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Effect of hydrotropes on solubility, mass transfer coefficient and thermodynamic properties of the drug Meftal Spas

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ABSTRACT

Meftal spas acts as a pain killer and can be used for fever. The time taken by the drug to act in the human body is longer. It is a partially water soluble drug. By using hydrotropic solubilization technique, the solubility can be increased. Increasing the soluble reduces the time taken by the drug to act in the human body. Hydrotropes such as nicotinamide, urea, sodium benzoate, sodium acetate were used. The study was carried out under the influence of a wide range of hydrotropic concentrations (0 to 3mol/L). It is observed that the solubility of Meftal spas increases with the increase in hydrotropic concentration. Mass Transfer Coefficient was calculated. To ascertain the hydrotropic aggregation behavior, thermodynamic properties such as Gibb's free energy, enthalpy, and entropy of the system were studied. Maximum enhancement factor for solubility and mass transfer coefficient have been calculated along with Effectiveness of the drug.

KEY WORDS: Meftal Spas, Hydrotropes, Solubility, Mass transfer coefficient, Thermodynamic properties.

1. INTRODUCTION

Commercially now a days, there are lots of drugs available. But very few are very effective. For example, when we have a fever, the drug that we immediately take is paracetamol. Why?? The reason being; it reduces fever almost immediately after the consumption of drugs. We can say that the residence time taken by the drug in the human body is very less. There by increasing its efficiency.

Meftal spas acts as a pain killer. It has a residence time of about 15-40 minutes. It is far too long for a pain killer. It also has side effects such as vomiting, and nausea. This is mainly because of the improper solubilization of the drug in the human body which results in nausea and vomiting.

The Effectiveness of a drug depends ultimately upon the solubility of the drug. Solubility is the one of the important parameters of the drug. It is also known that the side effects of some drugs are the result of their poor solubility. The ability to increase the aqueous solubility can thus be a valuable aid in decreasing the side effects of certain drugs. This is true for any orally administered solutions and drugs. Decreasing the residence time taken by the drug in the human body will ultimately result in increased effectiveness. This also reduces the side effects caused by the drug.

Meftal spas are comprised of two major compositions. It comprises of Mefenamic Acid and Dicyclomine Hydrochloride. We can decrease the residence time by increasing the solubility of the drug using Hydrotropy. Hydrotropes are a class of Chemical compounds used for several fold increase in aqueous solubility of certain solutes, which are sparingly soluble in water under normal conditions. This increase in solubility in water is probably due to the formation of organized assemblies of hydrotrope molecules at critical concentrations.

Hydrotropy is suggested to be superior to other solubilization methods, such as micellar solubilization, miscibility, co solvency and salting in. It is independent of pH, has high selectivity and does not require emulsification. It only requires mixing the drug with the hydrotrope in water. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system. It is economical, safe, environment and user friendly method.

When these Hydrotropes are added to Meftal spas it increases the solubility of the drug there by decreasing the residence time of the drug taken inside the human body. Hydrotropes taken include urea, nicotinamide, sodium benzoate, and sodium acetate.

Since Meftal spas are partially water soluble drug, addition of Hydrotropes results in a several fold increase in the solubility of the drug. A study on the effect of hydrotrope of various concentrations and at different temperature of the drug is done. It has been observed that a minimum hydrotropic concentration is needed for a minimum raise in solubility. This has been termed as Minimum Hydrotropic Concentration (MHC). A maximum increase in solubility is seen at a particular hydrotropic concentration, after which there won't be any appreciable increase in solubility. This is termed as Maximum Hydrotropic Concentration, C_{max}.

1.1. Selection of Hydrotropes: Various Hydrotropes such as Urea, Nicotinamide, Pyrogallol, Citric Acid, Sodium Tri basic citrate, Sodium benzoate, Sodium Acetate were initially taken for this study. It has been observed that only urea, nicotinamide, sodium benzoate and sodium acetate gave favorable results. The reason being, the formation of the aggregation of molecules by hydrotropes was less, thereby the solubility level of the given drug remained unraised. Sodium Benzoate is naturally present in Berries that we consume on a day to day basis. It has no harmful

effects. Sodium Acetate is present in Vinegar and other food coating agents. Other hydrotropes such as Urea and Nicotinamide should not exceed more than 3 grams/Day.

