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SOLUBILIZATION OF PARACETAMOL USING NON-IONIC SURFACTANTS AND CO-SOLUBILIZERS

by

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ABSTRACT

The influence of certain aqueous non-ionic surfactants, cosolvents and cosolvent - surfactant blends on the enhanced solubility of paracetamol were studied. Dielectric constants of these solvent systems with and without paracetamol were determined. In several instances, paracetamol was increased in solubility by 5-7 fold, depending on the system used. Dielectric constants were affected to varying degrees by these systems.

The cosolvents, propylene glycol and glycerin apparently suppress micelle formation.

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PAST WORK

Suface-active agents of the non-ionic type vary chemically and are quite diverse in solubilizing power[1]. The generally accepted mechanism of increasing the solubility of non-aqueous soluble materials is by micelle formation. The type of micelle formed, is spheroid, cylindrical or laminar, is concentration dependent. Solubilization is considered to occur by setting up biphasic dispersions of different polarities. The heat of fusion for solids is an important consideration in its ability and capacity to be solubilized [2,3].

Cosolvents such as propylene glycol and glycerin alter in "polar" environment and typically increased solubility by this mechanism. It has been found, however, that surfactants and cosolvents used together are not additive with respect to enhanced solubility [4]. Temperature changes that are minor only slightly affect solubilization [5]. There may be some change in the chemical and biological properties of solubilized materials [6].

INTRODUCTION

In this study, an attempt was made to determine solubiity enhancement of paracetamol in various systems. Two liquids, glycerin and propylene glycol were used in aqueous co-solvent mixtures at 20, 30 and 40% W/V; and co-solvent mixtures with Tween 20 at 10% W/V concentration.

Various other solubilizing agents were used which included Tween 80, Myrj 53 and 59 & Brij 58 & 700 at concentration levels of 2.5, 5 & 10% W/V. There was also an attempt to relate the solubility

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changes to the dielectric constant changes of these solvent mixture with and without dissolved drug.

There were several interesting changes observed for the dielectric constants of these systems which aided in interpreting some of the solubility data determined in this study.

Some very surprizing and interesting results were obtained when the number of moles of drug (paracetamol) were disolved per mole of surfactant. In this case, the average molecular weight of the common name component in the surfactant mixture was used.

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MATERIALS AND APPARATUS

1. Tween 80, Tween 20, Myrj 53, Myrj 59, Brij 59, and Brij 700 (ICI Americas, Inc., Willington, Deleware, U.S.A.).
2. Paracetamol, Sigma Chem. Co., St. Louis, MO., U.S.A.
3. Glycerin, J.T. Baker Chemical Co., N.J., U.S.A.
4. Propylene glycol, J.T. Baker Chemical Co., N.J., U.S.A.
5. Electric oven, Blue M. Electric Co., Illinois, U.S.A.
6. Rotating bottles apparatus with thermostat, Percision Scientific Co., U.S.A.
7. Oscillometer, Sargetn Model V, Sargent and Co., Chicago, U.S.A.

EXPERIMENTAL

The dielectric constants were determined by the use of a (Sargent Model V) oscillometer by generating a calibration curve of known dielectric constants. Absolute ethanol (U.S. Industrial Chemicals Co.) and distilled water were used in small increments of composition variation in order to define the calibration curve. The readings

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produced for these known mixtures and known dielectric constants of these mixtures allowed for the graphic interpolation of dielectric constants for the unknown solvent systems used in this study. There was some day-to-day variability in the calibration curves produced, however, they tended to exhibit parallelism.

In all cases, the 10 cc cell was used and readings (instrument units) varied about 100 units out of readings of about 12,500 units for absolute ethanol and about 18,500 units for water. This six thousand unit spread was equivalent to a dielectric constant scan of 56.2 ($\epsilon_{H_2O} - \epsilon_{ETOH}$).

While this range of 6000 units for about 60 dielectric units should produce quite accurate results (100 units/1 dielectric constant unit), the variability was on the order of $\pm$ 1 - 2 dielectric constant units. Two factors are involved here, one is the graphic interpolation where linearity was assumed for 2.5% V/V increments of absolute ethanol in water. Minor laboratory temperature fluctuations occurred with changes in the calibration curve which showed some skewness at dielectric constant values higher than 60. This, of course, would be due, to the high aqueous content and its particular sensitivity to dielectric constant changes with temperature.

