Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 3, 2012

Research Article

ASSOCIATION MODEL OF HYDROTROPY FOR THE EFFECT OF HYDROTROPES ON SOLUBILITY AND MASS TRANSFER COEFFICIENT OF ACETYLSALICYLIC ACID

***,[1]S.THENESH KUMAR, [2]N.NAGENDRA GANDHI**

***,[1]Department of Chemical Engineering, Vel Tech High Tech Dr. Rangarajan Dr. Sakunthala Engineering College, Chennai 600062, India, [2]Department of Chemical Engineering, Alagappa College of Technology, Anna University, Chennai 600 025, India.**
Email: stheneshkumar@gmail.com

Received: 27 Apr 2012, Revised and Accepted: 27 Jun 2012

ABSTRACT

Hydrotropes enhance the solubility and mass transfer coefficient of water-insoluble or sparingly soluble acetylsalicylic acid in aqueous solutions. The solubility of acetylsalicylic acid is experimentally determined in aqueous solutions of hydrotropes such as sodium salicylate, sodium benzoate, nicotinamide and urea under a wide range of hydrotrope concentrations (0 to 3.0) mol/L and different system temperatures *T* = (303 to 333) K. The maximum enhancement factor value has been determined for both solubility and mass transfer coefficient. The effectiveness of hydrotropes was measured in terms of Setschnew constant K_s and reported for all hydrotropes used in this study. The solubility data was fitted in the Association model of hydrotropy to estimate the hydrotrope-hydrotrope K_{hh} and hydrotrope-solute K_{hs} association constants.

Keywords: Acetylsalicylic acid, Hydrotropy, Hydrotropes, Solubilization, Mass transfer coefficient, Association model

INTRODUCTION

The term hydrotropy[1] was defined as the large increase in the water solubility of a variety of hydrophobic compounds brought about by the addition of certain water-soluble organic compounds, named hydrotropes[2]. Hydrotropes comprise hydrophilic and hydrophobic moieties, with the latter being typically too small to induce micelle formation[3,4]. Hydrotropes are usually anionic compounds comprising of an aromatic ring substituted by a sulphate, sulfonate, or carboxylate group, typical examples of hydrotropes being sodium xylene sulfonate (SXS) or sodium benzoate[5-9]. This definition was later extended to cationic and neutral aromatic compounds.

Hydrotrope molecules seem to aggregate by a stacking mechanism of the planar aromatic ring present in their chemical structures[10]. This type of aggregation is believed to be at the origin of the solubilization process of sparingly soluble hydrophobic compounds in water, analogous to a micellization process. Nevertheless some aliphatic compounds such as short sodium alkanoates or alkyl sulphates show also a hydrotropic behaviour as it was observed for aromatic derivatives. For such aliphatic compounds the assumed stacking mechanism does not make sense.

Hydrotropy, showing typical sigmoidal solubilization profiles, from solubilization observed by cosolvency[11] and by salting-in effects showing a monotonic increase in the solubilizing ability with increasing co-solvent concentration. More generally, the solubilization of a hydrophobic compound in water by a co-solvent is known to increase slightly and monotonically at low and moderate co-solvent concentrations and to increase exponentially at very high concentrations[12].

This hydrotropy process goes beyond other conventional solubilization methods such as micellar solubilization, miscibility, co-solvency, salting-in, and so forth, since it offers high selectivity and unprecedented increase in solubility and mass transfer coefficient. The problem of emulsification which is normally encountered with surfactant solution is not found with hydrotrope solution.

Acetylsalicylic acid (Aspirin) is an analgesic, anti-inflammatory, antipyretic and also an inhibitor of platelet aggregation. It inhibits fatty acid cyclo-oxygenase by acetylation of the active site of enzyme and the pharmacological effects of aspirin are due to the inhibition of the formation of cyclo-oxygenase products including prostaglandins, thromboxanes and prostacyclin. Aspirin is a very common pain-killer drug, with a chemical formula of $C_9H_8O_4$ and it has two polar groups (-COOH and CH_3COO-) ortho-binding on the benzene skeleton, thus resulting in a dipole moment of 4.36 D.

