Bull. Pharm. Sci., Assiut University.
Vol 11, Part 1, pp 50-69 (1988).

INTERACTION OF TEMAZEPAM WITH CERTAIN MACROMOLECULES: IV-PHASE DIAGRAM OF TEMAZEPAM-POLYETHYLENE GLYCOL BINARY SYSTEMS.

B.A.Mulley[*], A.E.Aboutaleb[**], Aly A.Abdel Rahman[**] and S.M.Ahmed

School of Pharmacy, Bradford University, England[*]
and Dept. of Industrial Pharmacy, Faculty of Pharmacy,
Assiut University, Egypt .

ABSTRACT

Differential scanning calorimetery and hot stage microscopy were used to build up temperature-composition phase diagrams for temazepam-polyethylene glycol 2000, 4000 and 6000 physical mixtures and comprecipitates.

The phase diagrams showed the systems to be of the monotectic type, with the monotectic species being the pure drug.

Phase diagrams of the drug and the investigated polyethylene glycols helped in ruling out the possibility of forming solid solution or molecular compound within the concentration range of the components investigated.

Differential scanning calorimetery was also utilized for predicting the melting behaviour of temazepam and polyethylene glycols separately and as coprecipitates and physical mixture binary systems.

A good correlation was found between the position of the system on the phase diagram and its dissolution rate . The highest the carrier content, the nearest the system would be to the monotectic composition, the highest the release rate of the drug.

INTRODUCTION

The rate of absorption and/or the extent of biological availability are controlled by the dissolution rate in the gastrointestinal tract for water-insoluble drugs administered orally[1]. Therefore, efforts have been done to increase the dissolution rate of poorly water-soluble drugs[2-4]. Many techniques have been developed for this purpose viz: solvent deposition, lyophilization, solvate formation[5], salt and polymorphic formation[6], crystallization[7], and solid dispersion[8]. Solid dispersion is one of the widest techniques applied for the dissolution rate enhancement of drugs of low aqueous solubility. Since 1961, over 270 publications have reported the solid dispersion of more than 120 drugs in over thirty carriers[5]. Many works have been done to search for the mechanisms responsible for the modification of the drugs dissolution when presented in solid dispersion forms. Of the factors that may be responsible for such modification are: reduction of the particle size of the drug[9], increased wettability[8], microenvironmental solubilization[10], reduction of the drug or polymer crystallinity[11] and decrease in the activation energy needed for the drug dissolution[12]. Another factor contributing to the changes in drug dissolution from solid dispersions is the position of the solid dispersion on the temperature-composition phase diagram[13] of the drug and the carrier. Therefore, construction of the phase diagram for drug macromolecular system intended to be combined in a formulation, to modify the drug dissolution, is of considerable pharmaceutical interest. Additionally, it helps to shed some light on the drug-macromolecular interaction in solid state.

The purpose of the article is to construct the phase diagram dispersed in a polyethylene glycol carriers. Temazepam is a 1,4-benzodiazepine derivative; utilized in clinical practice as rapidly acting hypnotic drug[14]. In addition, a trial was done to find a correlation between the drug dissolution behavior and the position of the prepared systems on the phase diagram.

Interaction of Temazepam with Certain Macromolecules : IV-Phase Diagram of Temazepam-Polyethylene Glycol Binary Systems.

EXPERIMENTAL

Materials :

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

Polyethylene glycol 2000 (PEG 2000), (Hoechst, Farbwerke, Frankfurt West Germany).

Polyethylene glycol 4000 (PEG 4000) Koch-Light Ltd., Haverhill, (England).

Polyethlene glycol 6000 (PEG 6000), B.D.H. chemicals Ltd, Poole, England).

Apparatus: Du Pont differential scanning calorimeter connected to Du Pont 1091 Disk Momery, Du Pont Co., Analytical Instruments Division, Willmington, USA).

Hot stage microscope (Stanton Redcroft, London, England).

Dissolution apparatus (Erweka Apparatebau, GmbH ., West Germany).

CE 292 digital ultraviolet spectrophotometer C - C IL (Instrum - NTS, Cambridge, England).

Multipen Recorder (Rikadenki Mitsni Electronics Ltd, England).

Perkin-Elmer I.R. spectrophotometer 297 (Perkin-Elmer Ltd., Beaconsfield)

Vibration Mill Mkll and I.R. compressor unit (Research and Industrial company, England).

Preparation of the Binary Systems : (i) Physical Mixturs : A number of binary physical mixtures of temazepam with either PEG 2000,4000or 6000 were prepared by mixing accurately weighed quantities of the drug and the carrier so as to contain progressing 10% increase in concentration (0-100%) w/v as temazepam. Each component was screened to a particle size of 45-200 μ before mixing.

(ii) Coprecipitates : A portion of each of the physical mixtures was dissolved in 1 : 1 methanol-acetone. The solvent was evaporated in vacuo at room temperature. The residue was dried to a constant weight, pulverized and screened to a particle size of 45-200 μ.

Physical mixtures and coprecipitates were assayed for their temazepam content using the ultraviolet method of assay at 231 nm[15]. It was found that the presence of the PEGs investigated did not interfere in the spectrophotometric assay of the drug. The samples having 100 $\pm$ 5% w/w as temazepam were used for further investigation, others were discarded.

Phase diagram construction :

(i) Differential Scanning Calorimetry (DSC) : Samples (10 mg) of each of the physical mixtures or coprecipitates were placed in a crimped aluminium pan with pierced lid. The sample was program heated at a rate of 10°/minute in a dynamic nitrogen environment from 30-175°. Computerized procedures were utilized to mark both the thaw and final melting points of each of the plotted scanns. A cross section of the differential scanning calorimeter used in this respect is shown in Fig. 1 A.

(ii) Hot Stage Microscope : Samples (1 mg) were placed on a glass microscope cover slip which in turn was fixed to the hot stage. The stage was linked to a control unit (Fig. 1 B) which could be programmed to heat the sample from 30-175° at a rate of 10° C/ minute. A zoom stereoscope microscope was used to detect any changes occurred in the sample. The temperature at which the first sign of melting could be observed was considered as the thaw point (solidus melting point). The final disappearance of solids was considered as the final melting point (liquidus melting point).

Determination of the Dissolution Rate:

Dispersed particulate method was adopted for the determination of the release rate of the drug presented as coprecipitates. The coprecipitate composition was selected so as to represent three different regions on the phase diagrams viz : 1:1, 1:3 and 1:7 w/w drug to carrier ratio. Temazepam (8 mg., 45-200 U) or an accurately weighed seived (45-200 U) amounts of the coprecipitates having an amount of the drug were sprinkled over the surface of the dissolution medium (900 ml degased double distilled water of 37°C). The solution in the dissolution vessel was automatically pumped through a quartz flow cell of the spectrophotometer and then backed to the dissolution vessel. A filter tip was fixed to the inlet tube, also, the inlet and the exit of the tubes were fixed. The dissolution medium was agitated at a rate of 100 rpm. The absorbances of temazepam at 231 nm was recorded to give a continuous plot of absorbance versus time for 30 minutes. Sink conditions were maintained during the experiments.

Interaction of Temazepam with Certain Macromolecules : IV-Phase Diagram of Temazepam-Polyethylene Glycol Binary Systems.

Infre-Red Analysis (IR) : A quantitative IR analysis has been performed for temazepam-PEGs solid dispersions and physical mixtures. Samples of 1-2 mg were mixed with potassium bromide (IR quality) and were shaken in a vibrating ball mill. The resultant homogenous mixture was compressed into a disc in the compressor unit under vacuum and scanned from 4000 to 625 cm^{-1} with an empty pellet holder as a reference .

RESULTS AND DISCUSSIONS

Differential scanning calorimetry (DSC) and hot stage microscope (HSM) were found to be effective thermal methods for predicting the melting behavior of temazepam, PEGs and temazepam-PEG physical mixtures or solid dispersions. Combination of thermal events data helped in constructing the drug-PEG phase diagrams.

A. Melting Behaviour of Original Materials: Temazepam gave a single endothermic peak corresponding to fusion when subjected to thermal analysis (Trace I of Figs. 2-7) . Absence of thermal events before melting signifying that the drug did not decompose prior to melting. Since an exotherm following an endotherm was not observed, no polymorphs for this drug existed under these conditions. Guillory et al[16] claimed that pure compounds which do not exhibit polymorphism, do not contain solvent of crystallization and do not decompose prior to melting, generally exhibit a single endothermic peak corresponding to the fusion temperature.

PEGs exhibited a single endothermic peak at a lower temperature than that of the drug, as demonstrated by trace II of Figs. 3,5 and 7.

