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Thermodynamic Study On Hydrotropic Aggregation Behavior Of Mebendazole

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ABSTRACT

On investigation for the solubility and mass transfer coefficient of mebendazole through hydrotropy has been studied. This study was carried out using hydrotropes such as sodium salicylate, sodium benzoate and resorcinol under the influence of a wide range of hydrotrope

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concentrations [(0 to 3) mol L^{-1}] and different system temperatures [(303 to 333) K]. It has been distinctively observed and noted that the solubility of mebendazole increases with an increase in hydrotrope concentration and also with system temperature likely similar to the several organic compounds and drugs A Minimum Hydrotrope Concentration (MHC) in the aqueous phase was required to initiate significant solubilization of mebendazole. Consequent to the increase in the solubilization of mebendazole, the mass transfer coefficient was also found to increase with increase in hydrotrope concentration at 303 K. A threshold value similar to MHC is to be maintained to have an appreciable enhancement in mass transfer coefficient. The maximum enhancement factor, which is the ratio of the value in the presence and absence of a hydrotrope, has been determined for all sets of experimentations. To ascertain the hydrotropic aggregation behavior of mebendazole, thermodynamic parameters such as Gibb's free energy, enthalpy, and entropy of mebendazole were determined. The Gibb's free energy decreases with an increase in system temperature. The aggregation of hydrotropes was found to be exothermic in nature and favored by a positive value of entropy.

Keywords: Hydrotrope, Solubility, Mebendazole, Enhancement factor, Thermodynamics Properties.

INTRODUCTION

An overview on Hydrotropy

Hydrotropy is a unique and unprecedented solubilization technique in which certain chemical compounds termed as hydrotropes can be used to effect a several fold increase in solubility for sparingly soluble solutes under normal conditions. This increase in solubility in water is probably due to the formation of organized assemblies of hydrotrope molecules at critical concentration. Hydrotropes in general are water soluble and surface active compounds which can significantly enhance the solubility of organic solutes such as acids, esters, alcohols, aldehydes, ketones, hydrocarbons and fats. Hydrotropes are widely used in drug solubilization, detergent

formulation, health care and household applications as well as for being an extraction agent for fragrances.

Hydrotropes are amphiphilic substances composed mainly of hydrophilic functional group. Hydrotropes are organic salts that when present in aqueous solutions can substantially enhance the solubility of a variety of hydrophobic organic substances in the aqueous phase. Some typical hydrotropes are hydroxybenzenes, hydroxybenzoates, and benzenesulfonates which when present in significant concentration can enhance the solubility of hydrophobic compounds. Above a certain characteristic concentration, compounds aggregate to offer non-polar micro-domains to solubilize hydrophobic solutes.

Scope and Objective of the Project

- To study the effect of hydrotropes on the solubility of poorly water soluble drug mebendazole.
- To undertake this study under the influence of a wide range of hydrotrope concentration.
- Then by using the suitable hydrotrope from above study to increase the solubility of drug mebendazole.
- Thermodynamic parameter for used hydrotrope was calculated.

MATERIALS AND METHODS

System

- Mebendazole

Mebendazole Structure

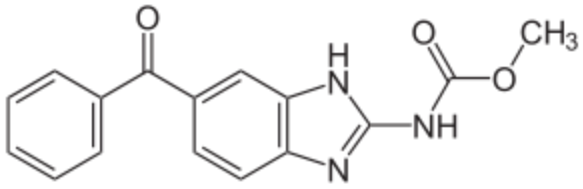

Figure : 3.1.1 Structure of mebendazole

3.1.1 Physical and Chemical Properties of Mebendazole

Molecular Formula	**:**	$C_{16}H_{13}N_3O$
Molecular Weight	**:**	295.293
Appearance	**:**	Small molecule
Odor	**:**	Characteristic fruity odour
Solubility	**:**	71.3 mg/L
Melting Point	**:**	288.5 °C

Available Dosage Forms and Dose

- Adult: Tablets are the available dosage forms for the adults.
- Round worm infestation - 100 mg twice daily for 3 days
- Tape worm infestation - 300 mg three times for every 3 days
- Maximum total daily dosage - 300 mg
- Trichinosis -200 to 400 mg orally three times a day for 3 days

Hydrotropes

Most commonly used hydrotropic agents for enhancing the solubility of drugs include

- Sodium salicylate,
- Sodium benzoate
- Resorcinol

Boiling point : 336 °C

Experimental procedure

Twenty tablets of mebendazole were weighed and powdered finely. The powder, equivalent to 300 mg mebendazole was accurately weighed and transferred to a conical flask, After

adding the 40 ml of hydrotropic solution of different concentration, (0.3,0.6,0.9,,,,3.0M) in water. The vials were shaken for 6 hours allowed to equilibrate with mechanically shaking and inter-mitten vortexing for 12 h at 25 ± 2 C. After completion of18 h each vial is centrifuged for 5 min at 2000 rpm. The supernatant of each vial was filtered through what man filter paper, filtrate should be characterized The properties of hydrotrope solution, such as viscosity, specific gravity, surface tension and specific conductance were determined for a range of hydrotrope concentration between 0.30 and 3.00 mol/L. This study on properties of hydrotrope solution is undertaken to propose a possible mechanism of hydrotropy.the solubility study were determined for a range of hydrotrope concentration between 0.30 and 3.00 mol/L.

