INTERACTION OF TEMAZEPAM WITH HYDROPHILIC MACROMOLECULES

VI-PREPARATION, DISSOLUTION CHARACTERISTICS AND
AGEING OF TEMAZEPAM SOLID DISPERSIONS

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ABSTRACT

Temazepam solid dispersions were prepared using the solvent and the fusion methods with certain hydrophilic carriers including polyethylene glycol 6000 (PEG 6000), Murj 52, polyvinyl pyrrolidone 10000 (PVP 10000), and polyvinyl pyrrolidone 40000 (PVP 40000).

It was found that the solvent method is preferable than the fusion method.

Thin layer chromatographic investigations revealed that there was no chemical degradation of the drug or the carriers through processing.

Intra Red analysis revealed that there was no evidence for complexation between temazepam and the investigated carriers nor decomposition of the drug.

Differential scanning calorimetry (DSC) investigations illustrated that the drug present in the co-precipitates in the amorphous form in the fresh samples as well as the aged-ones. HPLC in the aged samples proved no drug degradation.

INTRODUCTION

A solid dispersion is an ultrafine dispersions of a solid drug in a solid inert carrier. The dispersion of such a drug or drugs within a water-soluble carrier effectively causes a reduction in particle size of the dispersed drug. The pharmaceutical applications of solid dispersion systems were extensively reviewed1-3.
The application of solid dispersion technique in the pharmaceutical technology includes producing more efficient and predictable drug therapy for griseofulvin by dispersing it in PEG 6000 (1:9 w/w drug: carrier) by either solvent or fusion method\(^4\)-\(^7\).

The solid dispersion of acetyl salicylic acid in PEG 6000 has less injury for gastric mucosa\(^8\) than the drug alone. Granules of chlorpropamide-urea solid dispersion were prepared using a modified bowl granulator. Similarly, granules of indomethacin-PEG 6000 dispersions were prepared\(^9\).

The present work presents the preparation of solid dispersions of temazepam with different hydrophilic carriers in order to enhance its dissolution and subsequently its absorption. The investigation of the prepared dispersions by different techniques as well as ageing of these dispersions were performed.

**EXPERIMENTAL**

**Materials:**

Temazepam (Fabbrica Italiani Sintetici Laboratorio, Controllo Aite Montecchio (vicenza), Italy).

Polyethylene glycol 6000 (PEG 6000), (BDH Chemicals Ltd, Poole, England).

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

Polyvinyl pyrrolidone 10000 (PVP 10000), (Aldrich Chemical Co. Ltd., Gillingham, Dorset, England).

Polyvinyl pyrrolidone 40000 (PVP 40000), (Sigma Chemical Company, USA).

**Apparatus:**

Dissolution apparatus (Erweka Apparatebau, G. m.b.H., West Germany).


Perkin Elmer I.R. spectrophotometer 297 (Perkin Elmer Ltd, Beaconsfield.) USA.
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High pressure liquid chromatograph (HPLC) with variable wave length UV detector (Pye Unicam, England).

Methods:
Preparation of the Test Systems:

A- Solid dispersions:

1) Solvent method: This method was used for the preparation of 1:1, 1:3 and 1:7 w/w temazepam-PEG 6000 or Myrj 52 dispersions respectively. Both components were dissolved in a minimum amount (25 ml) of 1:1 acetone-methanol mixed solvent. The solvent was evaporated in vacuum at room temperature. The residue was dried to a constant weight in a vacuum desicator. The coprecipitates were pulverized and screened to a particle size of 45-200 μ. The same procedure was adopted for the preparation of 1:1 w/w temazepam PVP 10000 (as higher ratios of PVP 10000 interfered with the spectrophotometric assay of the drug as the former contains impurities) and 1:1. 1:2 w/w temazepam-PVP 40000 coprecipitates.

11) Fusion method: 1:1 and 1:3 w/w temazepam-PEG 6000 were mechanically mixed and melted using an oil bath. The beakers containing the melts were carefully dipped in ice. The solidified masses were dried in a vacuum desicator, pulverized and screened as before.

