



2-Chlorobenzoylthiourea-modified MCM-41 for Drug Delivery

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Abstract: Mesoporous 2-chlorobenzoylthiourea-modified MCM-41 (2-Cl-BT-MCM-41) was prepared for the first time and loaded with ibuprofen in a supercritical carbon dioxide (sC-CO₂) environment. 2-Cl-BT-MCM-41 was prepared and also characterized via XRD, FT-IR, SEM and BET techniques. The (100) and (110) reflections observed at low angle XRD show the mesoporous SiO₂ structure. The particule size of non-uniform spheres were observed at a range of 250-305 nm. BET surface areas were calculated as 1506 m² / g for MCM-41 and 306 m²/g for 2-Cl-BT-MCM-41, respectively. The absorption and releasing studies of ibuprofen were carried out in simulated body fluid. The result revealed that high adsorption capacity for drug with 2-Cl-BT-MCM-41 and slower drug release rate was achieved.

Keywords: Drug delivery system (DDS), mesoporous MCM-41, 2-chlorobenzoylthiourea.

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INTRODUCTION

Controlled drug delivery systems (DDS) are formulations that release a drug in a targeted area in the body. Materials obtained by encapsulation of clinically approved drugs will increase the therapeutic effect of the drug and reduce side effects. Biodegradable polymers, polymeric micelles, liposomes, magnetic nanoparticles, hydroxyapatites, calcium phosphate cement (CPC), xerogels, hydrogels and mesoporous silica are used as drug delivery systems. As a disadvantage, hydrolysis leads to deterioration of the polymer-based carrier structure, resulting in a rapid release of drug molecules and non-homogeneous distribution during the separation process. Research is underway to develop inorganic carriers to overcome these disadvantages of polymer systems. Controlled release of drugs from ordering mesoporous materials is an interesting field of application (1). High-order mesoporous silicates are very promising materials with a wide

range of possible applications (2). The porous web of these biocompatible materials can act as a reservoir for the maintenance of drug molecules by increasing the solubility and relative bioavailability of drug molecules. Among the mesoporous silicates, the MCM-41 has a high specific surface area (~ 1150 m²/g), a larger pore volume (~ 1 cm³/g), and smaller pore size (2-5 nm), thus being a drug carrier. MCM-41 has attracted more attention as a carrier for drug delivery (2). MCM has been tested for the transport and controlled release of aspirin (3), atenolol (4), captopril (5), coumarin derivatives (6), diflunisal (7), hydrochlorothiazide (8), ibuprofen (9-12), methotrexate (13), naproxine (9), sertraline hydrochloride (14), resveratrol (15), and others (16-17). The presence of high concentrations of silanol group on the silica surface makes it possible to modify the pore walls and surfaces by selecting appropriate organic groups. The surface of MCM-41 can be modified with chloropropyl, phenyl, benzyl,

mercaptopropyl, cyanopropyl, and aminopropyl groups (18).

The objective of this work was to study the ibuprofen adsorption and release behavior of 2-Cl-BT-MCM-41 in simulated body fluid. 2-Cl-BT-MCM-41 was prepared and also characterized via XRD, FT-IR, SEM and BET techniques.

MATERIALS AND METHODS

Synthesis of Compounds

Synthesis of MCM-41

Typically, 0.6 g of n-cetyltrimethylammonium bromide (CTAB) was first dissolved in 400 mL of deionized water. Then 3.5 mL of 2 mol/L NaOH was added to the solution, followed by adjusting the solution temperature to 80 °C. Subsequently, 2.5 mL of TEOS was added dropwise to the above solution with vigorous stirring. The mixture was stirred for another 2 h to give rise to white precipitates. The obtained solid product was filtered, washed with deionized water and ethanol, and then dried in air. The dried sample was calcined at 550 °C for 1 h in N₂ and followed by another 3 h in air to remove the organic template.

Synthesis of 2-Cl-BT-MCM-41

The MCM-41 was functionalized with 3-aminopropyltriethoxysilane in the toluene solution (refluxing for 24 h) according to the conventional procedure (19). After cooling, the modified mesoporous material was filtered out and washed several times with small portions of toluene and *i*-propanol to remove an excess of the modifier and possible products of hydrolysis. Finally, the modified mesoporous material was dried overnight in an oven at 95-100 °C under vacuum. The resulting material was designated as MCM-41-NH₂.

