Research Article

Study of Molecular Interactions of COOH-MCM-41 in Presence of Nicotinamide (A Hydrotropic Agent) in Ethanol and Application of NH$_2$-MCM-41 for Effective Drug Delivery of Aspirin

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ABSTRACT

The present study deals with the physico-chemical study of carboxylic modified MCM-41.COOH-MCM-41 with two different weight percent were synthesized by post-synthesis method which is a two step process. The initial step was the modification with 3-amino-propyltriethoxysilane, and the next was the reaction with succinic anhydride in toluene in order to obtain carboxylic modified mesoporous carriers. The carboxylic functionalized mesoporous materials were characterized by SEM, XRD, FT-IR spectroscopy. The density, viscosity and conductance of COOH-MCM-41(5 and 10 weight %) have been measured in the concentration range of 40 ppm-140ppm in ethanolic solution of hydrotropic agent nicotinamide at different temperatures ranging from 298.15 K to 313.15 K at an interval of 5 K. The density and viscosity data have been analyzed for the evaluation of limiting apparent molar volume(V_ϕ^0),), limiting apparent expansibility (E_ϕ^0), Falken-Hagen co-efficient (A_F), Jones-Dole co-efficient(B_J).From conductance measurement, dissociation constant, free energy, enthalpy, entropy, activation energy were calculated. The results have been discussed in terms of solute-solute; solute-solvent interactions. Again the drug loading and release study of amine modified MCM-41 were studied and the results were compared with unmodified parent MCM-41.Amine functionalized mesoporous systems are found to be appropriate drug delivery platforms having effective drug loading and controlled releasing capacity.1 gram of NH$_2$-MCM-41(10 wt. %)shows 175 mg aspirin loading, which is highest among all the three samples (MCM-41, 5 and 10 wt. % NH$_2$-MCM-41).MCM-41 shows highest aspirin release capacity due to weak drug-host interaction. This investigation would give valuable information regarding these drug carriers which would be helpful for the drug delivery of hydrotropic drugs.

Keywords: NH$_2$-MCM-41, SEM, Apparent molar volume, Nicotinamide, Aspirin.

INTRODUCTION

In recent years the mesoporous MCM-41 has proved itself as attractive candidate for many biomedical applications due to its large pore volume, uniform porosity, stable aqueous dispersion, excellent biocompatibility, in vivo biodegradability, and their facile functionalization with different organic groups. Presence of organic groups on the surface of ordered mesoporous materials determines many important properties of the materials such as adsorption capacity, hydrothermal stability, surface reactivity, hydrophobicity etc. The organophil surface modification of MCM-41 with appropriate functional group is found to be essential for effective delivery of water insoluble drugs[1-5] than the conventionally used other delivery systems as it enhances the adsorption capacity of drug molecules, modulating their release. In response to this issue, mesoporous materials functionalized with a variety of pendant organic groups have been achieved. The carboxylic-modified mesoporous materials are of great interest in nanomedicine applications because of the possibility of pH-response delivery[6] for controlled release of drug molecules with free amino functional groups. Again it has catalytic application in the view point that it has acidic group which is versatile for acid catalyzed reactions. The synthesis of this material is essential in the viewpoints of specific adsorption[7], ion-exchange, and catalysis since the carboxylic acid group is a well-known reactive group and possesses the ability to form hydrogen bonds with organic or inorganic species. The synthesis of COOH modified MCM-41 can be done by two methods, one-pot synthesis and post synthesis. The present study deals with the carboxyl modification by post synthesis method through a ring opening reaction with succinic anhydride. We have attempted to study the density, viscosity of COOH-MCM-41 in the solvent (ethanol) in presence of a hydrotropic agent (nicotinamide) at four different temperatures ranging from 298.15 K to 313.15 K with an interval of 5K that provides valuable information regarding molecular interactions taking place in the system.[8-11]

In recent years, modern drug discovery efforts have been producing active pharmaceutical substance having high therapeutic value but poor aqueous solubility and according to some estimates more than 50% of new chemical entities (NCE) exhibit poor water solubility which complicates the delivery of these compounds giving rise to the bioavailability problems, lack of in-vivo and in-vitro correlation, lack of patient compliance, and inter subject variations etc. The drug action, structure activity relationship, drug transport kinetics and in-situ drug release profile are explained by the physiochemical property; solubility. Different solubility-enabling formulations are used to tackle these solubility limitations, but care should be taken when using these formulations, because in some cases it was evident that the increased solubility afforded by the formulations in accompanied by a parallel decreased intestinal

permeability. Numerous, drug delivery systems like biodegradable polymers,[12] hydroxyapatite (HA),[13-15]calcium phosphate cement,[16, 17]xerogels,[18] hydrogels,[19,20] etc have been studied for controlled drug delivery. Along with the solubility issue, the delivery systems or carriers of these types of compounds have some problems like decreased bioavailability, increased chance of food effect, more frequent release from the dosage and higher interpatient variability. Although several formulation approaches including solid formulation approaches including solid dispersions, emulsion based systems and nanosizing have led to promising in vitro results, the number of marketed applications of these technologies remains very limited. To overcome this handicap and to enable oral delivery of these new chemical entities now constitutes one of the greatest challenges to the formulation scientists of pharmaceutical research.

Together with the growing number of poorly water double compounds, this emphasizes the need to explore new types of approaches. Novel drug delivery systems (DDS) are an area of keen interest in drug research to improve the pharmacokinetic profile of hydrophobic drugs. An ideal DDS should not adversely affect drug activity, be capable of delivering a therapeutic dose of drug, and allow homogenous drug loading and drug release. Ordered mesoporous, silica materials have recently attracted much attention because of their emerging applications in drug delivery.[21] since their first appearance in material science in the 1990s; these inorganic carriers have been used successfully as drug delivery systems. The large surface area allows the particles to be filled with drug like "Trojan Horse" (refers to a trick that causes a target to invite a foe into a securely protected bastion or place)., the particles will be taken up by certain biological cells through endocytosis (is a form of active transport in which a cell transports molecules into the cell by engulfing them in an energy-using process), depending on what chemicals are attached to the outside of the spheres. The high pore volume can fit in large amount of pharmaceutical entities.

