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TEMAZEPAM-ß-CYCLODEXTRIN AND TEMAZEPAM-MICROCRYSTALLINE CELLULOSE GROUND MIXTURES FORMULATED INTO TABLETS, CAPSULES AND SUPPOSITORIES

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تم فى هذا البحث صياغة المطحون المشترك للتيمازيبام مع البيتاسيكلوديكسترين وكذا المطحون المشترك التيمازيبام مع ميكروكريستالين السيليلوز على هيئة أقراص وكبسولات وأقماع. وقد تم تقويم الصيغ الجديدة المحضرة من حيث صفاتها الطبيعية ومعدل إتاحتها المعملى للتيمازيبام.

وقد أظهرت النتائج أن الأقراص المحضرة بإستخدام المطحون المشترك للتيمازيبام مع البيتاسيكلوديكسترين أو مع ميكروكريستالين السيليلوز لها صفات طبيعية معقولة ولها صفات إتاحة معملية اسرع من ذلك من تلك المحضرة بإستخدام التيمازيبام غير المعامل أو التيمازيبام المطحون بمفرده. وقد سلكت الكبسولات المحضرة مسلكا مشابها للأقراص وتفوقت فى الإتاحة المعملية عن الكبسولات التجارية التى تمت دراستها.

أما فيما يخص الأقماع المحضرة فقد أدى إستخدام واتيبسول هـ١٥ كقاعدة للأقماع إلى صفات إتاحة معملية بطيئة جدا بينما أدى إستخدام خليط من عديد إيثلين الجليكول ١٥٠٠ ، ٤٠٠ بنسبة ١:٩ إلى الحصول على أقماع لها صفات إتاحة معملية سريعة.

Temazepam-β-cyclodextrin and temazepam-microcrystalline cellulose ground mixtures were formulated into tablets, capsules and suppositories. The produced dosage forms were evaluated with regard to their physical properties and dissolution characteristics. Tablets containing temazepam-β-cyclodextrin or temazepam-microcrystalline cellulose ground mixtures showed reasonable physical properties and faster dissolution characteristics compared to those containing untreated temazepam or ground alone one. Capsules containing temazepam-β-cyclodextrin or temazepam-microcrystalline cellulose ground mixtures showed faster release characteristics compared to those containing untreated temazepam, the ground alone one or the commercial temazepam capsule form studied. With regard to the prepared suppositories, Witepsole H 15 gave rise to suppositories with a very slow release whereas, a mixture of PEG 1500 and PEG 400 (9:1 W/W) gave rise to suppositories with very fast release characteristics.

INTRODUCTION

Temazepam is one of the benzodiazepines widely used as anticonvulsant, sedatives, tranquilizers and hypnotics in psychotherapy. This group of drugs is known for their poor water solubility and it has become increasingly clear that the rate of absorption of this group from the GIT is slow and formulation dependent[1]. This fact represents a problem for these drugs whose rapid plasma appearance is therapeutically essential. In other words, fast dissolving forms with high aqueous solubility for rapid absorption are required in case of benzodiazepine therapy. Many techniques have been adopted to improve the water solubility and the dissolution characteristics of benzodiazepines and other poorly water soluble drugs. Among these techniques are: solid dispersion[2-5], inclusion complexation with cyclodextrins[6-8], crystallization in aqueous solutions of surfactants[9], roll mixing with cyclodextrins[10] and

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co-grinding with cyclodextrins and other excipients[11-14].

In a recent work[15], temazepam dissolution was markedly improved through co-grinding with β-cyclodextrin, hydroxypropyl β-cyclodextrin and microcrystalline cellulose. Obviously, the main goal of all the above mentioned techniques is the expected achievement of dosage forms with a fast release of the incorporated drug. Hence, the aim of the present work was the formulation of temazepam-β-cyclodextrin and temazepam-microcrystalline cellulose ground mixtures into tablets, capsules and suppositories. The produced dosage forms were to be evaluated with regard to their physical properties and dissolution characteristics.