RESULTS AND DISCUSSION

Effect of different hydrotrope concentration(C) on the solution Properties of mebendazole in water

The solubility of mebendazole in water in the absence of any hydrotrope is $2.415*10^{-4.}$ Mol/L.The effect of hydrotropes such as, Sodium salicylate, sodium benzoate and resorcinol on the solubility of mebendazole is discussed in this chapter.

Table 1. Effect of sodium salicylate concentration on the conductance of mebendazole in water**.**

C, mol/L	Conductance, (m ohm)
0.3	13.53
0.6	22.5
0.9	30.5
1.2	37.4
1.5	40.7
1.8	45.4
2.1	46.0
2.4	49.5
2.7	50.4
3	51.2

Table 2. Effect of sodium benzoate concentration on the conductance of mebendazole in water.

C,mol/L	Conductance, (m ohm)
0.3	7.4
0.6	12.6
0.9	16.3
1.2	19.3
1.5	20.9
1.8	22.4
2.1	23.5
2.4	24.2
2.7	24.7
3	24.8

Table 3. Effect of resorcinol concentration on the conductance of mebendazole in Water.

C,mol/L	Conductance, (m ohm)
0.3	0.008
0.6	0.009
0.9	0.009
1.2	0.010
1.5	0.011
1.8	0.011
2.1	0.012
2.4	0.013
2.7	0.013
3.0	0.013

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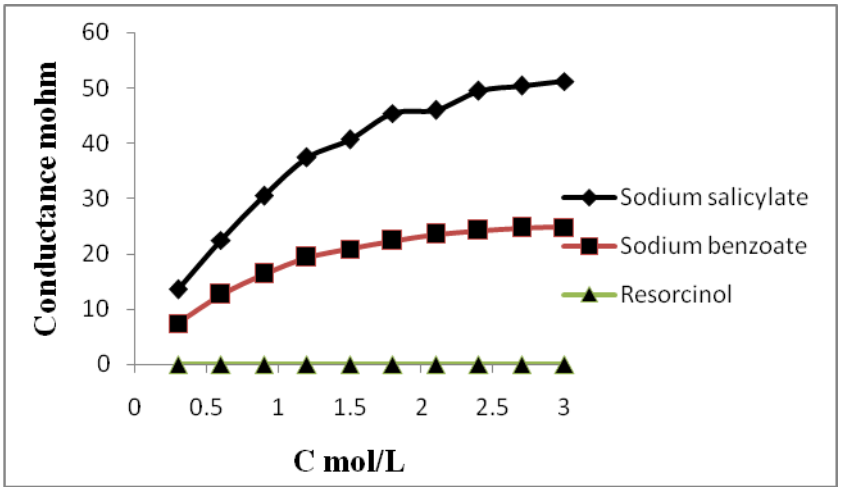

Figure 1: Effect of different hydrotrope concentration (c) on the conductance of mebendazole in water.

Table 4. Effect of sodium salicylate concentration on the specific gravity of mebendazole in water.

C,mol/L	Specific gravity
0.3	1.028
0.6	1.034
0.9	1.049
1.2	1.069
1.5	1.079
1.8	1.101
2.1	1.101
2.4	1.103
2.7	1.104
3.0	1.105

Table 5. Effect of sodium benzoate concentration on the specific gravity of mebendazole in water.

C,mol/L	Specific gravity
0.3	1.013
0.6	1.031
0.9	1.05
1.2	1.058
1.5	1.075
1.8	1.091
2.1	1.103
2.4	1.11
2.7	1.13
3.0	1.143

Table 6. Effect of resorcinol concentration on the specific gravity of mebendazole in Water.