There were some difficulties encountered in dealing with these rather viscous samples. However, they were overcome by draining the oscillometer cell for several minutes and rinsing with either liquid or sample twice and reading the instrument values in one minute intervals until a constant value was obtained.

The dielectric constants for Tween 20 & 80 were determined over the entire concentration range. The other surfactants and cosolvents dielectric constants were determined only at the concentrations of use in this study.

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All solvent systems were determined relative to the dielectric constant value with and without the drug, paracetamol, at saturation.

The solubility results were determined in the usual manner at 25°C by using an equilibrated (seven hour) sample filtered through a 0.22μ millipore syringe filtering assembly. The well known interference of small amounts of Tweens or glycerin and propylene glycol in the spectrophotometric analysis of paracetamol necessitated the use of a differential technique. A known amount of paracetamol in excess of its solubility was placed in the appropriate solvent systems and allowed to equilibrate. The entire sample was filtered, and the residue, including that washed out from the syringe remained on the millipore filter. The millipore filter was then dried to constant weight in an oven set at 70°C for 4 hours and was subtracted from the original amount put in to get the solubility value. This differential technique would give only approximate solubilities, and the intent here was to range-find these values to determine the effects of surfactants and cosolubilizers. The results were quite consistant and are discussed later.

RESULTS & DISCUSSION

The dielectric constants of paracetamol solutions of varying concentrations were determined and the results are illustrated in Figure 1. At saturation, paracetamol, i.e. 14 mg/ml decreases the dielectric constant of water from 78.5 to 70.1. As the concentration decreases, the dielectric constant increases and becomes asymptotic at low concentrations and approaches the value of the pure water.

The dielectric constants of Tween 20 and Tween 80 as binary mixture over the entire range of concentration were also determined.

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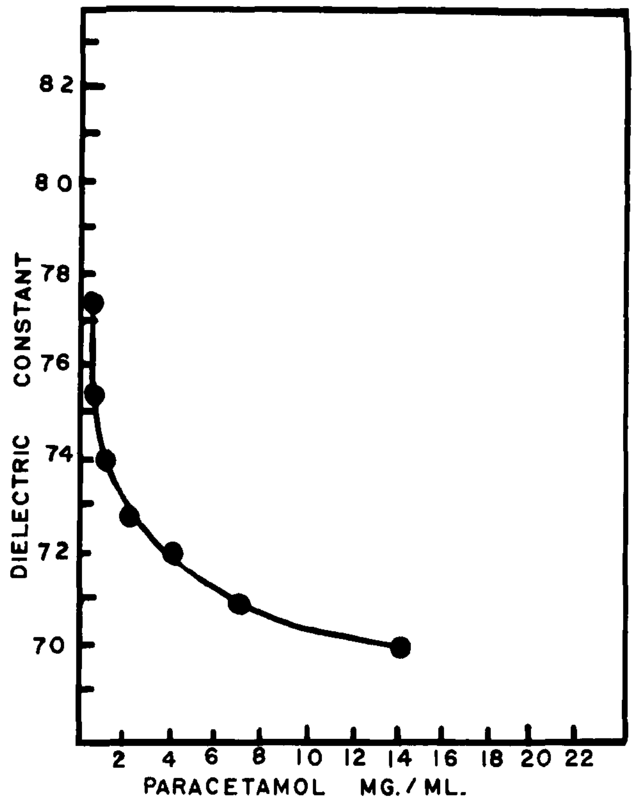

FIGURE I-

Fig.1: Effect of Variation of Paracetamol Concentration on Dielectric Constant of Water

The results are depicted in Figure 2. Tween 20 mixtures with water gave a strongly positive (greater than additive) curve particularly at lower concentrations. Tween 80, on the other hand seemed to be essentially invarient up to about 20% V/V and positively deviated. Between about 35-55% W/V Tween 80 (negatively disposed) an unpourable gelantinous mass exists for which dielectric constant values could not be taken. The remaining curve is negatively disposed from about 60 - 100% W/V Tween 80. It should be pointed out that, concentrations of 2.5, 5 and 10.0% W/V of both used in this study are all positively deviated from linearity.

