COMPARATIVE CHEMICAL STABILITY STUDIES OF THE SOLUBILIZED AND SUSPENSION LIQUID DOSAGE FORMS OF PARACETAMOL

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ABSTRACT

The formulation option of solubilizing the poorly water soluble Paracetamol powder B.P. was compared to the suspension option in which the chemical stabilities of the following three preparations were studied:

a. Co-solvent solubilized form (Elixir)
b. Surfactant solubilized form (Sodium Lauryl sulphate used)
c. Suspension form.

Accelerated stability studies were carried out on the preparations at the elevated temperatures of 40°C, 60°C and 80°C. The results were extrapolated to room temperature (25°C) by the use of the Arrhenius plot to obtain the degradation rate constants at room temperature from which shelf and half life were calculated. The study showed that at storage temperature of about 40°C and below, the Elixir was the most stable of the three preparations showing very little deterioration at those temperatures as given by the Arrhenius plot. This thus suggests that the Elixir should be the preferred liquid dosage form of paracetamol: However it must be stored at low temperature since its deterioration rate rapidly increase with increase in storage temperature, attaining a maximum at about 60°C above which deterioration rate was seen to decrease again. The suspension form was found to be more stable than the surfactant solubilized form.

INTRODUCTION

When a drug to be formulated as a Pharmaceutical liquid dosage form is poorly soluble in water, the formulating Pharmacists has a number of options to choose from as follows:

1. Use the Technique of solubilization by e.g use of Co-solvents, surface active agents (S.A.A) above their critical micelle concentration (C.M.C), complexation, chemical modification of drug (without changing biological activity, toxicity e.t.c) hydrotrophy e.t.c.
2. Formulate the drug as a suspension
3. If the drug is soluble in oil, the drug could be dissolved in a suitable oil and formulated as emulsion or the oily solution used. However, for oral preparations, it has been observed that some oil-soluble compounds are absorbed more completely when emulsified than when administered orally as an oily solution (Martin, Swarbrick and Cammarata 1969).

The drug under study i.e Paracetamol is a drug that is widely used for analgesic and antipyretic action in both adults and children. In children, the use of the liquid dosage form of Paracetamol would be more appropriate since children have difficulty in swallowing solid dosage forms like tablet and capsules. However, Paracetamol Powder B.P. is poorly soluble in water and the dose of 120mg cannot be dissolved in 5ml of water. In carrying out this study, it has been observed that most manufacturers market Paracetamol for Paediatric use in the form Elixir (a solubilized form), and it has been reported by Hamza and Paruta (1985) that Paracetamol in solution undergoes both hydrolysis and oxidation which could result in a Pinkish Colouration of the solution. Also there has been recent reports of toxicity of Paracetamol Elixir resulting from uncertain nature of propylene glycol used. The study therefore looked into the suspension option and compared the chemical stability of the solubilized and suspension forms. Since degradation of the most Pharmaceutical products is usually slow at room temperature, accelerated stability studies were conducted and the results extrapolated to room storage temperatures by the use of the Arrhenius plot.

MATERIALS AND EQUIPMENT

All material and chemicals were used as supplied by the manufacturers and are of Pharmaceutical grades. They include: Paracetamol Powder; Propylene glycol; glycerin; ethanol (96%); sodium Lauryl sulphate; tragacanth powder and sodium hydroxide pellets.

The equipment used include: U.V. Spectrophotometer (spectronic 21); dispensing balance; water bath with thermostat (Greenfield Oldman); pH meter; thermometer; glasswares, pestle and mortar.

METHODS

1. **Preparations**

The following formulations were freshly prepared:

a. **Co-solvent Solubilized form (Elixir)**

Paracetamol Powder B.P	**2.4gm**
Ethanol (96%)	10.0mls
Propylene glycol	10.0,mls
Distilled water	27.5mls
Glycerol to	100.0mls

b **Surfactants solubilized form**

Paracetamol Powder B.P.	2.4gm
Sodium Lauryl sulphate	1.0%
Distilled water to	100.0mls

The Paracetamol was dissolved in 50mls of 2% sodium lauryl sulphate solution and the volume made up to 100mls with more distilled water.

c. **Suspension form**

Paracetamol Powder B.P	2.4gm
Tragacanth Powder	2.0gm
Distilled water to	100.0mls

The suspension was prepared in the usual way. Colouring agents were omitted in all preparations to observe any colour change. All preparations had a pH of 6 - 7.

ii. ACCELERATED STABILITY STUDIES.

