Journal of Colloid and Interface Science 434 (2014) 218–225

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

www.elsevier.com/locate/jcis

# Modulating *in vitro* release and solubility of griseofulvin using functionalized mesoporous silica nanoparticles

Siddharth Jambhrunkar [a], Zhi Qu [a], Amirali Popat [b,c], Surajit Karmakar [a], Chun Xu [a], Chengzhong Yu [a,*]

[a] Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD 4072, Australia
[b] The School of Pharmacy, The University of Queensland, Brisbane, QLD 4072, Australia
[c] Mucosal Diseases Group, Mater Research Institute – The University of Queensland, Translational Research Institute, 37 Kent St, Woolloongabba, QLD 4102, Australia

ARTICLE INFO

*Article history:*
Received 25 May 2014
Accepted 9 August 2014
Available online 20 August 2014

*Keywords:*
Mesoporous silica
Surface charge
Hydrophobicity
Griseofulvin
Drug release
Solubility

ABSTRACT

Mesoporous silica nanoparticles (MCM-41) were used as a carrier system to study the influence of surface charge and hydrophobicity on solubility and *in-vitro* drug release behavior of Griseofulvin, a potent antifungal drug with low water solubility. Bare MCM-41 with a pure silica composition, MCM-41 after amino functionalization (MCM-41-$NH_2$) and methyl functionalization (MCM-41-$CH_3$) were used in this study followed by encapsulation of griseofulvin. Various characterization techniques have been employed to confirm the successful drug loading inside the nanopores. The surface functionalization on MCM-41 is found to have significant effect on griseofulvin's *in vitro* release and solubility. Both negatively and positively charged surface showed enhancement in solubility and drug release of griseofulvin. However, the hydrophobic modification led to a retarded drug release, which is caused by the poor wetting effect in the case of MCM-41-$CH_3$ nanoparticles.



## 1. Introduction

Relatively higher proportions of newly emerging drug molecules from high throughput screening are hydrophobic (poor aqueous solubility), posing a major obstacle in clinical applications [1,2]. Solubility enhancement is traditionally achieved by various processes such as salt formation, co-solvents, complexation, and solid dispersion to name a few. These techniques, however, suffer from uncontrolled precipitation, solvent toxicity and stability concerns [3–6]. The main emphasis for solubility enhancement till date in the pharmaceutical fraternity relies on particle size reduction, as reflected by Ostwald–Freundlich equation [7]. Particle size reduction techniques such as comminution, micronization and spray drying are conceived to be efficient, reproducible and economically viable. However, this process leads to induction of physical stress on drug particles, tendency to agglomerate on standing and is inapt for thermolabile drugs. The development of effective carrier systems provides another pathway to enhance the drug solubility as well as to control the release profile. Several delivery systems such as surfactant complexes, liposomes, hydrogels, and polymeric nanoparticles have been developed but suffer from synthesis complexity and poor biological stability [8–10].

Mesoporous silica nanoparticles (MSNs) such as MCM-41 [11] and SBA-15 [12], with unique features of ordered structure, high surface area, large pore volume, tunable pore size, ease of surface functionalization [13] and biocompatibility have attracted increased attention in drug delivery field since the last decade [14]. The influence of pore size of MSNs has been studied for drug, peptide, protein and enzyme immobilization [15–18]. MSNs provide an adjustable pore size at nanoscale for the confinement of drug molecules and hence the size of drug particles can be reduced at nanoscale leading to solubility enhancement [19–21]. MSNs surface functionalisation also plays an important role in drug encapsulation and release [22,23]. Surface functionalized MSNs with 3-aminopropyl triethoxysilane help in achieving high drug loading and slower drug release [13,22,24]. MSNs modified by 2-cyanopropyltriethoxysilane and mercaptopropyltrimethoxysilane improved drug efficacy by achieving high cell specificity when tested in cell lines [25,26]. MSNs were modified to obtain hydrophobic surface using 1, 1, 1, 3, 3, 3-hexamethyldisilazane, and ibuprofen release test showed that the drug release was inversely proportional to the degree of hydrophobicity [27]. Despite numerous studies highlighting the significance and advantage of MSNs for enhancing drug solubility and the effect of surface functionalization of MSNs on drug release, there is no study to compare the influence of surface charge and hydrophobicity on both drug solubility and drug release.

* Corresponding author. Fax: +61 7 3346 3973.
*E-mail address:* c.yu@uq.edu.au (C. Yu).

http://dx.doi.org/10.1016/j.jcis.2014.08.019
0021-9797/

Griseofulvin (GRIS), a potent antifungal drug, belongs to BCS class II and is slightly soluble in water [28]. Several studies have been reported addressing the solubility and/or dissolution enhancement of griseofulvin using processes such as solid dispersions [19,29], complexation with cyclodextrin [30], microemulsions [31] and deformable membrane vesicles [28]. In a recent study, an inclusion complex of griseofulvin – β-cyclodextrin was formed and grafted on the silica surface to study the adsorption kinetics, confirming the successful encapsulation of griseofulvin in β-cyclodextrin [32]. However, the drug release or solubility behavior was not reported. To date the encapsulation of GRIS inside MSNs has not been reported.

In this study, we report the influence of surface charge and hydrophobicity of MSNs on solubility and drug release behavior of griseofulvin in a series of MCM-41 materials (Fig. 1), including bare MCM-41, amino functionalized MCM-41 (MCM-41-$NH_2$) and methyl functionalized MCM-41 (MCM-41-$CH_3$). The surface modified MSNs were synthesized to obtain similar pore size to avoid the influence of pore size in further evaluations. Griseofulvin was encapsulated in the pore channels of MSNs by a simple rotavap technique. We studied the influence of surface chemistry on drug solubility and drug release by comparing negatively and positively charged MCM-41 with hydrophobic MCM-41-$CH_3$. To the best of our knowledge this is the first report to study the influence of surface modification of MSNs on griseofulvin's *in vitro* release and solubility.