The effect of hydrotropes on the solubility and mass transfer coefficient for a series of organic acids and esters such as salicylic acid[13], 2-nitrobenzoic acid, butyl acetate, ethyl benzoate, amyl acetate, methyl salicylate and benzyl acetate was studied in our earlier publications[14]. It has been observed that, in many two-phase reaction systems involving a sparingly soluble organic compound like acetylsalicylic acid, the mass transfer coefficient was found to be very low solely due to the poor solubility of acetylsalicylic acid in the aqueous phase. Since acetylsalicylic acid serves as raw material/intermediate for a wide variety of chemicals and allied products[15] and the separation of acetylsalicylic acid from any liquid mixture seems to be difficult, this hydrotropic technique can be adapted to increase the solubility as well as to separate such mixtures effectively. Data on various aspects of hydrotropic study on the solubility and mass transfer coefficient for acetylsalicylic acid + water system are reported for the first time.

MATERIALS AND METHODS

Acetylsalicylic acid and hydrotropes such as sodium salicylate, sodium benzoate, nicotinamide and urea, of purity 99.5% each, were procured from Navdeep Chemicals, Mumbai, India.

The experimental setup for the determination of solubility values consisted of a thermostatic bath and a separating funnel. For each solubility test, 100 ml of a solution of the hydrotrope of known concentration was taken in a separating funnel and an excess amount of acetylsalicylic acid was added. The separating funnel was immersed in a constant-temperature bath fitted with a temperature controller which could control the temperature within + 0.1 °C. The setup was kept overnight for equilibration. After equilibrium was attained, the solution was filtered from the remaining acid. The concentration of the dissolved acid in aqueous hydrotrope solutions was analyzed by UV-Vis spectrophotometer (1601, Shimadzu, Japan)[16-18]. All the solubility experiments were conducted in duplicate to check the reproducibility. The reproducibility was less than 2 %.

The experimental setup for the determination of the mass transfer coefficient consisted of a vessel provided with baffles and a turbine impeller run by a motor to agitate the mixture. The vessel used for mass transfer studies is of height 40 cm and of inner diameter 15 cm. The turbine impeller diameter is 5 cm, the width is 1 cm, and the length is 1.2 cm. It has four blades. The baffle is 40 cm high with a diameter of 1.5 cm. There are about four baffles that rotate at a speed of 600 rpm.

For each run, to measure the mass transfer coefficient, an excess amount of acid was added to the aqueous solution of the hydrotrope of known concentration. The sample was then agitated for a known

time of (600, 1200, 1800 and 2400) s. After the end of fixed time t, the entire mixture was transferred to a separating funnel. After allowing the sample to stand for some time, the solution was filtered from the remaining acid. The concentration of the solubilised acid in aqueous hydrotrope solutions at time t was analyzed as done for solubility determinations. A plot of –log [1 - C_b/C^*] versus t is drawn, where C_b is the concentration of acetylsalicylic acid at time t and C^* is the equilibrium solubility of acetylsalicylic acid at the same hydrotrope concentration. The slope of the graph gives $k_L a/2.303$, from which $k_L a$, the mass transfer coefficient was determined. Duplicate runs were made to check the reproducibility. The observed difference was less than 2 %.

RESULTS AND DISCUSSION

Solubility

The solubility of acetylsalicylic acid standard in water is 4.80x10^{-2} mol/L at 303 K, compared to "insoluble" as reported by John[19]. Thus, the solubility value of acetylsalicylic acid in water is in excellent agreement with the earlier reported values[19,20].

Experimental data representing the average of duplicate determinations on the effect of hydrotropes, i.e., sodium salicylate, sodium benzoate, nicotinamide and urea on the solubility of acetylsalicylic acid are plotted in Figs 1-4. Sodium salicylate is one of the hydrotropes used in this study. The solubility of acetylsalicylic acid in water at 303 K in the absence of any hydrotrope is 4.80x10^{-2} mol/L (Fig. 1). It has been observed that the solubility of acetylsalicylic acid in water increases significantly only after the addition of 0.20 mol/L of sodium salicylate in the aqueous solution. This concentration is referred to as the Minimum Hydrotrope Concentration (MHC).

Therefore, it is evident that hydrotropic solubilization is displayed only above the MHC, irrespective of system temperature. Since hydrotropy appears to operate only at significant concentrations of hydrotrope in water, most hydrotropic solutions release the dissolved acetyl salicylic acid on dilution with water below MHC. The knowledge of MHC values is necessary especially at industrial levels, as it ensures ready recovery of the hydrotrope for reuse.

