

## Key acceptability attributes of orodispersible films

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## Abstract

The features rendering ODFs as patient-centric formulations are widely discussed in the scientific literature. However there is a lack of research studies exploring ODF characteristics with a potential impact on end-user acceptability. The aim of this study was to identify the key ODF characteristics affecting end-user acceptability by developing *in vitro* test methods for the prediction of ODFs acceptability and correlate these formulation characteristics with the data obtained from human panel study. Four drug-free single-polymer films were prepared by solvent casting. Solutions of poly(vinyl) alcohol (PVOH) 30 KDa (P1), PVOH 205 KDa (P2), carboxymethylcellulose (CMC) 395 KDa (C1), and CMC 725 KDa (C2) were prepared. Texture analysis and Dynamic Mechanical Analysis (DMA) were used to assess film tack. Petri dish and drop methods were used for assessment of disintegration time. A human panel of 24 healthy young adults was employed to identify end-user acceptability criteria of the four study film samples. Texture analysis data of ODF tack were not found to be in agreement with the *in vivo* stickiness perceived in the mouth. However, measurement of the area under the adhesive force curve obtained by DMA correlated with *in vivo* stickiness perceived data for all samples. The disintegration times obtained by drop method were more comparable to human panel data than the petri dish method. Hence DMA and drop methods proved to be promising methodologies for the prediction of the end-user acceptability. The type and molecular weight of the film-forming polymer had a strong influence on stickiness perception, whereas only polymeric molecular weight influenced perceived disintegration time. The human panel study showed that Participant Reported Outcomes (PROs) for the stickiness perceived in the mouth and disintegration time of test films received significantly different scores between samples, and thus were identified as the key attributes with the potential to affect the end-user acceptability. ODF stickiness and disintegration time should therefore be considered at an early stage of the drug product design.

## Introduction

The term patient-centricity is currently used to describe drug products with characteristics that meet the needs of patient groups [1]. The quality attributes of pharmaceutical products should be optimised to ensure appropriate patient acceptability [2]. Orally administered pharmaceutical formulations, such as multiparticulates, orodispersibles, buccal tablets, buccal films, and chewable formulations, have been evaluated for their potential patient-centric features [3–5]. However, a harmonised approach towards the end-user acceptability testing of pharmaceutical formulations has not yet been fulfilled [1]. Recently, the definition of patient-centric drug product design was proposed [1], suggesting testing a drug product in the personal health and environmental context of the target patient population, or to collect such information during clinical trials, where appropriate. Design drivers could then be identified and used to achieve the desired design outputs of the drug product [1].

Orodispersible films (ODFs) are stamp-size polymeric thin films that rapidly dissolve upon contact with saliva. Although ODFs have been reported to contribute to improved patient compliance [6], and offer a wide range of characteristics with the potential of addressing the needs of different patient populations [7], their acceptability has not been explored in the context of final dosage form characteristics [8–10]. Patient acceptability has been defined as the ability and willingness to take a medication as intended [2].

As ODFs reside in the mouth until complete disintegration, taste, mouthfeel and texture are considered as the characteristics that are very likely to affect patient acceptability [11]. Moreover, the standard requirement for the disintegration time of orodispersible formulations is 3 minutes or less [12]. This guideline was introduced in order to allow a clear differentiation between dispersible and non-dispersible dosage forms. However, it also indirectly points to the central role played by disintegration time on patient preferences when choosing one type of dosage form over the other. Therefore, the disintegration time could also affect the acceptability of ODFs.

The assessment of the end-user acceptability of ODFs should focus on the identification of the needs of the patient/caregiver and key acceptability attributes of

the test product. Human panels have been widely used in food science in order to determine the customer acceptability of specific food products [13]. Techniques such as hedonic scales have also been used for the acceptability assessment of pharmaceutical products, especially in children [9], allowing the identification of patient needs. However, knowing whether a specific ODF product is acceptable to patients does not provide any information on how to identify the formulation attributes that can influence the acceptability of the end-user. For this purpose, human panels should be designed to allow the identification of ODFs key acceptability attributes through an appropriate selection of the test samples.

Such selection needs to account the acceptability property being studied, and how it can be influenced by modifying the formulation and/or process parameters of the particular product. For example, establishment of acceptability criteria of ODFs stickiness requires the test samples prepared with different types of polymers at varying molecular weights. This stems from the fact that the adhesive properties of the film forming polymer depend, among other parameters, on the molecular weight and type of film forming polymer [14]. Once a certain attribute is identified to influence participants' perception, it should be also aimed to develop an *in vitro* methodology to predict the end-user's acceptability at an early stage of the drug product development. Ideally, such a methodology should allow assessment of an outcome measure capable of describing the acceptability attribute in a quantitative way. In the case of stickiness, one of the appropriate methods would be measuring the adhesive force of the ODF sample upon detachment from a surface under hydrated conditions as a measure of tack. The adhesive force values of the test ODF samples measured at different time points can possibly describe how ODF tack changes over its disintegration time.

The aim of this study was to identify the key ODF characteristics affecting end-user acceptability by developing *in vitro* test methods for the prediction of ODFs acceptability and correlate these formulation characteristics with the data obtained from human panel study. Dynamic Mechanical Analysis (DMA) and texture analysis methods were developed to assess ODF tack and petri dish and drop methods were used to assess the ODF *in vitro* disintegration time. A human panel study was conducted in order to evaluate the perception of the healthy young adults' about the

stickiness and disintegration time of ODFs. The key acceptability attributes of polymeric ODFs were thereby established by assessing the relevant *in vitro* film properties and *in vivo* perceptive data.

