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Characterisation and sensory evaluation of placebo OrPhyllo™ orodispersible films as a versatile paediatric drug delivery platform.

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Abstract

Orodispersible films (ODFs) are a convenient form of paediatric drug delivery and for those with swallowing difficulties. They can be extemporaneously prepared in pharmacies using pre-formulated bases which simplify and fasten the process while reducing compounding errors. OrPhyllo™ is a water-based commercial vehicle for preparing polymeric ODFs. It is chemically compatible with various clinically relevant active pharmaceutical ingredients (APIs) at different drug loadings.

This study focuses on characterising placebo OrPhyllo™ films, including their morphological, mechanical, and textural properties, as well as physicochemical stability by thermal analysis and X-ray diffraction. After local ethical approval, healthy adults explored stickiness, mouthfeel, and disintegration of these 3×3cm ODFs following various modes of administration.

OrPhyllo™ ODFs (185±10µm thick) exhibited distinct surface characteristics, one side (lower) smoother and the upper side rougher, as observed and shown by scanning electron and atomic force microscopy. However, both sides demonstrated similar mucoadhesive properties and rapid disintegration (between 60 and 140s, depending on the method used). Both sides were well-accepted, whether administered on the tongue or in the cheeks, with minor differences in mouthfeel and fast disintegration perception. The hen's egg chorioallantoic membrane test showed no irritancy, supporting the good acceptability of these placebo ODFs. The films remained structurally stable over 6 months, with low residual moisture.

Keywords : orodispersible , thin films , rapid disintegration , administration , palatability , irritancy , orphyllo , extemporaneous

1. Introduction

The need for personalised dosing remains a critical area of research in paediatrics due to the lack of suitable commercial alternatives [1]. Despite recent global legislation aimed at improving the availability of age-appropriate formulations, paediatric patients frequently depend on extemporaneous preparations when commercially available, child-friendly dosage forms with tailored strengths are unavailable. Furthermore, compounded formulations can benefit patients of any age who have swallowing difficulties [2], as well as animals [3], by enhancing medication adherence and improving therapeutic outcomes.

A recent global survey highlighted that oral liquids remain the preferred dosage form for extemporaneous paediatric compounding, surpassing capsules and sachets. Liquid medicines offer flexibility in tailoring doses to meet the needs of children, but certain factors require careful consideration. One important aspect is flavour and palatability, as unpleasant tastes can influence acceptance and adherence, particularly in younger patients. Additionally, maintaining the stability of liquid formulations is essential, as they may be susceptible to environmental factors, including microbial contamination and chemical degradation, necessitating appropriate storage and monitoring, as well as proper shaking and handling by the patient to avoid under- or over-dosing. [4]

As a result, the World Health Organization (WHO) led a campaign in 2008 introducing flexible solid oral dosage forms which do not have to be swallowed whole, and therefore behave like a liquid at the point of administration from the patient's perspective; they come without safety, cost and storage considerations encountered with liquid medicines yet providing access to age-appropriate medicines. Amongst them are sprinkle capsules, multiparticulates, effervescent tablets, chewable tablets, dispersible tablets and orodispersible tablets or films. [5]

Orodispersible films (ODFs) are innovative drug delivery systems designed to dissolve rapidly upon contact with saliva, enabling the release of active pharmaceutical ingredients (APIs) directly into the oral cavity. They are a convenient alternative for any patients with swallowing difficulties. In fact, administration of therapeutics using ODFs has been found to be an acceptable alternative by children and healthcare professionals. [6,7] This dosage form typically consists of a thin polymeric matrix, often incorporating hydrophilic polymers, which facilitates swift disintegration without the need for water. [8] While emerging technologies of ODF fabrication, such as 3D printing, offer a myriad of benefits to formulation development, they require specialised equipment often inaccessible to smaller pharmacy settings. The regulatory framework for the implementation of new ODF technologies is under development, but in the meantime, the patients' needs remain neglected [9,10].

ODFs can be extemporaneously prepared in compounding pharmacies by solvent-casting a pre-formulated film base. For example, OrPhyllo™ is an ODF base developed by Fagron and composed of pullulan, xanthan gum, kappa carrageenan gum, potassium sorbate, soy lecithin, neohesperidin dihydrochalcone, thaumatin, and mannitol [11]. The base can be mixed directly with the API and palatability enhancers, allowing for customisation of API, dose strength, appearance and palatability of ODFs. Moreover, Orphyllo™ not only provides a simple process of ODF preparation but also lessens the risk of compounding errors by simplifying the formulation step, thereby diminishing the risk of contamination. The recent study by Polonini et al. showed compatibility with 9 tested APIs (vitamin B12, vitamin D3, 5-hydroxytryptophan, bromopride, coenzyme Q10, melatonin, resveratrol, tadalafil, vitamin C) for up to 180 days [11], suggesting the suitability of OrPhyllo™ for formulating diverse pharmaceutical agents.

While the negative effect of surface roughness on patient acceptability of tablets has been explored [12,13], it is less known for orodispersible formulations. Studies quantifying surface roughness of ODFs do not report human palatability data [14–16], indicating the important gap in the existing knowledge of the impact of physicochemical, morphological and topographical characteristics on the end user experience.

