CONDUCTANCE MEASUREMENTS OF MCM-41 AND TIO$_2$-MCM-41 IN PRESENCE OF NICOTINAMIDE (A HYDROTROPIC AGENT) IN ETHANOL FOR PARTIALLY SOLUBLE DRUGS

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ABSTRACT

The conductance measurements of MCM-41 and TiO$_2$-MCM-41(10 and 15 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 conductance data have been analyzed by Shedlovsky method to obtain Λ_0 and K_A. The thermodynamics parameters,such as change in enthalpy, entropy and free energy for the ion pair formation have been calculated from the value of ion association constant at constant temperature. The results have been discussed in terms of ion-ion, ion-solvent and solvent-solvent interactions and also the effects of various substituents(groups) were investigated. This investigation gave detailed information regarding pharmakokinetics and pharmakodynamics of these drug carriers.

KEY WORDS: TiO$_2$-MCM-41, Ethanol, Nicotinamide,Association constant.

1 INTRODUCTION

The application of mesoporous silica materials as drug carriers has shown a new hope to the researchers for the delivery of water insoluble drugs which is the major obstacle and challenge for most of the pharmaceutical companies[1].The modification of these materials by certain functional groups also affects the drug delivery activity of these materials[2].Considering this useful application of mesoporous material in medicinal field,we have attempted to study the density and viscosity of mesoporous MCM-41[3] which provides valuable information regarding molecular interactions taking place in the

system.Modification of internal pore surfaces of mesoporous materials with metal oxide surface groups is possible.Titania nanoparticle is a low cost,low toxic,highly stable,promising,semiconducting transition metal oxide which has proved itself very useful as an effective catalyst, photocatalyst,electrode material,and also as an improved drug delivery system(DDS)for cancer treatment. The titania containing MCM-41 were reported for the first time in 1994[4].The titania incorporation into the pores of MCM-41 increases its specific surface area(>200 m^2g^{-1}) in comparison to pure titania.So it is expected to have outstanding applications in mesoporous form.

The limiting molar conductivity(Λ_m^0), association constant(K_A), Walden products ($\Lambda_m^0\eta_0$),ΔH^0, ΔS^0 and ΔG^0 are used as a probe for getting insight into the dynamic aspects of ion-solvent interactions[5] .Literature reveals the study of molecular interactions of water insoluble drugs,aminoacids,and hydrotropic agents by conductance measurements[6-8]. Many work highlighted the effect of the solubility enhancers (hydrotropic agents)[9,10] and hence improved solubility of the drug,but no detailed explanation is available relating to the improvement phenomenon for a drug delivery system.Again conductometric study of mesoporous materials in presence of hydrotropic agent is seldom reported.

The presence of silanol groups on the surface of mesororous materials facilitates the reaction with alcohols,and the materials become stable in nonaqueous media like alcohol.Thats why we hav attempted to study the thermodynamics behaviour,conductometric properties of solute (MCM-41, TiO_2-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 at an interval of 5K. The data were analyzed by Shedlovsky method[8]. The thermodynamics parameters,such as ΔH^0; ΔS^0 and ΔG^0 for the association have been studied from the values of ion association constant at different temperatures. The calculated values have been used to discuss qualitatively the nature of different interactions. This study will provide better scope for structural elucidation,delivery activity,mechanism of action and hydrotropic solubilisation of these materials to act as potential carriers for most of the hydrophobic drugs.

2 MATERIALS AND METHODS

2.1. Materials

Cetylhexadecyltrimethylammoniumbromide(CTAB) used as structure directing agent, Tetraethylorthosilicate(TEOS) used as the silica source, ammonia solution used as mineralizing agent,and nicotinamide used as hydrotropic agent, respectively, were purchased

from Merck and Degussa P-25 as titania source(80% anatase,20% rutile) ,and Sodium hydroxide were purchased from Sigma-Aldrich.Ethanol used was of AnalaR grade and used after dehydration with molecular sieve over night.Deionized water (Sp. Cond. ~10^{-6} S cm^1) was used throughtout the experiment.

