INTERACTION OF TEMAZEPAM WITH CERTAIN MACROMOLECULES

VIII-FORMULATION OF TABLETS CONTAINING TEMAZEPAM SOLID DISPERSIONS

Aly A. Abdel Rahman*, A.E. Aboutaleb*, B.A. Mulley** and S.M. Ahmed*
Dept. of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Egypt* and School of Pharmacy, Bradford University, England**

ABSTRACT

Temazepam-polyethylene glycol 6000 (PEG 6000) coprecipitates has been formulated as tablets using direct compression technique. This coprecipitation was chosen as it exhibited an optimum drug release characteristic and could be easily handled and pulverized.

Differential scanning calorimetry (DSC) was utilized to check the compatibility of temazepam with Avicel pH 101 and magnesium stearate as well as the effect of ageing on the formulated coprecipitates, at different storage conditions. It was concluded that the drug is compatible with those tablet excipients, and no detectable changes resulted from ageing.

Compression of the formula containing 1:3 w/w temazepam-PEG 6000 coprecipitates produced good quality tablets having rapid disintegration and rapid dissolution rates. Tablets of 1:1 w/w ratio were highly compact and having a lower disintegration and a lower dissolution rates. This shows the importance of optimizing the formulations by finding out the correct quantity of excipients to maintain better dissolution properties.

The results obtained indicated that 1:3 w/w temazepam-PEG 6000 coprecipitates retains its higher dissolution when compressed as tablets. Additionally, this tablet formulation helped to provide temazepam in a high quality dosage form.

INTRODUCTION

The formulation of solid dispersions with various pharmacologically inert carriers is one of the techniques that potentially enhance the dissolution rate and extent of absorption of hydrophobic drugs. Ultimately, solid dispersions required formulation into dosage forms, either tablets or capsules. For the former, wet granulation techniques are unacceptable since aqueous
fluids would break down the dispersion destroying its fast release characteristics\(^1\). Solid dispersions may often be tacky and unhandable\(^2\), but when they are easy to pulverize direct compression, double compression, or encapsulation technique may be used. Direct compression with or without direct compression aids has been accomplished successfully for dispersions including certain drugs\(^3\)-\(^6\).

Temazepam is marketed as soft gelatin capsules containing solution of the drug in polyethylene glycol. From the technological point of view, the gelatin capsule is difficult to be manufactured and stored. In addition to the problem of leakage of the contents which seems to be a common fault with all temazepam capsules in the market, including the branded versions\(^7\), Maquire\(^8\) stated that the supply of temazepam formulated in soft gelatin capsules, however, is still presenting some problems. Many patients prefer one particular brand and refuse the others of different manufacturers because they observed inadequate or adverse clinical activity when they received a change. Maquire declared that this was not purely psychological, but there might be a fundamental difference in the pharmacokinetics of the drug. In a recent review, Ford\(^1\) mentioned many additional advantages for solid dispersions, that provide scope for the continued interest in solid dispersions. Of these advantages, maintaining the drug in a bioavailable form\(^9\), dosage reduction\(^10\) and cleaner manufacturing conditions\(^11\).

The aim of the present work is to develop a convenient dosage form of temazepam prepared in solid dispersions. As a result of the intensive studies done on solid dispersion of this drug with some hydrophilic carriers\(^12\), the best carrier, the optimum composition and the best method for the preparation of temazepam solid dispersions were chosen as a basis for the work done in this article. Based on these observations, temazepam-PEG 6000 coprecipitates were formulated as tablets.
EXPERIMENTAL

Materials and Methods:

Temazepam (Fabri
cia Italiana Sintetici, Laboratorio, Controllo Alte
Montecchio (vicenza), Italy).

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

Polyoxyethylene (40) stearate (Myrij 52), (Atlas Chemical Industries, Ltd, England).

Microcrystalline cellulose (Avicel pH 101), (F.M.C. International Food and Pharmaceutical Products, Ireland).

Magnesium stearate (B.D.H. Chemicals Ltd, Poole, England).

Apparatus:


Hp 8451 A Diode array-spectrophotometer, 98155 A with keyboard and 7470 A plotter (Hewlett packard, USA).


Roche friabilator, (J.E.L., Ludwigshafen, Rhein. W. Germany).

Methods:

Assay of Temazepam: Ultraviolet spectrophotometric method was adopted for temazepam determination alone or in various test preparations using a computerized HP 8451 Diode Array spectrophotometer. The drug absorbance was determined at 232 nm. The concentrations of temazepam were determined from the calibration curve which followed Beer's law.
Preparation of Temazepam-PEG 6000 Coprecipitates:

1:1, 1:3 and 1:7 Temazepam-PEG 6000 solid dispersions as well as controls were prepared by both solvent and fusion methods.\textsuperscript{12,13}

Characterization of the Produced Coprecipitates:

A- Ultraviolet Spectrophotometric Studies:

The U.V. studies of the pure and the processed temazepam (5 \( \mu \text{g/ml} \)) were carried out.\textsuperscript{13} The presence of the carrier did not interfere with the spectrophotometric assay of the drug, Fig. 1.