C,mol/L	Specific gravity
0.3	1.002
0.6	1.005
0.9	1.008
1.2	1.009
1.5	1.010
1.8	1.013
2.1	1.014
2.4	1.016
2.7	1.019
3	1.021

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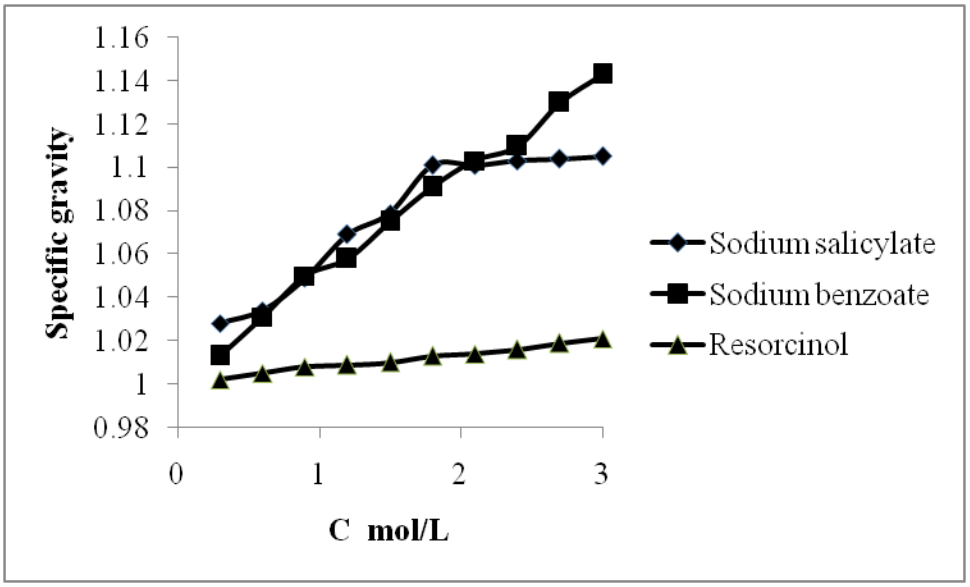

Figure 2. Effect of different Hydrotrope concentration (c) on the specific gravity of mebendazole in water.

Table 7.Effect of sodium salicylate concentration on the surface tension of mebendazole in Water.

C,mol/L	Surface tension
0.3	0.047
0.6	0.036
0.9	0.042
1.2	0.037
1.5	0.031
1.8	0.038
2.1	0.038
2.4	0.038
2.7	0.039
3	0.039

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Table 8.Effect of sodium benzoate concentration on the surface tension of mebendazole in water.

C,mol/L	Surface tension
0.3	0.064
0.6	0.053
0.9	0.036
1.2	0.042
1.5	0.031
1.8	0.032
2.1	0.025
2.4	0.032
2.7	0.026
3	0.026

Table 9.Effect of resorcinol concentration on the surface tension of mebendazole in water.

C,mol/L	Surface tension
0.3	0.052
0.6	0.052
0.9	0.047
1.2	0.041
1.5	0.041
1.8	0.036
2.1	0.03
2.4	0.03
2.7	0.024
3	0.024

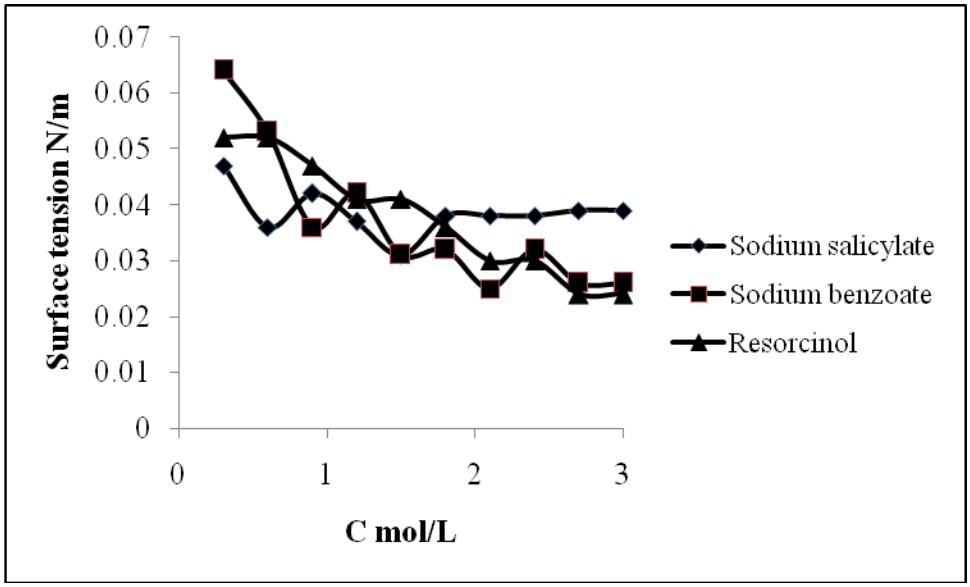

Figure 3. Effect of different hydrotrope concentration (c) on the surface tension of mebendazole in water.

