*Bull. Pharm. Sci., Assiut University*
*Vol, 8. Part 2, pp 171 - 185*

# INTERACTION OF 1,4-BENZODIAZEPINES WITH CERTAIN MACROMOLECULES II. CRYSTALLIZATION OF TEMAZEPAM IN PRESENCE OF HYDROPHILIC MACROMOLECULES

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## ABSTRACT

*Temazepam was crystallized from either ethanol or ethanol containing different concentrations of polysorbate 80, cetomacrogol 1000, Myrj 52 and PVP 40000 at 50°C. The produced treated crystals, as well as the untreated ones were subjected to solubility and computerized thermal studies, electron scanning microscopic examinations, determination of drug content and dissolution rates using particulate and intrinsic dissolution methods and employing recycling and automatic recording systems.*

*Crystallization of the investigated drug from ethanol containing the afore-mentioned additives enhanced the dissolution rate to a varying extent, as demonstrated by a decrease in the $T_{50\%}$ and the increase in the R.D.R. Decreasing the concentration of cetomacrogol 1000 and polysorbate 80 in the crystallization medium causes a gradual drop in dissolution rates.*

*Thermal analysis of the produced crystals revealed a negligible change in melting points and a slight change in the enthalpy of fusion ($\Delta H_f$).*

## INTRODUCTION

The availability of a poorly water-soluble or insoluble drug, dispersed as a solid dosage form, depends on its dissolution rate in the GIT. This rate is dependent upon the contact area between the substance and the liquid, and is also influenced by the crystal form, lattice structure and surface properties of the crystals[1].

Many methods have been used to enhance the dissolution rates of water insoluble drugs. The methods include, for example, salt and polymorphic formation[2], micronization, microcrystallization, solid dispersion, coprecipitation using inert water soluble carriers,[3-7] and adsorption onto an inert water-insoluble compound[8]. Crystallization of hydrophobic water-insoluble drugs in the presence of low concentrations of hydrophilic macromolecules is one of the techniques successfully used to enhance the dissolution rate of poorly water soluble or water insoluble drugs. Chiou and co-workers[9] modified the dissolution rate of chloramphenicol, sulphathiazole and predinsone by crystallizing them in 2.5% w/v polysorbate 80 aqueous solution. Crystallization of nalidixic acid, in the presence of different carriers, showed a great enhancement in its dissolution rate[10]. York and Al-Meshal[11] have examined relationships between the physicochemical properties and the crystallographic character of phenylbutazone crystallized in presence of hydroxypropylmethyl cellulose. They observed an increase in solubility and in intrinsic dissolution rate of the crystallized drug.

The aim of the present work is to investigate the effect of crystallization of Temazepam[12] in the presence of different concentrations of some hydrophilic macromolecules

on its in vitro dissolution rate. The macromolecules used in this study include: non-ionic surfactants of different chemical classes (polysorbate 80, cetomacrogol and Myrj52) and a hydrophilic polymer (polyvinylpyrrolidone 4000).

## EXPERIMENTAL

### Materials:

Temazepam, (Fabrica Italiana Sintetica, Laboratori Controllo Alte Montecchio Vicenzo, Italy). I.R. and M.P. measured agreed with reference determination.

### Macromolecules:

Polyoxyethylene (20-24) monohexadecyl ether (cetomacrogol 1000), polyoxyethylene (40) stearate (Myrj 52), (Atlas Chemical Industries Ltd., England), polyoxyethylene (20) sorbitan monooleate (polysorbate 80) (Sigma Chemical Company, U.S.A.) and polyvinylpyrrolidone 40000 (Sigma Chemical Company, U.S.A.).

### Apparatus:

- Shaking water bath (Grant Instruments, Cambridge Ltd, England).
- CE 292 Digital Ultraviolet spectrophotometer(Instrum=NTS, Cambridge, England).
- Multipen-recorder (Rikadenki Mitsni Electronics Ltd, England).
- Dissolution apparatus (Erweka-Apparatebau, G.M.B.H., W. Germany).
- Du Pont differential scanning calorimeter connected to Du Pont 1091 Disk Memory DuPont Co., Analytical Instruments Division, Wilmingotn, U.S.A).
- Electron scanning microscope (Cambridge Stereoscan 600, England).

