

INTERACTION OF TEMAZEPAM WITH CERTAIN MACROMOLECULES:
V-THERMODYNAMICS OF TEMAZEPAM SOLUBILIZATION.

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ABSTRACT

Temazepam was solubilized by series of non-ionic surfactant solutions including polysorbates, Eumulgins, Brijs, Myrjs and cetomacrogol as well as ionic ones including sodium lauryl sulphate and cetrимide at different temperatures. Among the non-ionic surfactant solutions investigated, polysorbate 80 was found to be the most efficient solubilizer at the different temperatures investigated, while Myrj 59 was the least. For the ionic ones, sodium lauryl sulphate proved to be more efficient than cetrимide.

Thermodynamic parameters for the solubilization of temazepam in polysorbates and Eumulgins were calculated in order to investigate the thermal process of micellar solubilization. These parameters include the heat of solution, ΔH , the free energy change for the transfer of temazepam from aqueous phase to micellar phase, ΔG and the entropy of solubilization, ΔS .

For all systems ΔG was a negative value indicating spontaneous solubilization. The positive values of entropy, ΔS , suggest a decrease in the degree of ordering when temazepam dissolved in the micellar phase. This positive values of entropy also implies that temazepam molecules penetrated into the micelle interior.

INTRODUCTION

Solubilization in surfactant solutions above the critical micelle concentration offers good approach to the formulation of water-insoluble drugs¹. This technique has attracted a great attention, not only for its intrinsic scientific interest but also it has many technical applications.

Surfactants are perhaps the most widely used group of pharmaceutical adjuvants. Although ionic surfactants have higher solubilizing efficiencies than the non-ionic ones, the latter are preferred, as they are less toxic to biological systems, effective as solubilizers at smaller concentrations due to their lower cmc values and compatible with most insoluble drugs².

The effect of surfactant structure and the role of different micellar regions on the solubilizing capacities of certain surfactants have been investigated^{3,4}.

Temperature has an effect on the extent of micellar solubilization which is dependent on the solubilizate structure and that of the surfactant⁵.

Solubilization of many water-insoluble pharmaceutical compounds has been published including 13 barbituric acid derivatives⁶, tolfenamic acid⁷, indomethacin^{8,9}, hydrocortisone, dexamethazone, testosterone and progesterone¹⁰.

In the present work temazepam was solubilized by different concentrations of non-ionic, anionic, and cationic surfactant solutions at different temperatures, then Vant Hoff plots were performed for the drug in the investigated solutions. The aim of this study was to solubilize this practically water-insoluble drug by different surfactant solution and to investigate the nature of interactions between temazepam and the surfactants used

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The loci of the drug within the micelles were also determined adopting Mukerjee's method¹¹. Furthermore, the thermodynamic parameters of the solubilized drug in different surfactant solutions were determined including the heat of solution, ΔH , the free energy change, ΔG , and the entropy of solubilization, ΔS .

EXPERIMENTAL

Materials :

Temazepam (Fabrica Italiana Sintetici, Laboratorio, Controllo Alte Montecchio (Vicenza), Italy) was of analytical grade, IR, UV and m.p. measured for the drug agreed with reference standard.

Surfactants :

Polysorbates : polyoxyethylene (20) sorbitan monopalmitate (polysorbate 40) and polyoxyethylene (20) sorbitan monooleate (polysorbate 80), (Sigma Chemical Company, U.S.A.).

Eumulgins : Cetyl stearyl alcohol with (20) ethylene oxide units (Eumulgin C 1000) and cetyl stearyl alcohol with (50) ethylene oxide units (Eumulgin C 1500), (Henkel International Dusseldorf, West Germany).

Myrj's : Polyoxyethylene (40) stearate (Myrj 52), Polyoxyethylene (50) stearate (Myrj 53) and polyoxyethylene (100) stearate (Myrj 59).

(Chemicals of Atlas Industries Ltd., England).

Brij's : Polyoxyethylene (20) cetyl ether (Brij 58) and polyoxyethylene (23) lauryl ether (Brij 35), (Atlas Chemical Industries Ltd., England).

Cetomacrogol 1000 : Polyoxyethylene (20-24) monohexadecyl ether (Atlas chemical Industries Ltd., England).

Sodium lauryl Sulphate : (BDH, Poole, England).

Cetrimide : (Thornton and Ross Ltd., England).

Apparatus :

Shaking water bath (Grant Instruments, Cambridge Ltd., England).

HP 8451A Diode array-spectrophotometer, 98155A Keyboard and 7470A plotter (Hewlett Packard, USA).

Methods : The solubilities of temazepam in different non-ionic surfactant solutions were determined as follows : an excess of the pure drug was shaken at a rate of 130 strokes min^{-1} with 10 ml of different concentrations of the surfactant solutions for 24 hours at various temperatures, 20, 25, 37 and 45°C. The suspension was filtered and an aliquot (2 ml) was taken and diluted to 50 ml with distilled water and assayed spectrophotometrically for its temazepam content at 232 nm. It was found that the presence of the surfactant solutions in the dilution range used neither interfered with the spectrophotometric assay of the drug nor they made any shift in its maximum absorbance.

RESULTS AND DISCUSSIONS

Effect of surfactant concentration on temazepam solubility :

At concentrations in excess of their reported cmc values¹², all surfactants investigated increased the solubility of temazepam. There is a linear relationship between temazepam solubilized and surfactant concentration, an observation which is in agreement with other reports⁹ concerning micellar solubilization. This linearity is shown in Fig.1.

Cloudness was not observed in these systems because of the relatively high content of oxyethylene moieties in all the non-ionic surfactants investigated, which gave rise to surfactants with relatively high cloud points¹². Furthermore, temazepam did not depress the cloud points of these surfactant solutions even at the highest temperature investigated.

Effect of surfactant molecular structure on temazepam solubility:

A- Effect of alkyl chain length (polysorbates and Brij)s :

On using either polysorbate or Brij series possessing different hydrocarbon chain for the same ethylene oxide moiety, for temazepam solubilization, it was found that the solubility of the drug increased by extending the hydrocarbon chain length from

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polysorbate 40 to polysorbate 80 and from Brij 35 to Brij 58 as shown in Fig. 1 and Table 1. This increase in the solubility by extending the hydrocarbon chain length is considered to be due to the increase in the hydrocarbon micellar interior volume ; the core volume of the micelle. This indicates that the drug is mainly solubilized within the cores of these micelles, which may be due to its non-polar nature. Therefore, the micellar core volume can be considered to be one of the main factors affecting the solubilization of this drug.

In an idealized picture of the spherical micelles, the alkyl portion of the micelle may be visualized as being directed inward. An increase in its length will result in micelles of larger sizes, which can accommodate more solubilizate¹³.

Table 1. shows the solubilizing capacities expressed as gm drug per gm surfactant, which actually are the slopes of the solubility isotherms.

B- Effect of polyoxyethylene chain length (Eumulgin and Myrj):

The effect of extending the polyoxyethylene chains in each of Eumulgin and Myrj series, is shown in Fig. 1 and Table 1. A pronounced decrease in temazepam solubility was obtained as shown in the following sequence: Eumulgin C1000 Eumulgin > C1500 and Myrj 52 > Myrj 53 > Myrj 59. This decrease in temazepam by extending the polyoxyethylene chain is due to the decrease in the relative volume of the micellar core compared to the total micellar volume. So, if the solubilized moiety is associated with the hydrocarbon interior of the micelle; the core, the solubility of the solute is expected to decrease by extending the polyoxyethylene chain length. El-Eini et al¹⁴ have found that the micellar size of surfactants decreases while hydration increases as the polyoxyethylene chain increases. Based on these findings, the decrease in temazepam solubility, upon

extending the polyoxyethylene chain length may be due to decrease in the micellar size and increase in micellar hydration.