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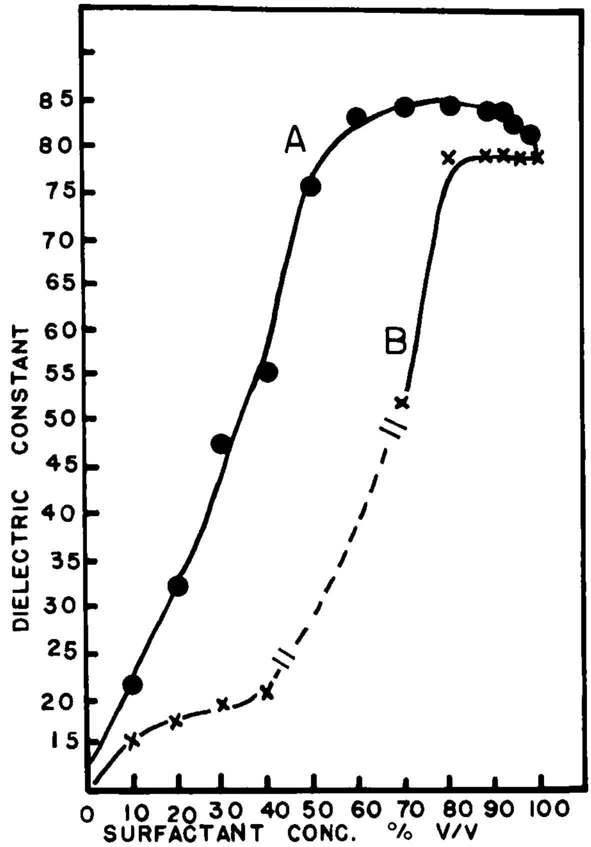

FIGURE 2 –

Fig.2: Effect of Tween 20 and Tween 80 concentration on Dielectric Constant of Water.

The dielectric constants of all the surfactants used in the present study at various concentrations are given in Table I. In this case, the dielectric constants are given for the surfactant - water system only; and the surfactant - water - drug saturated system.

The amount of solubilized drug is also shown for the systems studies. In all cases the dielectric constant increases with concentration except Tween 80 which is invarient. This would indicate that, these strongly hydrophilic surfactants (high HLB 15 - 18.8) are all positively deviated from linearity, and provide "localized environment"

Table I: Dielectric constants of the surfactant solvent systems with and without Paracetamol and the respective solubilities (mg/ml)

SOLUBILIZER CONC. (% W/V)		ϵ_{12} (S.A./WATER)	(DRUG CONC.) C_D (mg/ml)	ϵ_{123} (S.A./WATER/DRUG)
Tween 80	2.5	79.0	64	82.0
	5.0	79.0	74	83.1
	10.0	79.0	77	84.5
Tween 20	2.5	80.6	52	82.5
	5.0	82.9	68	84.6
	10.0	84.2	97	85.9
Myrj 53	2.5	75.9	64	80.8
	5.0	77.3	69	80.8
	10.0	79.4	78	81.0
Myrj 59	2.5	76.0	62	80.7
	5.0	77.0	63	79.0
	10.0	77.6	67	79.0
Brij 58	2.5	76.1	62	81.1
	5.0	77.6	62	81.0
	10.0	80.9	64	81.2
Brij 700	2.5	76.3	54	81.1
	5.0	77.6	61	81.0
	10.0	80.7	67	81.1

S.A. = Surface Active Agent

ϵ = Dielectric Constant

different from pure aqueous dipoles. The amount of solubilized drug usually increases with increasing surfactant concentration to only very small extents such as Myrj 59 or larger extents such as Tween 20, Brij 700 and Myrj 53. The increase in solubility compared to water with these agents goes from a low of 3.7/1 with Tween 20 at 2.5% to a high of about 7/1 with Tween 20 at 10%. The other solubilizing agents increase the ratio of solubility in any given system with respect to water between a ratio of about 3.9 - 5.6. It is interesting to note that, the dielectric constants of the final solutions of both