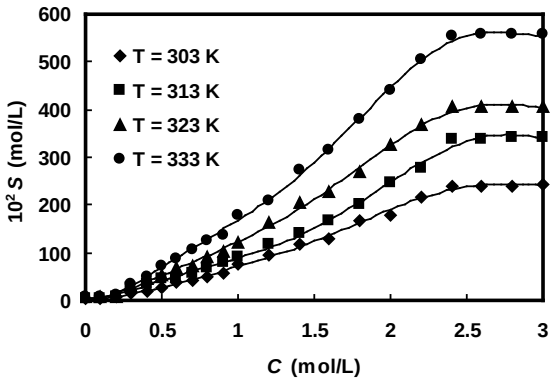

Fig. 1: Effect of sodium salicylate concentration (*C*) on the solubility (*S*) of acetylsalicylic acid in water at different temperatures

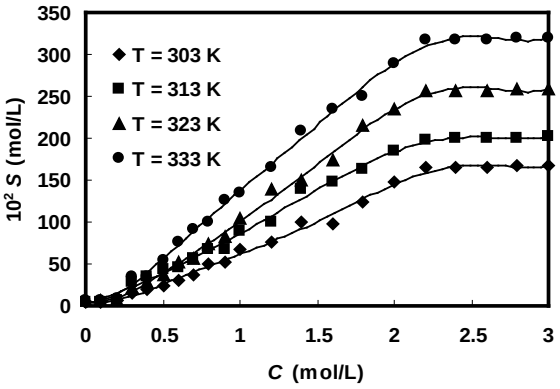

Fig. 2: Effect of sodium benzoate concentration (*C*) on the solubility (*S*) of acetylsalicylic acid in water at different temperatures

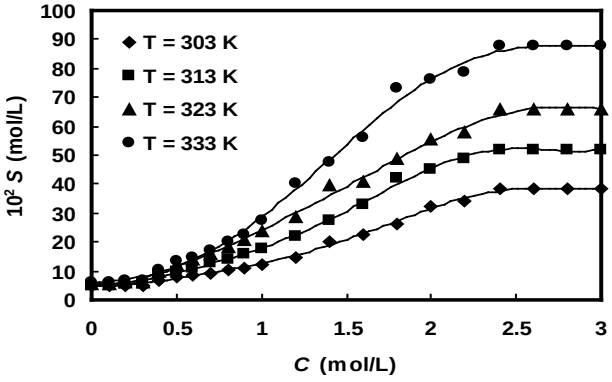

Fig. 3: Effect of nicotinamide concentration (*C*) on the solubility (*S*) of acetylsalicylic acid in water at different temperatures

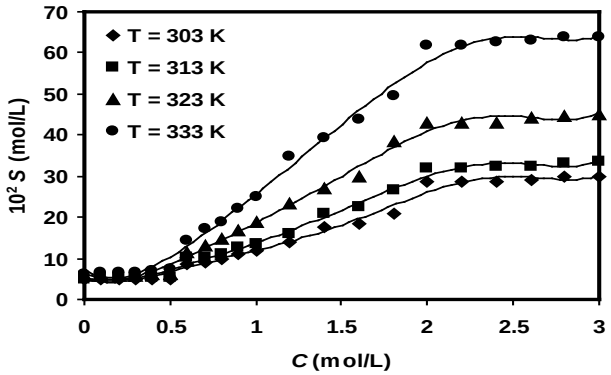

Fig. 4: Effect of urea concentration (C) on the solubility (S) of acetylsalicylic acid in water at different temperatures

The solubilization effect varies with concentration of hydrotrope (Fig. 1). In the present case, a clear increasing trend in the solubility of acetylsalicylic acid was observed above the MHC of sodium salicylate. This increasing trend is maintained only up to a certain concentration of sodium salicylate in the aqueous solution, beyond which there is no appreciable increase in the solubility of acetylsalicylic acid. This concentration of sodium salicylate (hydrotrope) in the aqueous solution is referred to as the maximum hydrotrope concentration (C_{max}). From the analysis of the experimental data, it is observed that further increase in hydrotrope concentration beyond C_{max} does not bring any appreciable increase in the solubility of acetylsalicylic acid even up to 3.00 mol/L of sodium salicylate in the aqueous solution.