## Methods

### I- Method of Crystallization:

Temazepam powder (1 gram) was dissolved in a minimum volume of ethanol (20 ml) containing either 0,1,2.5, 5% w/v polysorbate 80,1,2.5, 5% w/v cetomacrogol 1000, 5% w/v Myrj 52 or 5% w/v PVP 40,000, at 50°C. The system was allowed to cool slowly overnight at room temperature. The crystals were separated by filtration, thoroughly washed with fresh ethanol and dried in a vacum desiccator over shavings of hard paraffin. The crystals were screened to a particle size of 45-200 μ and used for further investigations.

### II- Characterization of the produced crystals:

#### 1. Solubility Studies:

An excess of the produced Temazepam crystals was shaken with 10 ml of different concentrations of the investigated macromolecule solutions for 24 hours in a constant temperture water bath at 37 ± 0.2°C. 2 ml of the suspension were filtered and 1 ml of the filtrate was diluted to 50 ml with distilled water and the concentration was determined by measuring the UV absorption of Temazepam at 232 nm. Equilibration beyond 24 hours did not increase the solubility.

#### 2. Thermal Studies:

Using the DSC technique, crystals (5-9 mg) were placed in a crimped aluminium sample pan with pierced lid. The sample was programheated at a rate of 10°/ minute in a dynamic nitrogen environment from 30-175°. Determination of transition temperature and energy were made by a computerized procedure. The instrument was calibrated with indium. Duplicate measurement were carried out on each sample.

3. Microsopic Studies:

Electron micrography was done for the prepared crystals mounted on double sided adhesive tapes and photographed using electron scanning microscope (25 kv B.S.E.D.).

4. Determination of drug content in the crystallized powder:

The crystallized drug (25 mg) was dissolved in ethanol (50 ml), then 1 ml of the solution was diluted to 50 ml distilled water and assayed spectrophotometrically at 232 nm. The presence of trace of the macromolecules investigated neither interferred in the spectrophotometeric assay of Temazepam nor made any shift in the maximum absorbance of the drug.

5. Dissolution Studies:

Dissolution characteristics of the crystallized drug were studied by the dispersed particulate and intrinsic dissolution methods[13].

## RESULTS AND DISCUSSION

Table (1) shows the $T_{50\%}$ and R.D.R. values (relative dissolution rates) for Temazepam crystals: untreated, crystallized in absolute ethanol and in different types of macromolecules as calculated from the dissolution profiles ,(Figures 1-3). Inspection of the results revealed, that crystallization of the investigated drug in presence of any of those macromolecules enhanced its dissolution rate to a varying extent, as demonstrated by a decrease in the $T_{50\%}$ and an increase in the R.D.R. The increase in the dissolution rate has the following order: untreated Temazepam equals Temazepam crystallized in ethanol < in 5% w/v PVP 4000 < 5 % w/v Myrj 52 < in 5% w/v polysorbate 80 < in 5% w/v cetomacrogol. Decreasing the concentration of cetomacrogol and polysorbate 80 in the crystallization medium caused a gradual drop in the dissolution rate.

Similarity in dissolution rates for untreated Temazepam to that crystallized from ethanol indicates that the increase in the dissolution rate is not due to solvate formation . Dissolution rate constants mentioned in Table 1 ( calculated from slopes of the amount dissolved against time using static disc method under Sink condition , Fig. 4) show also an increase in dissolution rate.

Fig. 5 shows the DSC peaks accompaning melting of Temazepam crystals. The Figure and the data (M.P. and $\Delta H_f$) mentioned in Table 1 indicate a negligible change in melting points. Further inspection for the table reveals a slight change in the enthalpy of fusion ($\Delta H_f$) that directly reflects a change in internal energy, as well as a change in the disruption index[14]. A decrease in the onset slopes and broading of the melting endotherms ( the area near the arrows) in comparison with those for untreated Temazepam and that crystallized from ethanol are also observed. The last findings give an indication that the investigated macromolecules are included in Temazepam crystal itself, which actually accounts for the enhancement of the dissolution rate of the crystallized drug. The endothermic peaks also confirm that Temazepam has no polymorphs since no exotherm following the endotherm was observed.