2-Cl-BT-MCM-41 was synthesized via a reaction between aminopropyl-functionalized mesoporous silica (MCM-41-NH₂) and benzoyl isothiocyanate, which normally proceeds completely. A typical procedure included reaction of 9.04x10⁻⁶ mmol (2 g) of aminopropylsilica with 0.50 mL of 2-chlorobenzoyl isothiocyanate (25% excess) in toluene. The resulting solid was filtered out, washed with 50 mL of toluene and 50 mL of *i*-propanol, and dried under vacuum for 5 h at 90 °C. The final sample with the attached thiourea functionality had a light yellow color. Schematic illustration of the surface present in the 2-Cl-BT-MCM-41 is given in Figure 1.

Characterization

X-ray diffraction pattern was recorded on a Bruker D8 using CuK_α radiation, with the diffraction angle (2θ) at range of 10–80°. FT-IR spectrum was recorded on Perkin Elmer FT-

IR/FIR/NIR spectrometer Frontier ATR system. SEM measurements were recorded with a Jeol Sem-7100-EDX computer controlled digital model device. BET analyzes were done with Quantachrome Quadrasorb SI device. Absorbance measurements were performed with Pg Instruments UV-Visible spectrometer.

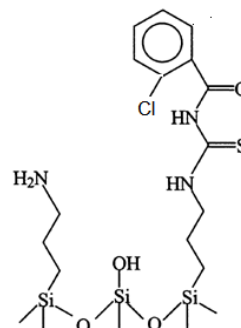


Figure: 1. Schematic illustration of the surface present in the 2-Cl-BT-MCM-41

Ibuprofen loading and release studies

Drug loading studies were carried out via supercritical carbon dioxide (scCO₂) system. 1 g of 2-Cl-BT-MCM-41 and 0.8 g ibuprofen were dissolved in 15 mL of ethanol and they were charged to the scCO₂ reaction unit at 40 °C and allowed to stand at 200 bar CO₂ for 2 hours. The reaction unit's valve was opened to reduce the CO₂ pressure and the drug loaded nanostructures were obtained.

The in vitro drug delivery was performed by soaking the sample powder into a simulated body fluid, SBF, at 37 °C and at pH of 7.4, maintaining the ratio SBF volume (mL) per adsorbed ibuprofen mass (mg) equal to 0.8:1. Continuous magnetic stirring was maintained during the delivery to avoid limitation of the delivery rate by external diffusion constraints. The delivered ibuprofen concentration was monitored by UV spectrophotometry at 273 nm.

RESULTS AND DISCUSSION

FT-IR studies of MCM-41, MCM-41-NH₂ and 2-Cl-BT-MCM-41

FT-IR spectra of the MCM-41, MCM-41-NH₂ and 2-Cl-BT-MCM-41 are given in Figure 2a-c. Asymmetric vibration band of the O-H group is observed at 3356 cm⁻¹. The stretching and bending vibration bands of Si-O are observed at 1064 cm⁻¹ and 801 cm⁻¹, respectively. The results indicate the accuracy of the proposed MCM-41 structure. In the FT-IR spectrum of the MCM-41-NH₂, N-H vibration peaks were observed at 2850-2920 cm⁻¹. In the FT-IR spectrum of the 2-Cl-BT-MCM-41, aromatic C-H vibrations were observed at 3000 cm⁻¹. C=O vibrations also observed at 1700 cm⁻¹. FT-IR spectra confirm that the proposed structures are formed.



Figure 2: FT-IR spectrum of MCM-41.

