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ENHANCED SOLUBILITY OF PARACETAMOL BY VARIOUS HYDROTROPIC AGENTS

BY

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ABSTRACT

The increase in the aqueous solubility of paracetamol by the use of various hydrotropes was studied.

These agents were sodium glycinate, sodium gentisate, sodium salicylate and nicotinamide. All of these agents increased the aqueous solubility to varying degrees, with nicotinamide and sodium salicylate being the most efficient solubilizers.

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A conductance parameter was investigated as a mean of aiding interpretation of the solubility data. Dielectric constants could only be determined in the nicotinamide systems.

Ultra-violet spectral analysis, TLC, infra-red, and NMR techniques were utilized in order to elucidate the solubility mechanism. These tests indicate that no special bonding or complex formation exists for the sodium salt hydrotropes in these preliminary work. There is some evidence from UV & TLC analysis that nicotinamide and paracetamol enter into complex formation.

The other hydrotropic agents, in this study indicate the mechanism of solubilization is one of "salting - in" by causing miscibility of two formally immiscible liquid phases of ternary systems.

INTRODUCTION

Pharmaceutical systems have involved salts of organic acids as solubilizers for some practically insoluble or sparingly soluble drugs. These solubilizing agents are known as hydrotropes or hydrotropic agents.

The large amounts of hydrotropic agent needed to bring about increased solubility of sparingly soluble drugs were considered as an indication for another mechanism than micellar solubilization. Some workers have suggested that various forms of binding between solublizate and hydrotrope molecules would occur. Ueda (1,2) proposed that both factors of complex formation and salting in. played a part in the hydrotropic properties as shown by sodium benzoate.

Lawrence and Pearson (3) have studied the influence of a hydrotrope on a surfactant - solubilizate system. They indicated that, the addition of low hydrotrope concentrations increased the two liquid regions indicating a salting - out which they compared to similar salt effect suggested by Klevens (4). Higher concentrations of a hydrotrope caused a salting - in, yielding an increase in the area of the phase diagram which showed an isotropic solubilized system.

The effect of large concentrations of sodium benzoate on the solubility of caffeine is a classic example of hydrotropy applied to a pharmaceutical system (5). In addition, solubilization of benzoic acid with sodium benzoate and theophylline with sodium acetate and sodium glycinate are other examples (6,7).

The present study was undertaken to investigate the influence of certain hydrotropic agents on the increased solubility of paracetamol.

EXPERIMENTAL

Materials: Paracetamol[1], sodium salicylate[2], sodium gentisate[3], sodium glycinate[4], nicotinamide[5], silica gel [6] LK6DF, mineral oil[7],

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1 Sigma Chemical Company, St. Louis, MO., U.S.A.

2 Amend Drug and Chemical Co., N.J., U.S.A.

3 Sigma Chemical Company, St. Louis, MO, U.S.A.

4 Sigma Chemical Company, St. Louis, MO., U.S.A.

5 Metheson Coleman and Bell, division of Metheson Company, Inc. Norwood (Cincinnati), U.S.A.

6 Whitman Chemical Separation Inc., Clifton, N.J., U.S.A.

7 Chemalog Chemical Dynamics Corporation, Plainfield, N.J., U.S.A.

potassium bromide[8], chloroform[9], methanol[10], d_6-acetone[11], and deterium oxide[12].

Solubility Determination: This was achieved by use of the synthetic solubility method. In this method, gradually increasing weights of paracetamol were placed in glass ampoules followed by the aqueous solution of the hydrotropic agent, then sealed and transferred to a boiling water bath. Heating with occasional vigorous shaking is continued till clear solution were obtained. The ampoules were removed and kept undisturbed at ambient temperatures for ten days. where the maximum concentration of the drug that remained clear and beyond which no precipitation occurred was taken as the solubility of the drug. The weight increment in the serial solubility vials was about 2.5 mg/ml.

Thin - Layer Chromatography: A plate of silica gel LK6DF was used where the aqueous solutions of the hydrotropic agents alone as well as solubilized paracetamol in presence of each agent were spotted on the base line with the aid of microdropper. Then, the plate was left for twenty minutes to dry, transferred to solution jar where a solvent system composed of chloroform - methanol (90:10 V/V) was allowed to run for 20 CM. height to effect separation. Lastly, the plate was transferred to an oven maintained at 105°C for 5

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8 Beckman RIIC Ltd., London, England

9 MCB Manufacturing Chemicsts, Inc., Cincinnati, OH., U.S.A.

10 MCB Manufacturing Chemist, Inc., Cincinnati, OH, U.S.A.

11 Wilmad Glass Co., Inc. Buena, NJ, U.S.A.

12 Sigma Chem. Co., St. Louis, MO., U.S.A.

minutes and then subjected to iodine vapours for visualization of spots. The latter were outlined and their respective R_F values were determined.