2.2. Synthesis

The pristine MCM-41 was prepared as reported earlier[3].Various amounts of titania (0.30g and 0.45g)were added to 1.5 g of CTAB in 30 ml deionized water.Then 3 ml of TEOS and 45ml of ethanol were added and stirred for 30 minutes for hydrolysis.10.1 ml of ammonia solution was added at once to the reaction mixture causing immediate gel formation.Then the precipitate was filtered,washed several times with deionized water and dried at 80^0 C for 24 h.Calcination of the samples was carried out at 550^0 C for 5h.

2.3. Preparation of solution of MCM-41

The solutions of MCM-41, and TiO$_2$-MCM-41(10 and 15 weight %), were prepared by using 0.1 M solution of nicotinamide in ethanol as solvent. The concentration of the solutions ranges from 40ppm to 140ppm and the solutions were used on the same day.

2.4. Measurement of conductance

The conductance values of the solutions were measured by means of a conductivity meter (Elico make) at a cell constant of 1S cm^{-1} at different temperatures ranging from 298.15K to 313.15K at an interval of 5K.

3 Theoretical aspects

1. The molar conductance is calculated from the specific conductance value by the relation $\Lambda_m =1000$ k/c [1] Where Λ_m is molar conductance,k is the specific conductance and c is the concentration of the solution.

2. Then approximate limiting molar conductance (Λ_m^0) is obtained from the intercept of the plot between Λ_m and c$^{1/2}$ least squares method (10) using the equation $\Lambda_m= \Lambda_m^0 -S$ c$^{1/2}$ [2] Where S is the slope and Λ_m^0 is the intercept of the plot of Λ_m vs. c$^{1/2.}$

3. 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)$^{3/2}$ Λ_m^0 (3) Where η_0 and D are the coefficient of viscosity,dielectric constant of the solvent at temperature T.

4. The experimental data of conductance measurements of the solutions were analysed using the Shedlovsky extrapolation technique, [11]

$1/\Lambda_m S (Z) = 1/\Lambda_0 + K_A/ \Lambda_0^2 c\Lambda_m S (Z)$ (4) where $S(Z) = 1+Z+Z^2/2+Z^3/8$ and $Z = S(\Lambda_m c)^{1/2}/ \Lambda_m^{0\ 3/2}$ From the linear plot between $1/ \Lambda_m S (Z)$ and $c\Lambda_m S (Z)$, Λ_m^0 and K_A were evaluated from the intercept and slope, respectively.The procedure was repeated till constant values of Λ_m^0 and K_A were obtained.

5. The free energy change, ΔG^0 for the association process is calculated from the following relation $\Lambda G^0 = - RT \ln K_A$ [5] The heat of association ΔH^0 is calculated from the slope of the plot of $\ln K_A$ *vs* $1/T$ and the entropy change, ΔS^0 from Gibbs - Helmholtz equation, $\Delta G^0 = \Delta H^0 - T\Delta S^0$ [6]

6. The activation energy of the transport process is determined from the relation $\Lambda_m^0 = A\ e^{-Es/RT}$ or $\log \Lambda_m^0 = \log A - E_s/2.303RT$ [7]

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

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

4 RESULTS AND DISCUSSION

4.1. Characterization of materials

The Scanning Electron Microscopy (SEM) indicated the 2D hexagonal long range mesoscopic morphology of MCM-41, and TiO_2-MCM-41(10 and 15 weight %)(Figs1, 2, and 3). The uniform distribution of spherical particles representing the outer surface shows the typical siliceous material.
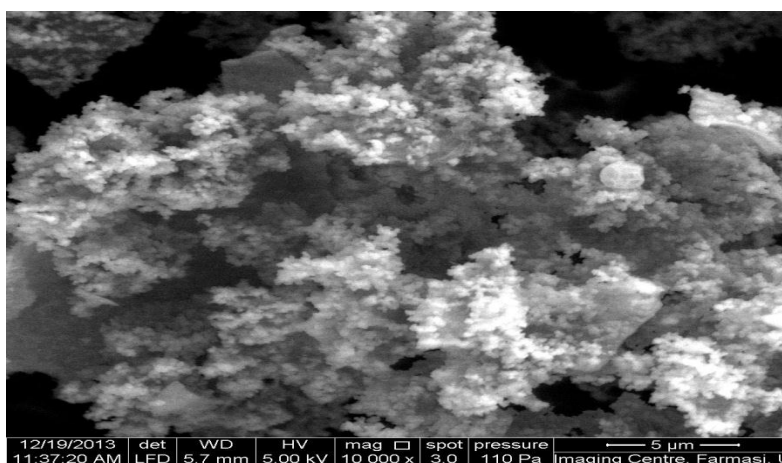