EXPERIMENTAL

Materials

- Temazepam (Fabrica Italiana Sintefici, Italy).
- β-cyclodextrin (Roqutte, France).
- Avicel PH 101; microcrystalline cellulose (FMC Corporation, Pennsylvania, USA).
- Magnesium stearate (Prolabo, France).
- Polyethylene glycols 1500 and 400, PEG 1500 and PEG 400 (Merck - Schuchardt 8011, Hohenbrunn bei, Müchen, Germany).
- Witepsole H 15 (Gattefossé, France).
- Temazepam hard gelatin capsules (CID Company, Assiut, Egypt).

Equipment

- Cupic mixer (Erweka Apparatabau, Germany).
- Coffee mill (Radar type 299. 210, France).
- Erweka TBT hardness tester (Erweka Apparatabau).
- Erweka TAB friabiliator (Erweka Apparatabau).
- Disintegration time test apparatus (Erweka Apparatabau).
- USP dissolution test apparatus (Erweka Apparatabau).
- Korsch tableting machine EK/0 (Perlin, Germany).
- Spectrophotometer (Uvedic 320, Japan).
- Erweka suppository hardness tester SBT (Erweka Apparatabau).

Methods

Preparation of temazepam-β-cyclodextrin and temazepam- Avicel ground mixtures:

Mixtures of temazepam with either β-cyclodextrin (1:4 W/W) or Avicel PH 101 (1:3 W/W) were ground for 10 minutes in the mentioned mill. On the other hand, temazepam, Avicel and β-cyclodextrin were separately ground in the same manner. All the ground samples were passed through a 80 μ sieve. Random samples from the ground mixtures were spectrophotometrically assayed for their temazepam content.

Preparation of tablets

The formula under test containing 1 % of magnesium stearate and the proper amount of Avicel PH 101 as excipient was mixed in the cubic mixer for 10 minutes at 25 r.p.m. Tablets containing 10 mg of temazepam were directly compressed using the Korsch machine equipped with 2 (8 mm flat) punches. Batches, 100 tablets each, were prepared. The machine settings were adjusted to produce tablets weighing 200 mg and having hardness of about 6 kg (Erweka) as possible.

Evaluation of the tablets

Uniformity of weight

Uniformity of weight of tablets was examined according to the USP XX on 20 randomly taken tablets.

Hardness

The hardness of 10 tablets of each batch was determined using the Erweka hardness tester. The mean hardness (crushing strength) was calculated.

Friability

The loss percentage of preweighed 20 tablets of each batch was deduced after revolving at 25 r.p.m. during 5 minutes. The test was repeated 3 times and the mean loss % was calculated.

Disintegration time

The time required for the disintegration of the different batches was determined according to the procedure of the USP XX.

Dissolution rate

The dissolution rate studies were carried using the USP apparatus equipped with baskets which were rotating at 100 r.p.m. in distilled water. Temperature was kept at 37°C. One tablet was introduced in each of the 6 baskets. Samples were withdrawn at suitable time intervals by the aid of pipettes with filter tips. The withdrawn samples were replaced by equal volumes of the dissolution medium. Samples were spectrophotometrically assayed for temazepam at 232 nm.

Drug content

Ten randomly taken tablets were individually assayed for their content of temazepam. Tablets were quantitatively dissolved in distilled water and spectrophotometrically assayed at 232 nm.

Preparation of capsules

The formula under test (the same formulas used in the preparation of the tablets) were manually filled into suitable hard gelatin capsules.

Evaluation of the capsules

The dissolution characteristics of the capsules in distilled water were investigated using the USP apparatus at 100 r.p.m. similarly to the case of the tablets.