Each of the three preparations were kept at 40°C, 60°C and 80°C in water baths. At one hour interval, sample were taken from each bottle of preparation over a period of 4 hours. The samples were then treated as given in the British Pharmacopeia (B.P.) extraction method under Paracetamol Elixir. Absorbances of extracts were taken at the maximum wavelength (↑ max) of 256nM using 1cm cell against a blank prepared in same manner omitting only the Paracetamol.

From Beer Lambert's Law

$$E = \frac{A}{CD}$$

Where E = Molar extinction coeff = E1% / 1cm, (given as 715 at 256nM
C = Concentration (mg/ml)
A = Absorbance
D = Pathlength of the cell = 1cm

$$\frac{C = A}{ED} = \frac{A}{715 \times 1}$$

$$\% \text{ Potency} = \frac{A}{715 \times 100}$$

The percentage potencies of sample of were calculated with that at zero time (to) representing 100%, and other % potencies were calculated as percentages of the to value.

The average of three determinations

RESULTS

TABLE 1: Analysis of Samples

(a) Elixir Samples

Time (hrs)	40°C		60°C		80°C	
	Absorbance	% Potency	Absorbance	% Potency	Absorbance	% Potency
0	0.268	100	0.268	100	0.268	100
1	0.264	93	0.246	92	0.176	66
2	0.245	92	0.204	76	0.170	64
3	0.244	91	0.177	66	0.167	62
4	0.233	87	0.162	60	0.141	53

(b) Surfactant Solubilized samples

Time (hrs)	40°C		60°C		80°C	
	Absorbance	% Potency	Absorbance	% Potency	Absorbance	% Potency
0	0.268	100	0.268	100	0.268	100
1	0.259	97	0.244	91	0.236	88
2	0.252	94	0.220	82	0.183	68
3	0.237	88	0.218	81	0.163	61
4	0.219	82	0.209	78	0.156	58

(c) Suspension Samples

Time (hrs)	40°C		60°C		80°C	
	Absorbance	% Potency	Absorbance	% Potency	Absorbance	% Potency
0	0.268	100	0.268	100	0.268	100
1	0.240	89	0.201	75	0.178	66
2	0.239	89	0.193	72	0.162	60
3	0.238	89	0.188	70	0.157	58
4	0.228	85	0.177	66	0.143	53

TABLE 2: Calculated results for 2nd order plots

(a) For Elixir Samples

$Co = 100\%, \frac{1}{Co} = 0.01$

Temp. (°C)	Time (hrs)	% Potency (C)	$\frac{1}{C}$	$\frac{1}{C} - \frac{1}{Co}$	$(\frac{1}{C} - \frac{1}{Co}) \times 10^{-3}$
40	1	93	0.011	0.001	1.0
	2	92	0.011	0.001	1.0
	3	91	0.011	0.001	1.0
	4	87	0.011	0.001	1.0
60	1	92	0.011	0.001	1.0
	2	76	0.013	0.003	3.0
	3	66	0.015	0.005	5.0
	4	60	0.017	0.007	7.0
80	1	66	0.015	0.005	5.0
	2	64	0.016	0.006	6.0
	3	62	0.016	0.006	6.0
	4	53	0.019	0.009	9.0

(b) For Surfactant Solubilized Samples

$Co = 100\%, 1/Co = 0.01$

Temp. (°C)	Time (hrs)	% Potency (C)	1/C	1/C - 1/C	$(1/C - 1/Co) \times 10^{-3}$
40	1	97	0.010	0	0
	2	94	0.011	0.001	1.0
	3	88	0.011	0.001	1.0
	4	82	0.012	0.002	2.0
60	1	91	0.011	0.001	1.0
	2	82	0.012	0.002	2.0
	3	81	0.012	0.002	2.0
	4	78	0.013	0.003	3.0
80	1	88	0.011	0.001	1.0
	2	68	0.015	0.005	5.0
	3	61	0.016	0.006	6.0
	4	58	0.017	0.007	7.0

TABLE 3: Calculated results for Arrhenius plot

	Elixir Samples			Surfactant solubilized samples			Suspension samples		
	40°C	60°C	80°C	40°C	60°C	80°C	40°C	60°C	80°C
Absolute temp (°A)	313	333	353	313	333	353	313	333	353
$1/T°A \times 10^{-3}$	3.2	3.0	2.8	3.2	3.0	2.8	3.2	3.0	2.8
Slope $= -K_t$ (zero order)							-1.17	-3.0	-4.5
Slope $= K_t \times 10^{-3}$ (2nd order)	0	2.0	1.37	0.67	0.67	1.0			
K_t (zero order)							1.17	3.0	4.5
$K_t \times 10^{-3}$ (2nd order)	0	2.0	1.37	0.67	0.67	1.0			

The Arrhenius plots were extrapolated to room temperature (298°A) to obtain the reaction rate constants at room temperature (K_{RT}) for the three formulations from which shelf and half lifes were calculated as presented in Table 4.

