

A STUDY ON THE SOLUBILITY AND  
STABILITY OF DIAZEPAM AND NITRAZEPAM  
IN BUFFERED MIXTURES

A.E. Aboutaleb, M.S. Mesiha and A. Abdel-Zaher  
Department of Industrial Pharmacy, Faculty of Pharmacy,  
University of Assiut, Assiut, Egypt.

*Diazepam and Nitrazepam were solubilized by a series of commercial non-ionic surfactant solutions buffered to pH 4, 6 and 7 at 35°C. These nonionic surfactants include Emulgin C 1000 and C 1500 and Brij 35 and 58. It was found that the surfactant and the drug molecular structure as well as the pH value affect the quantity of Diazepam and Nitrazepam solubilized.*

*The stability of Diazepam and Nitrazepam were studied in the formulated mixtures at controlled pH values. It was found that the formulated mixtures showed maximum stability for Diazepam and Nitrazepam in mixtures adjusted to pH 6.*

The solubility and stability of Diazepam in 30% sodium salicylate were studied<sup>1</sup>. It was found that the solubility and the dissolution rate of Diazepam were increased with increasing sodium salicylate concentration. Diazepam was also stable to photochemical decomposition in 30% sodium salicylate solution.

The mechanism of degradation of Diazepam and Nitrazepam was investigated<sup>2</sup>. The mechanism proposed was the cleavage of the seven membered benzodiazepine ring.

In this study the solubilization of Diazepam and Nitrazepam in buffered solutions of nonionic surfactants was studied in order to investigate the effect of pH value

of the solubilized systems containing both drugs.

A TLC method<sup>3</sup> was carried out for the separation of Diazepam and Nitrazepam from their degradation products.

## EXPERIMENTAL

### Materials:

Diazepam and Nitrazepam (Hoffman La-Roche, Basel, Switzerland) were of Pharmaceutical grade. The surface active agents were of commercial grades. They were used without purification. These surfactants include cetyl stearyl alcohol with (20) ethylene oxide units (Eumulgin C 1000), cetyl stearyl alcohol with (50) ethylene oxide units (Eumulgin C 1500), both were obtained from Henkel Intern. Dusseldorf, W. Germany. Polyoxyethylene (23) lauryl ether (Brij 35) and polyoxyethylene (20) cetyl ether (Brij 58) both from Atlas Inc. Delaware, U.S.A. The number between brackets indicates the number of ethylene oxide groups in the surfactants molecule.

Sodium dibasic phosphate, citric acid, sodium metabisulphite, glycerol, Methyl and propyl parabens were pure chemicals (BDH, Poole. U.K.) Silica gel G for thin layer chromatography, Chloroform and diethyl ether were from Merck, Schuchard, W. Germany.

### Solubility Determination:

The analytical method was followed for measuring the solubility of Diazepam and Nitrazepam by different non-ionic surfactant solutions.

An accurately weighed amount of about 50 mg of either Diazepam or Nitrazepam were equilibrated with 8 ml of the previously mentioned nonionic surfactant solutions adjusted to pH 4, 6 and 7 using Mc-Illivan buffer system in screw capped tubes. The tubes were shaken in a constant temperature water bath at 35<sup>o</sup>. The equilibrium was established by repetitive sampling technique. After equilibration, they were centrifuged to sediment excess solids. The tubes were then reequilibrated for further period of 24 hours to attain the desired temperature. Samples were withdrawn and diluted with distilled water prior to their assay by ultraviolet spectroscopy at 232 nm for Diazepam and at 260 nm for Nitrazepam. The same nonionic surfactant concentration of the specific pH value was used as a blank at each time. It was found that the presence of the studied nonionic surfactant solutions did not interfere with the assay, nor made any shift in the maximum absorbance for both Diazepam and Nitrazepam.

Formulation of Diazepam and Nitrazepam in Mixtures:

A solution containing 2.5% w/v EumulginC1000 in distilled water was used as solubilizing vehicle for Diazepam, and a solution of Brij 35 (2.5% w/v) in distilled water was used as the solubilizing vehicle for Nitrazepam. A mixed preservative of 0.18% w/v methyl paraben and 0.02% w/v propyl paraben was used in each mixture. 0.1% w/v sodium metabisulphite was incorporated as an antioxidant, while 20% w/v glycerol was incorporated as sweetening agent.

The final formulations were adjusted to pH 4, 6 and 7 using Mc-Illivan buffer. The quantity of both Diazepam and Nitrazepam solubilized in each formulated mixture was measured initially using TLC and it was found to be 0.11% w/v for Diazepam and 0.4% w/v for Nitrazepam.



Separation of Diazepam and Nitrazepam from their  
Degradation Products:

Thin layer chromatographic method<sup>3</sup> was used for separating both Diazepam and Nitrazepam from their degradation products using silica gel G as adsorbent and chloroform : diethyl ether (6:4) as the developing system. Both of the two drugs were visualized under ultraviolet light. Diazepam of  $R_f$  value of 0.53 showed three degradation products of  $R_f$  values of 0.92, 0.71 and 0.42 respectively. While Nitrazepam of  $R_f$  value of 0.56 showed three degradation products of  $R_f$  value of 0.88, 0.71 and 0.4. Thus the intact drugs could be separated from their degradation products and assayed quantitatively by measuring the eluted spots in ethanol at 232 and 260 nm for Diazepam and Nitrazepam respectively.