Preparation of the suppositories

Drug displacement for the two suppository bases studied [Witepsol H 15 and PEG 1500/PEG 400 (9:1)] was firstly determined. Suppositories were prepared using the melting technique by dispersing the drug or its mixture with β-cyclodextrin in the molten base. The molten mass was then poured into 3 g torpedo shape suppository mould.

Evaluation of the suppositories

Weight variation

20 suppositories of each formula were individually weighed. The mean and the coefficient of variation percent were calculated.

Content uniformity

The uniformity of temazepam content of the suppositories prepared was estimated on 10 suppositories from each batch. They were assayed individually.

Hardness

The hardness of the suppositories prepared were measured on 10 of each batch. The mean hardness was calculated.

Release characteristics

The release characteristics of 6 suppositories of each batch was determined in 500 ml of distilled water at 37 $\pm$ 0.5°C using the USP tablet dissolution apparatus at 50 r.p.m. Each suppository was included in a manually made metallic cage which was attached to the paddles of the apparatus. Samples were withdrawn, at suitable time intervals, using pippets with filter tips. The withdrawn samples were replaced by equal volumes of distilled water at 37 °C. The samples were spectrophotometrically assayed at 232 nm after being appropriately diluted.

RESULTS AND DISCUSSIONS

Temazepam tablets and capsules

Table 1 demonstrates the physical properties and drug content of the different temazepam tablets prepared. Tablets containing untreated temazepam or temazepam ground mixtures showed good weight uniformity with low values of coefficient of variation. On the other hand, tablets containing micronized temazepam with micronized β-cyclodextrin or micronized Avicel showed higher values of coefficient of variation. All batches showed a mean temazepam content of about 95 %. Similarly to the case of weight uniformity, tablets containing the coground mixtures showed superior drug content uniformity. This finding coincides with our previous finding[16] and indicates that cogrinding could be advantageous in the production of tablets of uniform weight in case of low dose drugs.

Table 1: Physico-chemical properties of different temazepam tablets.

Code Formula	Weight (g)		Hardness (Kg)	Friability loss %	% Drug content	
	Mean	C.V.%			Mean	C.V. %
1- Tema + ß-CD + Av.	0.2043	1.9	7.4	0.38	96.2	2.5
2- Micro. tema + Av.	0.1950	4.1	4.5	0.63	95.4	4.1
3- Micro. tema + micro. ß-Cd + Av.	0.1998	6.4	6.6	0.13	94.7	5.0
4- Tema + ß-CD (co-g) + Av.	0.2037	1.9	8.0	0.30	96.2	1.6
5- Tema + Av.	0.1821	4.4	3.9	1.40	95.1	4.3
6- Micro. tema + micro Av. + Av.	0.1830	5.45	4.0	1.10	95.3	5.1
7- Tema + Av. (co-g) + Av.	0.1830	3.89	4.0	1.10	96.2	2.1

- ß-CD : ß-cyclodextrin
- micro : micronized.
- Tema : temazepam.
- co-g : co-ground.
- Av. : Avicel PH 101

All batches showed reasonable hardness values (4-8 kg, Erweka) with low values of friability ranging from 0.13 to 1.4 %. Generally, tablets containing β-cyclodextrin with Avicel showed higher hardness and lower friability values than those containing only Avicel. It is worth mentioning that all the produced batches showed very fast disintegration with disintegration times ranging from 0.5 to 3 minutes.