Since 2001, when MCM-41 was purposed for the first time as controlled delivery system[22], much research efforts have been devoted to tailor the chemical properties of mesoporous carriers at the nanometer scale to achieve a better cause over loading and release of molecules of mesoporous carrier is selected according to the features of the guest molecules and the targeted application. Therefore different guest molecules have

been successfully confined into mesoporous silicas. Some of the molecules are drugs[23] others consisted of biological active species, such as proteins, e.g., bovine serum albumin (BSA)[24] and certain amino acids.[25]The textural properties (i.e., pore diameter, surface area and pore volume) of MCM-41 are key factors that govern molecules adsorption and release.[26] Moreover, functionalization of silica walls using different organic groups has been revealed as the main strategy to modulate molecule loading and release. The functionalization of organic amine (Amino propyl triethoxy silane, APTES) results in inhomogeneous surface coverage because the introduced organic molecules congregate near the entries to the mesoporous channels and on the exterior surface.

In continuation to our previous work[27-29], in the current paper we have studied the drug loading and release of amine modified MCM-41 taking Aspirin as model drug and compared the result with MCM-41. Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used for treating fever, pain, and inflammation in the body. It is one of the most commonly used drugs in the world Approximately 35,000 tons of this drug is produced and consumed annually. In addition to its small size, good pharmacological activity, and short biological half-life, it has a carboxyl group that can interact with the surface silanol groups or amino groups on the pore walls and may be useful for the controlled drug release. The chemical name for aspirin is acetylsalicylic acid. It is an ester derivative of salicylic acid and its common name is derived from the old German version of the name, acetylspirasaeure. Aspirin was first marketed commercially by the Bayer Company in Germany in 1899.The highly colored complex which forms between acetylsalicylic acid (aspirin) and iron (III) chloride enables us to determine colorimetrically the specific amount of acetylsalicylic acid present in a tablet. Since the intensity of the color formed is directly related to the amount of acetylsalicylic acid present, a series of solutions, each with a different concentration of acetylsalicylic acid, can be prepared and the absorbance of each solution measured. A calibration curve is then constructed and from this curve the amount of acetylsalicylic acid in a commercial aspirin product can be determined.

The complex ion is formed in two steps. First the acetylsalicylic acid is reacted with sodium hydroxide to form the salicylate dianion. Then the addition of acidified iron (III) ion produces the violet tetraaquosalicylatroiron (III) complex.

The complex is formed by reacting the aspirin with sodium hydroxide to form the salicylate dianion.
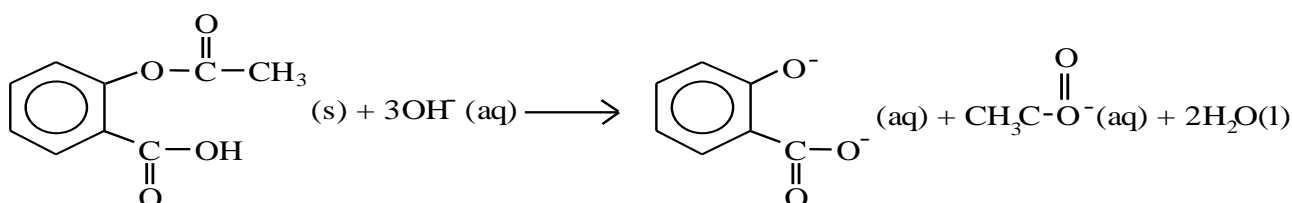
The addition of acidified iron (III) ion produces the violet tetraaquosalicylatroiron (III) complex.
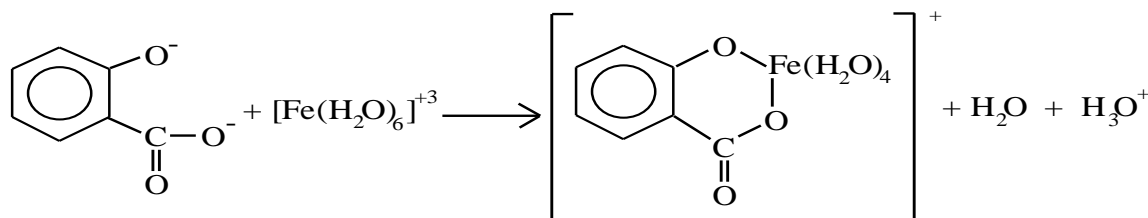
The loading and release of aspirin from MCM-41, and amine modified MCM-41 were investigated. We aim that; it will provide a better understanding of the interaction between the drug and the mesoporous host and how the modification affects the loading and release properties.

MATERIALS AND METHODS

Chemicals

Cetylhexadecyltrimethylammoniumbromide (CTAB), Tetraethylorthosilicate (TEOS), ammonia solution, Toluene, and nicotinamide were purchased from Merck, and 3-Amino propyltriethoxysilane (APTES), Succinic anhydride and Sodium hydroxide were purchased from Sigma-Aldrich. Methanol and Ethanol were of AnalaR grade and used after dehydration with molecular sieve over night. Deionized water (Sp. Cond. ~10^{-6} S cm^{-1}) was used throughout the experiment.

Synthesis

The mixture of CTAB (2.0 g), 2M NaOH (7ml) and water (480ml) was heated at 80^{0}C for30 min to attain a $_p$H≈12.3.To this clear solution, various amounts of TEOS (10.04ml and 5 ml) and 3-APTES (1.09ml) were added sequentially and rapidly via injection. Following the injection, a white ppt was observed after 3 min of stirring at 550 rpm. The reaction temperature was maintained at 80^{0}C for 2 hours. The products were isolated by a hot filtration, washed with excess amount of water and methanol and dried under vacuum (oven) for 8 hours at 110^{0}C, and powdered. Calcination was done by acid extraction for which a mixture of methanol (200ml), conc. HCl and as made materials were heated at 60^{0}C for 6 hours. The resulting surfactant removed solid products were filtered and washed with water and methanol and dried in oven for 8 hours at 110^{0}C.The samples are designated as NH$_2$-MCM-41(xx) where xx stands for 5 and 10 weight % of the samples.

