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IMPROVEMENT OF DISSOLUTION BEHAVIOR OF TEMAZEPAM

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ABSTRACT

The interaction between temazepam and ß-cyclodextrin (ß-CD) or hydroxypropyl ß-cyclodex rin (HPß-CD) was studied in aqueous solution. The attempets made to obtain temazepam-cyclodextrin complexes in the solid state through freeze drying or slow evaporation under nitrogen of equimolar solutions of temazepam-CD failed to separate these inclusion compounds. On the other hand, co-grinding of temazepam with ß-CD or HPß-CD although showed no evidence of formation of inclusion complexes, yet gave rise to very fast dissolution compared to non-treated temazepam or its physical mixtures with CD. Furthermore, the co-grinding of temazepam with Avicel PH 101 (microcrystalline cellulose) improved temazepam dissolution to nearly the same extent as those of ß-CD or HPß- CD.

INTRODUCTION

Temazepam is a member of benzodiazepines widely used as anticonvulsants, sedatives and hypnotics in psycotherapy. However, temazepam has both poor aqueous solubility and stability [1]. Recently, it has become increasingly clear that the rate of absorption of benzodiazepines from the gut after oral administration is formulation dependent. When given in solid forms, as tablets or capsules, dissolution of the drug is slow and the drug is therefore poorly available to the gut mucosa for absorption [2]. Obviously, a fast dissolving form of benzodiazepines with high aqueous solubility is desirable for rapid absorption in oral benzodiazepine therapy particularly in the treatment of acute convulsive attacks. Formation of inclusion complexes of many members of benzodiazepines with cyclodextrins were investigated in order to improve their dissolution and availability [3-5]. Through inclusion complexation or molecular encapsulation, an increased aqueous solubility and chemical or physical stability as well as an improved bioavailability and decreased gastrointestinal side effects could be achieved [3]. In contrary to the other members of benzodiazepines, the literature gave nothing about such treatment for temazepam.

In the present work, the interaction of temazepam with ß-CD and HPß-CD in water was investigated. Attempts were also made to obtain solid complexes of temazepam with CD by Freeze drying, slow evaporation under nitrogen and co-grinding. In addition, the effect of co-grinding with CD as well as microcrystalline cellulose on the dissolution characteristics of temazepam was explored.

Materials and Methods

Materials

Temazepam (Fabbrica Italiana Sintetici), ß-cyclodextrin and hydroxypropyl ß-cyclodextrin (Roquette, France), Avicel PH 101; microcrystalline cellulose (FMC Corporation, Pensylvania, 19061, USA).

Methods

Solubility studies

Solubility measurements were carried out according to the method of Higuchi and Conners [6]. Excess amounts of temazepam were added to aqueous solutions containing various concentrations of ß-CD and HPß-CD and were vigorously shaken at 20°C during 24 hours. Filtered aliquots were adequately diluted and spectrophotometrically assayed for their temazepam content.

Freeze drying

The solutions of equimolar mixture of temazepam with ß-CD and HPß-CD were freeze dried using a tray freeze dryer (DURA - DRY, FTS systems, INC. USA).

Co-grinding

Mixtures of temazepam and ß-CD (1:4 w/w) or HPß-CD (1:5 w/w) or Avicel PH 101 (1:3 w/w) were ground for 5 minutes using a small coffee mill (Moulinex, France).

Infrared absorption spectroscopy

It was carried out using a (Beckman, 4230, USA) spectrophotometer by KBr method.

Differential scanning calorimetry

The differential scanning calorimetry (DSC) was determined using a micro-differential scanning calorimeter. Peaks were recorded using a Beckman recorder. Samples were heated at a heating rate of 5°C / minute. The instrument was calibrated with an indum standard.

X-ray diffractometry

Powder X-ray diffraction patterns were measured using a Data MP Siemens D 500 diffractometer, Cu anode, voltage 35 kv, current 30 mA, scanning speed 2 degrees / minute.