Spectroscopic Studies: Solutions of the hydrotropic agents; sodium salicylate, sodium glycinate, sodium gentisate and nicotinamide in water as well as the solubilized aqueous systems of paracetamol prepared with each of these agents were subjected to spectrophotometric measurements in the U.V. range using a spectrophotometer[13].

Infra-Red Studies: Samples of the hydrotropic agents as well as the products of freez-drying[14] of solubilized paracetamol with these agents were subjected to I.R. measurements. Only 5 mg of each sample was mixed with 100 mg of potassium bromide and compressed as discs and measured by a spectrophotometer[15]. Those samples containing sodium glycinate either alone or as Lyophilized powder of solubilized paracetamol with this agent were measured as a thin film in mineral oil due to its virtual instantneous hygroscopicity.

NMR Studies: 60 mg of Lyophilized samples of solubilized paracetamol with sodium glycinate, sodium salicylate, sodium gentisate and nicotinamide as well as the individual components of each experiment were dissolved in deuterium oxide and the NMR spectra were recorded on a spectrometer[15]. The complete spectra were initially scanned, and then signals of interest were recorded

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13 Perkin Elmer - Hitachi 200, Hitachi Ltd, Tokyo, Japan

14 Freez-dryer 18 Labconco, Jefferson Scientific Hillwood, IL, U.S.A.

15 Varian Instruemnt Groups, Florhann, NJ, U.S.A.

three times to obtain the line width at half - height. The line widths thus measured were estimated to be accurate to $\pm$ 0.1 HZ. The normal operating probe temperature was kept at $0^{o}C$.

ELECTRICAL STUDIES

Nicotinamide in aqueous solutions could be determined relatives to its dielectric constant values of the use of the oscillometer. The three sodium salts, gentisate, glycinate and salicylate were also determined on the oscillometer[16] by measuring the number of units required to null the instrument needle. This was done at ambient temperatures, i.e. 23 - $25^{o}C$. These measurements were taken (R-values) on both the hydrotropic agents solutions and those solutions at paracetamol saturation.

Due to the high concentration of these agents in aqueous systems, the property being measured in some function of conductivity. It would be possible that some specific absorptive effects (concentration dependent) could take place and cause some small heating conviction currents in the positioned cell. This was minimized by taking readings quickly, using the same geometry (cell position), and rinsing with small amounts of sample prior to determining the R-values. Typically, conductance would be given in micronmicro-farads, but the R-value, though instrumental in nature is considered to be self-consistant and useful for these types of solutions.

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16 Sargent Chemical Oscillometer, Model V, Sargent and Co., Chicago, IL, U.S.A.

Data was also compiled as a function of the concentration of the hydrotropic agent, usually about 10 - 40% W/V and the comments given above also apply.

RESULTS AND DISCUSSION

The results of the solubility study are given in Table I. The solubility of paracetamol is about 15 mg/ml in water at ambient temperatures. It can be seen that the solubility values obtained with these agents varied over a wide range. Sodium gentisate at 20% W/V concentration gives about a 1.33 fold increase in solubility whereas nicotinamide increase solubility by 15-fold when expressed in mg/ml.

The solubilizing capacity is essentially an efficiency expression which indicates that nicotinamide has the greatest per mole solubilizing power, followed by sodium salicylate, sodium glycinate and sodium gentisate.

Oscillometric Studies - These studies were undertaken to determine if a possible mechanism of hydrotropy could be found.

Figure 1 depicts that, in case of sodium salts (gentisate, salicylate, glycinate), when the drug was added as the third component, the conductance (R-value) is decreased probably indicating a repression of dissociation of the sodium salts.