The saturation of the hydrotropic effect beyond C_{max} may be due to the non-availability of water molecules to form further aggregates comprising of additional MHC agglomerates. Similar to the MHC values, C_{max} values of hydrotropes also remained unaltered at increased system temperatures. The values of MHC and C_{max} of a hydrotrope with respect to acetylsalicylic acid may be useful in determining the recovery of the dissolved acetylsalicylic acid even to an extent of the calculated amount from hydrotrope solutions at any concentration between MHC and C_{max} by simple dilution with distilled water. This is the unique advantage of the hydrotropic solubilization technique.

From the experimental data plotted in Fig. 1, it can further be observed that, in order to achieve the particular solubility of acetylsalicylic acid, say 200x10^{-2} mol/L, the sodium salicylate concentration should be 2.07 mol/L at 303 K, 1.78 mol/L at 313 K, 1.44 mol/L at 323 K and 1.15 mol/L at 333 K in the aqueous solution. Thus it can be seen that as the system temperature increases, the concentration of sodium salicylate required in the aqueous phase to achieve a particular solubility of acetylsalicylic acid decreases. A similar trend has been observed for other systems also. It has also been observed that the solubilization effect of sodium salicylate was not a linear function of the concentration of the sodium salicylate. The solubilization effect of sodium salicylate increases with increase in hydrotrope concentration and also with system temperature[21].

A similar trend has been observed in the solubilization effect of other hydrotropes namely sodium benzoate, nicotinamide and urea. It has also been observed that the MHC values of hydrotrope used in this work range between (0.20 and 0.60) mol/L and the C_{max} values of hydrotropes range between (2 and 2.40) mol/L (Table 1). The highest value of solubilization enhancement factors φ_s, which is the ratio of solubility values in the presence and absence of a hydrotrope has been observed in the case of sodium salicylate as 88.01 at a system temperature of 333 K (Table 2).

Table 1: Minimum hydrotrope concentration (MHC) and maximum hydrotrope concentration (C_{max}) values for hydrotropes

Hydrotrope	MHC (mol/L)	C_{max} (mol/L)
Sodium salicylate	0.20	2.40
Sodium benzoate	0.20	2.20
Nicotinamide	0.40	2.40
Urea	0.60	2.00

Table 2: Maximum solubilization enhancement factor (φ_s) of acetylsalicylic acid

Hydrotrope	φ_s			
	303 (K)	313 (K)	323 (K)	333 (K)
Sodium salicylate	50.34	66.83	71.04	88.01
Sodium benzoate	34.80	39.45	45.28	50.50
Nicotinamide	8.03	10.22	11.56	13.88
Urea	6.26	6.55	7.90	10.12

φ_s is the maximum enhancement factor for solubility

Hydrotropic solubilization has been claimed to be a collective molecular phenomenon, possibly occurring by the intercalation or co-aggregation of a solute with the hydrotrope aggregates and the self-aggregation of hydrotrope molecules in aqueous solutions is considered to be a prerequisite for the enhanced solubility of the solute. Hydrotrope, above MHC, is expected to form organized loose nanoassemblies with distinct hydrophobic regions where the solute can be solubilized. The solute molecules may also take part in the aggregation process of the hydrotrope thereby forming co-aggregates with the hydrotrope molecules in the aqueous solutions. The formation of a stable co-aggregate depends on the molecular structure as well as the functional group(s) attached to the carbon skeleton of the solute as it would govern the intercalation of the solute between the hydrotrope molecules. The solubilization of a solute is influenced by its hydrophobic part and also the chain length of an alkyl group of a hydrotrope.

Most of the hydrotropes selected for the present study (sodium salicylate, sodium benzoate and nicotinamide) possess a hydrotropic centre having the parent benzene nucleus which can interact due to a large surface area and a mobile electron cloud known as an aromatic sextet. Thus, these site are available for non-bonded and Van der Waals interaction with water and acetylsalicylic acid. The molecules of water join to form cluster together. For solubilization, the ionized hydrotropes break this association and use the ion-dipoles of water for solvation.

This increasing hydrotrope concentration results in unassociated form of water to make cluster of the hydrotrope by hydrogen bonding and non-bonding interactions at the various centers of acetylsalicylic acid molecule. Thus, charge de-localization along with an increase in π–cloud area on hydrotropic molecule would account partially for difference in apparent drug solubility in the presence of various hydrotropes.