B- Physical mixtures:

Accurately weighed quantities of sieved temazepam and carriers (45-200 μ) were mechanically mixed in a ratio of 1:3, 1:7 w/w temazepam-PEG 6000 and 1:2 w/w temazepam-PVP 40000. With Myrj 52 as a carrier however the preparation of a homogeneous physical mixture proved to be impossible, because of its waxy nature.

Predetermined quantities of the prepared samples were assayed for its drug content using the UV method to insure uniformity of mixing.

Controls: Temazepam samples as controls were prepared: (a) Untreated and as received, (b) precipitated from 1:1 acetone-methanol, and (c)Fused. All were screened to produce 45-200 μ particles.
Characterisation of the Prepared Systems:

A- Ultraviolet Spectrophotometric Studies (UV): Stock solutions of the pure and the processed temazepam in absolute ethanol were prepared. Fractions of each stock solution were diluted with distilled water so as to contain 5 ug/ml temazepam. Spectral characteristics of the diluted solutions were scanned from 200-450 nm and plotted in a comparative manner.

B- Thin Layer Chromatographic Investigations: The dispersions prepared were analyzed using TLC to check the chemical stability of temazepam during processing. Both of the non-processed and the processed samples were dissolved in chlorform (5000 ug/ml) and approximately constant volumes of each were spotted on silica gel G-F 254 plates (Merk). The plates were developed using chlorform-acetone (9:1 v/v) solvent system and examined under UV light. The plates were also examined after spraying with 1% w/w potassium permanganate solution.

C- Infra Red Analysis (IR): A qualitative IR analysis using potassium bromide disc method has been performed for 2 mg temazepam-PEG 6000 solid dispersions and physical mixtures. PEG 6000 was considered as a representative of the investigated carriers.

D- Differential Scanning Calorimetric Investigations (DSC):

Ten mg of each of the prepared test preparations was placed in a crimped aluminium sample pan with a pierced lid. The sample was programmed heated at the rate of 10°C/minute in a dynamic nitrogen gas environment from 30-175°C. The melting endotherms are shown in Figs. 1-3. Duplicate measurements were carried out on each sample. The instrument was calibrated with an indium standard.

E- Determination of the Polymer Crystallinity in the Prepared Systems:

1:1, 1:3 and 1:7 physical mixtures and coprecipitates of temazepam-PEG 6000 were prepared. The same steps adopted for performing the DSC studies mentioned before were utilized for plotting the thermogram for each of the physical mixtures or coprecipitates (sample weight 4-10 mg).

The melting endotherms of the polymer were integrated to calculate the heat of fusion (ΔHf) and the transition temperature (C). ΔHf,s(KJ/mole) were used directly to evaluate the DSC crystallinity of the polymer, Fig.4 and Table 1.
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**F- Dissolution Studies:** Powdered temazepam (8 mg, 45-2000 U) or a certain weight of coprecipitate, melt or physical mixture (45-200 U), equivalent to 8 mg of the pure drug was sprinkled over the surface of 900 ml of the dissolution medium (deionized double distilled deaerated water of 37°C). A stirring paddle was used for agitating the solution at a rate of 100 r.p.m. The dissolution medium was automatically measured for its drug content in a continuous flow system. The dissolution results are seen in Figs. 5-7 and Tables 2,3.

**G- Solubility Studies:** Temazepam solubility in PEG 6000, Myrj 52, PVP 10000 and PVP 40000 solutions were measured as follows: An excess of the pure drug was shaken (130 strokes min.\(^{-1}\)) with different concentration of carrier solutions in water (10 ml) for equilibrium time of 24 hours in a constant temperature water bath of 37°C. An aliquot (2 ml) was taken and diluted to 50 ml with distilled water and assayed spectrophotometrically for its temazepam content at 232 nm, Table 4.