Synthesis of COOH-MCM-41 involves ring opening reaction of NH$_2$-MCM-41 with succinic anhydride in which amino modified silicas was added with succinic anhydride and refluxed in presence of toluene (Fig. 1). To remove adsorbed water azeotropic drying of amino modified silicas was made at 115 $^\circ$C by mixing 1 g of silica with 20 ml of anhydrous toluene. 6.6 mmol of succinic anhydride (assuming 2 wt. % of amino content on silica) was added to the mixture at 60 $\circ$C and treated for 24 h .The samples were dried by vacuum evaporation (0.04 Pa) at room temperature for 6 h. The samples are designated as

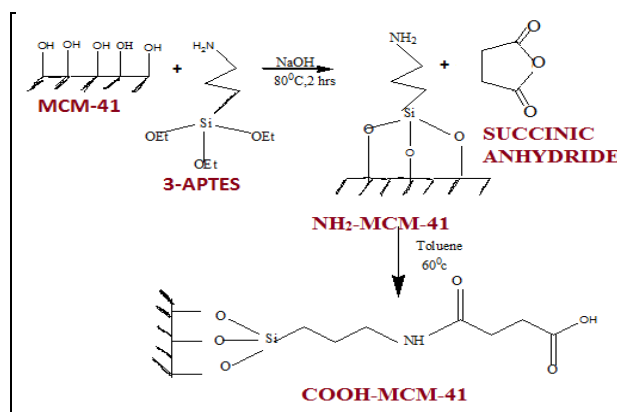COOH-MCM-41(xx) where xx stands for 5 and 10 weight % of the samples.

Figure 1: Synthesis of carboxylic modified MCM-41.

Preparation of solvent

0.1 M nicotinamide solution in ethanol was taken as the solvent for preparation of solution of COOH-MCM-41 which was prepared by dissolving 3.05 g nicotinamide (a hydrotropic agent) in 250 mL of ethanol.

Preparation of solution

The solutions of COOH-MCM-41 of six different concentrations; 40 ppm, 60 ppm, 80 ppm, 100 ppm, 120 ppm, and 140 ppm and 140 ppm were prepared by taking 0.002g,0.003g,0.004g,0.005g,0.006g,and 0.007g of samples in 50 ml measuring flask and made up to the mark by adding 0.1 M alcoholic nicotinamide solution. All solutions prepared are used on the same day. Then concentrations are converted from ppm scale to molar scale.

Measurement of density

The density values of ethanol + nicotinamide mixture and the solutions of the samples in ethanol + nicotinamide mixture were determined by relative measurement methods by using specific gravity bottle of 25mL capacity as described elsewhere[30]. Prior to measurements on the experimental solutions, the specific gravity bottle was calibrated to the respective temperatures using conductivity water. Densities of water at the studied temperatures were obtained from the literature.[31] At least five observations were taken and differences between any two readings did not exceed ± 0.02%. Measurement of density was done in the temperature

range 298.15K to 313.15K.The density of the solution was determined using the formula.

$$d_2 = (W_2/W_1) d_1 \qquad (1)$$

Where d_1 = density of water

d_2 = density of solution

W_1= weight of water

W_2= weight of solution

Measurement of viscosity

Viscosity measurements were made in a water thermostat maintained at appropriate temperatures varying within ±0.05K by using an Ostwald Viscometer as described elsewhere.[30] The flow time of water and solutions were measured with a digital stop clock with an accuracy of 0.01s. The viscosity values so obtained were accurate to within $±0.3×10^{-3}$Cp.The viscosity values of water at the experimental temperatures are obtained from the literature.[32]The solutions of MCM-41 varied over a concentration range of 40 ppm-140 ppm.

In Ostwald method, the time for a fixed volume of liquid to fall through into a reservoir under a variable pressure head is a function of the density and viscosity of the liquid and the dimensions of the viscometer. The time of flow and the density are measured and the viscosity of the test liquid is obtained relative to that of a reference liquid in the same viscometer from the relation,

$$\eta_1 /\eta_2 = d_1t_1/d_2t_2 \qquad (2)$$

η_1 =viscosity co-efficient of water

η_2 = viscosity co-efficient of solution

d_1 =density of water

d_2 = density of solution

t_1 = time flow of water

t_2 = time flow of solution

Measurement of conductance

The conductance measurements were carried out on a digital conductivity meter (Systronics, type 304) with a sensitivity of 0.1%.A dipping type conductivity cell with platinised electrodes(cell constant 1S cm^{-1}) was used. The measurements were made over the temperature range of 298.15-313.15 K by circulating water from a thermostatically regulated bath around the sample holder with double wall to maintain the temperature with a precision of ±0.05 K. The specific and molar conductances are expressed in terms of Scm^{-1} and Scm^2mol^{-1}, respectively. The ionic strengths of the solutions were kept as low as possible (10^{-4} to 10^{-2} M). The conductivites of the solutions of MCM-41, TiO_2-MCM-41(xx), NH_2-MCM-41(xx), and COOH-MCM-41(xx) were corrected for the contribution of the solvent.

$$\Lambda =1000 k/c \qquad (3)$$

where Λ = molar conductance,

k = Electrical conductivity (specific conductance)

c = molar concentration of the solution.

Calculation

From the density (d), viscosity co-efficient (η) data, the following parameters have been determined.

Apparent molar volume, V_ϕ was calculated by equation $(4)^{[33]}$

$$V_\phi = 1000 (cd_0)^{-1} (d_0\text{-}d) + Md_0^{-1} \qquad (4)$$

Where c is the molar concentration, d_0 is the density of the solvent, d is that of the solution and M is the molecular mass of the MCM-41.

Limiting apparent molar volume, V_ϕ^0 was determined by least squares method[33]by fitting the V_ϕ data to the Masson equation

$$V_\phi= V_\phi^0 + S_v c^{1/2} \qquad (5)$$

Where S_v is the slope of the plot of V_ϕ vs $c^{1/2}$ plot.

