Supporting information

Synthesis of Mesoporous Materials as Nano-carriers for an Antimalarial Drug

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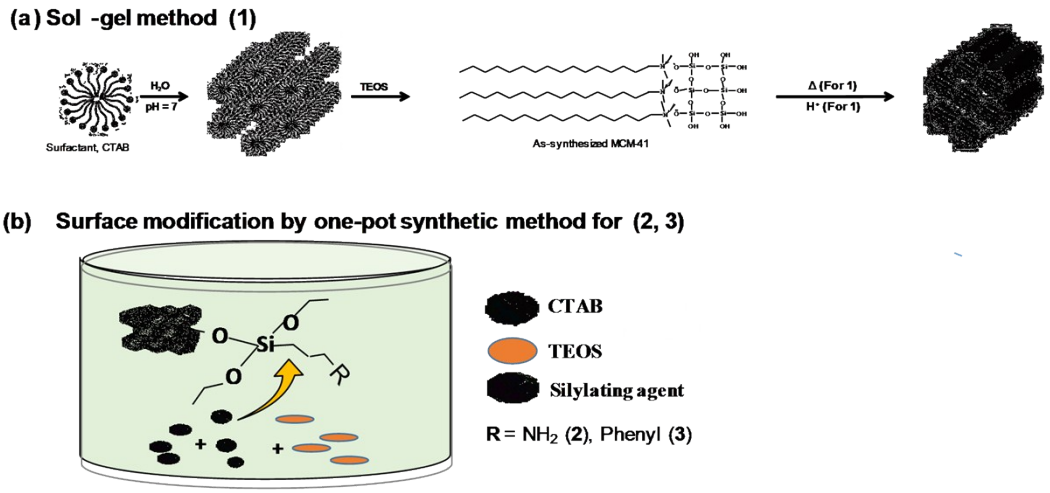
Experimental Section

Materials

All the materials and chemicals were of reagent grade and were used as purchased without further purification: Tetraethyl orthosilicate (TEOS), cetyl trimethyl ammonium bromide(CTAB), 3-aminopropyltriethoxysilane (APTES), 3-phenylpropyltrichlorosilane (3-PPTCS), and 3-trihydroxysilypropyl methylphosphonate (THMP) were purchased from Sigma Aldrich, sodium lauryl sulphate (SLS) from Wako, dialysis membrane,

arteunate drug ("d" represents ATS acronyms) were purchased from TCI. Deionized water, AR grade was used for all the preparation and purification.



Scheme S 1: Synthesis of MCM-41 and surface modified MSNs

Characterization

A Fourier Transform Infrared (FT-IR) spectroscopy spectrophotometer recorded on FTIR-8700 spectrometer was used to record infrared spectra of the MSNs. The samples were grounded with KBr to form pellet and KBr background spectrum was used for determining the samples' spectra over the range of 400 ~ 4000 cm^{-1}. The interior pores properties like surface area, pore size and volume were determined with nitrogen physisorption measurements at -196 ℃ by using a Micromeritics Tristar 3000 system. MCM-41, modified MCM-41 and their artesunate (ATS) encapsulated samples were degassed respectively at 120 ℃ for 6h on a vacuum line. The pore-size distribution was measured from the desorption branch of the isotherm using BJH model followed by gaussian fitting specific and surface area of the samples were calculated by using the Brunauer–Emmett–Teller (BET) equation methods. Differential scanning calorimetric study was performed on NETZSCH DSC 200F3 Maia using the crimp-aluminum pan. The measurement was carried out from 20 to 155 ℃ at heating rate of 10 K/min under nitrogen gas flow for two cycles to check the structural phase transition peak of the samples' molecular state. Thermogravimetric analyses were performed using a TG/DTA 6300 SII Seiko Instrument Inc, Japan at a heating rate of 10 ℃/min under a nitrogen purge a 40 ml/min. Powder X-ray diffraction (PXRD) patterns of the silica and silica loaded drugs were recorded on a Smart Lab Rigaku X-ray diffractometer with Fe-filtered Co radiation (Rigaku Corporation, Japan). The measurement conditions were as follows: target, CuKa; filter, Ni; voltage, 30 kV; current, 15 mA; scanning range, 2-25°; scanning speed, 4 ℃/min to measure the molecular state of the adsorbed drug. Transmission electron microscopy (TEM) structural images were obtained using a JEOL 1010 operated at 100 kV while JEOL-JSM 7600F operating at an accelerating voltage of 5.0kV was used to obtain field-emission Scanning Electron Microscope (SEM) micrographs / morphology of both unmodified and modified MSNs and their encapsulated materials. At first, the silica nanoparticles were dropped on the carbon-coated copper grid and then sputtered with thin film of platinum and gold to boost the silica conductivity before scanning. The amount of ATS drug loaded and released from mesoporous silica were determined using UV-3600 UV-VIS spectrophometer Shimadzu.