Table 10.Effect of sodium salicylate concentration on the viscosity of mebendazole in water.

C, mol/L	Viscosity(cps)
0.3	0.69
0.6	0.77
0.9	0.99
1.2	0.92
1.5	0.98
1.8	1.07
2.1	1.11
2.4	1.33
2.7	1.39
3.0	1.46

Table 11. Effect of sodium benzoate concentration on the viscosity of mebendazole in water.

C, mol/L	Viscosity(cps)
0.3	0.932
0.6	0.99
0.9	1.01
1.2	1.01
1.5	1.02
1.8	1.33
2.1	1.49
2.4	1.60
2.7	2.03
3.0	2.07

Table 12.Effect of resorcinol concentration on the viscosity of mebendazole in water.

C, mol/L	Viscosity(cps)
0.3	0.77
0.6	0.78
0.9	0.83
1.2	0.85
1.5	0.89
1.8	1.02
2.1	1.05
2.4	1.17
2.7	1.18
3.0	1.25

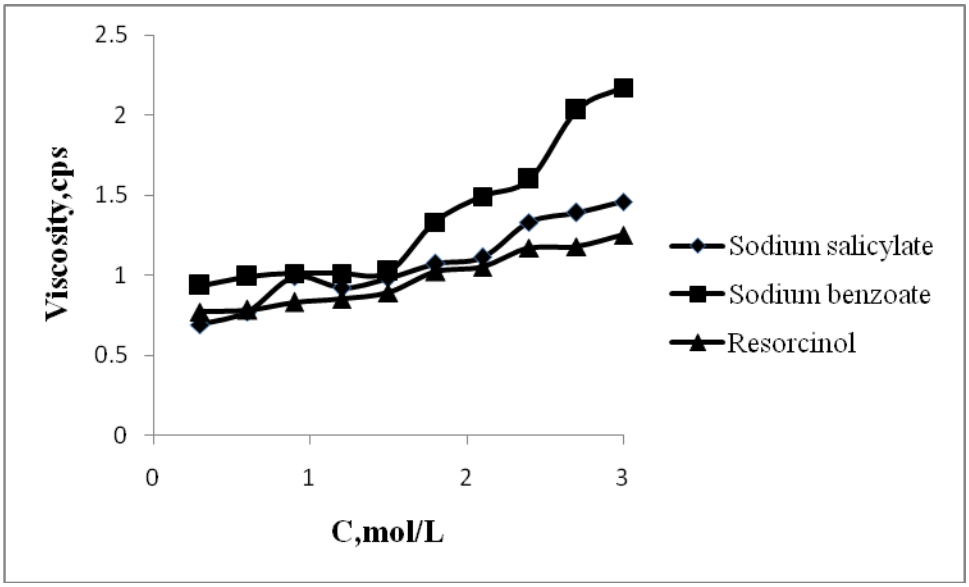

Figure 4. Effect of different hydrotrope concentration (c) on the viscosity of mebendazole in water.

The plots of specific gravity versus hydrotrope concentration showed a negative deviation that indicates an increase in partial molal volume upon aggregation, and this increase in volume may be due to expansion of the hydrocarbon portion of the molecule or its partial removal from the high compressive force of water.

The positive deviation in the viscosity plots indicates that aggregate formation is associated with an increase in viscosity of hydrotrope concentration, which is in agreement with the self-association of phenolic compounds. The surface tension plots showed a moderate decrease in surface tension on increasing the hydrotrope concentration as hydrotropes are not surface active agents . The deviation from linearity in specific conductance plots is strongly indicative of molecular aggregation . It was revealed interactions while at higher hydrotrope concentration, the molecular aggregation seems to be the possible mechanism of hydrotropic solubilization.

Effect of different hydrotrope concentration(C) on the solubility of mebendazole in water at various temperature

Table13. Effect of sodium salicylate hydrotrope concentration on the solubility of mebendazole in water at various temperatures.

C, mol/L	10^4S (mol/L)		
	T=298 K	T=303K	T=310K
0.1	3.13	3.15	3.19
0.3(MHC)	5.45	5.48	5.96
0.6	6.09	6.51	6.84
0.9	7.01	7.78	11.2
1.2	8.01	8.76	13.86
1.5	9.82	10.65	13.87
1.8	12.39	13.02	16.45
2.1	14.06	14.56	16.57
2.4(C_{Max})	14.84	14.91	17.15
2.7	14.87	15.23	17.36
3.0	14.87	15.45	17.43