Effect of temperature on the solubility of temazepam in surfactant solutions :

Temperature has an effect on the extent of micellar solubilization which is dependent on the structure of the solubilizate and that of the surfactant. In most cases the amount solubilized and the degree of interaction between the solubilizate and surfactant molecules increase with temperature. This effect has been considered due to changes in the aqueous solubility properties of the solubilizate and changes in the properties of the micelles⁵. From Table 1, it is clear that raising temperature results in an increase in the amount of temazepam solubilized.

The positive temperature effect could be interpreted according to the explanation proposed by McBain *et al*¹⁵ who assumed that temperature changes may bring about changes in surfactant orientation and changes of temperature may cause the solubilizate in the micelle, as well as, in water, the continuous phase, to change to varying extents. Other probable explanation was that on raising the temperature, the aggregation number will be increased, consequently the micellar volume will be increased, and so more solubilizate could be accommodated within the micelles. Furthermore, a decrease in the cmc of non-ionic surfactants was observed when the temperature was raised². Consequently, more monomers would be micellized at lower surfactant concentration, thus, the solvent power of the surfactant would be increased at higher temperatures.

Distribution coefficient of temazepam (Km):

The linearity between the amount of temazepam solubilized and the surfactant concentration indicates that the solubilization of temazepam follows the distribution law, according to which the drug partitioned between the aqueous phase and

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the micellar pseudophase¹⁵. Table 2 shows the distribution coefficient (K_m) of temazepam between the micellar phase and the aqueous continuous phase according to the partition model of solubilization, using the following equation :

$$K_m = C_m/C_w$$

where C_m is the concentration of the solute in the micellar phase gm/gm, and C_w is the concentration of the solute in the aqueous phase gm/gm which is equal to its water solubility at the temperature investigated. In this method, the density of the surfactant solutions was considered to be equal to that of water and the whole amount of the surfactant was assumed to be completely micellized, neglecting the monomer fraction. For the present work, these assumptions should not introduce significant errors, since relatively dilute solutions were used and the surfactants used have very low cmc values except cetr-imide and sodium lauryl sulphate. In these cases, the cmc values must be subtracted from the surfactant concentration used before the K_m calculation. Definition of the distribution coefficient in this way is subjected to the usual limitations; i.e., it is only applied strictly to low concentrations of solute and to the distribution of the same molecular species in the two phases.

The distribution coefficients K_m , of temazepam were found to be affected by both the surfactant molecular structure as well as the temperature of solubilization. Table 2 shows a decrease in K_m values with extending the polyoxyethylene chain in Myrj series, possibly due to decrease in micellar size¹⁴.

Although it was found that temazepam solubilities in water and in surfactant solutions increased with temperature, K_m values decreased. This was as a result of the complexity of temperature effect on the water solubility of the drug, as well as the changes in the micellar structure and properties at higher temperatures².

The higher the K_m value, the greater the amount of the solute that can be incorporated within the micelles, assuming that the solute is solubilized by partition between the micellar and aqueous phases.

Determination of temazepam location :

A theoretical treatment proposed by Mukerjee¹¹ was adopted to calculate the distribution of temazepam between the core and capsular regions of the micelles. Mukerjee has discussed the solubilization of benzoic acid derivatives by a series of polyoxyethylene surfactants (Myrj series) in terms of an equilibrium distribution between the two loci, the polyoxyethylene mantle and the hydrocarbon core. The amount of the solubilizate solubilized in the core and the capsular regions of the micelle was assumed to be proportional to the number of equivalents of the alkyl chain moiety (stearate), C_R , and the number of equivalents of oxyethylene groups, C_{EO} , respectively. The total amount solubilized in equivalent per liter of solutions, S , is then :

$$S = a C_{EO} + b C_R$$

where C_{EO} and C_R are the concentrations, in equivalent per liter of (EO) and (R) groups respectively, (a) and (b) are the proportionality constants. On dividing by C_{EO} one obtains :

$$S/C_{EO} = a + b C_R/C_{EO}$$

A plot of S/C_{EO} in equivalent per equivalent against C_R/C_{EO} gives linear curve with the intercept (a) representing the solubilization in the capsule (equivalent of solubilizate per equivalent of EO groups) and the slope (b) representing the solubilization in the core (equivalents of solubilizate per equivalent of R groups). Fig. 2 shows the plot of the data obtained on the solubilization of temazepam using Myrj series, according to the above equation at 25 and 37°C. The values of (a)

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are 48×10^{-5} and 57×10^{-5} and those for (b) are 0.102 and 0.118 as deduced from the plotted lines at 25 and 37°C respectively. It can be noticed that temazepam solubilized mainly in the micellar core. Further, the amount of the drug solubilized in the capsule increased on extending the polyoxyethylene chain from 40 (Myrj 52), 50 (Myrj 53) to 100 (Myrj 59) at the two temperatures investigated, Table 3.

Effect of ionic surfactants on solubilizing temazepam:

Solubilization of temazepam in sodium lauryl sulphate as an example of anionic surfactants and cetrimide for the cationic ones has been investigated, Table 1. From the increase in temazepam solubility by increasing surfactant concentrations, it is evident that micellar solubilization of the drug in these two ionic surfactants could be the possible mechanism. It is also apparent from the results that the ionic surfactants have higher solubilizing efficiencies than the non-ionic ones. The amount of temazepam solubilized in these two ionic surfactants was increased by raising the temperature from 25 to 37°C, i.e., positive temperature effect was observed, Table 1.

Calculation of thermodynamic parameters for the solubilization of temazepam in polysorbates and Eumulgins :

In an attempt to investigate the mechanisms of temazepam solubilization, some thermodynamic parameters controlling the process were derived. Fig. 3-6 show the effect of temperature on temazepam solubility in different concentrations of polysorbates and Eumulgins. It is evident from the plots that raising the temperature from 20 to 45°C caused an increase in temazepam solubility to varying extents depending upon the type and the concentration of the surfactant. The classical Van't Hoff type plots of the equilibrium solubilities of temazepam in polysorbates are represented in Figs. 7 & 8 which show reasonably good linear relationships. The heat of solution (ΔH) was calculated from the slopes of these plots using the following equation:

$$\text{Slope} = \Delta H / 2.303 R$$

where R is the gas constant (1.987 cal./deg.mole).

The free energy change (ΔG) for the transfer of temazepam from aqueous phase to micellar phase was calculated from the following thermodynamic relationship¹⁶.

$$\Delta G = -2.303 RT \log S_s / S_w$$

Where S_s / S_w is the ratio of the molar solubility of the solute in surfactant solution to that in water and T is the absolute temperature.

After the values of ΔG and ΔH have been calculated, the entropy of solubilization, ΔS (.Cal./deg.mole) could be calculated from the following equation:

$$\Delta S = (\Delta H - \Delta G) / T$$

The values of ΔH , ΔG and ΔS are listed in Tables 4 & 5.

Generally, the values of ΔH are positive, which indicates that the micellar solubilization of temazepam is an endothermic process. However, it was noticed that the values of ΔH in surfactant solutions are lower than that of water. As the heat required to break up the crystal will be the same for the dissolution in water as in a surfactant, either the heat of dilution differs from that in water, or an interaction between the drug and the surfactant molecules accounts for the difference in heat changes. Extending the hydrocarbon chain length from polysorbate 40 to 80 leads to a big change in the values of ΔH . However, extending the polyoxyethylene chain length from Eumulgin C1000 to Eumulgin C 1500 leads to a little change. This reflects the importance of hydrocarbon interior of the micelle as a major site for temazepam incorporation.

