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PREPARATION AND EVALUATION OF CLONAZEPAM SOLID DISPERSIONS

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ABSTRACT

Preparation of clonazepam solid dispersions was carried out using certain hydrophilic carriers including polyethylene glycol 2000, (PEG 2000) polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000), polyvinyl pyrrolidone 44000 (PVP 44000), Myrj 52, Myrj 53 and Myrj 59.

The solvent method was adopted for the preparation of the investigated solid dispersions which were subjected to ultraviolet, differential scanning calorimetry (DSC) and dissolution evaluation. It was found that dissolution enhancement was obtained from the prepared co-precipitates compared to the drug alone. The type of the carriers used, their chemical natures and their molecular weights have pronounced effects on the dissolution rate of the drug.

INTRODUCTION

Benzodiazepines are widely used as anticonvulsants, sedatives, tranquillizers and hypnotics in psychotherapy. They have become among the most commonly prescribed medications and have replaced prescriptions of short acting barbiturates and other sedative hypnotics[1]. Many biopharmaceutical studies on benzodiazepines have shown that their rapid plasma appearance is therapeutically essential. Moreover, it has become increasingly clear that the rate of absorption of this group of drugs from the GIT following oral administration is slow and formulation dependent[2].

It has become obvious that fast dissolving forms of benzodiazepines are required in order to enhance their absorption. Accordingly, several investigations have reported in this concern. Solid dispersion[3-6], cyclodextrin inclusion complexation[6-9] and grinding[10] were among the techniques successfully applied for enhancing the dissolution of certain benzodiazepines.

Interestingly, it was tried during this investigation to utilize solid dispersion technique for enhancing the dissolution rate of the practically water insoluble benzodiazepine member, clonazepam[1,4]. The factors affecting the drug dissolution rate including the type, the chemical nature and the molecular weight of the carriers were also investigated.

EXPERIMENTAL

Materials

-Clonazepam,(kindly obtained from Hoffman - La Roche, New Jersy, USA).

-Polyethylene glycols : PEG 2000, PEG 4000 and PEG 6000 (BDH, Poole, England).

-Polyvinyl pyrrolidone 44000 (PVP 44000) (BDH, Poole, England).

-Myrjs, Myrj 52 (Polyoxythylene (40) stearate), Myrj 53 (polyoxyethylene (50) stearate) and Myrj 59 (Polyoxyethylene (100) stearate, (Atlas chemical In-

dustries, Inc. willimington, Delaware, USA).

Other chemicals and solvents were of analytical grade.

Deionized double distilled water was used throughout this study.

Apparatus

-Dissolution apparatus (Erweka- DT-D, GmBH, Germany).

-Spectrophotometer (Pu 8620 UV/VIS, Holland).

-Spectrophotometer (555 perkin Elmer) for UV scanning.

-Dupont 9900 thermal analyzer and Dupont 912 DT-calorimeter (USA).

Methods

1-Preparation of clonazepam solid dispersions:

The solvent method[3] was adopted for the preparation of 1:3 or 1:7 (w/w) clonazepam : carrier respectively. The proportions selected was based on preliminary experiments. Both components were dissolved in 25 ml of 50% v/v acetone-methanol mixed solvent. The solvent was evaporated in vacuum at room temperature. The residue was dried to a constant weight in a vacuum desiccator, pulverized and screened to 75-200 u particle size. Clonazepam powder was subjected to the same procedures and was used as a control.

2-Characterization of the prepared coprecipitates :

A-Ultraviolet spectrophotometric investigation :

The UV method was used for the determination of clonazepam concentration at 310 nm[10]. UV scans (190 - 400 nm) were plotted in a comparative manner for solutions of the pure and processed clonazepam containing 10 mg/ml of the drug. It was found that the presence of the investigated carriers in the dilution range used did not interfere with the spectrophotometric assay of the drug.

B-DSC Studies :

Five mg sample of each of the prepared coprecipitates or the control was programme heated at the rate of 10°C/ minute in a dynamic nitrogen gas environment from 40 to 260°C[3]. The instrument was calibrated with indium standard.

C-In Vitro dissolution Studies:

Clonazepam, processed as the control, (15 mg, 75-200 u) or the prepared coprecipitates containing an equivalent amount of the pure drug was filled into colourless hard gelatin capsules. Each capsule was placed in the dissolution basket of the Erweka dissolution apparatus which was assembled to the motor shaft of the apparatus and rotated at 100 rpm, the dissolution medium was distilled water kept at 37°C.

RESULTS AND DISCUSSION

Clonazepam - PEG 6000 and Clonazepam - PVP 44000 coprecipitates were hard and pulverizable masses while coprecipitates containing PEG 2000, PEG 4000, and Myrjs were waxy in nature.

