutics 524 (2017) 141–147

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Effects of amine modification of mesoporous magnesium carbonate on controlled drug release

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ARTICLE INFO

Article history:
Received 18 January 2017
Received in revised form 24 March 2017
Accepted 25 March 2017
Available online 27 March 2017

Keywords:
Ibuprofen
Mesoporous
Magnesium carbonate
APTES
Controlled release
Surface functionalization

ABSTRACT

(3-Aminopropyl)triethoxysilane (APTES) was used to modify the surface of mesoporous magnesium carbonate (MMC). The as-synthesized MMC had an average pore diameter of ~5 nm, but amine grafting occurred preferentially on the walls of the largest MMC pores. Analysis of ibuprofen (IBU) loading and release showed that IBU remained stable in the amorphous phase in all the MMC and modified MMC samples. The kinetics of IBU release from the modified MMC were assessed and used to evaluate the effects of the different functional groups. The release rate showed that the release of IBU could be controlled by adjusting the amine surface coverage of MMC and also by changing the surface groups. It was concluded that the interaction between the grafted functional groups in the modified MMC and the OH in the carboxyl groups of IBU was the most important factor for prolonging the release of the drug. These results are expected to lead to investigation of other as yet unexplored applications for MMC, including using it as a plastic additive and for gas separation.

1. Introduction

Due to its ease of administration, low costs and high patient compliance, oral drug delivery is the most convenient and preferred route of administration in many therapeutic areas (Yu et al., 1996). One of the principal goals of oral drug administration is to ensure extensive, reliable bioavailability of the active pharmaceutical ingredients (APIs).

In 1995, the Biopharmaceutics Classification System (BCS) was introduced to classify APIs with respect to their aqueous solubility and membrane permeation. Recent advances in synthesis methodology, particularly for organic molecules, have allowed the development of new Class II drug candidates. These Class II drug candidates permeate the intestine well but have poor aqueous solubility. This poor solubility is one of the fundamental critical properties limiting the bioavailability of the drug after oral administration, and it has been estimated that it has impeded the formulation of more than 70% of newly developed substances (Vasconcelos et al., 2007). Some novel drug delivery systems appear to enhance the bioavailability of Class II APIs by improving their dissolution rate. These include micro-emulsions and self-emulsifying drug delivery systems, liposomal drug delivery systems and polymer-based drug delivery systems.

In addition to these methods, the application of nanotechnology in medicine has attracted a lot of attention in recent decades (Boisselier and Astruc, 2009; Moghimi et al., 2005). Various nanomaterials are now being widely investigated as potential drug carriers to facilitate controlled and targeted drug release. In comparison with organic lipids or polymer-based materials, inorganic nanoparticles have improved stability, are more controllable during synthesis and are easier to functionalize.

Since the late 1980s, mesoporous silica nanoparticles (MSNs) have attracted enormous interest with respect to their use in various bio-applications. Their most useful properties include their high surface area, adjustable particle size, tunable pore structure, and controllable surface chemical properties (Vallet-Regi et al., 2007). Of particular interest to drug development, it has been found that the dissolution of an API can be vastly improved if it is

Abbreviations: API, active pharmaceutical ingredients; APTES, (3-aminopropyl) triethoxysilane; BCS, biopharmaceutics classification system; BET, Brunauer-Emmet-Teller; BJH, Barrett-Joyner-Halenda; DFT, density functional theory; DSC, differential scanning calorimetry; ESCA, electron spectroscopy for chemical analysis; IBU, ibuprofen; ICP-OES, inductively coupled plasma-optical emission spectroscopy; IR, infrared; MMC, mesoporous magnesium carbonate; MSN, mesoporous silica nanoparticles; PTES, *N*-propyltriethoxysilane; S_{BET}, specific surface area; TGA, thermogravimetric analysis; XPS, X-ray photoelectron spectroscopy; XRD, X-ray diffraction.

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http://dx.doi.org/10.1016/j.ijpharm.2017.03.063
0378-5173/

loaded into the pores of MSNs in an amorphous state (Garcia-Bennett, 2011; Mellaerts et al., 2007; Vallet-Regi et al., 2007).

However, there are situations where the fast release of an API is not ideal, for example in the treatment of chronic symptoms such as those of rheumatoid arthritis, or rheumatic diseases. In these cases, it is necessary for the drug release/dissolution rate to be regulated (He and Shi, 2011; Rathbone et al., 2002; Slowing et al., 2008). To this end, the effects of amine modification of the MSNs on the release rate of the API have been tested. An aminosilane (typically (3-aminopropyl)triethoxysilane, APTES) is grafted on to the OH groups on the surface of the MSN. The interaction between the MSN and the incorporated drug particle is thus enhanced by the strong bonds (*e.g.* hydrogen bonds) formed between the amine groups on the modified MSN and the loaded drug. A number of studies have investigated the use of mesoporous silica modified with amine groups for sustained or controlled drug release; for example, (Ahmadi et al., 2014) found that the loading capacity of amine-modified SBA-15 nanoparticles was enhanced and the release of ibuprofen (IBU) was prolonged.

