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Polylactic acid coated SBA-15 functionalized with 3-aminopropyl triethoxysilane

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In the present study, a pH responsive polylactic acid coated SBA-15 functionalized with 3-aminopropyl triethoxysilane is reported. PLA has been coated on the functionalized SBA-15 by formation of amide linkage between amine functionalized SBA-15 and PLA. The amide linkage is confirmed by FTIR spectroscopic data. The materials are well characterized by FTIR, SEM, EDAX and XRD data. Using the PLA coated functionalized SBA-15 the controlled release of the drug ibuprofen has been studied. The successful delivery of ibuprofen has been achieved on the basis of its pH response.

Keywords: Mesoporous materials, Mesoporous silica, Silica, SBA-15, Functionalized SBA-15, Drug delivery

Mesoporous materials with regular geometries are drawing a lot of attention owing to their great potential in practical applications such as catalysis, adsorption, sensing, medical usage ecology, nanotechnology, chromatography, photonic devices, electronic devices, drug delivery and energy storage.[1-8] Over the past 30 years, there has been rapid growth in the area of drug delivery because drug delivery can bring solutions for both commercial and therapeutic problems associated with health care products. Apart from polymers and nanomaterials, microparticles,[9] porous materials,[10] smart materials like hydrogels[11] are also being used as drug carrier for drug delivery. Among the various materials used in drug delivery, mesoporous materials have other notable properties which include large surface area, adjustable pore diameters, modifiable surface properties and biocompatibility that are essential for drug delivery applications. Also, the pore size and pore volume of the mesoporous materials can be altered, and depending on the size and the surface chemistry of the pores, increased dissolution rate or sustained release of drugs can be achieved.[12,13]

The first report on ibuprofen loaded into mesoporous silica material MCM-41 was published by Vallet Regi in 2001.[14] Since then, numerous articles have been published on these materials with modified pore size and chemical modifications of the surfaces.[15] Because of the high solubility of highly porous (p-Si> 70%) materials in simulated body fluids (except in the simulated gastric fluid), many of them were used as drug carrier. Slowing *et al.*[16] discussed the advantages of using mesoporous materials for several drug delivery applications. The exciting progress on using mesoporous materials to penetrate various cell membranes in animal and plant cells is also reported.

Owing to the wide range of useful properties, these porous carriers have been used in pharmaceuticals for many purposes including the development of floating drug delivery systems, sustained drug delivery systems. Various types of pores like open, closed, transport and blind pores in the porous solid allow them to adsorb drugs and release them in a more reproducible and predictable manner.[10]

The triblock copolymer template made the mesoporous silica material, SBA-15, has large, controlled pore size and highly ordered hexagonal topology. These properties have opened the way to intriguing experiments inside the resulting channel structures.[17] By anchoring various functional groups on the internal surfaces, the sorption capacity and behavior of SBA-15 could be substantially altered. SBA-15 has a nanosilicate mesoporous composition which is prepared by surfactant templating mechanism. The structure of mesopore can be controlled by the volume of the precursors added such as copolymers and inorganic components.[18] The most commonly used structure directing copolymer is poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), commercially known as P123.

Mesoporous material SBA-15 has been used for both traditional drug delivery systems and implantable local drug delivery devices. These local drug delivery systems can be useful in bone tissue repair.[19] Song *et al.*[20] reported controlled drug delivery using functionalized SBA-15 in 2005.[20] SBA-15 materials were functionalized with amine groups by post-synthesis and one-pot synthesis. SBA-15