B. Melting Behavior of Temazepam-PEG Binary Systems:
DSC thermograms for temazepam-PEG 2000, 4000 and 6000 in physical mixtures or coprecipitates of a composition ranging from 10-

90% w/w are represented in Figs. 2-7. They all displayed similar characteristics. Examination of these thermograms gave an idea about the changes happened as the composition of the binary system varied. Generally, as the temazepam content decreased, the carrier content increased, the size of the first endotherm (the carrier endotherm) increased. Coincidentally, the size of the second endotherm (the drug endotherm) decreased. Further decrease in the drug content (40% w/w drug), disappeared the melting endotherm of the drug. This may be attributed to the presence of the drug as ultrafine crystallities, the size of which falls below the limit of the DSC analysis. For these conditions, hot stage microscope (HSM) was utillized for the determination of the final melting points of these systems.

C. Construction of Temazepam-PEG Phase Diagrams:

DSC thermograms were found to be more useful for the thaw point determination in constructing the phase diagrams of temazepam with PEGs, since the DSC and the differential thermal analysis are thought to be very sensitive and objective for this purpose[17]. These thaw points were used for the construction of the solidus lines. However, the liquidus lines of these diagrams were constructed from both DSC and HSM techniques. The thaw points and the final melting points determined are presented in Table 1.

Examination of the phase diagrams (Figs. 8-10) reveals that they all have similar characteristics. The liquidus line rises continuously from the melting point of the carrier to that of temazepam, and the solidus line passes horizontally through the melting point of the carrier. These features are characteristic for monotectic systems. Monotectics were first reported by Bowden[18] and applied to pharmaceutical systems by Kaur et al[19] and Grant et al[20]. Monotectic system can be regarded as an eutectic with an arm-missing system where the lower melting substance appears to melt independently of the higher melting one.

Interaction of Temazepam with Certain Macromolecules : IV-Phase Diagram of Temazepam-Polyethylene Glycol Binary Systems.

The rising liquidus curve on the left of each monotectic diagram corresponds to the solubility curve of the drug in the liquid excipient. Upon further examination of the phase diagram, it is possible to rule out the formation of solid solutions or molecular compounds within the concentration range investigated.

Correlation of Temazepam Release With its Phase Diagrams:

The position of a solid dispersion on the phase diagram, which determines the physical nature of the system, must be considered in relation to the rate of the drug dissolution. A summary of the dissolution rate of temazepam from the prepared solid dispersions is presented in Table 2. The dissolution of the drug presented in this table was calculated from the dissolution profiles. It is clear that, from the obtained results, the higher the carrier content in the solid dispersion, the nearer the system to the monotectic composition, the higher the drug release. This deduction is in agreement with Grant and Abougela[20] who have found that, the left region of the phase diagrams represents the composition region for the fastest release solid dispersions showing monotectic behavior. It is worth mentioning that the phase diagrams erected from the data of the drug-carrier physical mixtures were found to be similar to those determined from solid dispersions. This similarity gives a good indication that there was no evidence of the formation of solid complexes between the two components. This reveals that PEGs can only influence the dissolution rate of the drug by altering their surface properties such as surface area or the nature of the drug-water interfaces[2.19]. On the contrary, a decrease in the dissolution rate of nalidixic acid-PEG solid dispersion was observed and attributed to the presence of an interaction between the drug and the carrier[21]. Similarly, El-Banna et al[22] found that there is a good correlation between the release of hydrochlorothiazide-urea solid dispersions and the position of the selected samples on the phase diagrams. However, Goldberg et al.[10] have found that the dissolution rate of urea-acetaminophen fused mixtures at the eutectic composition was similar to that of the physically mixed samples.

Infra Red Analysis : The I.R. spectra for 1:3 and 1:7 w/w temazepam- PEG 6000 coprecipitates and the same ratio of the physical mixtures are shown in Fig. 14. The top spectrum of temazepam was found to be identical with a reference spectrum of the drug[23]. Both show NH and OH stretching from 3500 to 3300 cm^{-1} and C=O stretching at 1690 cm^{-1}. Those characteristic peaks were utilized for comparison of the I.R. charts of the processed drug with that of the reference sample.

Temazepam-PEG 6000 physical mixtures showed the absorption bands illustrating the presence of temazepam and the carrier- Additionally, it was found that the I.R. spectra of 1:3 and 1:7 w/w temazepam-PEG coprecipitates were identical to those of their respective physical mixtures. Also, the spectra showed no evidence of peak shift or variation in comparison with the reference spectrum.

On the bases of these observations, it is concluded that, there is no evidence of complexation between temazepam and the investigated carrier when they are in solid state, i.e., lack of solid interaction. In addition, it is clear from the spectra that coprecipitation method did not lead to any decomposition of the drug.

A lack of complexation has also been reported from a study of PEG 6000 fusion dispersions using tolbutamide[24]. succinylsulphathiazole and chlorpropamide[25]. On the other hand, PEG 4000 has been shown by I.R. analysis to complex, through hydrogen bonding, with several disubstituted barbiturates[26].

Table 1: Phase Transition Temperatures for Temazepam with Different Carriers Using DSC Technique and Hot Stage Microscope.

Composition (%w/w Temazepam)	Transition Temperatures (°C)													
	Temazepam-PEG 2000				Temazepam-PEG 4000				Temazepam-PEG 6000				Melts	
	Physical mixture		coprecipitates		Physical mixture		coprecipitates		Physical mixture		coprecipitates			
	Thaw	Final	Thaw	Final	Thaw	Final	Thaw	Final	Thaw	Final	Thaw	Final	Thaw	Final
00.0	50.2				55.9				58.9					
10.0	49.0	98.0*	46.4	90.0*	56.6	140.0*	53.5	99.0*	58.4	107*	54.6	114.0*	58.1	111*
20.0	51.3	117.5*	46.1	125.0*	56.6	149.0*	54.4	122.0*	58.6	126.5*	55.4	123.5*	58.4	120*
30.0	49.8	128.5*	46.3	137.0*	56.6	150*	54.4	134.0*	58.5	134.0*	55.9	134.0*	57.5	130*
40.0	49.2	135.6	46.7	139.7	56.8	150.5	54.4	135.3	58.3	139.2	54.8	136.2	58.0	139.3
50.0	50.0	143.1	46.7	150.2	57.2	153.8	55.1	150.0	58.6	147.1	54.9	145.1	58.0	143.8
60.0	49.4	149.2	48.4	151.3	57.3	155.9	54.6	150.3	58.8	152.0	55.8	150.7	57.9	151.0
70.0	49.2	154.1	46.9	152.9	57.3	158.7	54.1	133.0	58.6	154.4	55.7	156.4	57.0	156.0
80.0	49.8	154.3	47.8	155.5	57.4	159.8	54.8	157.7	58.8	156.5	55.4	158.0	56.4	157.5
90.0	50.1	156.9	48.9	158.3	57.9	161.9	55.3	158.9	59.0	158.4	56.2	159.1	57.2	158.0
100.0	---	162.0	---	162.0	----	162.0	----	162.0	----	162.0	-----	162.0	----	158.9

* Temazepam determined using hot stage microscope.

Table (2) Dissolution Half Lives* and R.D.R.** for Temazepam PEG Coprecipitates.

Carrier	Ratio of the drug: PEG (w/w)	T 50 % (minutes)	R.D.R (minutes) 6	10	20
Control drug# PEG2000		15.5	1	1	1
	1:1	7.4	5.0	3.5	2.0
	1:3	6.2	8.2	5.3	2.9
	1:7	2.4	15.0	8.5	3.8
PEG 4000	1:1	5.6	7.9	4.9	2.6
	1:3	4.6	10.0	6.3	3.1
	1:7	1.8	17.9	9.7	4.2
PEG 6000	1:1	4.3	10.3	6.6	3.2
	1:3	3.4	14.9	8.9	3.9
	1:7	1.9	20.5	10.8	4.5

\# Pure untreated drug in absence of macromolecules.

* It is the time in minutes for 50% of the dissolved amount of the drug.

** It is the ratio of the amount of the drug dissolved from coprecipitates divided by the amount dissolved from the pure drug at the same time interval.

Interaction of Temazepam with Certain Macromolecules: IV-Phase Diagram of Temazepam-Polylene Glycol Binary Systems.

