Materials Science and Engineering C 59 (2016) 585–593

Contents lists available at ScienceDirect

Materials Science and Engineering C

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

Mesoporous silica sub-micron spheres as drug dissolution enhancers: Influence of drug and matrix chemistry on functionality and stability

Laura Brigo [a,b], Elisa Scomparin [c], Marco Galuppo [c], Giovanni Capurso [e], Maria Grazia Ferlin [c], Valentina Bello [d], Nicola Realdon [c], Giovanna Brusatin [a], Margherita Morpurgo [c,*]

[a] Department of Industrial Engineering and INSTM Padova RU, University of Padova, via Marzolo 9, 35131 Padova, Italy
[b] Micro System Technology RU, Center for Materials and Microsystems, Bruno Kessler Foundation, via Sommarive 18, 38123 Trento, Italy
[c] Department of Pharmaceutical and Pharmacological Sciences, University of Padova, via Marzolo 5, 35131, Padova, Italy
[d] Department of Physics and Astronomy Galileo Galilei, University of Padova, via Marzolo 8, 35131 Padova, Italy
[e] Helmholtz-Zentrum Geesthacht, Institute of Materials Research - Dept. of Nanotechnology, Max-Planck-Strasse 1, D-21502 Geesthacht, Germany

ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form 30 September 2015
Accepted 12 October 2015
Available online 17 October 2015

Keywords:
Mesoporous materials
Nanoparticles
Microparticles
Drug dissolution enhancement
Anticancer oral therapy
Sol–gel process

ABSTRACT

Mesoporous silica particles prepared through a simplified Stöber method and low temperature solvent-promoted surfactant removal are evaluated as dissolution enhancers for poorly soluble compounds, using a powerful anticancer agent belonging to pyrroloquinolinones as a model for anticancer oral therapy, and anti-inflammatory ibuprofen as a reference compound. Mesoporous powders composed of either pure silica or silica modified with aminopropyl residues are produced. The influence of material composition and drug chemical properties on drug loading capability and dissolution enhancement are studied. The two types of particles display similar size, surface area, porosity, erodibility, drug loading capability and stability. An up to 50% w/w drug loading is reached, showing correlation between drug concentration in adsorption medium and content in the final powder. Upon immersion in simulating body fluids, immediate drug dissolution occurred, allowing acceptor solutions to reach concentrations equal to or greater than drug saturation limits. The matrix composition influenced drug solution maximal concentration, complementing the dissolution enhancement generated by a mesoporous structure. This effect was found to depend on both matrix and drug chemical properties allowing us to hypothesise general prediction behaviour rules.

1. Introduction

Scarce solubility of bioactive compounds is an important issue in pharmaceutical sciences since it has a negative impact on bioavailability and efficacy. Given that poor solubility is a common feature for many active molecules, several approaches have been suggested to improve their dissolution. Most of these rely on colloidal complex systems that act by enhancing the local solubility of the complexed drug — e. g. inclusion complexes, microemulsions, self-emulsifying drug delivery systems, solid solutions and dispersions, and salt formation [1–6]. More recently, an alternative/complementary strategy to implement drug availability has originated from the use of mesoporous silica-based materials. Such inorganic powder materials are characterized by a very large surface area, allowing for the adsorption of large amounts of drugs, which display enhanced dissolution thanks to the stabilization of their amorphous state and the large surface area available for the process [7,8]. These materials were originally developed as catalysts by Mobile (MCM41 = Mobile Composition of Matter 41) [9] but their use has expanded to several other areas, including the pharmaceutical industry [8]. Since the pioneering work of the group of Vallet-Regi in 2001, several papers have demonstrated the usefulness of diverse types of mesoporous silica, prepared through different routes, in improving drug dissolution [7–15]. Mesoporous silica is characterized by a stable and rigid framework, an ordered pore network, a large surface area and a pore volume which can change depending on the type of template used in the synthesis [8,16–18]. The pore network is generated by the polymerization of silica around cetyltrimethyl ammonium bromide (CTAB-MCM-41) [9] or PPO (SB-15) [19] micelles and by successive template removal, achieving pore diameters in the 2–6 nm range for MCM-41 and 4–13 nm range for SBA-15.