#### RESULTS AND DISCUSSIONS

The results for the solubilization of Diazepam and Nitrazepam in buffered nonionic surfactant solutions at pH 4, 6 and 7 are shown in Fig. 1-6. In all cases the nonionic surfactants can be arranged according to their solubilizing efficiency as follows: Eumulgin C 1000 > Brij 58 > Eumulgin C 1500 > Brij 53. Thus, the solubilizing effect increases by increasing the lipophilic moiety of the surfactant and *vice versa*

At zero concentration of the surfactant the effect of pH is more apparent. Both drugs were more soluble at pH 4 than at higher pH values. This may be due to the protonation of the nitrogenous centers of the benzodiazepine nucleus. This effect is evident in case of Nitrazepam at pH 4 for all concentrations of the surfactants. In the

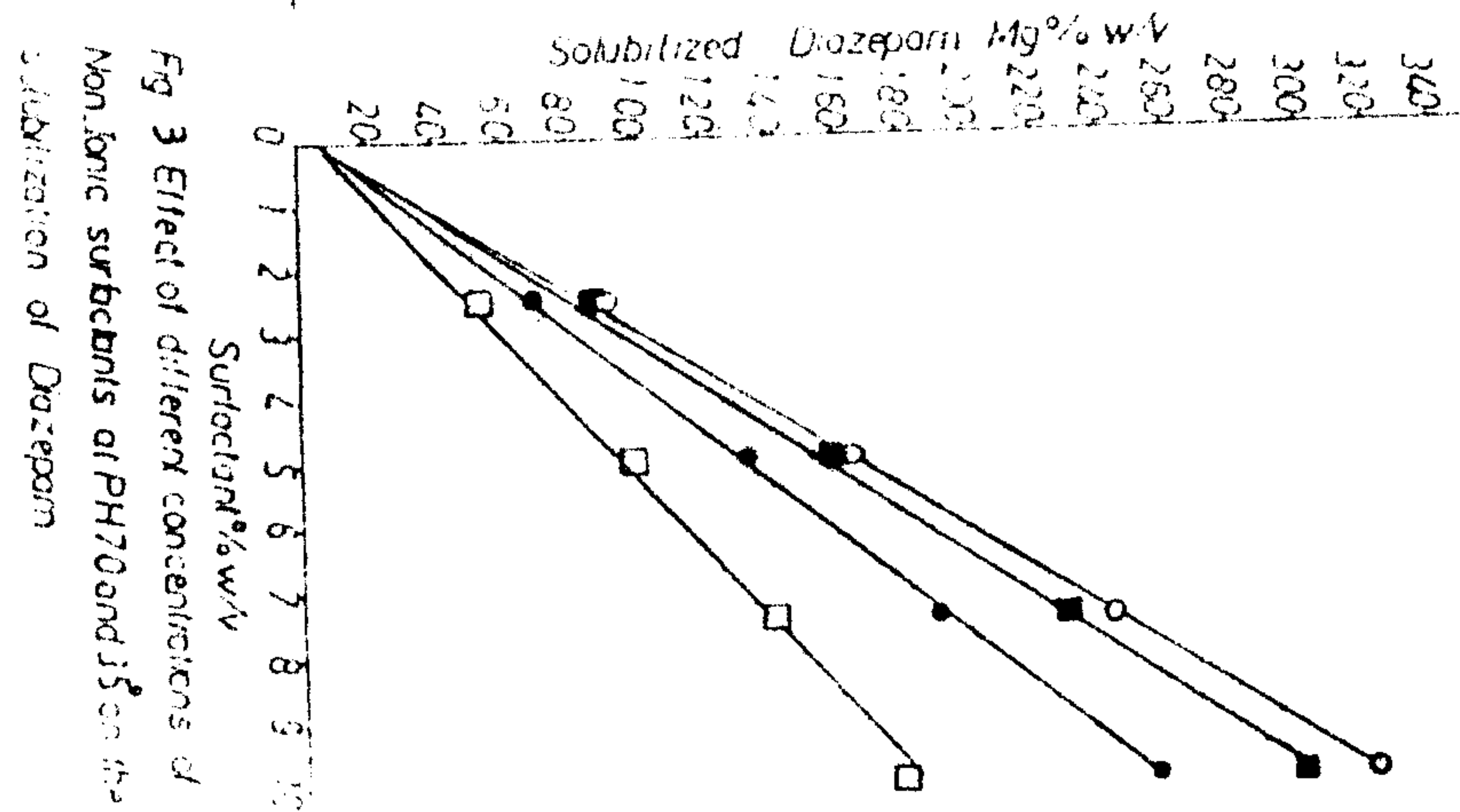
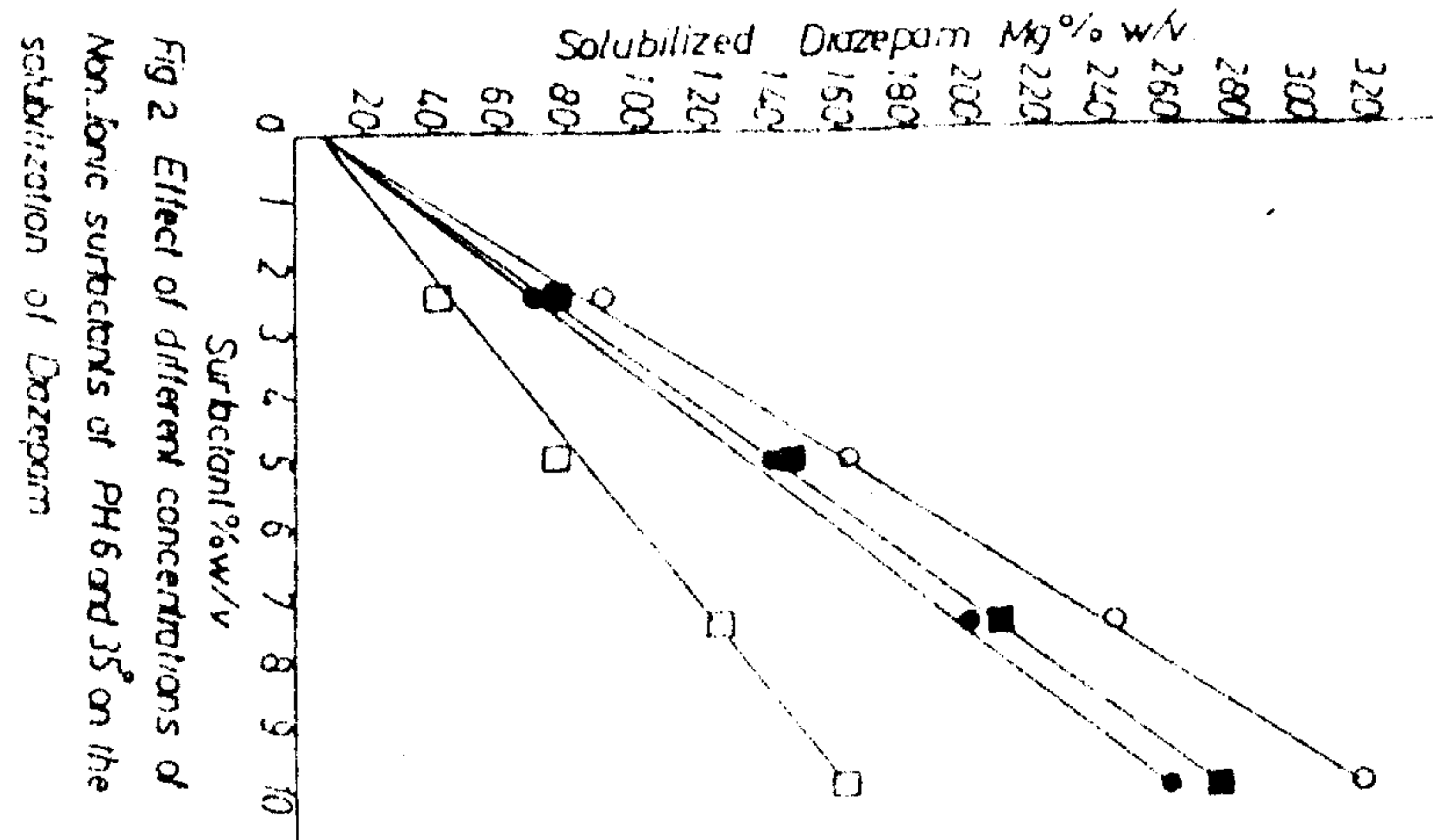
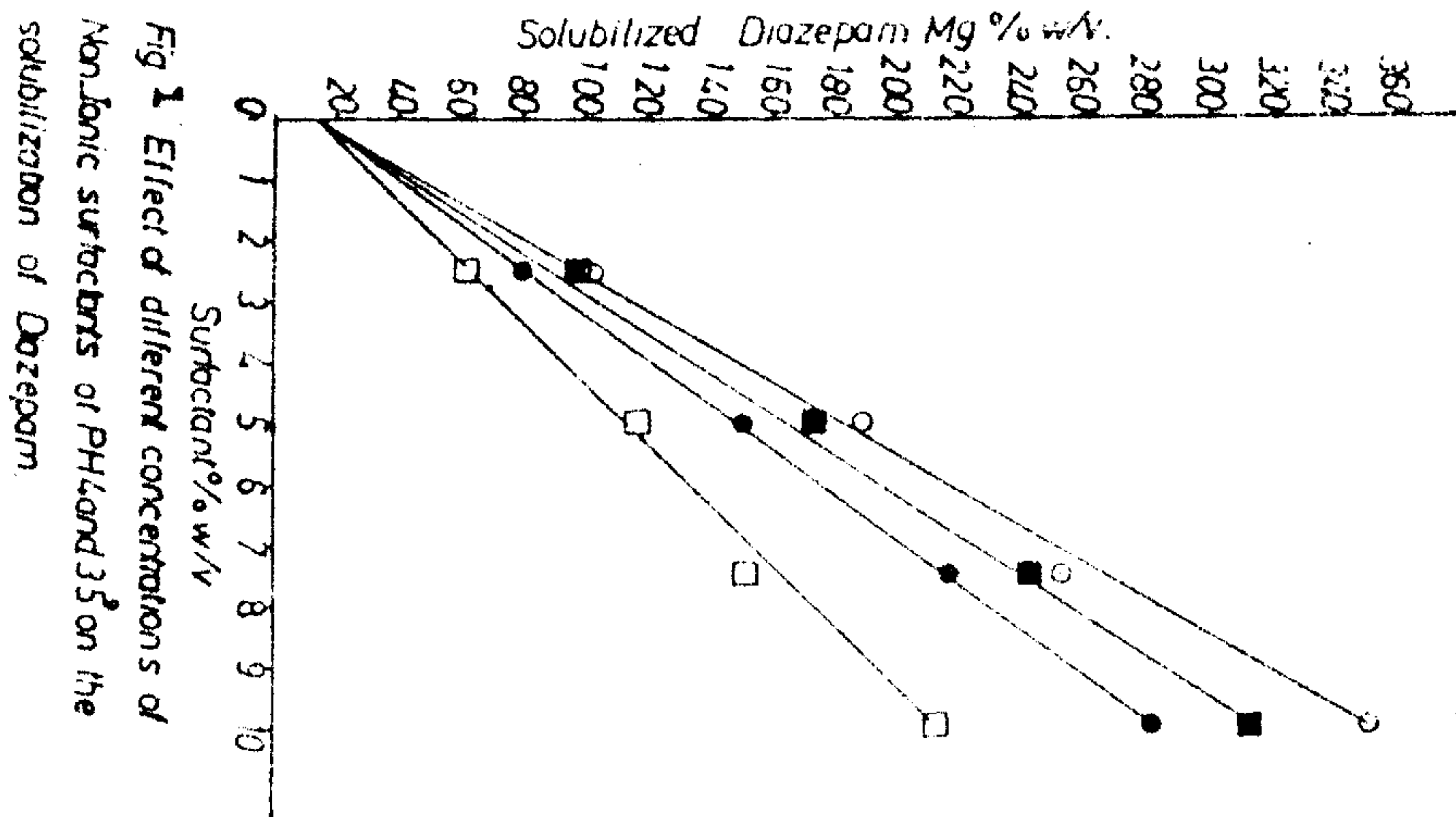
last case the role of surfactant type was masked by the role of the pH value. On the other hand, the effect of the buffer components should be considered, when discussing the solubilization at different pH values. The higher solubility of Nitrazepam at pH 4 may also be attributed to the solubilizing effect of excess citric acid relative to the sodium phosphate content. The sodium salt present at higher concentrations to attain the higher pH values may cause a salting out effect for the surfactant<sup>4</sup>.