Apparent molar expansibility, E_ϕ was calculated by using equation $(6)^{[33]}$

$$E_\phi = E_\phi^0 + (\alpha\text{-}\alpha_0) 1000 c^{-1} \qquad (6)$$

Where α and α_0 are the co-efficient of thermal expansion of the solution and solvent, respectively, and were obtained from the usual relation.[33,34]

Limiting apparent expansibility E_ϕ^0 was determined by least squares method by fitting the E_ϕ data to the Masson equation by equation (7)

$$E_\phi= E_\phi^0 + S_E c^{1/2} \qquad (7)$$

Where S_E is the slope of the E_ϕ vs $c^{1/2}$ plot.

The average molecular weight of MCM-41 solution was determined by equation (8)

$$M = (d\eta /n) ×10^6 \qquad (8)$$

Where n=40-60.

Then molecular weight of MCM-41 was determined by substracting molecular weights of ethanol and nicotinamide from it.

The relative viscosity of the solution was determined by Jones-Dole[34] empirical equation as follows:

$$\eta_{r =} \eta /\eta_0 = 1+A_F c^{1/2}+B_J c \qquad (9)$$

where η_r is the relative viscosity, η is the viscosity co-efficient of the solution , η_0 is that of the solvent, A_F is Falken-Hagen co-efficient and B_J is Jones-Dole co-efficient.

The constants A_F and B_J are the intercept and slope of the linear plots of $(\eta /\eta_0\text{-}1)/c^{1/2}$ vs. $c^{1/2}$, respectively.

The viscosity data have been analyzed on the basis of transition state theory from the relation,[35]

$$\Delta\mu_2^0{}^*= \Delta\mu_1^0{}^*+ (RT / \bar{V}_1^0)1000B - (\bar{V}_1^0 - \bar{V}_2^0) \qquad (10)$$

Where $\Delta\mu_2^{0*}$ is the contribution per mol of the solute to free energy of activation for   viscous flow of the solution.

$$\Delta\mu_1^{0*} = 2.303 \, R \, T \log (\eta_0 \, \overline{V}_1^0 / hN) \qquad (11)$$

Where h and N are Planck's constant and Avogadro number, respectively.

$\Delta\mu_2^{0*}$ is the contribution per mol of the solvent to free energy of activation for viscous   flow of the solution.

$$V_1^0 = M_{solvent} / d \qquad (12)$$

$$V_2^0 = V_\phi^0$$

The electrical conductance of the mesoporous samples were measured as functions of their concentration in the experimental solvent at different   temperatures. The molar conductance is calculated from the specific conductance value by the relation

$$\Lambda_m = 1000 \, k/c \qquad (13)$$

where Λ_m is molar conductance, k is the specific conductance and c is the concentration of the solution.

The approximate limiting molar conductance (Λ_m^0) is obtained from the intercept of the plot between Λ_m and $c^{1/2}$ by least squares method using the equation
$$\Lambda_m = \Lambda_m^0 - Sc^{1/2} \qquad (14)$$

Where S is the Onsagar slope and Λ_m^0 is the intercept of the plot of Λ_m vs. $c^{1/2}$.

The dielectric constant of the solvent is found out by using the relation

$$S = 82.4/\eta_0 (DT)^{1/2} + 8.2 \times 10^5 /(DT)^{3/2} \Lambda_m^0 \qquad (15)$$

Where η_0, D are the coefficients of viscosity, and dielectric constant of the solvent, respectively, at temperature T.

The experimental data of conductance measurements of the solution were analyzed using the Harned and Owen least square fitting technique[33] till a constant value of limiting molar conductance (Λ_m^0) is obtained
$$\Lambda = \Lambda_m^0 - (Ac^{1/2} / 1 + B \, c^{1/2}) \qquad (16)$$
Λ_m^0, A, B = Fitting parameters
From the linear plot between Λ_m and $c^{1/2}$, Λ_m^0 is evaluated from the intercept. The procedure was repeated till constant values of Λ_m^0 are obtained.

The dissociation constant K_d is obtained by the expression

$$K_d = (\alpha^2 c) / (1 - \alpha) \qquad (17)$$

The standard free energy change, ΔG^0 for the dissociation process is calculated from the following relation,

$$\Delta G^0 = - RT \ln K_d \qquad (18)$$

The heat of dissociation ΔH^0 is calculated from the slope of the plot of $\ln K_d$ vs $1/T$ and the entropy change, ΔS^0 from Gibbs - Helmholtz equation,

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \qquad (19)$$

The activation energy of the transport process is determined from the relation

$$\Lambda_m^0 = A \, e^{-Es/RT} \text{ or } \log \Lambda_m^0 = \log A - E_s/2.303RT \qquad (20)$$

Where A is the frequency factor, R is the gas constant and E_s is the Arrhenius activation energy. From the plot of log Λ_m^0 vs. $1/T$, the E_s values have been computed from the slope (= $- E_s/2.303 \, R$)

The Walden product ($\Lambda_m^0 \eta_0$) is calculated for the samples using the coefficients of viscosity of the solvent (η_0) at temperature T.

Drug loading and release

The MCM-41, NH_2-MCM-41(10 and 15 wt. %) were loaded with the aspirin by mixing the aspirin in ether until it dissolved and then adding the mesoporous materials with magnetic stirring for 12–24 h at 25 °C. The solution was filtered and dried at 25 °C overnight. Then loading amount of the drug is determined colourimetrically using iron (III) chloride with a Spectronic 20 set at 530 nm. For release profiles, 300 mg of the aspirin loaded materials were placed in a phosphate buffer solution with pH = 7.4 at 37.4 °C. The contents were stirred at ~50 rpm, and 5 mL aliquots were removed at regular intervals of time, diluted,   and   analyzed   in   UV-vis   nanodrop spectrophotometer at λ = 265 nm.