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For all systems ΔG was a negative value indicating spontaneous solubilization. At constant temperature, $-\Delta G$ decreased with increasing the hydrophilic chain length, i.e. from Eumulgin C1000 to Eumulgin C 1500. Additionally, $-\Delta G$ increased with increasing hydrophobic chain length, i.e., from polysorbate 40 to polysorbate 80. This indicates that the solubilizing efficiency was greater for more hydrophobic surfactants.

The positive values of entropy, ΔS , suggest a decrease in the degree of ordering when temazepam dissolved in the micellar phase. Barry et al.¹⁰ reported a negative value of entropy for polar drug molecules and positive change of entropy for non-polar or less polar drug molecules. In case of temazepam solubilization, the possible explanation for the positive values of entropy obtained might be interpreted considering, two opposing factors. The insertion of solubilized molecules in the micelles restricts molecular movements, i.e., a more ordered state, and provides a negative change in entropy. However, an opposing effect is produced to the water molecules when the non-polar molecules leave the aqueous phase for the micelle. The configurational entropy of water molecules increases due to break up of "iceberg" structure surrounding non-polar groups, i.e., a less ordered state produces a positive change in entropy¹⁰.

Hence, a net positive change in entropy might occur on temazepam solubilization as a result of the comparatively high positive value of that of water molecules. Furthermore, the location of solubilized molecules within a micelle has been suggested in terms of the sign of the standard entropy of solubilization⁶. It was noticed that there are positive values for embedding the drug in the micellar center and negative ones for adsorption on the micellar surface. In the present study, all values of entropies are positive, this implies that in this system temazepam molecules penetrated into the micellar interior.

Table 1: Effect of Surfactant Solution on Temazepam Solubility at different Temperatures

| Surfactant | Solubility of Temazepam g/g Surfactant x 10 ³ | | | |
|----------------------|--|-------|-------|------|
| | 20°C | 25°C | 37°C | 45°C |
| Polysorbate 40 | 20.2 | 20.7 | 26.0 | 30.3 |
| Polysorbate 80 | 36.7 | 38.7 | 44.4 | 45.4 |
| Eumulgin C 1000 | 29.1 | 29.9 | 36.1 | 38.8 |
| Fumulgin C 1500 | 24.2 | 27.8 | 32.0 | 34.8 |
| Brij 35 | --- | 24.8 | 29.6 | --- |
| Brij 58 | --- | 29.8 | 32.8 | --- |
| Myrj 52 | --- | 17.0 | 20.8 | --- |
| Myrj 53 | --- | 15.3 | 16.8 | --- |
| Myrj 59 | --- | 10.1 | 11.1 | --- |
| Cetomaorogal 1000 | --- | --- | 32.5 | --- |
| Sod. lauryl sulphate | --- | 360.0 | 371.6 | --- |
| Cetrimide | --- | 118.0 | 137.0 | --- |

Table 2: Distribution Coefficients (K_m) of Temazepam between the Micellar and Aqueous Phases at Different Temperatures.

| Surfactant | Distribution Coefficients (K _m) | | | |
|------------------------|---|---------|---------|---------|
| | at 20°C | at 25°C | at 37°C | at 45°C |
| Polysorbate 40 | 221.5 | 190.7 | 185.0 | 154.1 |
| Polysorbate 80 | 394.0 | 358.4 | 307.3 | 236.9 |
| Eumulgin C 1000 | 311.9 | 272.8 | 254.4 | 199.6 |
| Eumulgin C 1500 | 268.1 | 252.7 | 221.1 | 181.1 |
| Brij 35 | ----- | 229.5 | 206.3 | ----- |
| Brij 58 | ----- | 269.3 | 232.0 | ----- |
| Myrj 52 | ----- | 163.7 | 147.1 | ----- |
| Myrj 53 | ----- | 140.6 | 118.7 | ----- |
| Myrj 59 | ----- | 91.4 | 80.6 | ----- |
| Sodium lauryl sulphate | ----- | 3250.0 | 2572.9 | ----- |
| Cetrimide | ----- | 1078.0 | 972.1 | ----- |

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Table 3: Distribution of Temazepam between the Cores and the Capsules of the Myrj Micelles at Different Temperatures, Calculated by Mukerjee's Method.

| Surfactant | Surfactant Molecular weight | Weight of Ethylene oxide part | S/C _{E₀} at | | C _R /C _{E₀} | Ratio of the Amount of Temazepam in Capsule and core at | | |
|------------|----------------------------------|-------------------------------|---------------------------------|---------|--|---|--------|--------|
| | | | 25°C | 37°C | | 25°C | 37°C | |
| Myrj 52 | C ₁₇ E ₄₀ | 2046 | 1777 | 0.00307 | 0.00360 | 0.025 | 0.1558 | 0.1561 |
| Myrj 53 | C ₁₇ E ₅₀ | 2486 | 2177 | 0.00247 | 0.00279 | 0.020 | 0.1937 | 0.196 |
| Myrj 59 | C ₁₇ E ₁₀₀ | 4686 | 4417 | 0.00152 | 0.00179 | 0.010 | 0.4484 | 0.4520 |

Table 4: Thermodynamic Parameters for the Solubilization of Temazepam in Polysorbate Solutions.

| Surfactant Concentration (g w/v) | Polysorbate 40 | | | | | | Polysorbate 80 | | | | | |
|----------------------------------|----------------|-------|-------|-------|-------|-------|----------------|-------|-------|-------|-------|-------|
| | (20°) | (25°) | (37°) | (45°) | (20°) | (25°) | (37°) | (45°) | (20°) | (25°) | (37°) | (45°) |
| | ΔH | ΔG | ΔS | ΔG | ΔS | ΔH | ΔG | ΔS | ΔG | ΔS | ΔG | ΔS |
| 0.0 | 541 | | | | | 541 | | | | | | |
| 2.5 | 326 | -1105 | 3772 | -1039 | 3488 | 211 | -1412 | 4820 | -1358 | 4558 | -1326 | 4278 |
| 5.0 | 334 | -1455 | 4967 | -1390 | 4666 | 201 | -1739 | 5936 | -1749 | 5870 | -1720 | 5549 |
| 7.5 | 357 | -1639 | 5595 | -1605 | 5387 | 218 | -1977 | 6748 | -1963 | 6588 | -1959 | 6320 |
| 10.0 | 326 | -1829 | 6243 | -1777 | 5964 | 169 | -2164 | 7386 | -2132 | 7155 | -2121 | 6878 |

Table 5: Thermodynamic Parameters for the Solubilization of Temazepam in Eumulgin Solutions.

| Surfactant Concentration (% w/v) | Eumulgin C 10000 | | | | | Eumulgin C 1500 | | | | |
|-------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | (20°) | (25°) | (37°) | (45°) | | (20°) | (25°) | (37°) | (45°) | |
| 0.0 | ΔH 541 | ΔG ... | ΔS ... | ΔG ... | ΔS ... | ΔH 541 | ΔG ... | ΔS ... | ΔG ... | ΔS ... |
| 2.5 | 283 | -1265 | 4329 | -1209 | 4058 | -1280 | 3969 | -1127 | 3545 | 272 |
| 5.0 | 267 | -1627 | 5554 | -1591 | 5340 | -1615 | 5211 | -1508 | 4743 | 303 |
| 7.5 | 265 | -1856 | 5335 | -1814 | 6088 | -1842 | 5943 | -1754 | 5517 | 269 |
| 10.0 | 246 | -2027 | 5919 | -1981 | 6649 | -2014 | 6498 | -1919 | 6035 | 273 |

Where, ΔH is the enthalpy change (cal./mole), ΔG is the free energy change (K.cal./mole) and ΔS is the entropy change (cal./deg.mole) for the solubilization process.