2. MATERIALS AND METHODS

For each solubility test, about 25 ml of the drug previously saturated with distilled water and equal volume of a solution of the hydrotrope of known concentration is added. The solution of different concentrations of the hydrotrope is prepared by diluting with distilled water. They are kept in thermostatic bath for equilibrium purpose. The aqueous layer is carefully separated out. The solubility of the drug is calculated using a UV visible spectrophotometer.

For confirming the hydrotropic aggregation behavior, thermodynamic properties such as Gibb's free energy, enthalpy, and entropy of the system were studied.

The tests were repeated for reproducibility and it has been observed that an error of <2% was observed.

3. RESULTS AND DISCUSSIONS

3.1. Solubility analysis: The solubility of Meftal Spas showed an appreciable rise on the addition of 0.1 mol/L of sodium acetate, sodium benzoate, nicotinamide and urea concentration. This shows that the minimum hydrotropic concentration required is less than 0.1 mol/L for sodium benzoate, nicotinamide, urea, and sodium acetate.

It is then observed that the Minimum Hydrotropic Concentration required is 0.02 mol/L for sodium acetate, nicotinamide and urea concentrations. For Sodium Benzoate it has been observed that a minimum hydrotropic concentration of about 0.06 mol/L is needed for any appreciable change in the solubility values of the Drug-Hydrotrope System.

The particular concentration below which there is no appreciable change in the solubility level of Meftal Spas is termed as Minimum Hydrotropic Concentration (MHC). It has been observed that the Minimum Hydrotropic Concentration (MHC) is unaltered even after raising the temperature. The Solubility level of the drug rises as there is an increase in the hydrotropic concentration. A maximum increase in Solubility is seen at a particular hydrotropic concentration.

That hydrotropic concentration is termed as Maximum Hydrotropic Concentration, above which there is no increase in the solubility level. It is denoted by $C_{max.}$ The solubility enhancement factors for all the hydrotropes were calculated. It has been observed that a maximum enhancement factor is observed for sodium acetate**.**

3.2. Thermodynamic property analysis: The change in enthalpy, entropy and free energy accompanying the aggregation of hydrotrope is determined by the standard equations. The calculation is based on the MHC values. The standard free energy change (ΔG°) of aggregation per mole of the hydrotropes is given by,

$$\Delta G^\circ = RT \ln (X_{MHC}) \quad (1)$$

Where, X_{MHC} = solubility of meftal spas in mol/L.

The standard enthalpy (ΔH°) of aggregation can be found by Van't Hoff equation

$$\Delta H^\circ = -RT^2 \ln (\partial X_{MHC} / \partial T) \quad (2)$$

Where, the slope in the plot of ln X_{MHC} vs T at each temperature is taken as ln $(\partial X_{MHC} / \partial T)$

The standard entropy (ΔS°) of aggregation can be calculated from,

$$\Delta S^\circ = [(\Delta H^\circ - \Delta G^\circ)/T] \quad (3)$$

3.3. Setschenow constant: The effectiveness factor of each hydrotrope with respect to Meftal Spas at different system temperatures has been determined by analyzing the experimental solubility data for each case applying the model suggested by Setschenow,

$$\text{Log } [S/Sm] = K_s [Cs - Cm] \quad (4)$$

Where S and Sm are the solubility of Meftal Spas at any hydrotrope concentration Cs and the minimum hydrotrope concentration Cm, (same as MHC) respectively. The Setschenow constant (Ks) can be considered as a measure of the effectiveness of a hydrotrope at any given condition of hydrotrope concentration and system temperature. The Setscheow constant values of the hydrotropes, namely sodium acetate, sodium benzoate, urea and nicotinamide, for the Meftal spas + water system at different system temperatures are listed in Table 7. The highest value observed is 2.5162 in case of Sodium Acetate as the hydrotrope at 323 K.