B- Thin Layer Chromatographic Investigation:

The dispersions prepared were analyzed by TLC to check the chemical stability of temazepam during processing, as mentioned before.\textsuperscript{13} It was found that the processed Temazepam was stable and no signs of degradation appeared.

C- Differential Scanning Calorimetric Studies:

DSC of the freshly prepared coprecipitates as well as the stored ones were carried out\textsuperscript{12,13} in order to determine the transition temperature and the heats of fusion.

Tablet Formulation Compatibility of Temazepam with the Suggested Tablet Excipients:

DSC technique was used to check the compatibility of temazepam with Avicel PH 101 and magnesium stearate. Thermograms for individual substances and for 1:1 w/w physical mixtures of the drug with either Avicel PH 101 or magnesium stearate were plotted. Apparatus and procedures used are described before\textsuperscript{12,13}.

Tablet Compression:

Three solid dispersion formulae were chosen from detailed studies based on the dissolution work done\textsuperscript{12} and characteristics of the solid dispersions investigated\textsuperscript{12}.  

Each tablet was formulated to contain 10 mg temazepam.

**Formula A:** (control formula)

- Temazepam powder (45-200 U) 10 mg
- Magnesium stearate 1 mg
- Avicel PH 101 to 200 mg

**Formula B:**

- 1:3 w/w Temazepam-PEG 6000 coprecipitates 80 mg
- Magnesium stearate 1 mg
- Avicel PH 101 to 200 mg

**Formula C:**

- 1:7 w/w Temazepam-PEG coprecipitates 80 mg
- Magnesium stearate 1 mg
- Avicel PH 101 to 200 mg

**Formula D:**

- 1:3 temazepam-Myrj 52 coprecipitates 40 mg
- Magnesium, stearate 1 mg
- Avicel PH 101 to 200 mg

The ingredients of each formula, except magnesium stearate, were blended in a glass jar for 25 minutes. Magnesium stearate, was sieved in and blended for an additional 5 minutes. A Manesty single punch tablet machine with concave surface was used to compress the tablets. Compression force was adjusted to give tablets of suitable hardness.

Many attempts were done to compress formula D using 1:3 w/w temazepam-Myrj 52 coprecipitates, this proved to be impossible due to cracking of the tablets produced.

**Properties of the Compressed Tablets:**

a) **Tablet Dimensions:** The height and diameter of each tablet were measured using a screw gauge micrometer. Results given are the average of ten tablet determinations.

b) **Tablet Hardness:** The tablet crushing strengths (kg) of eight tablets were determined using the Heberlein hardness tester.

C) **Disintegration time:** The disintegration of the tablets was studied at 37 ± 0.5°C using the disintegration test apparatus of the British
pharmacopoeia with the disc. Values are the average of two determinations.

d) Uniformity of Drug Content: Five tablets were selected randomly from each batch. Each tablet was ground in a mortar, washed quantitatively into a volumetric flask with absolute ethanol. The contents of the flask were shaken well for 30 minutes, filtered and 2.5 ml of the filtrate was diluted to 50 ml with distilled water. The diluted aqueous solution was assayed for its temazepam contents.

f) Dissolution Rates: The dissolution rates of the tablets was determined using Erweka dissolution apparatus. The dissolution medium was 900 ml distilled water of 37°C. The dissolution medium was automatically measured for its drug content in a continuous spectrophotometric flow system. A filter tip was fixed to the inlet tube, also, inlet and exit of the tubes were fixed. Agitation of the dissolution medium was accomplished by a stirrering paddle at a rate of 100 r.p.m. A cylindrical stainless steel basket was fixed to the end of the rotating shaft instead of the blade. One tablet was placed in the basket and the dissolution profile of the drug was recorded and drawn at 232 nm for 30 minutes.

RESULTS AND DISCUSSION

Since it was believed that incorporation of solid dispersions into tablets provides a dosage form with fast release properties relative to test tablets of untreated drug, a trial was made to apply this technique to prepare good quality tablets of temazepam, to evaluate the effects of tabletting on the drug release from solid dispersions.

The selection of the most suitable dispersion carrier, drug:carrier ratio and the best method of preparing the solid dispersions for the construction of the tablet formulae were based on the data obtained from the dissolution rate studies. Those preparations provided solid dispersions having the highest dissolution rates were selected.
Direct compression technique was chosen to manufacture solid dispersion tablets, as it is advantageous in terms of low cost, simplicity and product stability. Microcrystalline cellulose was used as a directly compressible vehicle for the preparation of temazepam solid dispersion tablets. Magnesium stearate was selected as a lubricant.