**The Effect of Ageing in Certain Storage Conditions on the Properties of Temazepam Coprecipitates:**

1:3 and 1:7 w/w temazepam-PEG 6000 coprecipitates were stored at 4, 37 and 45°C. The coprecipitates were also stored in a temperature and humidity controlled room, 20°C/40% or at 20°C/75% relative humidity provided by saturated sodium chloride solution. Samples were stored in tightly sealed containers except those tested for humidity. After eight months, the rate of the drug dissolution from the stored samples were determined as mentioned before, (Figs. 8-10). Sieved temazepam powder (45-200 U) was treated similarly.

HPLC and DSC were utilized to predict any changes that might happened for the drug upon storage.

A) **HPLC Investigation for the aged Samples:** HPLC procedure was used for the assay of temazepam content of the aged coprecipitates and to check the presence of possible decomposition products.

A pye Unican high pressure liquid chromatograph equipped with a UV detector and a partisil-10 ODS reversed phase column; 25 cm length, 4.5 mm i.d. was used.
The flow rate was set at 2 ml/minute and pressure of 2500 psi. The column was kept at ambient temperature and the recorder chart speed was 1 cm/minute. Quantitation of the drug was done by peak height method. The mobile phase used was a mixture of acetonitrile, methanol and water (20:20:60 v/v) containing 0.005 M of 1-pentane sulphonic acid. Diazepam was used as internal standard. A standard solution containing 10 µg/ml of fresh and pure temazepam and diazepam dissolved in the mobile phase was prepared. Hundred ul of the prepared standard solution was injected to check the suitability of the above mentioned conditions for the assay method.

HPLC Calibration Curve of Temazepam: Stock solutions (100 µg/ml of both pure temazepam and pure diazepam in HPLC-grade methanol were prepared.

Solutions containing variable concentrations of temazepam (50, 25, 5 and 2 µg/ml) and a constant concentration of diazepam (10 µg/ml) were prepared by pipetting suitable fractions of the stock solutions into a 10 ml volumetric flasks and diluting them to volume by the mobile phase. Hundred ul of each of the dilute solutions were injected. The peak height ratios of temazepam/diazepam were plotted versus temazepam concentration. Regression analysis was applied to construct the line of the best fit.

Assay of temazepam in the aged samples using HPLC: Solutions (100 µg/ml) of some of the aged temazepam and coprecipitates stored at various conditions were prepared by dissolving 10 mg of the drug or a certain weight of the coprecipitates containing an equivalent amount in methanol. One ml of the methanolic diazepam solution (10 µg/ml) and 1 ml of each of the methanolic solutions of the above prepared sample solutions were pipetted into a 10 ml volumetric flask and diluted to volume with the mobile phase. Hundred ul of each of the dilute solutions (10 ul/ml diazepam and 10 ul/ml temazepam were injected). The peak height ratios of temazepam/diazepam were measured and the temazepam concentration in µg/ml were determined from the calibration curve.

B- DSC Studies for the aged samples: DSC thermograms of temazepam stored at the previously mentioned conditions were drawn in comparison with that of the fresh sample. Additionally, DSC-thermograms of 1:3 w/w temazepam-PEG 6000 coprecipitates stored for 8 months at different storage conditions were compared with that of the fresh coprecipitates.
RESULTS AND DISCUSSIONS

UP 8451 Diode Array spectrophotometer with a built in computer has been used for temazepam assay in the different preparations. It was found that the presence of the macromolecules investigated did not interfere with the spectrophotometric assay of the drug if PVP concentration was lower than 0.0025 %.

TLC chromatograms of temazepam prepared systems showed a single fluorescent spot of the same $R_f$ value (0.67 cm) under UV light for both the pure and the processed drug. Similarly when the plates were sprayed with 1 % w/v potassium permanganate only one spot with the same $R_f$ value was obtained. Faint yellow spots ($R_f$ of zero) were visible on the base line for all the systems containing carriers but not for the pure and the fused drug samples.

The IR spectra for the prepared samples were carried out. The spectrum of temazepam alone was found to be identical with a reference spectrum of the drug. Both show NH and OH stretching from 3500 cm$^{-1}$ to 3300 cm$^{-1}$ and C = O stretching at 1690 cm$^{-1}$.