The scanning electron micrographs for the crystals,suggest a change in crystal habit. Fysh[15] has reported that the habit of crystals grown from aqueous solutions can be modified in different ways by addition of anionic or cationic surfactants, where adsorption of the additive takes place preferentially on certain faces of the crystals. These changes in crystal habit may have a minor effect in changing dissolution rate as seiving may also modify the crystal habits.

Surfactants were also shown to get adsorbed on solid surfaces due to their surface activity. This adsorption would undoubtedly increase the wettability of the crystals and thereby increase their dissolution rate[3]. This could explain the result for Temazepam crystallized in PVP 40,000 which shows the lowest disslution rate possibly because PVP has no surface activity.

Formation of a solid solution of the water-soluble macromolecule in the drug crystal may also enhance the dissolution rate[3]. The amount of macromolecule present in the crystals studied was too small to be detected by UV assay and had negligible effect on the solubility of the drug in the bulk solution, as shown in column 3 in Table 1. However, the macromolecule present inside and/or outside the crystal might enhance the solubility of the drug in the diffusion layer and consequently increase the dissolution rate. It is conceivable that such mechanism may be operating as surfactants were found to increase the dissolution rate of insoluble drugs.

Table (1): Properties* of Temazepam crystallized in the presence of different macromolecules

| Dissolution medium (% w/v) | | Solubility (ug/ml) | Thermal Analysis data m.p. °C | $\Delta H_f$ (c) (KJ/mole) | Disolution rate data: Static disk, dissolution rate constant (mg. $min^{-1} \times 10^3$) | Dispersed $T_{50\%}$ (a) minute | Particulate system R.D.R. (b) 10 | 20 |
|---|---|---|---|---|---|---|---|---|
| Cetomacrogol 1000 | 1.0 | 148.6 | 160.20 | 26.00 | - | 6.0 | 4.39 | 2.34 |
| | 2.5 | 151.0 | 160.25 | 26.50 | - | 5.7 | 4.71 | 2.53 |
| | 5.0 | 146.7 | 160.20 | 25.80 | 16.5 | 4.5 | 5.56 | 2.87 |
| Polysorbate 80 | 1.0 | 148.6 | 161.15 | 27.20 | - | 11.2 | 2.88 | 2.00 |
| | 2.5 | 149.4 | 161.20 | 27.40 | - | 6.7 | 3.93 | 2.17 |
| | 5.0 | 150.9 | 161.30 | 27.60 | - | 5.0 | 5.47 | 2.85 |
| Myrj 52 | 5.0 | 151.1 | 160.8 | 27.4 | 17.4 | 6.2 | 4.34 | 2.38 |
| PVP 40,000 | 5.0 | 146.0 | 160.6 | 27.5 | 13.5 | 10.8 | 2.37 | 1.54 |
| Distilled water : | | | | | | | | |
| for temazepam cryst. in ethanol | 0.0 | 145.1 | 161.0 | 26.40 | - | 14.2 | 1.00 | 0.988 |
| for temazepam untreated | 0.0 | 144.0 | 160.05 | 27.85 | 12.5 | 15.6 | 1.00 | 1.00 |

* Mean values of two or more determinations.

(a) $T_{50\%}$: Time required for 50% of the drug to dissolve.

(b) The relative dissolution rate : Ratio of the amount of temazepam dissolved from prepared crystals to that dissolved from untreated sample at the same time.

(c) $\Delta H_f$: latent heat of fusion obtained from integrated area under endotherm at the melting point.