The "hydrotropic" action of these substances probably resides in several operative mechanisms. The slight dissociative repression would cause the "release" of aqueous dipoles to the medium and create a slightly less polar environment in the overall solution. Since

Table I: Influence of Certain Hydrotropes on Synthetic Solubility of Paracetamol in Water

SOLUBILIZER	% (W/V)	SOLUBILIZED PARACETAMOL (mg/ml)	SOLUBILIZING CAPACITY MOLE PARACETAMOL/ MOLE HYDROTROPE
1- Sodium Gentisate[a]/ Water System	20	20.0	0.116
	30	32.5	0.126
	40	50.0	0.146
2- Sodium Salicylate[a]/ Water System	20	60.0	0.318
	30	90.0	0.318
	40	90.0	0.239
3- Sodium Glycinate/ Water System	20	90.0	0.289
	30	100.0	0.257
	40	112.5	0.161
4- Nicotinamide[a]/ Water System	20	150.0	0.609
	30	150.0	0.404
	40	225.0	0.455

a = These solutions at all concentrations were yellowish or pinkish off-color prior to solubilizing drug.

these organic salts can enter into various interactions such as Keesom, Debye and London type, it would be expected that the frequency of these depend on concentration of the hydrotropic agent. This is the general trend of increase in solubility of paracetamol with increased concentrations of hydrotropic agent. It would also be expected that, at these high concentrations of 20 - 40% W/V, these

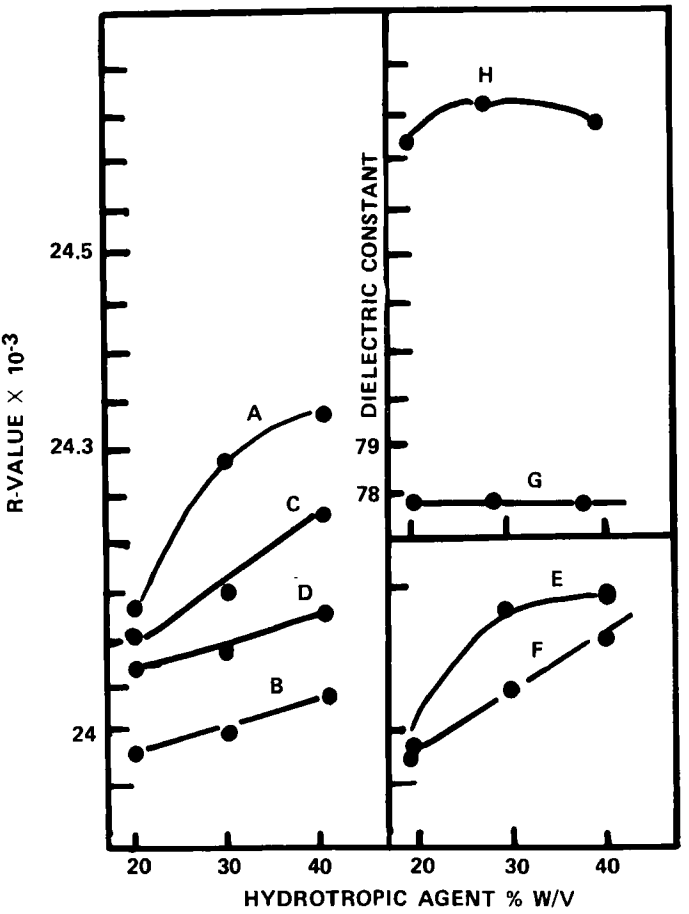

Fig.1 : Effect of variation of Hydrotropic Agents Concentration on R- Value of Water.

salts, while ionized would not be completely dissociated, and, could act as dipolar species in solution i.e., ion-pairs.

Nicotinamide, on the other hand, illustrated some interesting effects. In concentrations of 20 - 40% W/V, nicotinamide solutions have only a very small effect on dielectric constant of water, being only a few tenths below pure water as shown in Table II. At concentrations of 10 - 20% W/V, almost no change is evidenced in the dielectric constant of water.

Table II. Influence of Hydrotropic Agents on Electrical Charactistics of Water and Solubilized Paracetamol System

HYDROTROPIC AGENT	% (W/V)	R-VALUES[a] WITH PARACETAMOL	R-VALUES[a] WITHOUT PARACETAMOL (I.E. IN WATER)
1-Sodium Gentisate	20	24066	24085
	30	24080	24150
	40	24125	24230
2-Sodium Salicylate	20	23982	24104
	30	23996	24288
	40	24043	24339
3-Sodium Glycinate	20	23960	23980
	30	24046	24125
	40	24097	24140
		$E^{c}123$ Value	$E^{b}12$ Value
4-Nicotinamide	20	85.2	77.8
	30	86.2	77.8
	40	85.8	77.7

[a] R-Value = Instrument reading

[b] E123 Value = Dielectric Constant of solubilized paracetamol in water with nicotinamide

[c] E12 Value = Dielectric constant of nicotinamide in water

However, nicotinamide was found to dissolve large amounts of paracetamol, varying from about 1.5 to 4.5 times as much as the other agents used.