## 2. Experimental

### 2.1. Materials

Cetyl trimethylammonium bromide (CTAB), tetraethoxy orthosilicate (TEOS), (3-aminopropyl)triethoxysilane (APTES), chlorotrimethylsilane (TMCS), sodium lauryl sulfate (SLS) and griseofulvin (GRIS) were purchased from Sigma–Aldrich. Reagent grade sodium hydroxide (NaOH) was received from ChemSupply. Methanol AR and Toluene were purchased from RCI labscan and Merck, respectively.

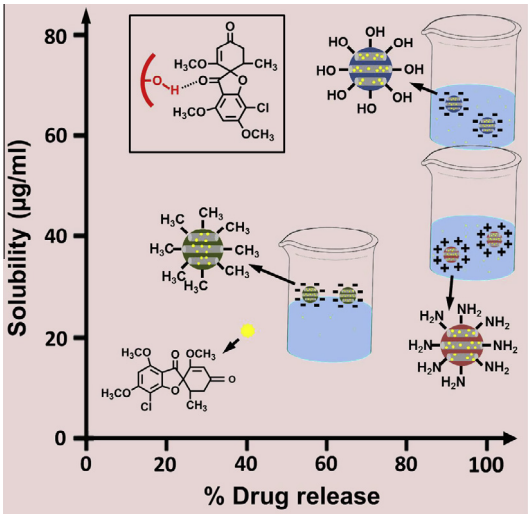


**Fig. 1.** A schematic representation comparing the solubility and *in vitro* drug release of griseofulvin from MCM-41-GRIS, MCM-41-$NH_2$-GRIS and MCM-41-$CH_3$-GRIS samples. Inset represents the binding of griseofulvin to the interior pore wall of MCM-41, MCM-41-$NH_2$ and MCM-41-$CH_3$ samples. Free drug is represented in yellow color. Inset shows the binding of GRIS in MCM-41. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

### 2.2. Characterization

X-ray diffractograms (XRD) and wide angle XRD (WXRD) were recorded on a Rigaku Miniflex X-ray diffractometer with Fe-filtered Co radiation ($\lambda$ = 1.79 Å). Transmission Electron Microscopy (TEM) images were obtained with a JEOL 1010 microscope operated at 100 kV. Scanning electron microscopy (SEM) characterization was performed using Hitachi SU3500 operated at 5 kV and working distance of 5.5 cm. Nitrogen physisorption measurements were carried out at −196 °C by using a Micromeritics Tristar II 3020 system. MCM-41, MCM-41-$NH_2$ and MCM-41-$CH_3$ samples were degassed at 100 °C whereas griseofulvin encapsulated MCM-41 (MCM-41-GRIS), MCM-41-$NH_2$ (MCM-41-$NH_2$-GRIS) and MCM-41-$CH_3$ (MCM-41-$CH_3$-GRIS) samples were degassed at 50 °C overnight on a vacuum line. The pore-size distribution was measured from the adsorption branch of the isotherm using BJH model. Fourier transform infrared (FTIR) spectra were recorded on ThermoNicolet Nexus 6700 FTIR spectrometer equipped with Diamond ATR (attenuated total reflection) Crystal. For each spectrum, 128 scans and 4 $cm^{-1}$ resolution was applied over the range of 400–4000 $cm^{-1}$. Particle size and zeta potential were measured on a Malvern Zetasizer Nano-ZS. The thermogravimetric analysis (TGA) was performed by a Setaram TG92 instrument with a heating rate of 5 °C/min in air flow. Griseofulvin concentration was determined using UV–VIS spectrophotometer (Shimadzu UV-2450).

### 2.3. Synthesis of MCM-41

MCM-41 synthesis was performed with slight modification to a previously reported method by Yang et al. [33]. Briefly, 1.0 g of CTAB was dissolved in 480 g of deionized water under stirring at room temperature followed by addition of 3.5 mL of NaOH (2 M) and increasing the temperature to 80 °C. Then, 6.7 mL of TEOS was added into the mixture as a silica source at 80 °C under continuous stirring for an additional 2 h. The resultant product was collected by filtration and dried at room temperature. The as-synthesized MCM-41 was divided into three parts. One-third of the material was subjected to solvent extraction process for the removal of surfactant template and labeled as MCM-41. Another one-third of the material was solvent extracted and used for the preparation of methyl modified MCM-41. The remaining as-synthesized material was utilized for the synthesis of amino modified MCM-41.

Surfactant template was removed by a reported method by Lu et. al. [34] with some modification. 0.3 g of as-synthesized material was added to 32 mL of methanol under stirring and the temperature was increased to 60 °C. To this suspension, 2.0 mL of conc. HCl was added and kept under continuous stirring for 36 h. Later the suspension was centrifuged and washed with methanol twice to ensure complete surfactant removal. The final product was dried at 50 °C overnight to be used for further studies.

### 2.4. Synthesis of amino modified MCM-41-$NH_2$

Amino modification was performed according to a published report with slight changes [35]. Typically, 0.4 g of as-synthesized MCM-41 was added to 25 mL of methanol under stirring at RT followed by the addition of 1.5 mL of APTES. The suspension was stirred overnight at RT. The amino functionalized MCM-41 with surfactant template still present in it was then retrieved by centrifugation and washed with methanol twice. The material was then dried at 50 °C overnight before subjected to solvent extraction process for surfactant template removal as described earlier.