This study therefore aimed to perform a thorough *in vitro* characterisation of placebo OrPhyllo™ ODFs, with a particular focus on the surface analysis, structural stability and mechanical properties. Additionally, this study introduces a novel way of testing oral irritancy of ODF using a hen's egg test chorioallantoic membrane model (HET-CAM). Finally, the *in vitro* results were correlated with the data obtained from a human palatability study, which focused on informing how to best administer the film in the oral cavity and its overall acceptability.

2. Methodology

2.1. Film preparation

The placebo OrPhyllo™ films were kindly provided by Fagron and prepared using a previously published method [11] in two main steps as follows: 1) reconstitution of the vehicle in water and 2) incorporation of an inactive ingredient, mannitol, which served as a diluent in place of the API. The vehicle was reconstituted by first transferring 22.5 g of the OrPhyllo™ film base into a PM jar 125 mL HV+LV (FagronLab™) and dispersing it with 50 g of purified water. Subsequently, 1 g of polysorbate 80 (as a surfactant), 3.75 g of polyethylene glycol 400 (acting as a plasticizer) and 1 g of simethicone 7-9245 emulsion 30% (to reduce bubble formation) were added. The mixture was then brought to a final mass of 100 g with additional water and then mixed and deaerated in a PM140 device (FagronLab™).

Next, mannitol (50 mg per film) was sieved, crushed and thoroughly mixed with the OrPhyllo™ film base until a paste-like consistency was achieved. This paste was spread onto glass plates using the

side D of a laminating apparatus (FILM-Rx, FagronLab™) and transferred to a film dryer (FagronLab™) set at 40°C for 40 minutes. After drying, the films were cut into 3 cm × 3 cm squares using a film cutter and packaged into individual laminated matte aluminium sachets. The sachets were stored at room temperature (15–30 °C) to simulate real-use conditions.

2.2. Morphological characterisation of films

2.2.1.Scanning electron microscopy

A sample of approximately 0.5 cm × 0.5 cm was cut from the ODF and mounted onto aluminium stubs (TAAB Laboratories, UK) with carbon-coated adhesive tabs, followed by sputter-coating with 20 nm gold for 2 minutes (Q150R coater, Quorum, UK) in an argon atmosphere. The coated samples were analysed with a cerium hexaboride thermionic filament scanning electron microscope (Phenom Pro, Thermo, Netherlands) connected to a secondary electron detector.

2.2.2 Atomic force microscopy (AFM)

The sample was fixed onto a glass slide with double-sided tape and mounted onto the sample stage. Atomic force microscopy (AFM) was performed using a nGauge (ISCPI, Canada) to characterise the surface morphology and roughness of the samples with a 20 μm × 20 μm scan size using an aluminium wedge tip chip. Six different areas on each side of the sample were scanned, excluding three data points with high noise. The roughness parameter analysed was arithmetic average roughness (Ra).

2.3 Surface analysis

2.3.1 Contact angle measurements

The hydrophobicity of ODFs was measured using a goniometer (FTA 1000USA). A water droplet (15 μL) was dispensed from a Gilmont micrometre syringe (Cole-Parmer Instrument Co. Ltd, UK) fitted to a 20-gauge blunt needle onto the film surface. The liquid droplet was allowed to stabilise on the film surface and photographed to allow for calculation of the contact angle using FTA 1000 software. Each sample was measured in triplicate, and the results are presented as mean ± standard deviation (n=3).

2.3.2 Mucoadhesion testing

Mucoadhesion experiments were carried out using a custom-made mucoadhesive probe on a TA-XT plus (Stable Micro Systems, UK). Bovine tongue tissue was obtained from Wetlab Ltd., sourced from Hereford oxen approximately 23 months old at the time of slaughter, with an average weight ranging between 0.9 and 1.2 kg. A film (1.5 cm^2) was attached to a 1 cm diameter cylindrical probe by double-sided adhesive tape. The bovine tongue tissue was placed onto the holder stage with the mucosal surface facing up. Before testing, artificial saliva (10 mM potassium chloride, 4 mM calcium

chloride, 2 mM sodium bicarbonate, 6.7 mM potassium dihydrogen phosphate, and 7 mM sodium chloride in deionised water) was dripped onto the tongue. The contact time between the probe and the tissue was 10 s with 60 g of force before pulling apart with a 2mm·s^{-1} removal speed. Each measurement was repeated in triplicate.

2.4 Mechanical properties of films

The mechanical properties of the film were analysed using a TA.XT.Plus texture analyser (Stable Micro Systems Ltd., UK). The puncture and tensile strength of the oral films were assessed to determine the films overall mechanical properties.