3.4. Solubility analysis: The graph is plotted for various concentrations of nicotinamide vs solubility of Meftal Spas. The Minimum MHC was found to be 0.02 mol/L, below which there is no change in solubility value. The solubility level of meftal spas increases with the increase in nicotinamide concentration. It reaches a particular concentration above which no change in solubility is seen. That particular concentration is termed as Maximum hydrotropic concentration. It is denoted as C_{max}. C_{max} is 1mol/L for nicotinamide-meftal system.

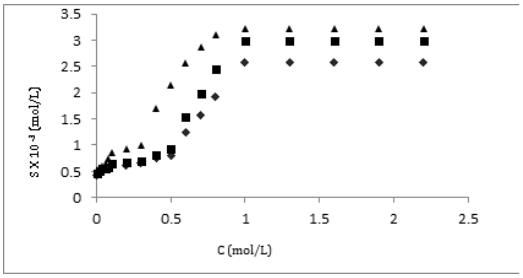

Figure.1. Effect of nicotinamide concentration (c) on solubility (s) of Meftal Spas in water at different system temperatures

Table.1. Effect of nicotinamide concentration (c) on solubility (s) of Meftal Spas in water at different system temperature

C(mol/L)	S, 10^{-3} (mol/L)		
	T=303 K	T=313 K	T=323K
0	0.435	0.4621	0.542
0.02 (MHC)	**0.491**	**0.514**	**0.563**
0.04	0.519	0.549	0.597
0.06	0.541	0.562	0.638
0.08	0.567	0.576	0.737
0.1	0.602	0.642	0.856
0.2	0.623	0.662	0.926
0.3	0.667	0.694	1.001
0.4	0.758	0.817	1.692
0.5	0.812	0.922	2.144
0.6	1.234	1.543	2.567
0.7	1.563	1.981	2.883
0.8	1.929	2.456	3.113
1.0 (C_{max})	**2.570**	**3.000**	**3.231**
1.3	2.570	3.000	3.231
1.6	2.570	3.000	3.231
1.9	2.570	3.000	3.231
2.2	2.570	3.000	3.231

Table.2. Effect of urea concentration (c) on solubility (s) of Meftal Spas in water at different system temperatures

C(mol/L)	S, 10^{-3} (mol/L)		
	T=303 K	T=313 K	T=323K
0	0.584	0.602	0.692
0.02 (MHC)	**0.596**	**0.633**	**0.761**
0.04	0.625	0.986	1.020
0.06	0.668	1.038	1.245
0.08	0.672	1.236	1.638
0.1	0.690	1.457	1.805
0.2	0.711	1.605	2.047
0.3	0.886	1.701	2.236
0.4	0.987	1.892	2.450
0.5	1.110	2.003	2.639
0.6	1.284	2.207	2.791
0.7	1.422	2.400	2.923
0.8	1.644	2.614	3.053
1.0	1.893	2.820	3.157
1.3	2.600	3.025	3.238
1.6	2.639	3.025	3.239
1.9 (C_{max})	**2.639**	**3.025**	**3.240**
2.2	2.639	3.025	3.241

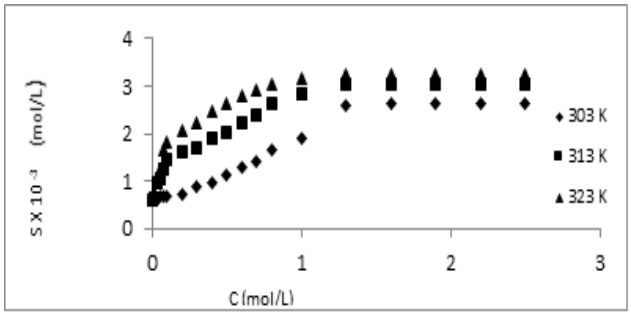

Figure.2. Effect of urea concentration (c) on solubility of meftal spas (s) in water at different system temperature

The graph is plotted for various concentrations of Urea versus solubility of Meftal Spas. The Minimum Hydrotropic Concentration (MHC) is 0.02 mol/L, below which there was no Change in solubility value. The solubility level increases as the concentration of Nicotinamide increases. It reaches a particular concentration above which no appreciable change in solubility is seen.

