

EFFECT OF COPRECIPITATE FORMATION AND CERTAIN NON-IONIC SURFACTANTS ON CHLORDIAZEPOXIDE RELEASE FROM CAPSULES.

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ABSTRACT

The solvent method was employed to prepare coprecipitates with certain carriers and the water-insoluble drug Chlordiazepoxide to enhance its dissolution rate. The investigated carriers were: poly-ethylene glycol 4000 (PEG 4000), Polyvinylpyrrolidone 44000 (PVP 44000) and α -cyclodextrin (α -CYC) in ratios 1:1, 1:3 and 1:7 (drug:carrier), respectively.

The dissolution rate of Chlordiazepoxide from its prepared coprecipitates using the previously mentioned carriers, especially α -CYC, was found to be higher than that of the drug alone in 0.1N HCl as a dissolution medium.

The effect of certain non-ionic surfactant solutions including Brij 35 and Eumulgin C1000 on the release of Chlordiazepoxide from the prepared coprecipitates was also investigated.

It was found that the investigated surfactants in the concentration used (0.1 % W/V), produced better drug release than the control, especially when PEG 4000 was used as a carrier.

The mode of interaction taking place between Chlordiazepoxide and the investigated carriers was studied by different techniques including UV, IR, chromatography and differential thermal analysis, where a complex formation between Chlordiazepoxide and the coprecipitating agents was revealed.

INTRODUCTION

Chlordizepoxide is used in the treatment of acute agitation such as that associated with panic states and it has been widely used in the management of alcohol withdrawal¹⁻⁴.

The drug belongs to the 1,4-benzodiazepine group which has lipophilic characteristics and is almost water-insoluble and is characterized by its low toxicity and its very weak side effects.

Absorption of slightly water soluble drugs is often a function of the dissolution rate of these substances in aqueous solutions^{5,6}. Therefore, it is of interest to increase the dissolution rate of poorly water-soluble drugs by incorporating them in solid dispersions or molecular dispersion in water-soluble polymers such as polyethylene glycols and polyvinyl-pyrrolidone.

Chou⁷ proposed that poorly water-soluble drugs can achieve faster dissolution rates when enmeshed in glass solutions of water soluble polymers.

The mechanisms and advantages of increasing the dissolution rates of poorly water-soluble drugs, solid coprecipitated in polyvinyl-pyrrolidone were described by Simonelli et al⁸ and by Said et al⁹.

PVP 11500, 40000 and 360000 were used for preparing solid coprecipitates of sulfathiazole⁸, Tolbutamide⁹, Reserpine¹⁰ and Chlorpropamide¹¹.

The present work is performed to enhance the dissolution rates of Chlordiazepoxide via coprecipitation and to investigate the effect of certain non-ionic surfactant concentration incorporated in the dissolution media on the dissolution rates of the drug.

Effect of Coprecipitate Formation and Certain Non-ionic Surfactants on Chlordiazepoxide Release From Capsules.

EXPERIMENTAL

Materials:

Chlordiazepoxide^a was purified by crystallization from alcohol. Polyvinyl-pyrrolidone 44000 (PVP 44000)^b, polyethylene glycol 4000^b (PEG 4000) and α -cyclodextrin^c (α -CYD) were the coprecipitating agents used.

Ethyl alcohol^b and concentrated hydrochloric acid^b were of analytical grade.

Brij 35^d and Eumulgin C1000^e were the non-ionic surfactants used. Geltin colourless capsules^f were used to perform the dissolution of the prepared coprecipitates.

Equipment:

Dissolution apparatus USP XX with PTFE paddles (Erweka dissolution tester).

Self recording spectrophotometer (Pye-Unicam SP 1750).

Single beam spectrophotometer (Pye-Unicam SP 400).

Infra Red spectrophotometer (Pye-Unicam SP 1025),

Differential thermal analysis Dupont 1090 instrument.

Methods:

Preparation of solid coprecipitates:

The solvent method was used to prepare Chlordiazepoxide coprecipitates with PEG 4000, PVP 44000 and α -CYD. The carrier was accurately weighed and dissolved in 50 ml of absolute ethanol. The powdered drug was accurately weighed in another 50 ml of absolute ethanol. The two solutions of

a- Hoffman La Roche, Basle, Switzerland.

b- B.D.H. Poole, England.

c- Sigma chemical company, U.S.A.

d- Atlas chemical industries Inc. Willimington, Delaware, USA.

e- Henkel International, Dusseldorf, West Germany.

f- Park Davis & Co, U.S.A.

the drug and the carrier in ratios of 1:1, 1:3 and 1:7 were mixed in a porcelain dish, the solvent was left to evaporate at room temperature and the dish was placed in a dessicator over calcium chloride. The residue was kept in an incubator at 37° till constant weight. The mass was then passed through set of sieves and particles of 100-200 μ were collected. The calculated amount of the powder was then packed into colourless capsules and stored in a dessicator at room temperature .

Dissolution rate studies:

The calculated amount of the drug and the carrier equivalent to 25 mg of the drug contained in a gelatin capsule was rapidly introduced into the suspended rotating basket. Stirring was maintained at a rate of 50 r.p.m. using a synchronous motor. The following dissolution media(500 ml) previously equilibrated at 37 C were used :0.1 N HCl, 0.1 N HCl containing 0.1% W/V Brij 35 and 0.1 N HCl containing 0.1% W/V Eumulgin C1000. Samples of 5 ml were withdrawn at different time intervals by means of immersion tube filter. One ml from the sample was pipetted and diluted to 25 ml of distilled water for the spectrophotometric analysis of the drug at 245 nm¹². The samples withdrawn were replaced by equal volumes of fresh solution of the dissolution media having the same temperature and the appropriate correction was made . Experiments were carried out in duplicates, from which the mean values were calculated. Figures 1-7 illustrate the dissolution behaviour of Chlordiazepoxide coprecipitated with different carriers and in different dissolution media investigated as well as the control.

Differential thermal analysis studies:

Certain weights of 1:1 drug: carrier coprecipitate systems were used for differential thermal analysis studies using 1090 instrument. All samples were run at a temperature range between 30-400 C° and at a scanning rate of 5° C/ minute. The instrument was calibrated using glass beads as a reference standard.

Effect of Coprecipitate Formation and Certain Non-ionic Surfactants on Chlordiazepoxide Release from Capsules.

RESULTS AND DISCUSSION

Figures 1, 4 and 7 show the dissolution profiles of chlordiazepoxide release from its coprecipitates with PEG 4000, PVP 44000 and α -CyD in 0.1 N HCl as a dissolution medium. PVP shows maximum release of the drug in the ratio of 1:3 while 1:1 and 1:7 ratios are nearly equal in their release (Fig 1.) The same findings are observed in case of PEG 4000 coprecipitates, Fig.4 with the exception that 1:7 coprecipitates attain higher release than 1:1 ratio. In case of α -CyD coprecipitates the 1:7 ratio attains the highest release percent of the drug, Fig.7

It is obvious that the release of the drug from the prepared coprecipitates is generally higher than the release from the control. This can be attributed to the explanation proposed by Chiou and Riegelman¹³ as follows: (a) the reduction of particles to the molecular and/or colloidal size; (b) possible solubilization of the carriers; (c) the absence of aggregation and agglomeration between fine particles and (d) increased wettability and dispersibility of the drug with dissolution medium.