2.4.1 Puncture strength

The puncture strength of oral films was evaluated using a TA analyser equipped with an HDP/FSR load cell. A 3 cm × 3 cm oral film was supported between plates with a 1 cm diameter circular aperture. The probe was lowered at a pre-test speed of 1 mm/s until it contacted the surface, after which a test speed of 2 mm/s was used until the film ruptured. During the test, the maximum force (F_{max1}) required to rupture the sample was recorded. Measurements were performed at three different points on each film, with results expressed as the mean ± SD. Puncture strength was calculated according to Equation 1:

$$PS(MPa) = \frac{F_{max1}}{\text{cross-sectional area of the film}} \qquad (1)$$

2.4.2 Tensile strength

The tensile properties of oral films were evaluated using a TA equipped with an A/TG load cell. An oral film measuring 3 cm × 1 cm was held between two clamps positioned 2.2 cm apart. The strip was pulled at a rate of 2 mm/sec, and the maximum force (F_{max2}) at which the film broke was recorded. Each batch was tested in triplicate, and findings were reported as mean ± SD. Tensile strength was calculated according to Equation 2:

$$TS(MPa) = \frac{F_{max2}}{\text{cross-sectional area of the film}} \qquad (2)$$

2.5 Physicochemical characterisation

2.5.1 Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was performed on a Discovery instrument (TA Instruments, Waters LLC, UK). Roughly 3 mg of film sample was loaded into an aluminium pan and heated from 40 to 400 °C at 10 °C/min under a 25 mL min^{-1} nitrogen flow. Data were recorded using the Trios software and analysed with TA Universal Analysis.

2.5.2 Differential scanning calorimetry (DSC)

Analysis was conducted using a Q2000 DSC (TA Instruments, UK). A small piece of film was placed inside a non-hermetically sealed aluminium pan (T130425, TA Instruments, Germany). DSC analysis was carried out from 0 ºC to 250 ºC at a temperature ramp of 10 ºC/min. Oxygen-free nitrogen gas at a purge rate of 50 mL min^{-1} was supplied to the furnace throughout the experiment.

2.5.3 X-ray diffraction (XRD)

X-ray diffraction (XRD) patterns of the samples and reference materials were obtained using a Miniflex 600 (Rigaku, Japan) diffractometer supplied with Cu-Kα radiation (λ= 1.5418 Å). A glass sample holder was used. The patterns were recorded in the 2Θ range of 3 - 50º at a speed of 0.5º min^{-1}. The generator voltage was set at 40 kV, and the current at 15 mA.

2.6 Disintegration testing

2.6.1 Petri dish experiment

Prewarmed simulated salivary fluid (SSF; Gittings et al., 2014) (2.5 mL) and a large mesh plate with internal 5 mm × 5 mm squares (Figure S1) were deposited in a 47 mm Petri dish and positioned between the springs of 37°C water bath under shaking rate at 70 rpm. A 3 cm × 3 cm oral film was placed in the Petri dish and the stopwatch was started. Film disintegration was defined as the single timepoint where structural integrity was lost [18]. Each film type was tested in triplicate (n=3), and the statistical analysis was performed using a one-way analysis of variance (ANOVA) followed by Turkey's post-hoc multiple comparison test (IBM SPSS V29).

2.6.2 Oral cavity model (OCM)

Disintegration testing using a bespoke oral cavity model (OCM) was performed as previously described [19,20]. A 3 cm × 3 cm oral film was placed at the median position of the silicone tongue and the compression sequence was introduced. Two seconds compression sequences were repeated with an increased applied pressure from 0-30 kPA. The compression was continued until the films disintegrated. The cavity was continuously irrigated with SSF, prepared as described in section 2.6.1, at a rate of 1.5 mL min^{-1} through a syringe driver, ensuring a thin layer of SSF formed on the tongue (Desai et al., 2020; Desai et al, 2022). A plan view was recorded at 30 images per second (Apple iPhone 13, Apple Inc., Cupertino, CA, USA). The recorded video files were analysed using MATLAB (MathWorks, Natick, MA, USA), which edge detection method was used to recognise changes in the area of the film during disintegration. Each film type was tested in triplicate (n=3). Statistical analysis was evaluated by MATLAB (MathWorks, Natick, MA, USA).

2.7 Irritancy testing

Fertilized Specific-Pathogen-Free (SPF) eggs obtained from White Leghorn chickens (sourced from Medeggs Ltd, UK) were incubated at a consistent temperature of 37 ± 1°C and a relative humidity of 50-60% for 10 days using a Marsh automatic incubator (Lyon Electric Company, Inc.). On the fourth day of embryo development (E4), each egg was carefully opened sterilely with sterilized forceps to expose the developing chorioallantoic membrane (CAM), after which the opening was immediately sealed using Sellotape® to preserve the internal conditions. The eggs were then returned to the incubator. On the tenth day of embryo development (EA10), the irritancy of the ODF was assessed employing the HET-CAM assay method. The ODFs were cut into uniform pieces measuring 15 mm x 15 mm and placed directly on the CAM. The experiment was conducted in triplicate, with a 0.1N NaOH solution as the positive control, 0.9% NaCl as the negative control, and SSF as the solution control.

2.8 Human sensory panel

2.8.1 Ethics and participants

A single-centre, single-blind crossover sensory study was conducted with 19 healthy adult volunteers who served as naïve sensory assessors. Their mean age was 25 ± 3.9 years (range 21 – 38 years), and the panel was balanced for sex, with 10 (53%) female and 9 (47%) male participants. Ethical approval was obtained from the UCL Research Ethics Committee (Project ID: 4612/039).