Dissolution studies

A through flow cells apparatus, Dissotest C Y (Sotax A. G., C H - 4008, Basel, Switzerland) was used to study the dissolution of temazepam in distilled water (1000 ml) at 37°C. Ten mg of temazepam or an equivalent amount of the ground mixture (containing 10 mg of temazepam) was introduced in each cell. The pump was adjusted to permit a flow rate of 40 ml/minute. 1 ml samples were withdrawn through tubes with filter tips. They were suitably diluted and spectrophotometrically assayed for their temazepam content at 232 nm.

RESULTS AND DISCUSSION

Solubility studies

Figure 1 and Figure 2 show the phase solubility diagrams of temazepam in presence of ß-CD and HPß-CD respectively. They indicate that the apparent solubility of temazepam increased linearly with the concentration of cyclodextrins at constant temperature. These phase solubility diagrams are classified as type A_L [6]. The increase of the solubility of temazepam in the presence of cyclodextrins is considered to be mainly due to the formation of an inclusion complex although some unspecific interactions of the drug molecule with the hydroxyl groups may also contribute. Hydrogen bonding, Van der walls forces and hydrophobic interactions between the guest and the host molecules were among the binding forces contributing to the inclusion process [7,8]. However, the most important parameter which determines whether an inclusion complex can be obtained and how strong is this complex is the relative size of the guest molecule and host cavity [9].

The infrared spectroscopic absorption (IR) of the ground mixtures

of temazepam 1/Avicel 3, temazepam 1/ß-CD 4 and temazepam 1/HPß-CD 5 showed neither physical nor chemical changes compared to the physical mixtures having the same ratios.

Figure 3 shows the X-ray diffraction patterns of temazepam and its ground mixtures with Avicel (1:3), ß-CD (1:4) and HPß-CD (1:5). The observed decrease in the intensity of diffraction peaks is due to the reduction in crystallinity caused by co-grinding (10) but hallow pattern characterising the formation of amorphous inclusion compounds was not observed.

Figure 4 shows the thermograms of temazepam and its ground mixture with Avicel (1:3), ß-CD (1:4) and HPß-CD (1:5). The endothermic peak due to the fusion of temazepam crystals was still found after co-grinding excluding the formation of new inclusion compounds [11]. Reduction in crystallinity of the ground mixtures could also be deduced from the reduction in the area of temazepam endothermic peak in the order HPß-CD < ß-CD < Avicel.

Dissolution studies

Figure 5 shows the dissolution profiles of temazepam, ground temazepam in addition to the physical and ground mixtures with ß-CD. Ground temazepam showed slower dissolution than non-treated temazepam. This could be attributed to the aggregation of the fine particles of the ground temazepam [12]. On the other hand, the physical mixtures of temazepam or ground temazepam with ß-CD (1:4) showed faster dissolution properties than those of non-treated temazepam. This is mainly due to the better dissociation and less aggregation of temazepam in that case. Temazepam 1: ß-CD 4 ground mixture showed the fastest dissolution among this series.

Figure 6 shows the dissolution profiles of temazepam, ground temazepam in addition to physical and ground mixtures of temazepam 1/ HPß-CD 5. A similar picture to that of ß-CD was obtained with the fastest dissolution characteristics obtained via co-grinding.

Figure 7 shows the dissolution profiles of temazepam, ground temazepam in addition to physical and ground mixtures of temazepam 1/ Avicel 3. A similar influence of that of cyclodextrins was obtained once again.

Figure 8 compares the dissolution behavior of the ground mixtures of temazepam with Avicel (1:3), ß-CD (1:4) and HPß-CD (1:5). As it could be easily seen, the three additives improved the dissolution behavior of temazepam with little discrimination. This enhanced dissolution characteristics upon co-grinding is explained on the bases of the molecular behavior of the drugs. Drug molecules in the ground mixture are inclosed by the hydrogen bonding between cellulose or cyclodextrin molecules. All molecules of the drug could be released simultaneously from the ground mixture [10, 13]. In addition, the effect of the reduced crystallinity and increased wettability could not be omitted.