It has been shown that 1:3 coprecipitates of the investigated carriers attain the highest release of the drug up to 100% release within 30 minutes (Figs, 1, 4 and 7). The initial increase of the dissolution rate of Chlordiazepoxide in the 1:3 ratio could be explained in terms of the dispersion effect of the carriers¹⁴.

The increase in the dissolution rate of the drug on using PVP 44000 as a carrier would be due to the formation of a very highly soluble complex or might be due to the formation of the amorphous form of the drug.

Table 1 illustrates the T50 and T80% of Chlordiazepoxide from the investigated coprecipitating agents. It is clear that the coprecipitate of the drug α -CyD, 1:7 is the fastest one concerning T50 and T80%. As regards to the effect of PEG 4000 and PVP 44000 in enhancing the dissolution rate of the drug in the 1:3 coprecipitate, it is clear that the former is more efficient than the latter.

The effect of 0.1%W/V Brij 35 & 0.1%W/V Eumulgin C1000 on the dissolution rates of the drug from the prepared coprecipitates was also investigated (Table 2). Chlordiazepoxide: PEG 4000 coprecipitate 1:3 containing 0.1% W/V Brij 35 in the dissolution medium represent the least T50 and T80% comparatively, hence the fastest dissolution rate of the drug, followed by the same preparation but containing 0.1 W/V Eumulgin C1000 in the dissolution medium. The high dissolution rate of the drug from PEG 4000 and PVP 44000 coprecipitates may be due to the possibility of water-soluble complex formation between the drug and PEG 4000 and PVP 44000¹⁵.

TLC examination of the investigated coprecipitates confirms the possibility of complex formation between the drug with PEG 4000 and PVP 44000 as two spots were separated from the coprecipitate sample on TLC plates. One spot has the same R_f value as for the drug (0.81) and another spot at the base line. This indicates that a fraction of the drug occurs free while the other fraction occurs as a complex with PEG 4000 and PVP 44000. The ratio of both fractions depend mainly upon the ratio of the coprecipitating agent to that of the drug in the preparation. These findings are also confirmed by the IR analysis of the drug and the investigated coprecipitating agents, Fig.8. The complex formed between the drug with PEG 4000 and PVP 44000 is confirmed by: (a) in IR-spectrum, the band characteristic for N-H stretching at 3400-3200 cm^{-1} showed a distinct shallowing due to its

Effect of Coprecipitate Formation and Certain Non-ionic Surfactants on Chlordiazepoxide Release from Capsules.

involvement in intermolecular hydrogen bonding with the polymer molecule (b) the IR-spectrum of PVP 44000 showed no noticeable change when precipitated with the drug except that the band at 1670 cm^{-1} characteristic for the carbonyl group stretching became deeper and appeared at 1660 cm^{-1} to 1640 cm^{-1} which is probably due to hydrogen bonding (c) the O-H stretching band of PEG 4000 at $3500\text{-}3300\text{ cm}^{-1}$ showed distinct shallowing also due to hydrogen bonding .

Another mechanism proposed by Sekikawa et al¹⁶ states that the drug in the coprecipitate is not in the crystalline form due to the inhibitory effect of PVP on the crystallization of the drug PVP solution¹⁷ or might be due to the formation of the amorphous form of the drug. PEG 4000 and α -CyD coprecipitates gave higher dissolution rates than those of PVP 44000. This effect may be due to finer dispersion than the increase in the wettability of Chlordiazepoxide. Ghanem et al¹⁸ proposed that the solubility of sulfamethoxazole in aqueous solutions of sugars was increased slightly only with those sugars having free carbonyl group.

The coprecipitation method, which has been widely tried using ethanol might hardly be used to obtain inclusion compounds of the drug with α -CYD in the solid powdered form. Following Hayashils¹⁹ patent, ethanol was used as a solvent but the inclusion compounds were not obtained for all non-steroidal anti-inflammatory drugs with cyclodextrins. The solvent themselves such as alcohols, benzene, n-heptane and cyclohexane were considered to be included in the cavities of the cyclodextrins^{20,21} and thus the inclusion compounds of the drugs might hardly be obtained from these solvents. Thus on using ethanol as a coprecipitating solvent with the drug and the

α -CyD, the latter is no longer considered as a complexing agent for the drug, yet it is considered as a coprecipitating agent. The last findings were more confirmed by the IR spectrum of the α -CyD-drug coprecipitates (Fig.8).

Figs. 2,3 show the dissolution profiles of Chlordiazepoxide release from its coprecipitates using PEG 4000 and PVP 440000 in the presence of 0.1% W/V Brij 35 in the dissolution medium. Generally the presence of the surfactant in the dissolution medium leads to an increase in the drug release from the control and the prepared coprecipitates. The amount of the drug released reached to 100% within 10 minutes especially on using drug: PEG 4000 in the ratio of 1:3. In case of PVP 44000, 1:1 ratio attains maximum dissolution rate.

The dissolution profiles of the drug released from its coprecipitates using the previously mentioned carriers in the presence of 0.1% W/V Eumulgin C1000 in the dissolution medium are shown in Figs. 3 and 6. The dissolution rate from the coprecipitate is faster than that of the drug alone especially at ratios of 1:3 (PEG coprecipitate) and 1:7 (PVP coprecipitate). The presence of surfactants in the dissolution medium in concentrations above their CMC values leads to a decrease in the surface tension and consequently increases the wettability of the solid drug which enhances its dissolution rate. Furthermore, the solvent power of the micelles present in the dissolution medium will be responsible for the increase in the solubility of this poor water soluble drug in the dissolution medium, hence dissolution rate enhancement.

UV, IR and TLC investigations were done in order to check any decomposition of the drug throughout the work and to figure out whether the coprecipitating agents used interfere in

Effect of Coprecipitate Formation and Certain Non-ionic Surfactants on Chlordiazepoxide Release from Capsules.

the spectrophotometric assay of the drug. The drug is found stable throughout the work and all the additives investigated did not interfere with the spectrophotometric assay of the drug nor they made any shift in the maximum absorbance.

TLC examination of Chlordiazepoxide coprecipitate with α -CyD using fluorescent silica gel and chlorform-methanol (10:1) as a developing system revealed that the coprecipitate resolved into one spot with R_f value of 0.81 which equals that of the free drug, indicating that no complex is formed between α -CyD and Chlordiazepoxide.