In this study, we attempted amine modification of the recently developed mesoporous magnesium carbonate (MMC) material. The synthesis of MMC was first reported by (Forsgren et al., 2013) in 2013. MMC is very porous, and has a high surface area and pore volume (Frykstrand et al., 2014). In addition, it interacts uniquely with water (Forsgren et al., 2013; Pochard et al., 2014, 2015), has antibacterial (Welch et al., 2016) and anticoagulant properties (Frykstrand et al., 2016), and is biocompatible (according to *in vivo* acute systematic toxicity and skin irritation tests as well as *in vitro* cytotoxicity evaluation) (Frykstrand et al., 2015). Investigation of MMC as a dissolution-enhancing drug carrier for poorly soluble substances (*e.g.* IBU and itraconazole) has shown promising results (Cheung et al., 2016; Zhang et al., 2014; Zhang et al., 2016a,b). Recent investigation of the nanostructure of MMC has shown that the average pore size can be controlled without the use of templates or surfactants (Cheung et al., 2016). In this study we investigated the possibility of modifying the surface of MMC by adding amine groups, in order to further improve the versatility of this material. We investigated whether grafting the amine (APTES) onto the surface of MMC can be used to control the release rate of loaded IBU and examined the effect of varying amine coverage. IBU has a short biological half-life (Rainsford, 2013) which makes prolonged release of it desirable; the goal is to have an initial burst release followed by a slow release to sustain the pharmacological effect for a longer period of time. It has previously been shown that using lipids, prolonged release of IBU can be achieved both *in vitro* and *in vivo* (Lamprecht et al., 2004). The effects of APTES-modified MMC were compared with those of *N*-propyltriethoxysilane (PTES)-modified MMC. PTES is very similar in structure to APTES, but instead of the amine groups it has a CH_3 group.

2. Experimental

2.1. Synthesis and surface modification of MMC

MMC was synthesized as described previously (Cheung et al., 2016). Briefly, 20 g of MgO (~325 mesh, Sigma-Aldrich) was dispersed in 300 mL of methanol (99.9% HPLC grade, J.T. Baker) by stirring at room temperature in a pressurized glass reaction vessel under 4 bar of CO_2 pressure for 48 h. Unreacted MgO was removed from the reaction mixture by centrifugation. The obtained reaction gel was dried into a powder under mechanical stirring at room temperature in a well-ventilated area. The average pore diameter of the resultant MMC was about 5 nm.

APTES was grafted onto the surface of the MMC particles under reflux. Prior to the experiment, all glassware was heated to 150 °C overnight, and the system was flushed with nitrogen gas during both the setup and the experiment to maintain an inert atmosphere. A drying tube packed with a drying agent and sealed with glass wool was attached to the top of the condenser to prevent moist air from entering the system and then all the other outlets were thoroughly sealed. MMC (5 g) was dispersed in anhydrous toluene (300 mL) in a three-necked round-bottom flask and then slowly heated in an oil bath to 110 °C. When the temperature had stabilized, APTES was added to the mixture (1–43 mmol/g) and the setup was left under reflux for 24 h. The mixture was allowed to cool and the modified MMC was then filtered off, washed with ethanol (2×50 mL) and dried overnight at 70 °C. The extent of APTES coverage was calculated using data obtained from CHN analysis and inductively coupled plasma-optical emission spectroscopy (ICP-OES, performed by MEDAC Ltd. UK; ICP-OES data are provided in the Supporting information). PTES modification of MMC was carried out using the same methods.

2.2. Characterization of amine-modified MMC

Powder X-ray diffraction (XRD) patterns were recorded using a Bruker D8 Twin Twin diffractometer (Billerica, Massachusetts, USA) with Cu–K_α radiation ($\lambda = 1.54$ Å) for $2\theta = 10.0$–$80.0°$ at room temperature. The instrument was set to operate at 45 kV and 40 mA. Thermogravimetric analysis (TGA) measurements were carried out using a Perkin Elmer TGA 7 instrument (Waltham, Massachusetts, U.S.); the samples were heated in air from room temperature to 850 °C at a heating rate of 5 °C min^{-1}. The morphology of the samples was examined using Zeiss LEO 1550 and 1530 electron microscopes (Oberkochen, Germany; operated at 2 kV), and an in-lens secondary electron detector was used for imaging. The specimens were mounted on aluminum stubs with double-sided carbon tape and were coated with Pd/Au prior to analysis to avoid charging effects. Differential scanning calorimetry (DSC) experiments were performed on a Q-2000 DSC instrument (TA Instruments, New Castle, United States) at a heating rate of 5 °C min^{-1} from −35 to 250 °C. Sample weights ranged from 4 to 6 mg, and all samples were sealed in aluminum pans for analysis.

The X-ray photoelectron spectroscopy (XPS) experiments were conducted on a Phi Quantum 2000 scanning electron spectroscopy for chemical analysis (ESCA) microprobe instrument. Prior to analysis, the samples were sputter-cleaned using argon ions for 10 min at 200 V to remove surface-adsorbed contamination. A full spectrum was recorded, along with energy-resolved spectra for Mg2p, Si2p and N1s. During data acquisition, an electron beam of 20 mA was used with argon ions to neutralize the non-conducting sample. The peak fitting data were obtained with CasaXPS software, the curves were fitted using Gaussian-Lorentzian functions, and the background was subtracted using a Shirley function. The spectra were calibrated against the C1s peak at 284.5 eV for adventitious carbon.

Infrared (IR) spectra were obtained using a Varian 670-IR Fourier transform IR spectrometer (Santa Clara, USA) coupled with a Varian 670-IR IR microscope and a Linkam THM-600 (Tadworth, UK) heating stage (room temperature to 600 °C). The sample was put on a small piece (0.5×0.5 cm^2) of clean aluminum foil and placed on the heating stage. With this setup, the IR beam goes through the sample, is reflected by the aluminum foil, and is then detected by a mercury-cadmium-telluride (MCT) detector. The samples were heat-treated to 150 °C *in situ* under dry nitrogen (using gas purged from the spectrometer/microscope system) to remove adsorbed water before data collection. Transmission-based IR spectra of the water-free samples were recorded for a sample area of 100×100 μm^2 (600–4000 cm^{-1} with 4 cm^{-1} resolution). 128 background spectra were recorded and accounted for. The sample spectra are reported as signal averages of 128 scans.