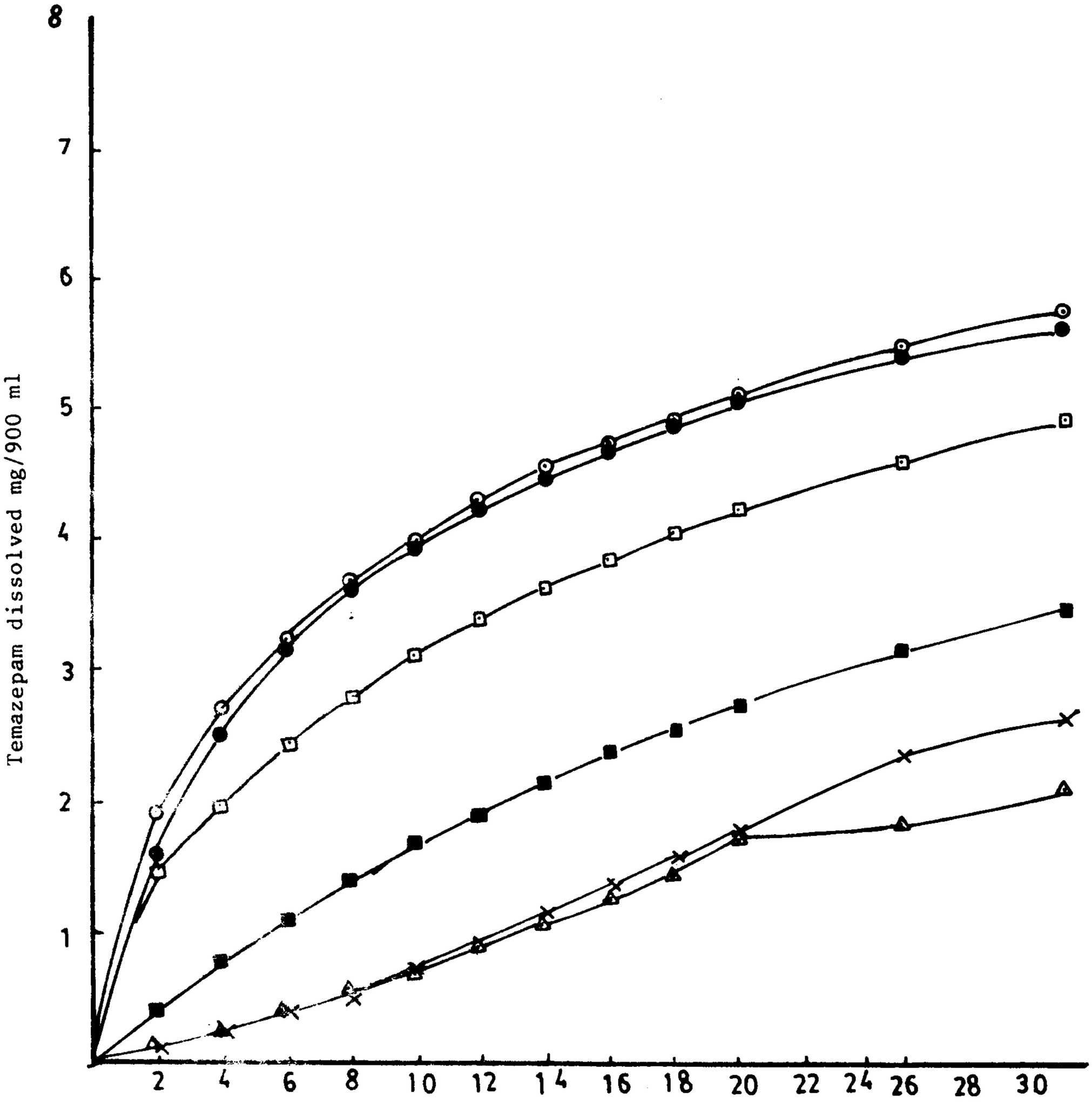


Fig.(1): Dissolution, Rate of Temazepam Powder-Crystallized in 5% w/v of Different Macromolecules using Dispersed Amount Method.

Key:

× untreated temazepam powder (as received)
Δ Temazepam recrystallized from ethanol
○ Temazepam recrystallized from Cetomacrogol 1000.
● Temazepam recrystallized from polysorbate 80 .
□ Temazepam recrystallized from Myrj 52.
■ Temazepam recrystallized from PVP 40,000.