DTA investigations were carried out in order to investigate the thermal behaviour of the drug and its prepared coprecipitates. The thermograms of Chlordiazepoxide coprecipitates are shown in Fig.9, illustrating the differential thermal reactions relevant to each product. Chlordiazepoxide on thermal treatment undergoes one main endothermic reaction, starting at 230 C and ending at 248 C. PVP on DTA has an endothermic reaction, starts at 135 C and ends at 145 C with a peak at 140 C. Endothermic curve peaks are caused by fusion or melting transition. The DTA of Chlordiazepoxide coprecipitates with PVP prepared by the solvent method declare that it has two clear flattened endothermic reactions. One starts at 80°C and ends at 140°C with a peak at 130 C while the second starts at 210 C and ends at 238 C with a peak at 225 which gave a complex endothermic peak in this temperature range.

The DTA of PEG 4000 shows a characteristic endothermic reaction starting at 45 C, ending at 72 C with a maximum peak at 60°C .

A broad exothermic reaction starting at 135 C also occurs. The coprecipitates prepared by the solvent technique show an endothermic reaction nearly similar to that of PEG 4000. A second exothermic reaction starts at 145 C, ends at 195 C with its peak at 160 C. A masking effect has been noted for second endothermic peak of the drug in this temperature region. Apparently a complex has been formed between the drug and PEG 4000²². Thus, it can be concluded that the drug interacts physically with PEG 4000 and PVP 44000 on coprecipitation.

Effect of Coprecipitates Formation and Certain Non-ionic Surfactants on Chlordiazepoxide Release from Capsules.

Table 1. Data relevant to T50 and T80 % of Chlordiazepoxide and its coprecipitates in 0.1 N HCl.

Type	Ratio drug:carrier	T50% (Min)	T80% (Min)
Control	---	9.5	>120
PEG Coprec.	1:3	7.5	12
PVP Coprec.	1:3	12	18
α -CyD Coprec.	1:7	4.00	6.5

Table 2. Data relevant to T50 and T80% of Chlordiazepoxide and its coprecipitates in 0.1 N HCl containing 0.1% W/V surfactant concentration.

Type	Ratio drug:carrier	0.1%W/V In dissolu- tion media	T50% (Min)	T80% (Min)
Control	---	Brij 35	8.5	20
PVP Coprec.	1:1	Brij 35	5	15
PVP Coprec.	1:7	Eumulgin C1000	5	20
Control	---	Eumulgin C1000	9	35
PEG Coprec.	1:3	Brij 35	3	5
PEG Coprec.	1:3	Eumulgin C1000	3.5	7.5

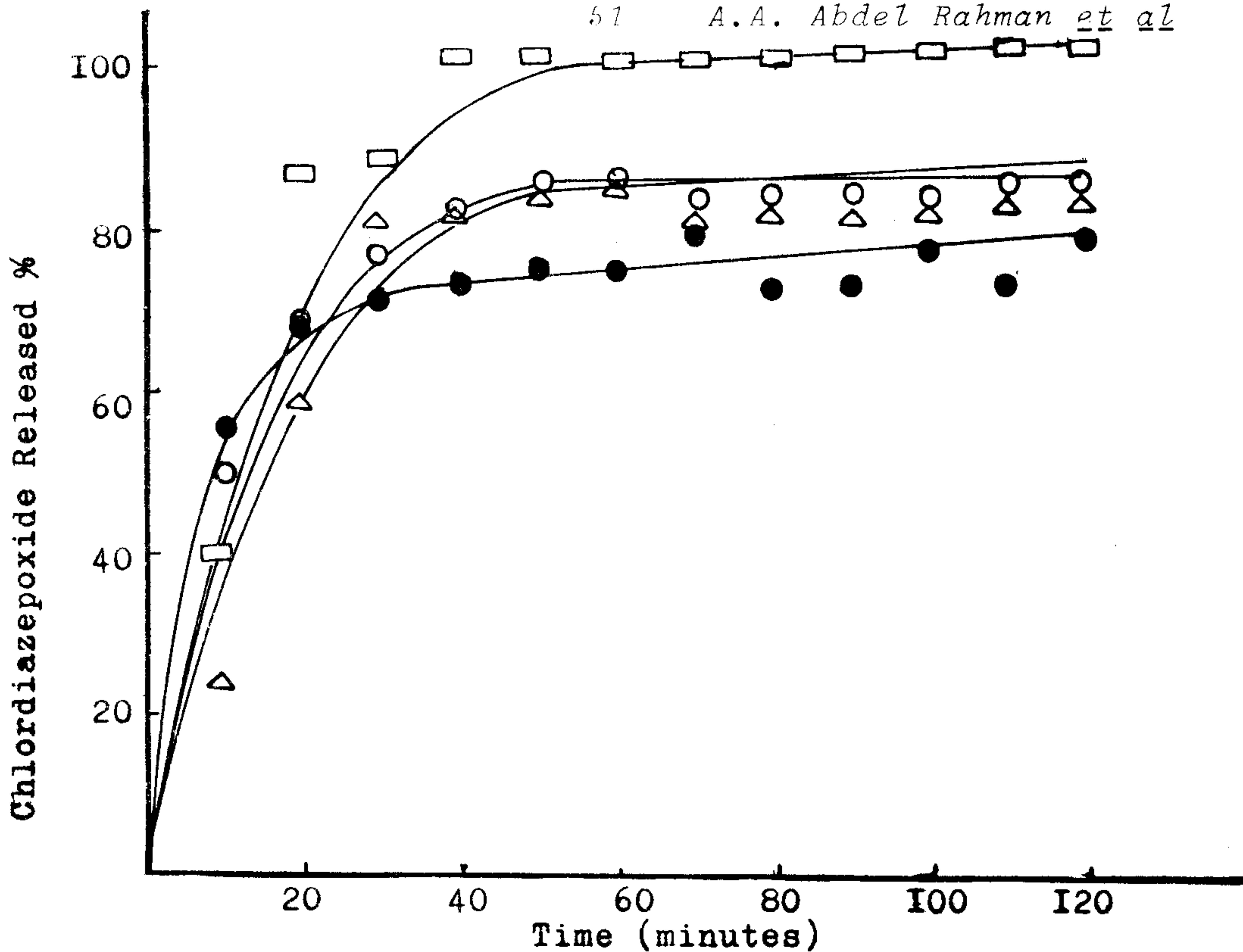


Fig.(1): Release of Chlordiazepoxide from its coprecipitates using PVP as a coprecipitating agent in 0.1 N HCl at 37 C
 Key: ● control ○ 1:1 coprecipitate □ 1:3 coprecipitate
 △ 1:7 coprecipitate