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S/CE₀ = 1000

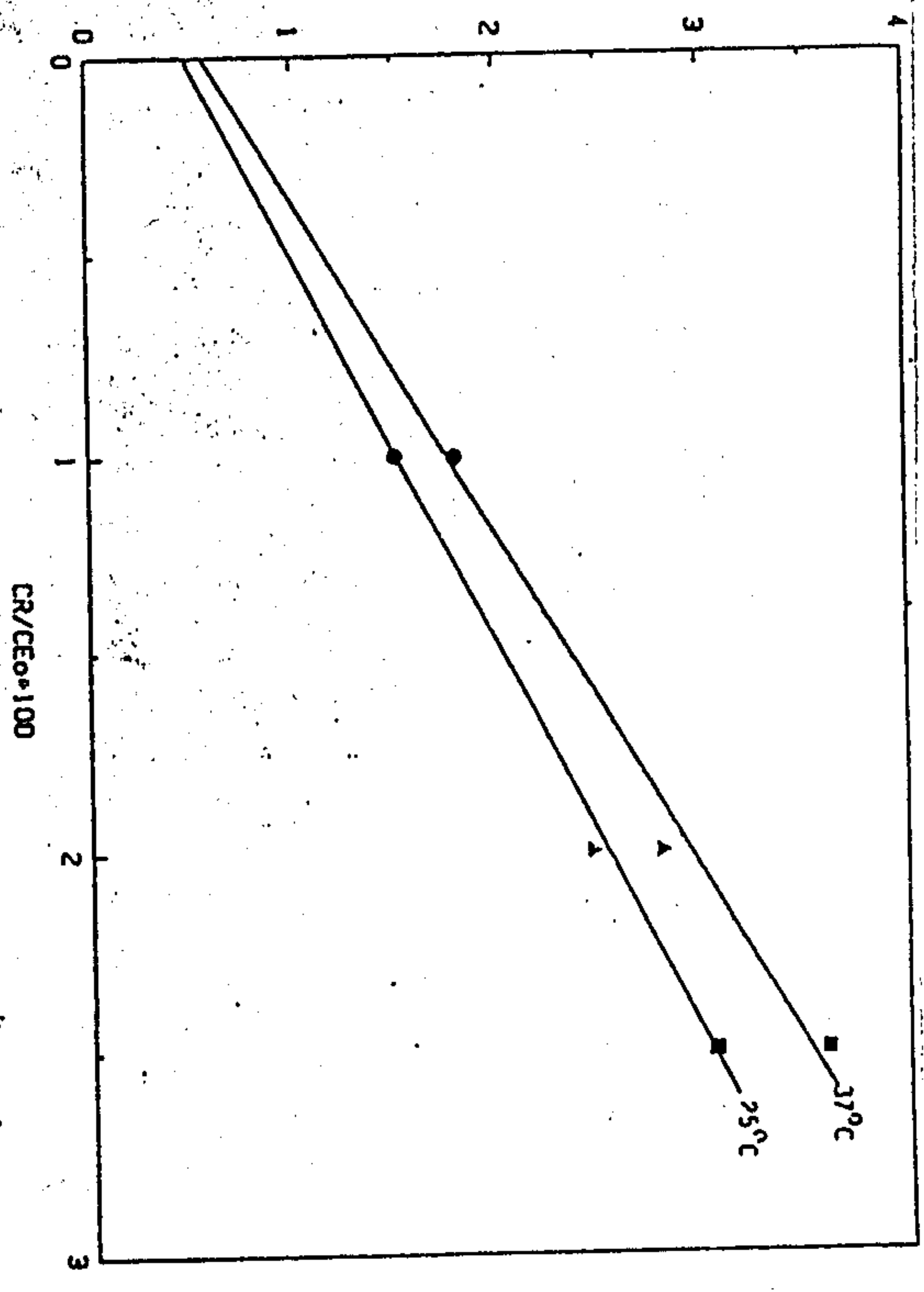


FIG (2) MICELLAR SOLUBILIZATION OF TEMAZEPAM IN MYRJ5 (AT 25&37°C) ACCORDING TO MUKERJEE'S METHOD.