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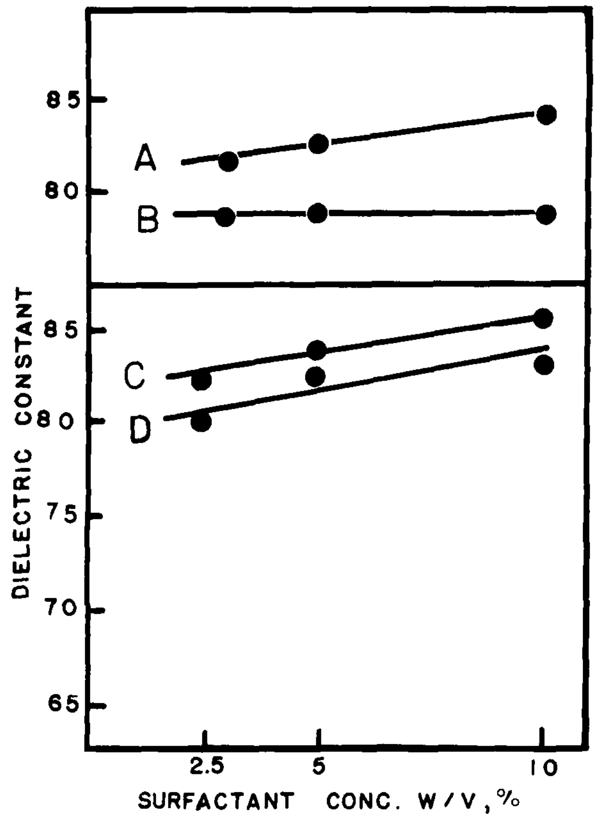

FIGURE 3 —

Fig.3: Effect of variation of Surfactants Concentration with and without Paracetamol on Dielectric Constant of Water.
A: Tween 80/ Water / drug ; B:Tween 80 / Water.
C; Tween 20/ Water / drug ; D:Tween 20 / Water.

Tween 80 and Tween 20 - water - drug showed increases in value with the concentration increase. This suggests that, the paracetamol modified the dielectric constant of the surfactant solutions to varying degrees. Except for Tweens (20 & 80), Myrj and Brij compounds with paracetamol gave a "leveling" effect, that is, very little change in value as the concentration changed.

Both the Tweens gave linear increases of dielectric constants for the final solutions, which were greater in magnitude than that of the surfactant - water system. These data are graphically illustrated in Figures 3 and 4.

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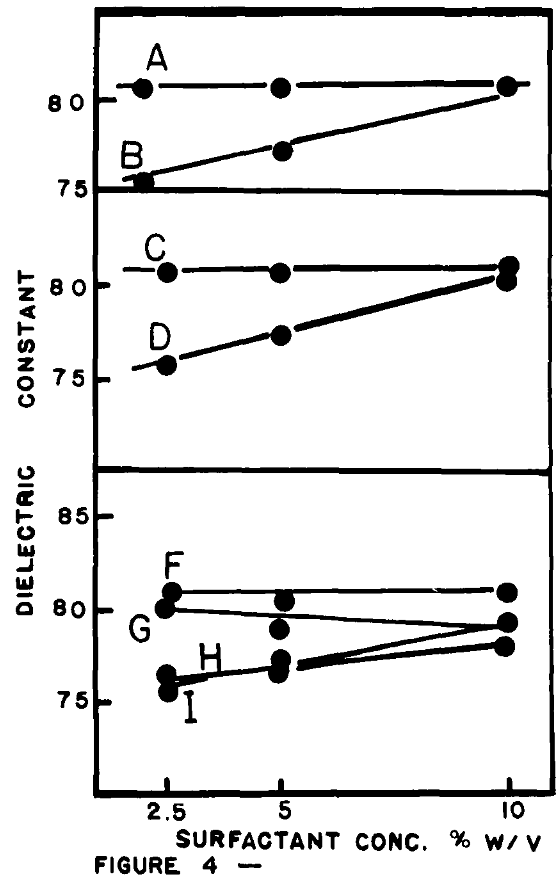

Fig.4: Effect of variation of Surfactants Concentration with and without Paracetamol on Dielectric Constant of Water.
A: Brij 700 / Water / Drug; B: Brij 700 / Water.
C: Brij 58 / Water / Drug; D: Brij 58 / Water.
F: Myrj 53 / Water / Drug; H: Myrj 53 / Water.
G: Myrj 59 / Water / Drug; I: Myrj 59 / Water.

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Table II: Dielectric constant and paracetamol solubility values for cosolvent blends with and without Tween 20 (10 % W/V).