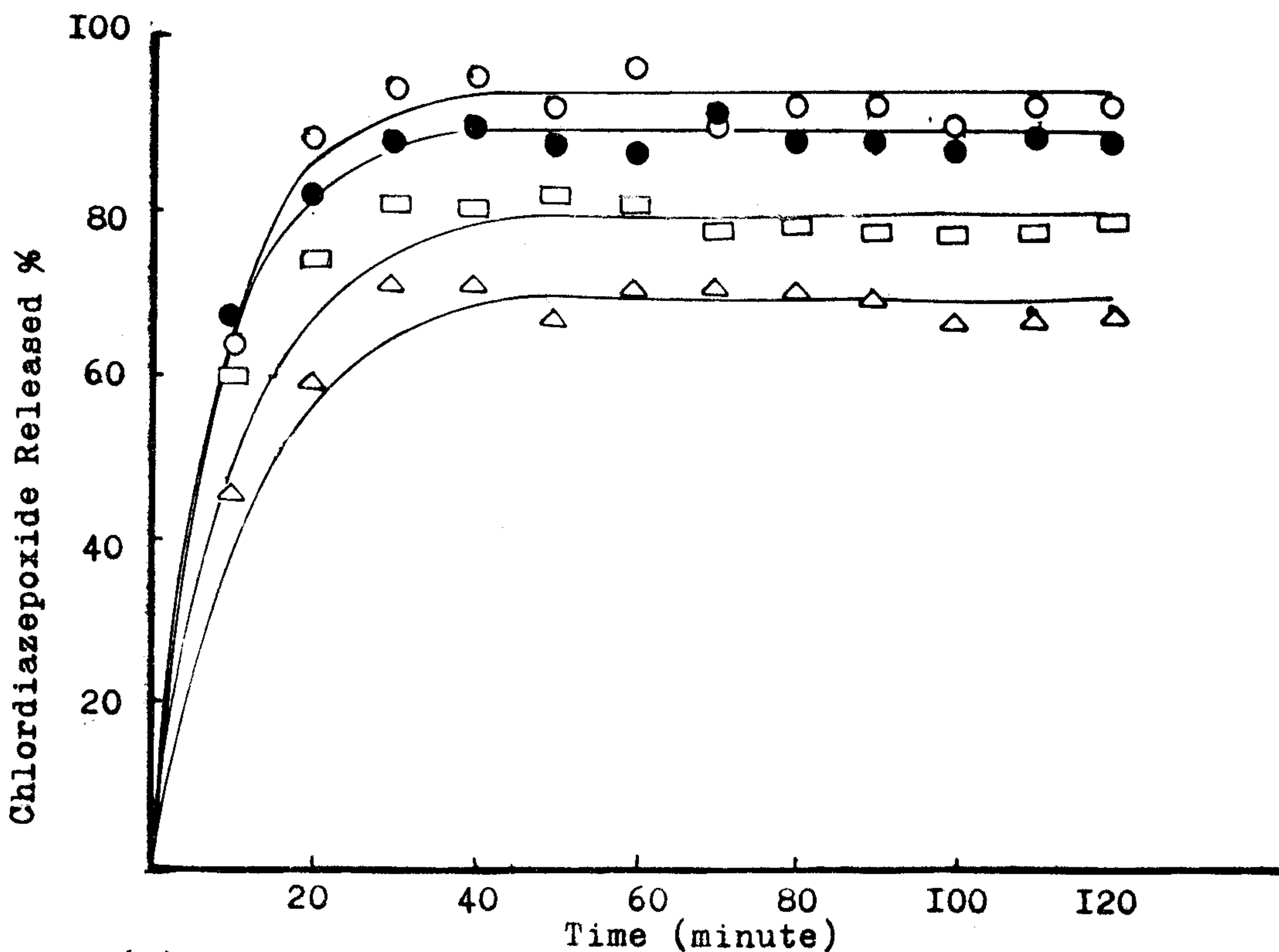


Fig.(2): Release of Chlordiazepoxide from its coprecipitates using PVP in 0.1 N HCl containing 0.1%w/v Brij 35
 Key: The same as Fig.(1)

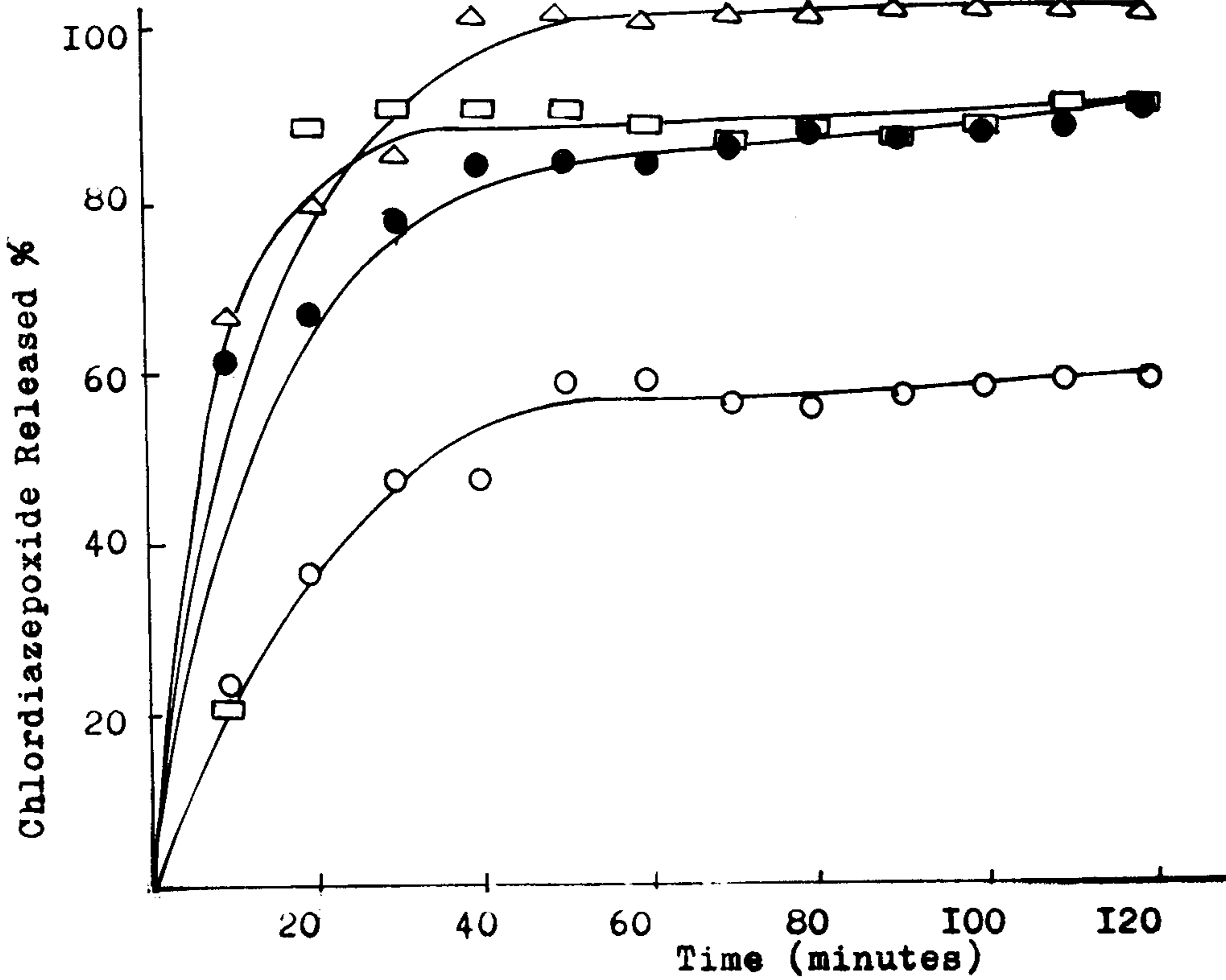


Fig.(3): Release of Chlordiazepoxide from its coprecipitates using PVP in 0.1 N HCl containing 0.1%w/v Eumulgin CI000
Key: The same as Fig.(I)