The experimental solubility values were fitted into an Association model proposed by Koparkar and Gaikar for the hydrotropic solubilization which illustrates the aggregation behaviour of hydrotrope and subsequent association of a solute with the hydrotrope assemblies[22]. The model characterizes the hydrotrope-hydrotrope and hydrotrope-solute associations with mass-action law assuming that hydrotrope molecules associate in a stepwise manner to form oligomers and multimers such that the association constant becomes weaker on addition of subsequent hydrotrope molecules. The association constant for an *n*-mer of hydrotrope with a monomer is related to the dimerization constant (K_{hh}, L/mol), i.e., $K_n = K_{hh}/n$.

The concentration of a monomeric hydrotrope molecule, [H_1], is related to the total hydrotrope concentration (C_s, mol/L) through the following equations

$$C_s = \sum_{n=1}^{\infty} nH_n \qquad (1)$$

or

$$C_s = H_1[2\, e^{K_{hh}H_1} - 1] \qquad (2)$$

Also the model assumes that the hydrotrope assemblies cosolubilize the solute, where an *n*-mer is capable to take up maximum of "(n - 1)" solute molecules and that the solutes' association with the hydrotrope assemblies becomes weaker on addition of an extra solute molecule in the same manner as the hydrotrope aggregation process. The total solute concentration associated with all hydrotrope aggregates is given by eq 3

$$S_T = 2\left(\frac{K_{hs}}{K_{hh}}\right)[S_1]\left[e^{K_{hh}H_1} - (1 + K_{hh}H_1)\right] \qquad (3)$$

The hydrotrope-solute association constant (K_{hs}, L/mol) and hydrotrope-hydrotrope association constant (K_{hh}) were thus calculated for acetylsalicylic acid and hydrotrope by fitting the experimental solubility data in eqs 2 and 3. The free solute concentration in the solution [S_1], (in mol/L) was taken equal to the solubility of acetylsalicylic acid in water, at the corresponding temperatures.

The values of K_{hh} and K_{hs} for hydrotropes at different temperatures are given in Table 3. The Association model inherently predicts an increase in the solubility of the solute. Table 3 shows that hydrotrope-hydrotrope association constant (K_{hh}) to be much smaller than that of the hydrotrope-solute association constant (K_{hs}) for all hydrotropes. Although the hydrotrope aggregates are formed in aqueous solutions, their aggregation tendency is much weaker than that of hydrotrope-solute co-aggregation. With the increase in temperature, the association constants K_{hs} and K_{hh} also increase. Probably temperature induces a significant change in the aggregate structures, thereby causing more solute to be solubilized in the hydrotrope solutions.

Table 3: Association constants (K_{hh}, K_{hs}) values for acetylsalicylic acid and hydrotropes

Hydrotrope	*T* (K)	K_{hs} (L/mol)	K_{hh} (L/mol)	RMSE
Sodium salicylate	303	58.428	2.144	0.475
	313	81.700	2.868	0.615
	323	87.829	2.711	0.733
	333	115.630	3.274	1.009
Sodium benzoate	303	17.379	0.363	0.347
	313	19.387	0.381	0.366
	323	22.875	0.401	0.460
	333	25.215	0.400	0.569
Nicotinamide	303	3.659	0.077	0.371
	313	4.867	0.097	0.409
	323	5.458	0.096	0.503
	333	6.877	0.110	0.594
Urea	303	2.763	0.058	0.369
	313	2.952	0.059	0.416
	323	3.671	0.065	0.515
	333	4.892	0.078	0.608

RMSE: Root mean square error

Both K_{hh} and K_{hs} increase in the order of sodium salicylate > sodium benzoate > nicotinamide > urea. This indicates that the hydrotrope-hydrotrope and hydrotrope-solute associations are driven by hydrophobicity of the hydrotrope structure. With the increase in the number of carbon atom in the hydrotrope structure, its hydrophobicity also increases and results in an increased solubility of the solute in the hydrotropic solutions.

