Novel approach to disintegration testing of orodispersible films: *In vitro* oral cavity simulator

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**Background**

- Previous studies have confirmed that orodispersible films (ODFs) (Fig. 1) are acceptable dosage forms for preschool children, and infants (Orlu et al., 2017).
- ODF disintegration is a key characterisation parameter, not only for quality control purposes (Ph. Eur. 2016), but also as an indicator of the end-user acceptability (Scarpaci et al., 2018).
- There are currently no standard *in vitro* methods for the disintegration assessment of ODFs.

**Rationale**

- There is the need for *in vitro* predictive decision support tools to be implemented in the pharmaceutical industry, in order to guide the drug product design.

**Aim**

- To adapt a mechanical oral cavity model for the measurement of *in vitro* disintegration of ODFs.

**Methods**

**1. ODF sample composition**

<table>
<thead>
<tr>
<th>ID</th>
<th>Polymer</th>
<th>Molecular weight (kDa)</th>
<th>Concentration (w/v)</th>
<th>Size (cm²)</th>
<th>Dye</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Poly(vinyl) alcohol</td>
<td>30</td>
<td>5%</td>
<td>6</td>
<td>Red (0.4% w/v)</td>
</tr>
<tr>
<td>P2</td>
<td>Poly(vinyl) alcohol</td>
<td>205</td>
<td>5%</td>
<td>6</td>
<td>Red (0.4% w/v)</td>
</tr>
<tr>
<td>C1</td>
<td>Carboxymethylcellulose</td>
<td>395</td>
<td>1%</td>
<td>6</td>
<td>Red (0.2% w/v)</td>
</tr>
<tr>
<td>OD</td>
<td>Carboxymethylcellulose</td>
<td>725</td>
<td>1%</td>
<td>6</td>
<td>Red (0.2% w/v)</td>
</tr>
<tr>
<td>Listerine</td>
<td>Multiple</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>Green</td>
</tr>
</tbody>
</table>

**2. Oral cavity simulator**

- The original design of the Oral Cavity Simulator (OCS) involves a silicone body mimicking the human tongue, moving vertically, and applying a controlled compression onto a clear flat acrylic plate mimicking the human palate (Fig. 2).
- Four dyed ODFs were prepared by solvent casting (Tab. 1), and positioned on the tongue. Listerine® breath strips were also tested as benchmark.
- A camera (Sony RX100 M4) was positioned above the acrylic plate, and a video of disintegration was recorded. A compression and retraction phase of 0.7s was followed by a pause of 2s.
- Listerine® breath strips were also tested as benchmark.
- Four dyed ODFs were prepared by solvent casting (Tab. 1), and positioned on the tongue. Listerine® breath strips were also tested as benchmark.
- A camera (Sony RX100 M4) was positioned above the acrylic plate, and a video of disintegration was taken (Fig. 2).

**3. Video analysis**

- A video data processing program was developed using Matlab (MathWorks, Natick, MA, USA).
- From the video file, a frame was extracted at the beginning of the compression sequence during the ‘open’ position.
- The background and ODF areas were selected manually by a ‘crop’ function from the first extracted image (Fig. 3 a, and b).
- A manual thresholding function allowed to accurately define the film area (Fig. 3 d)
- One frame was subsequently extracted at each compression sequence during the ‘open’ position.
- For each extracted frame, the Red, Green, and Blu signal intensities were recorded from each pixel of the background and film areas.

**4. Signal intensity calibration**

- Two methods for the determination of the ODF signal intensities were developed: 1. Red-green method, and 2. Difference method.
- The signal intensity was calculated with each method on a ODF strip of known thickness.
- The ODF volume reduced linearly in samples P1 and Listerine®, and in a non-linear fashion in the other samples.
- A difference in ODF breakdown behaviour was observed between PV0H-based and CMC-based films (Fig. 5 b).
- Proportionality between *in vitro* data and previously reported in vivo measured perceived disintegration time (Fig. 6 a and b) was maintained.

**Results**

- The average ODF % volume reduction at 180 s was > 90% for sample P1 and Listerine®, and 85%, 48%, and 37% for samples C1, P2, and C2 respectively (Fig. 5 a).
- The lower molecular weight ODF of each polymeric species disintegrated faster than their high molecular weight counterparts.
- The ODF volume reduced linearly in samples P1 and Listerine®, and in a non-linear fashion in the other samples.
- A difference in ODF breakdown behaviour was observed between PV0H-based and CMC-based films (Fig. 5 b).
- Proportionality between *in vitro* data and previously reported in vivo measured perceived disintegration time (Fig. 6 a and b) was maintained.

**Discussion**

- The presence of non-linear regions in the disintegration profile, and the increase of disintegration time of high-molecular-weight ODF might depend on: 1. Hydration and disentanglement of long polymeric chains in liquid media. 2. Higher availability of substitution groups responsible for hydrogen bonding (Linxrazier et al., 1997)
- Adhesion mechanisms between polymeric chains and acrylic material (Tripathi et al., 2016)
- The difference in breakdown behaviour of ODF might be explained by the availability of different substitution groups (Linxrazier et al., 1997)

**Conclusions**

- A mechanical oral cavity simulator designed to mimic the adult oral cavity was adapted for the *in vitro* measurement of the disintegration behaviour of ODFs.
- The OCS could detect differences in disintegration behaviour of ODFs prepared with different film-forming polymers.
- Results maintained proportionality with previously reported in vivo data on perceived disintegration time in the adult population, potentially informing on the end-user acceptability.
- As the anatomical, and physiological features of the infant’s oral cavity can be mimicked in the OCS, the model holds potential to predict in *vitro* disintegration behaviour of paediatric orodispersible dosage forms.

**References**