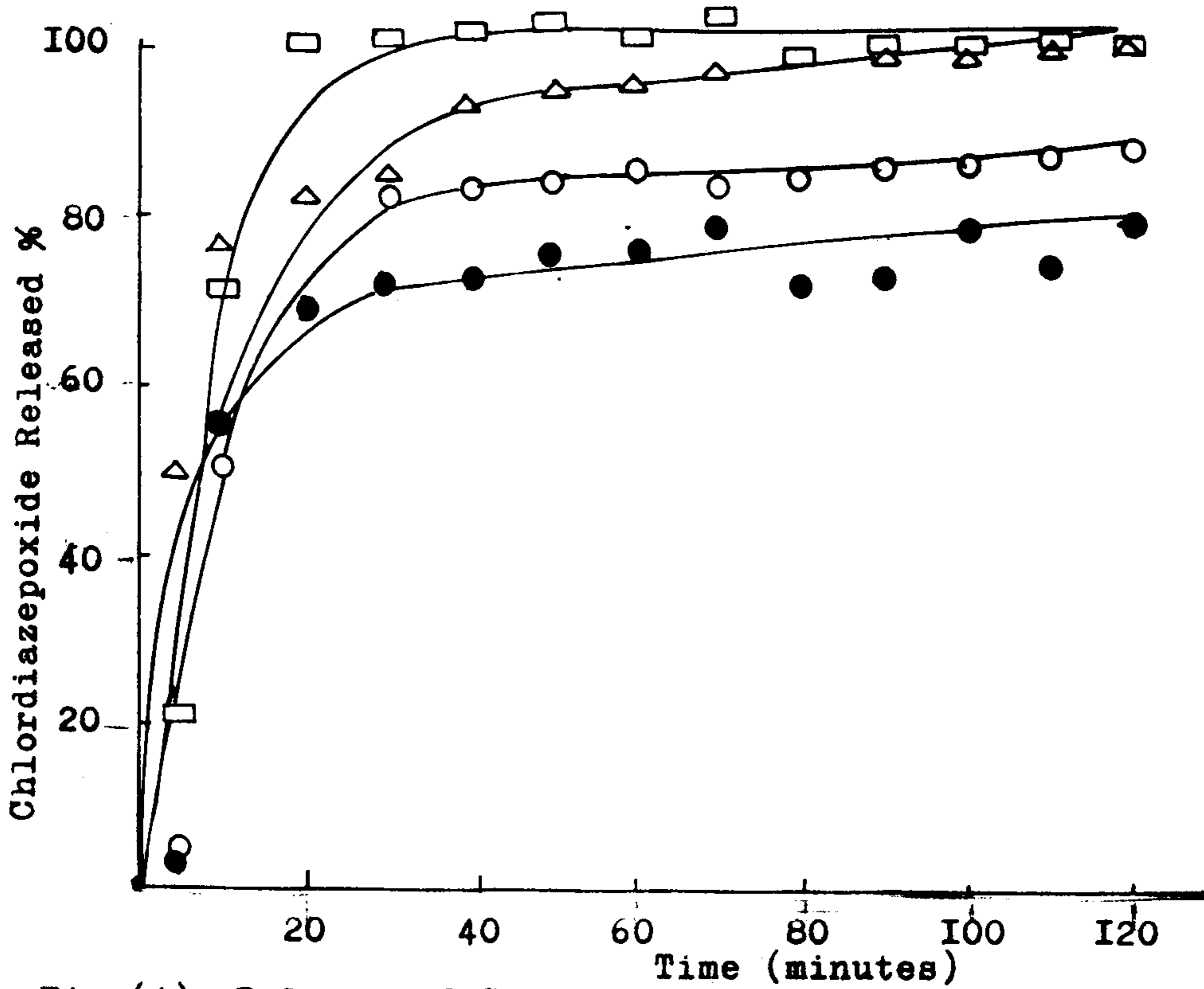


Fig.(4): Release of Chlordiazepoxide from its coprecipitates using PEG 4000 in 0.1 N HCl
Key: The same as Fig.(I)