Classically, these materials are obtained through a high pressure condensation step, which is followed by calcination to remove the organic template. The resulting powders have a non-homogenous shape, while the calcination step does not permit inserting organic functional residues during the synthesis process. As a consequence, if organic functional residues need to be inserted onto the silica surface additional synthetic steps [20] are to be performed.

Here we investigated the potentials of a kind of mesoporous MCM41 sub-micron sized particles obtained through a low temperature Stöber-

* Corresponding author.
E-mail address: margherita.morpurgo@unipd.it (M. Morpurgo).

http://dx.doi.org/10.1016/j.msec.2015.10.039
0928-4931/

like synthetic process [21–23], in which template removal is achieved through a HCl/EtOH washing procedure, bypassing calcination [24]. This method, which was introduced by Etienne [24] in 2001, not only generates mesoporous materials directly in round-shaped particles, but also allows inserting organic moieties in the silica network directly along the one step synthetic process. So far, this kind of matrix has not been investigated as a pharmaceutical excipient. In this work, the potential of these MCM41 materials has been addressed through a series of experiments in which we evaluated a) if and how the spheres are capable of acting as dissolution enhancers for poorly soluble drugs; b) if and how the presence of an alkylamino function in the silica network and the drug chemical properties (namely the hydrophobic, and ionisable residues) affect the drug adsorption and dissolution enhancement properties; and c) if the material's properties are preserved along storage.

To this end, we selected two poorly soluble drugs as model compounds: the first one is a cytotoxic compound, 7-phenyl-3*H*-pyrrolo [3,2-*f*]quinolin-9(6*H*)-one (MG-2477), characterized by high potency [25,26] but very low solubility. It is a non-ionic molecule and – as the majority of anticancer compounds – it is characterized by extremely poor solubility in an aqueous environment. Indeed, despite the strong biological activity of this class of compounds, their hydrophobic nature generally leads to poor aqueous solubility and low bioavailability. For this reason they are normally administered through the slow infusion of large volumes of low concentrated solutions. Recently, the oral administration of anticancer agents (anticancer oral therapy — AOT) has also been investigated and, indeed, there has been an increase in the number of approved oral drugs for cancer therapy. AOT is in principle more convenient and allows better patient compliance. However, in order for it to be successful, immediate bioavailability of the active compound after oral administration is necessary, thus necessitating improving the slow dissolution profile. In particular, MG-2477 is a powerful chemotherapeutic molecule, acting mainly through the inhibition of tubulin polymerization, that displays strong cytotoxicity towards fast replicating cells, but low toxicity for resting ones [25,26]. Its antiproliferative properties make it a good candidate for use in anticancer oral therapy, therefore justifying the search for an oral formulation strategy capable of improving its bioavailability after administration.

The second drug is ibuprofen ((RS)-2-(4-(2-methylpropyl) phenyl)propanoic acid), an acidic (pKa = 4.49) poorly soluble compound that has often been used as a model in mesoporous silica gel investigations [10,11,14,27,28]. The two drugs display opposite pH dependence in their solubility behaviour, namely ibuprofen is more soluble in a neutral–basic environment, whereas MG-2477 is more soluble in an acidic solution (see Supplementary data). By using in parallel these two drugs with both pure mesoporous silica and amino-functionalized mesoporous silica particles, we investigated the effect of both the drug and the matrix chemical properties on the drug adsorption and dissolution behaviour. In addition, we performed a preliminary investigation on the effect of storage on the stability of the matrices, before and after drug adsorption, in view of a potential industrial application.

2. Materials and methods

2.1. Materials and instrumentations

Hexadecyl-trimethyl-ammonium bromide (CTAB) (99+%) and tetraethoxysilane (TEOS) were obtained from ACROS (Geel, Belgium). Ammonia solution (NH_4OH) (30 wt.%), 3-aminopropyltriethoxysilane (APTES), and all other chemicals were purchased from Sigma-Aldrich (St. Louis, MO). Double-distilled grade water was used in all experiments, except for matrix erosion assays, which were carried out in ultra-pure water obtained by inverse osmosis (milli-Q grade). FUI-grade ibuprofen was obtained from FRANCIS (Varese, IT). Ibuprofen concentration in aqueous buffers was determined by UV–vis analysis (264 nm) (Varian Cary 50) on the basis of calibration curves measured for each investigated buffer. The detection limit was about 100 μg/ml.