Mass Transfer Coefficient

The mass transfer coefficient of acetylsalicylic acid + water system in the absence of any hydrotrope was determined as 2.57×10^{-4} s^{-1} at 303 K (Table 4). The effect of different hydrotropes on the mass transfer coefficient of acetylsalicylic acid at different hydrotrope concentrations is also given in the same table. It can be seen that a threshold value of 0.20 mol/L is required to effect significant enhancement in the mass transfer coefficient of acetylsalicylic acid + water system, as observed in the case of solubility determinations. The mass transfer coefficient of acetylsalicylic acid + water system increases with increase in sodium salicylate concentration. The maximum enhancement factor for mass transfer coefficient of acetylsalicylic acid + water system in the presence of sodium salicylate was found to be 39.23 (Table 4). A similar trend in the mass transfer coefficient enhancement (φ_{mtc}) of acetylsalicylic acid has been observed for other hydrotropes also namely sodium benzoate and nicotinamide. The highest value of φ_{mtc} (39.23) has been observed in the presence of sodium salicylate as hydrotrope at C_{max} of 2.40 mol/L.

Table 4: Effect of hydrotrope concentration (C) on the mass transfer coefficient (k_La) of acetylsalicylic acid

Hydrotrope	C (mol/L)	$10^4 k_La$ (s^{-1})	φ_{mtc}
Sodium salicylate	0.00	2.57	-
	0.10	2.70	1.05
	0.20[a]	3.50	1.36
	0.30	5.99	2.33
	0.50	10.51	4.09
	0.70	14.55	5.66
	0.90	20.07	7.81
	1.20	23.41	9.11
	1.60	43.38	16.88
	2.20	78.49	30.54
	2.40[b]	100.82	39.23
	2.60	105.42	41.02
	2.80	111.64	43.44
	3.00	115.21	44.83
Sodium benzoate	0.00	2.57	-
	0.10	2.60	1.01
	0.20[a]	3.30	1.28
	0.30	3.40	1.32
	0.50	4.00	1.56
	0.70	5.12	1.99
	0.90	6.71	2.61
	1.20	10.4	4.04
	1.60	22.92	8.92
	2.00	49.40	19.22
	2.20[b]	71.73	27.91
	2.40	69.67	27.11
	2.60	72.50	28.21
	2.80	75.10	29.22
	3.00	76.82	29.89
Nicotinamide	0.00	2.57	-
	0.10	2.58	1.00
	0.20	2.62	1.02
	0.30	2.90	1.13
	0.40[a]	3.34	1.30
	0.50	3.60	1.40
	0.70	4.20	1.63
	0.90	5.40	2.10
	1.20	8.25	3.21
	1.60	11.23	4.37
	2.00	14.98	5.83
	2.20	17.30	6.72
	2.40[b]	21.82	8.49
	2.60	22.60	8.81
	2.80	23.60	9.21
	3.00	23.93	9.31
Urea	0.00	2.57	-
	0.10	2.57	1.00
	0.20	2.57	1.00
	0.30	2.60	1.01
	0.40	2.65	1.03
	0.50	2.65	1.03
	0.60[a]	3.55	1.38
	0.70	3.65	1.42
	0.90	4.42	1.72
	1.20	5.78	2.25
	1.60	9.48	3.69
	1.80	11.51	3.79
	2.00[b]	14.73	5.73
	2.20	15.39	5.99
	2.40	17.55	6.83
	2.60	20.33	7.91
	2.80	22.82	8.88
	3.00	23.03	8.96

φ_{mtc} is the enhancement factor for mass transfer coefficient. [a] MHC is the minimum hydrotrope concentration. [b] C_{max} is the maximum hydrotrope concentration.

CONCLUSIONS

The solubility and mass transfer coefficient of acetylsalicylic acid in aqueous hydrotrope solutions of sodium salicylate, sodium benzoate, nicotinamide and urea has been increased in a differential manner with hydrotrope concentration. The highest value of solubilization enhancement factors φ_s, has been observed in the case of sodium salicylate as 88.01 at 333 K. Among the hydrotropes sodium salicylate is found to exhibit more association with

acetylsalicylic acid and hence higher association constants i.e. K_{hh} = 3.274 L/mol and K_{hs} = 115.630 L/mol at 333 K. The recovery of the dissolved acetylsalicylic acid from hydrotrope solution is ensured at any hydrotrope concentration between MHC and C_{max} by simple dilution with distilled water, which alters the solution properties of hydrotrope aggregates instantaneously affecting the MHC agglomerates. This also facilitates the reuse of hydrotrope solution, which will eliminate the huge cost and energy normally involved in the separation of the solubilized acetylsalicylic acid from its solution. The unprecedented increase in the solubilizing effect of hydrotropes is attributed to the formation of organized aggregates of hydrotrope molecules at a particular concentration