That particular concentration is termed as maximum hydrotropic concentration. It is denoted as C_{max}. C_{max} is 1.9 mol/L for Urea-meftal system. The graph is plotted for various concentrations of sodium benzoate vs solubility of meftal spas. The MHC is 0.06 mol/L, below which there is no change in solubility values. The solubility of Meftal Spas increases as the concentration of sodium benzoate increases. It reaches a particular concentration above which no change in solubility is seen. That particular concentration is termed as Maximum hydrotropic concentration. It is denoted as C_{max}. C_{max} is 0.8 mol/L for Sodium Benzoate -Meftal system.

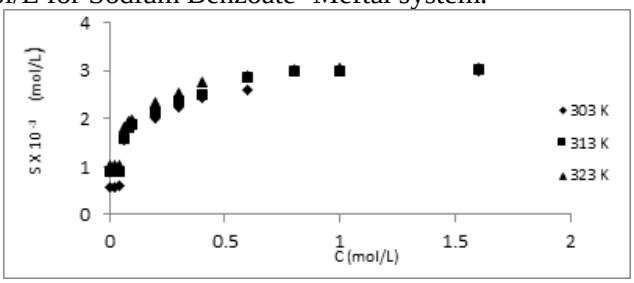

Figure.3. Effect of sodium benzoate concentration (c) on solubility (s) Meftal Spas in water at different system temperatures

Table.3. Effect of sodium benzoate concentration (c) on solubility (s) Meftal Spas in water at different system temperatures

C(mol/L)	S, 10^{-3} (mol/L)		
	T=303 K	T=313 K	T=323K
0	0.57	0.89	1.02
0.02	0.57	0.89	1.02
0.04	0.59	0.90	1.02
0.06(MHC)	**1.55**	**1.60**	**1.80**
0.08	1.81	1.82	1.93
0.1	1.94	1.88	1.98
0.2	2.02	2.14	2.35
0.3	2.23	2.36	2.52
0.4	2.44	2.51	2.77
0.6	2.61	2.87	2.89
0.8(C_{max})	**2.99**	**3.00**	**3.01**
1.0	2.992	3.00	3.07
1.6	2.992	3.01	3.07

The graph is plotted for various concentrations of Sodium Acetate versus solubility of Meftal Spas. The Minimum Hydrotropic Concentration (MHC) is 0.02 mol/L, below which there was no Change in solubility value. The solubility level increases as the concentration of Sodium Acetate increases. It reaches a particular concentration above which no change in solubility is seen. That particular concentration is termed as Maximum hydrotropic concentration. It is denoted as C_{max}. C_{max} is 0.2 mol/L for Sodium Acetate -meftal spas system.

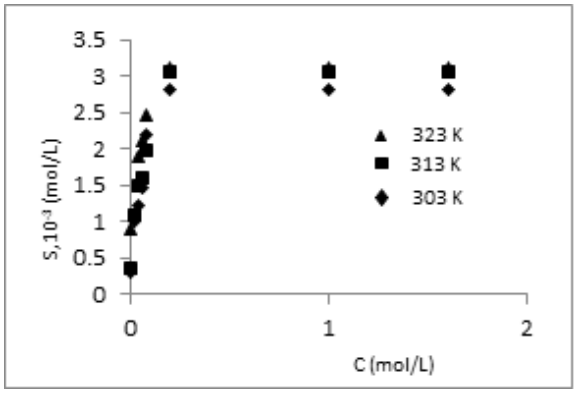

Figure.4. Effect of sodium acetate concentration (c) on solubility of Meftal Spas (s) in water at different temperatures

Table.4. Effect of sodium acetate concentration (c) on solubility (s) Meftal Spas in water at different system temperatures

C(mol/L)	S, 10^{-3} (mol/L)		
	T=303 K	T=313 K	T=323K
0	0.3143	0.3700	0.9061
0.02(MHC)	**1.0112**	**1.0847**	**1.0951**
0.04	1.2113	1.4885	1.9051
0.06	1.4569	1.6001	2.1173
0.08	2.2051	1.9853	2.4569
0.2(C_{max})	**2.8112**	**3.0675**	**3.1069**
1.0	2.8112	3.0675	3.1069
1.6	2.8112	3.0675	3.1069