A surprising phenomenon was observed for these ternary systems of paracetamol - water - nicotnamide. All of these saturated systems at 20, 30 and 40% W/V nicotinamide concentration, the dielectric

constant was substantially greater than 78.5 (the value of pure water at 25°C).

Since it was known that nicotinamide in concentrations of 20 - 40% W/V had very little effect on dielectric constant of water, the added paracetamol in rather high concentration up to a saturated solution must be involved. It is difficult, at this stage, to suggest a mechanism for this increase in dielectric constant when it is known that paracetamol in low concentration (14.2 mg/ml) decreases the dielectric constant of water by about 8.5 units. Yet, concentrations of 150-225 mg/ml apparently increase the dielectric constant of water by increasing its value by 8-9 units. Further studies may aid in elucidating more precisely the operative mechanism relating to the above phenomenon.

Ultra-violet spectral analysis of freshly prepared solutions and the resultant peaks are given in Table III.

Paracetamol in water gives a peak at 245 nm. Sodium glycinate would not possess a UV spectra; and mixtures of paracetamol - sodium glycinate - water give only the paracetamol peak at 244 nm, as expected. Thus, no "complex" formation occurs in this system. In the case of sodium gentisate - paracetamol - water system, the gentisate peak at 319 nm remains constant, but the paracetamol peak of 245 nm. undergoes a slight hypsochromic shift to 229 nm. While this does indicate an electronic change in the paracetamol molecule; there is no concurrent change in the gentisate molecule. This mitigates against "complex" formation in this system.

The sodium salicylate - paracetamol - water system is somewhat more complex. For these spectra, this is a noted bathochromic

Table III: U.V. Spectral Analysis of Hydrotropic Agents With and Without Solubilized Paracetamol

SYSTEM	PEAK, N.M.
Paracetamol/Water	245 nm.
Sodium Glycinate/Water	-
Sodium Gentisate/Water	319 nm.
Sodium Salicylate/Water	292 nm.
Nicotinamide/Water	263 nm.
Paracetamol/Sodium Glycinate/Water	244 nm.
Paracetamol/Sodium Gentisate/Water	229 nm. 319 nm.
Paracetamol/Sodium Salicylate/Water	257 nm. 325nm.
Paracetamol/Nicotinamide	292 nm.

shift of 12 nm. for the paracetamol and a 33 nm. shift for the salicylate. Although it seems that electronic changes (chromophores) are occuring with both substances in solution, there are only modifications in where the peaks occur and not in their abolution.

The nicotinamide - paracetamol - water system was unique among those studied.

In this case, both the paracetamol and nicotinamide "normal" peaks are dramatically shifted bathochromically by 47 nm and 29 nm respectively.

The apparent "loss" of both the paracetamol 244 nm peak and the nicotinamide 263 nm peak indicates the formation of a new chromophore (or complex) with different electronic make-up.

Elucidation of Solubilization Mechanism:

A complete study using thin-layer chromatography, infra-red spectrum and NMR characteristics were carried out in order to elucidate the solubilization mechanism of paracetamol with the hydrotropes. Each solubilized system was investigated separately comparable with individual components and the results obtained are shown in Tables IV and V. The NMR and IR measurements were done for lyophilized samples of solubilized paracetamol with the hydrotropes.

(I) Paracetamol:

It is obvious that the determined R_F of paracetamol equals 0.43 while the characteristic shoulders in I.R. are at 1180 cm^{-1} representing acetate group, at 1400 - 1600 cm^{-1} denoting aromatic group, at 1650 cm^{-1} for (c=o) group and at 3100 cm^{-1} for ($co-NH_2$) group that shields the (OH) group.

The NMR studies of paracetamol in d_6-acetone show a peak of δ = 2.5 denoting (CH_3) group, another peak δ = 4.8 that represents both the (NH) and (OH) groups and a quartet δ = 7.8 denoting the para-substituted dramatic ring (original charts are available for any inquiry).