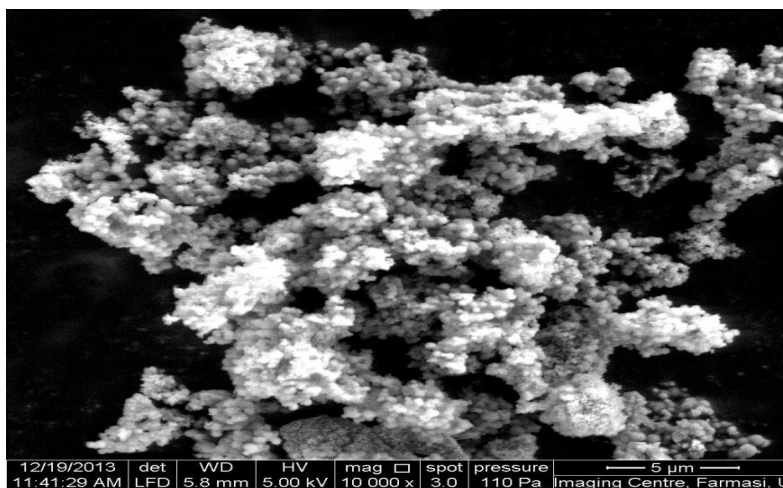**Fig 1. SEM image of mesoporous MCM-41**

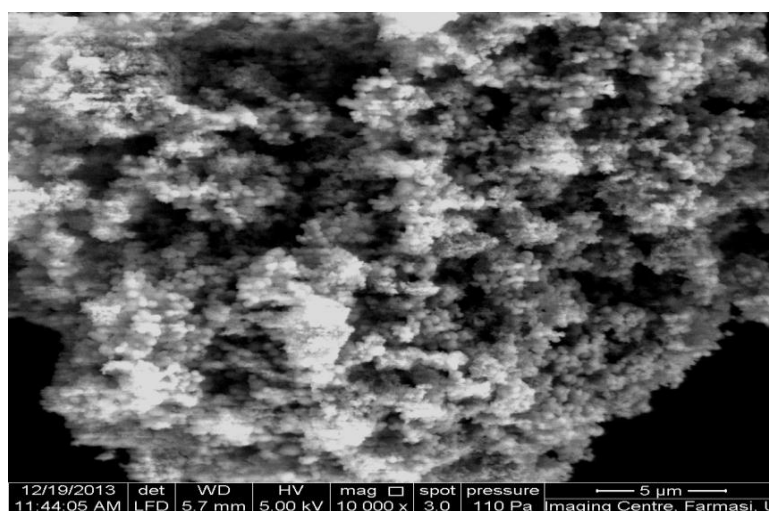**Fig 2. SEM image of mesoporous TiO$_2$-MCM-41(10 weight %)**

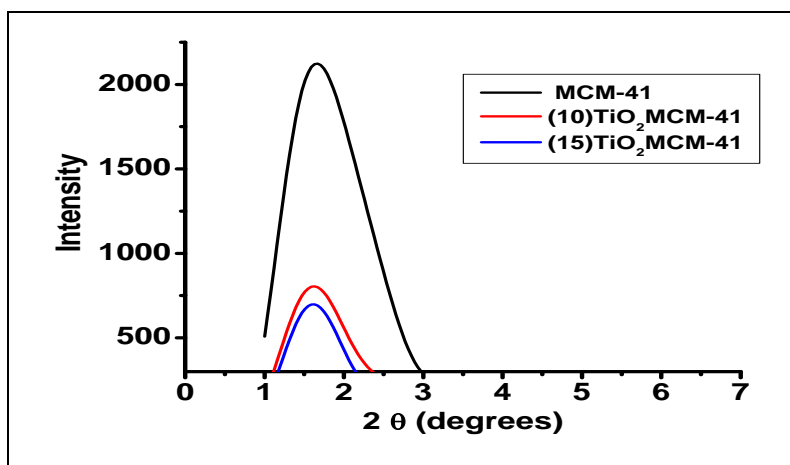**Fig 3. SEM image of mesoporous TiO$_2$-MCM-41(15 weight %)**