Compatibility of Temazepam with the Suggested Tablet Excipients:

Differential scanning calorimetry was utilized to check the compatibility of temazepam with the suggested tablet excipients.

The DSC thermogram of temazepam (Trace 1 of Fig. 2) showed a melting endotherm at 162°C, with a heat of fusion ($\Delta H_f$) of 27.5 kJ/mole. The DSC thermogram of Avicel PH 101 (Trace 2 of Fig. 2) showed no characteristic features at the temperature of interest (35-175°C).

As a rule, if the DSC thermogram of an equal mixture of the drug and the excipient reflects the characteristic features of the thermograms of each component, it could be concluded that there is no interaction between them, i.e., there is no physicochemical incompatibility, and vice versa. It was found that the DSC thermogram of 1:1 w/w mixture of temazepam-Avicel PH 101 (Trace 3 of Fig. 2) showed the combined features characteristic of the thermograms of each component. The heat of fusion, kJ/mole, was found to be quantitatively identical to the predicted value of temazepam (27.5 kJ/mole) indicating no incompatibility under these conditions.

DSC thermograms of magnesium stearate (Trace 2 of Fig. 3) showed two broadened transitions at about 72°C and 100°C respectively. DSC thermogram of 1:1 w/w temazepam-magnesium stearate (Trace 3 of Fig. 3) combined the features characteristic of the thermograms of each component, but with a slight broadening of the temazepam melting endotherm. The heat of fusion of temazepam (27.5 kJ/mole) was found to be quantitatively identical to the predicted value indicating no incompatibility between temazepam and magnesium stearate under the condition of the test.
In a similar manner, El-Shattawy\textsuperscript{19} has found that anhydrous ampicillin was compatible with Avicel PH 101, Avicel PH 105, Elcema F 150, STA-RX 1500 and Cab-O-Sil, while incompatible with sorbitol and dicalcium phosphate dihydrate.

Therefore, DSC can distinguish between those excipients unlikely to cause a problem and those that may cause troubles and thereby a more rational approach to early formulation designs could be established. Although it can be conclusively studied that an incompatibility interaction will occur during storage at room temperature, this method can give an early warning of such a possibility\textsuperscript{12}.

In order to predict any thermal and crystalline changes that may happen on ageing of temazepam coprecipitates intended to be formulated into the tablets under investigation, DSC of some of the stored samples were compared with those of fresh ones, Fig. 4 & 5. Fig. 4, shows the effect of ageing on temazepam stored at 37 and 45°C. It is obvious that there is no change in the shape of the thermogram. Only a slight increase in melting point about (1-2°C) was observed on ageing. This increase is possibly due to a very slight increase in the crystal size or due to the trapped air.

Fig. 5 shows the effect of storage conditions (20°C/75% R.H, 37 and 45°C) on 1:3 w/w temazepam-PEG 6000 coprecipitates. It is obvious that the fresh and the aged samples are very similar, showing one melting endotherm of PEG 6000 and in both cases disappearance of the characteristic melting endotherm of temazepam. This clearly indicate that temazepam is still present in the stored coprecipitates as very fine crystallites or the amorphous form. Thus ageing of the formulated coprecipitates did not produce any detectable changes.
Properties of Temazepam Tablets:

Tablets prepared from temazepam and its PEG 6000 dispersions by the direct compression technique have a white and shiny appearance. Table 1 shows the properties of the prepared tablets. Generally, these results indicate the possibility of producing directly compressed temazepam tablets having satisfactory properties. Although it is believed that there is a great chance of drug content per tablet variation, it was found that temazepam tablets prepared using this technique have reasonable uniformity of drug content.

