Enhanced oromucosal permeation of midazolam HCl released from mucoadhesive buccal films using methylated β-cyclodextrins

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INTRODUCTION
Midazolam is commonly used for preoperative sedation in children. But, peroral or buccal administration is not licensed for premedication in children [1]. In anaesthesia practice, off-label use of tablets or injection solution administered by mouth is usual. Therapeutic success is reduced due to a delayed onset of action, poor bioavailability and a bitter taste of midazolam.

Aim of this study was to develop a mucoadhesive buccal film (MBF) representing a child appropriate dosage form. Methylated β-cyclodextrins were used to improve buccal absorption and therefore therapeutic efficacy.

MATERIALS AND METHODS
For MBF production midazolam HCl (MidHCl; Caelo), heptakis-(2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB; Cyclolab), randomly methylated β-cyclodextrin (RAMEB; Cyclolab), hypromellose (HPMC, Pharmaco® 506, Sartorius), ethyl cellulose (Aqualon® EC N50, Ashland), anhydrous glycerol (Caelo), ethanol 96 % (Fisher Scientific) and distilled water were used. MBFs were prepared by solvent casting technique (Coatmaster® 500, Erichsen). Wet film thickness of the drug layer was adjusted to 500 μm. The backing layer was cast on the top of the drug layer with a wet film thickness of 300 μm. After drying, films were cut into rectangular pieces (6 cm²) with a drug load of 5 mg.

Table 1. Labeling and composition of MBFs.

<table>
<thead>
<tr>
<th>Drug layer</th>
<th>MidHCl</th>
<th>Mid_RAMEB</th>
<th>Mid_TRIMEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam HCl</td>
<td>1.67 %</td>
<td>1.67 %</td>
<td>1.67 %</td>
</tr>
<tr>
<td>RAMEB</td>
<td>9.33 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC</td>
<td>-</td>
<td>6.67 %</td>
<td>-</td>
</tr>
<tr>
<td>Glycerol</td>
<td>15 %</td>
<td>15 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Distilled water</td>
<td>80.33 %</td>
<td>66 %</td>
<td>73.66 %</td>
</tr>
<tr>
<td>+ Backing layer</td>
<td>8 %</td>
<td>3 %</td>
<td>99 %</td>
</tr>
</tbody>
</table>

Solid state properties of raw materials and MBFs were investigated by X-ray diffraction (XRD, X’PertPro, PANalytical). Dry film thickness and weight of single layer films were determined using a micrometer screw (Mitutoyo) and an analytical balance (Sartorius). Slide frame method was used to investigate disintegration time of different MBFs. Cell viability and permeation studies were performed at the Fraunhofer IGB using an reconstructed human epidermis model (RhE model) of the oral mucosa (Figure 1).

RESULTS AND DISCUSSION

Solid state properties
XRD patterns of starting material and films are displayed in Figure 2. MidHCl and TRIMEB reveal crystalline structures. However, the complex of MidHCl and TRIMEB is amorphous. RAMEB is an amorphous substance. The XRD pattern of the corresponding MidHCl inclusion complex does not show peaks of the crystalline drug. Both types of β-cyclodextrins completely incorporate the drug. The film forming polymer HPMC is a semi-crystalline substance with a low crystalline fraction.

Figure 2. XRD patterns of starting material and MBFs (n = 3)

Thickness, weight and disintegration time of film formulations
Figure 3 shows the results of film characterization. Thickness and weight of films varied depending on the load of solid material within the formulation. Highest thickness and weight was observed for MBF Mid_RAMEB (89 ± 2.91 μm / 67.21 ± 1.05 mg). However, formulation with pure MidHCl showed lowest thickness and weight (48 ± 1.22 μm / 33.78 ± 0.71 mg). Disintegration time of films with MidHCl and Mid_TRIMEB was decreased (8.08 ± 1.24 s / 10.16 ± 2.06 s) compared to Mid_RAMEB (21.36 ± 2.41 s).

Permeation studies
MBFs containing Mid_TRIMEB showed increased permeation through the RhE model compared to MBFs made with MidHCl and Mid_RAMEB (Figure 4). The permeation rate of MBFs containing Mid_TRIMEB is particularly increased for the first 120 min.

Figure 4. Permeation of midazolam using an oromucosal RhE model (mean ± sd; n = 3; model 1–3 = cell models reconstructed from different donor keratinocytes)

RAMEB mainly interacts with the closed-ring form of midazolam, which is pharmacologically active but less water-soluble [2]. In contrast, TRIMEB stabilizes the more flexible and water-soluble open-ring form of midazolam, which ensures overall solubility even in the small saliva volume at physiological pH and facilitates buccal transport of midazolam [3].

CONCLUSION
MBFs containing MidHCl or corresponding RAMEB-TRIMEB-complexes were developed successfully. MBFs containing Mid_TRIMEB show enhanced permeation through the human oral mucosal model. In-vivo studies need to be made further explore the potential of improved bioavailability using a complex of midazolam and TRIMEB and its safety for premedication in children.