Temazepam-PEG 6000 physical mixtures and coprecipitates showed the absorption bands illustrating the presence of temazepam and the carrier. Also, those spectra showed no evidence of peak shift or variation in comparison with the reference spectrum, i.e. no evidence for complexation between temazepam and the investigated carrier in the solid state. Both TLC and IR spectroscopy proved that the coprecipitation method lead to neither complexation nor decomposition of the drug.

Fig. 1 shows the melting endotherm of temazepam coprecipitated with PEG 6000. It shows a single melting endotherm for the carrier at 60°C Whereas Myrj 52, Fig. 2, shows a forked melting endotherms for the carrier. Similar reports
suggested that double melting endotherms of some carriers were due to either two molecular weight fractions or due to two configurations in the solid state. Coprecipitates containing 50% temazepam (1:1 w/w temazepam-carrier) show a small endotherm of the drug in addition to the endotherm of the carrier in both PEG- and Myrj 52. These small endotherms are due to the melting of temazepam. Disappearance of the melting peak of temazepam on increasing the carrier concentration (as illustrated by 1:3 and 1:7 w/w drug: carrier ratios) indicated that the drug in those test preparations might have lost its crystalline structure. In other words, this indicate the presence of the drug in an amorphous from or in extremely fine crystallities. Similar findings were found by Takayama et al.\textsuperscript{15,16}.

However, the thermogram of 1:2 w/w temazepam-PVP 40000 coprecipitate, Fig. 3, show two melting endotherms. The first endotherm, at lower temperature, is broad with no measurable peak temperature corresponding to that of PVP. The second one is attributed to the melting of the crystalline temazepam.

Recently, Ford et al.\textsuperscript{17} stated that the crystallinity of the polymer controls the drug release rate from solid dispersions during dissolution rate study.

The crystallinity of PEG 6000 coprecipitated with temazepam was chosen as a representative example to investigate the effect of the polymer crystallinity on temazepam release rate. A calibration curve was constructed by plotting $\Delta H$ values obtained upon integration of the melting peak of the polymer in a physical mixture with temazepam, Fig. 4. From the $\Delta H_f$'s obtained upon melting of the coprecipitates, the percent crystallinity of PEG 6000 was calculated (referred to the calibration curve), Table 1. It is clear from the results obtained, Table 1 and Fig. 1, that temazepam in a solid dispersion with PEG 6000 tend to decrease the crystallinity of the polymer\textsuperscript{17}. 
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The dissolution profiles of temazepam-Myrj 52 and temazepam-PVP 40000 physical mixtures and solid dispersions are shown in Figs. 5 and 6, while Table 2 shows the T 50% and the RDR for temazepam solid dispersions and physical mixtures with PEG 6000, Myrj 52, PVP 10000 and PVP 40000. Examination of these profiles show that presenting the drug in the form of a solid dispersion enhanced the release rate over that of the pure untreated drug. To account for this effect and thus enable a valid comparison between the drug release rate from varying compositions, T 50%'s and RDR's were calculated.
(The relative dissolution rate is the ratio of the amount of the drug dissolved from physical mixture or coprecipitate divided by the amount dissolved from the pure drug at the same time interval), Table 2. The RDR of temazepam after 6 minutes were plotted against the composition of the test preparations, Fig. 7. Generally, the release rate of temazepam become greater with increasing the carrier content.

1:1, 1:3 w/w drug-PEG 6000 were prepared according to the solvent and the fusion methods. Table 3 shows the data for the dissolution rates of temazepam-PEG 6000 solid dispersions prepared by the two methods indicating the superiority of the former. The total surface of the drug, seems the most likely explanation for the difference.