As 1:7 w/w temazepam-PEG 6000 coprecipitate in powder form showed the highest dissolution rate, it was expected that the drug release rate from formulated tablets would be superior. Actually, this is not the case as those tablets showed the lowest dissolution, Table 1. Comparison of the T50%'s and the relative dissolution rates of the prepared tablets gave the rank order for the dissolution of test tablets: 1:3 w/w coprecipitate > untreated temazepam > 1:7 w/w coprecipitate tablets. Upon further examination of the results in Table 1, it is clear that the poor dissolution of the tablets prepared from 1:7 w/w temazepam-PEG 6000 coprecipitate was due to the poor disintegration properties of the tablet. This could be noticed in tablets containing higher proportion of PEG 6000 than those of 1:3 w/w coprecipitate tablets. It appears that high PEG 6000 content is undesirable during direct compression of solid dispersions because it produces highly compacted and tacky tablets resulting in delaying disintegration. Ford has concluded that tablets containing high PEG 6000 levels were hard and capping occurred during compression. The present results indicate that direct compression of 1:3 w/w temazepam-PEG 6000 coprecipitate (Formula B) produces tablets having very rapid disintegration and a high dissolution rate. This shows the importance of optimizing formulations by finding the correct quantity of excipients to maintain good dissolution properties without tackiness.
Fig. 6 shows the marked superiority in dissolution rate of the 1:3 w/w temazepam - PEG 6000 coprecipitate tablets over the drug alone and 1:7 w/w temazepam -PEG 6000 coprecipitates in tablets. This effect may be partially due to the rapid disintegration of the former tablets when they become in contact with the dissolution medium. This fact, beside the other mechanisms which lead to a higher drug release from its coprecipitate may account for the observed higher dissolution rate for the tablets containing this ratio of the coprecipitating agent.
Interaction of Temazepam With Certain Macromolecules
VIII-Formulation of Tablets Containing Temazepam
Solid Dispersions

Fig. 1: UV-absorption spectra of Temazepam (1), 1:1 w/w Temazepam-PEG coprecipitate (2) and 1:7 w/w Temazepam-PEG 6000 coprecipitate (3).

Fig. 2: DSC thermograms of Temazepam (1), Avicel PH 101 (2) and 1:1 w/w Temazepam-Avicel PH 101 mixture.
FIG. 3: DSC THERMOGRAMS OF TEMAZEPAM (1), MAGNESIUM STEARATE (2) and 1:1 W/W TEMAZEPAM-MAGNESIUM STEARATE MIXTURE.
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Fig. 4: The Effect of Ageing on DSC Thermogram of Temazepam of
Temazepam Stored At Various Conditions.

Key: A, Fresh Sample  B, Sample Stored at 37°C.
     C, Sample Stored at 45°C.

Fig. 5: The Effect of Ageing on DSC Thermograms of 1:3 w/w
Temazepam-PEG 6000 Coprecipitate Stored at Various Conditions.

Key:  A, Fresh Sample
     B, Sample Stored at 20°C. -75 % R.H. for 8 months
     C, Sample Stored at 37°C for 8 months.
     D, Sample Stored at 45°C for 8 months.
PEG 6000 COPRECIPITATES IN TABLET FORM: MEAN OF 4 DETERMINATIONS.

FIG. 6: DISSOLUTION PROFILES OF TEMAZEPAM TABLETS (CONTROL AND

TIME (minutes) vs TEMAZEPAM RELEASED (mg)

KEY

+ I.7%, CTR

* I.3%, CTR

CTRL
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<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Hardness (kgf)</th>
<th>Friability (%)</th>
<th>Dissolution Parameters R.D.R (min.)</th>
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<td>2.41</td>
<td>0.24</td>
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**Table 1:** Physical properties of tablets prepared by direct compression of Remazetham solid dispersions.
REFERENCES

تفاعلات التيمازيبام مع جزيئات كبيرة معينة:

- صياغة آقراص تحتوي على المتراسات الطلبية للتيمازيبام

على عبد الراوحت عبد الرحمن - أحمد السيد أبو طالب - براين أرثر ميل - سيد محمد أحمد
قسم الميبلة الصناعية - كلية الصيدلة - جامعة أسوان - مصر
كلية الصيدلة - جامعة براد فورد - إنجلترا.

صُنعت متراسات التيمازيبام مع عديد ايثلين جليكول ٤٠٠٠ كيأتم روص وتعضبله.

وقد اختُبر هذا المتراسب لأنه أعطي أعلى معدل اتاحة كما أنه من السهل تناوله وتعضبله.

ولكن استخدم المسح التفاعلي السريري وذلك لاختبار توافق التيمازيبام مع الأفيسب ٢٠٠ وضرات المافينسيوم وكذلك تأثير التخزين على المتراسات في ظروف تخزين مختلفة. ولقد استنتج أن التيمازيبام متوافق مع المواد المدكورة والمستخدمة كمواد للقراص، ولم تحدث كذلك أي تغييرات ملموسية بالتخزين.

وقد نتجت اقراس لها معدل اتاحة وتفتت سريع وذلك عند كيس المتراسات التي تحتوي ١:٣ وزنًا على وزن من التيمازيبام: عديد ايثلين جليكول ٤٠٠٠ و.١.

أما الأقراس التي تحتوي على نسبة ٧:١ فقد نتجت أقراس عالية التحمس ونها معدل تفتت واتاحة أقل.

وهذا يوضح أهمية نسبة المخادف في تحقيق اتاحة أعلى للالتزامات المفعمة.

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