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PRODUCT DEVELOPMENT STUDIES FOR THE SELECTION OF AN IDEAL SOLVENT SYSTEM FOR DIAZEPAM IN INJECTABLE FORMULATIONS.

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ABSTRACT

The low water solubility of diazepam necessitates the use of non-aqueous vehicles in its injectable formulations. Increased solubility of a compound is achieved by the following ways : (a) Solubilization, (b) use of co-solvent, (c) complexation and (d) altering the pH. The last method is not applicable because diazepam is incapable of accepting or donating a proton or hydroxyl ion in the prescribed pH range (6.2-6.9). In most of the commercial injectable solutions of diazepam, propylene glycol is often used as co-solvent which may result in pain at the injection site and precipitation in intravenous solutions, resulting in thrombophlebitis. In tropical countries there is another problem of discoloration of the injectable solution due to degradation products during storage.

With these problems in mind, the present study was undertaken to reassess the situation in a newer perspective. In this study PEG 400 was used to replace propylene glycol entirely in an effort to develop a non-precipitating, stable and less painful diazepam injection. Encouraging results were obtained. These are being reported in this paper.

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INTRODUCTION

Problems such as precipitation of diazepam in aqueous environment of blood[1] or on dilution of infusion with I.V. fluids[2-4], pain at injection site and discoloration of commercial formulations due to enhanced degradation of diazepam by ionic moieties[5, 6], provided the impetus for the present work. The relative stabilities of the developed PEG formulations with different buffer systems were also studied.

EXPERIMENTAL

Materials : All reagents used were of analytical grade. Methanol was of spectro grade. Diazepam R.S. and Diazepam I.P.[7] were supplied by courtsey of Central Drug Laboratory, Calcutta and Indian Drugs and Pharmaceutical Ltd. respectively.

Methods : In equilibrium solubility studies using a mechanical shaker, diazepam was assayed spectrophotometrically in acidified methanol at 360 nm and in stability studies, the method given by Nudelman and Waisbaum[8] was adopted. This was based on the separation of diazepam from its degradation products by TLC and subsequent spectrophotometric estimation at 360 nm.. The data obtained was compared with the standard data obtained by processing known amount of standard diazepam in the same way and in the same manner.

In order to see the applicability of micellar solubilization technique for solubilization of diazepam, a test was carried out using polysorbate 80 (0.0 to 0.1% w/v in glass distilled water)

The dielectric requirement of a solute is an important factor for solubilization[9] . The absolute solubility of a solute may vary considerably in two different solvents of the same dielectric constant but the solubility profile as a function of dielectric constant appears to be similar for a solute in a wide variety of solvent systems. Hence, the solubility of diazepam in dioxane-water blends of different dielectric constants at room temperature (26 deg. C) was determined by Universal Dielectrometer Type OH - 301.

Four solvent mixtures were prepared as follows :

Solvents (% v/v)	Solvent mixtures			
	1	2	3	4
PEG 400	40.0	50.0	60.0	70.0
Ethyl alcohol	10.0	10.0	10.0	10.0
Benzyl alcohol	1.5	1.5	1.5	1.5
Purified water	48.5	38.5	28.5	18.5

Solubility of diazepam in these solvent mixtures were determined at room temperature. The final filtrate was stored in the refrigerator (4 deg. C) overnight, again filtered and analysed. The results are given in table 1.

The A.D.C. of each mixture was calculated by neglecting the volume changes and using the D.C. of each solvent from literature with the help of the equation, A.D.C. = $[\Sigma\{(\%\ of\ A \times D.C.\ of\ A) + (\%\ of\ B \times D.C.\ of\ B) + ...\}]/100$.

The relationship of log of solubility with % of PEG 400 and A.D.C. is shown in fig. 1.