COSOLVENT CONC. (% W/V)	CSA/H_2O ∈ 12	$CSA/H_2O/D$ ∈ 123	mg/ml CD	$CSA/H_2O/D/T20$ ∈ 234	mg/ml CD
Propylene glycol					
20	70.1	68.1	99	66.4	92
30	65.2	63.2	87	63.2	74
40	60.0	59.3	90	59.9	75
Glycerin					
20	72.0	71.3	100	70.4	73
30	68.1	66.2	92	66.5	70
40	64.0	62.1	100	61.3	70

CSA= Cosolvent

In Table II, the dielectric constant and solubility data is given for the cosolubilizers, propylene glycol and glycerin in the presence and absence of 10% Tween 20. The choice of Tween 20 at a concentration of 10% W/V resided in the fact of being able to dissolve the largest amount of paracetamol among the surfactants used.

As expected, the dielectric constant of the propylene glycol - water and glycerin - water systems decreased with increasing concentration of cosolvent. Paracetamol in the concentrations noted in the data decrease the dielectric constants of propylene glycol - water and glycerin - water at 20, 30 & 40% W/V by small amounts.

The solubility data is interesting insofar as it indicates invariance in the cosolvent systems although glycerin - water systems seem to be slightly better than propylene glycol. When 10% water is replaced by 10% Tween 20, the solubility decreases.

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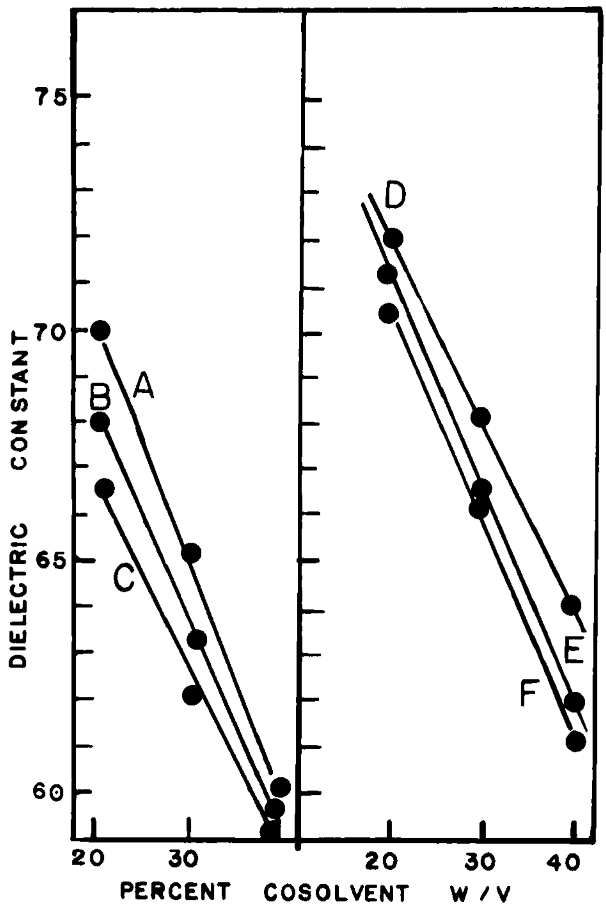

Fig.5: Effect of variation of Propylene Glycol and Glycerin Concentration on Dielectric Constant of Water.
A: Propylene Glycol / Water; B: Propylene Glycol/ Water / Drug ;C: Propylene Glycol/Water/Drug/Tween20.
D: Glycerin/ Water ; E: Glycerin /Water /Drug.
F: Glycerin/Water/Drug/ Tween 20.

The dielectric constants are changed only by very minor amounts indicating only a small change in overall polarity. There would seem to be a dramatic change in the micellization properties of Tween 20 in the presence of semipolar solvents such as glycols & glycerin

The solubilities of paracetamol for all these systems have been given in the appropriate tables and are plotted in Figures 6 & 7.