KEY
 ■ MYRJ 52
 ▲ MYRJ 51
 ● MYRJ 55

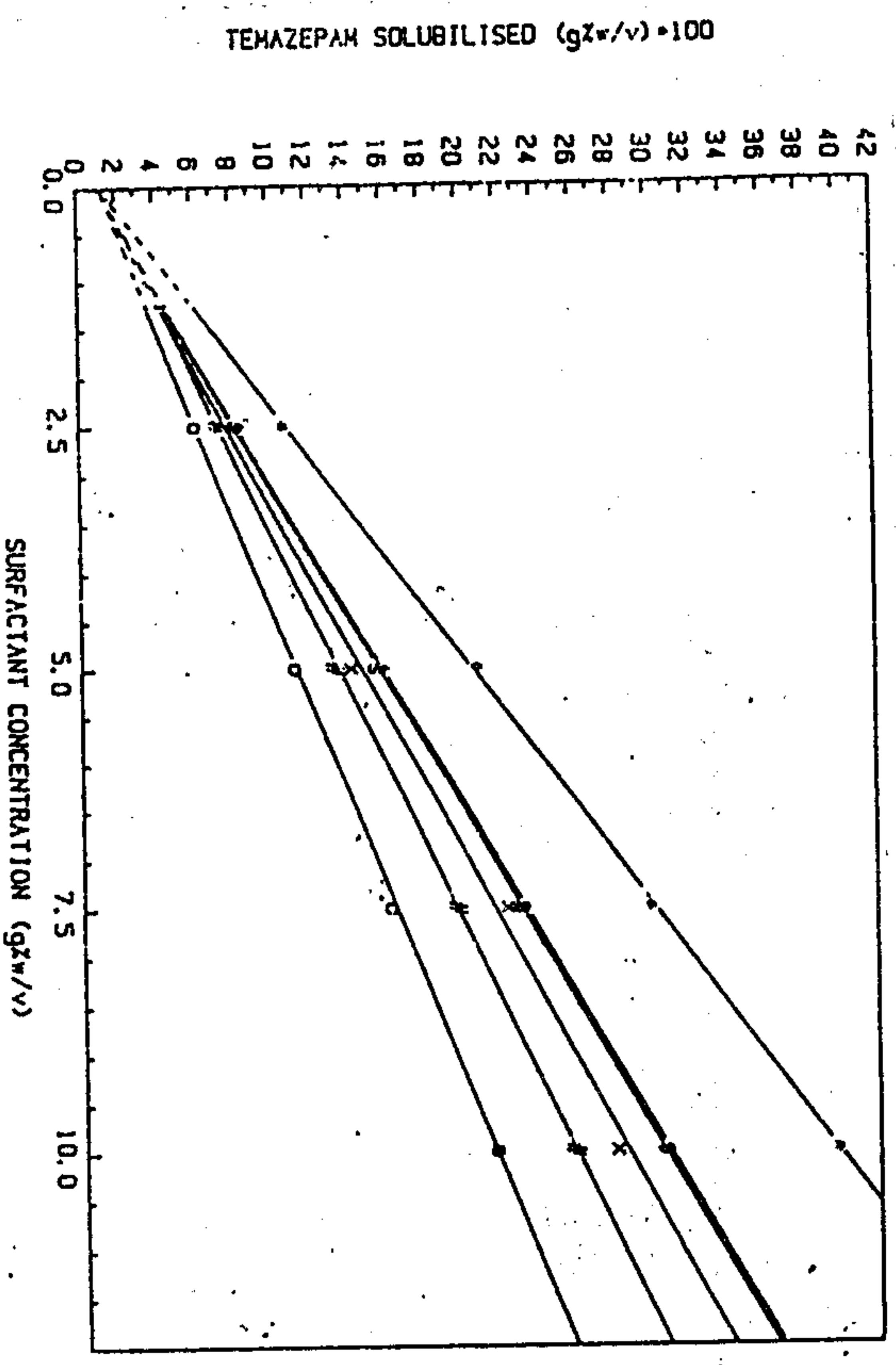


FIG (1) SOLUBILITY OF TEMAZEPAM IN DIFFERENT NON-IONIC SURFACTANT SOLUTIONS at 25°C.

KEY
 ○ POLYSORBATE 40
 ● POLYSORBATE 80
 + EDMULIN C1000
 * EDMULIN C1500
 # 93J 35
 \$ BRJ 58

TEMAZEPAM SOLUBILISED (gZw/v) * 100

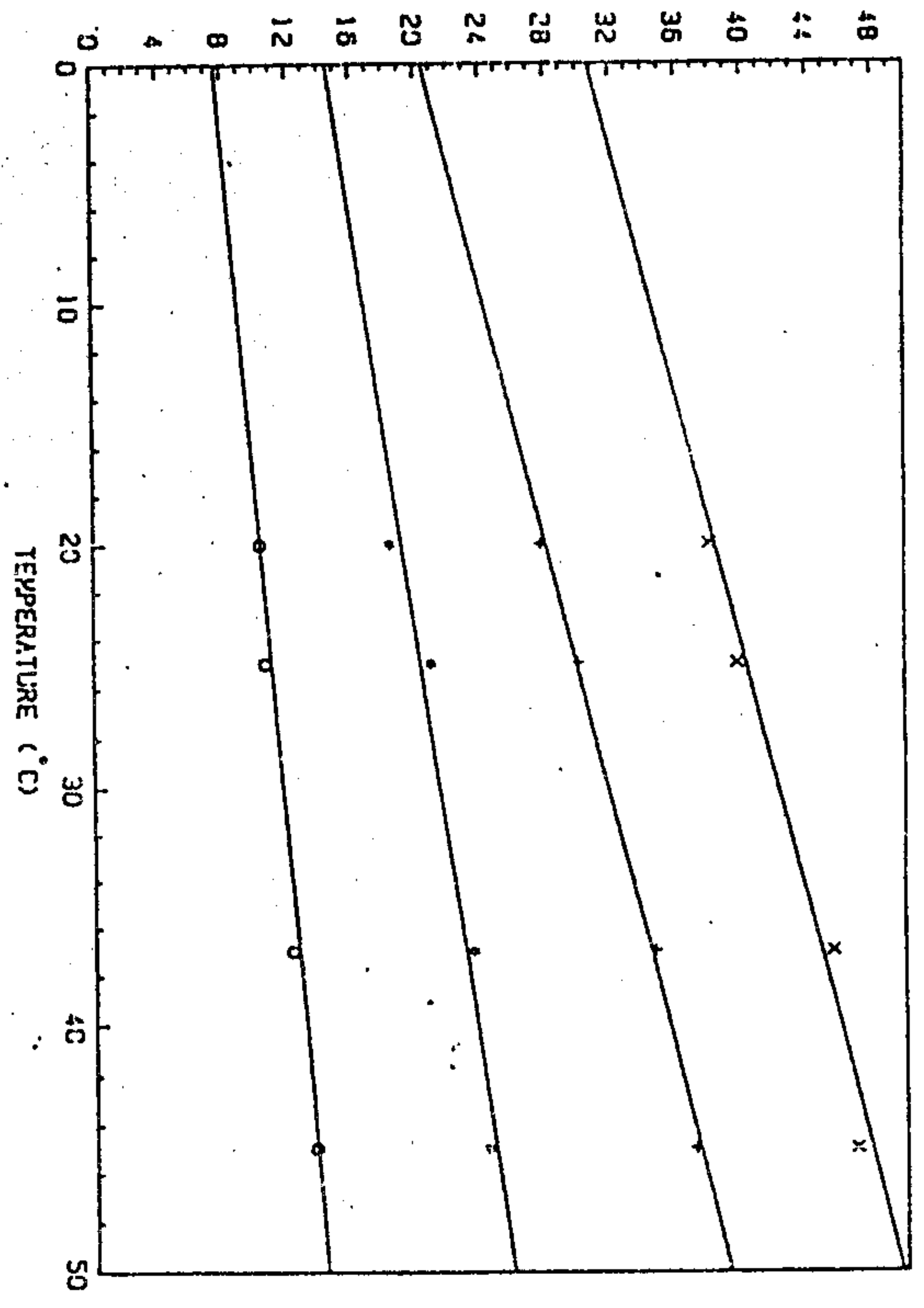


FIG. 4 : EFFECT OF TEMPERATURE ON THE SOLUBILITY OF TEMAZEPAM IN DIFFERENT CONCENTRATION OF POLYSORBATE 80 SOLUTIONS.