### Materials and methods

#### Materials

EMPROVE® Poly(vinyl) alcohol 4-88 (30 KDa) and 44-88 (205 KDa) were purchased from Merck Millipore (Darmstadt, Germany). Aqualon Blanose Carboxymethylcellulose 12M31P (395 KDa) and 7HF-PH (725 KDa) were provided by Ashland Aqualon Functional Ingredients (Wilmington, Delaware, U.S.). Sterile water for injection was purchased from Gibco (Grand Island, New York, U.S.) Listerine PocketPacks® breath strips (Listerine®) and NiQuitin® strips (NiQuitin®) were purchased from Johnson & Johnson (Skillman, New Jersey, U.S.) New Brunswick, New Jersey, U.S.), and Omega Pharma (Brentford, Middlesex, U.K.) respectively.

#### Drug-free test film preparation by solution casting

Four single-polymer test samples were prepared by solvent casting. Two samples were made of poly(vinyl) alcohol 30 KDa (P1), and 205 KDa (P2) respectively. Two samples were prepared with carboxymethylcellulose 395 KDa (C1) and 725 KDa (C2) respectively. The solvent casting method described in [15] was adapted to prepare PVOH-based films. A 5% (w/v) PVOH solution was prepared in sterile water under stirring. The solution was heated to 75-90 °C (depending on PVOH grade) until a visible clarity was obtained, and then allowed to cool to room temperature. A 1% (w/v) CMC solution was prepared in sterile water and stirred until clear. A 7.5 mL of PVOH or 15 mL of CMC solution were poured in a casting mould comprising a 10 cm diameter silicone ring (Shenzhen Yimeifen Technology, Guangdong, China) placed on top of a food safe acetate sheet (Tierrafilm - Nac Industrial, London, U.K.). The mould was then heated to 50 °C on a hot plate (IKA Labortechnik, Staufen, Germany) for two hours. The film was then peeled off, cut to size, and stored in a 10% RH (generated

using phosphorus pentoxide – Sigma-Aldrich, Gillingham, U.K.) and room temperature for at least one week.

#### Measurement of ODF thickness

Drug-free test ODF thickness was measured using a thickness gauge (Mercer Ltd, Manchester, U.K.). Thickness measurements were taken on 5 different location (at the four corners and at the centre) of 3 x 2 cm cast films, as reported by [16].

#### Adhesive force measurements of drug-free ODFs by texture analysis

The adhesive force of drug-free ODF samples was measured using a TA.XT Plus texture analyser (Stable Microsystems Ltd., Godalming, Surrey, U.K.) equipped with a 30 kg load cell. The testing method was adapted from [17,18] and [18]. A 1 x 1 cm<sup>2</sup> film with a thickness of 60 µm for PVOH films and 20 µm for CMC films was cut and placed on a non-conductive double-sided adhesive tape (SPI supplies, West Chester, Pennsylvania, U.S.) and attached to a microscope slide (Thermo Scientific, Braunschweig, Germany). The microscope slide was positioned under the TA.XT probe (6 mm cylindrical) and 200 µL of warm water (37°C) was deposited on top of the film. The probe was lowered at a test speed of 0.4 mm/second. A force of 2.308 N was applied to the sample and maintained for 12 seconds, before the probe was withdrawn at 0.4 mm/second. Data were visualised using Exponent software (Exponent v6, Stable Microsystems Ltd., Godalming, Surrey, U.K.).

#### Adhesive force measurements of drug-free ODFs by Dynamic Mechanical Analysis (DMA)

The adhesive force of drug-free and commercial test ODF was analysed using a Q800 Dynamic Mechanical Analyser (TA Instruments Delaware, US) equipped with 1.2 cm diameter steel compression clamps. The DMA was operated in controlled force mode. The film sample was cut into a circle of 12 mm diameter, mounted onto the lower clamp and secured by non-conductive double-sided adhesive tape. The clamps were kept separated by applying a negative force of -0.8 N, until the initial temperature of

37°C was reached. A 450 µL of warm water (37°C) was deposited on top of the film. Immediately after, the clamps were brought together and a force of 2.649 N was applied. The clamps were then withdrawn by ramping the force at -25 N/min to -8 N. Data were analysed using Universal Analysis 2000 v.4.5A (TA Instruments Waters LLC, Delaware, US). The adhesive force values were obtained at the intersection between the force curve and the ordinate of the displacement ramp at its onset point. The area under the curve (AUC) of the adhesive force versus time plot was calculated from time 0 to the corresponding *in vivo* maximum disintegration time reported by the human panel participants. If the *in vivo* disintegration time was found to last less than 1 minute, the corresponding AUC of the *in vitro* adhesive force was calculated for 60 seconds (from x=0 to x=60). Likewise, if the *in vivo* disintegration time was found to last between 1 and 3 minutes, the corresponding AUC of the *in vitro* adhesive force was calculated for 180 seconds (from x=0 to x=180).

#### Measurement of disintegration time by the petri dish method

ODF test samples of 6 cm<sup>2</sup> were placed in a 9 cm petri dish and covered with 2 mL deionised water at 37 C° under gentle shaking (70 rpm) [19]. The disintegration time of the sample was taken when the test film started breaking as observed visually.

#### Measurement of disintegration time by drop method

ODF samples of 6 cm<sup>2</sup> were placed between two metallic plates having a semicircular hole on one side. The film surface was therefore exposed on both sides. The plates were placed in a lifted position at 1 cm from the base of the apparatus and maintained parallel to the ground. A drop of 200 µL deionised water at 37 C° was deposited onto the exposed surface of the film, and the time required for the drop to fall and touch the apparatus base was taken. The method was adapted from Preis et al., 2012.

#### Data analysis

Experimental data obtained by texture analysis and DMA and both the disintegration time methods were analysed using a Kruskal-Wallis test followed by Dunn's multiple

comparisons test (Prism 7, GraphPad Software Inc.). Differences between petri dish and drop methods were analysed using the Mann-Whitney test (Prism 7, GraphPad Software Inc.).