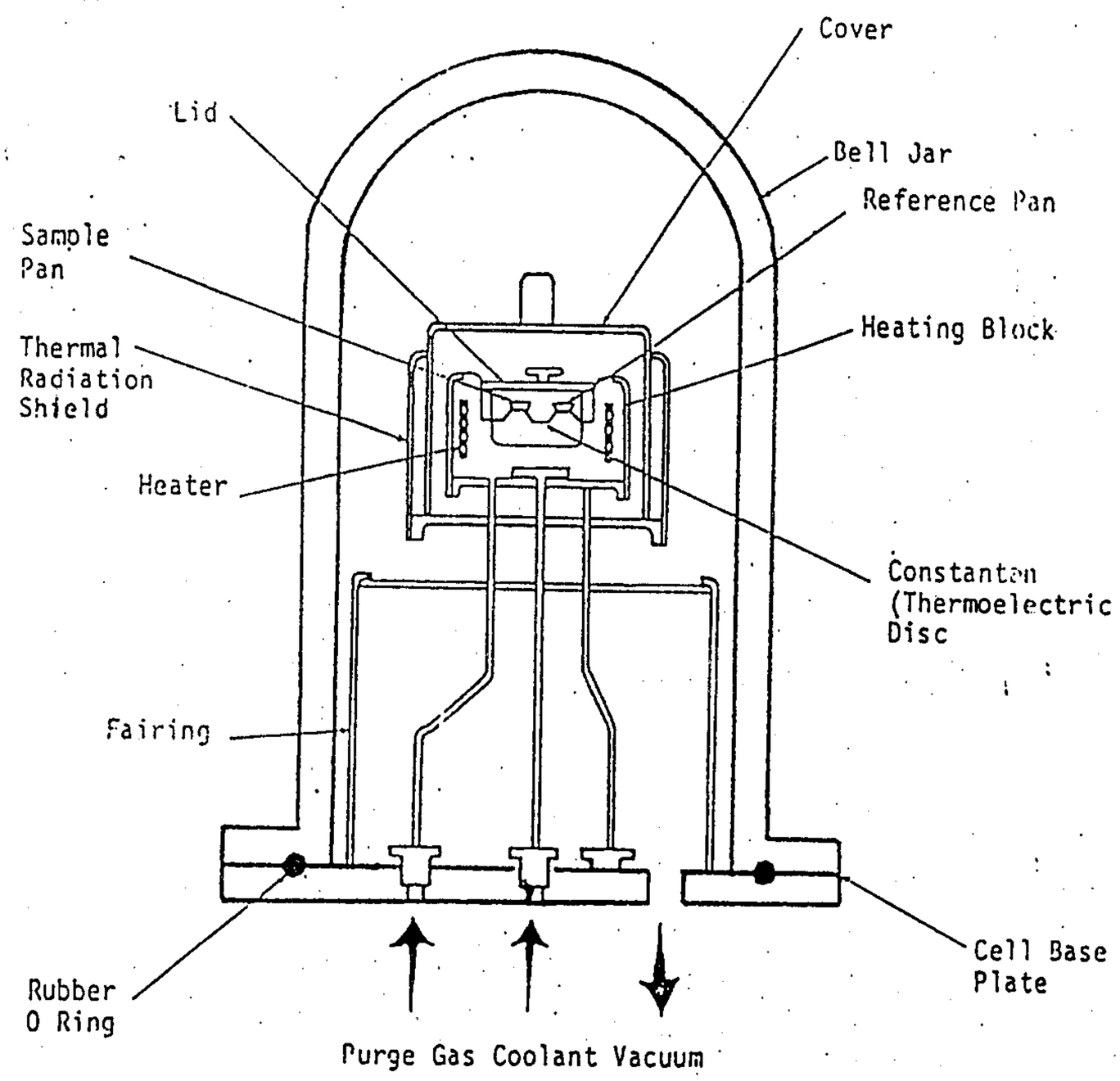

FIG. 1 A :CROSS SECTION OF DIFFERENTIAL SCANNING CALORIMETER.

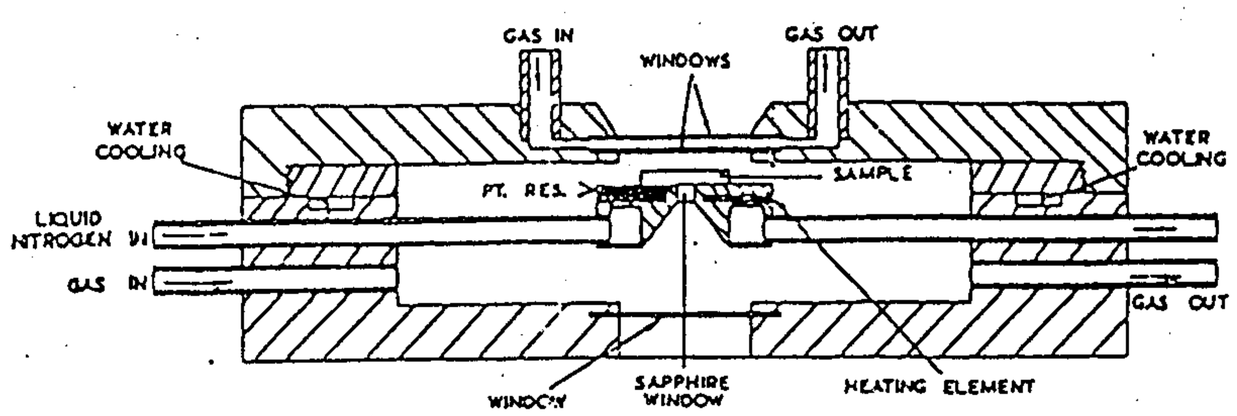

FIG.1 B: CROSS SECTION OF THE THERMAL CELL OF THE HOT STAGE MICROSCOPE.

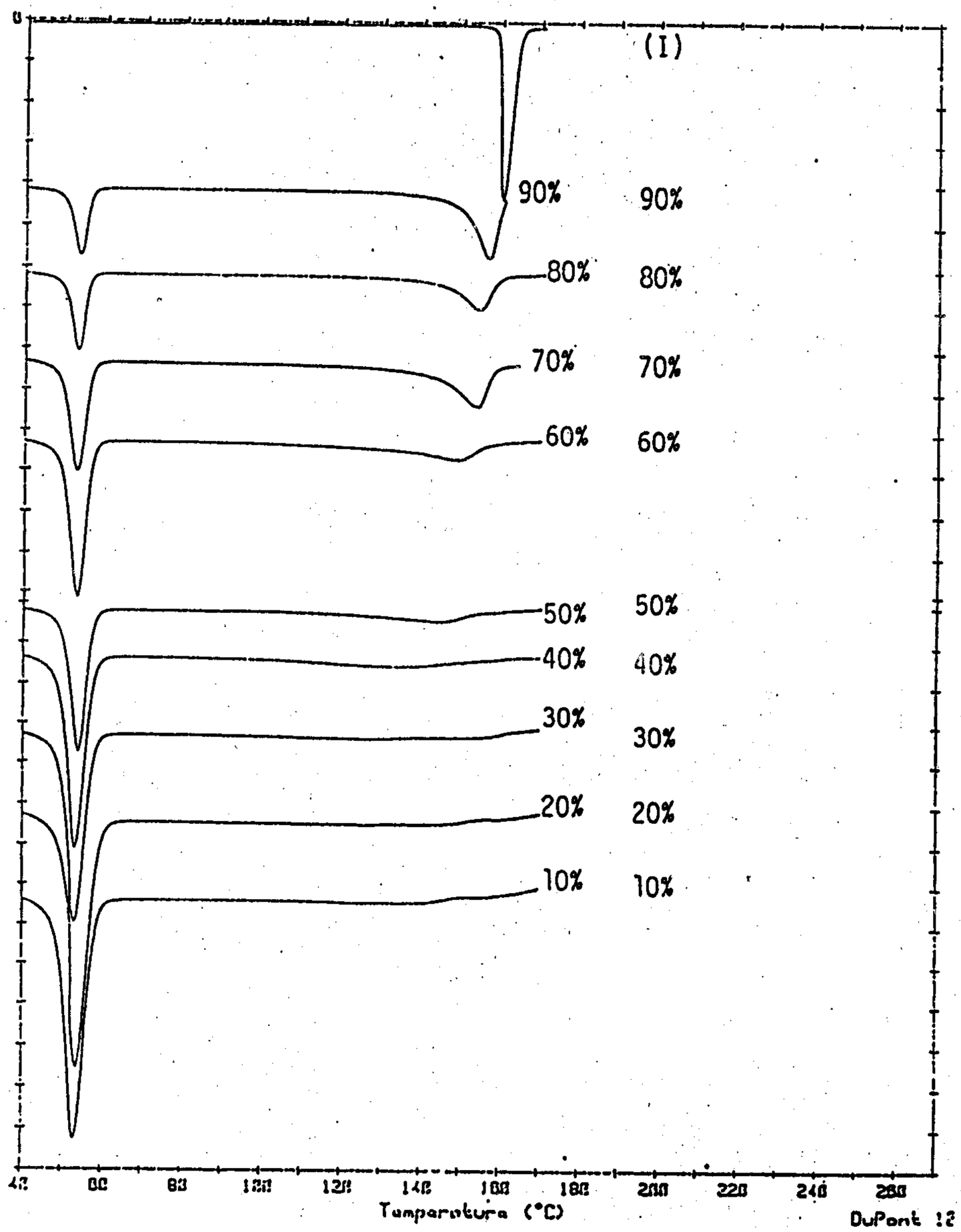

FIG. 2 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 2000 PHYSICAL MIXTURE.(I) TEMAZEPAM ALONE, % VALUES REPRESENT THE PERCENT OF TEMAZEPAM PRESENT IN THE FINAL MIXTURES.

Interaction of Temazepam with Certain Macromolecules: IV-Phase Diagram of Temazepam-Polylene Glycol Binary Systems.