Attempts to obtain temazepam-cyclodextrin inclusion complexes

Several attempts were made to obtain solid complexes of temazepam-ß-CD or Pß-CD using co-evaporation under nitrogen, freeze drying and co-grinding of equimolar amounts of the drug and CD. Generally, no strong complex has been formed as proved by the IR, X-ray and DSC studies. This may be due to the unsuitability of the methods or due to the formation of weak complexes.

The latter assumption is more likely to occur since the stability constant values, calculated from the phase solubility diagrams according to Higuchi equation [6], were found to be 181 and 481 for tem-ß-CD and tem-HPß-CD complexes respectively. Similarly, Andersen and Bundgaard [3] failed to prepare solid complexes of some benzodiazepines. Uekama *et al* [4] stated also that α- and ß-CD did not yield solid complexes with some benzodiazepines. Accordingly, it could be concluded that temazepam molecule was not fit to the cyclodextrin cavity [9].

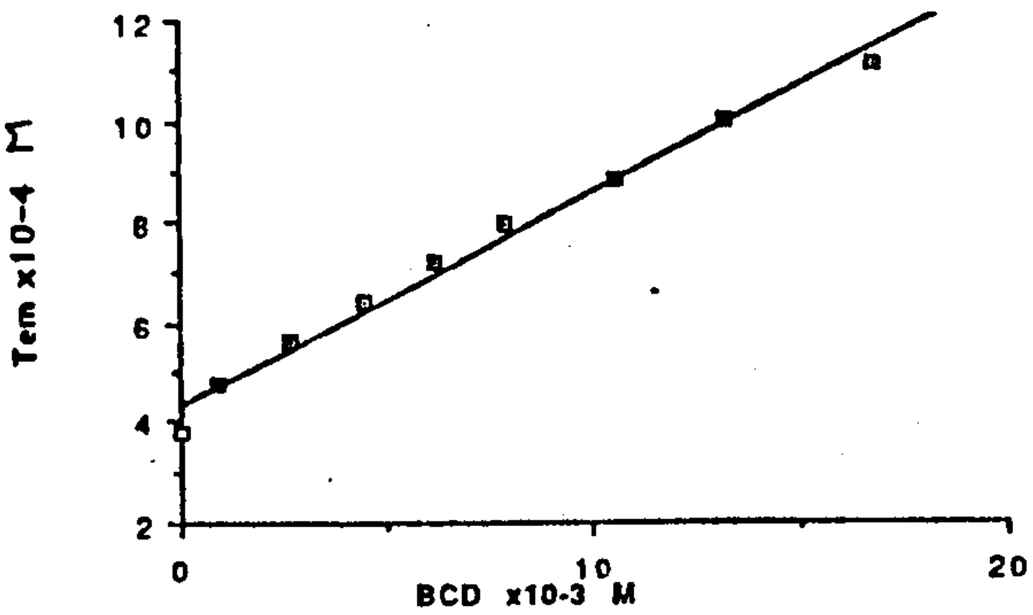

Fig. 1 : Solubility of temazepam as a function of B-CD in water at 20°C.