Analysis of the mixtures for the intact drug content using TLC chromatography at various time intervals showed that in all cases when the logarithm of percent concentration of either Diazepam or Nitrazepam ( $\log C$ ) in weeks, a straight line was obtained, denoting that the degradation of both drugs is a first order reaction. From this straight line correlation of the instability velocity constant "K" and the half life values " $t_{1/2}$ " were calculated and shown in Table 1.

The effect of the pH on the stability of Diazepam and Nitrazepam in mixture at 35°C is shown in Table 6 and Figures 7,8. Mixtures containing Diazepam or Nitrazepam were adjusted to pH 4, 6 and 7 in order to investigate the role of the pH values of the mixtures on the stability of the drugs. It is clear that adjusting the pH of the mixture at pH 6 has the greatest stabilizing effect on both Diazepam and Nitrazepam, while adjusting the mixture to pH 7 is nearly equal in its stabilizing effect of Diazepam to that having pH 4 but less stable Nitrazepam mixture was obtained at pH 7.

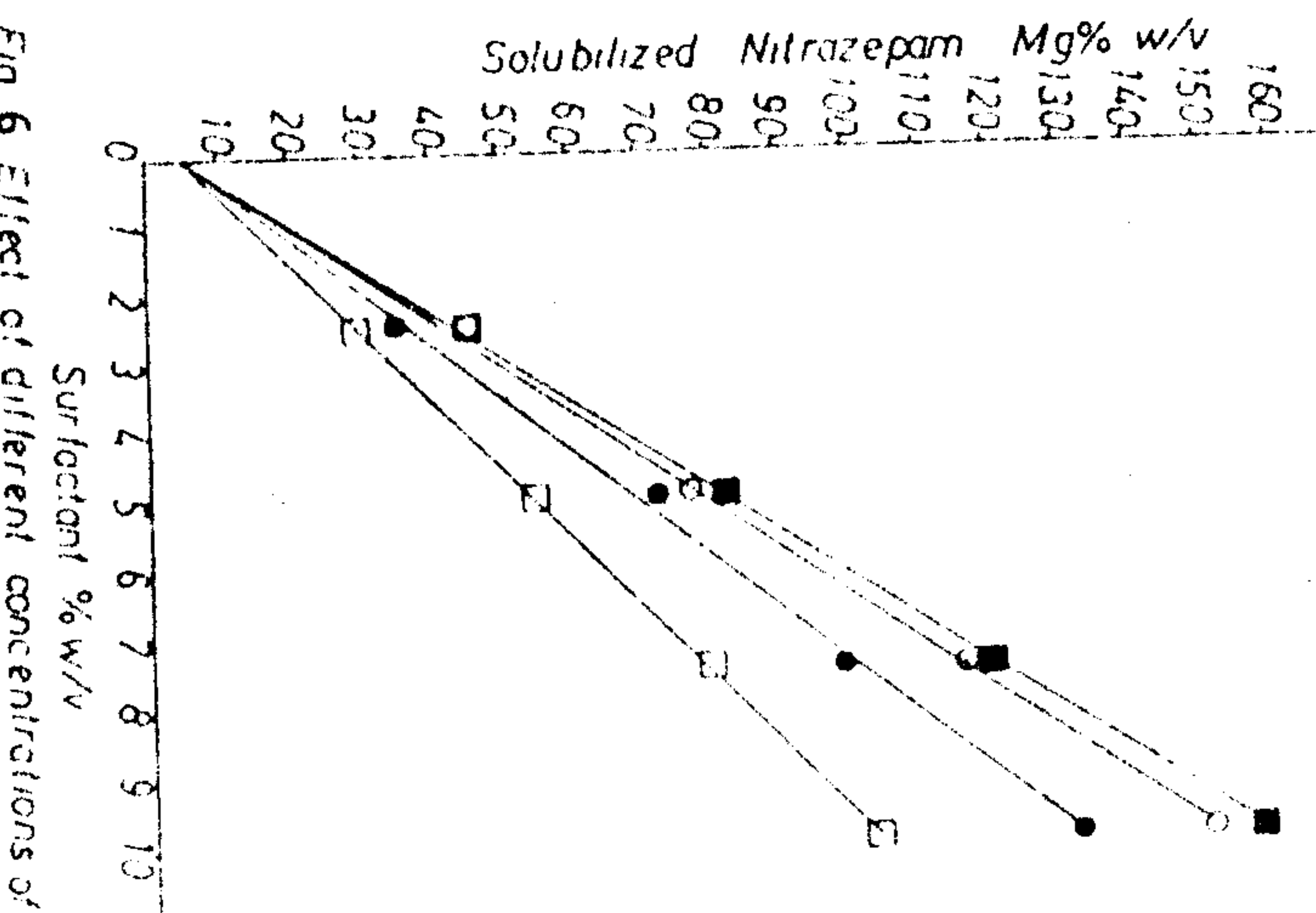
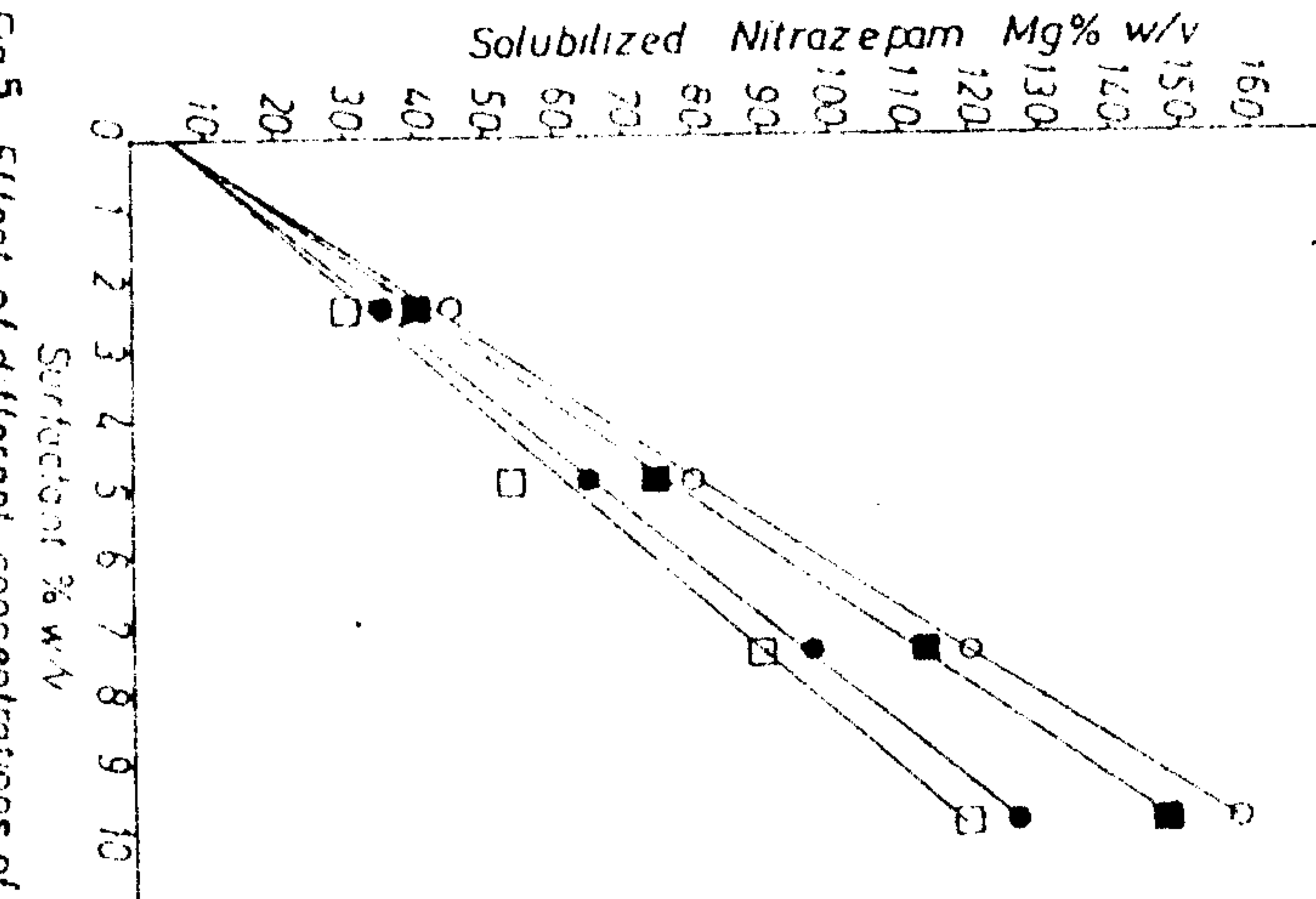
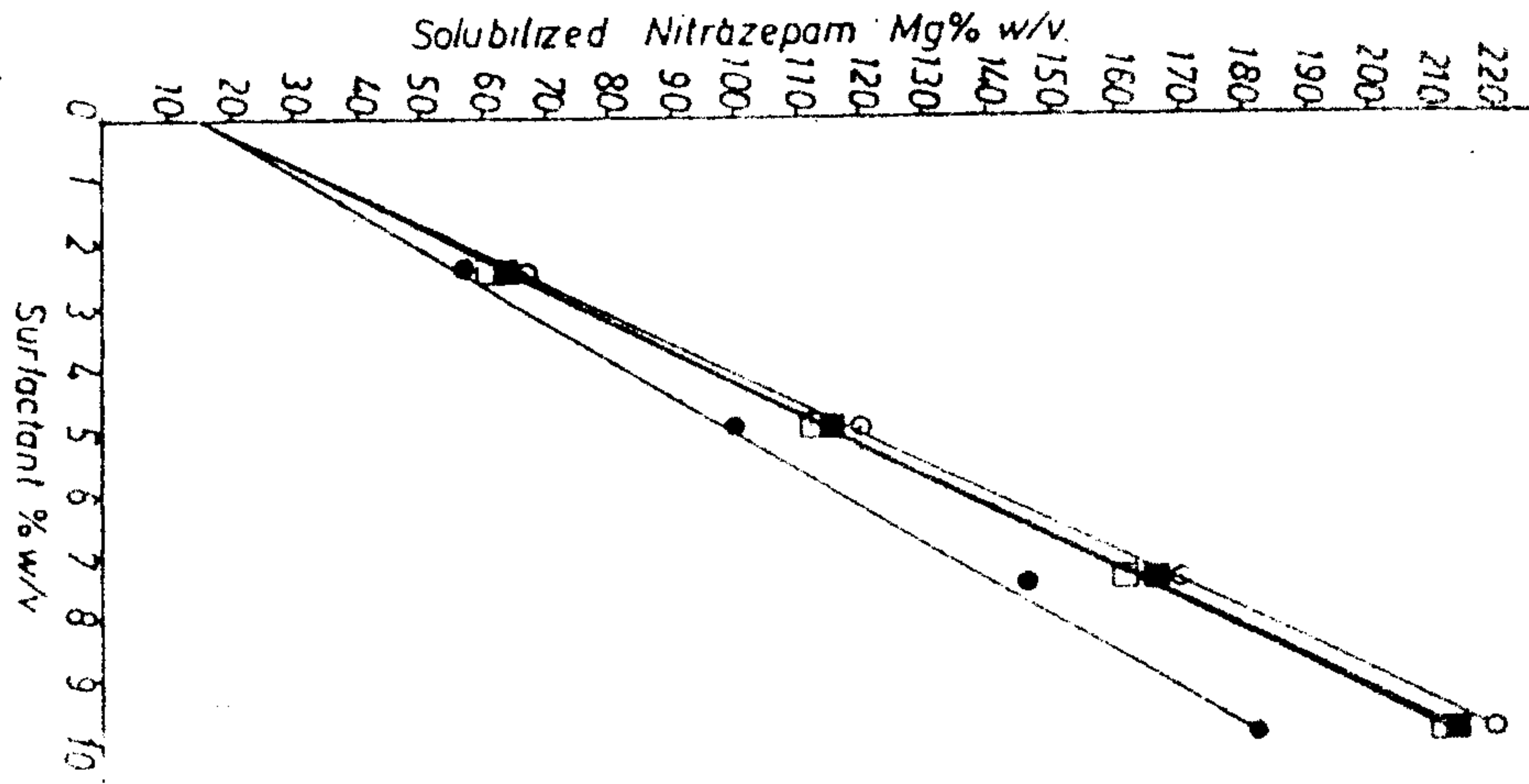
Table 1: Stability of Diazepam and Nitrazepam in mixture of different pH values at 35°C