Ultraviolet scans were done to characterize clonazepam solid dispersions as shown in Figure. 1. Generally, there was an exact similarity between the UV spectra of the pure and the processed drug, which indicated that the drug molecule remained unchanged after coprecipitation with the selected carriers. Also, this indicated the absence of interaction between the drug and the investigated carriers. Similar results on temazepam solid dispersions were obtained by Ahmed[3].

DSC has gained remarkable population in the last ten years as one of the most valuable thermal analysis methods. This technique was utilized to characterize clonazepam coprecipitates and to check the interactions, if any, between the drug and the carriers. Most of the prepared samples showed similar behaviour. The melting endotherm of clonazepam was found at 240. 77°C, Figure. 2, which was disappeared when the coprecipitates 1:3 or 1:7 w/w PEG 6000 were scanned. The disapearance of clonazepam melting endotherm in the coprecipitates signifying the existance of the drug in the amorphous form or in the extremely fine crystallites or molecular dispersion which could not be detected by DSC. Similar findings were obtained[11,12] upon melting of indomethacin, phenylbutazone and tolbutamide solid dispersions.

Clonazepam prepared coprecipitates exhibited higher dissolution rates than clonazepam precipitated from the same solvent (the control), Figures 2-6. Each release profile is characterized by a fast initial phase followed by a lower prolonged one. The initial fast rate could be attributed to the release of the drug present in a state of very fine subdivision optimally wetted. As the carrier was depleted, the second prolonged phase started. The relative dissolution rate (RDR) of the prepared coprecipitates are summarized in Table 1. As the carrier content was increased from 1:3 to 1:7 w/w ratio, the release rate became higher. This effect was demonstrated by the increased RDR values in the higher ratio of the carrier. Another factor that affected the release of the drug from the prepared solid dispersions was the chemical nature of the carrier. So, it was observed that the dissolution rate enhancement followed the following order Myrjs > PVP > PEG series with the exception of 1:7 ratio Myrj coprecipitates which exhibited lower RDRs than those of PVP at 45 and 90 minutes.

Although Myri 52 has the same average molecular weight as PEG 2000, the former enhanced clonazepam dissolution more than the latter. That is because Myrjs, lowered the surface tension of the dissolution medium since they are surface active agents. Moreover, PEG increased the viscosity of the dissolution medium more than Myrjs at lower concentration, which also insures the superiority of the Myrjs[13].

Table 1 and Figure. 10 demonstrate the effect of carrier molecular weight on the release rate of clonazepam from its copricipitates with PEG (s) and Myrjs. It seems that increasing the carrier molecular weight led to a decrease in the drug release. This effect was obvious upon increasing the molecular weight of the PEG carriers from 2000 to 4000 or 6000. However, no significant difference was observed between the effect of PEG 4000 and 6000. On the other hand, increasing the molecular weight of Myrj from 52 to 53 led to a sharp decrease in the drug release behaviour whereas, Myrj 59 showed in between release characteristics. Actually, no general trend could be held true for the effect of carrier molecular weight on the drug release from coprecipitates. This finding is in agreement with the literature. In some cases, a decrease in the dissolution rate had been observed upon increasing the carrier molecular weight[14] or, the opposite effect happened in other cases[15]. Furthermore, no significant effect of the molecular weight on the release of drugs was detected[16]. Some authors[14,15] owed such effects to the changes in the viscosity of the dissolution medium as the carrier molecular weight increased or decreased. Under the present experi-

mental conditions, the changes in viscosity of the dissolution medium resulting from changes in the carrier molecular weight may play a minor role. The main reason for this being the low concentration of the carrier added during each experiment since all the dissolution tests were done under sink conditions. Finally, the narrow range of molecular weights selected may be another reason for the observed conflection in the dissolution behaviour.

Briefly, the factors which may be responsible for improvement of clonazepam dissolution from solid dispersion are increased wettability, decreased crystallinity, decreased particle size, microenvironmental solubilization of the drug and the reduction of the crystallinity of the carrier. Enhancing clonazepam *in vitro* dissolution rate from the prepared solid dispersions should decrease the influence of this parameter on the initial steps of absorption and thereby could increase the drug bioavailability.

Table 1: Relative Dissolution Rate (RDR's)* of Clonazepam Solid Dispersions.