Table.5. Maximum enhancement factor for solubility analysis Φ_s

Hydrotrope used	Φ_s		
	303 K	313 K	323 K
Nicotinamide	5.91	6.49	5.96
Urea	4.52	5.02	4.63
Sodium Benzoate	5.25	3.36	3.10
Sodium Acetate	8.94	8.29	3.43

Table.6. Minimum Hydrotropic Concentration (MHC), Standard free energy (ΔG°), Standard Enthalpy (ΔH°), and Entropy (ΔS°) of the system

Hydrotrope Used	T (K)	ΔG° (KJ/mol)	ΔH°(KJ/mol)	ΔS° (KJ/mol)
Nicotinamide	303	-19.40	-3.69	0.052
	313	-19.94	-8.78	0.036
	323	-20.33	-10.99	0.029
Urea	303	-18.93	-4.67	0.047
	313	-19.40	-12.25	0.023
	323	-19.55	-13.04	0.021
Sodium Benzoate	303	-16.38	-3.90	0.041
	313	-16.78	-4.56	0.039
	323	-16.96	-13.1	0.012
Sodium Acetate	303	-17.37	-5.28	0.077
	313	-17.77	-5.91	0.076
	323	-18.32	-6.41	0.075

3.5. Thermodynamic properties: Gibb's free energy decreases as the temperature increases as shown in Table 6. All the Enthalpy values were negative. Hence the reaction is exothermic. All the entropy values were positive, indicating that the hydrotropic aggregation is favored entropically. But there is a decrease in entropy as the temperature increases. This may be due to the effect of self-aggregation becoming poor at higher temperatures.

Table.7. Setschenow constant (k_s) values of the selected drug using various hydrotropes

Hydrotrope Used	K_s		
	303 K	313 K	323 K
Sodium Benzoate	0.39	0.37	0.30
Sodium Acetate	2.47	2.51	2.52
Urea	0.34	0.36	0.34
Nicotinamide	0.73	0.78	0.77

3.6. SEM analysis: Surface studies help us in determining the surface characters such as size, shape of the molecule is analysis.

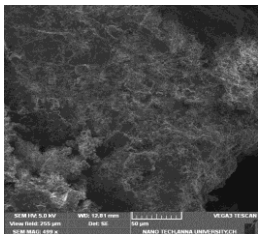

Figure.5.a. Meftal Spas powdered

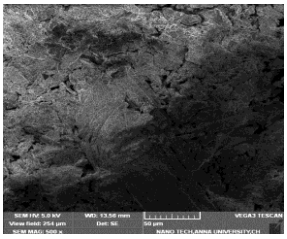

Figure 5.b. Meftal Spas + Sodium Acetate

In Figure 5.b we can see that the aggregate molecules are formed due to the addition of hydrotrope to the system. This aggregate molecules help in increasing the solubility of Meftal Spas. This conclusively proves that there is an increase in the solubility of Meftal Spas as a hydrotrope is added.

4. CONCLUSION

The solubility level of Meftal Spas showed an appreciable increase on the addition of hydrotropes such as nicotinamide, urea, sodium benzoate, sodium acetate.

Sodium benzoate and sodium acetate are preferred because they are human friendly and gave higher efficiency. It is clearly shown in SEM analysis that the formation of aggregate molecules is a result of the addition of hydrotrope to the system. Solubility analysis showed a maximum increase for sodium acetate. Thus making it an efficient hydrotrope. Maximum enhancement factor for solubility analysis of sodium acetate showed highest values. Mass transfer coefficient for enhancement factor showed a maximum increase for sodium acetate. Thermodynamic properties were calculated. It is seen that the Gibb's free energy decreases with an increase in the temperature. All the entropy values were reported positive, indicating that the reaction is favored entropically. Enthalpy values were negative, indicating that the reaction is exothermic.

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