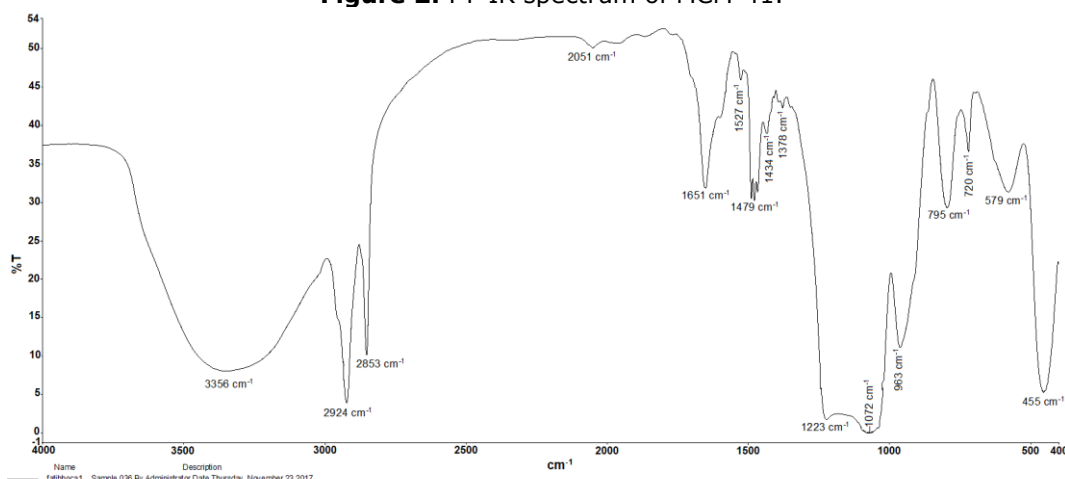


Figure 3: FT-IR spectrum of MCM-41-NH₂.

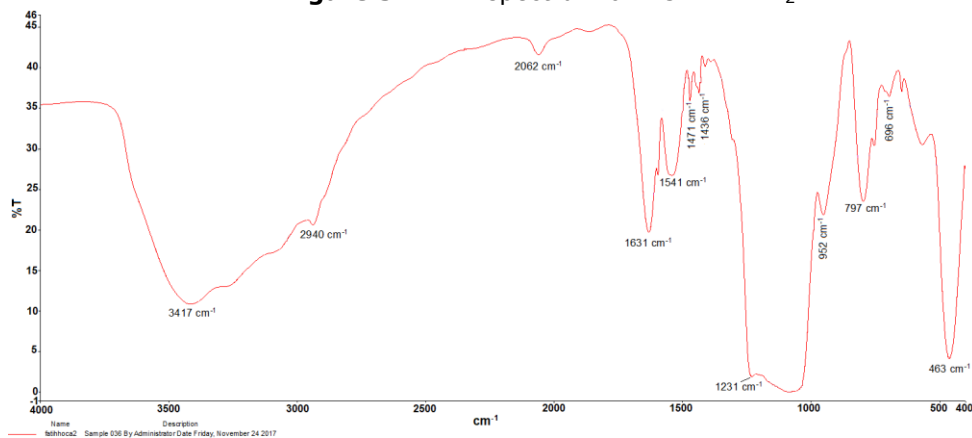


Figure 4: FT-IR spectrum of 2-Cl-BT-MCM-41.

XRD studies

The XRD pattern and low angle XRD patterns of 2-Cl-BT-MCM-41 are given in Figure 5a-b. The (100) and (110) reflections observed at low angle XRD show the mesoporous SiO₂ structure.

The broad band observed in the XRD powder pattern at 2 theta = 20° belongs to amorphous SiO₂. XRD results show that mesoporous 2-Cl-BT-MCM-41 has been successfully synthesized.

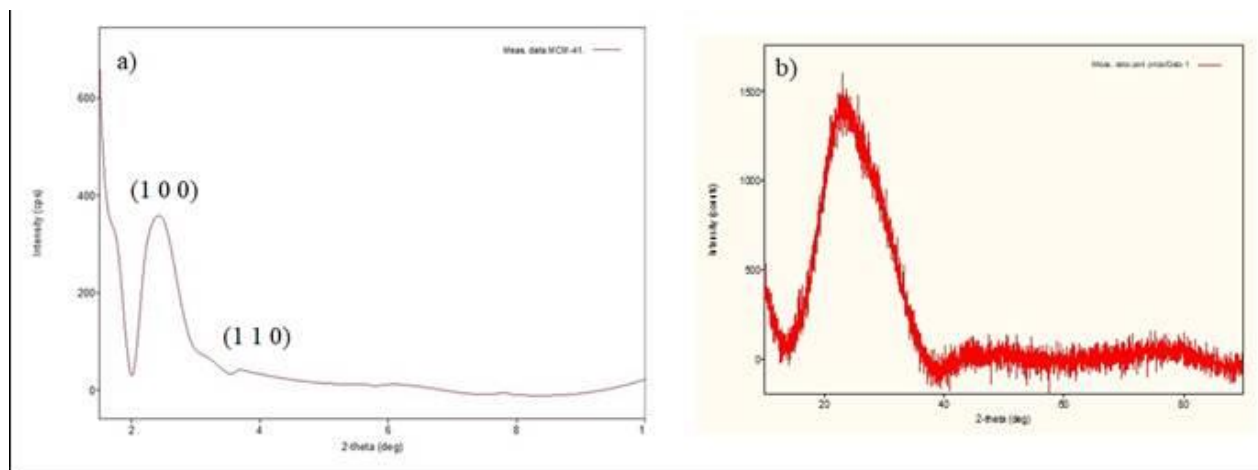


Figure 5: XRD powder patterns of MCM-41 a) Low angle XRD pattern, b) XRD pattern.