KEY
 ○ 2.5 gZw/v
 * 5 gZw/v
 + 7.5 gZw/v
 x 10 gZw/v

TEMAZEPAM SOLUBILISED (gZw/v) * 100

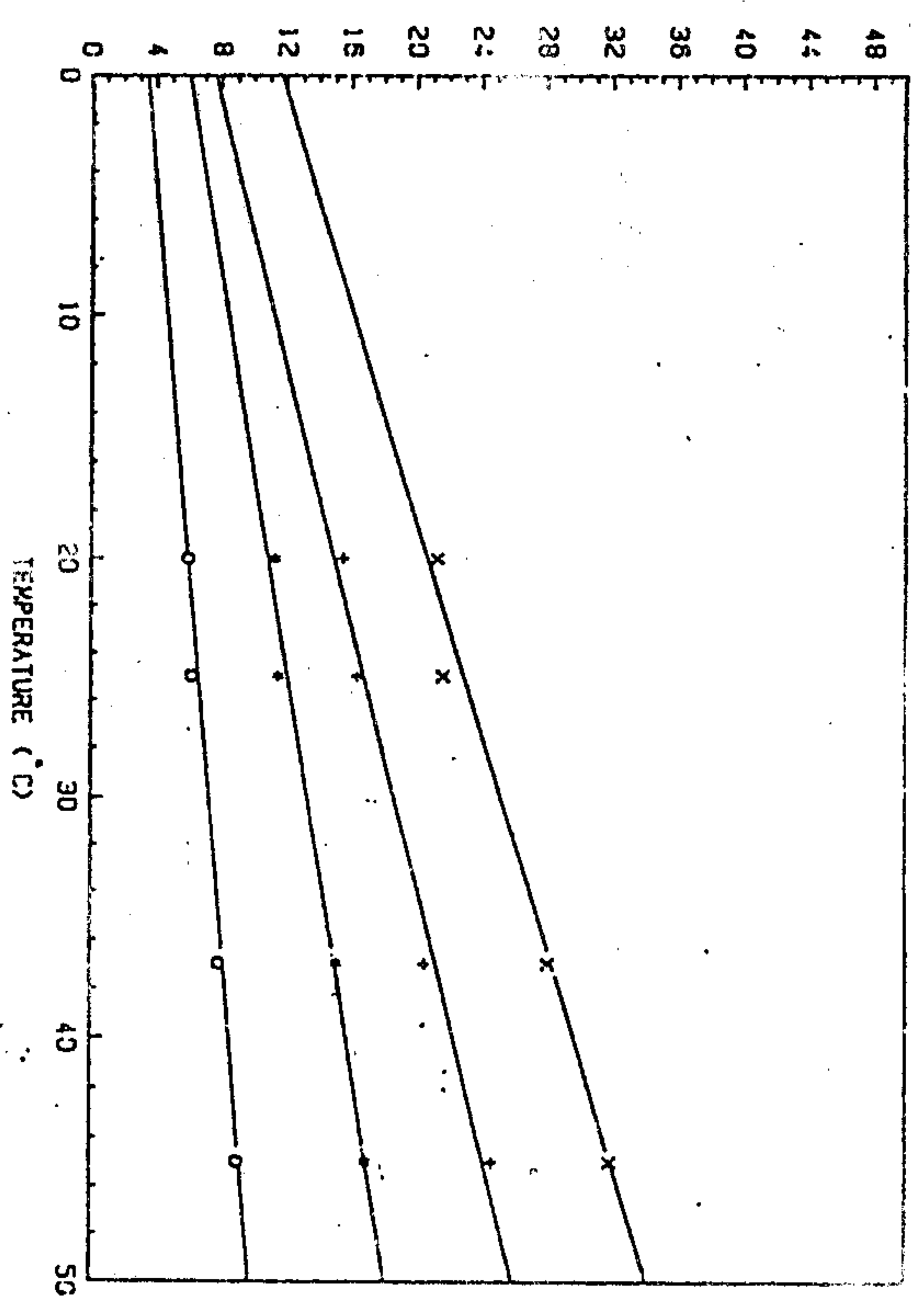


FIG. 3 : EFFECT OF TEMPERATURE ON THE SOLUBILITY OF TEMAZEPAM IN DIFFERENT CONCENTRATIONS OF POLYSORBATE 40 SOLUTIONS.

KEY
 ○ 2.5 gZw/v
 * 5 gZw/v
 + 7.5 gZw/v
 x 10 gZw/v

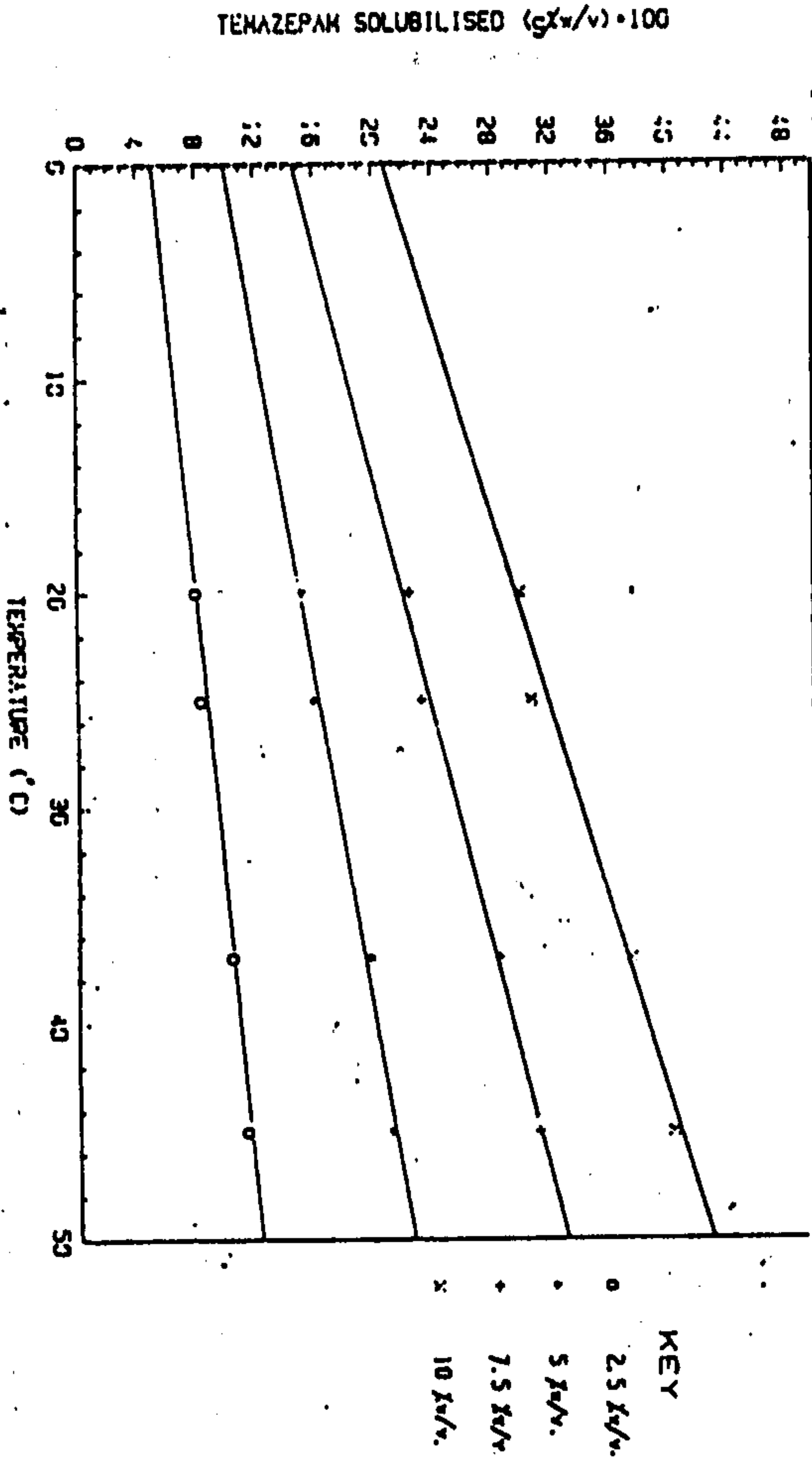


FIG. 5 : EFFECT OF TEMPERATURE ON THE SOLUBILITY OF TEMAZEPAM IN DIFFERENT CONCENTRATIONS OF EMULGIN C 1000 SOLUTIONS.