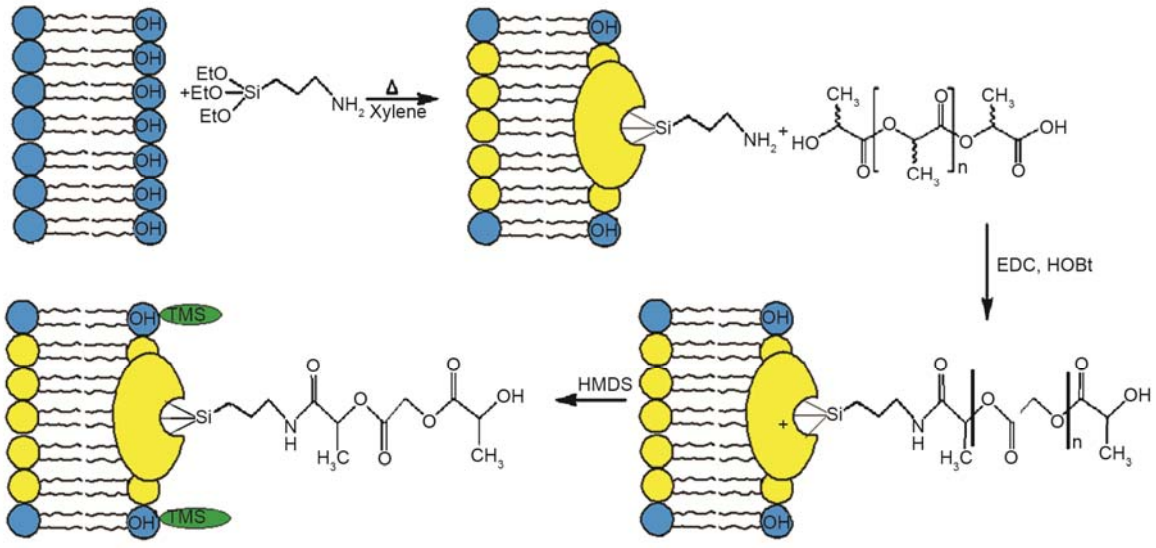
functionalized by one-pot synthesis is found to be more favorable for the adsorption and release of drug due to the balance of electrostatic interaction and hydrophilic interaction between the drug and the functionalized SBA-15 matrix. Michal Moritz *et al*. [21] reported the application of SBA-15 mesoporous material as carrier for drug formulation systems.

SBA-15 mesoporous material has been used as a matrix in three different drug formulations as powders, granules and tablets. Submicron particles with modified surface were synthesized by Shen *et al*.[22] by a simple one-pot synthesis approach and used as drug carrier for controlled release. They coated MgO on the surface of SBA-15 and used the material as a drug carrier in pH responsive drug delivery.[22]

Polymeric materials are very attractive for various applications due to ease of preparation and flexibility towards alteration of chemical and physical properties via molecular synthesis. In order to be used for controlled drug delivery, the polymer must be chemically inert and free of leachable impurities with appropriate physical structure, minimal undesired aging, and be readily processable. Some examples are poly(2-hydroxy ethyl methacrylate),[23] poly(N-vinyl pyrrolidone),[24] poly(methyl methacrylate),[25] poly(vinyl alcohol),[26] poly(acrylic acid),[27] polyacrylamide,[28] poly(ethylene-co-vinyl acetate),[29] poly(ethylene glycol),[30] poly(methacrylic acid),[31] polylactides (PLA),[32] polyglycolides (PGA),[33] polyanhydrides,[34] and polyorthoesters.[35] Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways.[36]

SBA-15 can be synthesized by the hydrothermal process through liquid templating mechanism.[37] It possesses ordered non-intersecting hexagonal channels. The walls of these mesoporous materials are amorphous silica. SBA-15 has got higher mechanical and thermal stability as compared to MCM-41 (Mobile Crystalline Material).[38]

In this work, for the synthesis of SBA-15, pluronic 123 (P123) was used as template material and tetraethylorthosilicate (TEOS) as silica source (Scheme 1). For drug encapsulation and coating, polymeric drug carrier (i. e., polylactic acid PLA) was chosen. Polymeric drug carriers are biocompatible, pH responsive, and target specific, zero release profile before reaching the target. The polymeric coating was required because unmodified MSNs cannot release the drugs. In human bodies, the pH is different in different parts and hence we can easily target systems by pH responsive polymeric coating. Ibuprofen was loaded on amine functionalized SBA-15. After the absorption of ibuprofen into the pores, it was centrifuged and the supernatant was analysed under UV visible spectroscopy at 263.5 nm to evaluate ibuprofen adsorbed on the silica nanoparticles. The ibuprofen loaded amine functionalized SBA-15 was



Scheme 1

coated with PLA by forming an amide linkage between –COOH group of PLA and $–NH_2$ group ibuprofen loaded SBA-15 (Scheme 1), leading to the successful incorporation of PLA in SBA-15. The amide formation was confirmed by FTIR spectroscopy. The peak at 1650 cm^{-1} in IR spectrum of the PLA coated SBA-15 confirmed the successful formation of amide linkage.