Synthesis

Preparation of MCM-41 (1)

The unmodified mesoporous silica nanoparticles were synthesized by Beck et al.

procedure with slight modification. Briefly, 1.34 g, 3.66 mmol hexadecyltrimethylammonium bromide (CTAB) was suspended in distilled water (480 mL) and raised the temperature to 50℃ to form a clear solution. Thereafter NaOH (2 M) solution (Ca 4 mL) was added to the solution (pH= 12-13) with constant stirring and when the temperature reached 80 ℃ the tetraethyl orthosilicate (TEOS) (6.7 ml, 30mmol) was dropped slowly and stirred for 2 h. The resulting product was filtered and washed severally with distilled water and methanol until the pH is 7.0 dried in vacuo overnight. The as-synthesized MCM-41 produced was calcined at 550 ℃ for 5h to remove the surfactant template and denoted as unmodified **1**.

Co-condensation method of synthesizing Modified MSNs (2, 3)

Co-condensation method i.e. one-pot synthetic method was adopted by modifying the previously reported in the literature. CTAB (1.34 g, 3.66 mmol), NaOHaq (4.0 mL, 2.0M), and H_2O (480 mL, 26.67 mol) was heated at 80℃. To this clear solution, TEOS (6.25 g, 38 mmol), 1.8 mL THMP was added after 10 min and each silylating agent was added were added sequentially and rapidly via injection. (TEOS: APTES: PPTCS) in 1: 0.08: 0.25 ratios for **2** and **3** respectively. The reaction temperature was maintained at 80℃ for 2 h. The products were isolated by a hot filtration, washed with distilled water and methanol, and dried under vacuum. Surfactant template was removed in the samples **2, 3** by acid solvent extraction method.

ATS loading in MCM-41 and Modified MSNs

Similar reported procedure was followed with slight change for loading the ATS drug in the mesoporous silica nanoparticles. MCM-41 (50 mg) was soaked in 10 mL of ethanol solution of ATS 100 mg (1:2 w/w) for 72h with constant mixing to allow full absorption of the drug inside the silica, the mixture flask was covered with aluminium foil to protect the drug from light The drug loaded samples were separated from the solvent mixture by centrifugation for 30minutes at 4000 rpm and washed with about 5 mL of ethanol to remove surface attached drugs. The residue i.e. adsorbed drug was dried in vacuum while the supernatant which contained small unabsorbed drug was determined after dilution using Beer-Lambert UV-Vis absorption spectrophotometer at 281.5 nm wavelength standard calibration curve. However, the actual amount of ATS loaded in the MSNs was calculated by removing the weight of ATS in the supernatant from the initial amount of ATS used. The loaded drugs were named **1d**, **2d**, and **3d** accordingly.

Equation formula for Drug Loading

Drug loading (**DL %**) = Weight of ATS in MSNs / weight of ATS-silica composite X 100%

Entrapment efficiency (**EE%**) = Weight of ATS in MSNs / weight of initial ATS loaded X 100%

***In-vitro* artesunate dissolution procedure**

The ATS loaded silica (**1d**, **2d**, **3d**) equivalent to 2 mg of the ATS drug was weighed and suspended in 1 ml of 0.5 % SLS buffer. This suspension was then placed in dialysis bag (Sigma Aldrich) with 10 kDa molecular weight cutoff and was immersed into 9 ml of 0.5 % SLS at 37 ℃ with continuous stirring at pH 7.0. At predetermined time intervals, 1 mL of the samples were withdrawn and immediately replaced with an equal volume of dissolution medium to keep the volume constant. Pure ATS release was studied along with silica-drug composite to compare the in vitro drug release profile by weighing 2 mg of pure ATS and suspending it in 0.5 % SLS similar to that of MCM-41-ATS These samples were then properly diluted and analyzed for ATS content at 281.5 nm using UV-VIS spectrophotometer.

