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Organo-bridged silsesquioxane incorporated mesoporous silica as a carrier for the controlled delivery of ibuprofen and fluorouracil

Fozia Rehman [a,b,*], Khalid Ahmed [a], Abdur Rahim [a,b,*], Nawshad Muhammad [b], Sarah Tariq [b], Usaid Azhar [b], Asif Jamal Khan [c], Zaib us Sama [d], Pedro L.O. Volpe [a], Claudio Airoldi [a]

[a] Institute of Chemistry, University of Campinas, UNICAMP, P.O. Box 6154, 13084-971 Campinas, SP, Brazil
[b] Interdisciplinary Research Centre in Biomedical Materials (IRCBM), COMSATS Institute of Information Technology, Lahore, Pakistan
[c] Shaanxi Key Laboratory of Earth Surface System and Environmental Carrying Capacity, College of Urban and Environmental Sciences, Northwest University, Xian 710127, China
[d] Department of Chemistry, Women University Swabi, KPK, Pakistan

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ABSTRACT

Mesoporous silica based drug carriers were synthesized and characterized by FTIR, NMR spectroscopy, elemental analysis, nitrogen adsorption, thermogravimetry, scanning and transmission electron microscopy and X-rays diffraction. Zeta potential was measured with zetasizer. The synthesized materials were tested as a drug carrier for ibuprofen, ibuprofen sodium dihydrate and 5 fluorouracil. Silica with long organic surface chains and ordered mesoporous network showed a high loading capacity for ibuprofen (22.0 wt%), ibuprofen sodium dehydrate (48.0 wt%) and 5 fluorouracil (9.4 wt%). The long hydrophobic chains enhanced the drug adhesion to the silica surface which eventually delayed the release of the drug and hence presented a sustained and controlled release profiles. The study suggests that the synthesized materials have potential as controlled drug release systems where prolonged drug therapeutic effects are required. This study also suggests that the 5 fluorouracil loaded nano-carriers in the form of films, mats or cream could be a potential candidate for skin cancer treatment formulations.

1. Introduction

Ordered mesoporous materials such as mesoporous silica (SiO_2) are becoming a research focus in the past few years due to its high surface area, pore volume, tunable pore size/structure and controlled particle size [1–4]. Such characteristics impart flexibility to the material for various technological applications, such as adsorption, drug delivery, catalysis and immobilization of functional entities [5–8]. The application of nanotechnology in medicine and more specifically in drug delivery systems is the main focus of present research [9]. The ordered mesoporous materials are used to facilitate the dose incorporation and duration of drug effect, to overcome the limitations such as repeated dosing, which cause inconvenience to the patients. Particle size, morphology, volume and pores geometry, all are the important parameters that determine the release of drug molecules form carriers. Recently, various drug delivery systems reported the use of porous silicates as drug carriers [10–12]. Previous studies were designed to demonstrate that these materials can release the biologically active substance in a controlled manner and found that these mesostructured carriers are the more effective matrix for the prolonged distribution of drug molecules [13–15].

SBA-15 is a well-known ordered mesoporous material due to its chemical, mechanical and thermal stability along with highly ordered hexagonal topology and large pores [16,17]. Furthermore, it has been found to exhibit better hydrophobicity as compared to other well-ordered mesoporous silica such as MCM-41, MCM-48 etc. [18] However, it has been reported that pure silica materials having free silanol groups on walls of mesoporous channels provide weak intermolecular hydrogen bonding with most organic groups that result in low drug loading capacity and initial fast release of therapeutic agents [19,20]. Thus, the use of these materials as a carrier of controlled drug delivery systems is limited. Modification of silica surface is an important feature that can lead to alteration of chemical properties, the inductance of optical properties, [21] surface hydrophobization, [22] excellent adsorption capacity, [23] sensitive to heat [24] and photocatalytic activity [25]. Previously it has been reported that surface alteration of mesoporous silicates through organosilane functionalization can increase the drug-silica interactions and ultimately could affect the degree of drug loading and release profile [26].

Ibuprofen is a recognized analgesic and anti-inflammatory drug having fast elimination rate, and the commonly prescribed drug by the

* Corresponding authors at: Interdisciplinary Research Centre in Biomedical Materials (IRCBM), COMSATS Institute of Information Technology, Lahore, Pakistan.
E-mail addresses: foziaics@yahoo.com (F. Rehman), abdurrahim@ciitlahore.edu.pk, foziaics@yahoo.com (A. Rahim).

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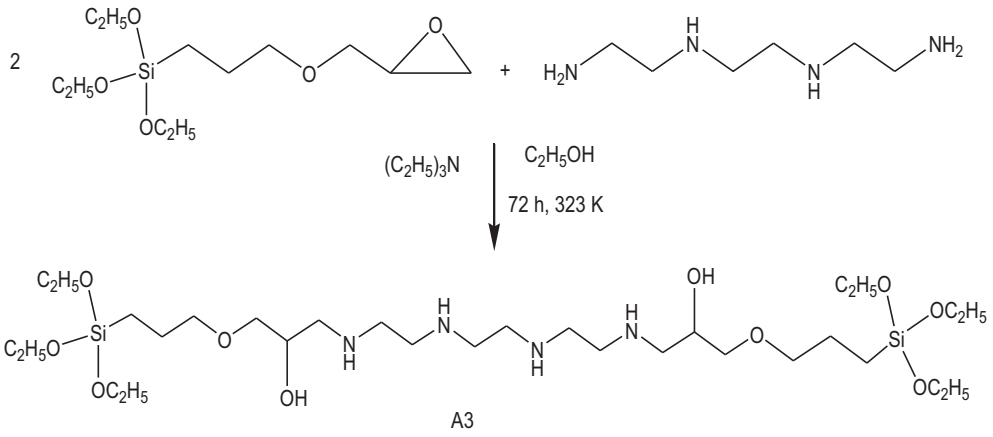

Fig. 1. Schematic representation of the formation of organic bridged silsesquioxanes for the surface modification of SBA-15.

