Impact of Gelatin Type and pH on the Disintegration Time and Dissolution of Lyophilised Midazolam-HCl Tablets

W. Ibrahim¹, H. Gieseler², I. Zimmermann¹
¹ Department of Pharmacy and Food Chemistry, University of Würzburg, Germany
² Division of Pharmaceutics, University of Erlangen, Germany

Introduction:

Tablets and capsules are the most commonly used pharmaceutical dosage form. However, some patients like children and elderly people have difficulty in swallowing these solid forms. A freeze dried dosage form is one of the preparations which was developed to improve the compliance of such patients. The porous structure of these tablets helps the rapid disintegration in the mouth without the requirement of water. The formulation of a tablet consists of the active ingredient which must be dispersed in a water soluble amorphous polymer (e.g. gelatin or dextrin), a bulking agent (e.g. mannitol), a buffer as well as flavours and sweeteners to cover the taste of the drug (1,2).

The goal of this work is to investigate the impact of gelatin type and the formulation pH on the disintegration time and therefore on the available Midazolam-HCl.

Material and methods:

Freeze drying procedure:
Four different formulations were prepared with Midazolam-HCl as active ingredient. An overview of the differences between the formulations is given in the Table 1. Freeze drying was performed by a Christ Delta 24-KD laboratory scale freeze-dryer (Martin Christ, Osterode, Germany). 1 mL of the formulation was filled into the blisters with Diameter of 16 mm and depth of 7 mm. The blisters were frozen in LN₂ and subsequently placed in the freezer at -20 °C for 20 hours. Primary drying was performed at a shelf temperature of +5 °C and a chamber pressure of 0.160 mbar for 15 h. Secondary drying was carried out at shelf temperature 40 °C, pressure 0.120 mbar for 2 hours.

Table 1: The differences between the formulations

<table>
<thead>
<tr>
<th>Differences</th>
<th>Form 1</th>
<th>Form 2</th>
<th>Form 3</th>
<th>Form 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin Bloom-Zahl</td>
<td>195</td>
<td>60</td>
<td>195</td>
<td>60</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>3.7</td>
<td>3.7</td>
<td>-</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

SEM:

Scanning Electron Microscopy images depict the porous structure of the lyophilised tablet on the top surface (Pic. 1A) or under the thin outer layer on the side (Pic.1B). The vertical section demonstrates the lamellar structure in the middle of the tablet (Pic. 1C) or tube-shaped structure at the bottom edge of the tablet (Pic. 1D). Both are typical for fast freezing with LN₂. SEM is not the appropriate technique to observe alteration in the cakes between formulations which lead to differences in the dissolution rate.

Results and discussion:

Collapse temperature, \( T_g \) with and without annealing:
The collapse temperature \( T_g \) was determined by using a Linkam FDCS 196 freeze drying stage and an Olympus BX 40 microscope. It was found between -16 °C and -10 °C in the four investigated formulations. However, the suspended Midazolam-HCl in the formulations (3 and 4) lead to higher \( T_g \). The glass transition temperature without annealing was about -30 °C and about -15 °C after annealing. These values indicate the importance of the annealing in the freeze drying cycle, as well as underline the roll of crystalline mannitol in enhancement the product’s resistance against the structure loss.

SEM:

Residual Moisture content:
Figure 4 shows that the residual moisture content of the freeze-dried tablets is approximately same in the four formulations and it is around 1.5% w/w.

SEM:

Conclusions:

- Gelatin with smaller bloom number improves the disintegration time without any significant influence on the other physical-chemical properties.
- The formulations with a pH of 3.7 showed better availability of Midazolam-HCl than these with a pH of 5.0.

References:


Figure 1. Collapse Temperature, \( T_g \) with and without annealing of each formulation.

Figure 2. XRD patterns of the formulations.

Figure 3. Comparison of the dissolution rate of the formulations.

Figure 4. Residual moisture of the Formulations

Picture 1. SEM images of a freeze dried tablet.