pH	Diazepam		Nitrazepam	
	$K \text{ (week)}^{-1}$	$t_{\frac{1}{2}} \text{ (weeks)}$	$K \text{ (week)}^{-1}$	$t_{\frac{1}{2}} \text{ (weeks)}$
4	0.042	16.38	0.018	38.28
6	0.034	20.08	0.011	59.23
7	0.042	16.26	0.021	25.95



○ Bismulglin C1000, ● Bismulglin C1500, □ BR13 35, ■ BR13 58





○ Eumulgin CI000, ● Eumulgin CI500, □ Brilj 35, ■ Brilj 58



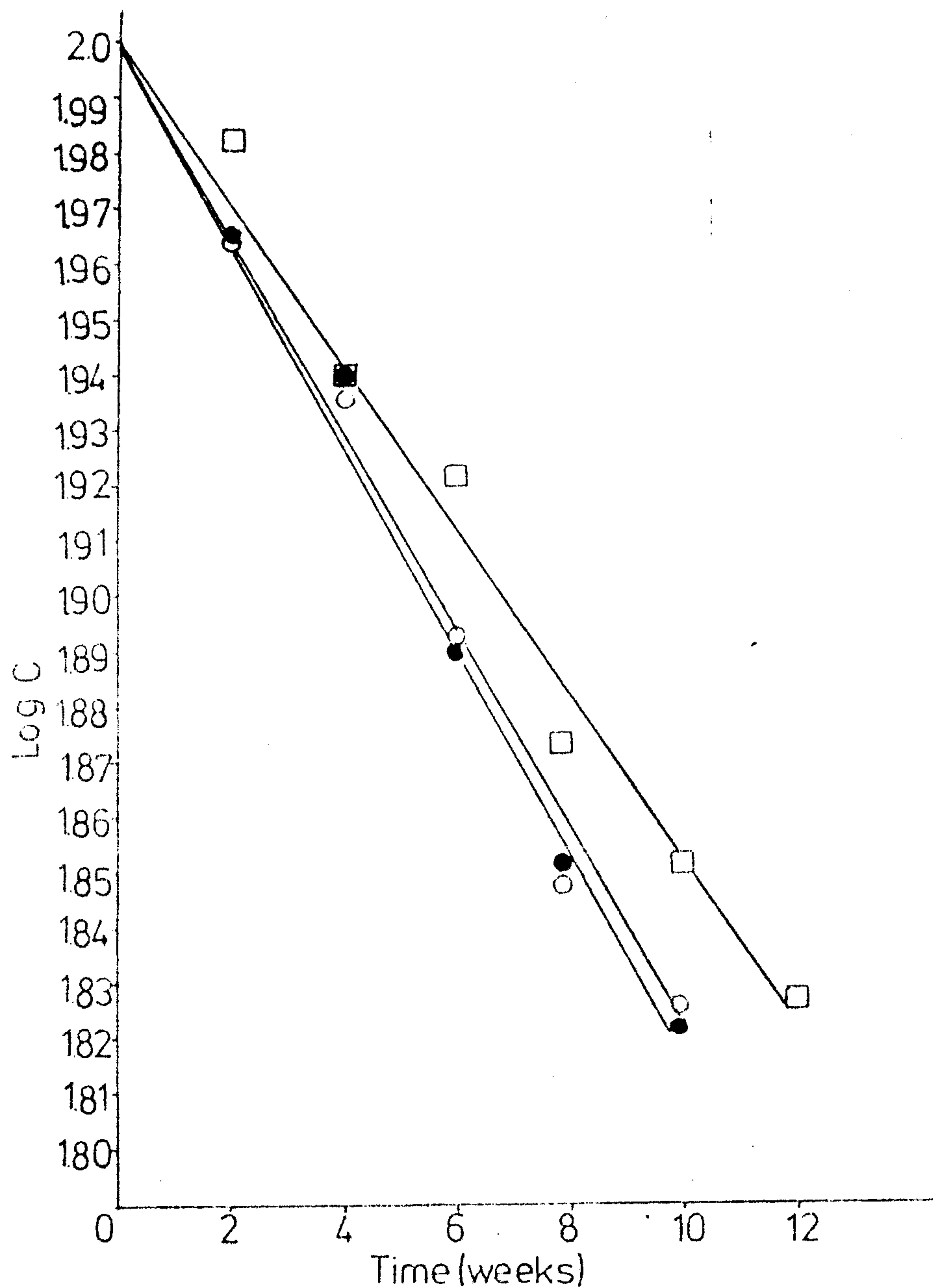


Fig. 7 Effect of the PH on the stability of Diazepam in mixtures at 35°.