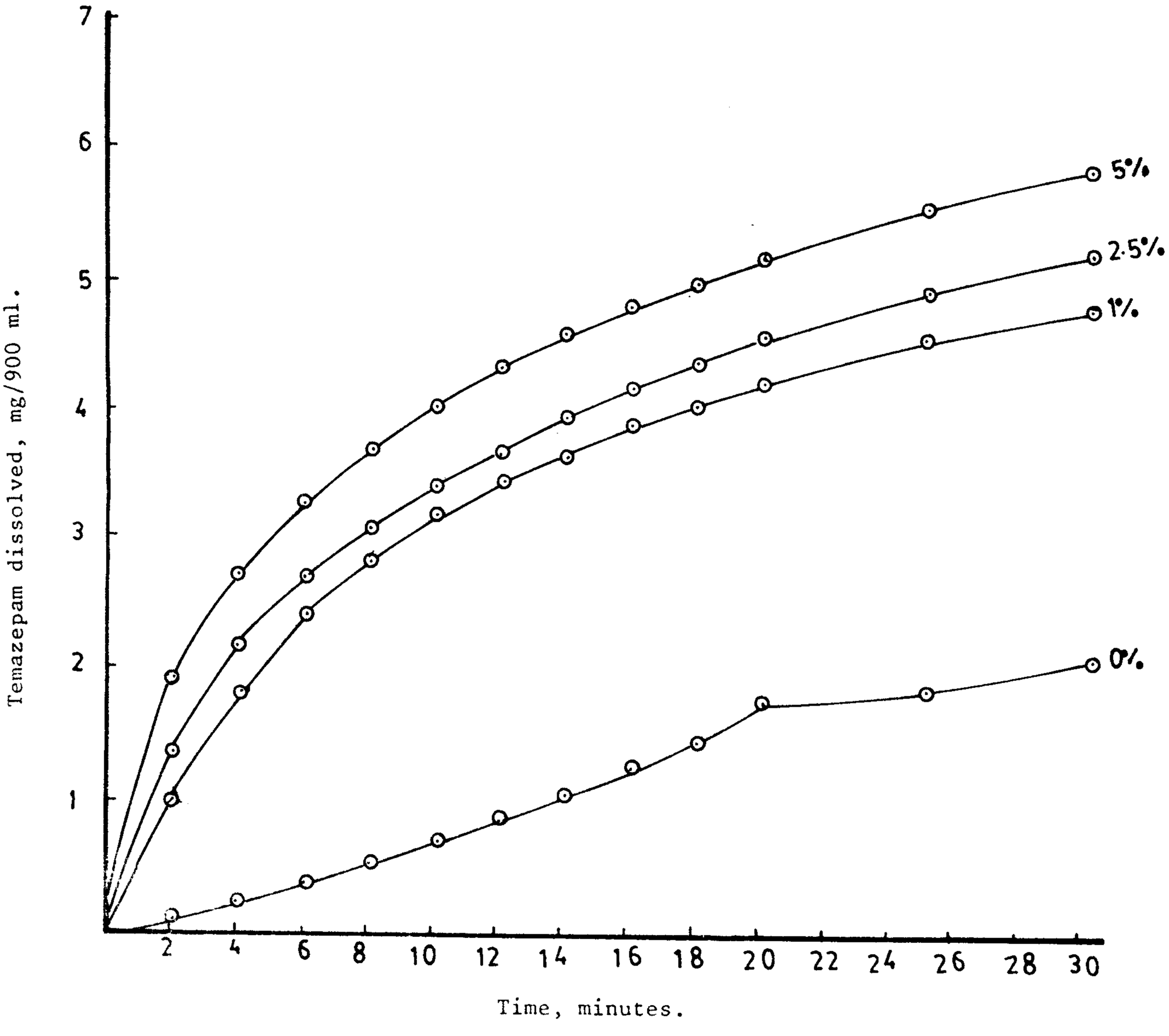


Fig.(2): Dissolution Rate of Temazepam Powder Crystallized in Different Concentrations (% w/v)Cetomacrogol using Dispersed Amount Method.

*Interaction of 1,4-Benzodiazepines with Certain Macromolecules II. Crystallization of Temazepam in Presence of Different Hydrophilic Macromolecules.*