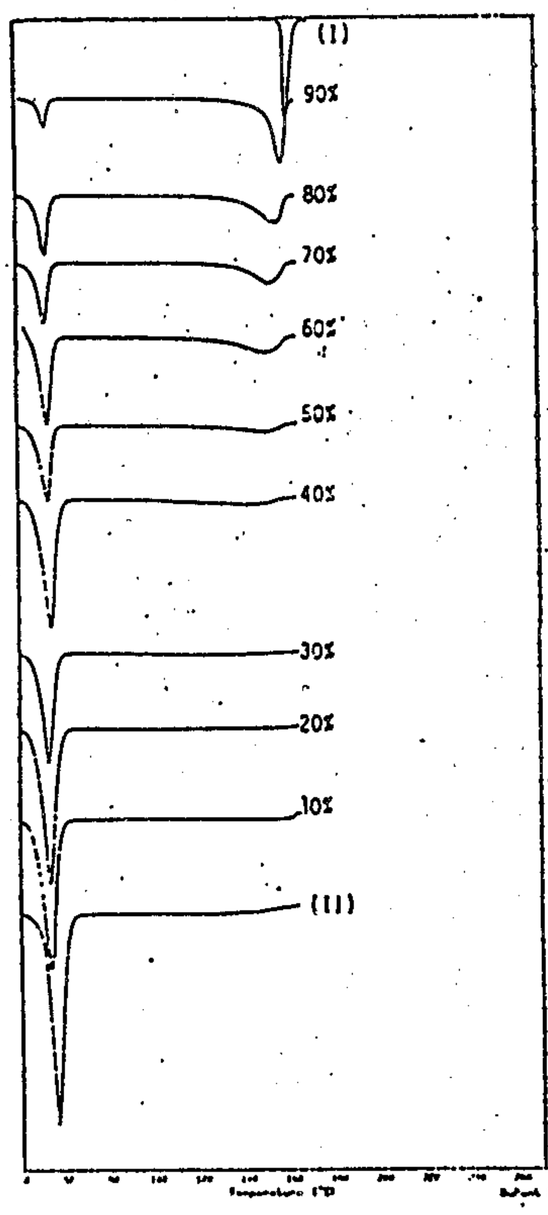

FIG.3 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 2000 COPRECIPITATES.(I) TEMAZEPAM ALONE,(II)PEG 2000 ALONE. % VALUES REPRESENT THE PERCENT OF TEMAZEPAM PRESENT IN THE FINAL SOLID DISPERSIONS.

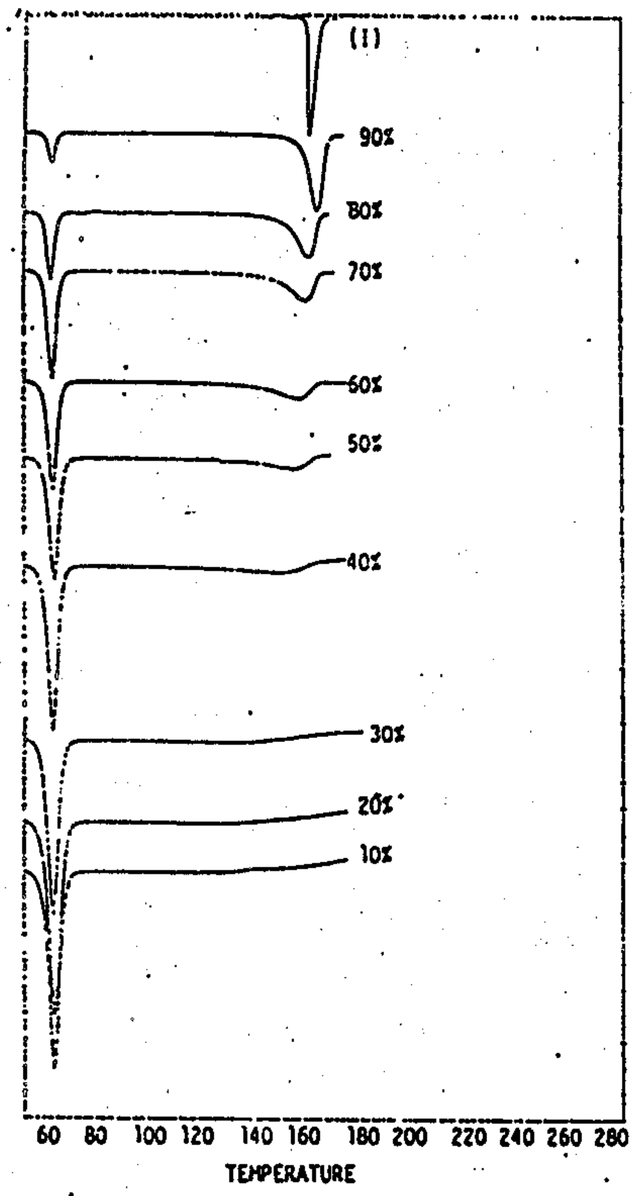

FIG. 4 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 4000 PHYSICAL MIXTURES.(I) TEMAZEPAM ALONE, % VALUES REPRESENT THE PERCENT OF TEMAZEPAM PRESENT IN THE FINAL MIXTURES.

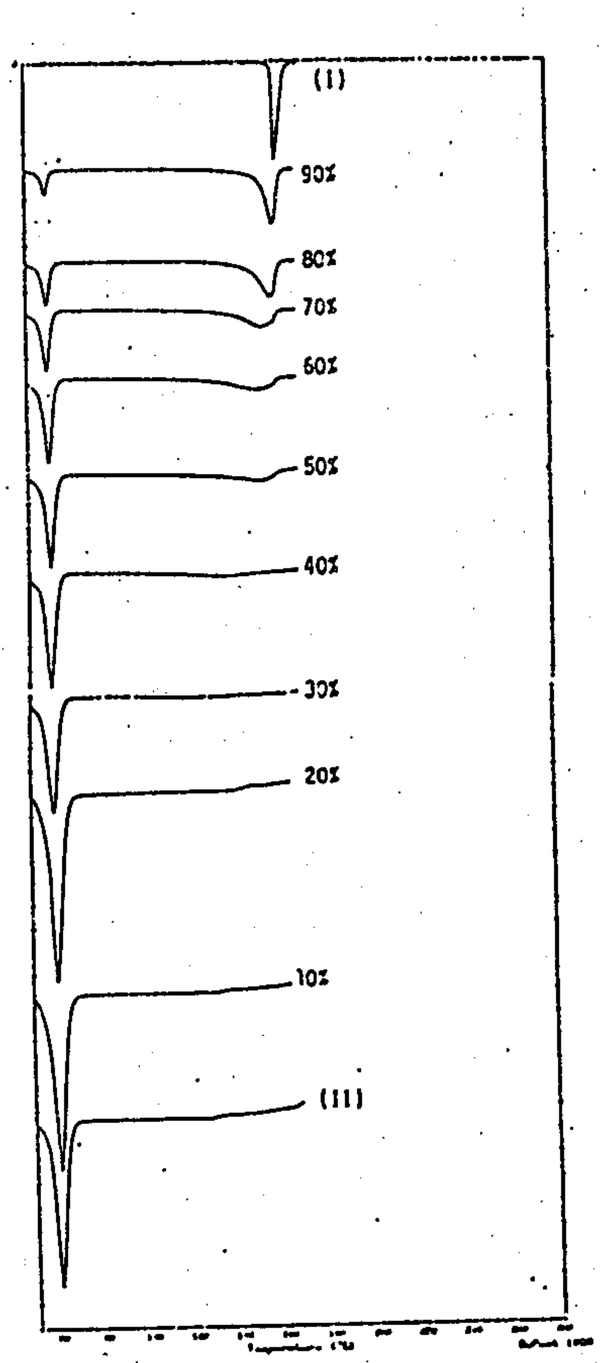

FIG. 5 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 4000 COPRECIPITATES (I) TEMAZEPAM ALONE, (II) PEG 4000 ALONE. % VALUES REPRESENT THE PERCENT OF TEMAZEPAM PRESENT IN THE FINAL SOLID DISPERSIONS.