TABLE 4: Calculated shelf and half lifes of Preparations

Preparation	K_{RT} (% hr^{-1})	Order of reaction	Rate Equation	Shelf life (hrs)	half life (hrs)
Elixir form	0	2nd	1/C-1/Co	Very long	Very long
Surfactant solubilized form	0.0005	2nd	"	2.0	20.0
Suspension form	0.64	Zero	Co-C=Kt	15.6	80.6

DISCUSSIONS

Koshy and Lach (1961) have reported that Paracetamol undergoes degradation to give P-aminophenol and acetic acid as follows:

OH OH

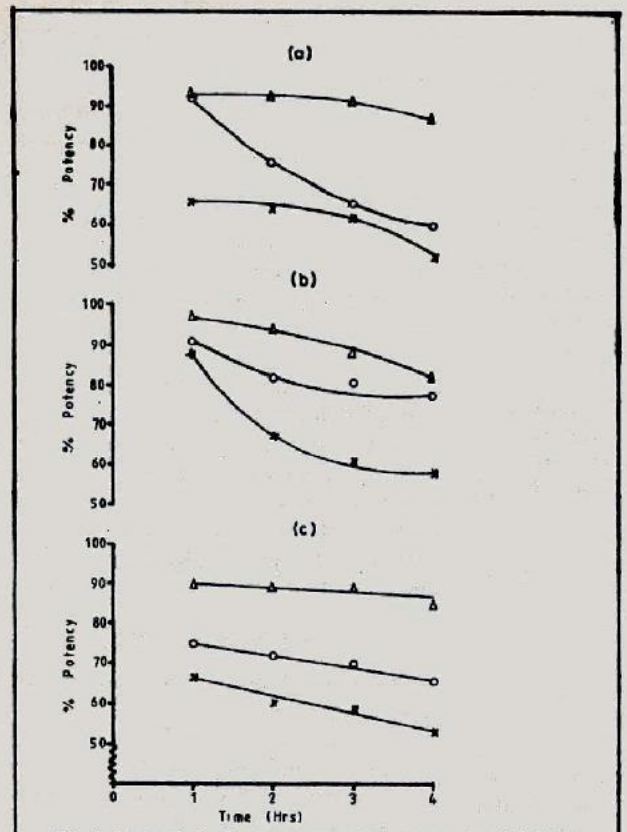


Fig. 1. Plot of % Potency against time for (a) Elixir (b) Surfactant solubilized (c) Suspension Formulations.

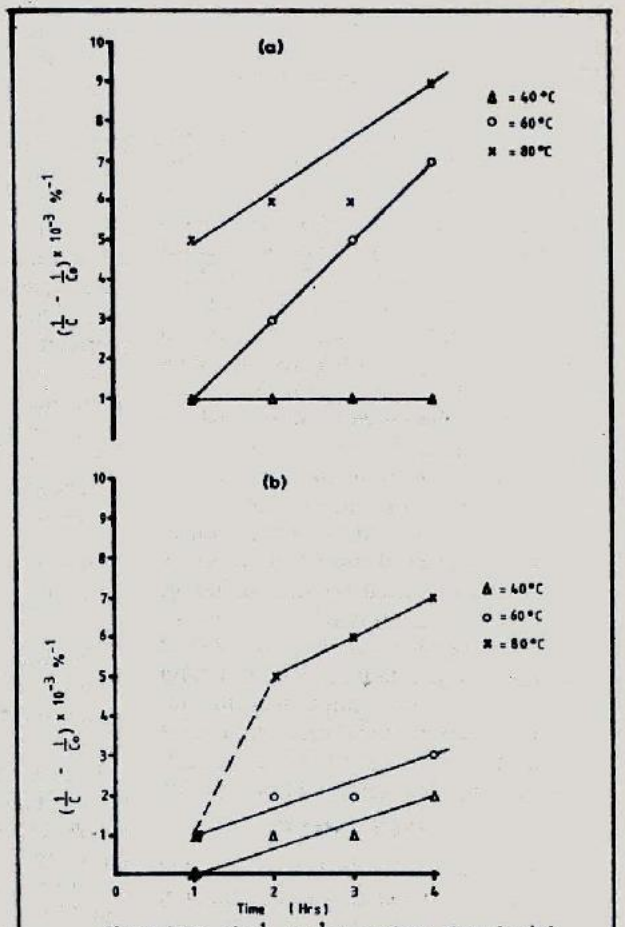


Fig. 3. Plot of $(\frac{1}{C} - \frac{1}{C_0})$ against time for (a) Elixir (b) Surfactant Solubilized Formulations