RESULTS AND DISCUSSION

Characterization of materials

The Field Emission Scanning Electron Microscopy (FE-SEM)   and   Fourier-Transform-Infrared spectroscopy (FTIR) of mesoporous COOH-MCM-41 is shown in Fig. 2 (A and B). FE-SEM indicated the 2D hexagonal long range mesoscopic morphology of COOH-MCM-41).The uniform distribution of spherical particles representing the outer surface shows the typical siliceous material.
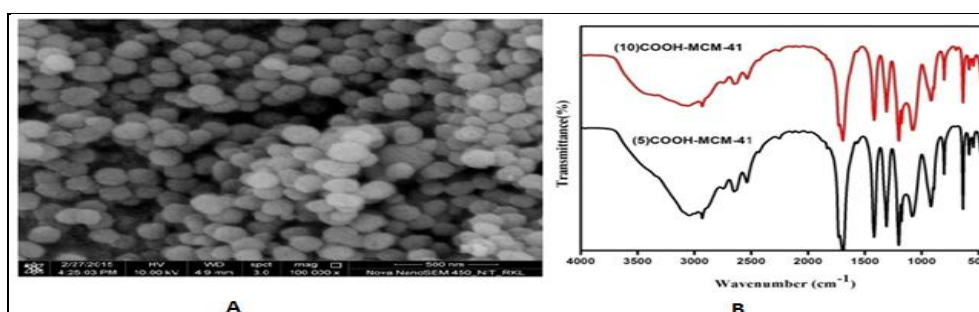

Figure 2: FE-SEM (A) and FTIR (B) image of COOH-MCM-41.

The symmetric and asymmetric stretching vibration bands characteristic for carboxylate (COO–) groups can be found at 1555 and 1411 cm^{-1} in both samples, respectively. The band at 1626 cm^{-1} is registered only in the spectrum of MCM-41COOH and it can be associated with the presence of amide groups (-NH-CO) strongly hydrogen bonded in the network. In the spectrum of the COOH-MCM-41 sample two additional bands appear. The band at 1697 cm^{-1} can be attributed to the strongly hydrogen bonded COOH groups. This is an indication of the fact that the number of carboxylic groups is higher; they can be found in close vicinity and can interact with each other or with the neighboring silanol groups. The shoulder at 1717 cm^{-1}

is characteristic of non dissociated, "free" carbonyl groups. The weak band at 1770 cm^{-1} can be associated with the unreacted succinic anhydride in the sample. The CH$_2$ deformation vibration of hydrocarbon chains can also be detected at the 1350–1450 cm^{-1} regions.[36]

Densiometric study

The values of parameters V_ϕ(m^{3}mol^{-1}), V_ϕ^0(m^{3}mol^{-1}), S_v (m$^{9/2}$mol$^{3/2}$), E_ϕ(m^{3}mol^{-1}K^{-1}),E_ϕ^0(m^{3}mol^{-1}K^{-1}),S_E(m$^{9/2}$mol$^{-3/2}$K^{-1}) for solutions of COOH-MCM-41(5),COOH-MCM-41(10) of different concentrations and temperature are calculated from density values by using equations 4-7 and are represented in Table 1.

Table 1: Values of parameters V_ϕ(m^{3}mol^{-1}), V_ϕ^0(m^{3}mol^{-1}), S_v (m$^{9/2}$mol$^{3/2}$), E_ϕ(m^{3}mol^{-1}K^{-1}),E_ϕ^0(m^{3}mol^{-1}K^{-1}),S_E(m$^{9/2}$mol$^{-3/2}$K^{-1}) for solutions of COOH-MCM-41(5),COOH-MCM-41(10) of different concentrations and temperatures.

COOH-MCM-41(5) in 0.1 M nicotinamide in ethanol

Temp(K)	c×10^7 moldm^{-3}	V_ϕ×10^{-7}	V_ϕ^0×10^{-7}	S_v×10^{-10}	E_ϕ×10^{-5}	E_ϕ^0×10^{-6}	S_E×10^{-9}
298.15	2.633	0.305			0.374		
	3.950	0.655			1.378		
	5.267	1.044	-93.688	125.170	4.915	-50.036	66.850
	6.584	0.458			3.900		
	7.900	1.021			5.304		
	9.217	1.109			0.866		
303.15	2.633	0.067			0.227		
	3.950	0.434			1.274		
	5.267	0.522	-55.930	74.724	3.592	-37.555	50.174
	6.584	0.134			3.822		
	7.900	0.785			8.661		
	9.217	0.799			0.840		
308.15	2.633	0.115			0.113		
	3.950	0.724			1.219		
	5.267	1.751	-112.52	150.341	3.636	-30.216	40.370
	6.584	0.943			3.842		
	7.900	0.933			5.215		
	9.217	1.050			0.791		
313.15	2.633	0.357			-0.021		
	3.950	0.856			1.126		
	5.267	1.589	-140.48	187.698	3.544	-29.437	39.329
	6.584	1.043			3.788		
	7.900	1.807			5.237		
	9.217	1.234			0.762		

DISCUSSION

The value of V_ϕ^0 is negative for COOH-MCM-41(5) which means weak solute-solvent interaction where as its positive value for COOH-MCM-41(10) indicates strong solute-solvent interaction.[35]However, the solute-solvent interaction is greater for carboxyl modified MCM-41 than that of unmodified MCM-41.That means interaction of the material with solvent molecules increases with

increase in weight % of -COOH group. The value of S_v indicates solute-solute interaction. Its positive value for COOH-MCM-41(5) indicates strong solute-solute interaction and reverse case for COOH-MCM-41(10). Negative value of E_ϕ^0 means no caging effect in both weight %. A perusal from Table 1 indicates that the solution of COOH-MCM-41(10) is highly favored in the solvent (ethanol). The caging effect is absent in carboxyl modified samples as shown by the negative value.

COOH-MCM-41(10) in 0.1 M nicotinamide in ethanol.