REFERENCES

1. Neuberg C. Hydrotopy. Biochem Z 1916; 76: 107-108.
2. Balasubramanian D, Srinivas V, Gaikar VG, Sharma MM. Aggregation behaviour of hydrotrope compounds in aqueous solution. J Phys Chem 1989; 93:3865-3870.
3. Ooya T, Moo Huh K, Saitoh M, Tamiya E, Park K. Self-assembly of cholesterol-hydrotropic dendrimers conjugates into micelle-like structure: preparation and hydrotropic solubilization of paclitaxel. Sci Technol Adv Mater 2005; 6:452-456.
4. Srinivas V, Balasubramanian D, When does the switch from hydrotropy to micellar behavior occur? Lagmuir 1998; 14:6658-6661.
5. Agarwal M, Gaikar VG. Extractive separation using hydrotropes. Sep Technol 1992; 2:79-84.
6. Jain AK. Solubilization of indomethacin using hydrotropes for aqeous injection. Eur J Pharm Biopharm 2008; 68:701-714.
7. Agrawal S, Pancholi SS, Jain NK, Agrawal GP. Hydrotropic solubilization of nimesulide for parenteral administration. Int J Pharm 2004; 274:149-155.
8. Badwan AA, EI-Khordagui LK, Salesh AM. The solubility of benzodiazepines in sodium salicylate solutions and proposed mechanism for hydrotropic solubilization. Int J Pharm 1982; 13:67-74.
9. Evstigneev MP, Evstigneev VP, Hernandez-Santiago DB, Davies. Effect of a mixture of caffeine and nicotinamide on the solubility of vitamin (B_2) in aqueous solution. Eur J Pharm Sci 2006; 28:59-66.
10. Coffman RE, Kildsig DO. Effect of nicotinamide and urea on the solubility of riboflavin in various solvent. J Pharm Sci 1996;85: 951-954.
11. Bauduin P, Renoncourt A, Kopf A, Touraud D, Kunz W. Unified concept of solubilization in water by hydrotropes and cosolvents. Langmuir 2005; 21:6769-6775.
12. Nicoli S, Zani F, Bilzi S, Bettini R, Santi P. Association of nicotinamide with parabens: effect on solubility, partition and transdermal permeation. Eur J Pharm Biopharm 2008; 69:613-621.
13. Maheshwari RK, Chavada V, Varghese S, Year KS. Analysis of bulk sample of salicylic acid by application of hydrotropic solubilization method. Indian J Pharm Sci 2008;70:823-825.
14. Nagendra Gandhi N, Dharmendira Kumar M, Sathyamurthy N. Effect of hydrotropes on solubility and mass-transfer coefficient of butyl acetate. J Chem Eng Data 1998; 43:695-699.
15. Agrawal S, Pancholi SS, Jain NK, Agrawal GP. Hydrotropic solubilization of nimesulide for parenteral administration. Int J Pharm 2004; 274:149-155.
16. Revathi R, Ethiraj T, Saravanan VS, Ganeshan V, Saranya V, Sengottuvel T. New spectroscopic determination of nifedipine using hydrotropic solubilization. Int J Pharm Pharm Sci 2010; 2:74-76.
17. Maheswari RK, Chandrawanshi HK, Gupta N. Quantitative estimation of aspirin in tablets and bulk sample using metformin hydrochloride as hydrotropic agent. Int J Pharm Pharm Sci 2010; 2:20-23.
18. Pareek V, Tambe S, Bhalerao S, Shinde R, Gupta L. Spectrophotometric estimation of cefprozil by using different hydrotropic agents. Int J Pharm Pharm Sci 2010; 2:82-87
19. John, A. D. Lange's Handbook of Chemistry, 13th ed. New York: McGraw-Hill; 1987.
20. Perry RH. Perry's Chemical Engineer's Handbook, 7th ed. New York: McGraw-Hill; 1997.
21. Wagle VB, Kothari PS, Gaikar VG. Effect of temperature on aggregation behaviour of aqueous solution of sodium cumene sulfonate. J Mol Liq 2007; 133:68-76.
22. Gaikar VG, Phatak PV. Selective solubilization of isomers in hydrotrope solutions: o-/p- chlorobenzoic acids and o-/p-nitroanilines. Sep Sci Technol 1999; 34:439-459.