Fig 4. XRD image of mesoporous MCM-41, TiO2-MCM-41(10 weight %, 15 weight %)

X-ray diffractogram of pure MCM-41 as well as titania modified MCM-41, a diffraction peak at 100 in low ɵ region is characteristics of long range ordered hexagonal MCM-41 mesoporous phase. This peak still remains even after modification with TiO_2, which indicates that, modification has no adverse effect on ordered mesoporous structure of MCM-41.But, the intensities of Bragg's peak decrease which may be due to the decrease in mesoscopic order due to titania deposition on MCM-41(Fig 4).

FTIR investigations

Fig 5 is the FTIR image of MCM-41 and TiO_2-MCM-41 (10 weight %, and 15 weight %) between 1000-4000 cm^{-1} wave number. The absorption peak at 3738 cm^{-1} is due to the free silanol groups.The broad band between 3100-3600   cm^{-1} is due to physically adsorbed water.The peaks between 1620-1601 cm^{-1} are due to H-O-H stretching vibration in the Si-O-Si structure.
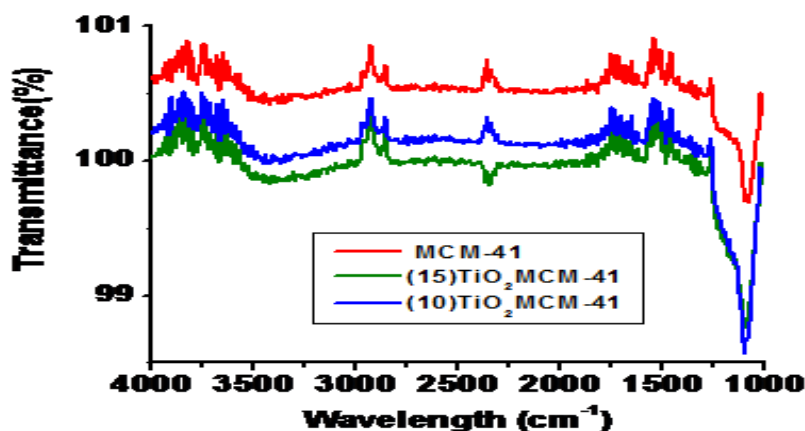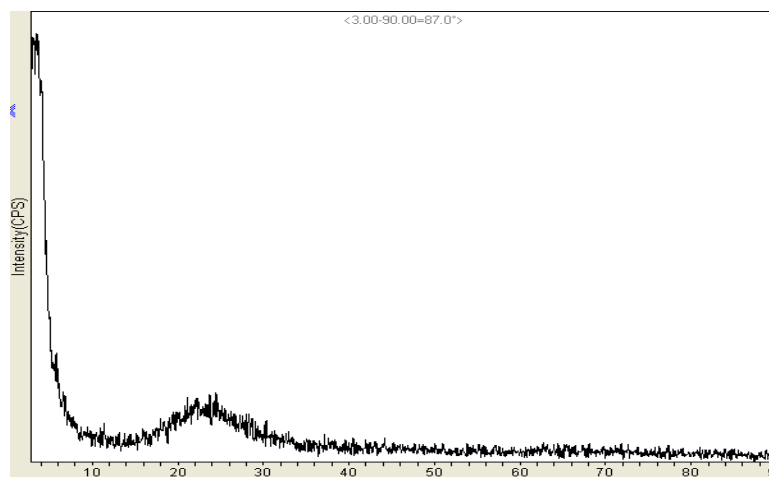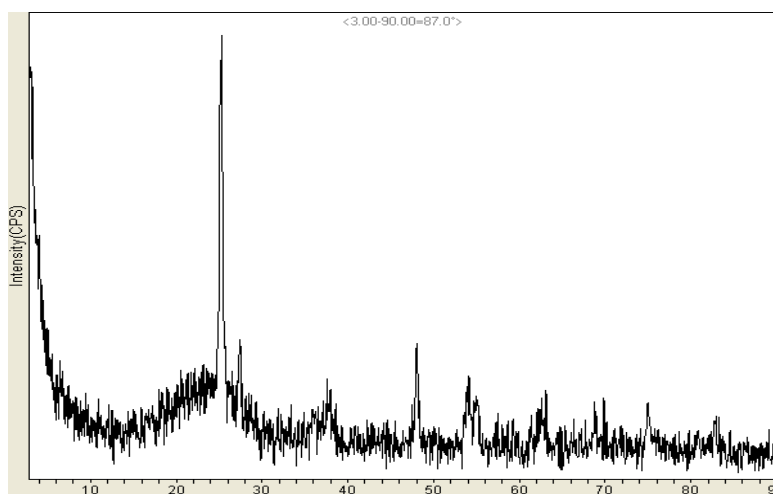