298.15	2.660	0.066			25.843		
	3.991	1.026			16.605		
	5.321	0.443	0.413	-0.010	13.479	-161.23	0.0214
	6.651	0.170			4.318		
	7.982	0.034			3.777		
	9.312	0.693			15.052		
303.15	2.660	1.252			25.815		
	3.991	1.694			16.819		
	5.321	1.038	2.727	-2.343	13.479	-161.46	0.0214
	6.651	0.682			4.318		
	7.982	0.429			3.777		
	9.312	0.615			15.052		
308.15	2.660	3.877			25.919		
	3.991	3.828			16.992		
	5.321	1.924	8.035	-7.962	13.482	-161.93	0.0215
	6.651	0.664			4.262		
	7.982	0.146			3.705		
	9.312	1.570			15.056		
313.15	2.660	3.989			25.774		
	3.991	3.526			16.551		
	5.321	2.482	6.520	-5.44	3.452	-160.70	0.0213
	6.651	0.822			4.213		
	7.982	0.690			3.692		
	9.312	2.957			15.130		

Viscometric study

The Values of parameters A_F ($dm^{3/2}mol^{-1/2}$), B_J ($dm^3 mol^{-1}$), $\overline{V}_1{}^0$(m^3), $\Delta\mu_1{}^0*$($kJ\ mol^{-1}$), $\Delta\mu_2{}^0*$($KJ\ mol^{-1}$) for solutions of COOH-MCM-41(5), COOH-MCM-41(10) of different concentrations at different temperatures are calculated by using equations 9-12 and are represented in Table 2.

Table 2: Values of parameters A_F ($dm^{3/2}mol^{-1/2}$), B_J ($dm^3 mol^{-1}$), $\overline{V}_1{}^0$(m^3), $\Delta\mu_1{}^0*$($kJ\ mol^{-1}$), $\Delta\mu_2{}^0*$($kJ\ mol^{-1}$) for solutions of COOH-MCM-41(5), COOH-MCM-41(10) of different concentrations at different temperatures.

Parameters	COOH-MCM-41(5)				COOH-MCM-41(10)			
	298.15	303.15	308.15	313.15	298.15	303.15	308.15	313.15
A_F	494.4	5027	5893	5132	-122	-157.0	-222.0	-93.00
$B_J \times 10^{-4}$	-66.05	-671.6	-787.3	-685.7	11.70	18.52	28.04	8.85
$\Delta\mu_1{}^{0*}$	67.30	68.17	69.02	69.85	67.30	68.17	69.02	69.85
$\Delta\mu_2{}^0 \times 10^{-9}$	-6.629	-677.2	-808.2	-716.5	11.58	18.69	28.83	9.29
$B/V_\phi{}^0 \times 10^3$	0.705	12.007	6.996	4.881	28.329	6.808	3.491	1.357

Identical conclusions in regard to solute-solute and solute-solvent interactions are obtained from the viscometric and apparent molar volume data. The negative values of coefficient A_F for COOH-MCM-41(10) indicate the presence of weak solute-solute interaction, which may be attributed to the formation of a sheath of ethanol molecules around the solute resulting in the weakening of solute-solute interaction. The positive value of B_J in COOH-MCM-41(10) may be ascribed to the increased solute-solvent interactions owing to the structure making tendency of the solute in the solvent.[37,38] $\Delta\mu_2{}^0$, the Gibbs free energy of activation for viscous flow of solution is positive; this suggests that there is strong interaction between the solute and solvent molecules in the transition state than in the ground state.

Conductometric study

It is found that, limiting molar conductance (Λ^0_m) increases with increase in temperature up to 35^{0}C then decreases. It follows our basic concept that with increase of temperature mobility of ions increases so conductance value increases. This is due to the fact that the increased thermal energy results in greater bond breaking and also variation in vibrational, rotational and translational energy of molecules lead to higher frequency and higher mobility of ions. However at high temperature, conductance decreases due to solvation of ions. Greater the weight %, greater is the conductance value. 10 weight % of COOH-MCM-41 has greater value of conductance than 5 weight % COOH-MCM-41 due to presence of more COO$^-$ ions. The thermodynamic parameters K_d (dm^3 mol^{-1}), $\Lambda_0\eta_0$, ΔG^0 (kJ mol^{-1}), ΔH^0 (kJ mol^{-1}), ΔS^0 (kJ mol^{-1} K^{-1}) and Es(kJ mol^{-1}) at different temperatures calculated by using equations 17-20 and are represented in Table 3.

Table 3: Thermodynamic parameters K_d (dm^3 mol^{-1}), $\Lambda_0\eta_0$, ΔG^0 (kJ mol^{-1}), ΔH^0 (kJ mol^{-1}), ΔS^0 (kJ mol^{-1} K^{-1}) and Es(kJ mol^{-1}) of at different temperatures.

COOH-MCM-41(5 weight %)

Temp (K)	Conc.c×10^7 (Moldm^{-3})	K_d×10^7	$\Lambda_0\eta_0$	ΔG^0	ΔH^0	ΔS^0	E_s
298.15	2.633	0.705	5308.739	40.824	77.171	0.121	-25870.569
	3.950	0.056		47.100	184.401	0.460	
	5.267	0.497		41.693	277.587	0.791	
	6.584	0.560		41.396	203.135	0.542	
	7.900	0.120		45.211	268.189	0.747	
	9.217	0.720		40.773	212.060	0.574	
303.15	2.633	2.454	8338.201	44.171	77.171	0.108	-26304.421
	3.950	0.012		51.764	18.4401	0.437	
	5.267	7.980		35.395	277.587	0.798	
	6.584	0.352		43.258	203.135	0.527	
	7.900	0.005		53.973	268.189	0.706	
	9.217	0.065		41.683	212.060	0.562	
308.15	2.633	0.127	3824.986	46.575	77.171	0.099	-26738.272
	3.950	0.0004		61.070	184.401	0.400	
	5.267	24.099		33.147	277.587	0.793	
	6.584	1.712		39.923	203..135	0.529	
	7.900	0.246		44.890	268.189	0.724	
	9.217	3.116		38.388	212.060	0.563	
313.15	2.633	4.841	732.3612	37.864	77.171	0.125	-27172.124
	3.950	10.004		35.963	184.401	0.474	
	5.267	134.37		29.210	277.587	0.793	
	6.584	27.024		33.386	203.135	0.542	
	7.900	11.240		35.671	268.189	0.742	
	9.217	42.285		32.220	212.060	0.574	