2.8.2 Samples

Placebo OrPhyllo^{TM} films with no active ingredients were used. Samples were prepared as described in 2.1 under the supervision of a registered pharmacist. All samples were blinded using a 3-digit product code and presented to participants in a randomized order, generated according to a Latin-square Williams Design Plan to minimize presentation bias.

2.8.3 Study procedure

Participants were seated individually at computer stations where a questionnaire, designed using Qualtrics software (SAP America Inc., Seattle, Washington, USA), was displayed to record their responses. Participants were required to cleanse their palates before and after testing each sample.

Participants evaluated four placebo ODFs administered in four different ways: ODFs were applied onto the tongue or inside the cheek, with evaluations made for both the smooth and rough sides of the films. Participants assessed the stickiness, mouthfeel, and overall sensory experience using a 5-point smiley face scale. Additionally, they recorded the time required for each film to dissolve by using a stopwatch, starting when the film was administered and stopping when they felt it had disintegrated entirely. Open-ended comments were also collected to gain further insights into participant experiences. Finally, participants were asked to choose their preferred administration method.

Ordinal data from the study were assigned discrete numerical values (1 = extremely uncomfortable; 2 = somewhat uncomfortable; 3 = neither comfortable nor uncomfortable; 4 = somewhat comfortable; 5 = extremely comfortable) and analysed using a Friedman analysis of variance, followed by Dunn's post hoc test (GraphPad Prism 10 Software Inc.).

3. Results and discussion

3.1. Morphology and topography of OrPhyllo™ films

When OrPhyllo™ paste was deposited onto a glass support, the lower side of the film formed a smooth and shiny surface, while the upper side appeared rougher (Figure 1). In solvent casting, the side of the film that contacts the glass plate is smoother due to the uniform base and slower solvent evaporation, providing more time for even spreading. Conversely, the side exposed to air is rougher due to faster solvent evaporation and environmental factors like airflow. [21].

ODFs should be sufficiently thin to adhere to the mucosa without causing discomfort and be thick enough to facilitate handling and manipulation. [22] Currently, there are no standardised criteria for the thickness of ODFs; however, it is generally required to fall within 5 and 200 µm [23]. The OrPhyllo™ used in this study was within the recommended range with a thickness of 185 ± 10 µm.

Scanning electron micrographs (Figure 2a) confirmed the apparent roughness of the surface. Needle-shaped deposits were observed on the upper side of the film, which could suggest the crystallisation of OrPhyllo™ paste ingredients on the surface. To further investigate the surface topography, 2D (Figure 2b) and 3D (Figure 2c) atomic force microscopy was performed, from which average surface roughness (Ra) (Figure 3a) was calculated.

The upper side of OrPhyllo™ film exhibited a mean Ra of 677 ± 164 nm, which was statistically significantly higher ($p=0.0094$) than that of the lower side (192 ± 70 nm) (Figure *3*a). Surface roughness has the potential to influence the patient acceptability of the ODF negatively [24]. Formulation particulates left after disintegration can impair mouthfeel and acceptance, with smaller particles being preferred over larger ones due to the latter's negative impact on the sensory experience [25]. The threshold for sensory detection of surface roughness is unknown. Still, a preliminary *in vivo* study performed by Centkowska *et al.* reported the roughness of 5 µm as acceptable [21]. This value is significantly higher than the roughness of the upper side of our films (Ra=677 nm), suggesting their acceptability for *in vivo* testing.

Smoother films could exhibit better adhesion to the mucosal surface, enhancing the film's retention time in the oral cavity. To investigate this, the adhesion of the films to cow's tongue was tested using a texture analyser (Figure 3b). While the detachment force was higher for the lower side of the films, suggesting better mucoadhesion on the smooth surface, there was no significant difference between the tested sides.

Measuring the contact angle between a water droplet and film surface is often performed to characterise material wettability and could act as a good predictor of film behaviour in an aqueous environment. Generally, a material with a water contact angle below 90° is considered hydrophilic, while contact angles equal to or more than 90° correspond to a hydrophobic surface [26]. Formulation wettability will largely depend on the structure and hydrophilicity of the excipients [27]. Increased surface roughness may lead to faster drug release kinetics [28], potentially due to increased surface area, leading to faster wetting, disintegration and film dissolution. Our study observed a decrease in contact angle from 37.18° on the lower side to 31.95° on the upper side (Figure *3*c). Although the difference is statistically significant (*p=0.0003*), both film sides are still considered highly hydrophilic.

It should be noted, however, that the disintegration rate of the sample may influence the results, potentially complicating their correlation with *in vivo* findings

3.2. Physicochemical composition of films upon storage

ODFs are often composed of hygroscopic excipients to accelerate disintegration in the mouth [29]. While appropriate shelf life can be ensured by using vacuum-sealed pouches, the films may be prone to changes in physical form once opened. To simulate the end-user experience, the films were kept at room temperature (15–30 °C) with no humidity control and analysed after one and six months using TGA, DSC and XRD (Figure 4). Sample weight loss of around 5% observed in TGA in the 75-125 °C range can be potentially attributed to water evaporation, suggesting mild atmospheric water uptake upon storage (Figure 4a). The results also indicate appropriate thermal stability of OrPhyllo™ films, with degradation starting to occur around 250 °C. Similarly to TGA data, the broad endotherm at around 100 °C observed in DSC trace of 6 months-old OrPhyllo™ film (Figure 4b) suggests the slight tendency to absorb moisture, possibly due to the hydrophilic components of the OrPhyllo™ base. X-ray diffractograms (Figure 4c) reveal the highly crystalline nature of the film, which is unchanged upon storage.