## Human panel on healthy young adults

### Acceptability study

A single centre, single blind, crossover human panel study was carried out in three sessions taking place in different days. All participants received four coded drug-free film test samples in a randomised sequence order in each session. Samples were randomised using the free webpage service Random.org (<https://www.random.org/>).

### Participants

The study was conducted at UCL School of Pharmacy. 24 healthy male or female adults, able to understand and speak English, and aged between 18 and 35 (average age 26) years were recruited. Volunteers who received dental care up to 15 days before the tests, anaesthetics into the mouth within 24 hours prior to the study, or taking any medicinal treatments altering saliva production were excluded from the study. Volunteers with any known excipient hypersensitivity or with any sensory disorders affecting the mouth were also excluded.

### Ethical considerations

This study was approved by the UCL Ethics Committee on 10 October 2016 (UCL Ethics ID: 8249/001). Data collection, storage and handling were performed in compliance with the Data Protection Act 1998, and approved by the UCL Data Protection Office (Data Registration Number: Z6364106/2016/08/68). Written consent was obtained from the participants before any part of the study was initiated, and after receiving exhaustive information on the study procedure, including the assessment of any potential risk involved.

## Study design

The study design of each session is summarised in Figure 1

### *Intended place for Figure 1*

Each participant was seated at a computer station and was presented with one of the four test ODF samples at a time and a stopwatch. Participants were asked to pick the ODF test sample from a petri dish, place it into the mouth, and simultaneously start the time count. During the assessment, researchers scored the participant sample intake performance and their reaction to the sample in a 2 point score system (Table 1). Then, participants were instructed to stop the stopwatch as soon as the film test sample had disintegrated in their mouth. They were then asked to rate several ODF characteristics on a 5 points hedonic facial scale ranging from “extremely uncomfortable” to “extremely comfortable” with a neutral response in the centre [9] (Figure 2). Hedonic scales are used as a method for the determination of the organoleptic properties of foods [21]. In particular, the 5 point hedonic scale has been used for the assessment of medicine palatability in children [9]. A 2 score point-based MAS has been used in the medicine acceptability in the paediatric population [22].

### *Intended place for Figure 2*

The disintegration time was noted and a multiple choice question on the duration of sample disintegration was answered by participants. After an interval of 10 minutes, the other 3 ODF test samples were presented in sequence. Participants were then invited to perform a ranking exercise on the stickiness of the 4 ODF test samples.

## Data collection

Researchers assessed the facial expression (0 points = positive face or signs of approval; 1 point = no facial expressions; 2 points = signs of distress), the jaw movements (0 points = no jaw movements until swallowing; 1 point = 1 to 3 chews until swallowing; 2 points = more than 3 or repeated chews or observed tongue

movements until swallowing), and the sample intake (0 points = ODF swallowed without loss; 1 point = ODF spat out with partial loss; 2 points = ODF spat out completely) as shown in Table 1. The results obtained were referred to as Researcher Reported Outcomes (RROs).

*Intended place for Table 1*

ODF sample size perceived on handling, thickness perceived on handling, stickiness perceived on handling, size perceived in the mouth, thickness perceived in the mouth, stickiness perceived in the mouth, and disintegration time were evaluated by participants on a computerised questionnaire (<https://www.qualtrics.com/>), using a [five point hedonic facial scale](#). Participants also reported whether the disintegration time of the ODF test sample was less than 1 minute, between 1 and 3 minutes, or more than 3 minutes on a multiple choice question. The resulting scores obtained by participants after the acceptability testing of the film samples were defined Participant Reported Outcomes (PROs). A second assessment of the stickiness of test ODF samples was carried out by means of a ranking exercise. Ranking was performed in order to detect differentiation between samples that were similar in acceptability [13]. In this study, participant willingness was assessed based on PROs expressed as comfort/discomfort to the sample and RROs expressed as MAS score on facial expression. Participant ability was assessed based on the RROs expressed as Medicines Acceptability Scale (MAS) score obtained from the jaw movements and sample intake assessment.

### Statistical analysis

PROs were converted into numerical values (1 = extremely uncomfortable; 2 = somewhat uncomfortable; 3 = neither comfortable nor uncomfortable; 4 = somewhat comfortable; 5 = extremely comfortable) [23] and analysed as ordinal variables using a Friedman analysis of variance followed by Dunn's post hoc test (Prism 7, GraphPad Software Inc.) [13]. The same score allocation system and statistical analysis method was used for the stickiness ranking exercise (1 = least sticky, 4 = most sticky). RROs consisted of three items, each one that could be scored from 0 (least acceptable) to 2 (most acceptable) points. The scores of all the three items were summed and the total

MAS score was calculated for each sample. The MAS total score differences between samples were calculated using the Friedman's test followed by Dunn's post hoc test for multiple comparisons (Prism 7, GraphPad Software Inc.) [13].

The ODF characteristics that showed significant differences between sample PRO scores were identified as key acceptability attributes of the test ODFs. Sample-related effects (e.g. type of film-forming polymer and polymeric molecular weight) on the acceptability of ODF samples were analysed using a Wilcoxon signed rank test (Prism 7, GraphPad Software Inc.). Study design-related effects (e.g. memory effect) were analysed using Friedman's test followed by Dunn's post hoc test for multiple comparisons (Prism 7, GraphPad Software Inc.).

## Results

### Thickness of drug-free ODF formulations

Study ODF samples were prepared as tabulated in Table 2. All the formulations were transparent, colourless, and tasteless. Listerine® and NiQuitin® were analysed as controls.

### *Intended place for Table 2*

### Adhesive force ODF measurements performed by texture analysis

The adhesive force required to detach the surface of the cylindrical probe from the test ODF sample was measured by texture analysis. Results are presented in Figure 3.