The solubility of temazepam in the investigated carriers at different concentrations is shown in Table 4. The possibility of this effect to occur depends on the ability of the carrier to be partially and completely dissolved creating an area of high carrier concentration immediately surrounding the drug particle during the early stage of dissolution process. It follows that, for the temazepam carrier systems, as the carrier content in the solid dispersion composition is lowered, the concentration of the carrier in the diffusion layer will decrease, and as a consequence, the degree of microenvironmental solubilization will be reduced.
Many dispersions contain molecularly dispersed drugs, are susceptible to changes during storage.\textsuperscript{22-25}

Temazepam-PEG 6000 coprecipitates were selected as an illustrative example for this purpose. Table 5 shows the dissolution profiles of temazepam alone and its coprecipitates (1:3 and 1:7 ratios) after 8 months storage at various conditions. It could be concluded that the storage of temazepam at 4\degree, 20\degree-40 \% R.H., 37 and 45\degree C caused little change in the drug T 50\% which may be considered negligible as it is, within experimental error. For coprecipitates kept at 4 \degree C, 20\degree-40\% R.H., and 37\degree C. The T 50\% of the drug remained substantially constant, whereas for those kept at 45\degree C a decrease in dissolution rate relative to that of the fresh sample was observed. In an attempt to fully assess the causes for that change in dissolution rate, DSC and HPLC techniques were used.

DSC was used to detect change in the crystalline state of temazepam within the dispersions. In addition, HPLC was used to check the chemical stability of the drug.

A) \textbf{HPLC:} It is preferred as it differentiates, between the drug and its degradation products if any.\textsuperscript{26}

It was found from the chromatogram for temazepam that the retention time is 6.25 minutes and the internal standard, diazepam, have a retention time of 10.5 minutes. Plotting of the peak height ratios versus temazepam concentration gave a straight (r equals 0.9999) line. Table 6 shows the analysis data for temazepam contents for some coprecipitates stored for 8 months. These data clearly indicate that coprecipitates stored at lower temperature (20\degree C-40\% R.H.) were stable and no degradation could be observed. However, coprecipitates stored at 45\degree C showed slight degradation which lead to drop in the content of intact temazepam. The presence of certain level of impurities in PEG may be responsible for the observed degradation.\textsuperscript{27}

Similar findings were observed by Khalil et al.\textsuperscript{28} upon examination of the stability and dissolution rates of corticosteroids coprecipitates.
B) **DSC**: DSC of some of the stored samples were compared with those of the fresh ones. Fig. 8 shows the effect of ageing on thermograms of temazepam stored at 37 and 45°C. It is obvious that there is no change in shape of the thermogram, only slight increase in melting point (about 1-2°C) was observed in comparison with the melting endotherm of the fresh pure drug, trace A. This increase is possibly due to a very slight increase in the crystal size\(^29\) or due to the trapped air.

Comparison of the thermograms of 1:3 w/w temazepam-PEG 6000 coprecipitates stored for 8 months at different storage conditions with those of the fresh ones is shown in Fig. 9. It is obvious that the thermograms 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 a very fine crystallities or amorphous, the size of which falls below the limit of the DSC analysis. As concluded from the DSC investigation ageing of the samples did not produce any detectable changes in the state of temazepam coprecipitates even those stored at 45°C.

Thus the observed decrease in the dissolution rate cannot be explained on the basis of the changes in the drug crystals, but to the degradation of a small portion of temazepam which has been detected by HPLC.
Table 1: DSC-Crystallinity of PEG 6000 Coprecipitated with Temazepam

<table>
<thead>
<tr>
<th>Temazepam Concentration (w/w)</th>
<th>Percent Crystallinity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>95.5</td>
</tr>
<tr>
<td>20</td>
<td>95.0</td>
</tr>
<tr>
<td>30</td>
<td>93.0</td>
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<td>40</td>
<td>92.5</td>
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<td>50</td>
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<td>60</td>
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<tr>
<td>70</td>
<td>86.5</td>
</tr>
<tr>
<td>80</td>
<td>85.0</td>
</tr>
<tr>
<td>90</td>
<td>80.6</td>
</tr>
</tbody>
</table>

* Mean of five determinations at least.

Table 2: Dissolution Half Lives and R.D.R. for Temazepam-Macromolecule Coprecipitates and Physical Mixtures.