(II) Paracetamol - Sodium Gentisate Solubilizate:

The IR peaks of sodium gentisate are exhibited at 3400 cm^{-1} denoting (OH) group, at 1600, 1500, 1460 and 1400 cm^{-1} representing the aromatic ring, and at 1650 cm^{-1} indicating (c=o) group. On the other hand, the IR peaks of a Lyophilized sample of paracetamol - sodium gentisate solubilizate are shown at 3200 - 3400 cm^{-1} as a

Table IV: IR Spectra of Solubilized Paracetamol with Hydrotropes (freez dried) Comparable With Individual Components Using Potassium Bromide Discs

	CHARACTERISTIC PEAKS AT WAVE NUMBER (cm^{-1})						
	I	II	III	IV	V	VI	VII
1-Paracetamol	-	1180	1400-1600	1650	-	-	3100
2-Sodium Gentisate	-	-	1460	1500	1600	1650	3400
3-Solubilized Paracetamol with sodium gentisate	-	-	1400,1460	1500	1600	1650	3200-3400
4-Sodium Salicylate	758		1446,1480	1580	-	3005-3045	3400
5-Solubilized Paracetamol with Sod. salicylate	-	-	1390-1490	-	1600	1650	3200
6-Sodium Glycinate	910	-	-	1570	-	2900	3300-3400
7-Solubilized paracetamol with sodium glycinate	-	1150	-	-	1665	2660-2680	2900
8-Nicotinamide	700	1130	1400-1440	-	1600-1620	1670	3070-3400
9-Solubilized Paracetamol with nicotinamide	-	1190	1400	-	1600	1670	3070-3400

Table V: R_F Values of Solubilized Paracetamol Solutions with hydrotropes Comparable with Individual Components using Chloroform - methanol (90:10 V/V) as Eluant

SYSTEM	R_F OF PARACETAMOL	R_F OF SOD. GENTISATE	R_F OF SOD. SALICYLATE	R_F OF SOD. GLYCINATE	R_F OF NICOTINAMIDE
1-Paracetamol Solution in water	0.43	-	-	-	-
2-Sod. Gentisate Solution in water	-	0.83	-	-	-
3-Sod. Salicylate Solution in water	-	-	0.19	-	-
4-Sod. Glycinate Solution in water	-	-	-	0.0	-
5-Nicotinamide Solution in water	-	-	-	-	0.36
6-Solubilized Paracetamol with Sod. Gentisate	0.43	0.083	-	-	-
7-Solubilized Paracetamol with Sod. Salicylate	0.43	-	0.19	-	-
8-Solubilized Paracetamol with sod. glycinate	0.43	-	-	0.0	-
9-Solubilized Paracetamol with Nicotinamide	0.43	-	-	-	0.36

broad and small forked ones indicating the presence of both (NH2) and (OH) groups. Also, peaks at 1600, 1500, 1460 and 1400 cm^{-1} that represented the aromatic rings of both the drug and the solubilizer are evidenced. Consequently, it seems obvious from the previous findings that no change has occurred in the characteristic peaks of both the drug and the solubilizer when brought into solubilized system together.

In addition, the TLC indicated that the spot of solubilized paracetamol with sodium gentisate has separated into 2 spots of R_F = 0.43 and R_F = 0.083, being identical with those of individual components.

The NMR peaks of sodium gentisate were shown as a singlet δ = 5.2 that indicates hydroxyl group and a multiple δ = 7.5 which represents an aromatic ring. However, a solublized drug with sodium gentisate showed a singlet δ = 4.6 that indicates both NH2 and hydroxyl groups and multiple δ = 7.5 which denotes the aromatic rings of both the drug and sodium gentisate.

In conclusion, the aforementioned observations reveal that, no indication for a fixed chemical interaction between the drug and the hydrotrope leading to complex formation.

(III) Paracetamol - Sodium Salicylate Solubilizate:

The IR peaks of sodium salicylate were shown at 3400 cm^{-1} denoting the hydroxyl group, at 3005 - 3045 cm^{-1} representing (CH) aromatic, at 1580, 1480 and 1446 cm^{-1} denoting the aromatic ring, and at 1110 cm^{-1} indicating asymmetric Keto group. Also, a peak at 758 cm^{-1} was shown that denotes ortho-substitution of the aromatic

ring. On the other hand, solubilized paracetamol with sodium salicylate exhibited IR peaks at 3200 cm^{-1} as a fork peak of amino group, at 1600, 1490 and 1390 cm^{-1} denoting the aromatic ring, at 1650 cm^{-1} representing the keto group. Hence, it could be concluded that no missing or broadening of any of the characteristic peaks of both the drug and the hydrotrope when brought into solution in a solubilized manner.