Fig 5.FTIR image of mesoporous MCM-41 and TiO_2-MCM-41(10 weight %, and15 weight %).

a

b

Fig 6.Composite diffractogram of MCM-41(a) and 15 weight % TiO$_2$-MCM-41

Fig 6 depicts the composite diffractogram of MCM-41 and (15 weight %) TiO$_2$-MCM-41 which shows the XRD pattern from 0-100^0 of 2θ value. The peak at 24^0 confirms the hexagonal array in neat and modified MCM-41 and the peak at 25.2^0 and 27.3^0 confirms the retention of anatase phase in TiO$_2$.These figures are more authentic proof for retention of hexagonal structure and rutile phase.

4.2. Conductance measurements

It is evident from Table 1 that the values of specific conductance(k),molar conductance(Λ_m) and limiting conductance(Λ_m^0) increase regularly with increase in temperature for MCM-41 and TiO$_2$-MCM-41(10 weight %,and15 weight%), indicating less solvation or higher mobility of the ions in the solvent systems studied. 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[12].But it is found that,specific and molar conductance of MCM-41 are greater than that of the titania modified TiO$_2$-MCM-41.Between 10 weight %,and15 weight % TiO$_2$-MCM-41,the conductance value of latter is more than that of former except for 140 ppm at 40^{0}C. The reason is that in the surface of MCM-41 is embedded with large number of pendant –OH groups(8-27%) which exist as oxonium ions when dissolved in solvent.But in TiO$_2$-MCM-41,the silanol groups undergo co-condensation with titania forming Si-O-Ti bonds which exist as a monolayer in the inner walls of TiO$_2$-MCM-41(Fig 7).So conductivity decreases with titania loading .But with increase in weight % of titania, more Ti-O-Ti bonds are formed which forms more TiO$^-$ ions when dissolved in the solvent increasing the conductance