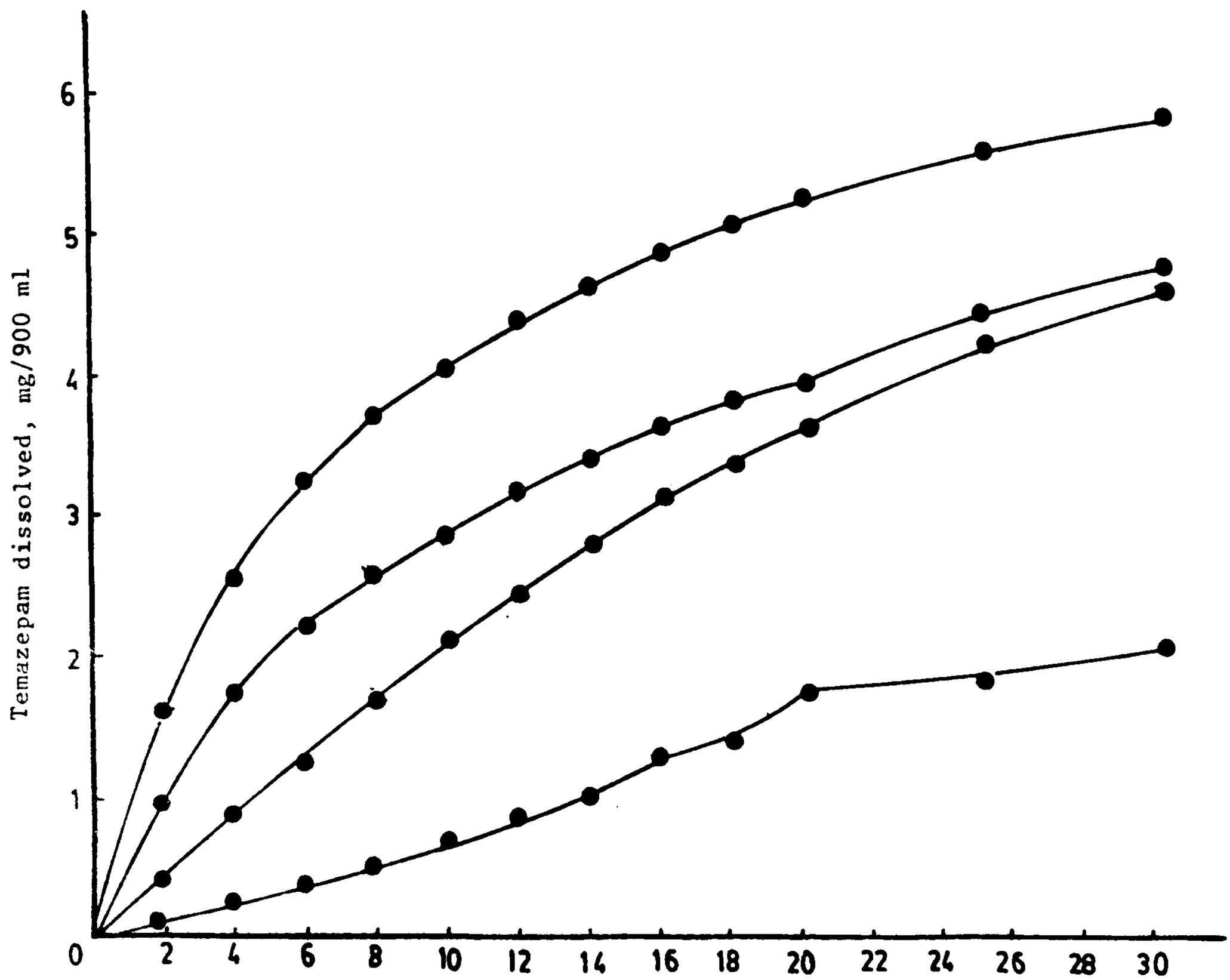


Fig.(3): **Dissolution Rate of Temazepam Powder Crystallized in Different Concentrations (Percent w/v) Polysorbate 80 Using Dispersed Amount Method.**