The TLC done reveals that, the spot of solubilized paracetamol with the aid of sodium salicylate has separated into 2 spots of R_F = 0.43 and R_F = 0.19 that are identical with those of individual paracetamol and sodium salicylate respectively.

The NMR studies discloses that sodium salicylate showed a singlet δ = 5.1 denoting (OH) group and a multiple δ = 7.5 that represents the aromatic ring. Furthermore, the Lyophilized sample of solubilized drug with sodium salicylate exhibited a singlet δ = 3.2 that represents (CH3) group of paracetamol, another singlet at δ = 5.7 of both (OH) and (NH) groups of the drug and sodium salicylate. Also, it showed a multiple δ = 8.2 which represents the aromatic rings of both the drug and sodium salicylate. Consequently, it seems obvious that not interaction occurred between paracetamol and sodium salicylate in aqueous solution and that solubilization process bears no relation to complexation being mere hydrotropy.

Paracetamol - Sodium Glycinate Solubilizate:

sodium glycinate showed IR shoulders at 3300 - 3400 cm^{-1} as a fork peak that denotes (NH2) group and at 2900, 1570 and 910 cm^{-1} that represent (CH2) group. Nevertheless, the Lyophilized sample of

solubilized paracetamol with sodium glycinate showed shoulders at 2900 cm^{-1} denoting (CH2) group, at 2660 - 2680 cm^{-1} representing aromatic ring, at 1665 cm^{-1} indicating keto group and at 1150 cm^{-1} denoting (NH) group.

The TLC of a spot of solubilized drug with sodium glycinate gave 2 spots of R_F = 0.43 and R_F = zero values that were identical with those of paracetamol and sodium glycinate respectively.

The NMR of sodium glycinate revealed 2 singlets, one at δ = 3.6 of (CH2) group and the other at δ = 5.3 of (NH2) group. On the other hand, the Lyophilized sample of solubilized paracetamol with sodium glycinate exhibited a peak at δ = 2.2 denoting (CH3) group of paracetamol, another one at δ = 3.3 representing (CH2) group of sodium glycinate. Also, a peak at δ = 4.5 for amino group of both paracetamol and sodium glycinate and a quartet at δ = 7.2 for para-substituted aromatic ring of paracetamol were shown.

In conclusion, the aforementioned evidence reveal that no special or specific interaction does exist between paracetamol and sodium salicylate and that the encountered solubilization mechanism is hydrotropy.

Paracetamol - Nicotinamide Solubilizate:

Nicotinamide exhibited IR shoulders at 3070 - 3400 cm^{-1} as a fork peak denoting amino group and at 1400 - 1420 and 1600 - 1620 cm^{-1} representing aromatic pyridine ring. Also, it showed a peak at 1670 cm^{-1} indicating keto group and two other peaks at 1130 and 700 cm^{-1} denoting pyridine ring. However, a Lyophilized sample of solubilized drug with nicotinamide exhibited peaks at 3070 - 3400

cm^{-1} as a fork one denoting amino group, at 1400 and 1600 cm^{-1} representing aromatic ring, at 1670 cm^{-1} indicating keto group and at 1190 cm^{-1} denoting acetate group. These peaks were shown side by side those of nicotinamide mentioned above.

The TLC of a spot of solubilized drug with nicotinamide has separated into two spots with the same R_F values characteristic for paracetamol and nicotinamide but without sharp cut off.

The NMR of nicotinamide showed a triplet at δ = 8 - 9.5 denoting pyridine ring, a doublet at δ = 8.8, another doublet at δ = 9.5 and a singlet at 6 - 5.4 denoting (NH2) group. Furthermore, the Lyophilized sample of solubilized paracetamol with nicotinamide showed the same NMR peaks described before for both of nicotinamide and paracetamol alone.

It could be concluded that no specific interaction does exist between paracetamol and each of sodium gentisate, sodium salicylate, sodium glycinate and nicotinamide during solubilization process. Consequently, this process is mediated through "hydrotropy" rather than any other postulated mechanism.

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