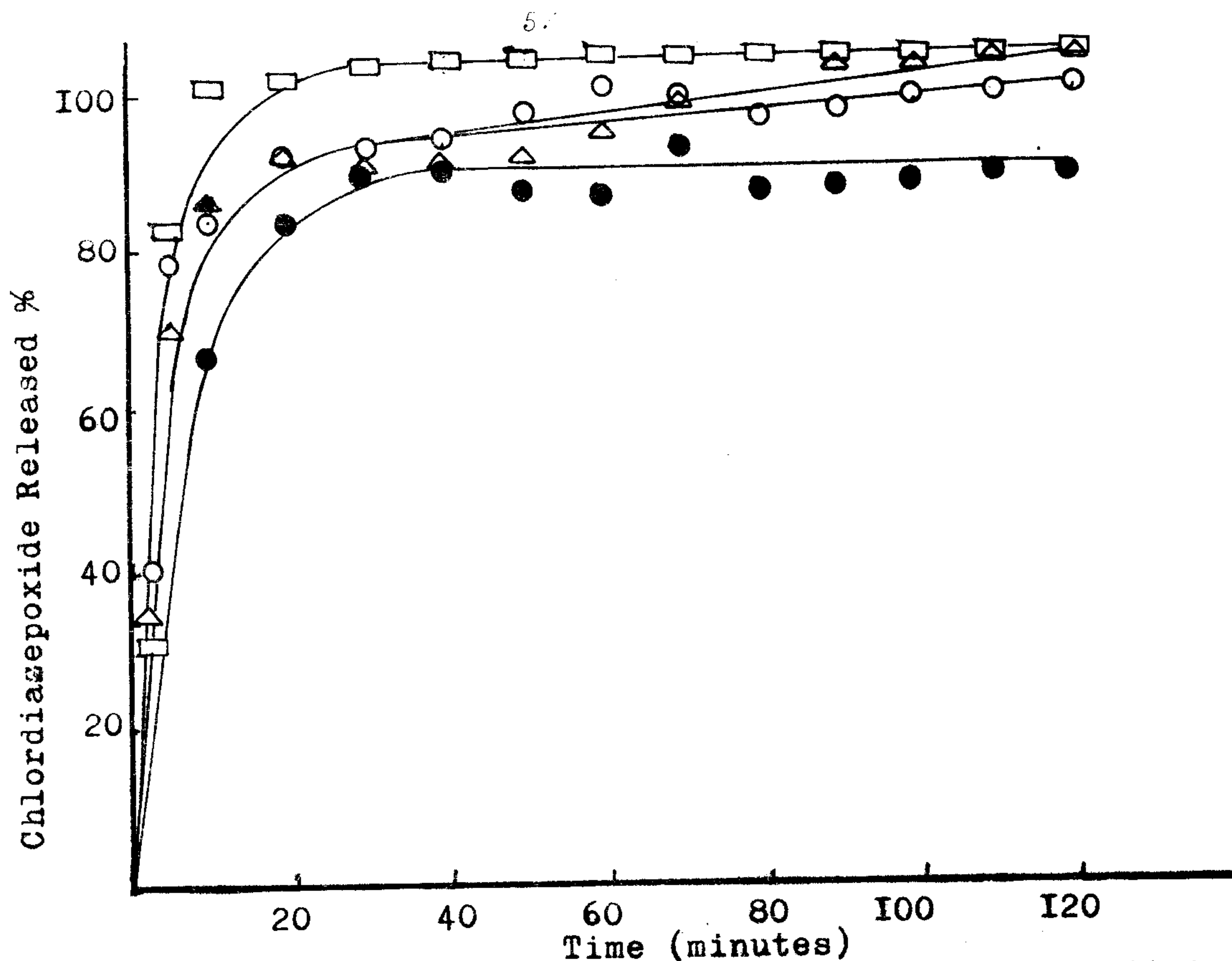


Fig.(5): Release of Chlordiazepoxide from its coprecipitates using PEG 4000 in 0.1 N HCl containing 0.1%w/v Brij 35
Key: The same as Fig.(I)

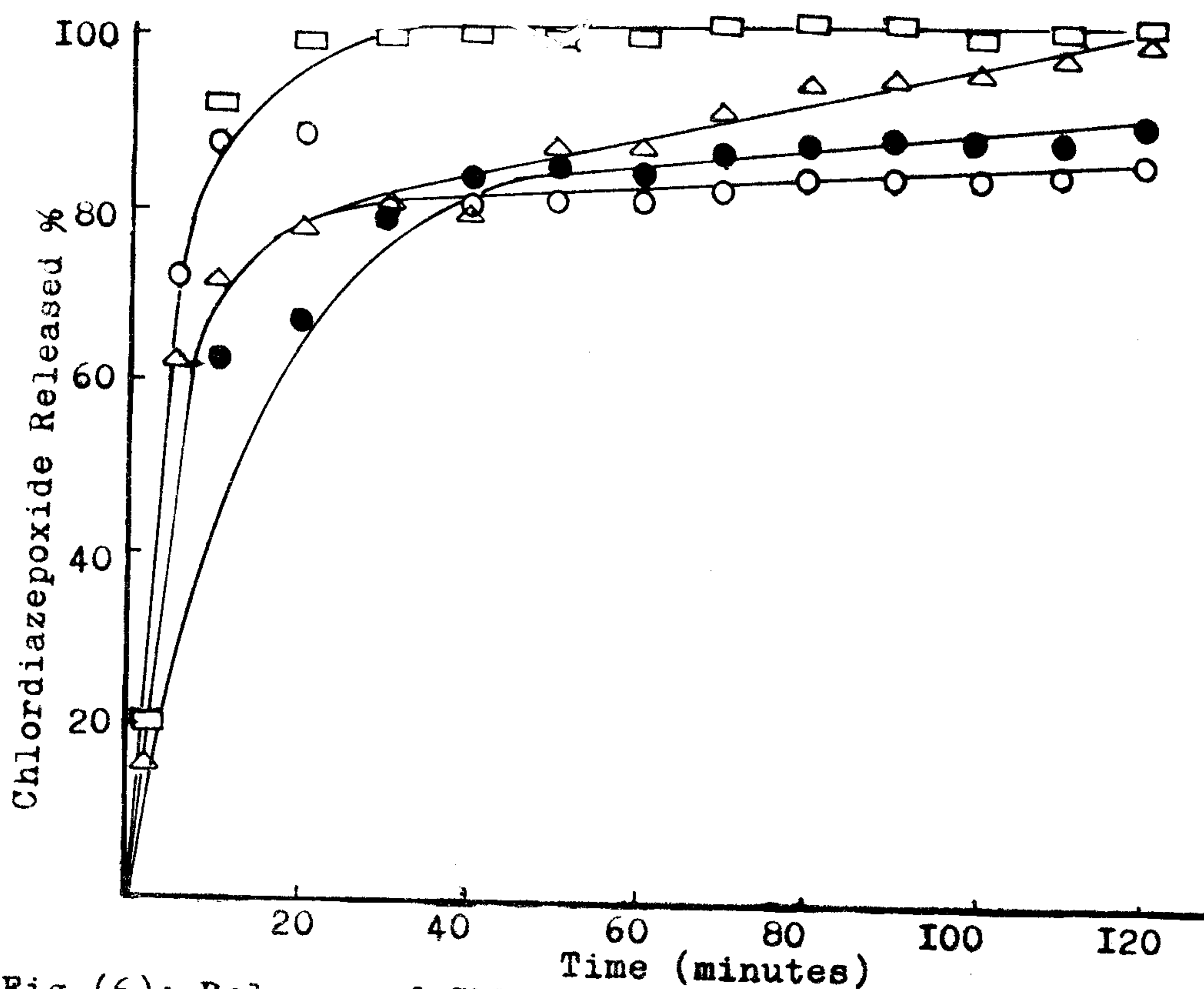


Fig.(6): Release of Chlordiazepoxide from its coprecipitates using PEG 4000 in 0.1 N HCl containing 0.1%w/v Eumulgin
Key: The same as Fig.(I)

Effect of Coprecipitate Formation and Certain Non-Ionic Surfactants on Chlordiazepoxide Release From Capsules.