### *Intended place for Figure 3*

Texture analysis showed ODF adhesive force values ranging from 0.105 N/mm<sup>2</sup> to 0.603 N/mm<sup>2</sup>. After 10 seconds of hydration time, samples P1 and P2 reached maximum adhesive force values of  $0.430 \pm 0.005$  N/mm<sup>2</sup> and  $0.478 \pm 0.063$  N/mm<sup>2</sup> respectively. After 60 seconds of hydration, the adhesive force of samples P1 and P2 stabilised around 0.200 N/mm<sup>2</sup> and 0.290 N/mm<sup>2</sup> respectively. Sample C1 reached

0.157 ± 0.006 N/mm<sup>2</sup> after 10 seconds and maintained similar adhesive force values until 240 seconds. The adhesive force of sample C2 was 0.105 ± 0.001 N/mm<sup>2</sup> at 10 seconds, increasing to 0.151 ± 0.004 N/mm<sup>2</sup> at 60 seconds and maintaining similar values until 240 seconds. Overall, the two CMC-based test ODF formulations (C1 and C2) showed adhesive force values below 0.200 N/mm<sup>2</sup> for the whole hydration time, whereas the two PVOH-based formulations (P1 and P2) maintained adhesive force values always above 0.180 N/mm<sup>2</sup>.

The Kruskal-Wallis followed by Dunn's multiple comparison test showed significant difference in adhesive force existing between P2 and C1 ( $p < 0.001$ ), and between P2 and C2 ( $p < 0.05$ ).

Adhesive force ODF measurements performed by Dynamic Mechanical Analysis

The adhesive force of the four test ODF samples and of two marketed ODF formulations (Listerine® and NiQuitin®) was assessed by DMA. Results are reported in Figure 4.

*Intended place for Figure 4*

C1 showed the highest adhesive force among all the test ODF samples assessed, with values of 0.037 ± 0.001 N/mm<sup>2</sup> at 10 seconds of hydration time, reaching a peak of 0.044 ± 0.001 N/mm<sup>2</sup> at 60 seconds, and decreasing to 0.040 ± 0.002 N/mm<sup>2</sup> at 120 seconds, to 0.015 ± 0.001 N/mm<sup>2</sup> at 180 seconds, and to 0.011 ± 0.001 N/mm<sup>2</sup> at 240 seconds. P2 and C2 maintained similar adhesive force values for the whole hydration time, although fluctuations were detected in both the test ODF samples. C2 showed a faster increase in adhesive force (to 0.024 ± 0.001 N/mm<sup>2</sup> at 10 seconds) than P2 (to 0.022 ± 0.001 N/mm<sup>2</sup> at 60 seconds). P1 and Listerine® showed the same adhesive force value at 10 seconds of hydration time (0.009 N/mm<sup>2</sup>). However, P1 maintained similar adhesive force for the whole hydration time, whereas Listerine® adhesive force decreased until reaching a minimum of 0.002 ± 0.001 N/mm<sup>2</sup> at 120 seconds and maintaining the same value until 240 seconds. NiQuitin® maintained an

adhesive force of  $0.002 \text{ N/mm}^2$  until 180 seconds, then increased to  $0.009 \pm 0.001 \text{ N/mm}^2$  at 240 seconds. Overall, the two marketed formulations and the test ODF formulation P1 showed adhesive force values lower than  $0.010 \text{ N/mm}^2$  for the whole hydration time, whereas P2, C1, and C2 showed values that maintained almost always above  $0.010 \text{ N/mm}^2$ . The Kruskal-Wallis followed by Dunn's multiple comparison test showed significant difference in adhesive force existing between Listerine® and samples C1 and C2 ( $p < 0.05$ ), and between NiQuitin® and samples C1 and C2 ( $p < 0.05$ ). The area under the adhesive force curve by the disintegration time of each sample was  $0.502 \pm 0.04 \text{ N/mm}^2 \cdot \text{s}$  in sample P1,  $2.034 \pm 0.05 \text{ N/mm}^2 \cdot \text{s}$  in sample C1,  $3.034 \pm 0.12 \text{ N/mm}^2 \cdot \text{s}$  in sample P2, and  $3.652 \pm 0.20 \text{ N/mm}^2 \cdot \text{s}$  in sample C2. There was no significant difference in AUC between samples pairs except from P1 and C1 ( $p < 0.05$ ).

#### Disintegration time measured by the petri dish method

The *in vitro* disintegration time measured by the petri dish method evidenced a relatively fast disintegration of samples C1, P1, P2 and Listerine®, with mean values of  $25.4 \pm 0.2$ ,  $7.2 \pm 0.8$ ,  $55.8 \pm 2.8$ , and  $12.9 \pm 0.6$  seconds respectively (Figure 5). Sample C2 showed a much longer disintegration time ( $262.0 \pm 11.2$ ) seconds, whereas NiQuitin® always disintegrated in more than 4 minutes (data not shown). A significant difference was found between samples C2 and P1 ( $p < 0.05$ ).

#### *Intended place for Figure 5*

#### Disintegration time measured by drop method

The *in vitro* disintegration times of the four ODF test samples assessed by the drop method showed that samples C1 and P1 took  $19.3 \pm 3.0$  and  $14.6 \pm 1.0$  seconds to dissolve respectively (Figure 5).

Sample C2 disintegrated *in vitro* in  $202.6 \pm 10.9$  seconds, beyond 3 minutes time. Sample P2 disintegration was  $113.3 \pm 20.0$  seconds. Listerine® took  $14.9 \pm 0.3$  seconds to dissolve, whereas NiQuitin® always took more than 4 minutes (data not

shown). Significant differences were found between the disintegration time of samples C2 and P1 ( $p < 0.05$ ). No significant difference was found between the two methods.