3.3. The influence of mechanical properties on disintegration profile

Mechanical properties, such as tensile and puncture strength or flexibility, directly impact the ease with which these films can be handled, their resistance to breaking or tearing and their overall performance during disintegration in the oral cavity. Achieving a balance between adequate mechanical strength and rapid disintegration is crucial; overly rigid films can hinder disintegration and affect the mouthfeel, while excessively fragile films may break too easily, resulting in inconsistent drug delivery. The mechanical properties, including both tensile and puncture strength, are influenced by the composition and manufacturing process of the films, including the choice of polymers, plasticizers and other excipients, as well as the method of film formation. [30,31]

Puncture strength, a measure of film's resistance to penetration, ensures that the films can withstand mechanical stresses encountered during manufacturing, transportation and storage without tearing or breaking. Adequate puncture strength is particularly important for maintaining the integrity of the films when they are handled by consumers, thereby preventing premature damage that could compromise the dosage form's efficacy and safety. The films tested in this study showed a puncture strength of 0.025 MPa ± 0.002.

Tensile strength, on the other hand, measures a film's ability to resist forces that attempt to pull it apart. This property is crucial for understanding the film's mechanical behaviour under stress, directly impacting its application performance. High tensile strength indicates that the film can endure stretching and bending forces without breaking, ensuring that it can be applied and administered effectively by the patient. OrPhyllo™ ODFs exhibited a tensile strength of 2.654 MPa ± 0.48.

Although both properties are crucial for the success of an orodispersible formulation, there is no consensus on the target values for mechanical strength studies [32,33], highlighting a significant gap in the existing regulatory and scientific framework for the development of ODFs.

3.4. In vitro disintegration behaviour

Similarly to mechanical properties, no standardised criteria are currently defined for target disintegration time, but values under 3 min are often quoted as preferential [11]. Additionally, the standard pharmacopeial disintegration testing apparatus may not be suitable for thin films due to the large vessel volume and applied motion. However, the Petri dish test can provide preliminary insights into the disintegration behaviour of ODFs during the early stages of formulation development.

Presently, OrPhyllo™ films achieved complete disintegration around 60 seconds in the Petri dish test. This value agrees with previous studies by Polonini et al. (2023), who tested the same film matrix and manufacturing method to produce OrPhyllo™ films containing various APIs. Their study reported an average disintegration time of 46.94 seconds as measured using a USP disintegration test apparatus.

A major limitation of the Petri dish disintegration test is the lack of consideration for tongue movements and pressure applied to the film during swallowing. Therefore, the OCM disintegration model was implemented to better mimic oral cavity function, namely salivary flow, tongue pressure and swallow cycle (Desai et al., 2022b). The OCM disintegration profiles further provide a detailed look at the dissolution process over time, offering real-time disintegration dynamics that highlight the gradual breakdown of the films, with complete dissolution within 140 s. Additionally, the disintegration profiles for both sides of the OrPhyllo™ film are consistent, indicating that surface roughness did not introduce apparent differences in the film disintegration behaviour.

Oral irritancy testing

The HET-CAM model is an effective preclinical assay for evaluating the biocompatibility and irritancy of drug delivery systems. This model involves applying the drug delivery system to the chorioallantoic membrane of a fertilised hen's egg, which provides a rich vascular network and a tissue environment that closely mimics human physiology. By monitoring the membrane for signs of vascular damage, haemorrhage or inflammatory responses, the potential irritant effects and overall safety profile of the drug delivery system can be assessed. Recent studies have demonstrated the applicability of the CAM model in assessing oral irritation and its potential as a human buccal mucosa model due to its structural similarity to human oral mucosa, albeit without a mucus layer. [34–36]

Visual observations of the vascular responses of the CAM surface following the application of the test substances showed negligible irritancy for both the lower and upper sides of the ODFs, as well as for the SSF and 0.9% NaCl (Figure 6). In contrast, the positive control (0.1N NaOH) exhibited a strong irritancy response, as evidenced by the high cumulative score. The lack of significant vascular reactions (hyperaemia, haemorrhage or coagulation) supports their safety profile regarding oral irritancy. The negligible irritancy scores for the ODFs, regardless of their surface texture (rough or smooth), indicate that the films are safe for application on the mucosal membrane.

3.5. Human sensory evaluation

To simplify the study instructions for the participants, the lower side of films was referred to as 'smooth' and the upper side as 'rough'. Figure 7 reports the studied properties, including film stickiness, mouthfeel, in vivo disintegration time, overall sensory experience, and preferred administration method.