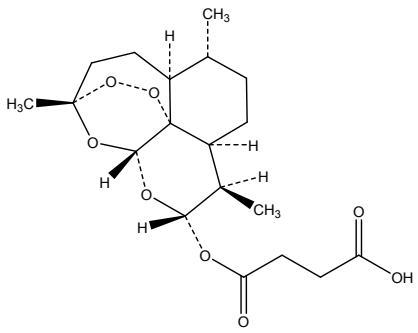


Figure S1 Chemical structure of Artesunate (ATS).

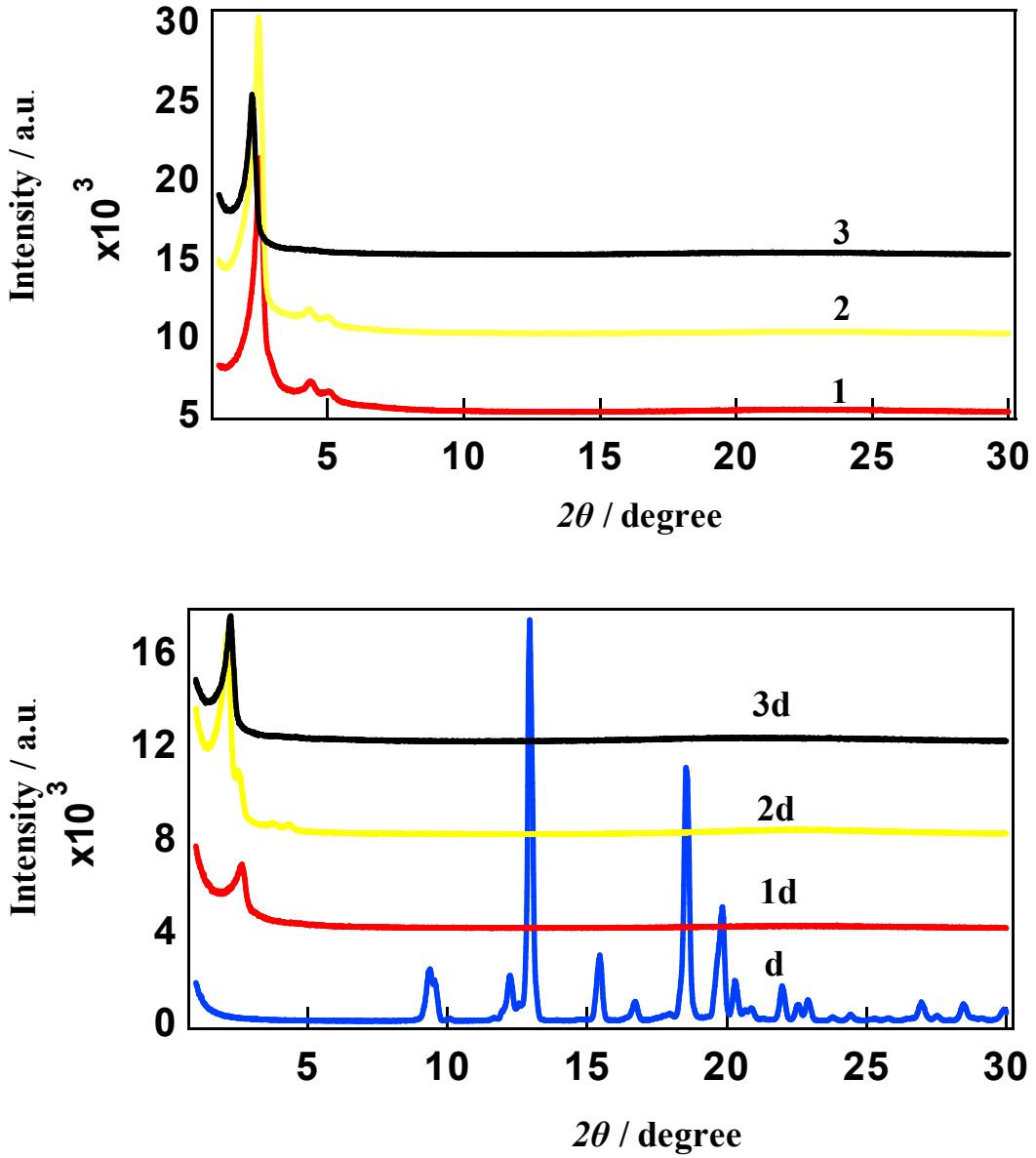


Figure S 2 PXRD pattern of MCM-41 (**1**), Modified MSNs (**2,3**)and their ATS loaded materials (**1d,2d,3d**)