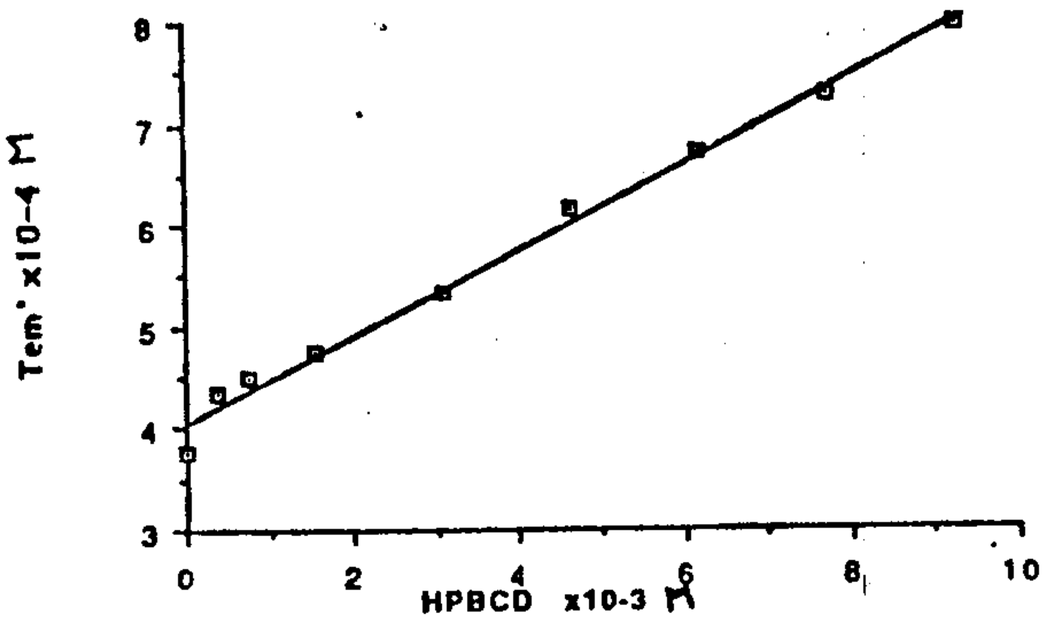

Fig. 2 : Solubility of temazepam as a function of HPß-CD in water at 20°c.