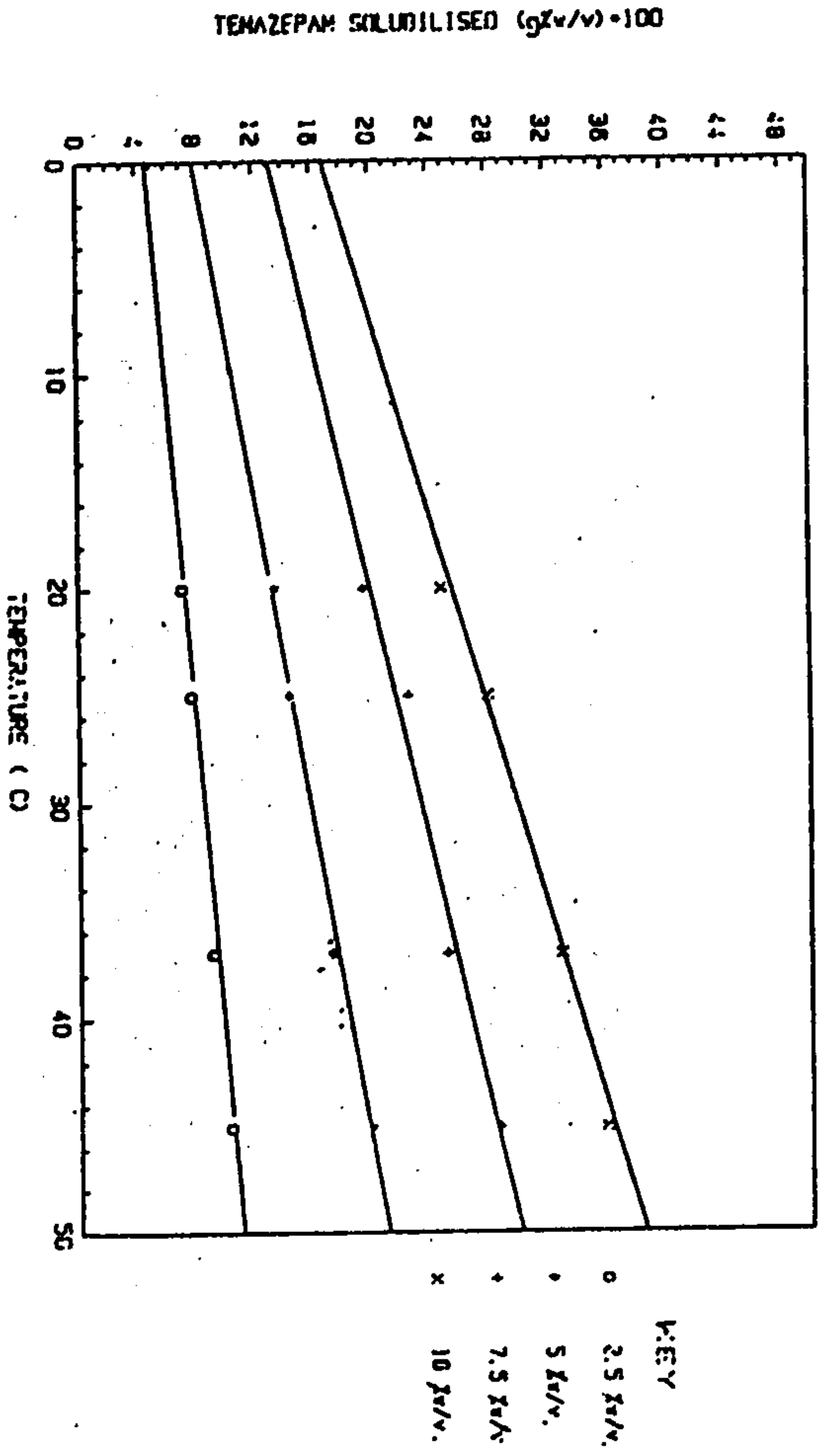


FIG. 6 : EFFECT OF TEMPERATURE ON THE SOLUBILITY OF TEMAZEPAM IN DIFFERENT CONCENTRATIONS OF EMULGIN C 1500.

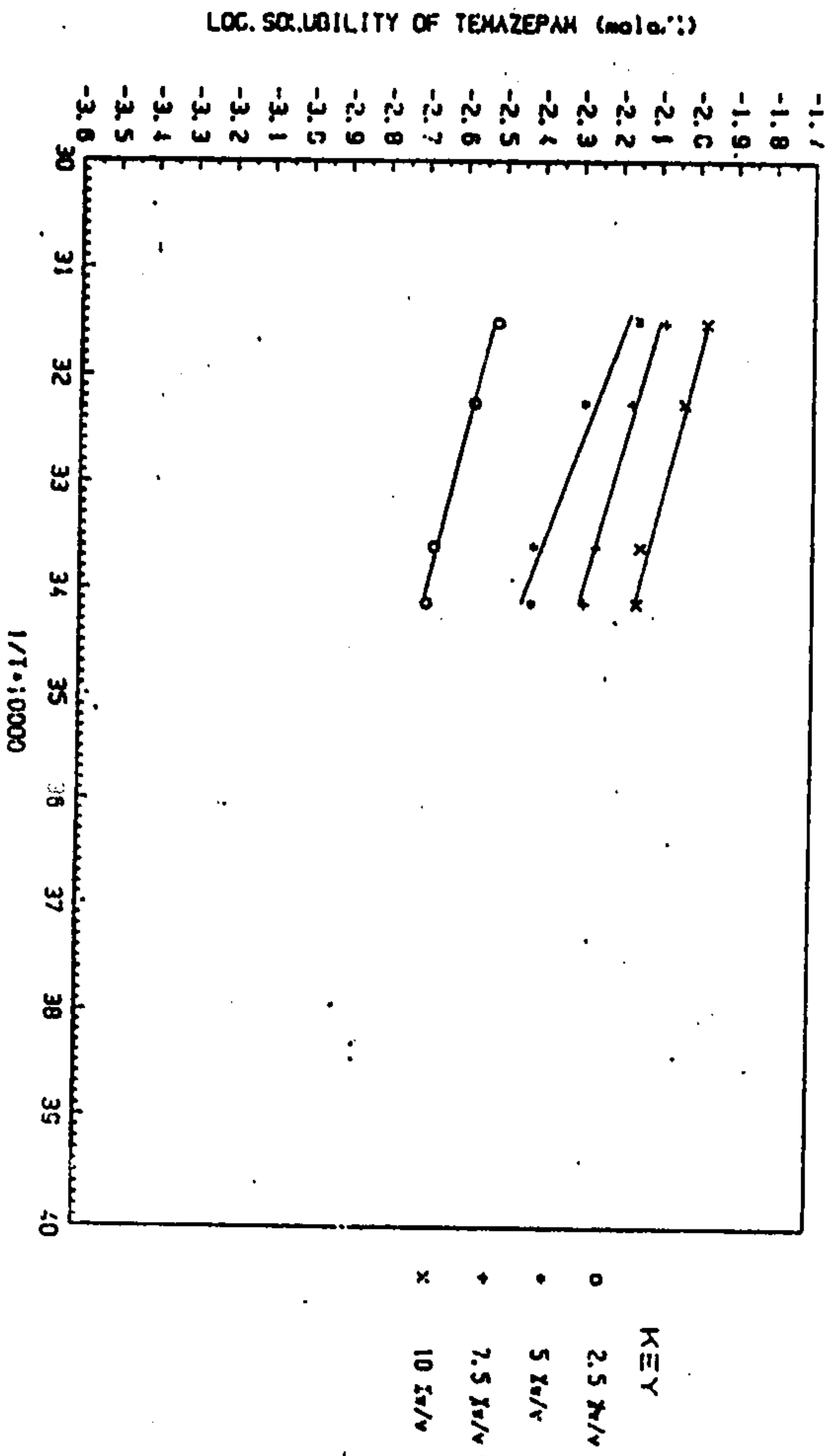


FIG (7) VAN'T HOFF PLOTS FOR THE SOLUBILITY OF TEMAZEPAM IN POLYSORBATE 40 SOLUTIONS.