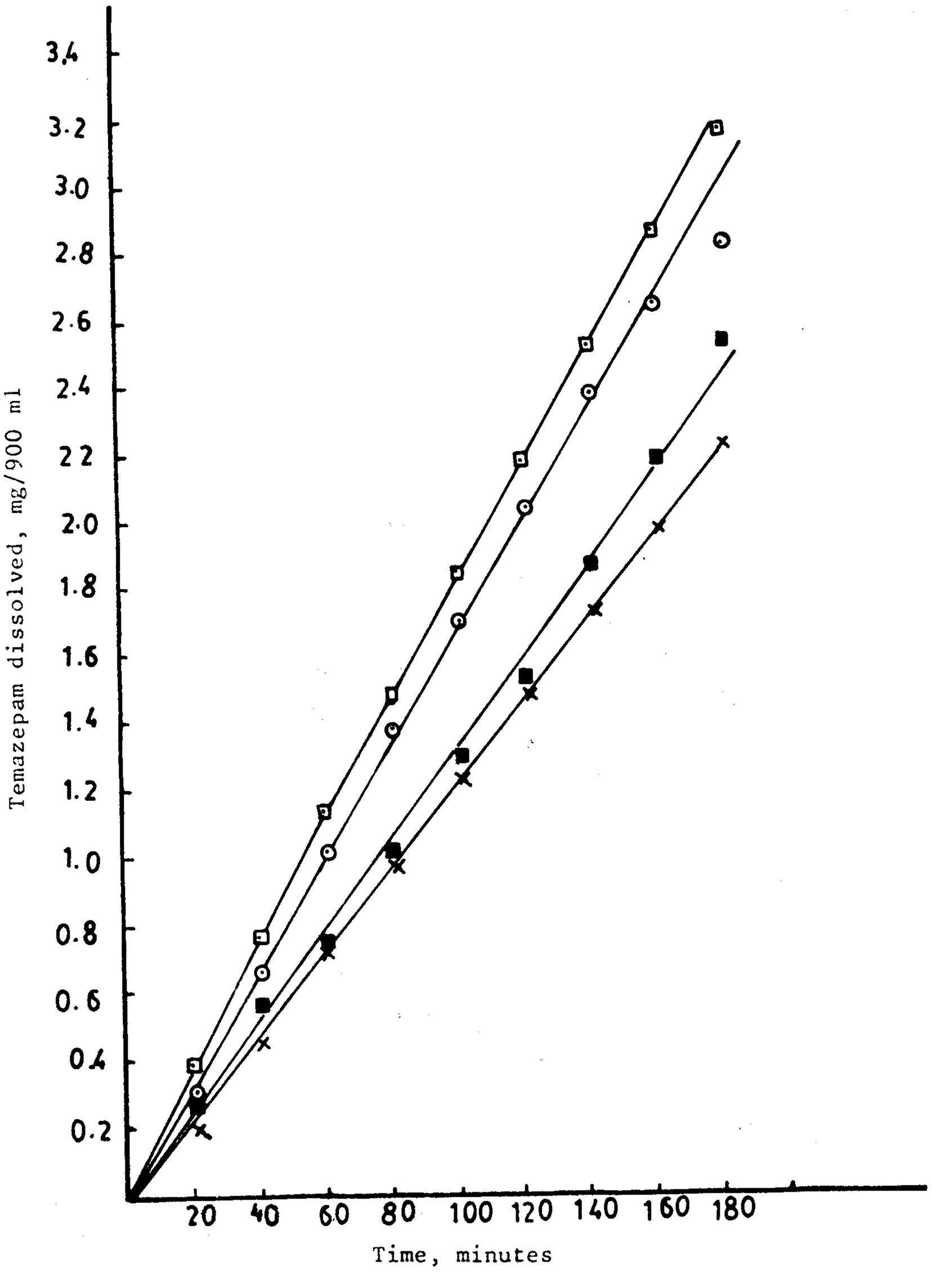


Fig.(4): Dissolutinn Rate of Temazepam Crystallized in 5% w/v of Different Macromolecules Using Static Disc Method.

Key : As Mentioned before, Fig. 1.