SEM studies

Surface investigations of the prepared 2-Cl-BT-MCM-41 were carried out by FE-SEM. SEM micrographs are given in Figure 6. SEM images showed non-uniform spheres at a range of 250-305 nm.

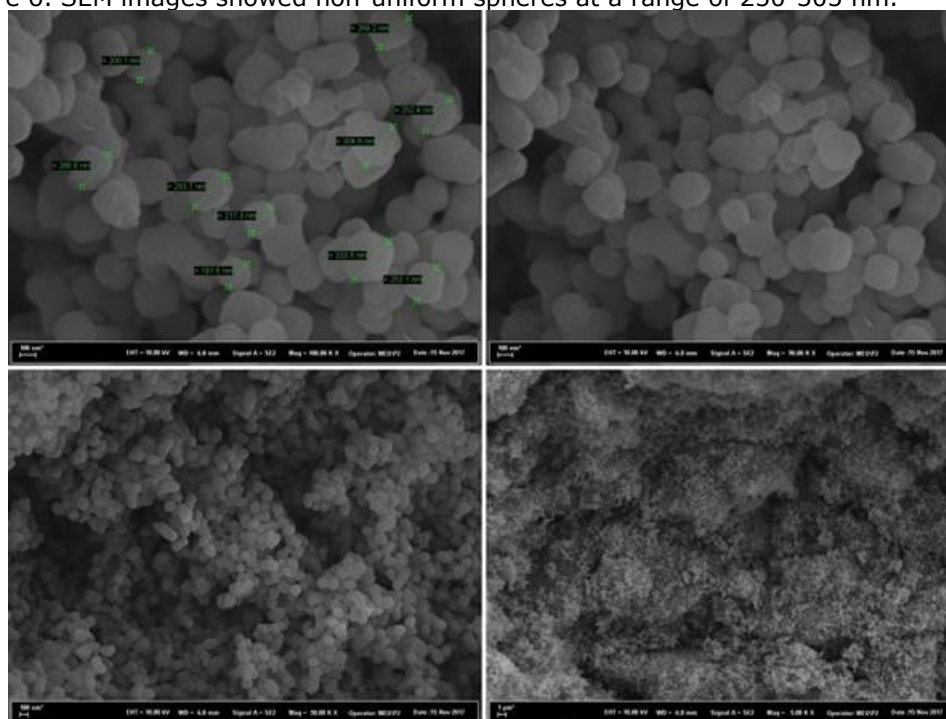


Figure 6: SEM images of 2-Cl-BT-MCM-41.

In vitro Ibuprofen Releasing Studies

To examine the drug release profiles, the cumulative percentages of drug release were plotted against time. The release behavior of ibuprofen from 2-Cl-BT-MCM-41 was investigated in the PBS solution for 66 hours. Release of ibuprofen from 2-Cl-BT-MCM-41 in PBS solution

(pH = 7.4; 37 °C) is given in Figure 7. Wave swing is observed in the drug release profiles. This behavior is due to unbalanced distribution of drug molecules from layered matrices, diffusibility, number of layers and thickness, and fluctuations in drug release are observed (20).