Fig. 1 shows the dissolution profile of temazepam-β-cyclodextrin tablets. Generally, tablets containing temazepam-β-cyclodextrin ground mixture exhibited a very enhanced release of temazepam compared to those containing untreated temazepam. On the other hand, tablets containing the ground alone temazepam showed faster dissolution than those containing untreated temazepam. This is due to the reduction in particle size and hence the increase in the surface area. Moreover, the inclusion of ground alone β-cyclodextrin resulted in further enhancement of the dissolution characteristics of the untreated temazepam. This is due to the presence of β-cyclodextrin and its surfactant like characteristics[17]. Fig. 2 shows the dissolution profiles of temazepam-Avicel tablets. The profiles were nearly similar to those of temazepam-β-cyclodextrin tablets. Tablets containing temazepam-Avicel ground mixture showed faster dissolution characteristics than those containing untreated temazepam. In the same time, tablets containing ground temazepam with or without ground Avicel exhibited faster dissolution than those containing untreated temazepam. This is mainly due to the reduction in the particle size and hence the augmentation in the surface area. In contrary to the case of β-cyclodextrin, the presence of ground Avicel didn't improve the release of temazepam. A general look on Fig.s 1 and 2 indicates that tablets containing temazepam-β-cyclodextrin ground mixtures had faster rate and greater extent of dissolution than those containing temazepam-Avicel ground mixtures.

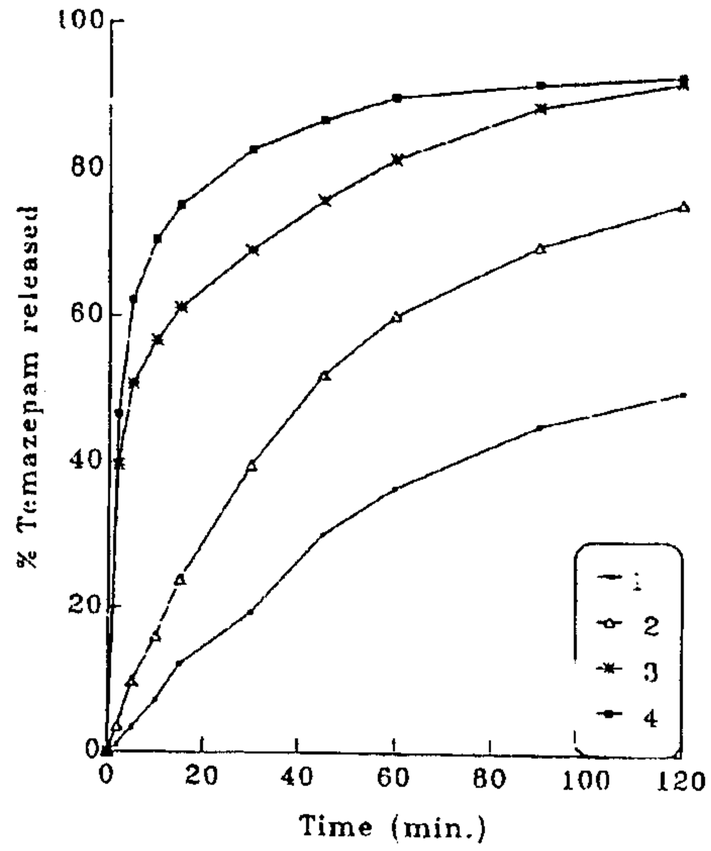

Fig. 1: Mean % Temazepam released from different Temazepam-ß-CD tablets.

1- Temazepam + ß-CD + avicel
2- Micronized temazepam + Avicel
3- Micronized Temazepam + Micronized ß-CD + Avicel
4- Temazepam + ß-CD (Co-ground) + Avicel.