COOH-MCM-41(10 weight %)

Temp (K)	Conc.c ×10^7 (Moldm^{-3})	K_d×10^7	$\Lambda_0\eta_0$	ΔG^0	ΔH^0	ΔS^0	E_s
298.15	2.660	2.718	10222.01	37.481	51.784	0.047	1697.300
	3.991	0.00084		57.501	240.848	0.614	
	5.321	0.329		42.710	70.348	0.092	
	6.651	0.598		41.232	42.776	0.005	
	7.982	0.010		51.203	64.194	0.043	
	9.312	0.070		46.536	73.950	0.091	

	2.660	1.817		39.124	51.784	0.041	
	3.991	0.124		45.878	240.848	0.643	
303.15	**5.321**	0.337	12891.46	43.371	70.348	0.088	1725.764
	6.651	0.383		43.047	42.776	-0.00089	
	7.982	0.015		51.166	64.194	0.042	
	9.312	0.048		48.278	73.950	0.084	
	2.660	4.427		37.488	51.784	0.046	
	3.991	0.032		50.078	240.848	0.619	
308.15	**5.321**	0.453	10802.56	43.328	70.348	0.087	1754.228
	6.651	0.503		43.058	42.776	-0.0009	
	7.982	0.0045		55.137	64.194	0.029	
	9.312	0.074		47.948	73.950	0.084	
	2.660	6.196		37.221	51.784	0.046	
	3.991	0.231		45.782	240.848	0.622	
313.15	**5.321**	1.373	8575.596	41.145	70.348	0.093	1782.692
	6.651	1.392		41.109	42.776	0.005	
	7.982	0.065		49.056	64.194	0.048	
	9.312	0.304		45.070	73.950	0.092	

A perusal of Table 3 shows that, the dissociation constant K_d, is found to be positive for both weight % of COOH-MCM-41. The Walden product is greater for 10 weight % of COOH-MCM-41. The free energy change, ΔG^0 values are positive i.e., the association process is favored over the dissociation process in the solvent. [39] Dissociation process is endothermic or energy absorbing for both weight % of COOH-MCM-41. The positive entropy values indicates the increase in randomness due to dissociation. The activation energy is found to be positive for 10 weight % of COOH-MCM-41 and negative for 5 weight % of COOH-MCM-41. [40]

Aspirin loading

Loading of Aspirin into mesoporous materials was confirmed by FTIR analysis (Fig. 3) using Jasco FTIR (Model 4100, Japan).
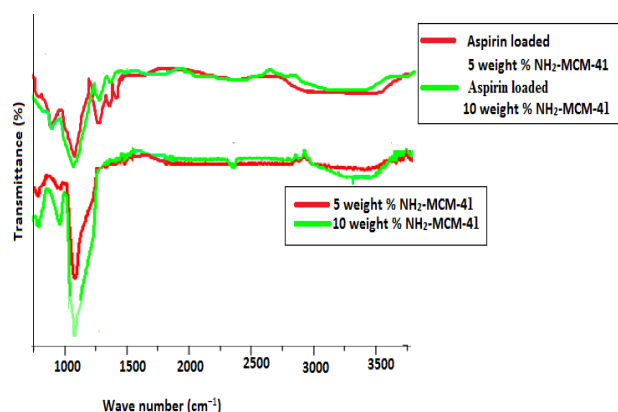

Figure 3: FTIR image of NH_2-MCM-41 and aspirin loaded NH_2-MCM-41.

In amine modified MCM-41, a peak due to N-H bending vibration is observed at 1532 cm^{-1}. The spectra of amine modified MCM-41 and aspirin loaded amine modified MCM-41 nearly similar due to the overlapping vibrations of aspirin and NH_2-MCM-41. The peak at nearly 1700 cm^{-1} attributed due to carbonyl group of COOH of aspirin is found to be absent in the Fig.3. This is due to the strong interaction between carbonyl group and amine group in the drug loaded samples.

Aspirin loading to MCM-41, NH_2-MCM-41(5), and NH_2-MCM-41(10) were calculated by Beer-Lambert's Law. [41-43] It is found that the loading of aspirin into APTES functionalized MCM-41 was enhanced by 20–70% relative to the unfunctionalized MCM-41. The increase in aspirin loading in the amine functionalized MCM-41 materials is attributed to the favorable amine group and aspirin interaction (Fig. 4). In parent MCM-41, aspirin is weakly bound to silanol groups. But, in amine modified samples, there exist a stronger interaction between the $-NH_2$ group, and $-COOH$ group, which increases the drug loading capacity of the later. [44] The amount of functionalization governs the drug loading. With increase in weight % of amine, Aspirin loading increases for our two samples. But further increase in weight % of amine (data not shown), loading of Aspirin decreases due to pore blocking.
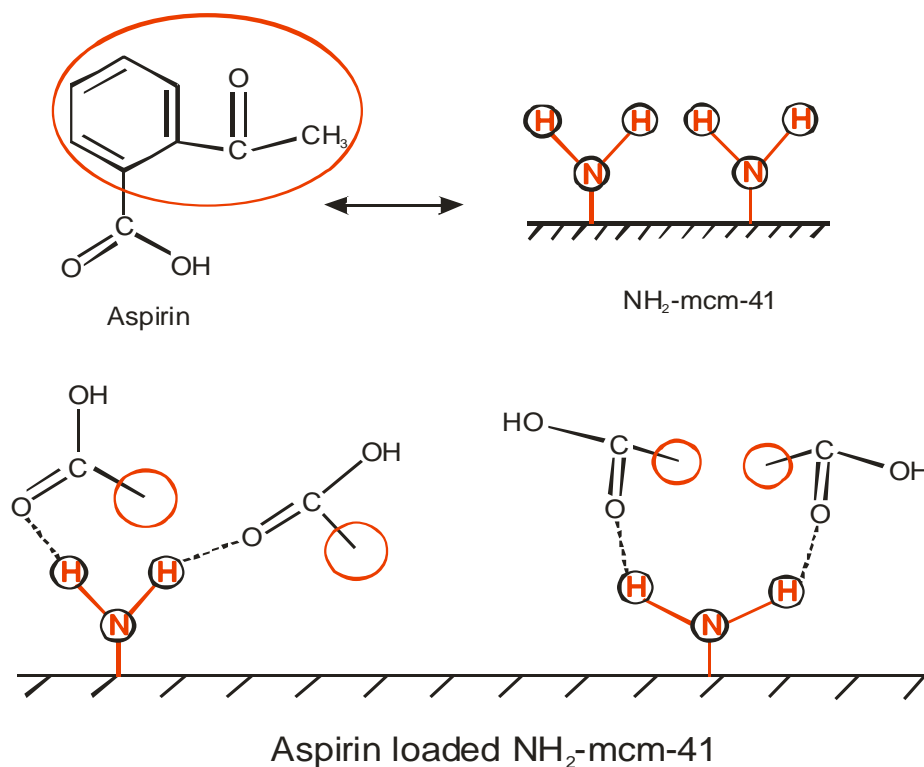
Figure 4: Mechanism of Aspirin loading of on NH₂-MCM-41.