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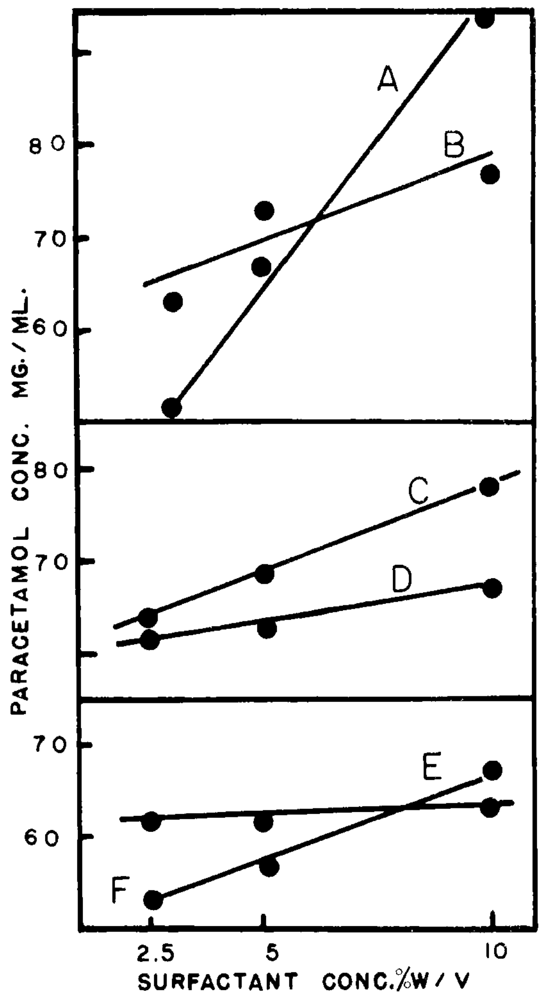

FIGURE 6 —

Fig.6: Effect of variation of Surfactants Concentration on Solubilized amount of Paracetamol in water.
A: Tween 20 ; B: Tween 80; C: Myrj 53; D:Myrj 59.
E: Brij 700 ; F: Brij 58.

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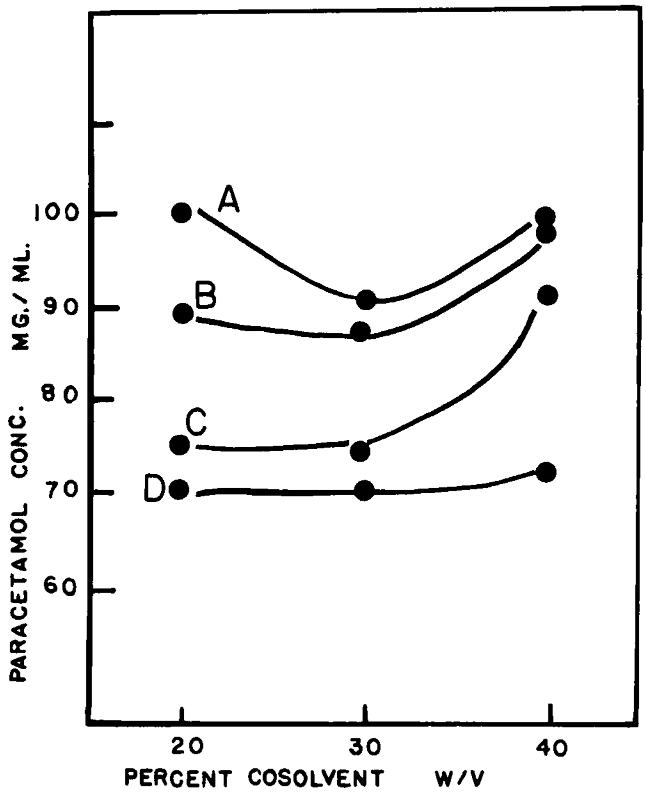

FIGURE 7 -

Fig.7: Effect of variation of Propylene Glycol and Glycerin Concentration with and without 10% W/V of Tween 20 on Paracetamol Solubility in Water.
A: Glycerin/Water ; B:Propylene Glycol/ Water.
C: Propylene Glycol/ Tween 20; D: Glycerin/ Tween 20.

For the surfactants, the solubility expressed in mg/ml increased with concentration to varying degrees.

The only exception to this was found for Brij 58 which was invarient with increasing concentrations. An interesting aspect of the solubility data was (except for Tween 20 at 10%) that the magnitudes of solubility did not vary substantially which may be an indication of the high hydrophilic nature of all the surfactants used (high HLB values).

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In the case of the cosolvents, propylene glycol and glycerin the solubility values were above those achieved by surfactants alone and about the same magnitude given previously in the presence of surfactant. Again, it can be pointed out, that, the cosolvent liquids suppress micelle formation and consequently lower the solubilization of the solute.

