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

Mariagiovanna Scarpa[1]; Andrew Redfearn[2]; Ben Hanson[2]; Mine Orlu[1]

[1] UCL School of Pharmacy, University College London, Department of Pharmaceutics, 29-39 Brunswick Square, London WC1N 1AX – UK, m.scarpa@ucl.ac.uk; m.orlu@ucl.ac.uk

[2] UCL Department of Mechanical Engineering, University College London Roberts Engineering Building, Torrington Place, London WC1E 7JE – UK, a.redfearn.12@ucl.ac.uk; b.hanson@ucl.ac.uk

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 (Scarpa et al., 2018).
- There are currently no standard *in vitro* methods for the disintegration assessment of ODFs.

Fig.1: An image of ODF

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 1: Composition of drug-free study samples, and Listerine® breath strips.

ID	Polymer	Molecular weight (kDa)	Concentration (w/v)	Size (cm^2)	Dye
P1	Poly(vinyl) alcohol	30	5%	6	Red (0.4% w/v)
P2	Poly(vinyl) alcohol	205	5%	6	Red (0.4% w/v)
C1	Carboxymethylcellulose	395	1%	6	Red (0.2% w/v)
C2	Carboxymethylcellulose	725	1%	6	Red (0.2% w/v)
Listerine®	Multiple	-	-	6	Green

2. Oral cavity simulator

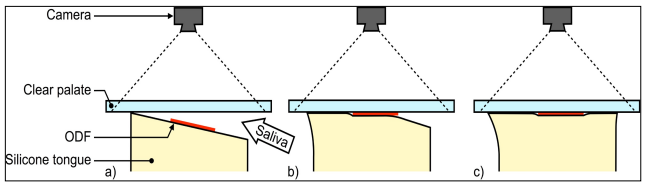
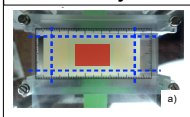


Figure 2: Adaptation of oral cavity simulator for ODF disintegration assessment. ODF is placed onto the silicone tongue, and artificial salivary fluid is sprayed inside the cavity (a); the silicone tongue is moved upwards (b), and presses against the acrylic plate (c).

- 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 compression and retraction phase of 0.7s was followed by a pause of 2s.
- Simulated salivary fluid (SSF) was sprayed inside the oral cavity every two compression cycles, in order to achieve a 1.5 mL/min flow rate (Gittings et al., 2015).
- A camera (Sony RX100 M4) was positioned above the acrylic plate, and a video of the dissolving ODF was taken (Fig. 2).

3. Video analysis



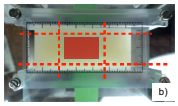
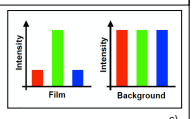
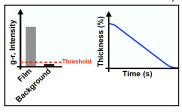


Figure 3: Crop function to select background (a), and ODF (b) area from each extracted frame. Film and background signal intensity recording (c). Manual thresholding and film estimated thickness vs time plot (d).





- A video data processing program was developed using Matlab (MathWorks, Natik, 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

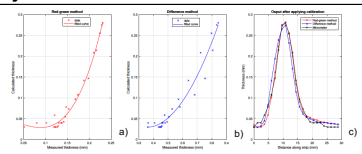


Figure 4: Thickness calibration of the image analysis Red-green (a), and Difference (b) methods, and comparison with real thickness values (c).

- Two methods for the determination of the ODF signal intensities were developed:
  1. **Red-green method**: the two highest signals from the film area were extracted and subtracted to the background signal.
  2. **Difference method:** all three signals were subtracted from the background signal.
- The signal intensity was calculated with each method on a ODF strip of known thickness.
- The Difference method better correlated with the real ODF thickness, and was used for further image analysis (Fig. 4).
- The volume of the dissolving ODF (area x thickness) expressed in percentage of the first extracted frame was plotted vs. time.

Results

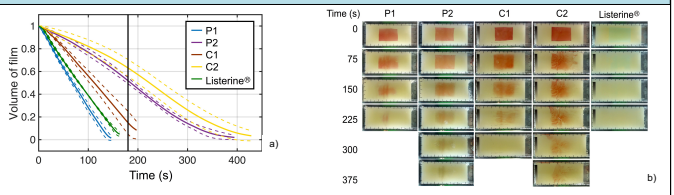


Figure 5: Percent film volume reduction vs. time plot of the four single-polymer ODF samples, and Listerine® (a). Extracted frames of the dissolving ODF samples at different time points (b).

- 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 PVOH-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.

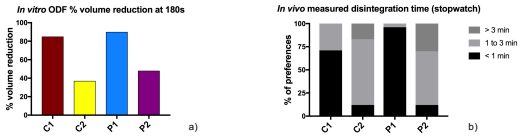


Figure 6: *In vitro* measured percent film volume reduction vs. time (a). *In vivo* perceived disintegration time measured by stopwatch (b) from Scarpa et al., 2018.

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 (Linossier et al., 1997)
3. 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 (Linossier et al., 1997)

Conclusions

- A mechanical oral cavity simulator designed to mimic the adult oral cavity was adapted for the *in vitro* meaurement 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

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