Tested Solid dispersions	Ratio of drug carrier (w/w)	R.D.R.(min) 15	45	90
Control		1	1	1
Clonazepam-PEG 2000	1:3	4.9	4.2	2.5
	1:7	7.3	5.0	2.7
Clonazepam-PEG 4000	1:3	3.3	3.5	1.9
	1:7	7.3	7.1	3.8
Clonazepam-PEG 6000	1:3	3.2	3.7	1.9
	1:7	8.7	6.4	3.4
Clonazepam-PVP 4400	1:3	5.0	6.5	2.9
	1:7	10.7	12.0	6.25
Clonazepam-Myrj 52	1:3	10.0	7.6	4.4
	1:7	16.0	9.5	5.2
Clonazepam-Myrj 53	1:3	5.0	4.5	3.2
	1:7	13.0	10.3	5.3
Clonazepam-Myrj 59	1:3	7.7	6.7	4.2
	1:7	12.3	10.0	5.2

Control: Pure drug precipitated from 50% v/v methanol acetone mixed solvent.

*R.D.R. 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.

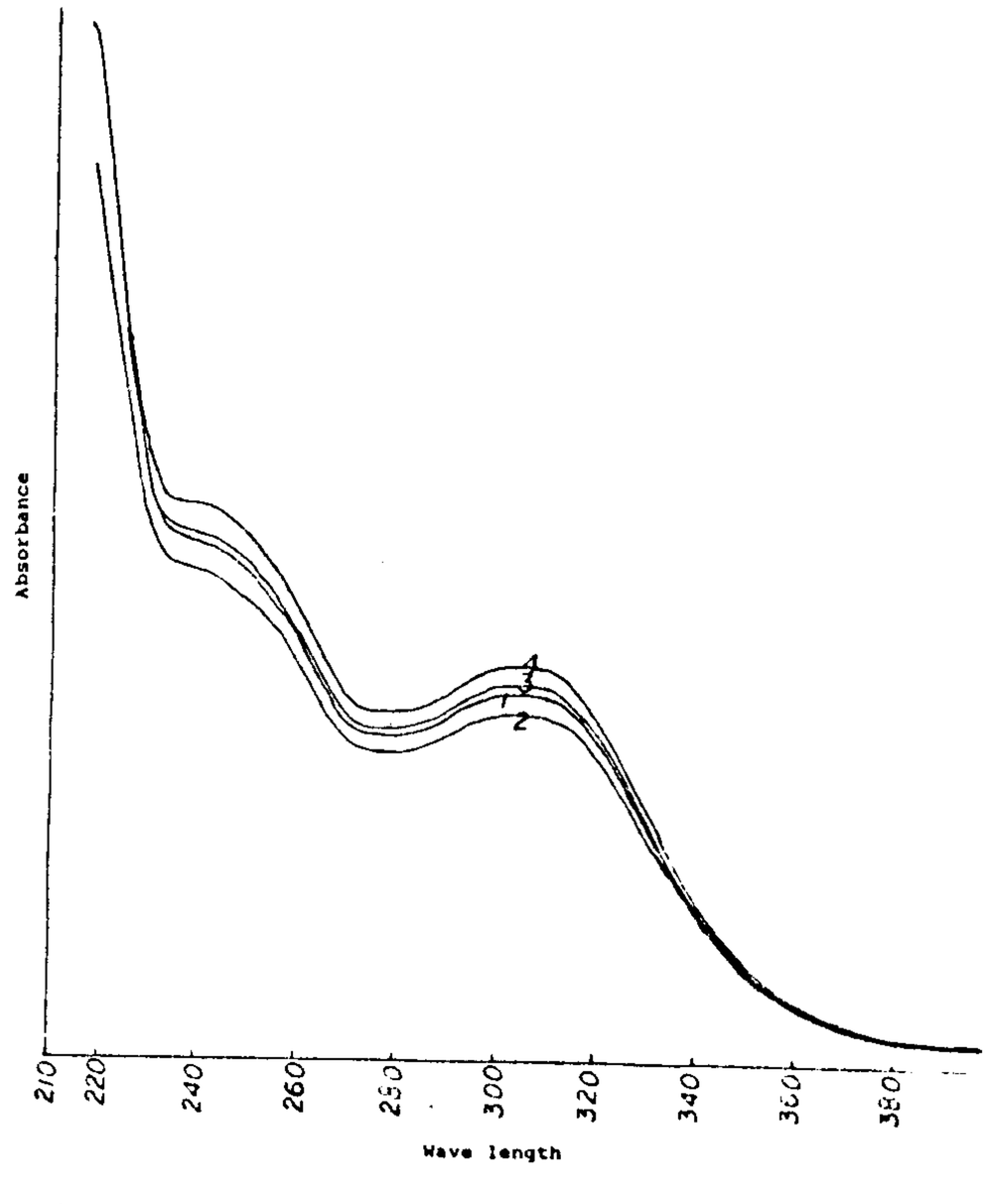

Fig. 1: U.V. absorption spectra of clonazepam (1), and of its coprecipitates, 1:3 w/w PEG 2000 (2), 1:7 w/w PVP 44000 (3) and 1:7 w/w Myrj 52 (4).