value.The limiting molar conductance of all the samples shows no regular change in conductance value with titania loading.However, molar conductance decreases with increase in concentration upto 80 ppm and reaches maximum at 100 ppm.Then different trend is followed by the three samples.(Fig 8)
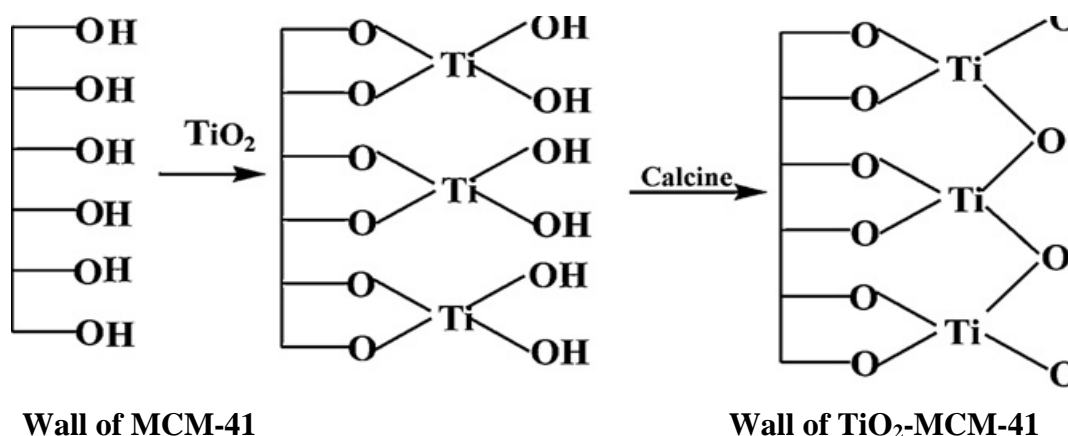

Wall of MCM-41   **Wall of TiO$_2$-MCM-41**

Fig 7.Mechanism for titania loading

A perusal of table 2 shows that association constant (K_A) shows no regular trend with increase in temperature.The Walden product is the highest for MCM-41which indicates weak solvation of the ions. It is known that the variation of Walden product reflects the change of solvation. As the weight percentage of titania increases, there is a variation trend observed in Walden product values.From this value it is found that TiO$_2$-MCM-41(15 weight %) is highly solvated in the solvent.It is evident that the activation energy, E_s, is positive for all the samples in the solvent. The free energy change, ΔG^o, values are positive for all the systems studied. This shows that the dissociation process is favoured in the solvent. The positive values of ΔH^o shows that the association process is endothermic in nature and the negative values of ΔS^o indicates that randomness is decreased in the solvent system.

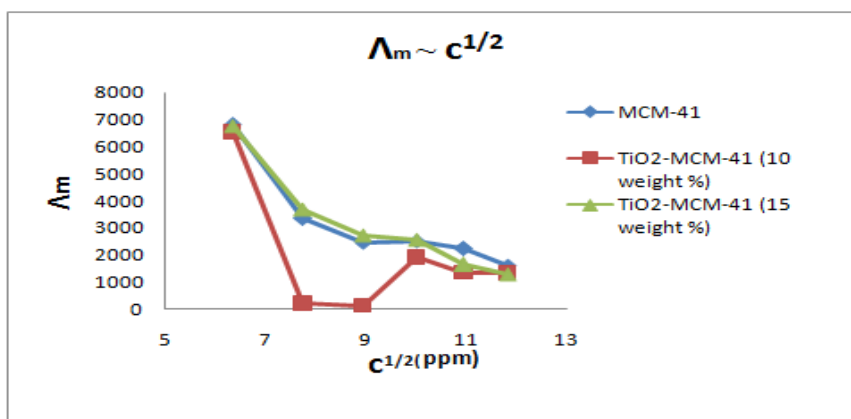**Fig 8. Plot of molar conductance Λ_m vs c$^{1/2}$ for solutions of MCM-41, TiO$_2$-MCM-41(10 weight %), and TiO$_2$-MCM-41 (15weight %) at 298.15K.**

Table 1. Values of Specific conductance (k) (Scm^{-1}), molar conductance (Scm^{2}mol^{-1}) and limiting molar conductance (Λ_m^0) (Scm^{2}mol^{-1}) for different concentrations of MCM-41 and TiO$_2$-MCM-41 (10 weight %, and15 weight %)in ethanolic nicotinamide solution at different temperatures.