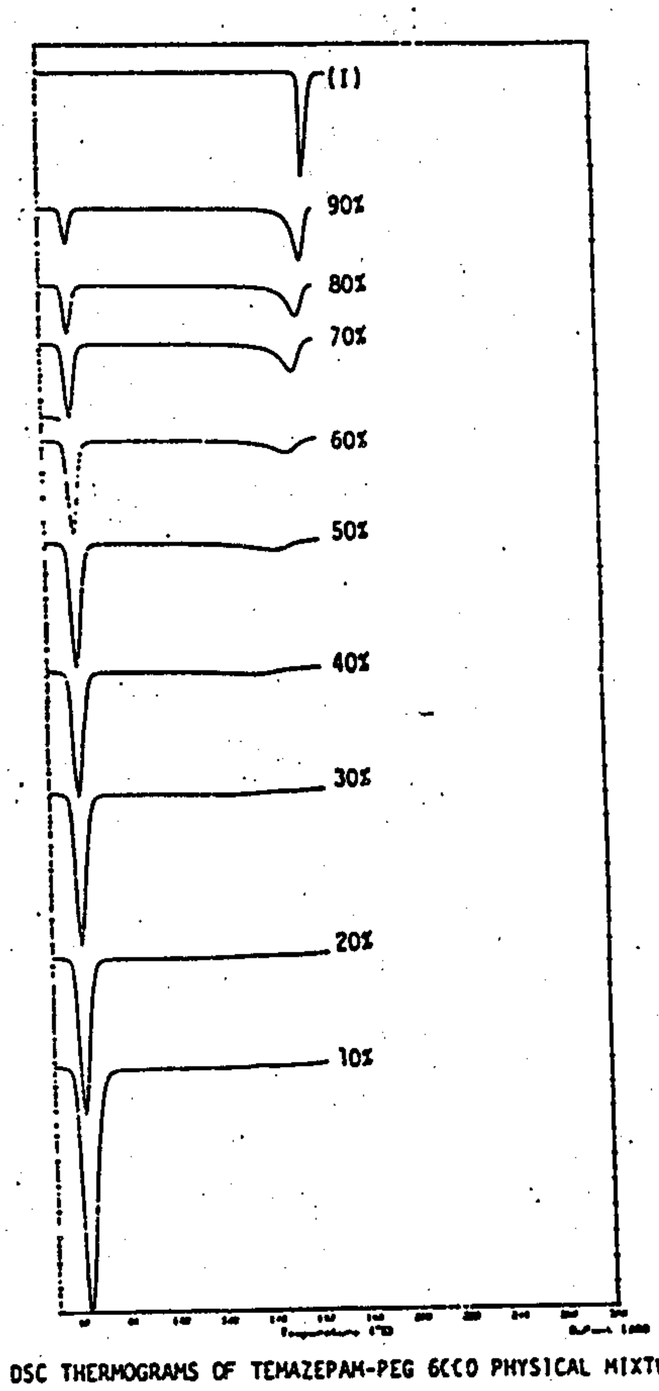

FIG. 6 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 6000 PHYSICAL MIXTURES. (I) TEMAZEPAM ALONE, % VALUES REPRESENT THE PERCENT OF TEMAZEPAM PERCENT IN THE FINAL MIXTURES.

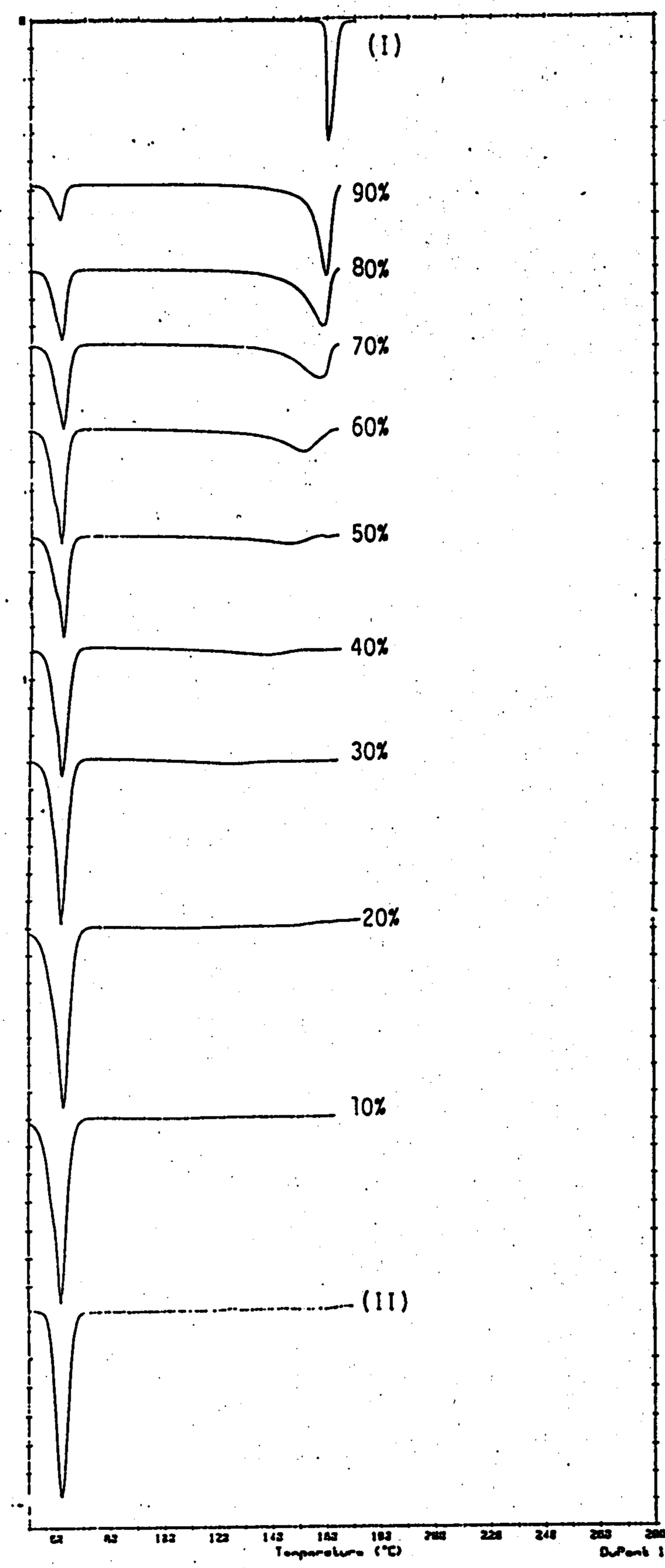

FIG. 7 : DSC THERMOGRAMS OF TEMAZEPAM-PEG 6000 COPRECIPITATES (I) TEMAZEPAM ALONE,(II) PEG 6000 ALONE.% VALUES REPRESENT THE PERCENT OF TEMAZEPAM PRESENT IN THE FINAL SOLID DISPERSIONS.

Interaction of Temazepam with Certain Macromolecules: IV-Phase Diagram of Temazepam-Polylene Glycol Binary Systems.

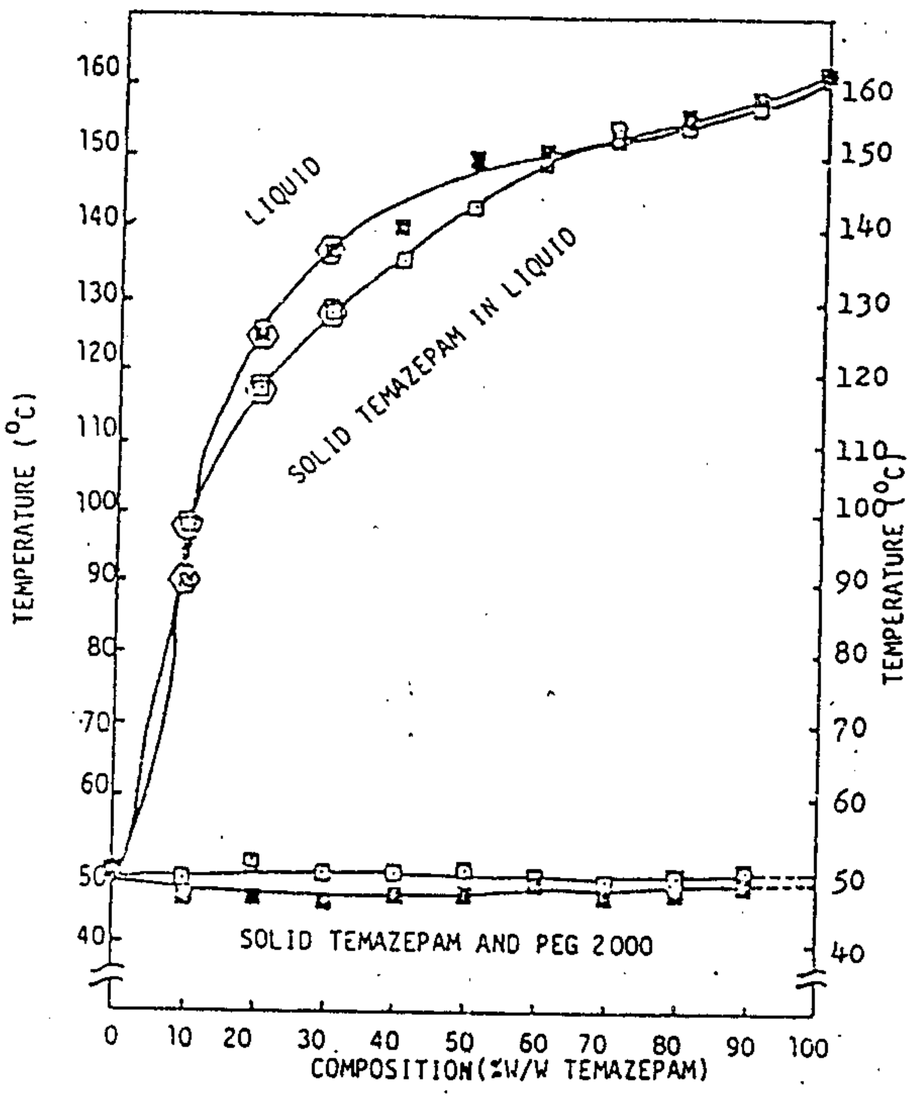

FIG. 8 : PHASE DIAGRAM FOR TEMAZEPAM-PEG 2000 SYSTEM.