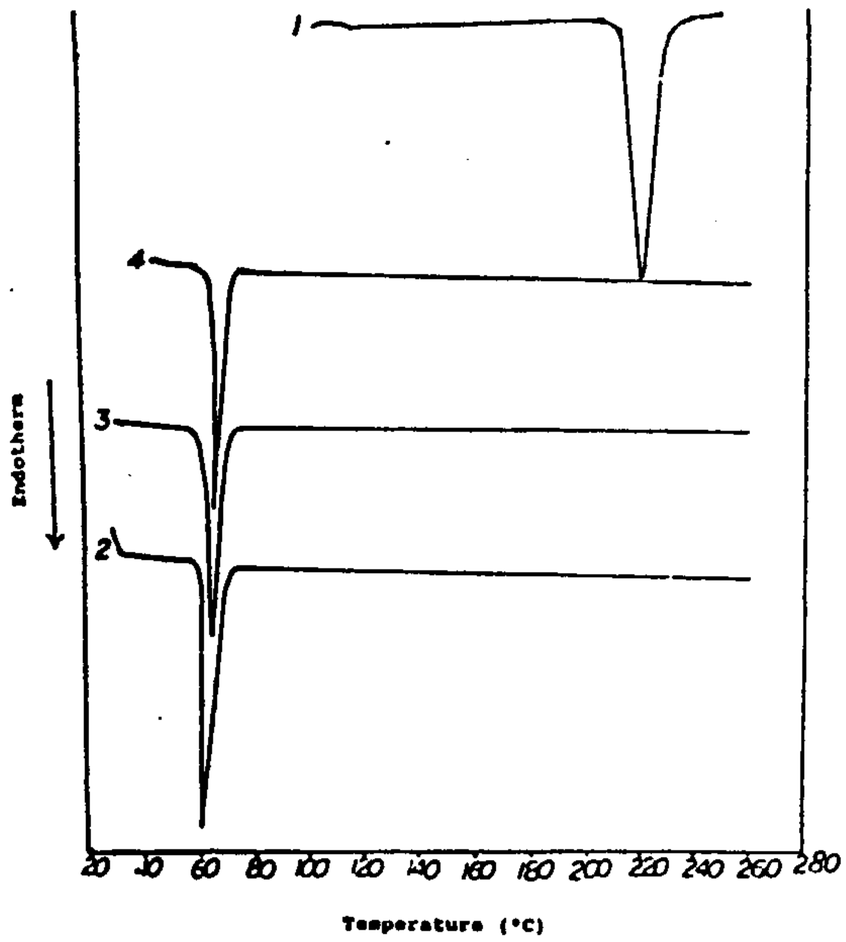

Fig. 3: DSC thermograms of clonazepam - PEG 6000 coprecipitates, clonazepam alone (1), PEG alone (3), 1:3 w/w clonazepam - PEG 6000 coprecipitate and 1:7 w/w clonazepam - PEG 6000 coprecipitate.