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Ratio of Drug:Macromolecule</th>
<th>T50 (minutes)</th>
<th>R.D.R. (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.3</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.9</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:3</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 6000</td>
<td>1:1</td>
<td>4.8</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>1.2</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>1:7</td>
<td>0.5</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>6.00</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myrj 52</td>
<td>1:1</td>
<td>4.8</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>1.2</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>1:7</td>
<td>0.5</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>6.00</td>
<td>9.6</td>
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<tr>
<td>PVP 10,000</td>
<td>1:1</td>
<td>5</td>
<td>7.5</td>
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<tr>
<td></td>
<td>1:2</td>
<td>3.00</td>
<td>12.0</td>
</tr>
<tr>
<td>PVP 40,000</td>
<td>1:1</td>
<td>1.00</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>6.00</td>
<td>7.8</td>
</tr>
</tbody>
</table>

# Pure drug in absence of macromolecules.
* R.D.R. = Relative Dissolution Rate is the ratio of the amount of the drug dissolved from physical mixtures or coprecipitates divided by the amount dissolved from the pure drug at the same time interval.
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Table 3: Dissolution Half-Lives and R.B.D. of Temazepam-
PEG 6000 Solid Dispersions Prepared by the Solvent
and the Fusion Methods.

<table>
<thead>
<tr>
<th>System</th>
<th>Solvent Method</th>
<th>Fusion Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T50X (minutes)</td>
<td>T50X (minutes)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Control</td>
<td>15.5</td>
<td>1</td>
</tr>
<tr>
<td>1:1 w/ temazepam-PEG 6000</td>
<td>4.3</td>
<td>10.3</td>
</tr>
<tr>
<td>1:3 w/ PEG 6000</td>
<td>3.4</td>
<td>14.9</td>
</tr>
</tbody>
</table>

* Pure drug in absence of macromolecules.

Table 4: Solubility of Temazepam in Different Macromolecule
Solutions at 37°C.

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Temazepam Solubility (mg/wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macromolecule concentration (%v)</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>14.64</td>
</tr>
<tr>
<td>Myrj 52</td>
<td>16.00</td>
</tr>
<tr>
<td>PVP 40,000</td>
<td>14.52</td>
</tr>
<tr>
<td>PVP 10,000</td>
<td>14.52</td>
</tr>
</tbody>
</table>

Temazepam water solubility is 14.4 mg%.

Table 5: Effect of Ageing on the Dissolution Rates of Temaze-
ptam from its Coprecipitates Stored at Different Con-
ditions.

<table>
<thead>
<tr>
<th>System</th>
<th>Fresh Sample</th>
<th>Stored for 8 Months at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20°C</td>
</tr>
<tr>
<td>Temazepam alone</td>
<td>T50X (min)</td>
<td>15.5</td>
</tr>
<tr>
<td>1:1 w/ Temazepam-PEG 6000 coprecipitate</td>
<td>T50X (min)</td>
<td>3.37</td>
</tr>
<tr>
<td>1:3 w/ Temazepam-PEG 6000 coprecipitate</td>
<td>T50X (min)</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Table 1: Percentage Temazepam Remainder (HPLC determined) in Aged Samples Stored for 8 Months.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Storage Conditions</th>
<th>Temazepam Remaining (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:3 (w/w) Temazepam-PEG 6000 coprecipitate</td>
<td>20°C (40% R.H.)</td>
<td>99.4</td>
</tr>
<tr>
<td>1:7 (w/w) Temazepam-PEG 6000 coprecipitate</td>
<td>45°C</td>
<td>94.6</td>
</tr>
<tr>
<td>1:3 (w/w) Temazepam-PEG 6000 coprecipitate</td>
<td>60°C</td>
<td>54.4</td>
</tr>
<tr>
<td>1:7 (w/w) Temazepam-PEG 6000 coprecipitate</td>
<td>70°C</td>
<td>44.4</td>
</tr>
<tr>
<td>Temazepam alone</td>
<td></td>
<td>34.4</td>
</tr>
</tbody>
</table>

FIG. 1: DSC Thermograms of Temazepam-PEG 6000 Coprecipitates (1) Temazepam alone, (11) PEG 6000 alone. % values represent the percent of temazepam present in the final solid dispersions.
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Figure 2: DSC thermogram of Temazepam-HPM 52 coprecipitates.