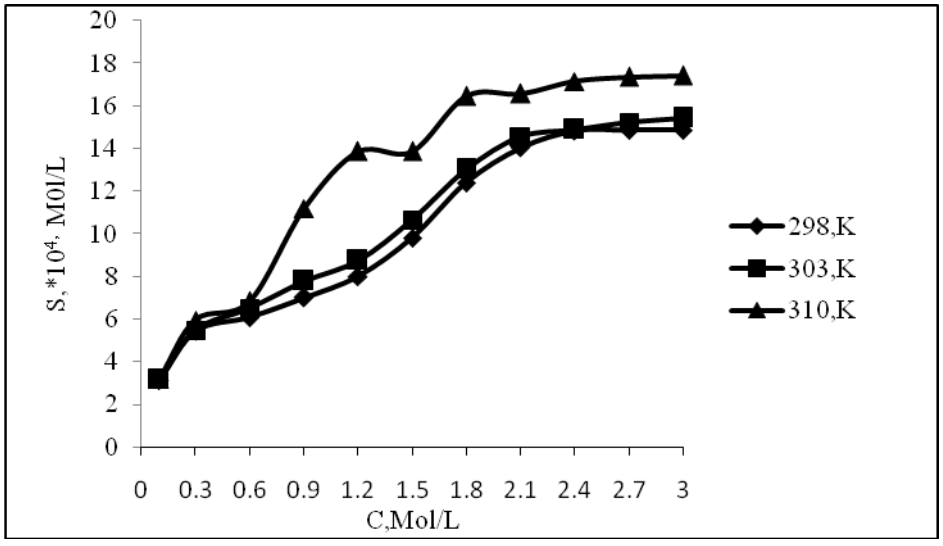

Figure 5. Effect of sodium benzoate hydrotrope concentration on the solubility of mebendazole in water at various temperatures.

The graph is plotted for various concentration of sodium salicylate concentration versus solubility of mebendazole at different temperatures (298,303,310K). it was observed that the solubility of mebendazole in water did not show any appreciable increases until sodium salicylate concentration of 0.3 mol/L.Therefore it is evident that a Minimum Hydrotrope Concentration (MHC) of 0.3 mol/L. It was required to initiate a significant increase in the aqueous solubility of mebendazole. The maximum hydrotrope concentration ($_{Cmax)}$ from graph is 2.4 mol/L beyond which there is no appreciable increase in solubility was observed. The solubility of mebendazole which is practically insoluble in water has been increased to maximum value of 17.95 Mol/L in the presence of sodium salicylate hydrotrope at system temperature of 310K.

Table 14. Effect of sodium benzoate hydrotrope concentration on the solubility of mebendazole in water for various temperatures.

C, mol/L	10^4S (mol/L)		
	T=298 K	T=303K	T=310K
0.1	3.6	3.63	3.66
0.3(MHC)	6.44	6.59	6.71
0.6	10.42	11.04	12.62
0.9	13.84	14.02	15.89
1.2	14.91	15.76	17.54
1.5	15.01	17.29	19.45
1.8	17.91	19.67	21.78
2.1	22.99	24.12	25.98
2.4	23.57	26.13	27.7
2.7(C_{Max})	24.32	27.02	28.98
3.0	25.16	27.06	29.12

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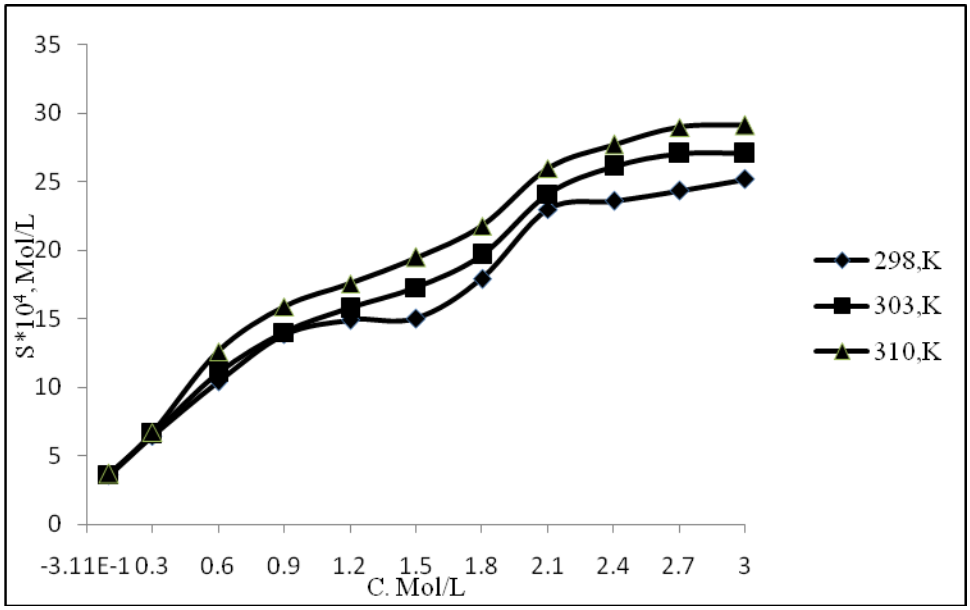

Figure 6. Effect of different hydrotrope concentration on the solubility of mebendazole in water for various temperatures.