MG-2477 was synthesized at the Department of Pharmaceutical and Pharmacological Sciences (Dr. Ferlin lab) of the University of Padua. MG-2477 is a strongly fluorescent compound and its concentration in solution was assessed by means of fluorescence measurements (λ_{exc} = 272 nm, 5 nm bandwidth, λ_{em} = 495 nm, 10 nm bandwidth) (Jasco FP 6200) on the basis of calibration curves experimentally obtained. The detection limit was below 100 ng/ml.

2.1.1. XRD

X-ray diffraction patterns (XRD) were registered on a Bruker AXS D8 Advanced X-ray (Bruker, Germany) diffractometer, with a copper Kα radiation (0.15418 nm). Angular scans in the 1.5–9° range were collected with a step size of 0.02° using 100 mg samples of mesoporous powder.

Fourier Transform Infrared (FT-IR) absorption spectra of mesoporous powders dispersed in KBr were recorded in the 4000–400 cm^{-1} range by Fourier transform infrared spectroscopy (FT-IR) (Jasco FT/IR-620.) with an accuracy of 4 cm^{-1}.

Surface area and porosity properties were calculated starting from nitrogen adsorption-desorption isotherms obtained at 77 K, using a Quantachrome Autosorb iQ. Samples were degassed at 120 °C for at least 12 h under vacuum (before starting data acquisition, all samples displayed a pressure variation lower than 5 mTorr in a 15 min interval). For each sample three different batches of powder were measured, obtaining definitely compatible results within the experimental error. Nitrogen absorption isotherm data were analysed by the BET (Brunauer–Emmett–Teller) method to retrieve the specific surface area [29], and the plots of the corresponding pore size distribution were obtained from the desorption branches of the isotherms by using BJH (Barrett–Joyner–Halenda) model [30] and from a NLDFT (non-linear density functional theory) model applied to the adsorption branches [31,32].

TEM analysis has been performed with a Jeol 3010, operating at 300 kV equipped with a Gatan slow-scan CCD camera (Mod. 794), in order to investigate the film structure. S-TEM analysis has been performed at CNR-IMM Institute (Bologna, Italy) with a field-emission gun (FEG) scanning microscope (FEI Tecnai F20 Super Twin) operating at 200 kV with an electron beam size of about 1 nm FWHM and equipped with an high-angle annular dark field (HAADF) detector.

2.2. Synthesis of mesoporous silica

Mesoporous silica particles were obtained at room temperature through the ammonia-catalysed hydrolysis of alkoxysilanes in the presence of CTAB as the template. A typical synthesis involved the dissolution of CTAB in a round bottom flask in a water:ethanol:30% ammonia (100:100:25 volume ratio) mixture, to a final concentration of 21 mg/ml (5.8 mM), followed by the addition of the alkoxysilane precursor(s). After 2 h stirring at room temperature, the resulting solution was centrifuged for solid precipitation. Powders were washed with water, then with absolute ethanol, dried under vacuum, and finally heated at 70 °C for 3 h. Template removal was performed suspending powders in a 1 M solution of HCl in ethanol (1 g/100 ml) and stirring for 24 h at room temperature. Such mixtures were centrifuged, the solvent removed, the powders dried under vacuum and analysed by FT-IR spectroscopy. This procedure was repeated until the characteristic CTAB IR absorption bands in the spectral range of 2900–2800 cm^{-1} progressively disappeared.

Two different types of powders were obtained: 1) a silica-based system, in which only TEOS was used as an alkoxysilane precursor ("T" formulation), and 2) an amino-functionalised silica-based matrix ("TA" formulation), in which TEOS and APTES were used as precursors in 90:10 M ratio. For the TA formulation, the two synthesis precursors were mixed together in a separate vessel prior to addition to the CTAB