A comparison of the loading of aspirin for the different samples is provided in Fig. 5(A).

Aspirin release

The % of drug release as a function of time for MCM-41, NH₂-MCM-41(5 wt. %), and NH₂-MCM-41(10 wt. %) were calculated and plotted in Fig. 5(B). From the plot it is found that, not less than 40% of the labeled amount of $C_9H_8O_4$ is dissolved in 30 minutes. The release of Aspirin becomes constant after 4 hours. It is found that MCM-41 shows highest drug releasing capacity among the three.

This may be due to the weak interaction of drug and MCM-41which results in the increase in drug releasing rate. NH₂-MCM-41(10 wt. %) shows lowest drug release capacity, this may be due to strong hydrogen bonding between amino group and carboxyl group. So, the release profile for aspirin can be controlled by amine modification of the mesoporous MCM-41.
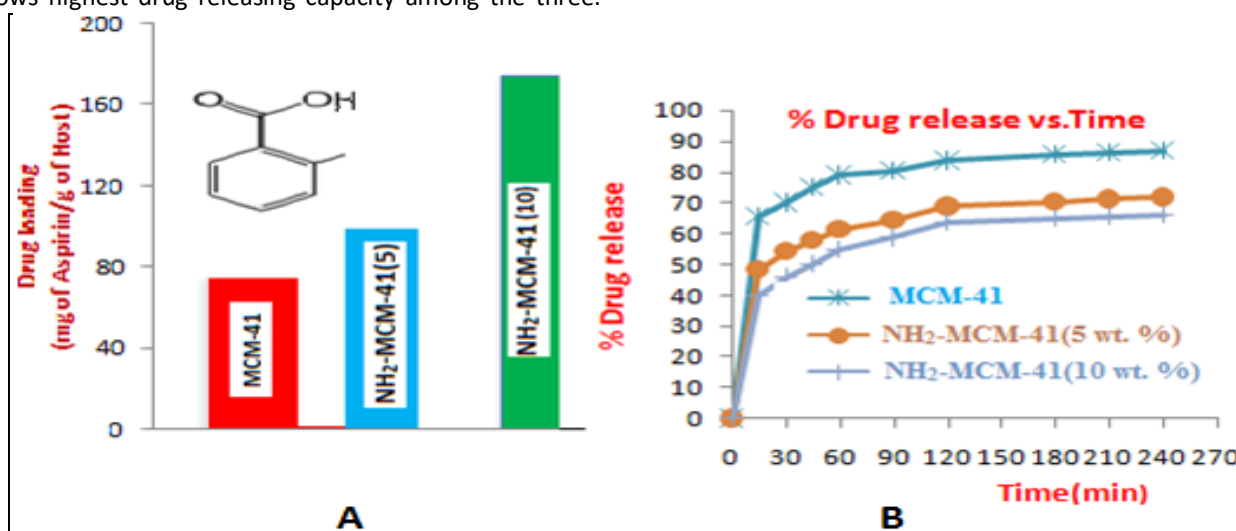

Figure 5: The loading (A) and in vitro release(B) of Aspirin from MCM-41, NH₂-MCM-41(5), and NH₂-MCM-41(10).

CONCLUSION

It is found that 10 weight % COOH-MCM-41 is solvated in the solvent (ethanol in presence of nicotinamide), as found from the positive values of V_ϕ^0 and B_J. The negative values of coefficient A_F for COOH-MCM-41(10) indicates

the presence of weak solute-solute interaction, which may be attributed to the formation of a sheath of ethanol molecules around the solute resulting in the weakening of solute-solute interaction or solute-co-solute association. The transition state treatment of viscosity data indicates

that there is strong interaction between the solute and solvent molecules in the transition state than in the ground state for COOH-MCM-41(10).Amine functionalized MCM-41 is found to be a novel carrier for drug delivery of aspirin. The -NH$_2$ group present on the surface of amine modified MCM-41 provide ample opportunities for drug molecules like aspirin, having –COOH group to be loaded on its surface and thereby providing controlled release of the drug. The rate of loading of aspirin increases with increase in weight % of amine. The in vitro release of Aspirin is more for MCM-41. It is found that 78 % of release occurs within 60 minutes. Whereas it can be decreased to 61 % for amine modified MCM-41.So amine functionalization of MCM-41 is found to be fruitful for the controlled release of Aspirin. 10 wt. % NH$_2$-MCM-41 shows highest drug loading capacity, lowest drug release capacity among the three samples (MCM-41, COOH-MCM-41(5), and COOH-MCM-41(10) due to the stronger interaction between amino group and carboxyl groups of the amine modified MCM-41, and aspirin respectively.

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