PROs from exploratory pilot study on ODF mouthfeel assessment

#### Participants reported outcomes

24 volunteers were recruited, all of whom completed the study. 16 participants were females and 8 were males. The average age was 26 years. No adverse effects associated with sample intake or discomfort were reported by the participants during and after the study.

Median and Interquartile range of the PRO are summarised in Table 3.

*Intended place for Table 3*

Among all the ODF characteristics analysed, size perceived on handling, thickness perceived on handling, and stickiness perceived on handling were all evaluated somewhat comfortable by the participants, with no significant differences among test ODFs (Table .

*Intended place for Figure 6*

The size perceived in the mouth was evaluated somewhat comfortable by participants (data not shown) with no differences in scores among samples. With regards to sample thickness perceived in the mouth (data not shown), C1 and C2 had both a real thickness of around 20  $\mu\text{m}$ , whereas P1 and P2 were approximately 60  $\mu\text{m}$  thick. As expected, significant differences were found between C1 and P2 ( $p_{1st\ session} < 0.05$ ;  $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.01$ ). However, a difference was also found between P1 and P2 ( $p_{2nd\ session} < 0.05$ ). Significantly different stickiness perceived in the mouth was found between C1 and P1 ( $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.001$ ), and between P1 and P2 ( $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.01$ ). However, only the difference between C2 and P1 was significant in all the three sessions ( $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.001$ ), and was deemed robust evidence that led to the selection of stickiness as

an ODF critical acceptability characteristic. Overall, P1 was evaluated as the most acceptable sample with respect to stickiness (Fig. 6a). The disintegration time of the test ODF samples was considered between somewhat comfortable and extremely comfortable for C1 and P1, and somewhat uncomfortable for C2 and P2, suggesting the influence of the polymeric molecular weight on the perception of film disintegration time (Fig. 6b). Significant differences were found between C1 and P2 ( $p_{1st\ session} < 0.001$ ;  $p_{2nd\ session} < 0.01$ ;  $p_{3rd\ session} < 0.01$ ) C2 and P1 ( $p_{1st\ session} < 0.001$ ;  $p_{2nd\ session} < 0.0001$ ;  $p_{3rd\ session} < 0.0001$ ), and P1 and P2 ( $p_{1st\ session} < 0.0001$ ;  $p_{2nd\ session} < 0.0001$ ;  $p_{3rd\ session} < 0.001$ ) PROs in all the three sessions. Therefore, disintegration time was also selected as a key acceptability characteristic for ODFs. A difference in the disintegration time PROs between C1 and C2 was only found in the third ( $p_{3rd\ session} < 0.001$ ).

#### Identification of memory effect

The randomisation of sample order was adopted to cancel any potential effect on PROs. However, after first exposure to the four samples, the potential for participants to recognise them despite their encoding was still present. Friedman's test was used to assess whether PROs significantly changed across the sessions, despite the sample order randomisation. The results obtained were used to identify any potential correlation between PROs and sessions that could lead to the hypothesis of the presence of a "memory effect" affecting participant responses. There was no significant difference between sessions in the PROs for stickiness in the mouth for all the samples analysed. No significant differences between sessions were also found for the disintegration time PROs in all samples except P1, where there was a difference between session 2 and 3 ( $p < 0.05$ ). However, as this difference was only found in one sample and only between two sessions, the result observed might be due to a random effect.

#### Sample stickiness ranking

At the end of each session, participants were asked to rank the four test ODF samples from the most sticky to the least sticky. A score of 4 was assigned to the most sticky

sample and a score of 1 to the least sticky [24]. Median values and interquartile ranges are represented in Figure 7.

#### *Intended place for Figure 7*

The most sticky sample was C2, followed by C1, P2, and then P1. Significant differences were found between C1 and P1 ( $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.05$ ), between C2 and P1 ( $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.0001$ ;  $p_{3rd\ session} < 0.05$ ), and between P1 and P2 ( $p_{1st\ session} < 0.05$ ;  $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.05$ ).

#### *In vivo disintegration time measurement*

The disintegration times of the samples were measured by each participant by means of a stopwatch. Participants were asked to indicate whether the sample disintegrated in less than 1 minute, between 1 and 3 minutes, or more than 3 minutes in a multiple choice question. Response percentages are reported in Figure 8.

#### *Intended place for Figure 8*

Overall, P1 and C1 disintegrated in less than 1 minute, as reported by the majority of participants in all the three sessions. C2 and P2 took between 1 and 3 minutes to disintegrate according to the majority of participants in all the three sessions. P1 was reported to disintegrate in less than 1 minute by 96% of participants (1<sup>st</sup> and 3<sup>rd</sup> sessions) and by 92% in the 2<sup>nd</sup> session, between 1 and 3 minutes by 4% (1<sup>st</sup> and 3<sup>rd</sup> sessions) and by 8% (2<sup>nd</sup> session), and in more than 3 minutes by 0%. P2 disintegrated in less than 1 minute according to 12% (1<sup>st</sup> and 3<sup>rd</sup> session), and 8% (2<sup>nd</sup> session) of participants, between 1 and 3 minutes for 58% (1<sup>st</sup> session), 67% (2<sup>nd</sup> session), and 46% (3<sup>rd</sup> session) of participants, and in more than 3 minutes for 30% (1<sup>st</sup> session), 25% (2<sup>nd</sup> session), and 42% (3<sup>rd</sup> session) of participants.