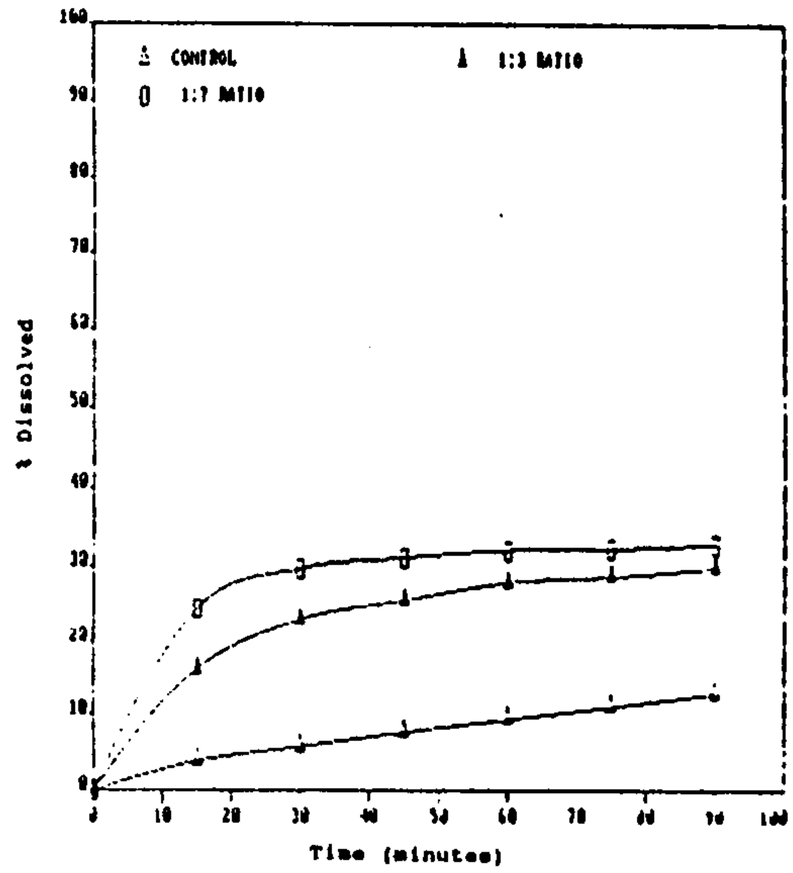

Fig. 31 Dissolution profiles of clonazepam - PEG 2000 coprecipitates.

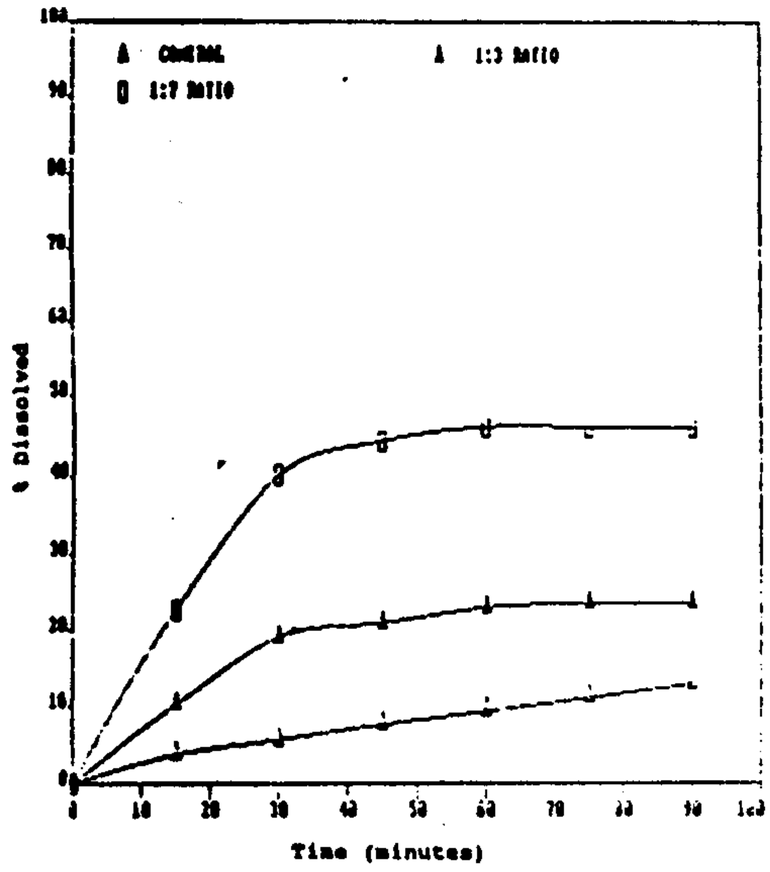

Fig. 4: Dissolution profiles of clonazepam - PEG 4000 coprecipitates.