Figure 3: DSC thermogram for 1:2 w/w Temazepam-PVP 40,000

coprecipitates.

Figure 4: Effect of Temazepam on the melts of PEG 4000

gained from ESC-adsorption.
FIG 5: DISSOLUTION PROFILES OF TEMAZEPAM-WYRJ 52 COPRECIPITATES.

FIG 6: DISSOLUTION PROFILES OF TEMAZEPAM-PVP10000 (A) & PVP40000 (B) COPRECIPITATES (COP) AND PHYSICAL MIXTURE (MIX).
Interaction of Temazepam with Hydrophilic Macromolecules VI—Preparation, Dissolution Characteristics and Ageing of Temazepam Solid Dispersions.

Figure 7: Dissolution Rate—Composition Profiles for Temazepam COP Precipitates (COP) & Physical Mixture (MIX)

Figure 8: The Effect of Ageing on DSC Thermogram of Temazepam Store:
Key: A. Fresh Sample.
B. Sample Stored at 52°C.
C. Sample Stored at 4°C.
Fig. 9: The effect of aging on DSC thermograms of LD/HM coprecipitated material stored at various conditions.

**Key:**
- A. Fresh sample.
- B. Sample stored at 20°C, 75% R.H. for 8 months.
- C. = = = 37°C for 8 months.
- D. = = = 45°C for 8 months.
REFERENCES

تفاعلات التيمازيبام مع رسوبات كبيرة محلية للماك 6 تحذير
وخصائص الاتاحة وتأثير التخزين على التيمازيبام من مشتقات الصلبة

على عبد الظاهر عبد الرحمن ـ أحمد السيد أبوطالب ـ براين آرثر مللي ـ سيد محمد أحمد
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وقد وجد أن طريقة الإذابة أفضل من طريقة الانغامية في التحضير.

وقد كشفت كروماتوجرافيا الطبقة الصلبة وكذلك الإختيارات تحت الحفر الصغيرة أن لا يوجد أي تحلل كيميائي للعقار أو الحوامل موضع الدراسة خلال التحضير أو الدراسة.

وقد كشف التحليل التفاضلي السريع أن العقار متواجد في المتراسات المحضررة في الصورة الفيبر بولورية أو الصورة البليورية المختصرة.

وقد حسبت النسبة المئوية للبلازما عديد ايثيلين جليكول 2000 وذلك في حرارة الانغامية المعطاه من المتراسات المختصرة. وقد وجد أن التيمازيبام يقلل من مدة حياة عدد ايثيلين جليكول 2000 في المتراسات المحضررة.

وقد وجد أن صياغة العقار في مشتقات صببة وكذلك زيادة نسبة المكونة للحوامل في المتراسات المحضررة يؤدي إلى زيادة ملحوظة في معدل اتاحية العقار.

وقد درست تأثير التخزين فترة سبعة أشهر في ظروف معينة على المتراسات الصلبة المحضررة.

وقد استخدم كروماتوجرافيا السوائل تحت فضفاض تحليل التفاضلي السريع في دراسة تأثير التخزين على شبات المتراسات الصلبة المحضرية وخصائصها. وفقا لنتائج أثبتت النتائج أن التخزين في درجة حرارة مختارة (40 درجة مئوية / رطوبة 70%) تسبب تحلل كيميائي بينما التخزين في درجة حرارة عالية نسباً (60 درجة مئوية) سبب قليل من التحلل.

وقد أدت التحليل التفاضلي السريع أن الأشكال الحرارية للعينات المخزنة متماثلة تماماً من العينات المحمرة خديها مما يثبت أن التيمازيبام في مشتقاته المخزنة مازال موجوداً في شكل البليوري الدقيق في العينات المخزنة لثماني سنوات.

وقد ثبت أيضاً أن التخزين لن ينتج أي تغيير ملموس في الصورة البليورية الدقيقة للتيمازيبام حتى عند التخزين عند 40 درجة مئوية.

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