For stability study of experimental formulations, the solvent mixture containing 55% PEG 400 was chosen to reach a compromise between % of water and syringability of the formulations. The composition of the experimental formulations are given below :

Composition	Formulations		
	1	2	3
1. PEG 400 (% V/V)	55.0	55.0	55.0
2. Ethanol (% V/V)	10.0	10.0	10.0
3. Benzyl alcohol (% V/V)	1.5	1.5	1.5
4. Water [glass distilled (% V/V)]	33.5	33.5	33.5
5. Diazepam (% W/V)	0.525	0.525	0.525
6. Ascorbic acid (% W/V)	0.100	0.100	0.100
7. Buffer	"B"	"P"	

'B' = Benzoate buffer to pH 6.5 (Total buffer conc.0.10 mole/lit.) and
'P' = Phosphate buffer to pH 6.5 (Total buffer conc. 0.06 mole/lit.)

TABLE - 1

Solvent Mixture	Solubility at 26deg. C (mg/ml)	Solubility at 4 deg. C (mg/ml)	Approximate Dielectric Constant (A.D.C.)
1	4.375	2.675	46.69
2	9.000	5.500	40.09
3	15.600	10.800	33.48
4	26.530	22.750	26.87

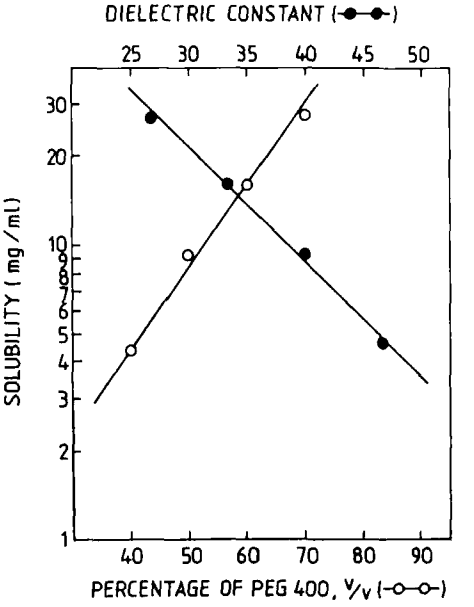

FIGURE 1

Plot of solubility of Diazepam at 26°C as a function of percentage of PEG 400 and dielectric constant of the injectable vehicle.

Ascorbic acid is used as an antioxidant and complexing agent. The use of ethanol is to reduce the viscosity and thereby improve the syringability of the preparations. Benzyl alcohol is used as a bacteriostatic agent, solubilizer and local anaesthetic. First two formulations were buffered and the third one was kept as control. The pH was adjusted to 6.5 with triethanolamine.

After the solutions were prepared, they were filtered and stored in sealed amber colored ampules. They should be sterilized by filtration. But here they were autoclaved at 121 deg. C at 15 lbs/sq. inch pressure for effective 15 minutes to observe the change in pH, if any. Then they were stored at room temperature and 53.5 ± 0.5 deg. C in a constant temperature oven. Some of the samples were stored in refrigerator to examine precipitation, if any. The contents of the ampules were assayed periodically. For periodic discoloration studies the samples were diluted 10 times with methanol and the % transmittances of these methanolic solutions were measured at 410 nm.

RESULTS & DISCUSSIONS

During solubility study in polysorbate 80 solution, it is observed that the highest solubility of 299.1 µg/ml is achieved at a polysorbate concentration of 0.02% (W/V). This solubility is quite low for injectable formulations. Therefore, polysorbate 80, alone can not be used to solubilize diazepam in an injectable formulation. But it can be used as an adjunct to other means of solubilization.

In the solubility study of diazepam in dioxane-water blends, it is observed that the D. C. of maximum solubility is about 10. This is a very low D. C. to be practicable.

In fig. 1. Log of solubility shows a linear relationship with the % of PEG 400 and A.D.C. of the medium, but absolute solubility at a particular dielectric constant is not similar to that obtained from solubility study. This might be due to solvent-solvent interaction.

In the stability study it is observed that the pH of the formulation with the phosphate buffer is not stable and decreased below 6.4. But pH of the other two formulations remains more or less constant.