# DSC

DuPont 1098

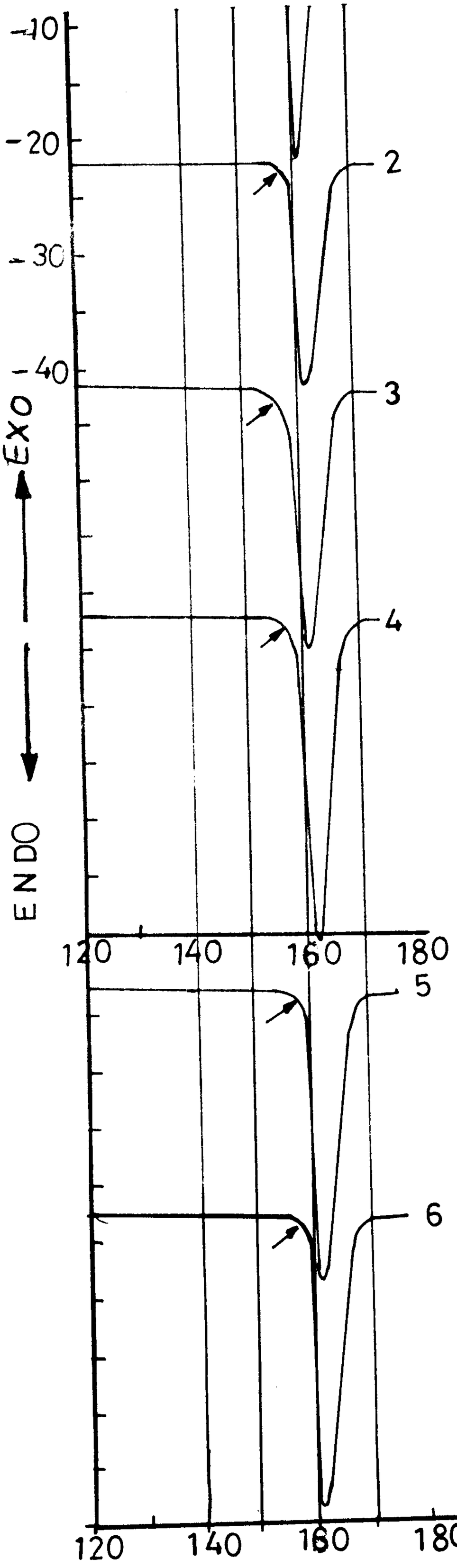


Fig.(5): DSC thermograms for Temazepam crystals

**KEY**

1, Untreated Temazepam

2, Temazepam crystallized in ethanol

3, Temazepam crystallized in 5%w/v polysorbate 80

4, Temazepam crystallized in 5%w/v cetomacrogol 1000.

5, Temazepam crystallized in 5%w/v Myrj 52.

6, Temazepam crystallized in 5%PVP 40,000.

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# تفاعلات مجموعة ار٤ ـ بنزوديازبين مع بعض الجزئيات الكبيرة : تبلر التيمازيبام فى وجود بعض الجزئيات الكبيرة المضافة للماء

براين آرثر مللى ـ احمد السيد ابو طالب ـ على عبد الظاهر عبد الرحمـــــن
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تم تبلر التيمازيبام من الكحول الاثيلى بمفرده او الكحول الاثيلى المحتوى على تركيزات مختلفة من عديد البوليسوربات ٨٠ ، السيتوماكروجول ١٠٠٠، الميرج٥٢ وعديد الفينيل بيروليدون ٤٠٠٠٠ وذلك عند درجة حرارة ٥٠ مئوية .

ولقد درست البللورات المحضرة فى وجود المواد المضافة وايضا البللورات المحضرة فى عدم وجودها من ناحية الذوبان وكذلك من ناحية تاثير التحليل الحرارى وايضا تم فحصها بالميكروسكوب الالكترونى وكذلك تعيين محتواها الدوائى ودراسة الاتاحة للتيمازيبام من خلالها وذلك بطريقتى الجزئيات المبعثرة والاتاحة من سطح ثابت . ولقد استخدم فى تعين الاتاحة نظام دائرى اوتوماتكى يسجل بطريقة اتوماتيكية الكمية المتاحة من العقار.

ولقد وجد ان بلورة العقار موضوع البحث من الكحول الايثيلى المحتوى على الاضافات المذكورة يسرع من معدل الاتاحة بدرجات متفاوته كما ان نقص السيتوماكروجول ١٠٠٠ وعديد البوليسوربات ٨٠ فى وسط التبلور سبب نقصا متدرجا فى معدل الاتاحة .

ومن دراسة التحليل الحرارى على البللورات الناتجة وجد ان هناك اختلاف قليل فى درجات الانصهار للبللورات وايضا فى Δ h مما يعكس تغييرا فى الطاقة الداخلية للبللورات وايضا فى فهرس عدم الثبات الداخلى للبللورات .

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*received in 10/12/1985 & accepted in 6/4/1986*