3.5.1. Film stickiness

Adhesiveness, or stickiness, refers to the degree to which a material clings to the tongue, gingiva, teeth or palate, potentially counteracting lubrication and hindering its removal from the oral cavity [24]. The mucoadhesive characteristics of ODFs are crucial for enhancing drug delivery as they allow the film to adhere to the oral mucosa to deliver a fixed dose (Wang et al., 2022). The location where the film adheres, such as the tongue or buccal cavity, may also impact this perception, as different areas of the mouth have varying sensitivities to texture and pressure. For patients, the stickiness can play a crucial role in the overall experience of using oral films and is particularly beneficial in administering medication to uncooperative patients, such as children, by reducing the likelihood of the medicine being spat out (Scarpa et al., 2017). However, excessive stickiness can lead to a sticky texture once wetting of the film occurs, creating an unpleasant mouthfeel that may negatively impact patient compliance (Krampe et al., 2016).

The human sensory evaluation of stickiness indicated that placing the rough side of the film on the tongue was rated as neither uncomfortable nor comfortable. In contrast, the other three methods were generally perceived as somewhat slightly more comfortable (Figure 6a). Overall, the stickiness of our films was considered generally acceptable, with no significant differences observed across various modes of administration or surfaces. This finding aligns with the results of the mucoadhesion test, which showed no significant difference in maximum detachment force between the two sides of the film, indicating comparable mucoadhesion strength and that surface roughness did not play a part in the mucoadhesive properties of the film. However, research suggests that stickiness perception may be influenced by a combination of mucoadhesion force and disintegration time [37]. Furthermore, Abdelhakim et al. suggest that acceptance of stickiness can vary significantly between individuals [38]. These indicate that further studies are needed to determine whether in vitro mucoadhesion results can accurately correlate with *in vivo* conditions. It is to be noted that presently that adhesion need to be sufficient adhesion so that when applied on the cheek or on the tongue mucosa the film stays in place but it is not the intention to deliver the drug transmucosal.

3.5.2. Mouthfeel

Most participants discerned textural differences between smooth and rough surfaces in the open comment section, corresponding to the differences in surface roughness observed with AFM (Figure 3). Notably, these textural differences appeared to influence sensory evaluations: the rough surface applied to the tongue received a lower median mouthfeel rating of 3, compared to a median of 4 for the other methods (Figure 7b). This suggests that the tongue is more sensitive to the film's roughness; however, the overall sensory perception of the rough side remained somewhat comfortable, indicating that the rough ODF surface is generally acceptable to users. The likely explanation is that the film disintegrated sufficiently rapidly to prevent the rough texture from affecting the acceptability of the formulation by volunteers.

3.5.3. *In vivo* disintegration time

The median disintegration times ranged from 67 to 82 seconds, and the means from 67 to 96 seconds, indicating no significant variability among the administration methods (Figure 7c). However, participant comments on disintegration time revealed a notable pattern: rough surface applied to the mucosa (tongue or cheek) tended to be perceived as disintegrating moderately or quickly by the majority of participants (Figure 7d). In contrast, about half of the respondents reported a slow disintegration rate for methods with the smooth surface applied to the mucosa (tongue or cheek).

The disintegration times between 1-2 min observed in the sensory panel were slower than the disintegration times observed in the Petri dish but faster than those recorded using the OCM method

(Figure 5). This may be due to inconsistencies in how disintegration is defined across different methods. In the Petri dish method, disintegration time is marked by the point at which the film begins to lose its structure [39], which is typical for *in vitro* studies. However, the endpoint of the observation of OCM is the time when the film completely disappears on the silicone tongue. Similarly, for human panels, the disintegration time is often perceived as the moment when the film completely disappears, as the film may continue to adhere to the oral mucosa even after losing its structure. Studies have shown that disintegration times are significantly longer when the endpoint is defined as complete film dissolution [40], consistent with our results. The findings of Samprasit et al. further proved that the *in vivo* disintegration time of oral films is longer than their *in vitro* disintegration time (Samprasit et al., 2017).

Two human panel studies have investigated the disintegration time of ODF and its impact on user comfort. One study by Scarpa et al. found that disintegration times between 1 and 3 min led to somewhat discomfort among participants. In contrast, films that disintegrated in less than 1 min were rated as comfortable to extremely comfortable [37]. Another study reported that most participants felt somewhat comfortable when the ODFs disintegrated within 1 min or less [38]. For our placebo films, the disintegration times across all four dosing methods ranged consistently between 1 to 2 min, with no significant differences observed. However, when administering the films with the rough surface facing downward, over 70% of volunteers reported fast or moderate disintegration times, suggesting that the rough surface provides an acceptable disintegration speed. In contrast, 42% of volunteers rated the disintegration speed of the smooth surface as slow. This result highlights that film surface texture may affect user perception of film disintegration time and agrees with our observation of higher surface wettability on the lower/rough surface of the film (Figure 3).