The effect of the type of film forming polymer and its molecular weight on stickiness and disintegration time perception

The influence of the type of film forming polymer ( $p_{1st\ session} < 0.001$ ;  $p_{2nd\ session} < 0.05$ ;  $p_{3rd\ session} < 0.0001$ ) and polymeric molecular weight ( $p_{1st\ session} < 0.001$ ;  $p_{2nd\ session} < 0.01$ ;  $p_{3rd\ session} < 0.05$ ) were assessed on the stickiness perceived in the mouth PROs. Both the effects also influenced the outcomes of the stickiness intensity ranking exercise, with  $p_{1st\ session} < 0.001$ , and  $p_{2nd\ session} < 0.05$  for the type of polymer effect, and  $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.01$ ;  $p_{3rd\ session} < 0.05$  for the molecular weight effect. The type of polymer effect was found to be not significant in the 3<sup>rd</sup> session. A strong molecular weight effect was found affecting the disintegration time PROs ( $p_{1st\ session} < 0.0001$ ;  $p_{2nd\ session} < 0.0001$ ;  $p_{3rd\ session} < 0.0001$ ), but the type of polymer effect was not significant. Similarly, the molecular weight effect was found significant in the in vivo disintegration time PROs ( $p_{1st\ session} < 0.0001$ ;  $p_{2nd\ session} < 0.0001$ ;  $p_{3rd\ session} < 0.0001$ ), while no type of polymer effect was found.

#### RROs from exploratory pilot study on ODF mouthfeel assessment

RRO collection and analysis, as described in Kraus et al., 1999, was slightly modified. Three items (participant facial expression, participant jaw movements, and sample intake performance) were scored between 0 and 2 by researchers, as explained above.

For each test ODF sample, the total score of the three assessed items was calculated. Median and Interquartile range are summarised in table

#### *Intended place for Table 4*

As shown in Figure 9, median total MAS scores were between 3.5 and 4 for C1, 4 for P1, between 3 and 4 for C2, and 3 for P2. None of the samples scored higher than 4. As almost all participants experienced no difficulty in taking the samples, the intake score median was 2 in all samples, with very narrow interquartile range, and little between-sample variability. Only one participant experienced a partial loss of sample C1 in one session. Therefore, the ability to take the test ODFs was not influenced by any of the samples characteristics. Jaw movement scores varied between the samples and it was the most discriminative item among all. Facial expression also had little between-sample variability.

Friedman's and Dunn's multiple comparisons tests on total MAS scores showed significant differences in acceptability between C1 and P2 ( $p_{1st\ session} < 0.001$ ;  $p_{2nd\ session} < 0.001$ ), between C2 and P1 ( $p_{3rd\ session} < 0.01$ ), between C2 and P2 ( $p_{1st\ session} < 0.05$ ), and between P1 and P2 ( $p_{1st\ session} < 0.01$ ;  $p_{2nd\ session} < 0.001$ ;  $p_{3rd\ session} < 0.05$ ). Only the difference between P1 and P2 was significant in all the three sessions.

*Intended place for Figure 9*

## Discussion

### Texture analysis

The adhesive force measurement of the four test ODF samples by texture analysis showed higher adhesive force values exhibited by P1 and P2 than C1 and C2, with little discrimination between the two molecular weights of the CMC-based films. Orodispersible films are not necessarily designed to have mucoadhesive characteristics, however a certain degree of mucoadhesion can occur due to the intrinsic characteristics of the film forming polymers [3]. Despite the marked difference in properties and purpose, orodispersible and buccal films could share mucoadhesive behaviour. The influence of the polymeric molecular weight on mucoadhesive strength in buccal films was proven by Akbari et al., 2014. Therefore, a difference in the adhesive force between test ODF samples C1 and C2 was expected. Although quantitative measurements of the adhesive force of films made exclusively of the two types of polymer are not available to the authors knowledge, it is known that CMC is used for the formulation of mucoadhesive dosage forms such as mucoadhesive buccal patches [26,27], buccal films [28] and buccoadhesive tablets [29,30]. CMC is also widely recognised as a highly mucoadhesive polymer [27,31,32]. PVOH is used, in combination with other polymers, in the formulation of mucoadhesive patches [32], however it is less commonly used in buccal film formulations. Since the two polymers are commonly used for different purposes and in different proportions, lower PVOH, and higher CMC adhesive force values were expected. Higher discrimination between test ODF samples was provided by DMA. This method allowed detection of a clear difference between the adhesive force profiles of samples C1 and C2, and between

P1 and P2. Surface properties might be responsible for the results observed in the texture analysis of the test ODF samples. The Texture Analyser probe used to assess the adhesive force of the test films was made of Perspex, as opposed to the stainless steel plates used in DMA, which might have established specific interactions with the surface of the test films. Moreover, the contact time of the probe with the film sample was a key factor for the adhesive force outcome, as reported by Repka et al., 2005. In this respect, shorter or longer contact times might have given different results. In the texture analysis experiment, a contact time of 12 seconds was adopted in order to obtain the closest possible experimental conditions to the DMA. In the method used to operate the DMA, the contact time could not be controlled as it was a function of the force ramp and sample adhesive force. Therefore, in order to make the two methods comparable, the average contact time from the DMA was calculated and used in the texture analysis method. In the texture analysis measurement, however, the contact force was maintained constant for the duration of the whole contact time, whereas the contact force in DMA was constantly decreased with the contact time until detachment of the plates. The possible experimental conditions applied during texture analysis and DMA might have determined the marked difference between the adhesive force values obtained.