KEY: ⊡ physical mixtures (DSC)
■ Coprecipitates (DSC)
⊛ , ⊡ HSM-Temperatures

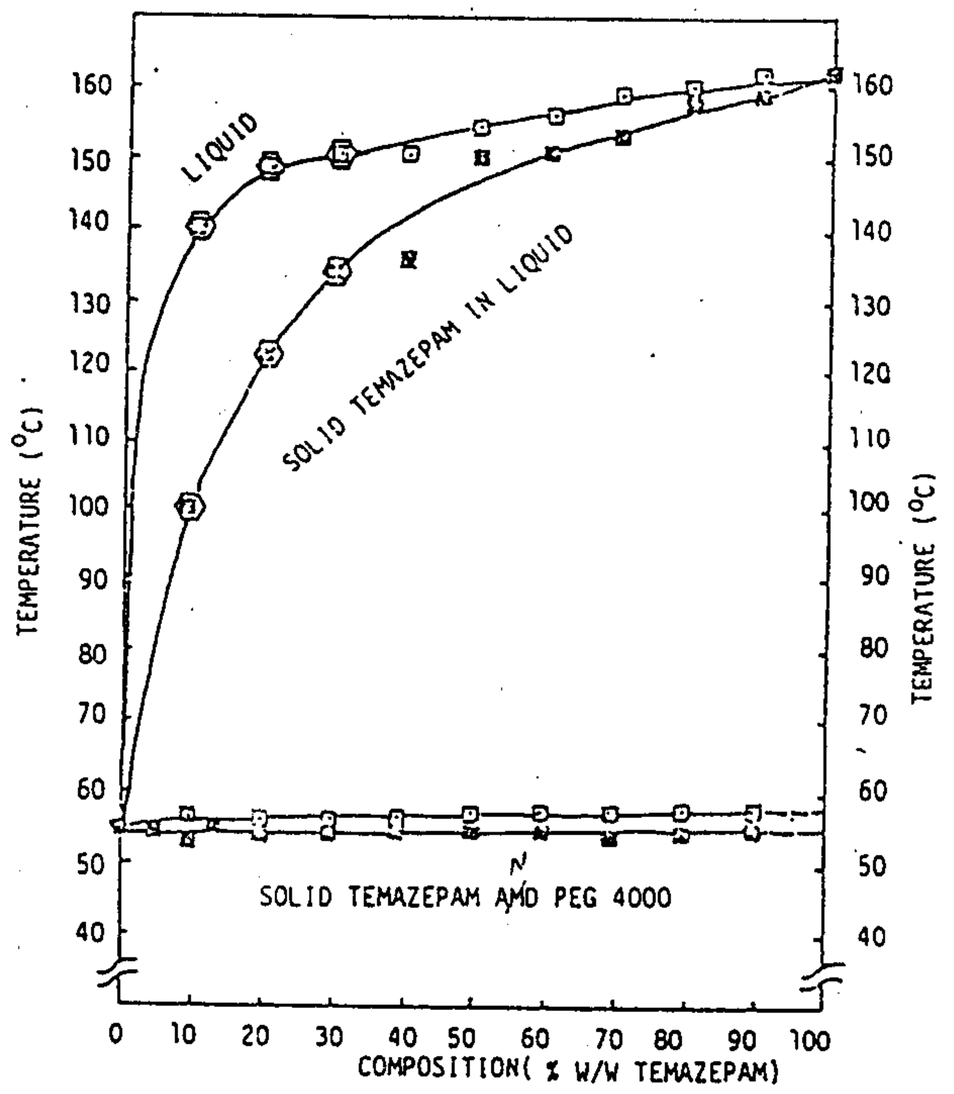

FIG. 9 : PHASE DIAGRAM FOR TEMAZEPAM-PEG 4000 SYSTEM.

KEY: AS MENTIONED BEFORE.

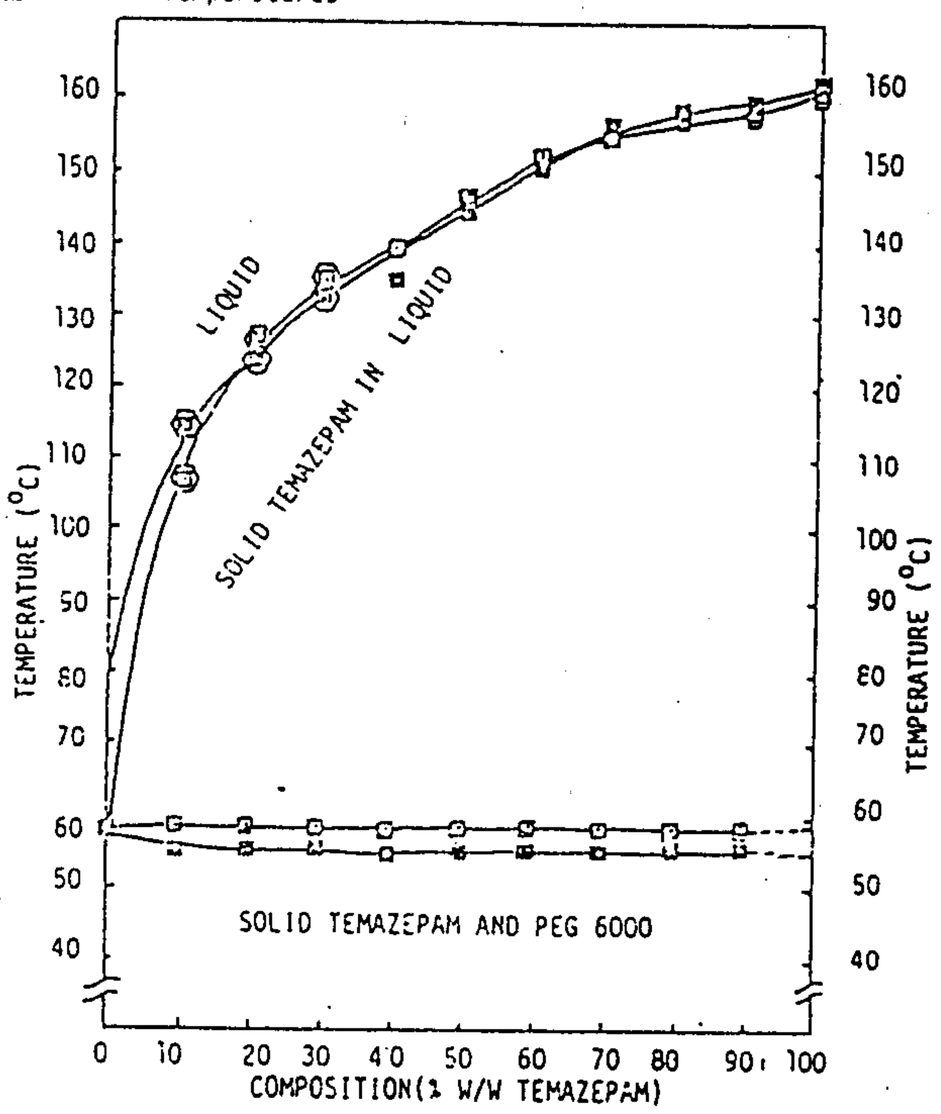

FIG. 10: PHASE DIAGRAM FOR TEMAZEPAM-PEG 6000 SYSTEM

KEY: AS MENTIONED BEFORE.