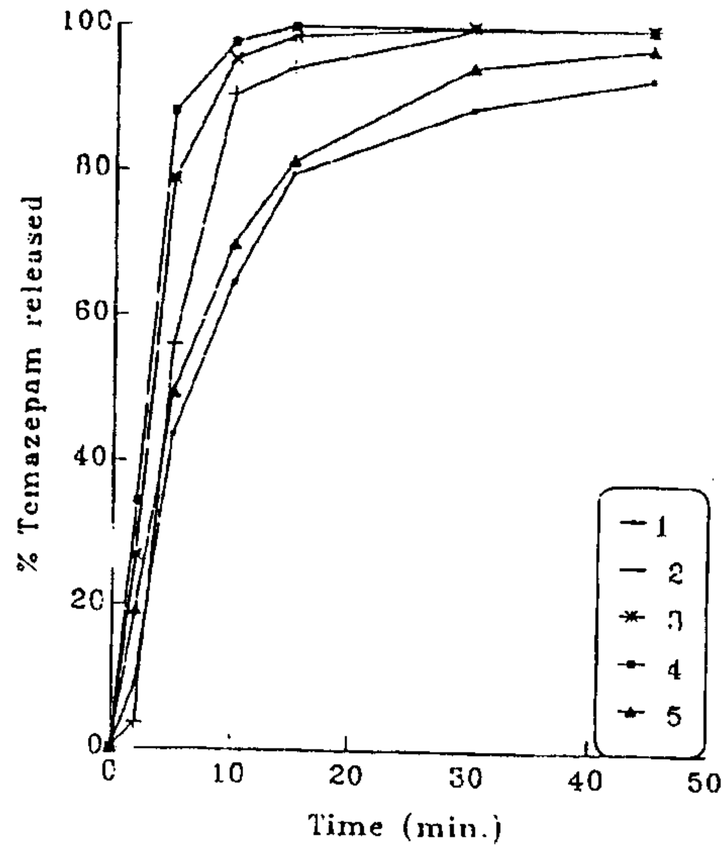

Fig. 3: Mean % Temazepam released from different Temazepam-ß-CD Capsules.

1- Temazepam + ß-CD + Avicel
2- Micronized temazepam + Avicel
3- Micronized Temazepam + Micronized ß-CD + Avicel
4- Temazepam + ß-CD (Co-ground) + Avicel.
5- Commercial Capsules.

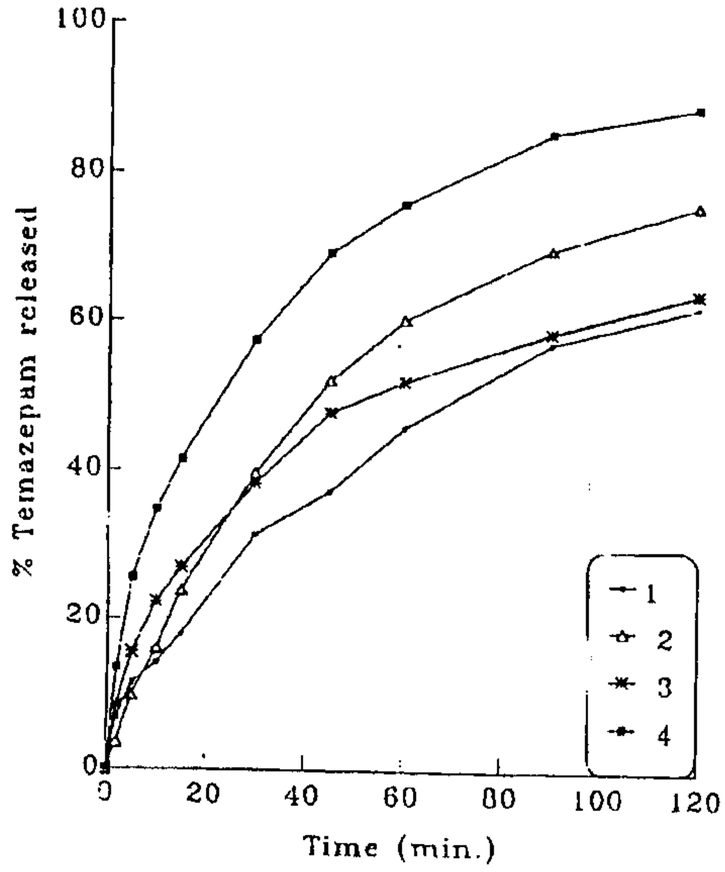

Fig. 2: Mean % Temazepam released from different Temazepam-Avicel tablets.