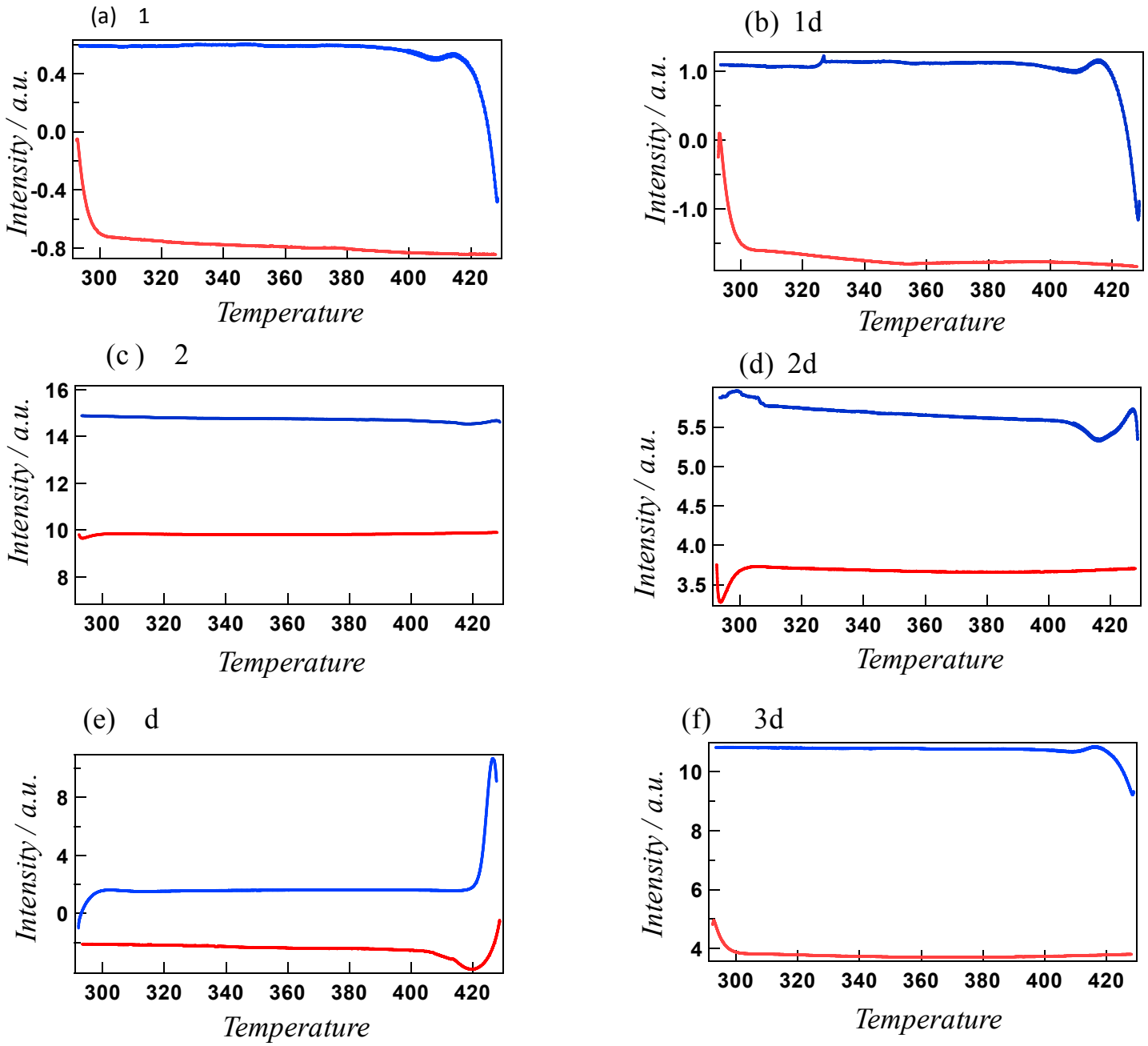


Figure S 3 DSC of MCM-41 (**1**), Modified MSNs and their loaded ATS drug

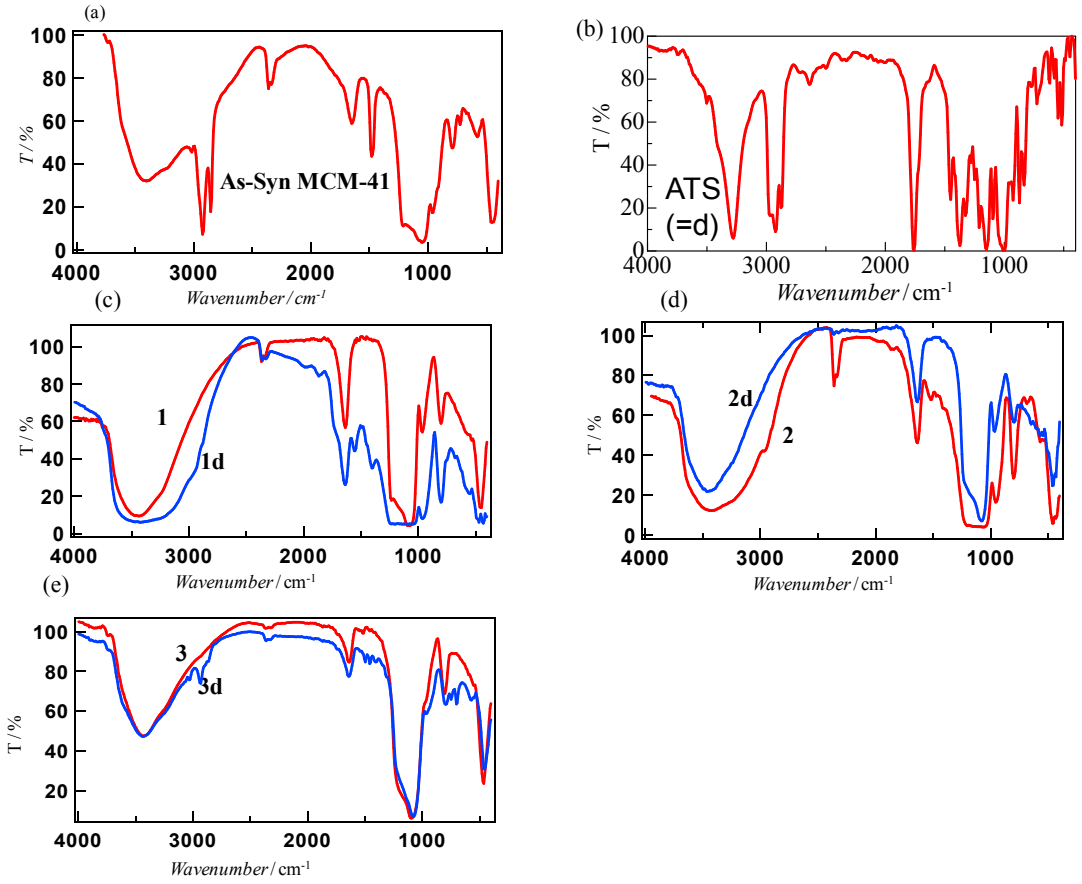


Figure S 4a FT-IR spectra for (a) As-synthesized MCM 41 (b) Artesunate drug (c) MCM-41 and ATS loaded MCM-41(**1, 1d**) (d) Amine modified MCM-41 and ATS loaded MSNs (**2, 2d**) (e) Phenyl modified MCM-41 and ATS loaded MSNs (**3, 3d**)