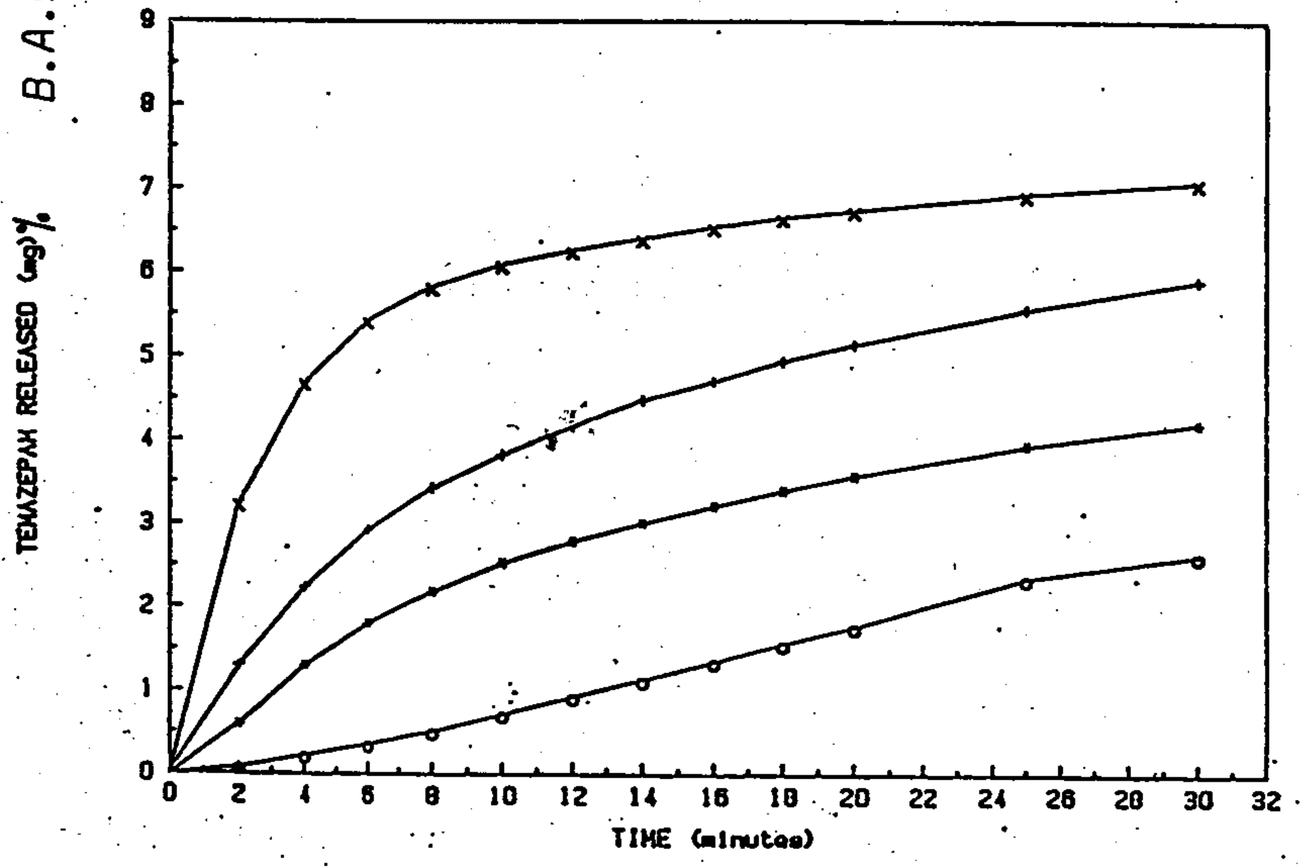

FIG (11)DISSOLUTION PROFILES OF TEMAZEPAM-PEG 2000 COPRECIPITATES

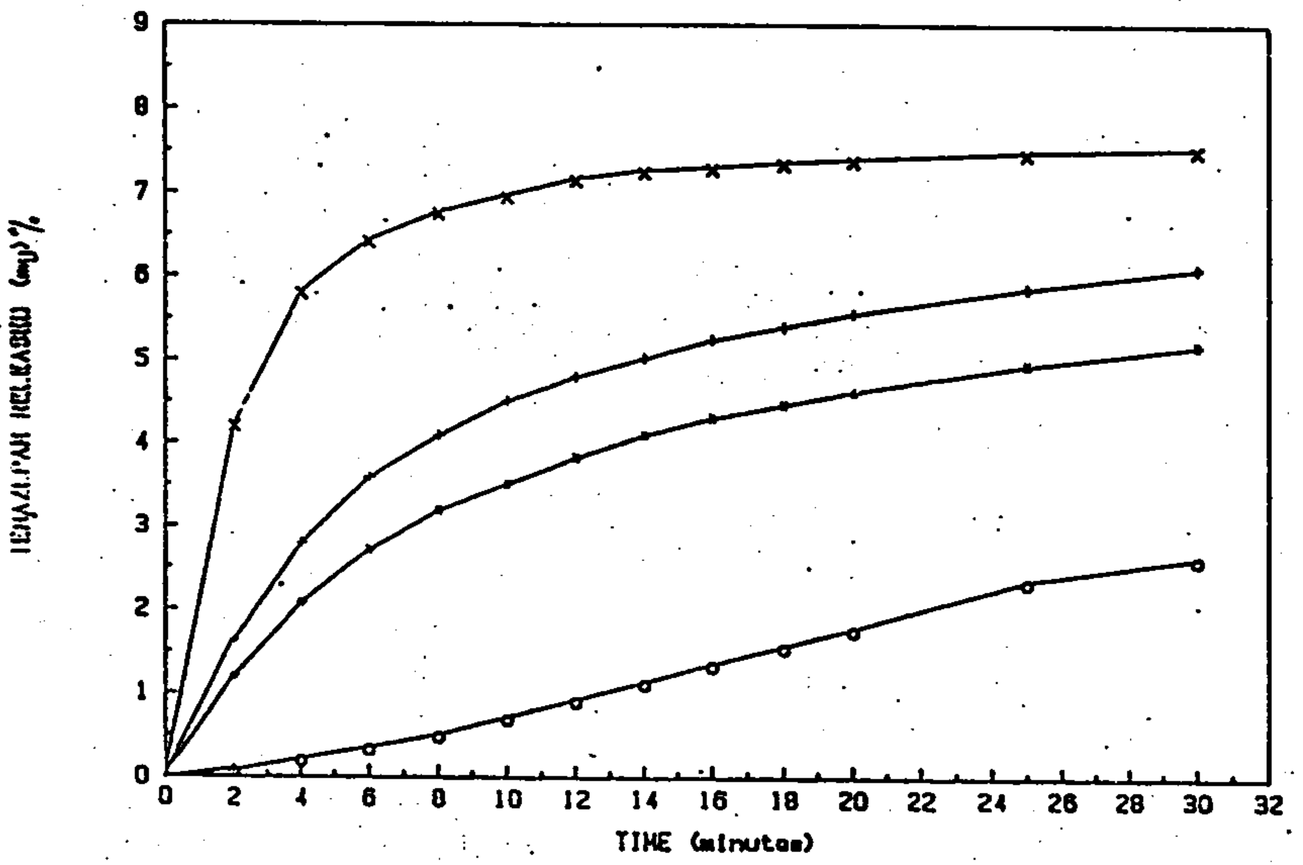

FIG (12)DISSOLUTION PROFILES OF TEMAZEPAM-PEG 4000 COPRECIPITATES.

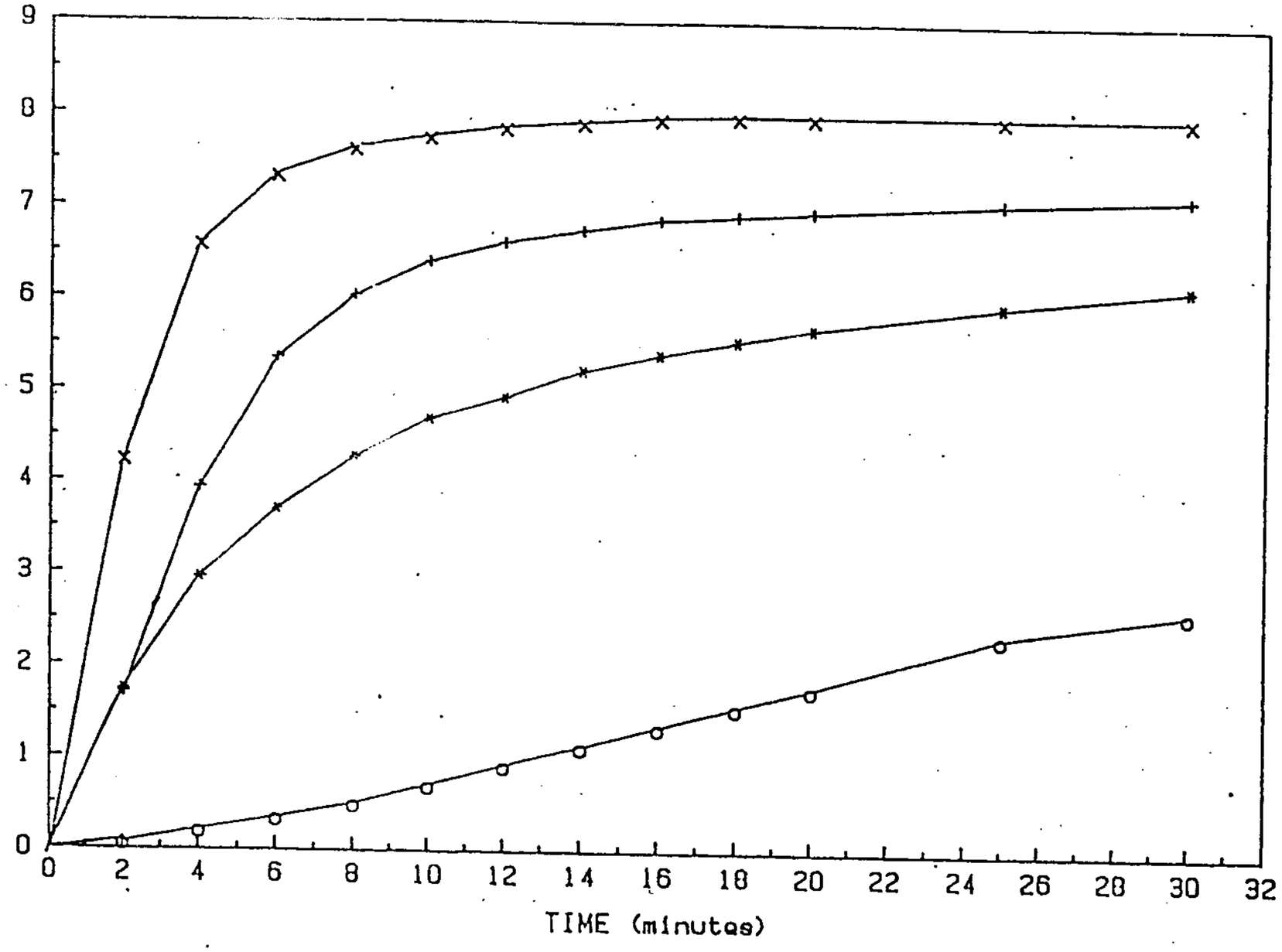

FIG (13)DISSOLUTION PROFILES OF TEMAZEPAM-PEG6000 COPRECIPITATES.