While it is recognized that, the surfactants used are mixtures of various components, an average molecular weight was obtained for each one used in this study. This was accomplished by determining the molecular weight of the common name component such as Polyoxyethylene 50 stearate for Myrj 53 and Polyoxyethylene 20 sorbitan mono-oleate for Tween 80.

These values are given in Table III in terms of moles of paracetamol dissolved per mole of surfactant and are illustrated in Figure 8.

Since this plot gave a series of non-linear curves, there also seemed to be parallelism of these curves for the individual surfactants. Tween 80 produced a curve with intermediate values for the ratio, was about parallel to the other five curves; and was used to unitize the results. These are found in Table III and plotted in Figure 9.

These results show that, Myrj 53 and Brij 700 have much greater solubilizing power with respect to moles dissolved to the extent of about two fold and three - fold respectively.

All the other surfactants have values around seven tenths to unity compared to Tween 80. There are some important practical aspects relating to this work. All the solutions were kept after solubility analysis and stored at ambient temperatures in order to note any

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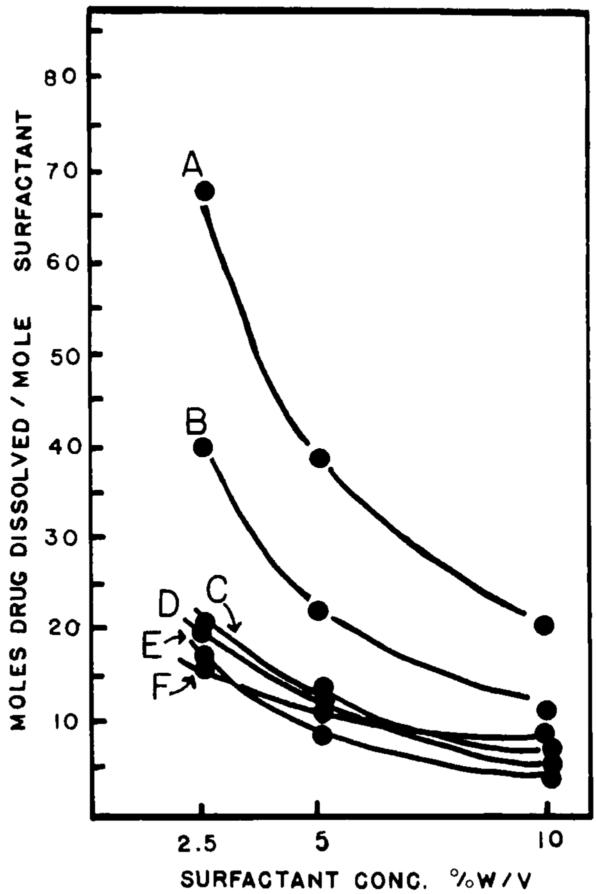

FIGURE 8 -

Fig.8: Effect of variation of Surfactants Concentration on Mole/Mole Solubility of Paracetamol in Water.
A: Brij 700; B: Myrj 53 ; C: Myrj 59; D:Tween 80; E: Tween 20, F: Brij 58.

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TABLE III: Moles of Paracetamol dissolved per Mole of surfactant and its relation ratio defining Tween 80 as unity.

SURFACTANT	%W/V	MOLES PARACETAMOL/MOLE SURFACTANT [a] (AVE. MOLE WT.)	
Tween 80	2.5	22.3	R = 1
	5.0	12.8	R = 1
	10.0	6.7	R = 1
Tween 20	2.5	16.9	R = 0.80
	5.0	11.1	R = 0.87
	10.0	7.9	R = 1.17
Mrij 53	2.5	40.9	R = 1.84
	5.0	22.4	R = 1.75
	10.0	12.7	R = 1.90
Mrij 59	2.5	23.8	R = 1.07
	5.0	12.0	R = 0.94
	10.0	6.4	R = 0.95
Brij 58	2.5	18.2	R = 0.82
	5.0	9.1	R = 0.72
	10.0	4.7	R = 0.70
Brij 700	2.5	68.6	R = 3.08
	5.0	38.1	R = 2.96
	10.0	20.9	R = 3.10

[a] see discussion of moleculer weight of surfactants

R = ratio (all values divided by Tween 80 values at a given conc. of surfactant)