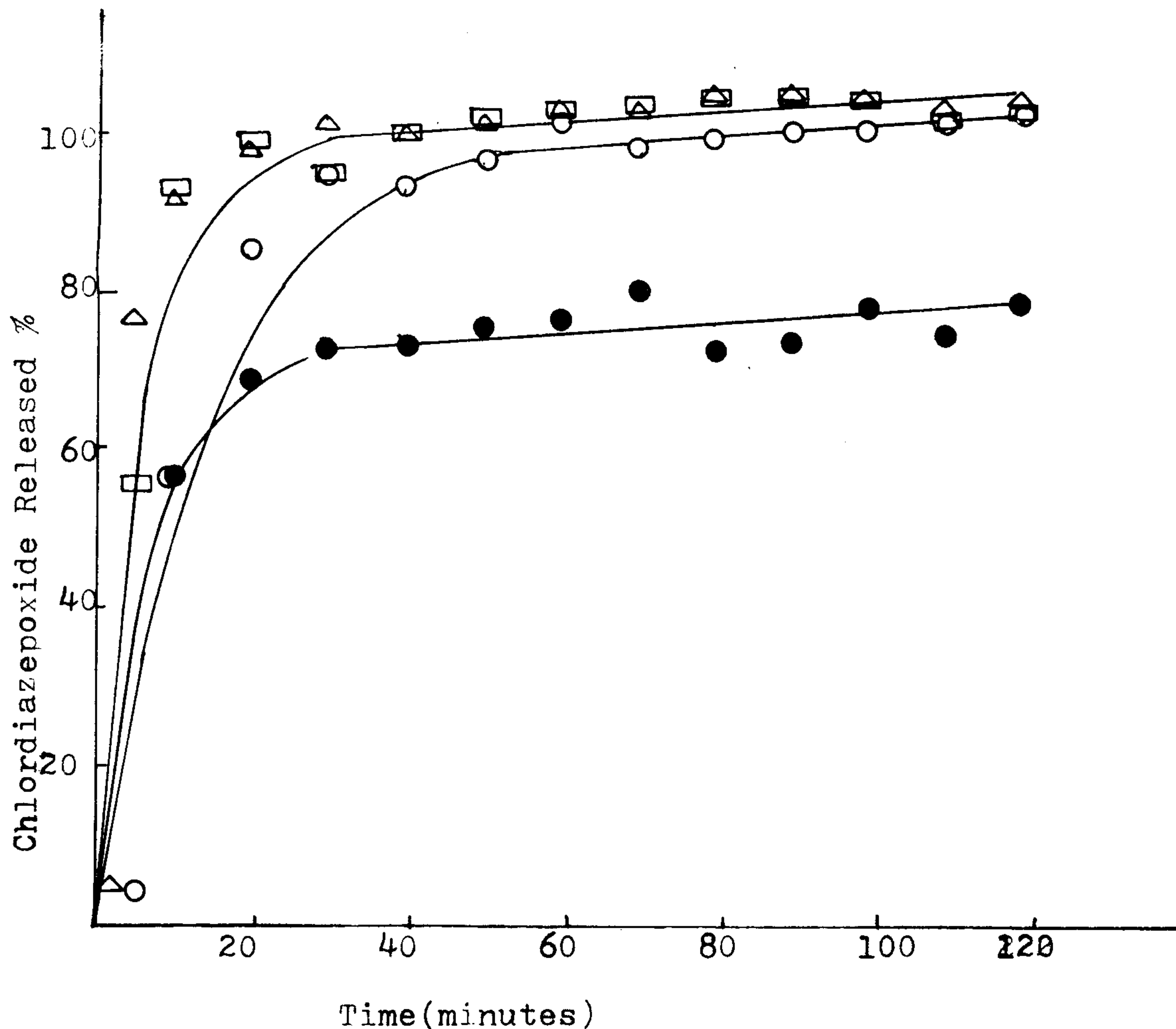


Fig.(7): Release of Chlordiazepoxide from its coprecipitates using α -Cyclodextrin in 0.1 N HCl
Key: The same as Fig.(1)

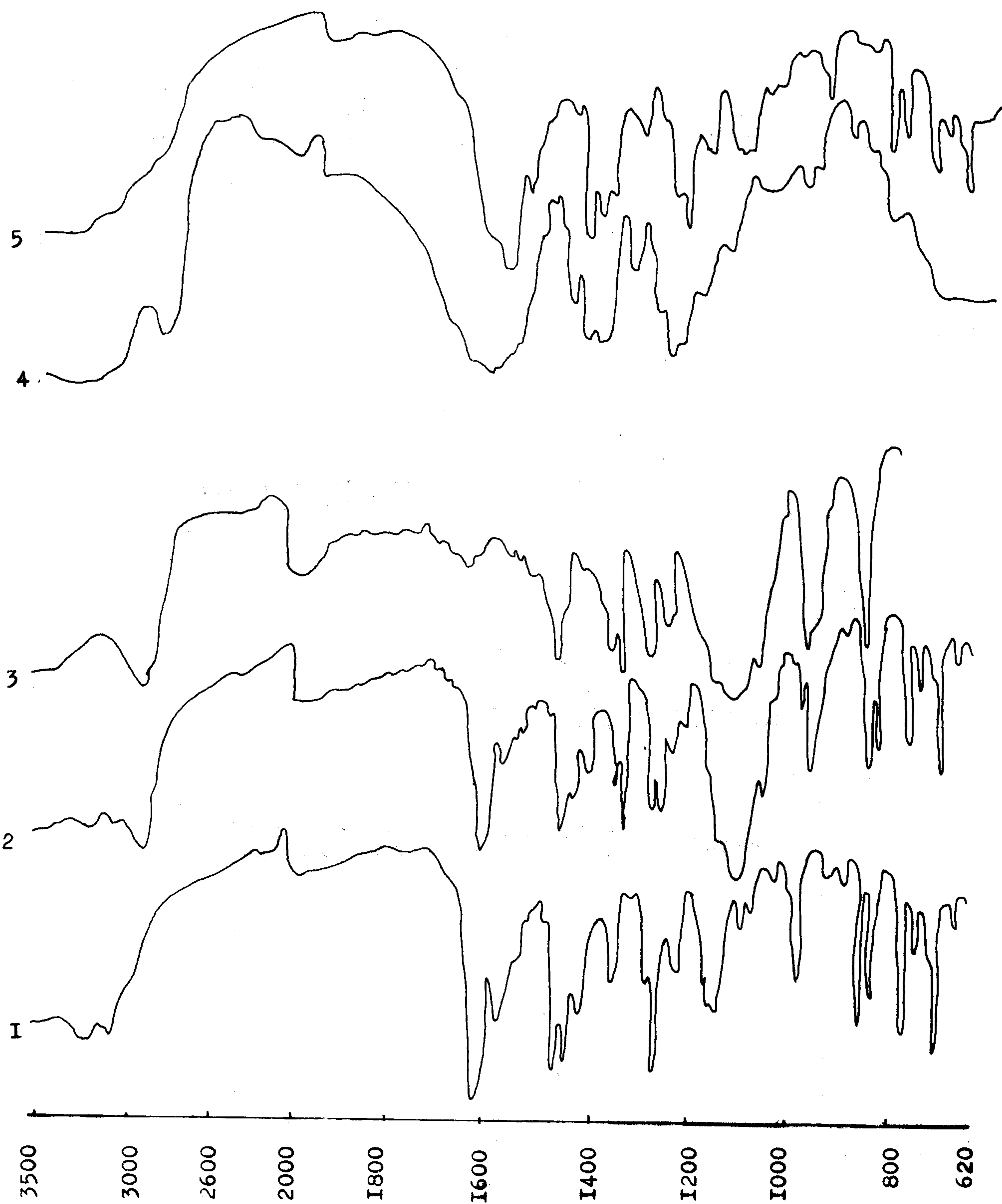


Fig.(8): Effect of PVP 44000 and PEG 4000 on the IR spectrum of Chlordiazepoxide

Key: 1-drug alone 2-drug/PEG coprecipitate 3-PEG alone
4-PVP alone 5-drug/PVP coprecipitate

Effect of Coprecipitate Formation and Certain Non-Ionic Surfactants on Chlordiazepoxide Release From Capsules.

