STABILITY STUDY OF ORAL LYOPHILISATE OF MIDAZOLAM-HCL IN DIFFERENT PACKING MATERIAL

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Introduction

Midazolam, a short-acting benzodiazepine, has become one of the most frequently used preanaesthetic medications to alleviate the stress and fear before surgery for both adults and children. Although IV or IM administration can typically assure a rapid effect, they may provoke a dramatic effect on the patient compliance. On the other hand, oral administration can presents some important drawbacks, such as difficulties in swallowing and extensive first pass effect. However, a freeze-dried dosage form could avoid the disadvantages. The highly porous structure supports a rapid disintegration in the mouth without the requirement of water [1].

The purpose of this study was to evaluate the stability of a midazolam-HCl-lyophilisate in different package materials. The characteristics of the final product with regard to drug content, disintegration time, residual moisture, crystallinity and macro- and microscopic morphology were examined.

Material and Methods

Freeze drying procedure

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Filling in blister</th>
<th>Freezing in LN₂</th>
<th>Annealing</th>
<th>Primary drying</th>
<th>Secondary drying</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{Formulation}</td>
<td></td>
<td></td>
<td>\text{T = -20 °C}</td>
<td>P = 0.160 mbar</td>
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<tr>
<td>Stabil. Agarose</td>
<td></td>
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<td>\text{T = +5 °C}</td>
<td>P = 0.120 mbar</td>
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<tr>
<td>Mannitol</td>
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<tr>
<td>Citric acid monohydrate</td>
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<tr>
<td>Gelatine B [60 Bloom]</td>
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<tr>
<td>Dextrose</td>
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<tr>
<td>Peppermint aroma</td>
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<tr>
<td>T = 40 °C</td>
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</table>

Storage conditions

3 batches of the freeze-dried tablets were stored in PVC-blisters (Lauer Fischer, Germany). The other batch was divided in two parts and stored in 100 mL tightly-closed glass bottles. Storage stability was tested over 24 weeks under long term conditions (RH = 60%, T = 25 °C) and over 4 weeks under accelerated conditions (RH = 75%, T = 40 °C).

Scanning Electron Microscopy (SEM)

After gold-palladium sputtering-coating the morphology of the lyophilisate was examined using a scanning electron microscope DSM 962 (Zeiss GmbH, Germany).

Karl-Fischer Titration

The determination of the residual moisture in tablets was performed using a Mitsubishi Moisture Meter (model CA-06) and a Mitsubishi Water Vaporizer (model VA-06).

X-Ray Powder Diffraction (XRPD)

X-ray diffraction investigations were performed by means of a Philips model X’pert MPD using Cu Ka radiation at 40 kV/40 mA (0-45 θ).

Results and Discussion

Macro- and microscopic morphology

Under long term storage conditions tablets in the glass bottle and in blisters showed a decrease in diameter (measured with a ruler) of about 9% after 24 weeks. The tablets stored in the glass bottle under accelerated conditions showed intensive shrinkage (ca. 25%). Therefore, these tablets could not be used for the purpose of final product testing. Shrinkage could be correlated with change in the microscopic structure depicted in the SEM-images as a wavelike surface (Fig. 1).

Disintegration time

The disintegration time of the freeze-dried tablets was determined according to the test described in the Ph. Eur. for oral lyophilisates using a beaker glass filled with 200 mL distilled water. The disintegration time was defined as the time necessary for the tablets to completely disintegrate until no solid residue is visually left in the beaker. It was found that during the complete storage period there was no significant change in disintegration time. In average, tablets consistently disintegrated in less than 60 seconds.

Residual moisture content

During the period of storage the moisture content increased by about 2% in both container systems. However, water acts as a plasticizer reducing the glass transition temperature of the amorphous material [2]. Therefore this increase in residual moisture content could be related to the overall degree of shrinkage.

XRD

The diffraction patterns of the tablets in Fig. 5 showed sharp peaks at 9.7° and 20.4° 2θ that are characteristic of the 6-polymorph of mannitol. No significant change in crystallinity could be detected during the storage time of 24 weeks.

Conclusion

- Lyophilisates of Midazolam-HCl for oral administration are stable for 24 weeks under long term storage conditions in blisters and glass bottle.
- Lyophilisates which were stored at accelerated conditions in a glass bottle showed a significant shrinkage after 4 weeks.
- Based on the present investigations, it is not recommendable that storage conditions exceed T = 25°C and RH = 60% for this product.

References