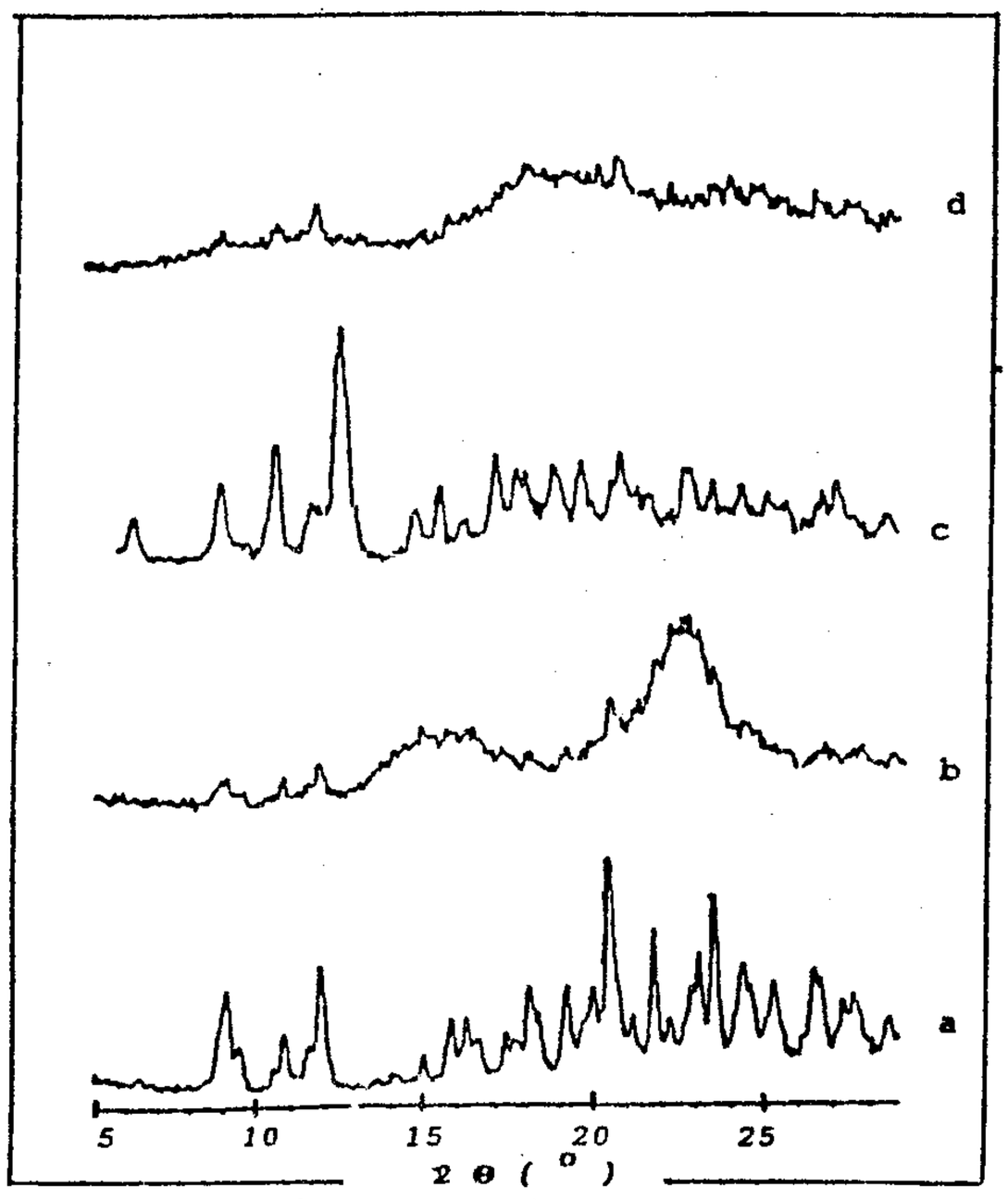

Fig. 3 : Powder X - ray diffraction patterns of temazepam and its ground mixtures.
a- temazepam
b- temazepam / Avicel
c- temazepam / ß-CD
d- temazepam / HPß-CD