#### ODF tack measured by DMA and stickiness acceptability

DMA was found to be more discriminative towards sample adhesive forces than texture analysis. The low adhesive force and AUC values shown by sample P1 corresponded to a high stickiness acceptability score (between 4 and 5 = somewhat comfortable to extremely comfortable) reported by the participants. Moreover, P1 was ranked as being the least sticky among the samples with a median rank score of 1 out of 4. The disintegration time of sample P1 was reported to be fast (less than 1 minute) by the vast majority of the participants, and was evaluated between “somewhat comfortable” and “extremely comfortable”. The total MAS acceptability median score for sample P1 was 4. Furthermore, the adhesive force profile of sample P1 did not differ significantly from marketed ODF formulations such as Listerine® and NiQuitin®. Samples C2 and P2 showed medium adhesive force and the highest AUC values compared to the other samples. This corresponded to stickiness acceptability scores

between 2 and 3 in both the samples (between “somewhat uncomfortable” and “neither comfortable nor uncomfortable”) and to stickiness median ranking score between 2.5 and 3. The disintegration times of C2 and P2 were both identified as between 1 and 3 minutes by the majority of participants, however P2 disintegration time longer than 3 minutes was also reported. With respect to acceptability, the disintegration time of samples C2 and P2 was considered between “somewhat uncomfortable” and “neither comfortable nor uncomfortable” (between 2 and 3). The total MAS acceptability median score was between 3 and 4 for C2 and 3 for P2, corresponding to the lowest MAS median values recorded. Sample C1 had much higher adhesive force values than the other samples analysed.

With regards to stickiness acceptability, the ODF sample received a median score between 2 and 3 (between “somewhat uncomfortable” and “neither comfortable nor uncomfortable”), exactly like samples C2 and P2. Moreover, its stickiness ranking score was between 2.5 and 3, like in sample P2. Considering the high adhesive force value detected by DMA, C1 was expected to receive a higher stickiness ranking score and lower stickiness acceptability score by participants. However, sample C1 exhibited a fast disintegration time (less than 1 minute), which was considered between “neither comfortable nor uncomfortable” and “somewhat comfortable” (between 3 and 4) by participants. A total MAS score between 3.5 and 4 confirmed the higher acceptability of this test ODF sample over C2 and P2. This figure could be explained by the lower AUC value than samples C2 and P2.

In test samples P1, C2 and P2 low stickiness and fast disintegration time corresponded to more acceptable ODFs. The more the stickiness and disintegration time increased, the more the acceptability of the test ODF samples decreased. This correspondence was not found in sample C1, where high adhesive force values did not lead to poor acceptability scores assigned by participants. However, the integration of the AUC for the *in vivo* disintegration time of C1 provided values that better correlated with the *in vivo* stickiness acceptability score (Figure 10).

*Intended place for Figure 10*

This result suggests that stickiness perception might be influenced by the combined effect of adhesive force, intended as the stimulus intensity, and disintegration time, intended as the stimulus duration. As the stickiness profile of C1 changed considerably over the course of 1 minute, it is reasonable to assume that the physical and rheological properties of the sample also changed with time [34]. Hutchings and colleagues described a similar phenomenon in relation to food processing [35]. Volunteers were asked to chew samples of whole and blended cashew nuts, and rate the stickiness intensity of the samples over time on a 9 points score system. The stickiness intensity of whole cashews rose over time and was rated less intense on average than blended cashews. Moreover, the total duration of the assessment (mastication time) was significantly shorter for blended cashews. These data suggest an existing relationship between stickiness perception, degree of oral processing, and processing time. In the case of ODF samples, the influence of disintegration time and physicochemical properties of the films on stickiness perception might have led participants to feel sample C1 as more acceptable than C2 and P2. This finding could also explain the influence of the polymeric molecular weight on the disintegration time of all the ODF samples analysed. A short polymer chain, in fact, is responsible for a fast chain disentanglement, and faster disintegration of the polymeric layer in solution [36], and could therefore influence the oral processing time of the polymeric films. However, care must be taken when considering this rationale a sufficient theory of the ODF stickiness acceptability assessed in the present study. Stickiness perception is a complex phenomenon that can be greatly influenced by the temporary dominance of other sample attributes [37], by the functional context and type of the product analysed (food versus medicine; different types of food) [38], and by the great complexity of human somatosensory system [39,40].

Little information is available on the ODF stickiness perception as potential acceptability-influencing attribute (Visser et al., 2017). ODF stickiness was mentioned in few works with regards to observations on its potential impact on manufacturing and mechanical properties [42–45]. Krampe and colleagues observed that the “gummy nature” of films might contribute to the mouthfeel of the dosage form [11]. This study confirmed the influence of the sample stickiness on ODF acceptability of healthy young adults, as well as the influence of formulation parameters such as film forming polymer type and molecular weight.

## Disintegration time

The differences in the *in vitro* disintegration time measured by petri dish and drop methods were not statistically significant. The petri dish method showed results with a smaller interquartile range than the drop method, however the latter returned disintegration times in better agreement with the *in vivo* data. Sample C1 had a disintegration time of 25.4 seconds with petri dish method, and of 19.3 seconds with the drop method, both in good agreement with the disintegration time measured *in vivo* (Table ). The disintegration time of sample C2 was overestimated in both the *in vitro* methods, however the drop method gave closer values to the *in vivo* disintegration time. This result agreed with the reported disintegration time of the majority of participants to the *in vivo* study. However, the 30%, 25%, and 42% of participants reported that P2 disintegrated in more than 3 minutes. The disintegration time of sample P1 was shorter when measured by the petri dish method; however both methodologies returned data in agreement with the *in vivo* testing. Sample P2 disintegrated in 55.8 seconds when measured by the petri dish method, slightly underestimating the corresponding disintegration time measured *in vivo*. On the other hand, the disintegration time of P2 measured by the drop method fell in the centre of the time interval reported by participants (113.0 seconds). Listerine® had a comparable disintegration time between the two methods.