3.5.4. Overall sensory evaluation

The overall sensory evaluation of various ODF administration methods (smooth versus rough surfaces; tongue versus cheek placement) demonstrates high acceptability for the films, with both median and mean scores around 4 (Figure *7*e). In open comments, concerns were raised about the size of the samples relative to the method of administration. Two participants mentioned that the sample size was too large for comfortable administration on the tongue. In contrast, four individuals noted that the size of the sample was overly large when placed inside the cheek

Despite similar sensory attributes and disintegration rates, approximately two-thirds of participants overall favoured the tongue, with about one-third preferring the cheek (Figure *7*f). This is likely due to the larger size of the films, which made placement in the cheek more challenging. Notably, the rough surface on the cheek was the least favoured, selected by only one participant. Preferences for other methods were relatively balanced and showed no significant difference between male and female volunteers, indicating a gender-neutral selection in this limited sample size. Exploration of

ODF size was outside of the scope of this work but would be an important parameter to explore in future work bearing in mind that decreasing the surface area could affect other aspects such as the handleability of films. Additionally, the influence of adding potentially aversive APIs on cross-modal perception and acceptability should be evaluated in further studies.

While children are not small adults, healthy adult volunteers can overcome safety, ethical and methodological limitations encountered if sensory studies were to be run with children. Moreover, regulatory guidance (Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2) suggests information on palatability can be acquired in the early stages of development from adult panels.

4. Conclusion

The comprehensive in vitro characterisation of ODFs produced with OrPhyllo™ demonstrated low residual moisture and strong thermal stability, confirming their suitability for pharmaceutical applications. Surface morphology analysis revealed distinct but complementary characteristics between the smooth and rough sides of the films, which enhanced versatility without compromising mucoadhesion, disintegration time, or sensory acceptance. These findings affirm the robust and reliable performance of OrPhyllo™ ODFs under various conditions. Human sensory evaluation further highlighted the high acceptability of the films, with participants expressing favourable feedback across different administration methods. Notably, the tongue was the preferred site of application, confirming the product's suitability for easy and effective paediatric and patient-centred drug delivery. These results reinforce OrPhyllo™ as an adaptable solution for personalised medication, capable of supporting enhanced adherence and patient experience in clinical settings.

5. Acknowledgements

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6. Bibliography

[1] Walsh J, Schaufelberger D, Iurian S, et al. Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a conect4children expert group white paper. Br J Clin Pharmacol [Internet]. 2022;88(12):5034–5051.

[2] Carvalho M, Almeida IF. The Role of Pharmaceutical Compounding in Promoting Medication Adherence. Pharmaceuticals. MDPI; 2022.

[3] Davidson G. Veterinary compounding: Regulation, challenges, and resources. Pharmaceutics. MDPI AG; 2017.

[4] Fadda HM, Weiler H, Carvalho M, et al. Pediatric oral extemporaneous preparations and practices: International Pharmaceutical Federation (FIP) global study. European Journal of Pharmaceutics and Biopharmaceutics [Internet]. 2024;204:114483.

[5] Orubu ESF, Tuleu C. Medicines for children: Flexible solid oral formulations. Bull World Health Organ. World Health Organization; 2017. p. 238–240.

[6] Orlu M, Ranmal SR, Sheng Y, et al. Acceptability of orodispersible films for delivery of medicines to infants and preschool children. Drug Deliv [Internet]. 2017;24(1):1243–1248.

[7] Klingmann V, Pohly CE, Meissner T, et al. Acceptability of an orodispersible film compared to syrup in neonates and infants: A randomized controlled trial. European Journal of Pharmaceutics and Biopharmaceutics [Internet]. 2020;151:239–245.

[8] Chacko IA, Ramachandran G, Sudheesh MS. Unmet technological demands in orodispersible films for age-appropriate paediatric drug delivery. Drug Deliv Transl Res. Springer; 2024. p. 841–857.

[9] Ahmed M, Tomlin S, Tuleu C, et al. Real-World Evidence of 3D Printing of Personalised Paediatric Medicines and Evaluating Its Potential in Children with Cancer: A Scoping Review. Pharmaceutics. Multidisciplinary Digital Publishing Institute (MDPI); 2024.

[10] Tian Y, Orlu M, Woerdenbag HJ, et al. Oromucosal films: from patient centricity to production by printing techniques. Expert Opin Drug Deliv [Internet]. 2019;16(9):981–993.

[11] Polonini HC, Ferreira AO, Raposo NRB, et al. Compatibility Assessment of Novel Orodispersible Film Vehicle for Personalized Medicine with Selected Active Pharmaceutical Ingredients. J Pers Med. 2023;13(11).

[12] Hofmanová JK, Rajabi-Siahboomi A, Haque S, et al. Developing methodology to evaluate the oral sensory features of pharmaceutical tablet coatings. Int J Pharm [Internet]. 2019;562:212–217.

[13] Liu Y, Li P, Qian R, et al. A novel and discriminative method of in vitro disintegration time for preparation and optimization of taste-masked orally disintegrating tablets of carbinoxamine maleate. Drug Dev Ind Pharm [Internet]. 2018;44(8):1317–1327.

[14] Lee JH, Park C, Song IO, et al. Investigation of Patient-Centric 3D-Printed Orodispersible Films Containing Amorphous Aripiprazole. Pharmaceuticals. 2022;15(7).

[15] Panraksa P, Qi S, Udomsom S, et al. Characterization of hydrophilic polymers as a syringe extrusion 3D printing material for orodispersible film. Polymers (Basel). 2021;13(20).

[16] Reddy KA, Karpagam S. Cellulose Orodispersible Films of Donepezil: Film Characterization and Drug Release. Pharm Chem J [Internet]. 2017;51(8):707–715.