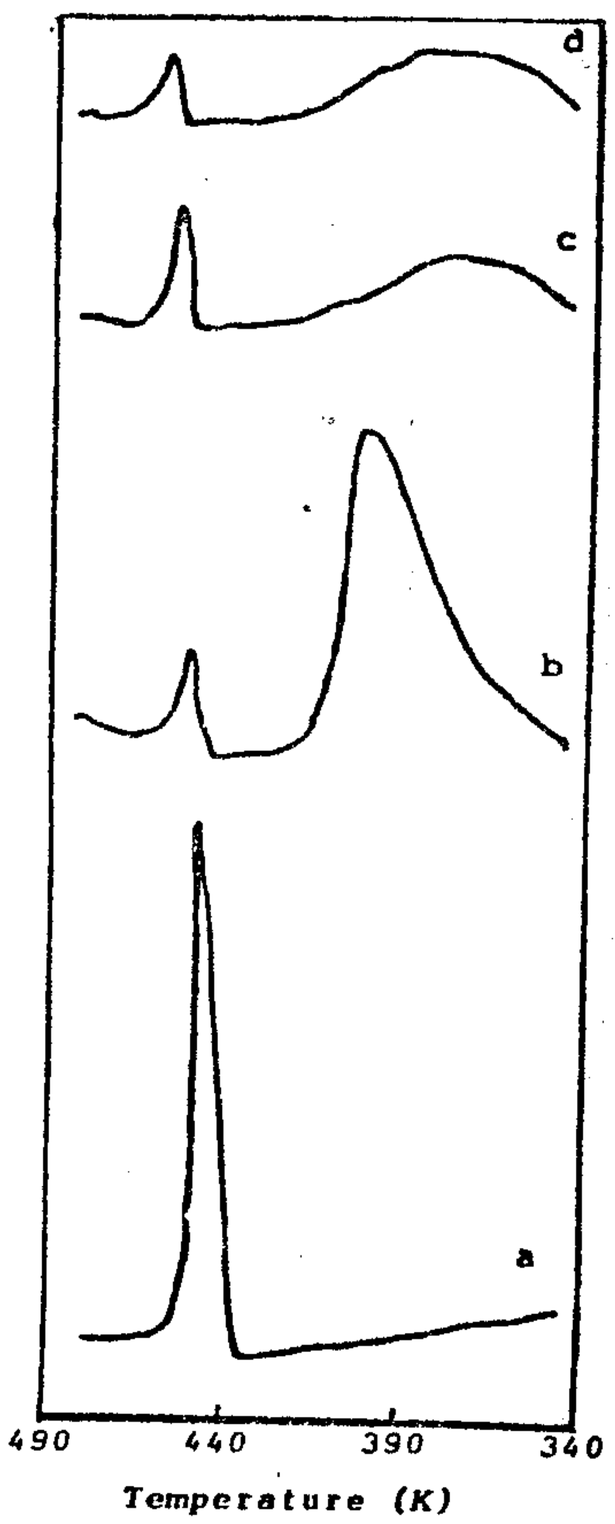

Fig. 4 : DSC thermograms of temazepam and its ground mixtures
a- temazepam
b- temazepam / ß-CD
c- temazepam / Avicel
d- temazepam / HPß-CD

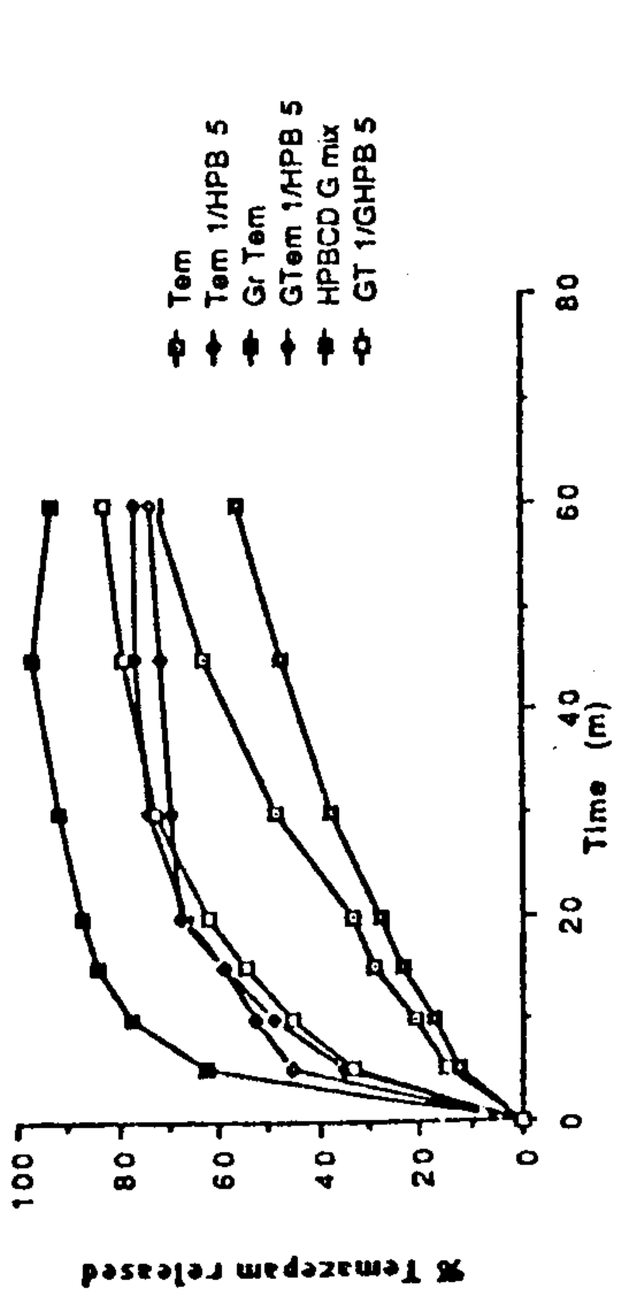

Fig. 6 Dissolution profiles of temazepam / HP8-CD systems.