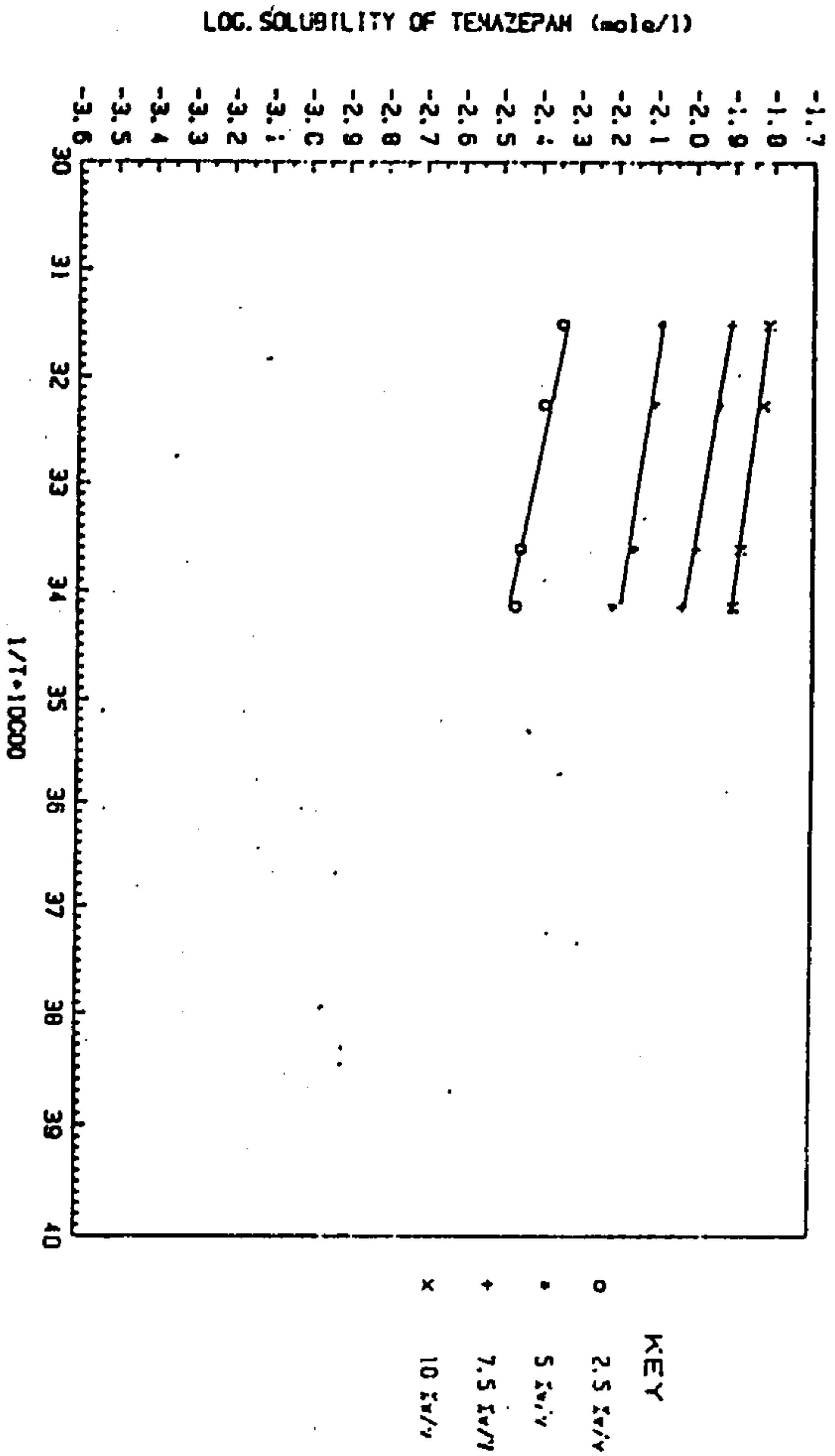


FIG (8) VAN'T HOFF PLOTS FOR THE SOLUBILITY OF TEMAZEPAM IN POLYSORBATE 80 SOLUTIONS.

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REFERENCES

- 1) J.G.Wagner "Biopharmaceutics and Relevant Pharmacokinetics". Drug Intelligence Publications, Hamilton, Illinois, 1971, P.98.
- 2) B.A."Mulley," Advances in pharmaceutical sciences "Edited by H.S.Bean, A.H.Beckett, and J.E.Careless, Academic Press, London, 1964, P. 87.
- 3) A.A.Ismail, M.W.Gouda, and M.M.Motawi, J. Pharm. Sci., 59, 220 (1970).
- 4) T.Arnarson, and P.H.El-Worthy, J. Pharm. Pharmacol., 32, 381 (1980).
- 5) D.Atwood, and A.T.Florence, "Surfactant systems" Chapman and Hall, London and New York, 1983..
- 6) C.Vaution, G.Treiner, F.Puisieux, and J.T.Cartensen, J. Pharm. Sci., 70, 1238 (1981).
- 7) O.Raunio and L.Turakka, Pharm. Ind., 44, 750 (1982).
- 8) N.M.Najib, M.S.Suleiman, Int, J. Pharm. 24, 165 (1985).
- 9) S.Y.Lin, and Y.Kawashima, Pharm. Acta Helv., 60, 339 (1985).
- 10) B.W.Barry, and D.I.El-Eini, J. Pharm. Pharmacol., 28, 210 (1976).
- 11) P.Mukerjee, J. Phys. Chem., 60, 1528 (1971).
- 12) P.Becher "Non-ionic surfactants" Edited by J.S.Martin. Marcel Dekker Inc., New York, 1967, P. 481.
- 13) J.Swarbrick, J. Pharm. Sci., 54, 1229 (1965).
- 14) D.I. El-Eini, B.W.Barry and C.T.Rhodes, J. Pharm. Pharmacol., 25, 166P (1973).
- 15) J.W.Mcbain, and E.Hutchinson "Solubilization and Related Phenomena " Academic Press Inc., NewYork, 1955, P. 11.
- 16) S.Feldman and M.Gibaldi, J. Pharm, Sci., 56, 370 (1967).

تفاعلات التيمازيبام مع جزئيات كبيرة معينة

ه - تذويب التيمازيبام والحرارة الديناميكية للتذويب

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أذيب التيمازيبام بواسطة سلسلة من منشطات السطح غير المتأينه تشمل
عديد السوربات ، الاملجينات ، البرج ، الميرج و اسيتوهناكروجول واستخدمت أيضا بعض
منشطات السطح المتأينه وتشمل لوريل الموديوم الكبريتي والستيريديد في درجات
حرارة مختلفة .

ولقد وجد أن عديد السوربات ٨٠ هو أكفا مذيب لهذا العقار بينما ميرج ٥٩
هو الاقل .

ولقد اتبعت دراسة أجراها العالم ماكرجى لتحديد مكان اذابة العقار فى
الشباك وذلك لمجموعة الميرج - ولقد وجد أن العقار يتواجد فى قلب الشباك بصفة
رئيسية .

ولقد حسبت الحرارة الديناميكية لتذويب التيمازيبام فى سلسلة عديد السوربات
الاملجين وذلك لدراسة النظام الحرارى للعملية الذوبانية فى الشباك .

وشملت هذه المعاملات الحرارية حرارة الاذابة (Δ ه) وكذلك تغيير الطاقة
الحره لنقل التيمازيبام من الوسط المائى الى الشباك (Δ ج) ، الانتروبي (Δ س) .

ولقد وجد أن Δ ج سالبة القيمة مما يبرهن أن عملية التذويب تلقائية
ووجد أن الانتروبي موجب القيمة مما يفسر نقص فى الترتيب عندما يذوب التيمازيبام
فى شبك المنشطات وأيضا يبرهن على أن التيمازيبام يخترق قلب الشباك .