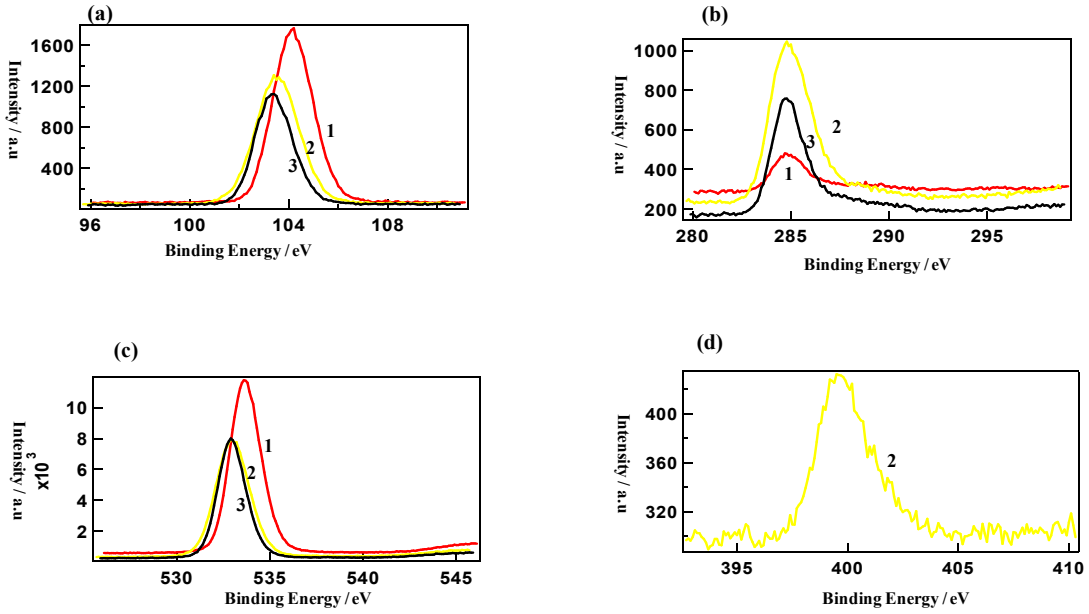


Figure S 4b XPS spectra for (a) Silicon (b) Carbon (c) Oxygen (d) Nitrogen binding energies

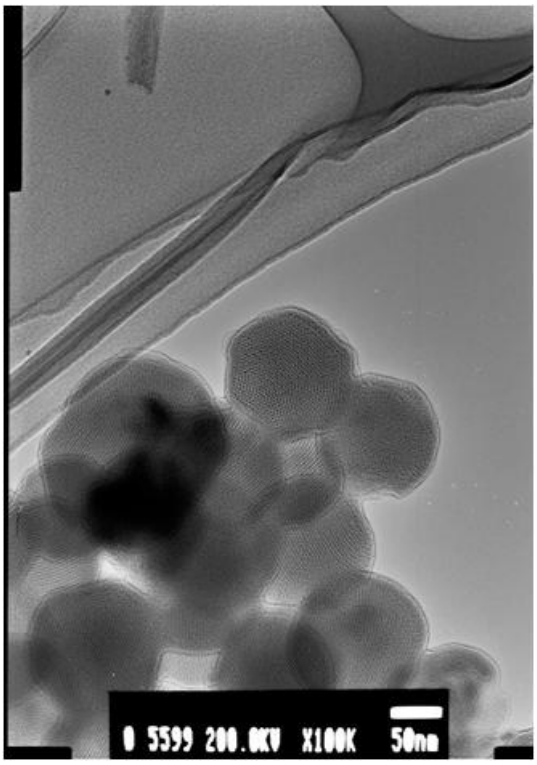


Figure S 5 Hexagonal 2-D well ordered structure of MCM-41(**1**) (TEM image).