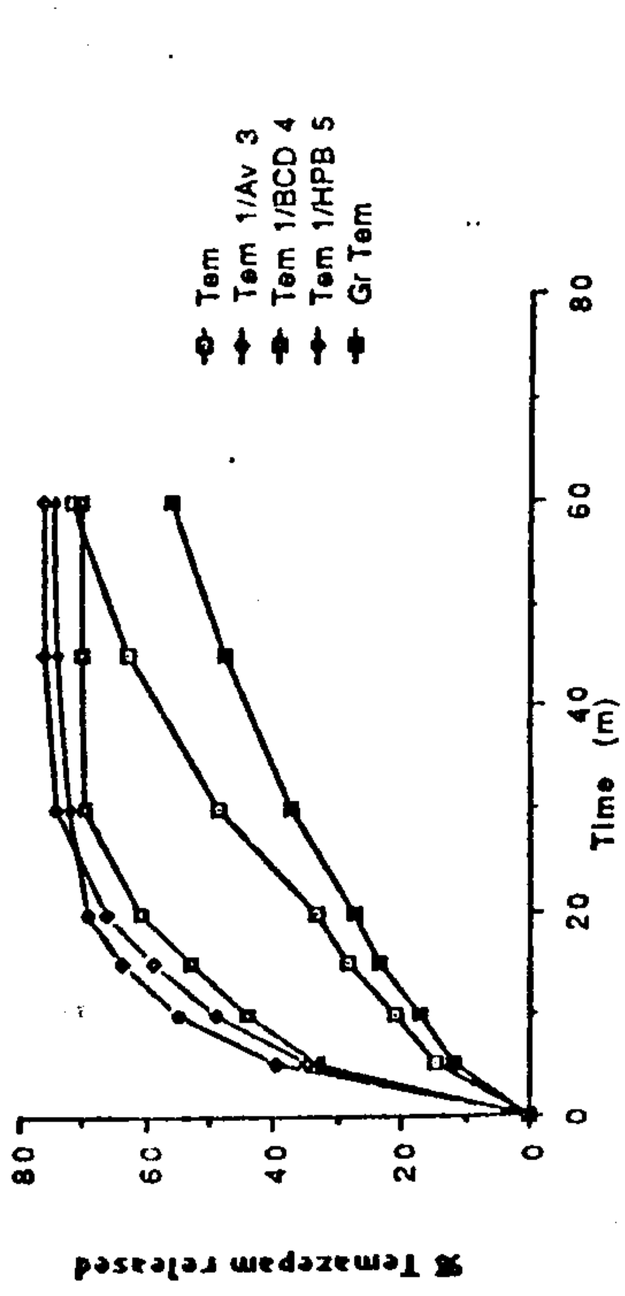

Fig. 8 : Dissolution profiles of ground temazepam (Gr tem), intact temazepam (Tem) and its ground mixtures with Avicel, 8-CD and HP8-CD.