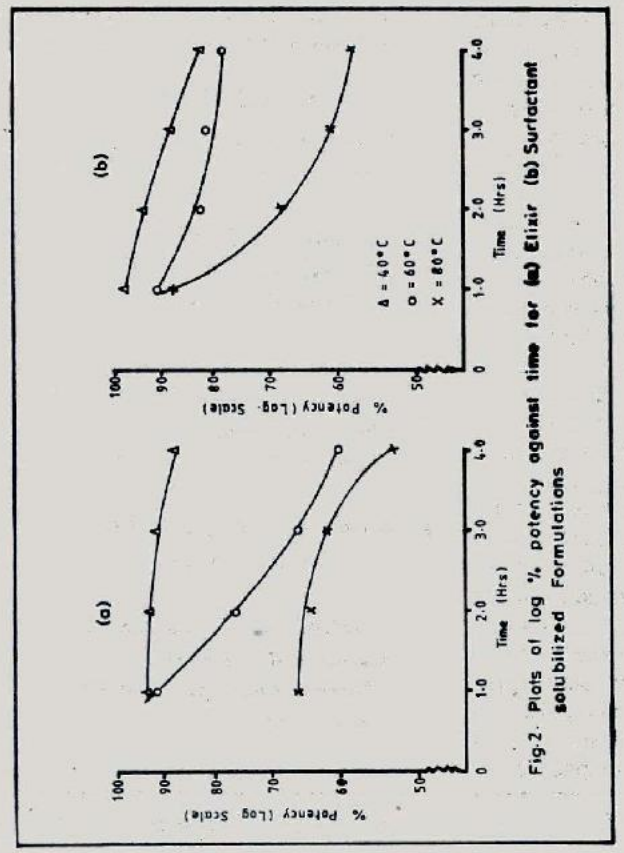


Fig. 2. Plots of log % potency against time for (a) Elixir (b) Surfactant solubilized Formulations

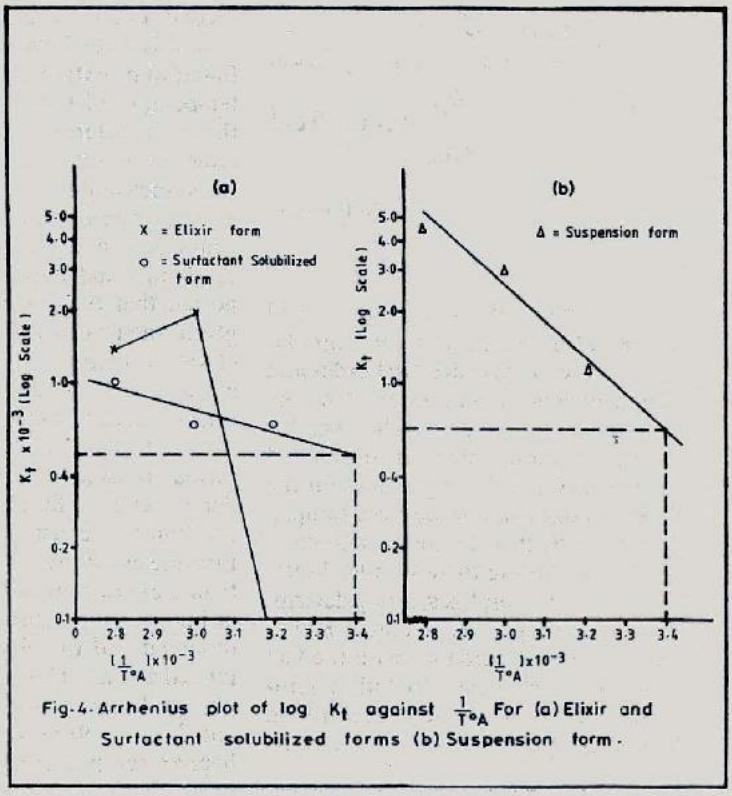


Fig. 4. Arrhenius plot of log K_t against $\frac{1}{T°A}$ For (a) Elixir and Surfactant solubilized forms (b) Suspension form.

were used in all cases .