The graph is plotted for various concentration of sodium benzoate concentration versus solubility of mebendazole at different temperature (298,303,310K). it was observed that the solubility of mebendazole in water did not show any appreciable increases until sodium benzoate concentration of 0.3 mol/L.Therefore it is evident that a Minimum Hydrotrope Concentration (MHC) of 0.3 mol/L It was required to initiate a significant increase in the aqueous solubility of mebendazole. The maximum Hydrotrope concentration ($_{Cmax)}$ from graph is 2.7 mol/L beyond which there is no appreciable increase in solubility was observed.The solubility of mebendazole which is practically insoluble in water, has been increased to maximum value of 28.98 Mol/L in the presence of sodium benzoate hydrotrope at system temperatutre of 310K.

Table 15. Effect of resorcinol hydrotrope concentration on the solubility of mebendazole in water for various temperatures.

C, mol/L	10^4S (mol/L)		
	T=298 K	T=303K	T=310K
0.1	2.45	2.47	2.56
0.3	2.49	2.55	2.83
0.6	2.81	2.82	3.12
0.9(MHC)	3.2	3.38	3.55
1.2	3.51	4.13	6.59
1.5	4.56	5.56	7.52
1.8	5.97	6.49	8.43
2.1	6.81	7.59	10.58
2.4	8.03	9.12	11.29
2.7(C_{Max})	9.53	10.18	11.99
3.0	9.78	10.53	12.12

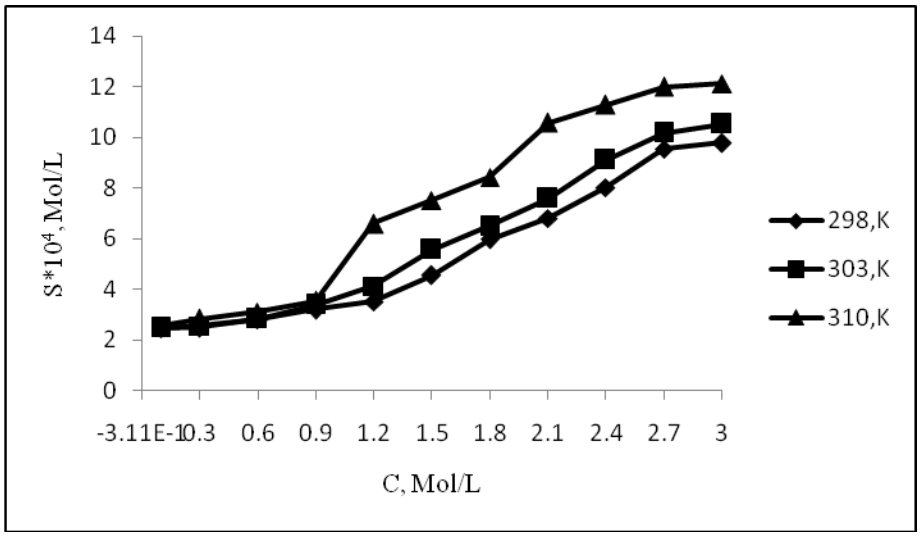

Figure 7. Effect of different hydrotrope concentration on the solubility of mebendazole water for various temperatures.

The graph is plotted for various concentration of resorcinol concentration versus solubility of mebendazole at different temperature (298,303,310K). it was observed that the solubility of mebendazole in water did not show any appreciable increases until resorcinol concentration of 0.9 mol/L. Therefore it is evident that a Minimum Hydrotrope Concentration (MHC) of 0.9 mol/L.It was required to initiate a significant increase in the aqueous solubility of mebendazole.the maximum Hydrotrope concentration ($_{Cmax)}$ from graph is 2.7 mol/L beyond which there is no appreciable increase in solubility was observed. The solubility of mebendazole which is practically insoluble in water has been increased to maximum value of 11.99 Mol/L in the presence of resorcinol hydrotrope at system temperature of 310K.

ENHANCEMENT FACTOR

Enhancement factor is defined as the ratio of solubility of the drug in the presence of hydrotrope to absence of Hydrotrope i.e., The solubility of the system at maximum concentration of the Hydrotrope to the solubility system in water.

ENHANCEMENT FACTOR CALCULATION

$$\text{Enhancement factor}(\varphi_s) = \frac{\text{Solubility value in the presence of Hydrotrope}}{\text{Solubility value in the absence of Hydrotrope}}$$

Table 16. Enhance factor for sodium salicylate.