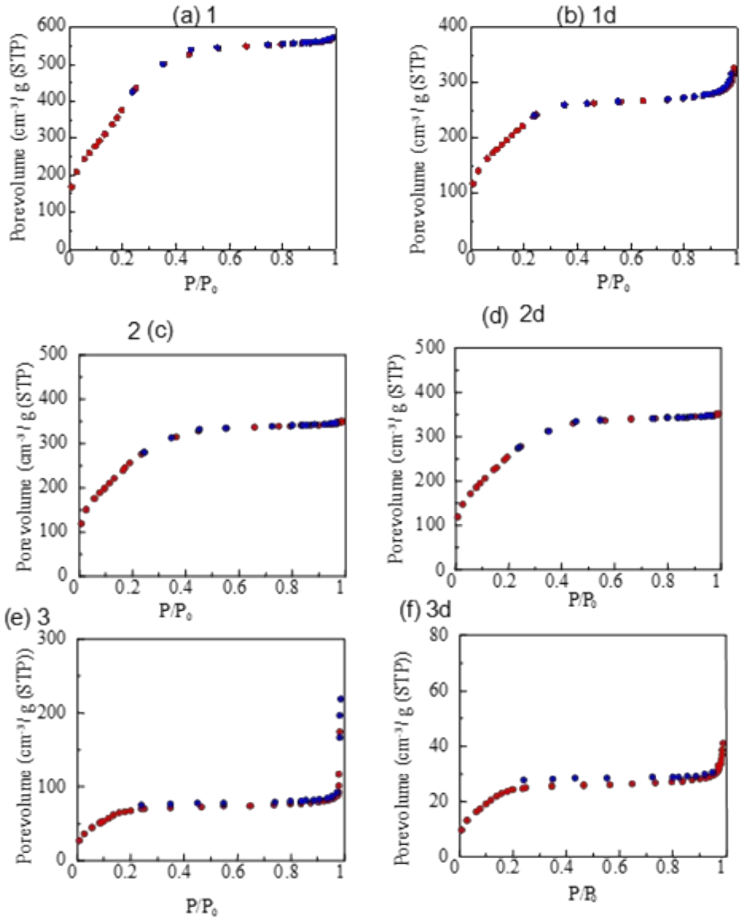


Figure S 6 N_2 sorption graph of (a)MCM-41(**1**) (b) ATS loaded unmodified MCM-41 (**1d**) (c) Amine modified MCM-41(**2**) (d) ATS loaded amine MCM-41(**2d**) (e) Phenyl modified MCM-41 (**3**) (f) ATS loaded phenyl MCM-41(**3d**)
(Adsorption isotherm curve = red line, desorption isotherm curve =blue line)

