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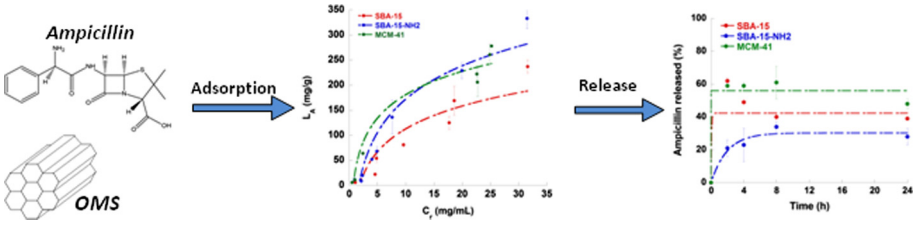
Adsorption and release of ampicillin antibiotic from ordered mesoporous silica

Valentina Nairi, Luca Medda, Maura Monduzzi *, Andrea Salis *

Department of Chemical and Geological Sciences, University of Cagliari-CSGI and CNBS, Cittadella Universitaria, S.S. 554 bivio Sestu, 09042 Monserrato, CA, Italy

GRAPHICAL ABSTRACT



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ABSTRACT

In this work the adsorption and the release of ampicillin - a β-lactam penicillin-like antibiotic - from MCM-41, SBA-15, and (amino functionalized) SBA-15-NH_2 ordered mesoporous silica (OMS) materials were investigated. The silica matrices differ for their pore size (SBA-15 vs. MCM-41) mainly, and also for surface charge (SBA-15 and MCM-41, vs. SBA-15-NH_2). OMS samples were characterized through small-angle X-rays scattering (SAXS), transmission electron microscopy (TEM), N_2 adsorption–desorption isotherms, Fourier transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), and potentiometric titrations. The quantification of immobilized and released ampicillin was monitored by mean of UV–Vis spectroscopy. Experimental adsorption isotherms evidenced that ampicillin's loading is not related to the pore size (d_{BJH}) of the adsorbent. Indeed the maximal loadings were 237 mg/g for SBA-15 (d_{BJH} = 6.5 nm), 278 mg/g for MCM-41 (d_{BJH} = 2.2 nm), and 333 mg/g for SBA-15-NH_2 (d_{BJH} = 5.6 nm). Loading seems, instead, to be related to the surface charge density (σ) of the sorbent surface. Indeed, at pH 7.4 ampicillin drug is negatively charged and likely prefers to interact with SBA-15-NH_2 ($\sigma_{SBA\text{-}15\text{-}NH2}$ = +0.223 C m^{-2}) rather than the slightly negatively charged silicas ($\sigma_{SBA\text{-}15}$ = −0.044 C m^{-2} and $\sigma_{MCM\text{-}41}$ = −0.033 C m^{-2}). Similarly, ampicillin release is affected by interfacial interactions. Indeed, we found a burst release from pure silica samples (SBA-15 and MCM-41), whereas a sustained one from SBA-15-NH_2 sample. We explain this behavior as a result of an attractive interaction between the protonated amino group of SBA-15-NH_2 and the negatively charged carboxylate group of ampicillin. In summary, in order to obtain a sustained drug release, the chemical nature of the matrix's surface plays a role which is more important than its textural features. SBA-15-NH_2 matrix is hence a suitable candidate for local sustained release of antibiotic drugs.

1. Introduction

Osseointegration was discovered in 1969 when Branemark observed that a piece of titanium inserted in a rabbit bone was

* Corresponding authors.
E-mail addresses: monduzzi@unica.it (M. Monduzzi), asalis@unica.it (A. Salis).

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not easily removed because anchored in the tissue [1]. The osseointegration process begins after the surgical insertion of an implant and is possible when the material is biocompatible, and allows for the spontaneous formation of hydroxyapatite layers [2]. However, after the implant insertion inflammatory processes (as periimplantitis) can occur [3]. This can cause the loss of the supporting bone [1] and different types of osteomyelitis [4]. These diseases can be treated with systemic administration of antibiotic or antiinflammatory drugs (via injection or ingestion) to prevent necrosis and bone neoformation that can degenerate in a chronic state [4,5]. This type of antibiotic therapy is highly inefficient. Indeed, only a low amount of drug can reach the infected region, so that the therapy needs to be repeated several times. Moreover, large amounts of administrated drugs can cause several drawbacks such as sensitivity, bacterial resistance, or superinfections. The proposed solution to all these problems is the *'in situ'* drug administration [5,6]. Nowadays different materials - i.e. antibiotic-impregnated cements, pastes, powders, degradable sponges or fleeces - are used in orthopedic surgery [7]. Nevertheless, only few nanomaterials can both easily be osseointegrated and slowly release antibiotic or anti-inflammatory drugs [5,8–11].

Ordered mesoporous silicas (OMSs), firstly synthesized in the early 90s [12,13], are interesting matrices for drug delivery [4,14–23]. Relevant features of OMSs are the high surface area (up to 1000 m^2/g), the narrow distribution of the pores size (2–30 nm), the high pore volume (1–3 cm^3/g) and the possibility to introduce several types of surface functional groups [24–30]. Moreover, OMSs display high biocompatibility [19,31–34] and allow for osseointegration if placed in a simulated body fluid [9,11]. All these features make OMSs very interesting matrices for biomedical applications as depot carriers for *'in situ'* controlled drug release. The use of OMS for drug delivery, dates back to 2001, when Vallet-Regì et al. studied the immobilization of ibuprofen on MCM-41 [35]. After that pioneering work the drug-loading capacity, and the sustained drug release from OMSs (i.e. MCM-41 and SBA-15) with different antibiotic or anti-inflammatory drugs - i.e. ibuprofen [36–38], gentamicin [39] and amoxicillin [25,40,41] - were widely investigated. Moreover, those studies showed how to modulate the drug loading and the release kinetics by functionalizing the surface of OMS samples [14,17,25,36,37,42,43], or by changing the pH, at which the drug loading is carried out [14,38,42,44,45].