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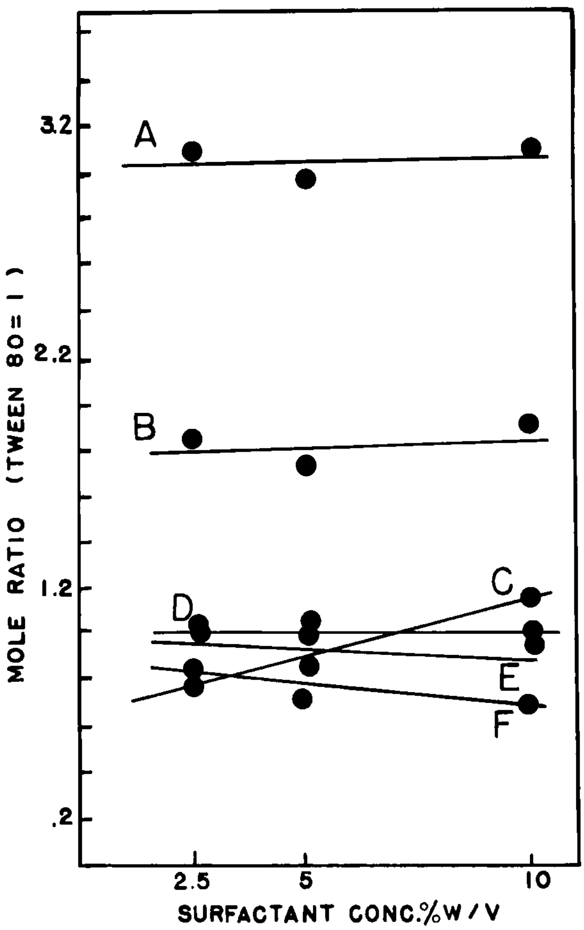

FIGURE 9 –

Fig.9: Effect of variation of Surfactants Concentration on relative number of moles needed to solubilize one mole of Paracetamol taking Tween 80 as unity.

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color change. Paracetamol, both hydrolyses and oxidizes in solution to a chromophore of pinkish discoloration which can be readily detected by visual observation.

It would be expected that, the surfactants would incorporate the paracetamol into the micelle and protect it from oxidation. The cosolvents propylene glycol and glycerin would also protect the drug by suppressing the formation of electron rich radicals in high concentrations. After 3 months, all of the surfactant solutions have remained clear except for Brij 58. This would indicate a satisfactory protection for the drug from oxidation degradation. The glycerin and propylene glycol solutions remained colorless after 3 months.

The mixed systems, glycerin or propylene glycol and Tween 20, operating with both mechanisms given above are also colorless after 3 months.

Another aspect of this data is the solubility enhancement achieved with surfactants, cosolvents and surfactant - cosolvent mixtures. The concentrations of about 60 - 100 mg/ml suggests at the lower end the possibility of a pediatric dose form with 300 mg/5 ml as a reconstitutable form with a shelf life of at least 3 months at ambient temperatures. At the higher end, 100 mg/ml suggests a 500 mg dose per teaspoonful with a stability of at least 3 months at 25^{o}C as well.

By scanning the data, a decision can be made about a liquid formulation by optimizing the solvent system components.

For example, glycerin at 20% W/V in water dissolves 100 mg/ml which is better than any of the surfactants in any concentration. In preparing a liquid pediatric form of this drug, it is obvious that an appropriate solution should be prepared at half - saturation

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(50 mg/ml). Otherwise, there would be some concern about the possibility of precipitation with thermal variations below ambient. For this reason, it would be quite difficult to prepare solutions of paracetamol at higher than pediatric levels.

Future studies are indicated in terms of mixed micelles and other solvent systems in order to enhance the solubility and minimize the oxidation of paracetamol.

REFERENCES

1. Mulley, B.A. "Advances in Pharmaceutical Sciences, volume 1, Academic Press, London, New York, 1964, p. 152.
2. Winsor, P.A., "Solvent Properties of Amphilphilic Compounds," Buttermoths, London, (1954), p. 127.
3. ibid., p. 135.
4. McBain, J.W., and Green, A.A., J. Am. Chem. Soc. 68, 1731-1736 (1946).
5. Kolothoff, I.M., and Graydon, W.F., J. Phys. Chem. 55, 699-712 (1951).
6. Bjaastad, S.G., and Hall, N.A., J. Ph. Sci. volume 56, no. 4, p. 504 (1967).

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