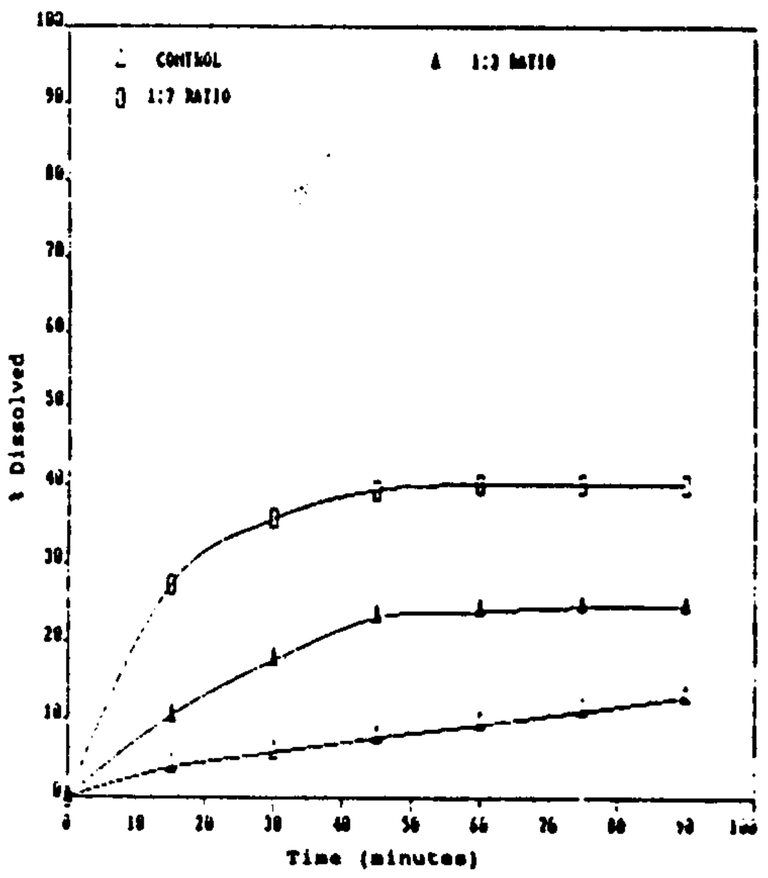

Fig. 5: Dissolution profiles of clonazepam - PEG 6000 coprecipitates.

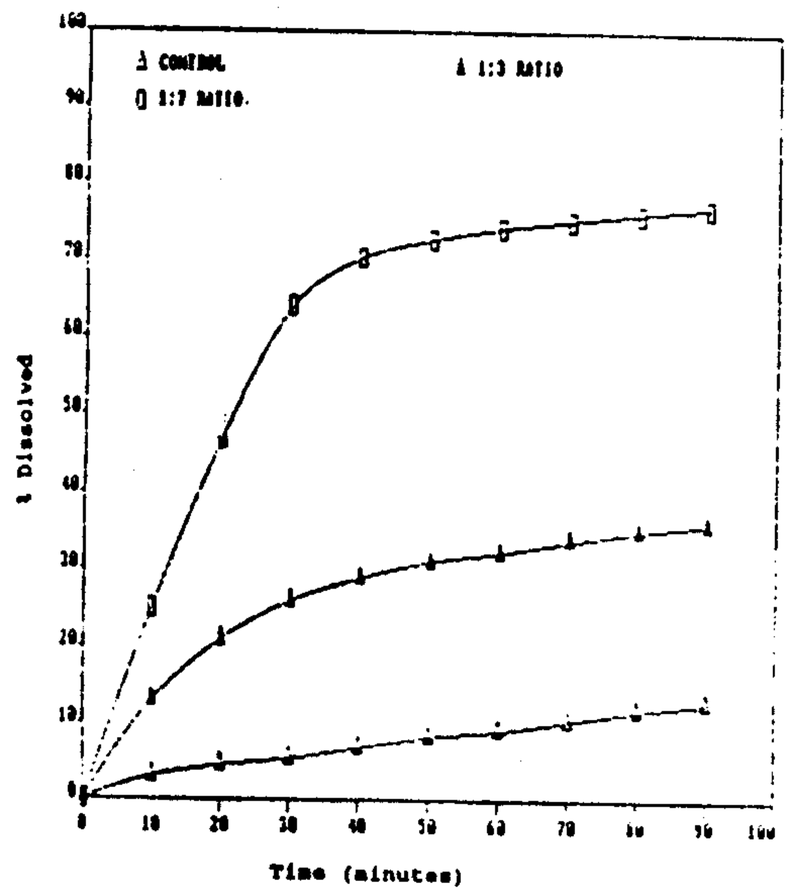

Fig. 6: Dissolution profiles of clonazepam - PVP 44000 coprecipitates.