1- Temazepam + Avicel
2- Micronized temazepam + Avicel
3- Micronized Temazepam + Micronized Avicel + Avicel
4- Temazepam + Avicel (Co-ground) + Avicel.

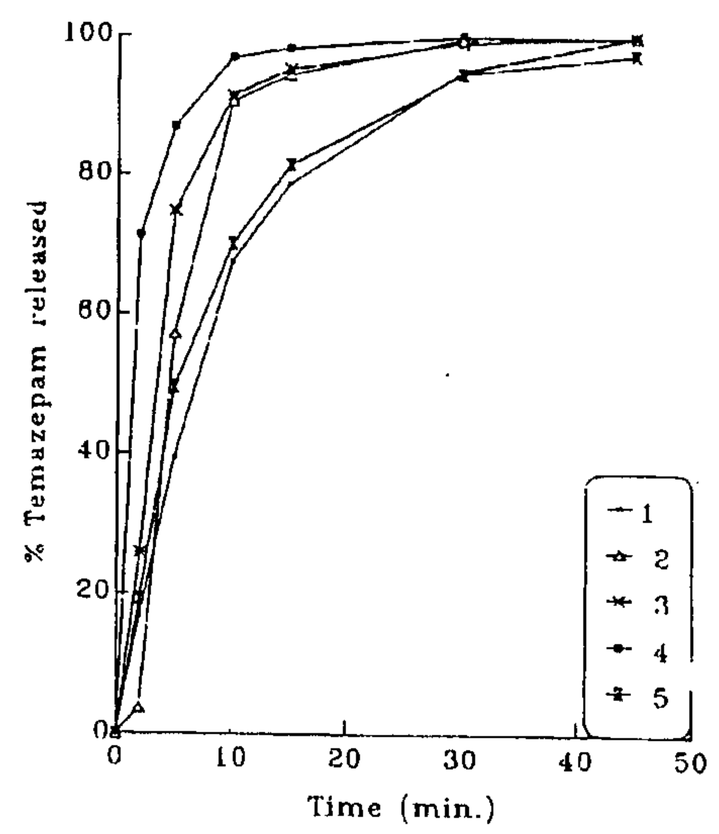

Fig. 4: Mean % Temazepam released from different Temazepam-Avicel Capsules.

1- Temazepam + Avicel
2- Micronized temazepam + Avicel
3- Micronized Temazepam + Micronized Avicel + Avicel
4- Temazepam + Avicel (Co-ground) + Avicel.
5- Commercial Capsules.

Manually filled hard gelatine capsules containing either temazepam-β-cyclodextrin or temazepam-Avicel systems showed very fast release characteristics (released 60% of its temazepam content in < 10 minutes) with the superiority of the capsules containing the ground mixtures as shown in Fig.s 3 and 4. Interestingly the commercial temazepam capsule brand studied showed a dissolution profile which is very similar to the prepared temazepam capsules containing untreated temazepam.

The reason behind the superiority of the dissolution characteristics of tablets and capsules containing the ground mixtures of temazepam may be due to the presence of the drug in a more energetic and less crystalline form in the ground mixtures and so dissolves faster. Other reasons and mechanisms such as the effect of the presence of cyclodextrins and increased wettability were previously discussed in details[11,15,16,18].

Temazepam suppositories

Table 2 shows the physico-chemical properties of different temazepam suppositories. All the prepared batches showed good uniformity in weight with low values of coefficients of variation. Similar results were obtained regarding the uniformity of drug content. The use of PEGs as a suppository base resulted in suppositories of lower hardness values than the use of Witepsol H 15.

Table 2: Physico-chemical properties of different temazepam suppositories.