Many factors could have determined the non-significant difference in the measured test ODF disintegration time between the two *in vitro* methods. The gentle shaking applied in the petri dish method might have affected the disintegration of the two PVOH-based films (P1 and P2), thus accelerating their disintegration, but not the disintegration of the two CMC-based films (C1 and C2), which seemed more affected by gravity and a smaller test surface area. The comparison between drop and petri dish method was carried out by Preis and colleagues in 2012 [19]. In all the test formulations, the petri dish method detected slightly faster disintegration times than the drop method with no formulation-dependency. The results of the present study suggested that both film-forming polymer type and molecular weight could have an effect on the disintegration time measured by the petri dish method, whereas only the film-forming polymer type had an impact on the disintegration time measured by the

drop method. Interestingly, only the molecular weight influenced both the disintegration time *in vivo* measurement and acceptability, and not the polymer type. A slightly lower film area-to-water volume ratio of the drop method (251.2 mm<sup>2</sup>/mL) compared to that of the petri dish method (300 mm<sup>2</sup>/mL) might play a role in providing slightly different disintegration data.

*Intended place for Table 5*

The European Pharmacopoeia set the standard for the disintegration time of orodispersible formulations to 3 minutes [12], however, there is no mention of the acceptability requirements of the end user. In the present study, the *in vivo* disintegration time of the two higher molecular weight samples (C2 and P2) was found to last between 1 and 3 minutes, and was perceived as somewhat uncomfortable by participants. On the other hand, samples which disintegration time was less than 1 minute were perceived between somewhat comfortable to extremely comfortable, independently from other film characteristics. Moreover, fast disintegration time samples obtained higher MAS scores, further confirming the influence of disintegration time on the end user acceptability of the test ODF samples. Only the molecular weight of the film forming polymer influenced the PROs of both *in vivo* disintegration time measurement and acceptability, as well as the *in vitro* disintegration time measured by petri dish, as also reported by [36].

#### Other PROs

PROs on the thickness acceptability of P2 differed significantly from those of the other test ODF samples. This result was not expected as P1 and P2 had comparable measured thicknesses (around 60 µm). Nevertheless, P2 was clearly stiffer than P1. As participants were not asked to assess the stiffness of the samples, they might have signalled the uncomfortable feeling conferred by the sample stiffness by giving low PRO scores to the thickness of P2. This observation was further supported by the comments participants gave after assessing sample P2.

Among all the characteristics assessed by participants, the stickiness perceived in the mouth, the disintegration time, and the thickness perceived in the mouth showed statistically significant differences between test ODF sample PROs. This suggests that such characteristics are key attributes determining the acceptability of ODFs in healthy young adults. Control characteristics such as size perceived on handling and in the mouth, which were the same in all the test samples, confirmed the validity of the method as participants did not perceive any difference in the size of the four samples. Other characteristics such as thickness perceived on handling and stickiness perceived on handling, did not produce different acceptability PROs in accordance with sample type.

There are currently no confirmed clinical implications of the stickiness and disintegration time influence on the young adults acceptability of ODFs, as the participants ability to take the film samples as instructed was not directly affected. However, in patients suffering from dry mouth syndrome, highly sticky or slow-dissolving ODF formulations might pose a more serious acceptability barrier. Highly sticky foods were reported to be associated with a higher risk of choking in older patients and patients with swallowing difficulties [46]. Conversely, highly sticky ODFs might simplify the administration to uncooperative patients or to patients requiring antiemetic drug treatment. A human panel with similar design carried out in specific patient groups (e.g. dry mouth syndrome, geriatric patients) could provide evidence of the acceptability requirements with respect to ODF stickiness and disintegration time. The DMA method developed could then become a useful tool for formulation scientists to obtain the *in vitro* prediction of ODF patient acceptability in an early drug development stage. The ODF disintegration time of the test samples could be obtained *in vitro* by drop method, as it proved to be a more biorelevant assessment methodology.

### Conclusion

In the present study a novel method for the identification of key acceptability attributes of ODF has been proposed. A human panel carried out in healthy young adults led to the identification of stickiness perceived in the mouth and disintegration time as key attributes of ODFs with potential to influence end-user acceptability. A DMA method

was developed for the *in vitro* assessment of ODF tack and results were in agreement with the stickiness evaluated *in vivo* by the human panel participants. Disintegration time data obtained by petri dish and drop methods were compared with *in vivo* data. The drop method provided data that better agreed with the disintegration time evaluated *in vivo*. Both ODF stickiness and disintegration time were influenced by at least one of the investigated formulation parameters (molecular weight of the film-forming polymer). DMA and drop methods hold potential to become a useful tool for the *in vitro* prediction of ODF acceptability at an early drug development stage and inform further studies aiming to extend the assessment of ODF acceptability criteria to other patient groups.

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Table captions:

Table 1: RRO of participants facial expression, participants jaw movements, and sample intake performance (with 0 = signs of distress/more than three repeated chews/film spat out completely; 1 = no facial expression/one to three chews/film spat out with partial loss; and 2 = positive face or other signs of approval/no jaw movements/film swallowed without loss).

Table 2: Composition and thickness of test ODF formulations.

Table : Median score values and interquartile range of PRO.

Table : Median score values and interquartile range of MAS RRO.

Figures captions:

Figure 1: Human panel study design. Figure 2: Sample question on acceptability attributes of ODFs.

Figure 3: Adhesive force measurements of drug-free ODF test samples by texture analysis (n=3).

Figure 4: Adhesive force measurements of drug-free ODF test samples by Dynamic Mechanical Analysis (n=3). Statistically significant difference in adhesive force was found between all the test ODF pairs ( $p \leq 0.0001$ , or  $p < 0.001$ ) except from Listerine® and NiQuitin®.

Figure 5: *In vitro* disintegration time of drug-free test ODFs measured by petri dish and drop method (n=3). Figure 6: PROs of (a) stickiness perceived in the mouth, (b) disintegration time (1 = extremely uncomfortable, 5 = extremely comfortable).

Figure 7: Stickiness intensity sample ranking.

Figure 8: Frequency of test ODF sample disintegration time.

Figure 9: RRO total MAS scores.

Figure 10: Comparison between stickiness perceived PROs and AUC values of the four ODF test samples. Low AUC values correspond to high PROs.