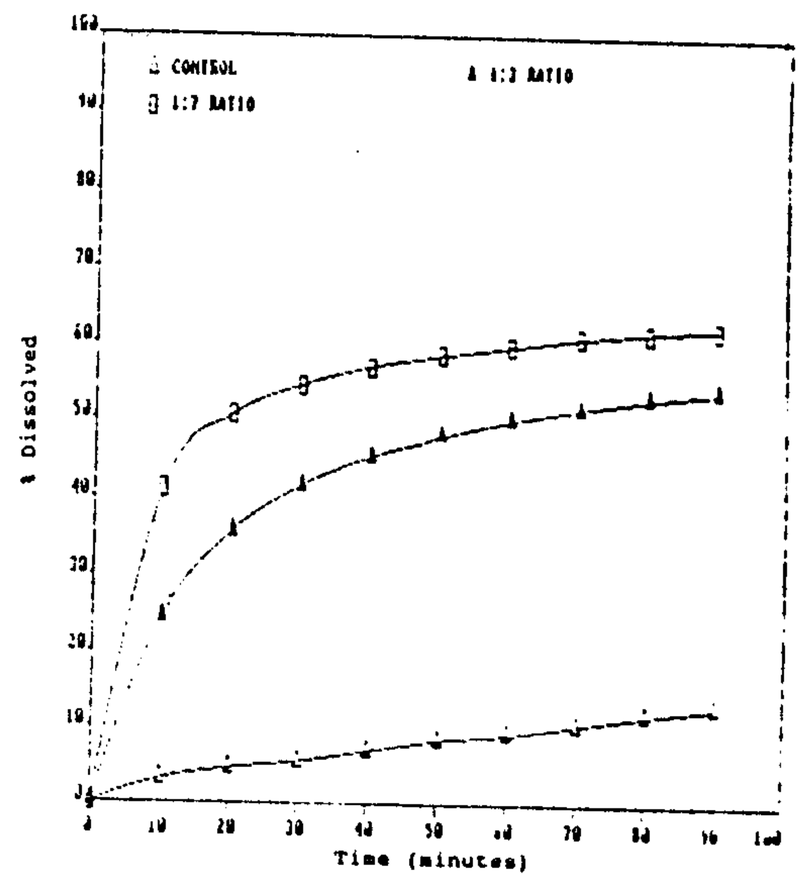

Fig. 7: Dissolution profiles of clonazepam - Myrj 52 coprecipitates.

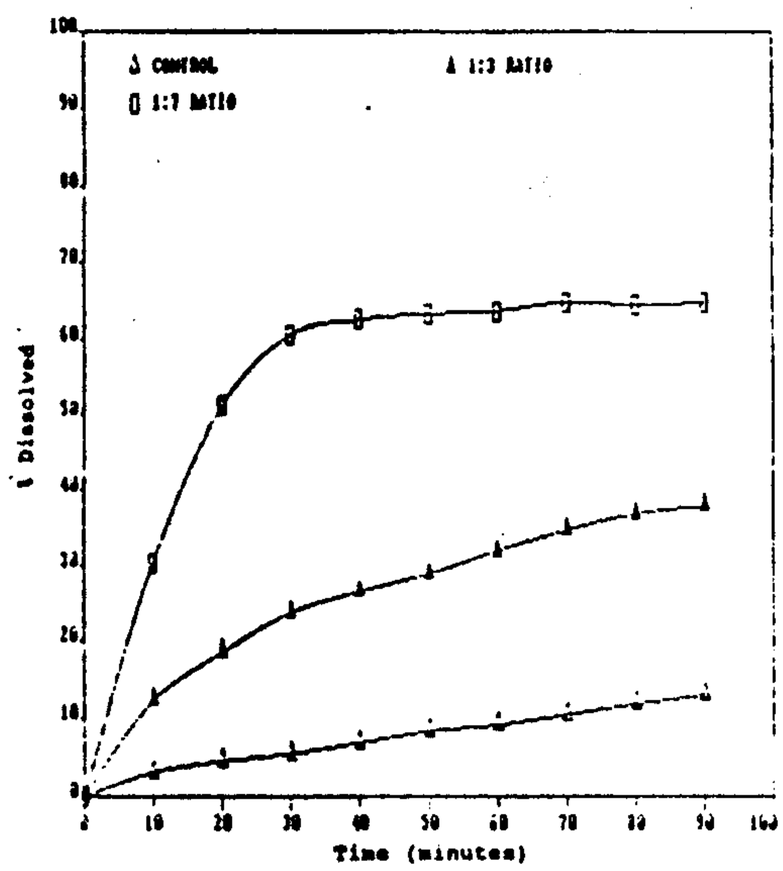

Fig. 8: Dissolution profiles of clonazepam - Myrj 53 coprecipitates.