Table 1
Percentages (%) of carbon (C) and nitrogen (N) and in mmol g^{-1} quantities, experimental ($C:N_{cal}$) and expected ($C:N_{exp}$), molar ratios and the degree of functionalization (δ) for SBA-15 and SBA-15GPTA.

Silica	C (%)	N (%)	C (mmol g^{-1})	N (mmol g^{-1})	$C:N_{EXP}$	$C:N_{CAL}$	δ (mmol g^{-1})
SBA-15	0.48	–	–	–	–	–	–
SBA-15GPTA	13.86	3.68	11.55	2.62	5.00	4.40	0.65

medical practitioner. Although Ibuprofen is extensively used in therapeutics, which is information about the physicochemical properties [27] and it has been controlled released efficiency on high surface area mesoporous materials [28]. Ibuprofen salts are well documented to be absorbed faster than the standard ibuprofen acid providing rapid onset of action [29,30]. A major antimetabolite, 5 fluorouracil, used widely against a variety of solid tumors, has erratic and unpredictable absorption from the gastrointestinal tract. It has a short half-life (10–30 min), requiring repeated administration [31,32]. Towards improved drug delivery, several nano-particulate carrier systems have been studied. Moreover, these systems may also significantly enhance the biological efficacy due to their high drug-load capacity [33]. The effectiveness of such drugs can be improved by loading drug into silica mesoporous channels to prevent the physiological degradation prior to absorption.

The present research focuses on the synthesis of SBA-15 mesoporous silica with hydrophobic organic functionalization to achieve controlled/sustained release of ibuprofen, its salt ibuprofen sodium dihydrate and anticancer drug 5 fluorouracil. Further, the modification of SBA-15 was done with long hydrophobic amine chains cross-linked with coupling/silylating agent. The synthesized materials were subjected to in vitro drug release investigations. The drug release profiles were studied and the conclusion was developed on sustained/controlled release capacity of the fabricated mesoporous silica materials. The schematic synthesis of functionalized silica is demonstrated in Fig. 1.

2. Experimental

2.1. Materials and methods

Analytical grade solvents/reagents were purchased and used as received. Tetraethylorthosilicate (TEOS), pluronic P123, triethylenetetramine (TETA), triethylamine, 3 glycidoxypropyltrimethoxysilane, ibuprofen (IUB), ibuprofen sodium dihydrate (IUB-Na), 5 fluorouracil (5-FU), sodium carbonate (Na_2CO_3), sodium chloride (NaCl), sodium sulphate (Na_2SO_4), potassium phosphate dibasic trihydrate ($K_2HPO_4 \cdot 3H_2O$), potassium chloride (KCl), calcium chloride ($CaCl_2$), sodium hydroxide (NaOH), tris(hydroxymethyl)amino methane ($NH_2C(CH_2OH)_3$ sodium bicarbonate ($NaHCO_3$), magnesium chloridehexahydrate ($MgCl_2 \cdot 6H_2O$) were Sigma Aldrich products. Xylene, ethanol, and hydrochloric were Synth products. Deionized water was used in this experiment.

2.2. Synthesis of mesoporous silica

To synthesize SBA-15 silica (2.0 g) [34], pluronic P123 (4.0 g) was dissolved in 24.0 cm^3 of deionized water and 60.0 cm^3 HCl

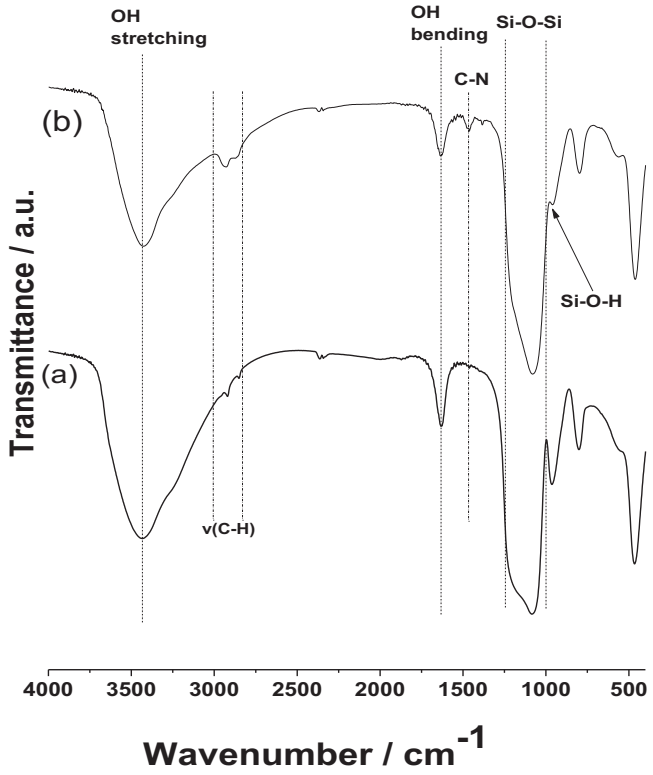

Fig. 2. IR spectra of (a) calcined SBA-15 and (b) SBA-15GPTA silicas.