Experimental

All chemicals used, viz., tetraethyl orthosilicate $Si(OC_2H_5)_4$ (TEOS, >99%), pluronic 123 (MW = 5800), amino propyl triethoxysilane (APTES), polylactic acid, dichloromethane, DCC and DMAP (amide coupling agents), were of analytical grade. FTIR spectra were recorded on a RXI Perkin-Elmer spectrometer using KBr pellets. The surface morphology was studied by scanning electron microscopy (SEM) (JEOL JSM 6360, Japan). The structural characteristics were analyzed by XRD data recorded on a Shimadzu X-ray diffractometer (XRD 6000, Japan) using a monochromatic X-ray beam from CuKα radiation.

SBA-15 was synthesized by the procedure previously reported under hydrothermal conditions using a triblock organic copolymer as a template.[17] In the typical synthesis, triblock copolymer (4 g), poly(ethyleneoxide)-poly(propylene oxide)-poly(ethylene oxide) (EO20-PO70-EO20) (Pluronic P123, MW = 5800) was dispersed in doubly distilled water (40 g) and 2 *M* aqueous HCl (120 mL) was added with stirring at ambient temperature (35 °C) for 3 h. Finally, tetraethylorthosilicate (4 g) was added to the homogeneous solution with stirring at 40 °C for 24 h to form a gel. The resultant gel was allowed to stand at 100 °C for 48 h in a Teflon Parr reactor, which led to crystallization under static hydrothermal conditions. The white solid product was filtered off, washed with warm distilled water for several times, and dried at 150 °C overnight. The solid product obtained was calcined at 540 °C in air for 24 h to remove the organic template.

For the preparation of aminopropyltriethoxysilane functionalized SBA-15, a suspension of aminopropyl-triethoxysilane (APTES) (0.45 g, 2 mmol) and calcined SBA-15 (1 g) in toluene (20 mL) was refluxed with continuous stirring under an inert atmosphere for 24 h. The resulting mixture was cooled to room temperature, filtered, washed with dry toluene and diethyl ether, and then dried under vacuum at ambient temperature. The dried material was further subjected to soxhlet extraction with dry dichloromethane for 24 h to remove the unreacted APTES. Finally, the functionalized SBA-15 solid product was dried at 70–90 °C under vacuum for 12 h.

Next, ibuprofen was loaded into the pores of amine functionalized SBA-15. Amine functionalized SBA-15 (100 mg) was soaked in concentrated ibuprofen solution (30 mg mL^{-1}) in hexane. The solution was sonicated for 1 min in a bath sonicator and kept in a shaker for 24 h at room temperature. After the absorption of ibuprofen into the pores, it was centrifuged and the supernatant was analysed under UV visible spectroscopy at 263.5 nm to evaluate ibuprofen adsorbed on the silica nanoparticles.

For the preparation of PLA coated SBA-15, polylactic acid was dissolved in dichloromethane. DCC (Dicyclohexylcarbodiimide) and DMAP were used as coupling agent which helps in the formation of amide linkage between amine functionalized SBA-15 and PLA. Then the ibuprofen loaded SBA-15 was added to the above solution and stirred overnight. The resultant product was filtered and washed with water in order to remove the urea byproduct. The product was dried in oven at 100 °C.

Results and discussion

The SEM images of SBA 15 before and after PLA coating shows rod-like shaped structure (Fig. 1(a) and (b)). The irregularity in the shape of the particle may be due to the increase in temperature during the surfactant removal step. The morphological studies show that the SBA-15 retained the structure even after drug loading and PLA coating.

The ordered mesoporous structure was confirmed by XRD characterization (Fig. 2). The 100 and 200 reflections represent the presence of mesopore and also confirm the hexagonal array of pores. All the samples show a well resolved reflection, indicating excellent structural ordering. SBA-15 mesoporous molecular sieves exhibited narrow pore size distribution. This indicates that all the materials even after the modification with amine, exhibit a well ordered two-dimensional hexagonal structure with linear arrays of pores which are arranged in regular intervals.