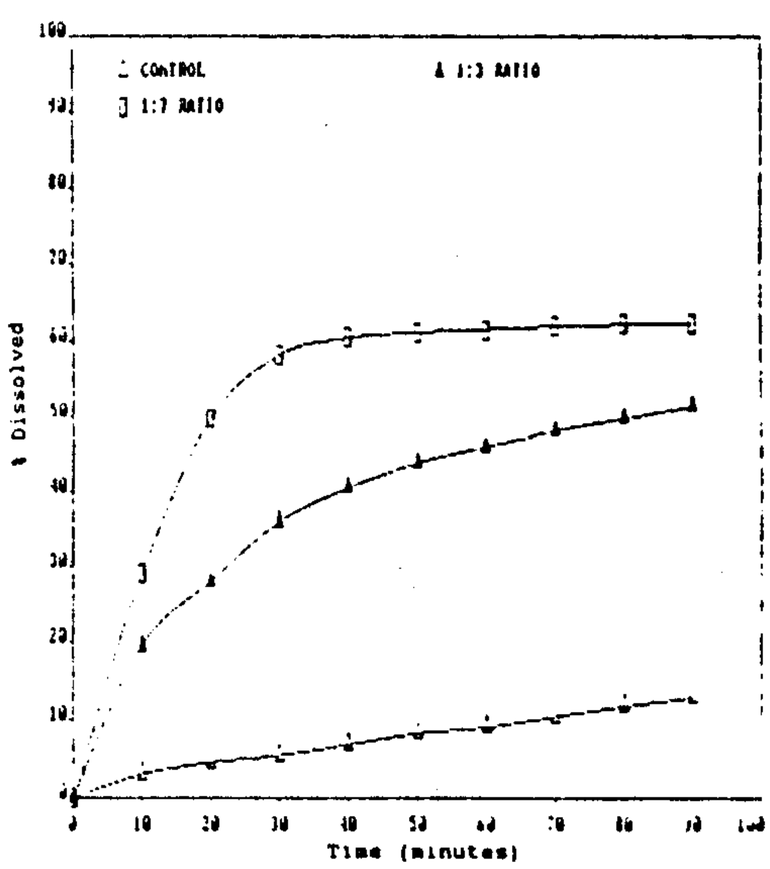

Fig. 9: Dissolution profiles of clonazepam - Myrj 59 coprecipitates.

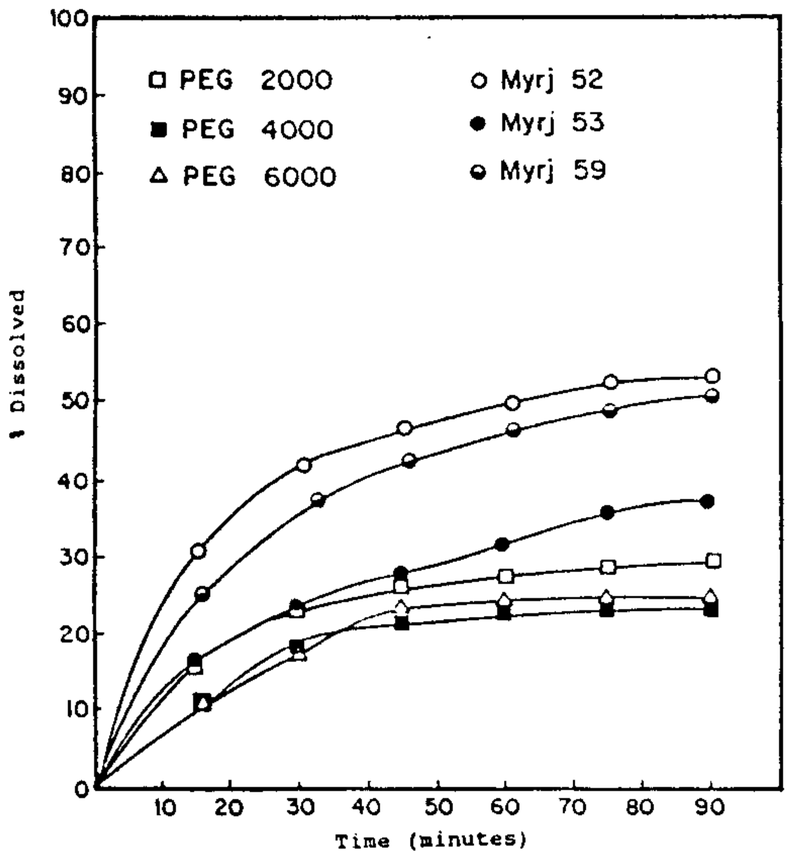

Fig. 10: Effect of carrier molecular weight on the dissolution of clonazepam from its coprecipitates (1:3 w/w) with PEG's and Myrjs.

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تحضير وتقييم المشتتات الصلبة للكلونازيبام

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حضرت المشتتات الصلبة للكلونازيبام باستعمال حاملات معينة محبة للماء مثل عديد ايثلين جليكول ٢٠٠٠ ، عديد ايثلين جليكول ٤٠٠٠ ، عديد ايثلين جليكول ٦٠٠٠ ، عديد الفينيل بيروليدون ٤٤٠٠٠ ، ميرج ٥٢ ، ميرج ٥٣ ، ميرج ٥٩.

ولقد استخدمت طريقة الاذابة لتحضير تلك المشتتات الصلبة التى درست خواصها بواسطة الاشعة فوق البنفسجية وكذلك التفاضل السعرى الحرارى وكذلك درس معدل اتاحة العقار من تلك المشتتات ولقد وجد أن معدل اتاحة العقار قد زاد من تلك المشتتات مقارنة بالعقار بمفرده ولقد وجد أن نوع الحامل وكذلك طبيعته الكيمائية ووزنه الجزيئى لهم تأثير على اتاحة العقار .

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