Graphical treatment of results

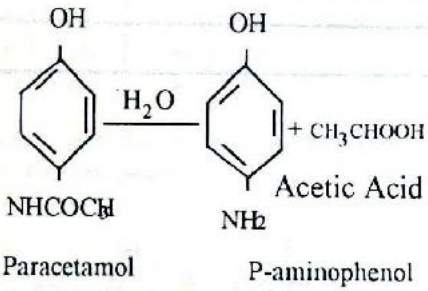
Graphs of % potency against time were plotted for each formulation at the various temperatures studied as shown in figure 1. For the plots that yielded curves, graph of log % Potency against time were plotted (figure 2). Since these plots yielded curves for Elixir and surfactant solubilized samples, the second order plots were constructed in which graphs of (1/C - 1/Co) against time were plotted as shown in figure 3, which yielded straight lines.

From the slopes of the straight line plots, the reaction rate constants were calculated at the various temperatures (Kt) for the three formulations as given in table 3 and used for the Arrhenius plot of log Kt against 1/ToA (figure 4).

The Arrhenius plots were extrapolated to room temperature (298°A) to obtain the reaction rate constants at room temperature (Krt) for the three formulations from which shelf and half lifes were calculated as presented in table 4.

DISCUSSIONS

Koshy and Lach (1961) have reported that Paracetamol undergoes degradation to give P-aminophenol and acetic acid as follows:



In this study, the graphical method was used for determining the degradation in which zero order, first order and second order plots were constructed. The zero order plot gave straight lines for the suspension sample while the second order plots yielded straight lines for the elixir and surfactant solubilized sample. This suggests that the suspension deteriorated according to zero order kinetics while the solubilized forms deteriorated according to second order Kinetics. This is in accordance with the fact that suspensions generally follow zero-order Kinetics since the concentration of drug in solution is kept constant by the reservoir of solid particles and so rate of decomposition becomes independent of the drug concentration.

In the case of the solubilized forms which deteriorated by second order Kinetics, degradation would depend on the concentration of two reaction,, one of the reactants been Paracetamol. For the elixir, the second reactant might be the limited amount of water or protective co-solvents (propylene glycol and glycerin), while for the surfactant solubilized preparations, the concentration of the protective micelles would be expected to influence degradation. When zero order reactions are compared to second order reactions two facts are observed as reported by Martin, Swarbrick and Cammarata (1969):

1. The shelf life for zero order reactions are longer
2. The time taken for reaction to be completed is much longer for second order reactions.

In pharmaceutical preparations, emphasis is laid more on the first fact, and the degraded products which might often be toxic should be within tolerable limits or that the % potency of the drug should be within acceptable limit usually 90% of original potency. Consequently drugs which undergo decomposition by zero order at room temperature are considered to be more stable chemically than those undergo first or second order decomposition reactions.

In this study however, the elixir was found to be extremely stable at storage temperature of 40°C and below and even though it deteriorated by second order Kinetics, it was much more stable than the suspension form which deteriorated by zero order Kinetics. This observation could be explained by the observation of Hamza and Paruta (1985) who reported that the co-solvents propylene glycol and glycerin afford stability to the elixir by suppressing the formation of electron rich radicals at high concentrations under storage temperature.

Despite the fact that the solubilized formulations deteriorated by second order Kinetics, differences exist in their reaction rate constants at low temperature, the elixir gave lower rate constants than the surfactant solubilized form, but at higher temperatures, a reversal was observed and the elixir gave a higher rate constants. This again could be explained by the observations of Hamza and Paruta (1985) who reported that at higher temperature, the protective mechanism of the co-solvent system may be reduced and infact may favour the formations of hydroxyl groups which hasten hydrolysis. These same workers also reported that surfactants in solution above their C.M.C form micelles which solubilize the Paracetamol and affords adequate protection to the Paracetamol against hydrolysis and oxidation bt preventing contact of the solubilizate (Paracetamol) with OH groups in the aqueous environment. However this protective mechanism may be less effective than the suppression of radial formation by co-solvent at room temperature. But as temperature increases within limits, micellar solubilization increases as reported by Florence et al (1977). Thus stability is enhanced as more of the drug will be taken up and protected in the micelles.

CONCLUSION

The result of the accelerated stability studies have shown that:

1. The solubilized forms of Paracetamol undergo degradation by second order Kinetics, while the suspension form undergoes degradation via the zero order Kinetics.
2. At storage temperatures of about 40°C and below the elixir was found to be the most stable of the three preparations and should thus be preferred liquid dosage form Paracetamol.
3. The suspension was more stable than the surfactant solubilized form at room storage temperature.

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