KEY o CONTROL

* 1:1w/wRATIO

\+ 1:3 RATIO

× 1:7 RATIO

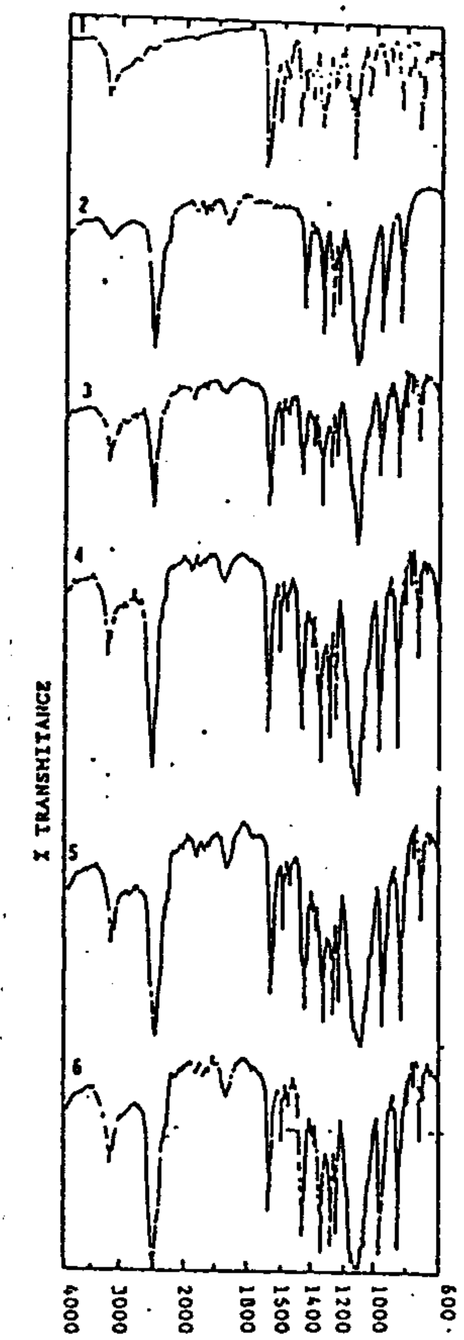

FIG. 14 EFFECT OF PEG 6000 AS SOLID DISPERSION CARRIER ON THE IR SPECTRUM OF TEMAZEPAM.

KEY: 1, TEMAZEPAM ALONE
2, PEG 6000 ALONE
3, 1:3 w/w TEMAZEPAM-PEG 6000 (Ph. Mix)
4, 1:3 w/w TEMAZEPAM-PEG 6000 (Cop.)
5, 1:7 w/w TEMAZEPAM-PEG 6000 (Ph. Mix)
6, 1:7 w/w TEMAZEPAM-PEG 6000 (Cop.)

REFERENCES

1) S.A.Kaplan, "Dosage Form Design" Swarbrick, ED.Lea & Febiger, Philadelphia, 1973, P. 20.

2) W.L. Chiou and S.Reigelman, J. Pharm. Sci., 58, 1505 (1969).

3) A.S. Geneidi and H. Hamacher, Pharm. IND., 42, 401 (1980).

4) A.N. El-Gindy, A.A.Shalaby and M.M.Abdel-Khalek, Drug Devel. Ind. Pharmacy, 8, 683 (1982).

5) J.L.Ford, Pharm. Acta Helv., 61, 69 (1981).

6) J.Halebliamn and W.McCrone, J. Pharm. Sci., 58, 911 (1969).

7) W.L.Chiou, S.J.Chen and N.Athanikar, ibid, 65, 1702 (1976).

8) C.Doherty and P.York, ibid., 76, 731 (1987).

9) W.L. Chiou, J. Pharm. Sci., 66, 989 (1977).

10) A.H.Goldberg, M.Gibaldi and J.L.Kanig, ibid., 55, 482 (1966).

11) J.L.Ford, A.F.Stewart and J.L.Dubois., Int. J. Pharm., 28, 11 (1986).

12) S.C.Shin, Arch. Pharm. Res., 2, 35 (1979).

13) B.J.Hargreaves, J.E.Pearson and P.Connor, J. Pharm. Pharmacol., 31, 47 (1979).

14) Extra-Pharmacopoeia (Martindale), 28 th Ed., Pharmaceutical press, London, 1982, p. 817.

15) E.G.Clark,"Isolation and Identification of Drugs" Vol. 2, the Pharmaceutical Press, London, 1975, P. 1099.

16) J.K.Guillory, S.N.Hwang and J.L.Lach, J. Pharm. Sci., 58, 301 (1969).

17) R.F.Schwenker and P.D.Gran "Thermal Analysis", Vol. 2, Academic Press, New York, 1969, p. 829.

18) S.T.Bowden, "The phase rule and the phase reactions", Macmillan and Co. Ltd., London, 1954, p. 153.

19) R.Kaur, D.J. Grant and T. Eaves, J. Pharm. Sci., 69, 1321 (1980).

20) D.J.Grant and I.K.Abougela, Anal. Proc., 545 (1982).

21) M.I.Fatouh, MSC. Thesis, Faculty of Pharmacy, El-Azhar Univ.,Egypt (1981).

22) H.M.El-Banna, Z.A.Gholmy and Y.Hammouda, Pharm. Acta Helv., 55, 244 (1980).

23) M.Terry, W.N.Price and J.C.Roberson "Instrumental Data for drug Analysis" Elsevier, New York, Amesterdam and Oxford, 1982, P.249.

24) S.A.Said, H.M.El-Fatatry and A.S.Genidi, Aust. J. Pharm. Sci., NC3, 42 (1974).

25) S.A. Said, H.M.El-Fatatary and M.S.El-Samaligih, ibid, NC3, 123 (1974).

B.L.Chang, N.O.Nuessle and J.W.Haney, J. Pharm. Sci., 11, 1787 (1975).

تفاعلات التيمازيبام مع جزئيات كبيرة معينه

٤ ـ تفاعلات التيازيبام مع عديد ايثيلين جليكولات فى مخاليط ثنائية طبيعية والشكل الفيزيائى الثنائى المرسوم لها

*براين آرثر مللى ، أحمد السيد أبوطالب ، على عبدالظاهرعبدالرحمن ،سيد محمد أحمد
قسم الصيدلة الصناعية ـ كلية الصيدلة ـ جامعة أسيوط،*كلية الصيدلة جامعة برادفورد انجلترا

استخدم التحليل السعرى التفاضلى المبرمج بالحاسب الالى والفحص الميكروسكوبى الحرارى لبناء أشكال فيزيائية ثنائية للتيمازيبام وعديد الايثلين جليكول ٢٠٠٠ ، ٤٠٠٠ ، ٦٠٠٠ وذلك فى مخاليط طبيعية ثنائية ومتراسبات ولقد أظهرت الاشكال الفيزيائية الثنائية أن النظام أحادى الانصهار أو مونوتكتكى .

والاشكال الفيزيائية الثنائية المرسومه للعقار وعديد الايثلين جليكولات موضوع الدراسة ساعدت على اثبات تكوين محاليل صلبه أو مركبات جزيئية فى التركيز المدروس للمواد موضوع الدراسة .

ولقد استغل التحليل السعرى التفاضلى لتحديد السلوك الانصهارى للتيمازيبام وعديد الايثلين جليكولات بمفردهم وفى المتراسبات المحضرة وفى المخاليط الطبيعية الثنائية لهم .

ولقد وجد أن هناك علاقه بين مكونات النظام على الشكل الفيزيائى الثنائى المرسوم ومعدل اتاحته ـ ووجد أنه كلما زاد تركيز الحامل كلما قرب النظام ليكون أحادى الانصهار ـ كلما زاد معدل الاتاحه .

---

received in 8/3/1988 - accepted in 18/8/1988