Temperature,K	**Solubility in the presence of hydrotrope**	**Solubility in the absence of hydrotrope**	**Enhancement factor(φ_s)**
298,K	14.84	2.40	6.18
303,K	14.91	2.40	6.21
313,K	17.95	2.44	7.36

Table 17. Enhance factor for sodium benzoate.

Temperature,K	Solubility in the presence of hydrotrope	Solubility in the absence of hydrotrope	Enhancement factor(φ_s)
298,K	24.32	2.40	10.13
303,K	27.02	2.40	11.26
313,K	28.98	2.44	11.88

Table 18. Enhance factor for sodium resorcinol.

Temperature,K	Solubility in the presence of hydrotrope	Solubility in the absence of hydrotrope	Enhancement factor(φ_s)
298,K	9.53	2.40	3.97
303,K	10.18	2.40	4.24
313,K	11.99	2.44	4.91

Table 19. Maximum enhancement factor (φ_s) of mebendazole.

Hydrotropes	Temperature, K		
	298K	303K	310K
Sodium salicylate	6.18	6.21	7.36
Sodium benzoate	10.11	11.26	11.88
Resorcinol	3.97	4.24	4.91

Table 20. MHC and C_{Max}values for hydrotropes.

Hydrotropes	MHC	C_{Max}
Sodium salicylate	0.3	2.4
Sodium benzoate	0.3	2.7
Resorcinol	0.9	2.7

From the above experimental work it has been notices that sodium benzoate is the best Hydrotrope to solubilize the drug mebendazole among the hydrotrope used. The maximum enhancement factor for mebendazole range at sodium benzoate Hydrotrope.

Effectiveness of hydrotropes.

The effectiveness factor of each hydrotrope with respect to butyl stearate at different system temperatures has been determined by analyzing the experimental solubility data for each case applying the model suggested by Setschenow and later modified by Pathak and Gaikar (1992),as given by the equation as follows.

$$\text{Log } [S/S_m] = Ks\ [C_s - C_m] \text{ --------- (1)}$$

where S and Sm are the solubility of mebendazole at any Hydrotrope concentration C_s and the minimum hydrotrope concentration C_m (same as MHC), respectively. The Setschenow constant Ks can be considered as a measure of the effectiveness of a Hydrotrope at any given conditions of hydrotrope concentration and system temperature. The Setschenow constant values of Hydrotropes namely sodium salicylate,sodium benzoate and resorcinol for the mebendazole + water system at different system temperatures are listed in Table 4.2.9. The value 0.265 has been observed as in the case of sodium benzoate as hydrotrope at 310K.

Table 21. Setschenow constant(k_s) values of hydrotropes with respect to mebendazole.

Temperature,K	**Hydrotrope**		
	Sodium salicylate	**Sodium benzoate**	**Resorcinol**
298,K	0.207	0.255	0.253
303,K	0.208	0.256	0.256
310,K	0.219	0.265	0.264

4.3 Aggeregation characteristics of hydrotrope at different temperature

Standard free energy

The change in enthalpy, entropy and free energy accompanying the aggregation of different hydrotrope solutions were further determined by the standard equations. The calculation is based on the MHC found usingsolubility . Using the charged pseudo-phase model, the standard free energy (ΔG^o) of aggregation per mole of hydrotropes is given by

$$\Delta G^o = RT \ln X_{MHC} \text{ ----------(2)}$$

Table 22. Standard free energyΔG^o values for hydrotropes at different temperature

Temperature,K	Hydrotropes		
	Sodium salicylate, ΔG^o	Sodium benzoate,ΔG^o	Resorcinol,ΔG^o
298,K	-18.62	-18.21	-19.94
303,K	-18.91	-18.45	-20.14
310,K	-19.14	-18.83	-20.47

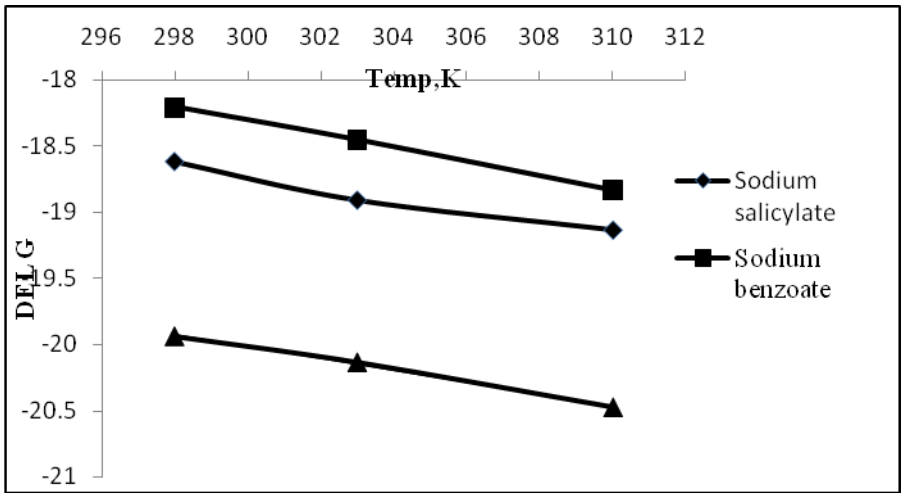

Figure 8. Standard Gibbs free energy vs temperature.