Code Formula	Weight (g)		Hardness (Kg)	% Drug content	
	Mean	C.V.%		Mean	C.V. %
1- W 15 + tema + ß-CD	2.317	2.0	4.7	97.3	2.0
2- W 15 + micro. tema	2.358	2.1	3.8	99.0	1.5
3- W 15 + micro. tema + micro ß-CD	2.340	2.11	4.0	98.1	1.3
4- W 15 + ß-CD + tema (co-g)	2.348	2.01	3.3	99.2	1.1
5- PEG + tema + ß-CD	2.911	1.50	1.4	100.0	1.5
6- PEG + micro. tema	2.903	1.52	1.2	99.6	1.2
7- PEG + micro. tema + micro. ß-CD	2.932	1.55	1.6	100.0	1.0
8- PEG + ß-Cd + tema (co-g)	2.925	1.56	1.4	100.0	0.7

- W 15 : Witepsol H 15
- ß-CD : ß-cyclodextrin
- PEG : PEG 1500/PEG 400 (9:1)
- Tema : temazepam.
- micro : micronized.
- co-g : co-ground.

Fig. 5 shows the release profile of temazepam-Witepsole H 15 suppositories in distilled water. All batches showed slow release characteristics (releasing nearly 20 % of its temazepam content during 2 hours). This is due to the lipophilic nature of temazepam which renders it difficult to leave the oleaginous base to the aqueous layer[6]. Interestingly, neither grinding temazepam alone nor its cogrinding with β-cyclodextrin were of good value for improving temazepam release from this suppository base. Meanwhile, the suppositories containing untreated temazepam released temazepam even faster than those containing the treated one (especially after 40 minutes and up). This may reveal that grinding which increases the surface area may have supported the interaction between temazepam and the oleaginous base.

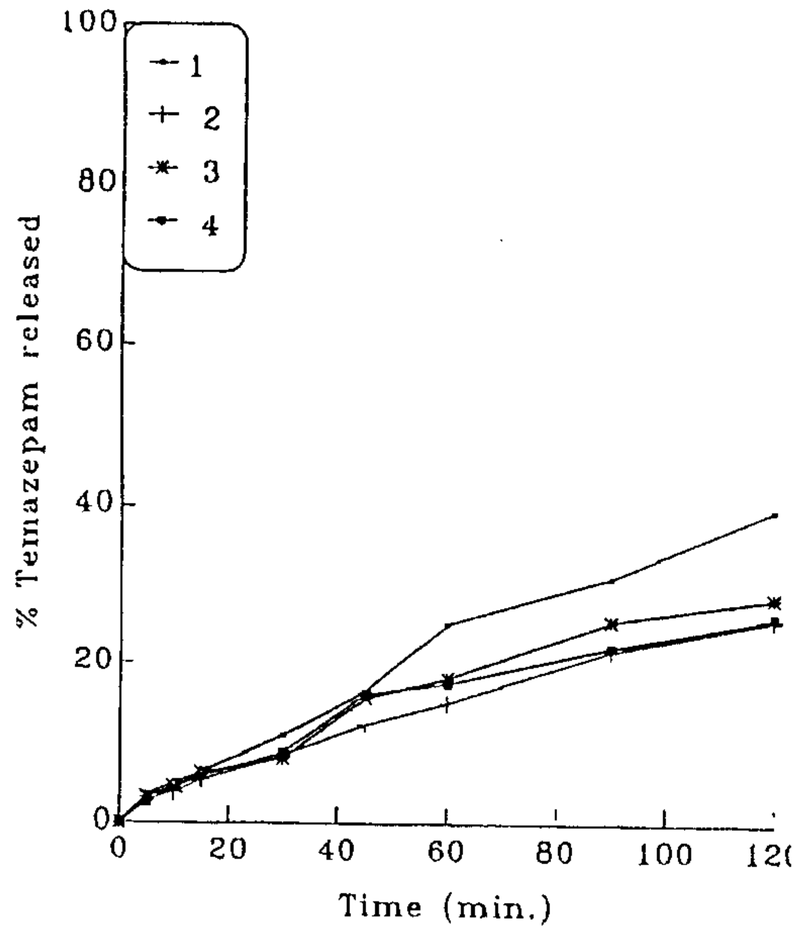

Fig. 5: Mean % Temazepam released from different Temazepam-witepsol H 15 suppositories.
1- Temazepam + ß-CD + Witepsol H 15.
2- Micronized temazepam + Witepsol H 15.
3- Micronized Temazepam + Micronized ß-CD + Witepsol H 15.
4- Temazepam + ß-CD (Co-ground) + Witepsol H 15.