Ampicillin is a penicillin-like molecule belonging to the class of β-lactam antibiotics, useful for the treatment of infections mediated by both gram-negative and gram-positive bacteria [5,7]. Ampicillin is usually administered in combination with sulbactam [46–48], a powerful and highly specific inhibitor of β-lactamases [49]. In particular, the therapeutic ampicillin dosage is 1.5–12 g/day for adults and 150 mg/kg/day for children [46]. After the administration, the maximal concentration of ampicillin in blood serum mainly depends on the patient's age. For adults (from 20 to 65 years) who have been administered with 2 g of ampicillin, the maximal measured concentration is about 80–110 μg/mL [50]. While for children (from 1 to 12 years) a dose of 40–80 mg/kg every 6 h results in an ampicillin concentration of 177–200 μg/mL [51]. Due to its high purity and low cost, ampicillin can be used as a model drug for a better understanding of the processes that regulate the adsorption and the release of therapeutic molecules from OMS-based depot systems. Recently, the release of ampicillin from different materials - amorphous silica, calcium silicate, silica/polycaprolactone, and $xCaO{\cdot}SiO_2$ - was studied [5,52]. These studies showed that the rate of release is affected by the chemical composition of the used material. Singh et al. used silica-based nanotubes for the adsorption and release of ampicillin [53]. They found that both adsorption and release rates are determined by the pore size of the carrier.

The aim of this work is to understand which, between the textural features and the chemical nature of the surface, plays the most important role to address the adsorption and release phenomena of ampicillin antibiotic from ordered mesoporous silica. To this purpose we compared the behavior of three different OMS samples, namely, SBA-15, SBA-15-NH_2 and MCM-41. In particular, we investigated the effect of pore size (SBA-15 versus MCM-41) and surface charge (SBA-15 versus SBA-15-NH_2) toward ampicillin adsorption (isotherms and kinetics) and release in simulated physiological conditions.

2. Materials and methods

2.1. Chemicals

Tetraethoxysilane (TEOS, 98%), pluronic copolymer 123 (EO_{20}-$PO_{70}EO_{20}$), cetyltrimethylammonium bromide (CTAB, >99%), (3-aminopropyl)triethoxysilane (APTES, >98%), sodium hydroxide, hydrochloride acid (37%), ampicillin sodium salt, acetic acid (>99.7%), sodium acetate (>99%), sodium dihydrogen phosphate (99.0%), and sodium phosphate dibasic (≥99.5%) were purchased from Sigma-Aldrich (Milan, Italy). Standard buffers at pH 1, 4, 6, 9, and 10 were purchased from Hanna Instruments (Szeged, Hungary). All chemical reagents were used without further purification.

2.2. Synthesis and characterization of SBA-15, MCM-41, and SBA-15-NH_2 samples

SBA-15 and MCM-41 were synthesized according to the methods reported in Refs. [27,54,55] respectively. We just remind that the synthesis occurs with a cooperative templating mechanism between TEOS and either Pluronic copolymer 123 (SBA-15) or CTAB (MCM-41). The organic surfactants were removed by calcination at 550 °C for 5 h. The functionalized SBA-15-NH_2 was prepared using APTES through a post-functionalization method described in Ref. [27]. The resulting solid was filtered and washed with acetone and dried overnight under vacuum at room temperature.

All materials were characterized through N_2 adsorption–desorption isotherms (texture), SAXS and TEM (structure), FTIR (functional groups), potentiometric titrations (surface charge density, σ), and thermogravimetric analysis (TGA). Textural analysis was carried out on an ASAP 2020 instrument, by determining the N_2 adsorption/desorption isotherm at 77 K. Before analysis MCM-41 and SBA-15 samples were heated at 250 °C at a rate of 1 °C/min under vacuum for 12 h, while SBA-15-NH_2 was heated at 110 °C at the rate of 1 °C/min under vacuum for 24 h. The Brunauer-Emmett-Teller (BET) and Barrett-Joyner-Halenda (BJH) method, calculated from the desorption branch of N_2 isotherm, were used to calculate surface area, pore volume and pore size distribution respectively. Small-angle X-ray scattering (SAXS) pattern was recorded with a S3-MICRO SWAXS camera system (HECUS X-ray Systems, Graz, Austria), as elsewhere reported [27]. Thin-walled 2 mm glass capillaries were filled with the sample for the scattering experiments. The scattering patterns were recorded for 1 h. Transmission electron microscopy (TEM) images were obtained on a JEOL 100S microscope, finely ground samples were placed directly onto formvar-coated electron microscopy nickel grids. Fourier transform infrared (FTIR) studies were conducted with a Bruker Tensor 27 spectrophotometer equipped with a diamond-ATR accessory and a DTGS detector. A number of 256 scans at a resolution of 2 cm^{-1} were averaged from wave