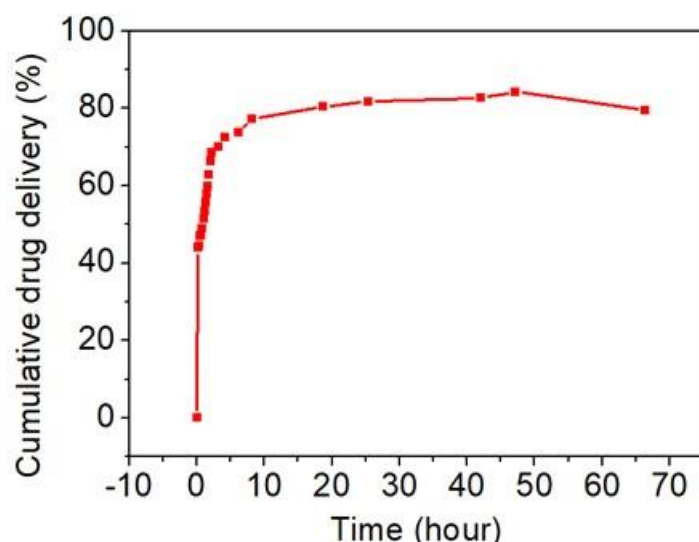


Figure 7: Release of ibuprofen from 2-Cl-BT-MCM-41 in PBS solution (pH = 7.4; 37 °C).

BET studies

For the prepared MCM-41, the BET surface area was calculated as 1506 m²/g and is compatible with the >1000 m²/g value given in the literature. In addition, the pore diameter of MCM-41 was

found to be 3.61 nm according to the literature. The surface area of 2-Cl-BT-MCM-41 was found to be 306 m²/g. Nitrogen adsorption (black) desorption isotherms of MCM-41 and 2-Cl-BT-MCM-41 are given in 8a-b.

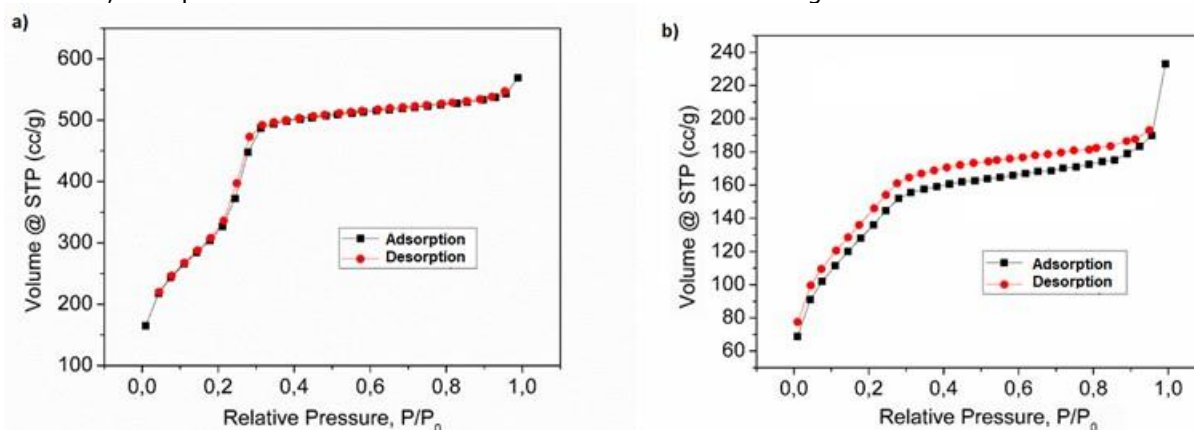


Figure 8: Nitrogen adsorption (black) desorption isotherms of a) MCM-41 and b) 2-Cl-BT-MCM-41.

CONCLUSION

In this study, mesoporous 2-Cl-BT-MCM-41 was synthesized by precipitation method. 2-Cl-BT-MCM-41 was characterized via XRD, FT-IR, SEM and BET techniques. FT-IR spectrum of the 2-Cl-BT-MCM-41, the aromatic vibrations (γ C-H) were observed at 3000 cm⁻¹. The carbon-oxygen vibrations (γ C=O) were also observed at 1700 cm⁻¹. The (100) and (110) reflections observed at low angle XRD show the mesoporous SiO₂ structure. The characterization results confirm that the proposed structures are formed. The surface morphology of the particles was determined by SEM micrographs. The particle size of non-uniform spheres were observed at a range of 250-305 nm. BET surface areas were calculated as 1506 m²/g for MCM-41 and 306 m²/g 2-Cl-BT-MCM-41, respectively. BET surface area is given as > 1000 m²/g value in the literature. Our BET results are compatible with the literature. Ibuprofen was loaded using supercritical carbon dioxide (sC-CO₂) environment. The absorption

and releasing studies of ibuprofen were carried out in simulated body fluid. The result revealed that high adsorption capacity for drug with 2-Cl-BT-MCM-41 and slower drug release rate was achieved. MCM 41 and 2-Cl-BT-MCM-41 bind with ibuprofen over weak hydrogen interactions. This causes slow releasing.

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