Fig. 6 shows the release profile of temazepam-PEG suppositories. As it could be easily observed a rapid release was achieved (releasing > 60 % of its temazepam content in < 10 minutes). This fast release may be due to the mechanism of drug release from this base which is the dissolution of the base in the aqueous medium, the absence of the hydrophobic interaction and the presence of β-cyclodextrin and PEGs with their surfactant like character [19,20].

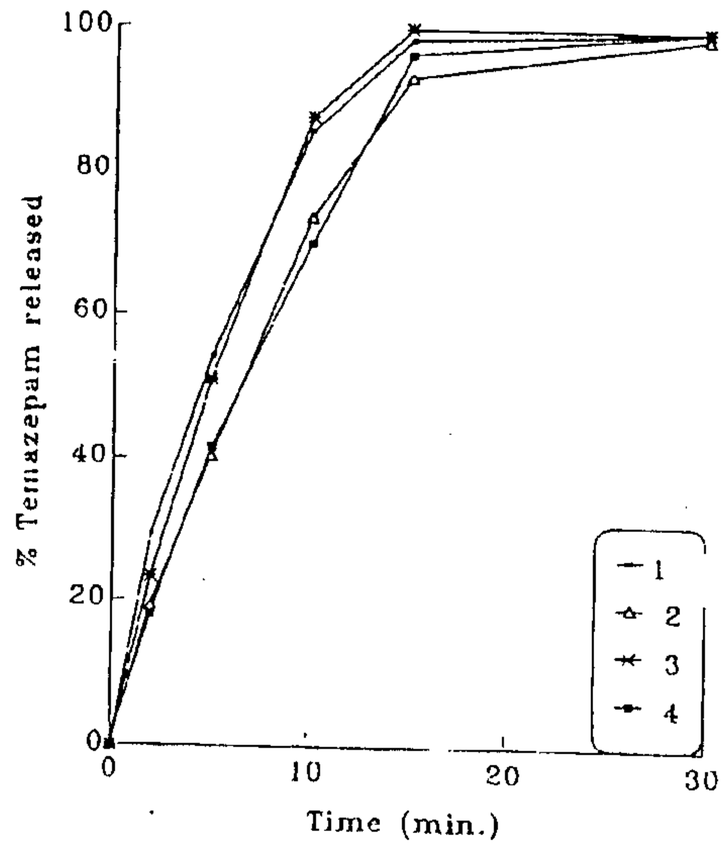

Fig. 6: Mean % Temazepam released from different Temazepam-PEG 1500/PEG suppositories.
1- Temazepam + ß-CD + (PEG 1500/PEG 400).
2- Micronized temazepam + (PEG 1500/PEG 400).
3- Micronized Temazepam + Micronized ß-CD + (PEG 1500/PEG 400).
4- Temazepam + ß-CD (Co-ground) + (PEG 1500/PEG 400).

CONCLUSIONS

From the results obtained throughout this study, it could be concluded that:

- Co-grinding technique of drugs with cyclodextrins or microcrystalline cellulose represents an easy way of improving the dissolution characteristics of poorly water soluble drugs such as temazepam.
- The co-ground mixture obtained could be easily incorporated into different dosage forms such as tablets, capsules and suppositories without loss of the induced

improvement in dissolution characteristics.

- Using PEG 1500/PEG 400 (9:1) as a suppository base, gave rise to temazepam suppositories with a very fast in vitro release characteristics.

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