No precipitation is found in any of the formulations after being kept for 10 days in refrigerator.

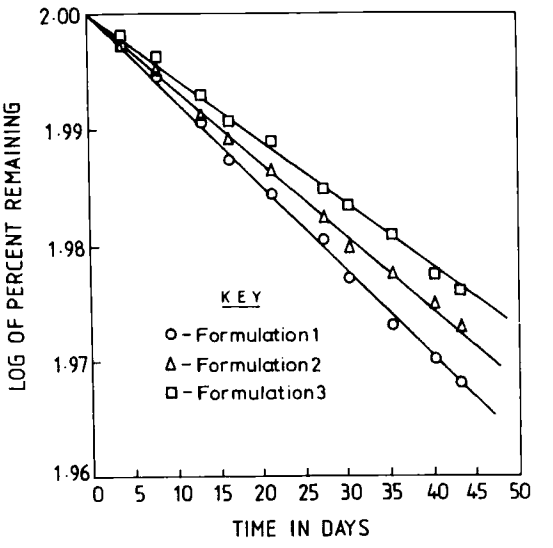

FIGURE 2

Log of % remaining versus time plot for Formulations stored at 26°C.

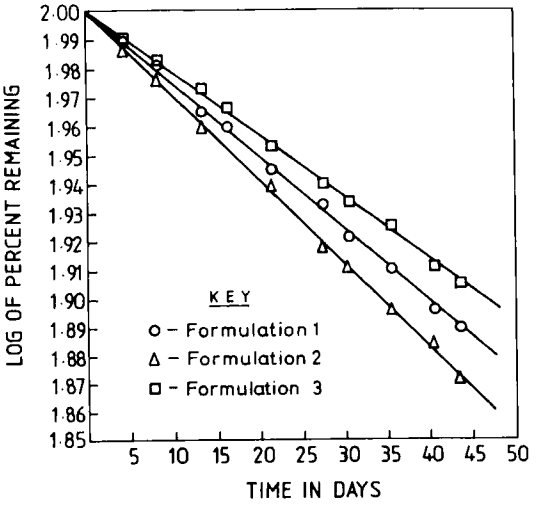

FIGURE 3

Log of % remaing versus time plot for Formulations stored at 53·5°C.

TABLE - 2

$K\ (days^{-1})$	Formulations		
	1	2	3
At 26 deg. C	7.575×10^{-4}	6.356×10^{-4}	5.585×10^{-4}
At 53.5 deg. C	2.606×10^{-3}	3.023×10^{-3}	2.243×10^{-3}

The results of periodic assay are given by the plots of log of % remaining vs. time (fig. 2 and 3). The apparent first order rate constants 'K' for each formulation at 26 deg. C and 53.5 deg. C are shown in table 2.

It is observed that the formulation containing phosphate buffer is more stable than the benzoate buffered formulation at room temperature but less stable at 53.5 deg. C. This shows that phosphate buffered formulation degrades more rapidly at higher temperatures. The benzoate buffered formulation shows more discoloration and is less stable than the unbuffered one. This may be due to the high ionic concentration associated with buffered formulations because ions catalyze the degradation and enhance discoloration. Low ionic strength of the unbuffered formulation may be the reason for its greater stability and lesser discoloration. At room temperature it is seen that virtually no discoloration is there on storage. The initial discoloration in other formulations both at room temperature and 53.5 deg. C may be attributed to ascorbic acid, the antioxidant used, which degrades to form brown coloured products.

Studies on formulation 3 indicate that unbuffered formulation can be used with a suitable antioxidant which itself shows no discoloration on storage. As this parenteral formulation contains oxidation susceptible diazepam, filling and sealing under nitrogen atmosphere prevent the degradation more efficiently. Since autoclaving of the formulations had a bearing on the stability and discoloration of diazepam, membrane filtration is adopted to eliminate the discoloration of the injectable solutions.

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