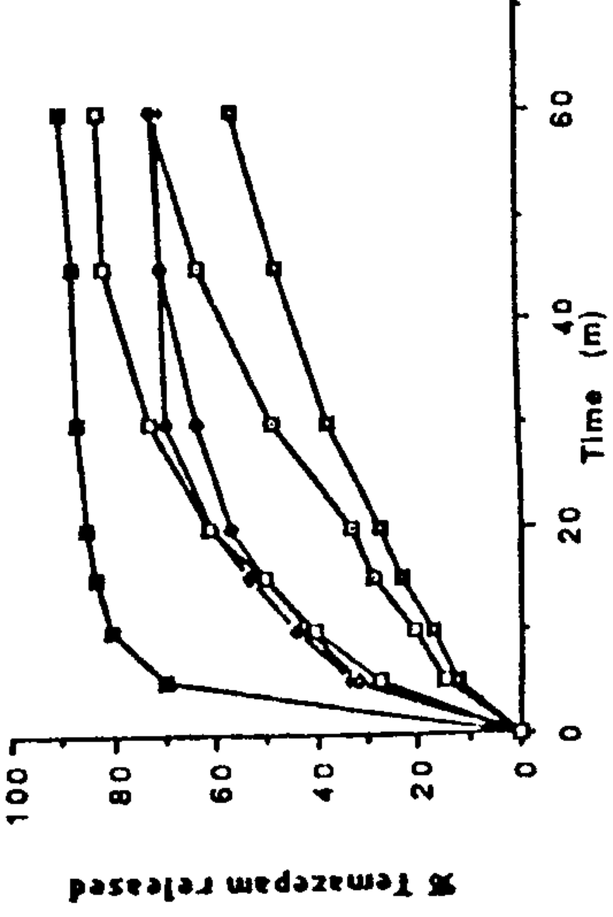

Fig. 5 : Dissolution profiles of temazepam (Tem), ground temazepam (Gr Tem) and mixtures with 8-CD.

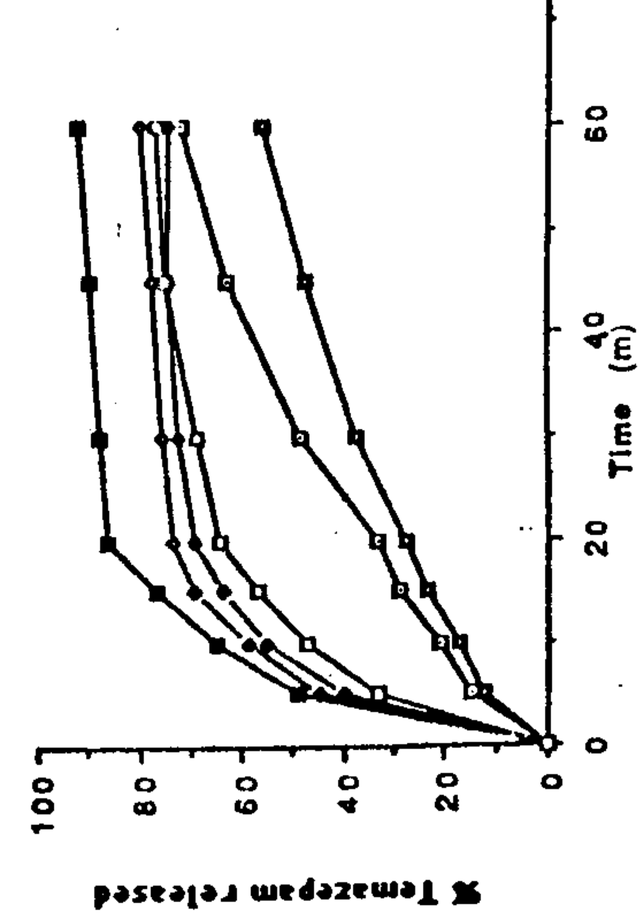

Fig. 7 Dissolution profiles of temazepam / Avicel systems.

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تحسين سلوك الاذابة للتيمازيبام بواسطة الطحن المتزامن مع البيتاسيكلوديكسترين وهيدروكسى بروبيل البيتاسيكلوديكسترين وكذا مع الميكروكريستالين سليولوز

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تم فى هذا البحث دراسة تداخل التيمازيبام مع البيتاسيكلوديكسترين والهيدروكسى بروبيل بيتاسيكلوديكسترين فى الحالة السائلة وكذلك تم عمل محاولات للحصول على منغمس التيمازيبام فى السيكلوديكسترينات فى الحالة الصلبة وذلك عن طريق التجفيف المجمد او التبخير البطىء تحت جو النيتروجين ولكن لم يتم الحصول على المنغمس فى الحالة الصلبة .

كذلك تمت دراسة تأثير الطحن المتزامن للتيمازيبام مع السيكلودكسترينات وميكروكريستالين السليولوز على معدل اتاحة التيمازيام وقد وجد ان عملية الطحن المتزامن للتيمازيام مع هذه المواد يؤدى الى معدل اتاحة سريع جدا وذلك بالمقارنة بالتيمازيام غير المعامل او خليطه الطبيعى مع هذه المواد بنفس النسب .

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