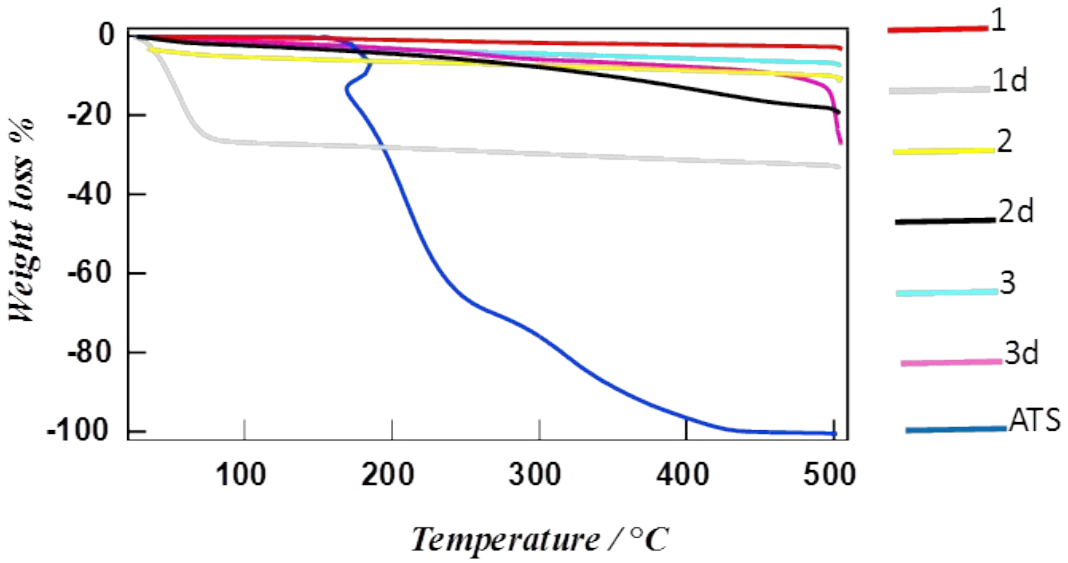


Figure S7 TGA of MCM-41 and MSNs loaded drugs

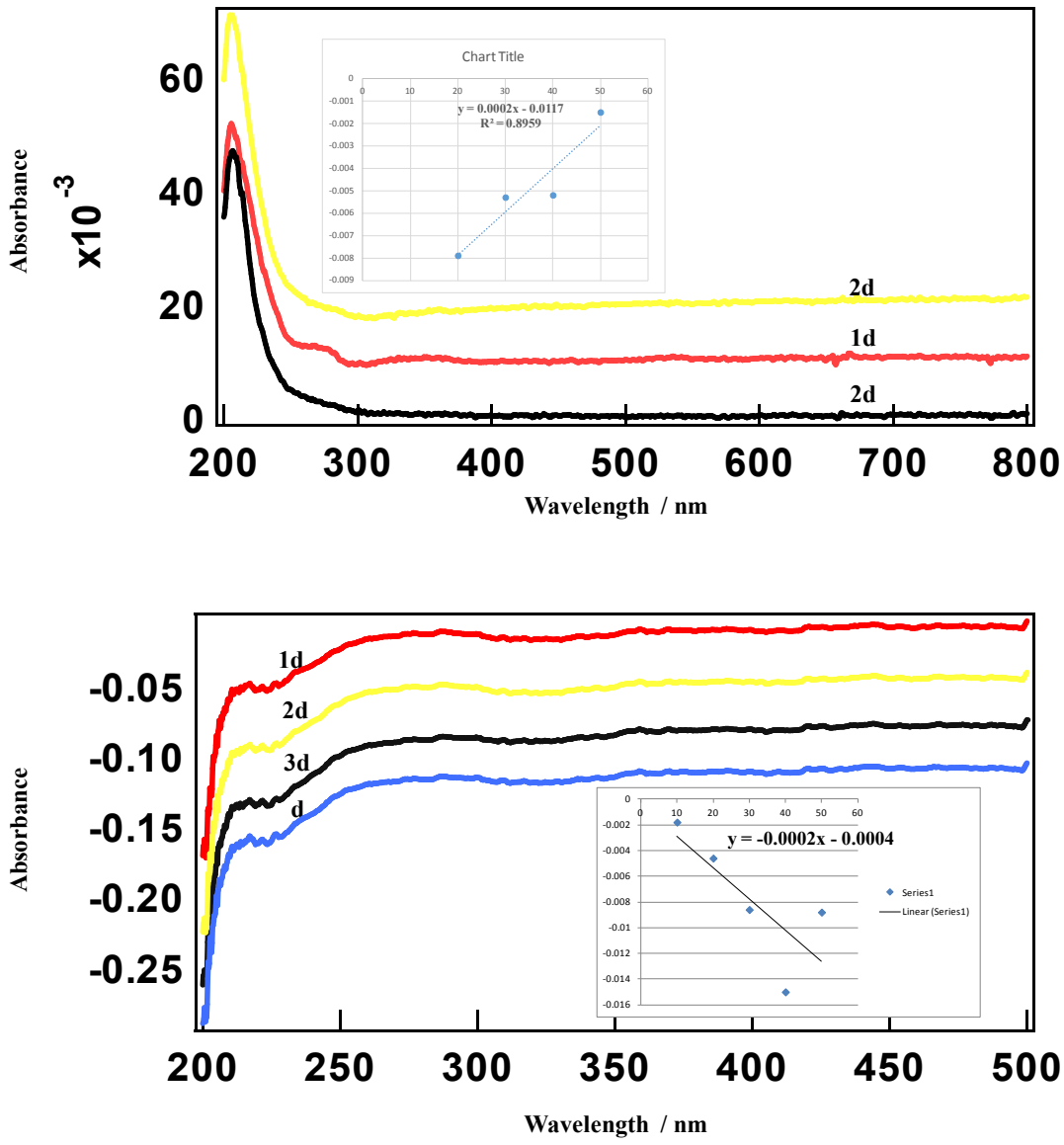


Figure S8 UV-Vis of ATS (i) Loading and (ii) Release