From the high intensity peak from the 100 plane, it was confirmed that the pore is free of any particles or surfactant templates (Fig. 2(a)). After ibuprofen loading, the diffraction peak intensities become a little weaker (Fig. 2(b & c)), indicating the presence of organic molecules inside the mesopores. The pore

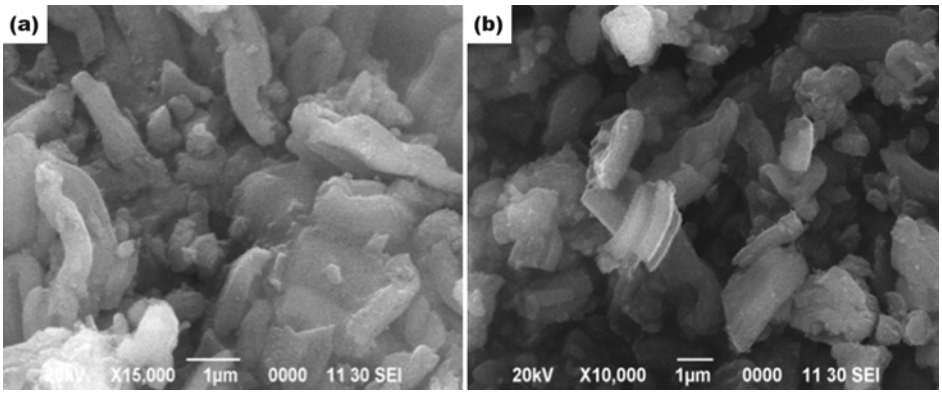


Fig. 1 — SEM images of functionalized SBA-15 before coating (a), and, (b) after PLA coating.

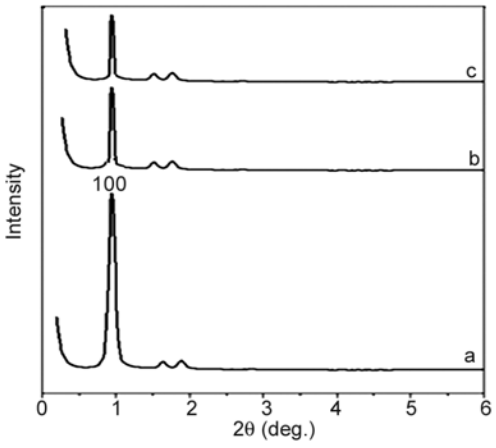


Fig. 2 — XRD patterns of (a) SBA-15 before coating, (b) SBA-15 after ibuprofen loading, and, (c) SBA-15 after PLA coating.

size of ~8 nm calculated from the XRD is found suitable for drug loading and other applications including catalysis.

From the SEM-EDAX analysis at various points of the sample, the loading of drug on PLA matrix was confirmed. The typical vibration modes of SBA-15 at 3328 cm^{-1} for OH and at ~1076 cm^{-1} for Si-O-Si and the sharp peak at 945 cm^{-1} for Si-OH are seen in the case of both pure SBA-15 and amine functionalized SBA-15. In the case of amine functionalized SBA-15, a small shoulder at 2934 cm^{-1}, ascribed to the CH stretching frequency of the aminopropylate triethoxy silane and a peak at 1515 cm^{-1}, due to the NH bending were observed. It is interesting to note that the intensity of the OH band significantly decreases after the end capping process, confirming that the free surface silanol groups present in the pore walls of ligand immobilized SBA-15 are capped with TMS groups.

To study the *in vitro* release of ibuprofen, ibuprofen loaded PLA coated mesoporous nanoparticles were mixed in different ranges of buffer solutions starting from pH 5 to 8 and shaken in a water bath maintained at 35 °C. In each trial, after a few minutes, aliquots were taken out, centrifuged and analyzed under UV visible spectroscopy at 263.5 nm. The PLA coated functionalized SBA-15 acts as a pH responsive shell, ensuring the release of the drug loaded under acidic conditions (Table 1). From Table 1 it is seen that the ibuprofen release was almost 100% within two hours. The release of drug was slow when the pH of the medium increased.This may be due to the protonation rate of amide nitrogen of the PLA coated functionalized SBA-15 under different pH conditions.

Table 1 – pH responsive drug release of ibuprofen by PLA coated functionalized SBA-15

No.	pH value	Time (h)	Drug released (%)
1	5	2	98
2	6	2	82
3	7	2	67
4	8	2	50

The main disadvantage is at undesirable pH, leaching will occur. Liu *et al.*[39] reported polyvinyl pyridine coated MSNs as a pH responsive drug delivery system. At high pH, this system formed a gel like structure stopping the drug release.[39] The drug ibuprofen release studies were carried out under different pH conditions. Mild acidic condition promotes protonation of amide NH leading to swelling of polymeric matrix. This resulted in the free release of drug molecules. Hence, altering pH can achieve a controlled release of the drug.

To conclude, a new method of coating PLA on amine functionalized mesoporous silica is reported. The drug ibuprofen release studies were carried out under different pH conditions. Mild acidic condition favours the successful release of the drug molecule.

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