Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Pharmaceutical Sciences 26 (2005) 365–373
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
www.elsevier.com/locate/ejps

Release evaluation of drugs from ordered three-dimensional silica structures

Isabel Izquierdo-Barba, África Martinez, Antonio L. Doadrio, Joaquin Pérez-Pariente, María Vallet-Regí *

Departamento de Química Inorgánica y Bioinorgánica, Facultad de Farmacia, Universidad Complutense, Pza, Ramón y Cajal s/n, ES 28040 Madrid, Spain

Received 11 January 2005; received in revised form 6 June 2005; accepted 21 June 2005
Available online 23 September 2005

Abstract

Cubic mesoporous structures with *Ia3d* symmetry, such as MCM-48 and large pore *Ia3d* material (LP-*Ia3d*), which present different pore size (3.6 and 5.7 nm, respectively), have been prepared, characterized and used as drug delivery systems. Ibuprofen and erythromycin have been chosen as drug models for delivery studies. The influence of the pore size at these structures has been studied and the results show that the delivery rate of drugs decreases with the pore size of the matrix. The influence of chemical nature of the pore surface on the delivery process has been also studied. In this case, the hydrophilic pore surface has been modified with hydrocarbon chains (C8 and C18 moieties) and the effect upon drug delivery of hydrophobic drugs like erythromycin has been studied. The results show a noticeable decrease of the delivery rate when the surface of the matrices is modified.

Keywords: Ordered mesoporous materials; Erythromycin; Ibuprofen; Three-dimensional matrices; Cubic structures; Functionalization

1. Introduction

Ordered mesoporous silicates, denoted M41S, have been the subject of much interest since they were first reported by Mobil researchers (Kresge et al., 1992). The synthesis and utilization of these materials have been investigated by many research groups because of their peculiar characteristics, such as a highly regular pore structure, uniform pore size, high surface areas and high thermal stability. These mesoporous materials are potential candidates for useful application in fields, such as catalysis, sorption, separation, optics, electronics, sensors, . . . (Stein, 2003; Monnier et al., 1993; Corma, 1997; Brunel, 1999). Recently, these ordered mesoporous materials had been used also as matrices in controlled drug delivery systems due to their high mesoporous volume which is usually close to 1 cm^3/g, and the very homogeneous pore size, which offers the possibility of embedding a large variety of organic molecules with therapeutic activity (Vallet-Regí et al., 2001, 2004; Ramila et al., 2003; Muñoz et al., 2003; Doadrio et al., 2004; Charnay et al., 2004; Horcajada et al., 2004; Lee et al., 2004). MCM-41 and SBA-15 silica structures which contain a hexagonal array of pores of ∼4 and ∼8 nm of diameter, respectively, have been successfully used as systems for the controlled release of drugs, such as ibuprofen, gentamicin and amoxicillin. These results suggest that several factors could affect the release profile of the hosted molecule, the pore size of the matrix and the nature of the host–guest chemical interaction among them.

In contrast with the unidirectional channels present in both MCM-41 and SBA-15 (Zhao et al., 1998), cubic structures with space group *Ia3d* (Kaneda et al., 2002; Sakamoto et al., 2004) have recently attracted much attention due to their unique penetrating bicontinuous channels networks which are very useful for applications requiring easy molecular accessibility and fast molecular transport. According to this

* Corresponding author. Tel.: +34 913941861; fax: +34 913941786.
E-mail address: vallet@farm.ucm.es (M. Vallet-Regí).

0928-0987/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2005.06.009

three-dimensional channel topology, cubic structures would also be attractive for developing systems aiming to release drugs in a controlled manner.

The syntheses of silica structures having cubic *Ia3d* symmetry both conventional MCM-48 and the large-pore counterpart have been reported (Kim et al., 1998; Che et al., 2003; Liu et al., 2002). They posses an ordered cubic arrangement of bidirectional mesoporous channels having ~3 and 6 nm of diameter, respectively. The large pore *Ia3d* has been synthesized using commercially available block-copolymer surfactant in strong acid media (Chen et al., 2003). It exhibits a pore size of ~6 nm of diameter, much larger than the 3.6 nm pore present in the MCM-48 structure. Indeed, the presence of micropores that connect the main bicontinuous channels has been evidenced. Moreover, the material possesses a wall thicker than that of MCM-48 structure, owing to its much larger unit cell. Therefore, the studies of these materials as drug delivery matrices will allow to determine the influence of pore size of the cubic structures as well as to compare them with unidirectional channel structure of similar pore size, like MCM-41 and SBA-15.