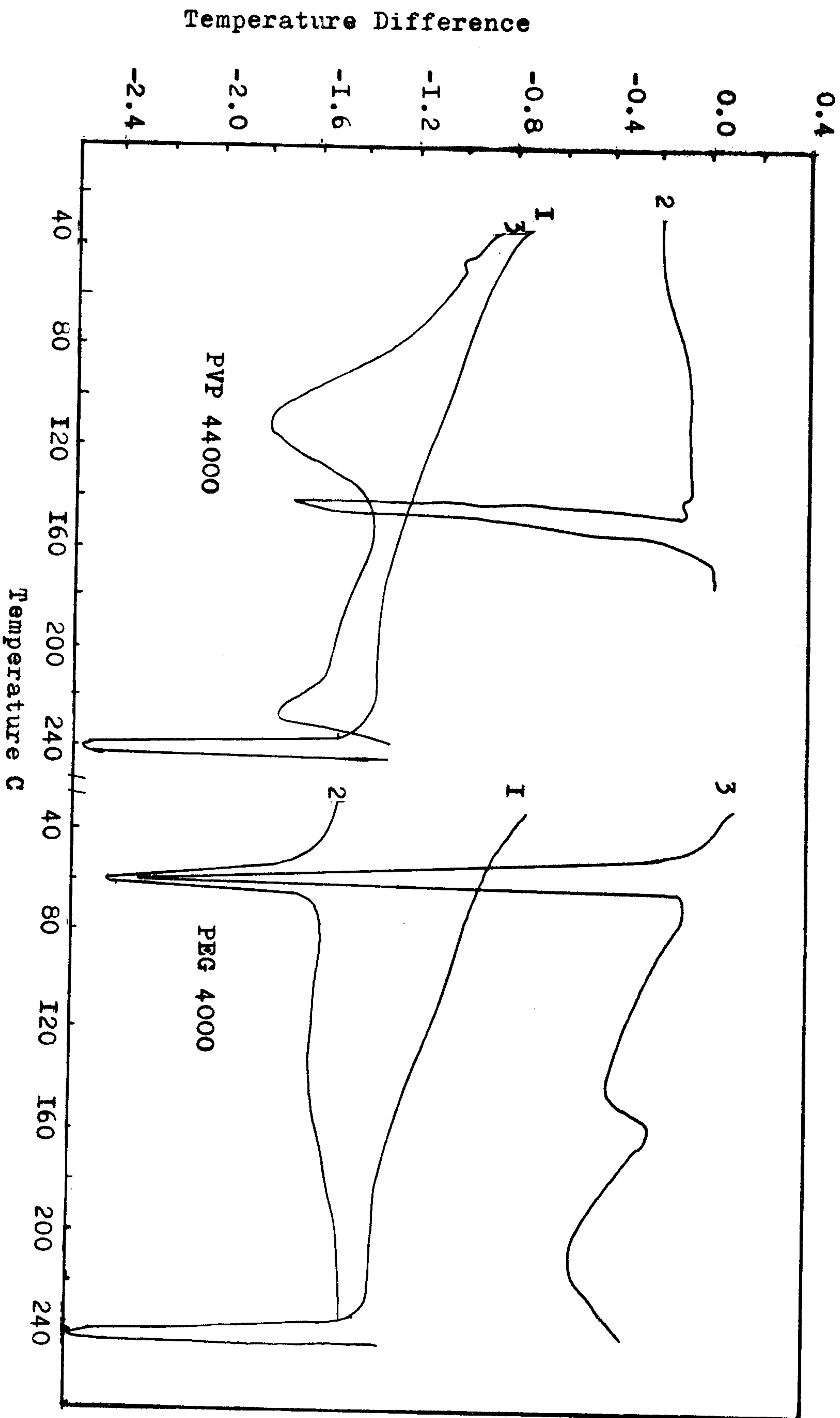


Fig. (9): DTA Thermograms of Chlordiazepoxide and its coprecipitates
Key: 1-Chlordiazepoxide alone 2-Carrier alone 3-Drug, Carrier coprecipitate I.1

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تأثير منشطات سطحية غير متأينة على اتاحة
الكلور ديازيبوكسيد من متراسباته

احمد السيد ابو طالب - على عبد الظاهر عبد الرحمن - ايمان مصطفى سامى
قسم الصيدلة الصناعية - كلية الصيدلة - جامعة اسيوط

استخدمت طريقة الاذابة لتحضير متراسبات الكلورديازيبوكسيد الذى لا يذوب
فى الماء مع بعض الحوامل وذلك للاسراع من معدل اتاحة هذا العقار.
ولقد كانت الحوامل المستخدمة هى عديد الايثلين جليكول ٤٠٠٠ ، عديد
الفيثيل بيروليدون ٤٤٠٠٠ ، الفا سيكلودكسترين .
ولقد وجد ان اسرع معدل للاتاحة للعقار فى متراسبات الكلورديازيبوكسيد
مع الفاسيكلودكسترين وذلك فى وسط ار . عيارى حامض الهيدروكلوريك كوسط
للاتاحة .

كما درس تأثير وجود بعض منشطات السطح غير المتأينة مثل ميرج ٣٥
والأمليجين س ١٠٠٠ على اتاحة الكلورديازيبوكسيد من متراسباته المحضرة .
ولقد وجد ان منشطات السطح غير المتأينة التى درست فى تركيز ار / وزنا
الى حجم اسرعت من معدل اتاحة الدواء خاصة عندما استخدمت عديد الايثيلين
جليكول كحامل .
ولقد درس ايضا التفاعل بين العقار والمتراسبات المدروسة وذلك باشعة الطيف
فوق البنفسجية وتحت الحمراء وكروماتوجرافيا الطبقة الرقيقة وكذلك بالتحليل
الحرارى التفاضلى .
ولقد اثبتت هذه الدراسة ان هناك تفاعل طبيعى بين العقار والحوامل التى
استخدمت والتى ثبت انها لا تتداخل مع تحليل الدواء بالاشعة فوق البنفسجية وايضا
لا يغير من موجة امتصاصه لتلك الاشعة .

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