Temp (K)	Conc.(ppm)	Specific conductance(k)			Molar conductance(Λm)			Limiting molar conductance (Λ_m^0)		
		MCM-41	TiO$_2$-MCM-41 (10 wt. (%)	TiO$_2$-MCM-41 (15 wt. (%)	MCM-41	TiO$_2$-MCM-41 (10 wt. (%)	TiO$_2$-MCM-41(15 wt. (%)	MCM-41	TiO$_2$-MCM-41 (10 wt. (%)	TiO$_2$-MCM-41 (15 wt. (%)
298.15	40	1.715	1.583	1.648	6784.2	6533.2	6767.9	1475.3	161.60	585.82
	60	1.267	0.071	1.345	3341.3	195.32	3681.9			
	80	1.253	0.067	1.335	2478.2	138.22	2740.7			
	100	1.587	1.148	1.561	2511.1	1894.7	2564.0			
	120	1.681	0.976	1.200	2216.5	1342.7	1642.4			
	140	1.424	1.123	1.101	1609.4	1323.8	1291.6			
303.15	40	2.091	1.766	1.836	8271.6	7288.4	7540.0	1475.4	784.52	569.54
	60	1.517	1.201	1.573	4000.6	3303.9	4306.0			
	80	1.454	1.189	1.509	2875.8	2453.0	3097.9			
	100	1.937	1.344	1.617	3064.9	2218.1	2656.0			
	120	1.957	1.077	1.343	2580.5	1481.2	1838.2			
	140	1.627	1.255	1.227	1838.8	1479.4	1439.4			
308.15	40	2.367	1.949	2.036	9363.5	8043.7	8361.3	1475.4	869.25	649.13
	60	1.762	1.333	1.856	4646.7	3667.1	5080.7			
	80	1.651	1.310	1.643	3265.4	2702.7	3373.0			
	100	2.287	1.543	1.764	3618.7	2546.6	2897.5			
	120	2.333	1.184	1.419	3076.2	1628.3	1942.2			
	140	1.827	1.387	1.338	2064.9	1635.0	1569.6			
313.15	40	2.643	2.132	2.243	10455	8799.0	9211.4	1475.5	930.79	698.26
	60	2.009	1.486	1.937	5298.1	4088.0	5302.4			
	80	1.857	1.431	1.804	3672.9	2952.3	3703.5			
	100	2.550	1.652	1.898	4034.9	2726.5	3117.6			
	120	2.804	1.307	1.587	3697.3	1797.5	2172.1			
	140	2.023	1.519	1.492	2286.4	1790.6	1750.3			

Table 2. Thermodynamics parameters K_A (dm^3 mol^{-1}), $\Lambda_m^0\eta_0$, ΔG^0 (KJ mol^{-1}), ΔH^0 (J mol^{-1}), ΔS^0 (J mol^{-1} K^{-1}) and E_s (J mol^{-1})in ethanolic nicotinamide solutions at different temperatures.

Temp (K)												
Param-eters	MCM-41				TiO$_2$-MCM-41(10 weight %)				TiO$_2$-MCM-41(15 weight %)			
T/K	298.15	303.15	308.15	313.15	298.15	303.15	308.15	313.15	298.15	303.15	308.15	313.15
$K_A\times 10^{-3}$	-42.56	-42.56	-42.56	-42.56	-39.22	-39.22	-39.22	-39.22	-32.39	-29.50	-30.06	-29.85
$\Lambda_m^0\eta_0$	14.500	13.069	11.781	10.547	1.588	6.949	6.940	6.653	5.758	5.044	5.183	4.991
ΔG^0	32.13	32.67	33.21	33.75	31.93	32.47	33.00	33.53	31.46	31.75	32.32	32.83
ΔH^0	0.52				2.95				3527.4660			
ΔS^0	-107.77	-107.77	-107.77	-107.77	-107.09	-107.09	-107.09	-107.09	-93.67	-93.04	-93.44	-93.56
E_s	49.1817				83419.6				10160.77			

5 CONCLUSION

The molar conductance of MCM-41, TiO2-MCM-41(10 and 15 weight %)has been measured in ethanolic nicotinamide solutions at temperatures ranging from 298.15 to 313.15 K.The conductance data have been analysed by Shedlovsky extrapolation technique.As the temperature increases,the conductance value goes on increasing for all the three samples.But,the conductance value of MCM-41is higher than that of the titania modified MCM-41.It has been observed that the walden product is higher for MCM-41 than that of the titania modified MCM-41.The ion-association constant and thermodynamics parameters have been discussed.The values of Es are positive for all the samples in the ethanolic nicotinamide solutions.

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