The interaction between mesoporous matrices and drugs is also decisive for designing controlled drug delivery systems for clinical applications. One of the characteristics of the mesoporous materials is the presence of a high concentration of silanol groups in the mesopores, which can be functionalized for the control of pore size and surface properties. The control of inner surface properties induced by such surface modification is required for the design of adsorption/desorption media for specific purposes. The first issue has been explored by using MCM-41 materials functionalized with aminopropyl groups and the results obtained for the ibuprofen delivery have been reported elsewhere (Muñoz et al., 2003; Ramila et al., 2003). Another possible chemical change is the modification of the surface by silanes with long hydrocarbon chains.

Several authors have studied the effect of the modification of amorphous silica gel with alkyl chains in delivery systems like dexmedetomidine and phytonadiona (Otsuka et al., 2000; Koteuso et al., 2001). This is a standard procedure to decrease the pore size and hydrophilic character of silica surfaces. Therefore, the incorporation of long hydrocarbon moieties is expected to increase the hydrophobic interaction between the matrix and the hydrophobic drugs, and hence the release profile would also be affected.

Ibuprofen and erythromycin have been chosen as drug delivery models. The ibuprofen, a molecule of hydrophilic characteristics having anti-inflammatory activity, was selected as a model drug due to its low solubility in water and its small molecular size; therefore, it is suitable for incorporation within the pores of MCM-48 and LP-*Ia3d* silica materials. The erythromycin belongs to the macrolide family of bactericide drugs. Simple modelling calculations (Chem Finder for Office, 2004, Cambridge Soft) show isolated erythromycin to adopt a quasi-globular conformation and it is larger than the ibuprofen molecule (see Fig. 1).

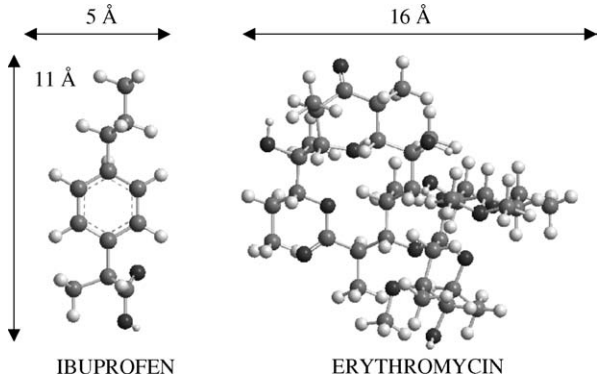

Fig. 1. Three-dimensional pictures of ibuprofen and erythromycin molecules.

In this work, a study of ibuprofen and erythromycin delivery from mesoporous matrices with cubic structure (*Ia3d* symmetry) (MCM-48 and large pore *Ia3d* material) that present different pore size (3 and 6 nm, respectively) is reported.

In order to imprint hydrophobic character to these matrices for improving their interaction with hydrophobic drugs (for example, erythromycin), a modification of the pore wall surface has been carried out. For this purpose, the Si–OH groups present in the pore wall have been functionalized with alkyl chains (C8 and C18).

2. Materials and methods

2.1. Preparation of materials

Mesoporous materials with cubic structure and different pore size denoted as MCM-48 and LP-*Ia3d* have been synthesized.

The MCM-48 material was prepared according to the method reported by Kim et al. (1998). 7.5 g of colloidal silica Ludox AS40 (40 wt% of SiO_2; Aldrich) was preheated at 343 K in a Erlenmeyer flask. An aqueous solution of 1 M NaOH was then slowly added to the heated Ludox with a vigorous magnetic stirring, to obtain a mixture with molar composition 0.25 Na_2O:1.00 SiO_2:12.5 H_2O. The resultant mixture became a clear sodium silicate solution after stirring continuously for 1 h at 343–353 K. After that, the solution was cooled to room temperature.

Hexadecyltrimethylamonium bromide (HTABr, Aldrich) (18.22 g) was dissolved in a mixture of distilled water and ethanol to give a solution of molar composition 1.0 HTABr:5.0 EtOH:120 H_2O. The above silica source was added to this surfactant solution at room temperature dropwise under vigorous magnetic stirring. The resulting gel mixture, with a molar composition of 1.4 SiO_2:1.0 HTABr:0.35 Na_2O:5.0 EtOH:144 H_2O was heated statically for 5 days at