● PH 4, □ PH 6, ○ PH 7

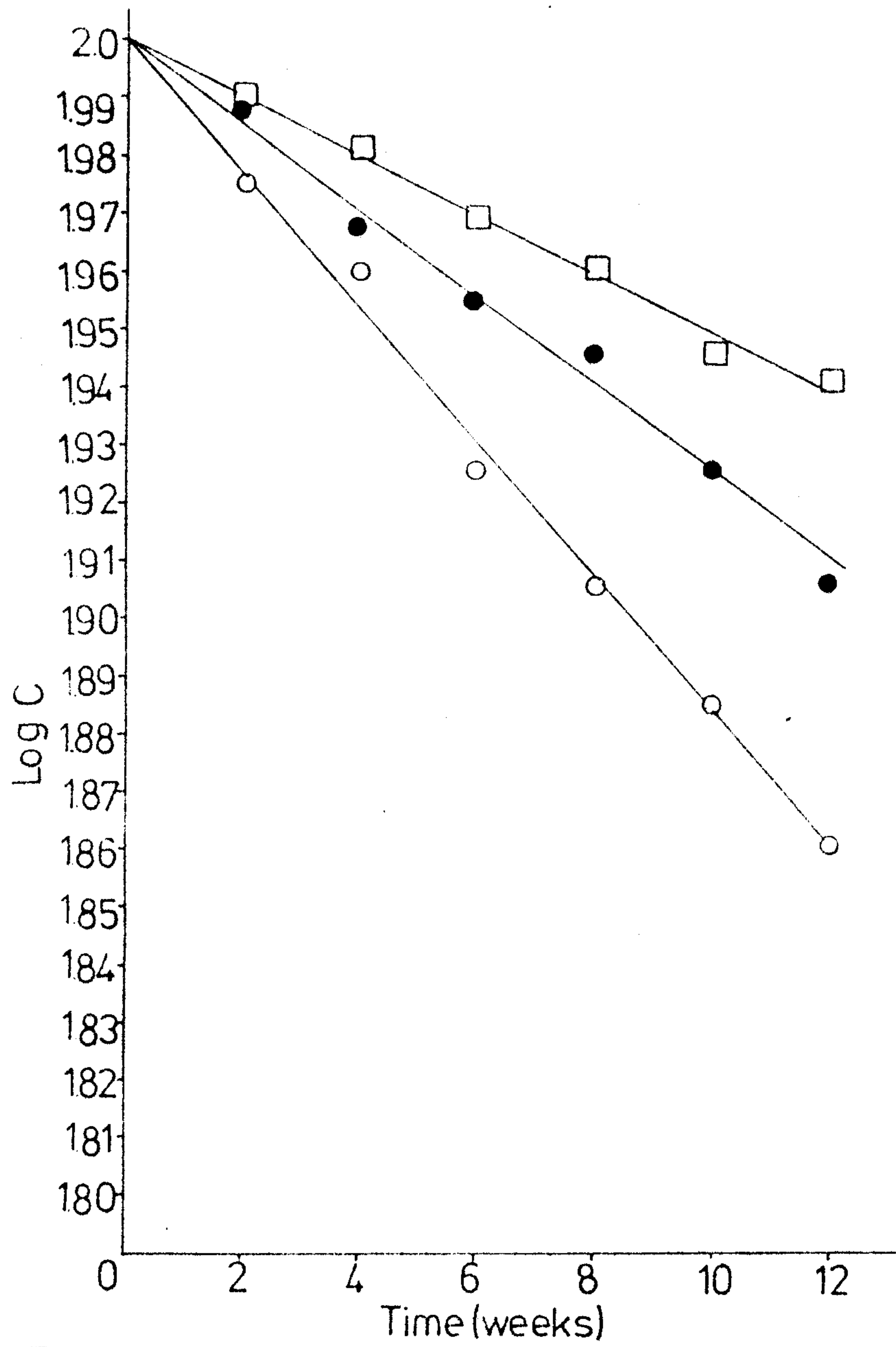


Fig 8 Effect of the PH on the stability of Nitrazepam in mixtures at 35.

● PH4, □ PH6, ○ PH7

REFERENCES

- 1) A.M. Saleh, S.A. Khalil and L.K. El-Khordawi, *Int. J. Pharm.*,  
5, 161 (1980)
- 2) W. Mayer, S. Erbe, G. Wolf, and R. Voigt, *Pharmazie* 29,  
10 (1974).
- 3) S.N. Tewari and S.K. Shukla, *Pharmazie* 31, 893 (1976).
- 4) P.H. Elworthy, A.T. Florence, and C.B. Macfarlane, "Solub-  
ilization by surface Active Agents, Chapman and Hall Ltd.,  
London, (1968).

دراسة على أذابة وثبات الديازيبام والنيترازيبام  
فى المخاليط المنظومة

أحمد السيد أبوطالب - منير صبحى مسيحة - على عبدالظاهر  
قسم الصيدلة الصناعية - كلية الصيدلة - جامعة أسيوط

أذيت الديازيبام والنيترازيبام بسلسلة من محاليل مشطات السطح  
غير المتأينة المنظورة الى أس هيدروجينى ٤ ، ٦ ، ٧ عند ٣٥ م . وشملت  
هذه المنشطات السطحية الأيمالجين س ١٠٠٠ و س ١٥٠٠ والبريج ٣٥ ، ٥٨ .  
وقد وجد أن التركيب الجزيئى للمنشط السطحى وللعقار وأيضا قيمة  
الاس الأيدروجينى تؤثر على كمية الديازيبام والنيترازيبام الدائبة .  
و درس ثبات الديازيبام والنيترازيبام فى المخاليط المصاغة عند قيم  
محكومة للاس الأيدروجينى وقد وجد أن أكثر هذه المخاليط ثباتا هى المحضرة  
عند أس هيدروجينى ٦ .