Figure 4.3.1. Shows the relationship between the standard free energy of both the hydrotropes and the temperature. The free energy decreases with increase in temperature.

Standard enthalpy

The standard enthalpy (ΔH^o) of aggregation can be foundby the Van't Hoff equation,

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$$\Delta H^o = - RT^2 (\partial \ln X_{MHC} / \partial T) \text{ --------- (3)}$$

The slope in the plot of $\ln X_{MHC}$ versus T at each temperature was taken as $(\partial \ln X_{MHC} / \partial T)$.

A linear plot was observed for both the hydrotropes as shown in Fig. 4. The values of enthalpy are negative which indicates the aggregation behaviour of exothermic nature.

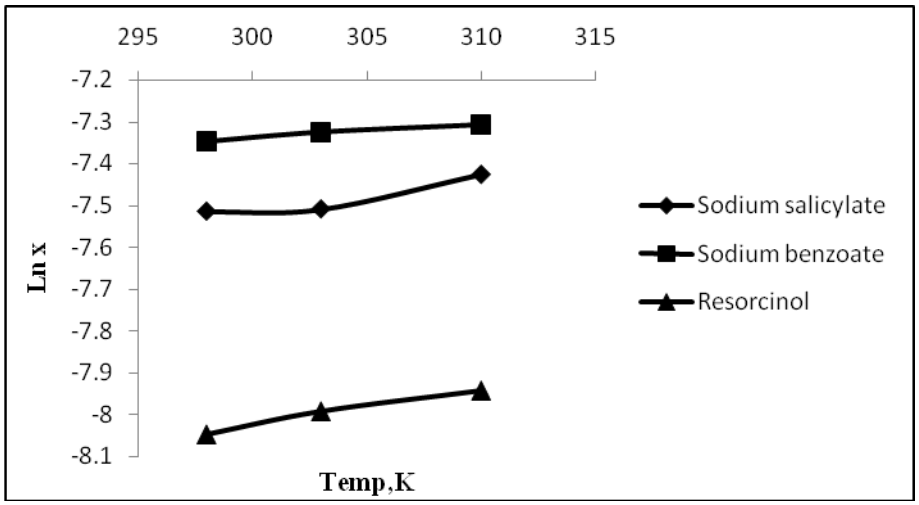

Figure 9. ln X_{MHC} vs. temperature

Standard entropy

The standard entropy (ΔS^o) of aggregation was calculated from

$$\Delta S^o = [(\Delta H^o - \Delta G^o) / T] \text{ ----(4)}$$

The entropy change in all cases is positive which confirms that aggregation of hydrotropes is favored entropically. However, the values are decreasing with increasing temperature . The reason might be self aggregation becomes poor at higher temperature because of enhanced molecular motion at increased temperature, change in enthalpy, eantrophy,and free enerergy hydrotropes at different temperature.

Table 23. The standard Gibbs free energy (ΔG^o), standard enthalpy(ΔH^o) and entropy (ΔS^o) for different hydrotrope at different temperatures.

Hydrotrope	Temperature, K	ΔG^{o} KJ/mol	ΔH^{o} KJ/mol	ΔS^{o} KJ/mol
Sodium Salicylate	298,K	-18.619	-5.169	0.0451
	303,K	-18.912	-5.343	0.0448
	310,K	-19.139	-5.702	0.0433
Sodium benzoate	298,K	-18.205	-2.215	0.0537
	303,K	-18.453	-2.291	0.0533
	310,K	-18.833	-2.444	0.0529
Resorcinol	298,K	-19.939	-5.906	0.0471
	303,K	-20.135	-6.106	0.0463
	310,K	-20.474	-6.392	0.0454

CONCLUSION

The solubility of mebendazole is found to to be maximum solubility is found to be 29.12 Mol/L In presence sodium benzoate at 310K. Sodium benzoate is more efficient for solubility of mebendazole as compared to sodium salicylate and resorcinol.From the thermodynamic studies it is found that sodium benzoate gives more self aggregation than other Hydrotrope.From FTIR spectral analysis no evidence of strong complex formation was obtained.

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