[17] Gittings S, Turnbull N, Roberts CJ, et al. Dissolution methodology for taste masked oral dosage forms. Journal of Controlled Release [Internet]. 2014;173:32–42.

[18] Desai N, Masen M, Cann P, et al. Modernising Orodispersible Film Characterisation to Improve Palatability and Acceptability Using a Toolbox of Techniques. Pharmaceutics. 2022;14(4).

[19] Desai N, Masen M, Cann P, et al. Modernising Orodispersible Film Characterisation to Improve Palatability and Acceptability Using a Toolbox of Techniques. Pharmaceutics. 2022;14(4).

[20] Desai N, Redfearn A, Macleod G, et al. How do orodispersible tablets behave in an in vitro oral cavity model: A pilot study. Pharmaceutics. 2020;12(7):1–10.

[21] Centkowska K, Ławrecka E, Sznitowska M. Technology of orodispersible polymer films with micronized loratadine—influence of different drug loadings on film properties. Pharmaceutics. 2020;12(3).

[22] Pacheco MS, Barbieri D, da Silva CF, et al. A review on orally disintegrating films (ODFs) made from natural polymers such as pullulan, maltodextrin, starch, and others. Int J Biol Macromol [Internet]. 2021;178:504–513.

[23] Bala R, Khanna S, Pawar P, et al. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm Investig. 2013;3(2):67.

[24] Asiri A, Hofmanová J, Batchelor H. A review of in vitro and in vivo methods and their correlations to assess mouthfeel of solid oral dosage forms. Drug Discov Today [Internet]. 2021;26(3):740–753.

[25] Krampe R, Visser JC, Frijlink HW, et al. Oromucosal film preparations: points to consider for patient centricity and manufacturing processes. Expert Opin Drug Deliv [Internet]. 2016;13(4):493–506.

[26] Lee Y, Kim K, Kim M, et al. Orally disintegrating films focusing on formulation, manufacturing process, and characterization. J Pharm Investig [Internet]. 2017;47(3):183–201.

[27] Yang B, Wei C, Yang Y, et al. Evaluation about wettability, water absorption or swelling of excipients through various methods and the correlation between these parameters and tablet disintegration. Drug Dev Ind Pharm [Internet]. 2018;44(9):1417–1425.

[28] Kalosakas G, Martini D. Drug release from slabs and the effects of surface roughness. Int J Pharm [Internet]. 2015;496(2):291–298.

[29] Salawi A. An Insight into Preparatory Methods and Characterization of Orodispersible Film—A Review. Pharmaceuticals. MDPI; 2022.

[30] Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. European Journal of Pharmaceutics and Biopharmaceutics [Internet]. 2011;77(2):187–199.

[31] Janigová N, Elbl J, Pavloková S, et al. Effects of Various Drying Times on the Properties of 3D Printed Orodispersible Films. Pharmaceutics. 2022;14(2).

[32] Takeuchi Y, Ikeda N, Tahara K, et al. Mechanical characteristics of orally disintegrating films: Comparison of folding endurance and tensile properties. Int J Pharm [Internet]. 2020;589:119876.

[33] Alaei S, Omidi Y, Omidian H. In vitro evaluation of adhesion and mechanical properties of oral thin films. European Journal of Pharmaceutical Sciences [Internet]. 2021;166:105965.

[34] Wannaphatchaiyong S, Heng PWS, Suksaeree J, et al. Lidocaine loaded gelatin/gelatinized tapioca starch films for buccal delivery and the irritancy evaluation using chick chorioallantoic membrane. Saudi Pharmaceutical Journal [Internet]. 2019;27(8):1085–1095.

[35] Kaewbanjong J, Wan Sia Heng P, Boonme P. Clotrimazole microemulsion and microemulsion-based gel: evaluation of buccal drug delivery and irritancy using chick chorioallantoic membrane as the model. Journal of Pharmacy and Pharmacology [Internet]. 2017;69(12):1716–1723.

[36] Tay SLM, Heng PWS, Chan LW. An investigation of the chick chorioallantoic membrane as an alternative model to various biological tissues for permeation studies. Journal of Pharmacy and Pharmacology [Internet]. 2011;63(10):1283–1289.

[37] Scarpa M, Paudel A, Kloprogge F, et al. Key acceptability attributes of orodispersible films. European Journal of Pharmaceutics and Biopharmaceutics [Internet]. 2018;125:131–140.

[38] Abdelhakim HE, Williams GR, Craig DQM, et al. Human mouthfeel panel investigating the acceptability of electrospun and solvent cast orodispersible films. Int J Pharm [Internet]. 2020;585:119532.

[39] Ouda GI, Dahmash EZ, Alyami H, et al. A Novel Technique to Improve Drug Loading Capacity of Fast/Extended Release Orally Dissolving Films with Potential for Paediatric and Geriatric Drug Delivery. AAPS PharmSciTech [Internet]. 2020;21(4):126.

[40] Turković E, Vasiljević I, Drašković M, et al. Orodispersible films — Pharmaceutical development for improved performance: A review. J Drug Deliv Sci Technol [Internet]. 2022;75:103708.

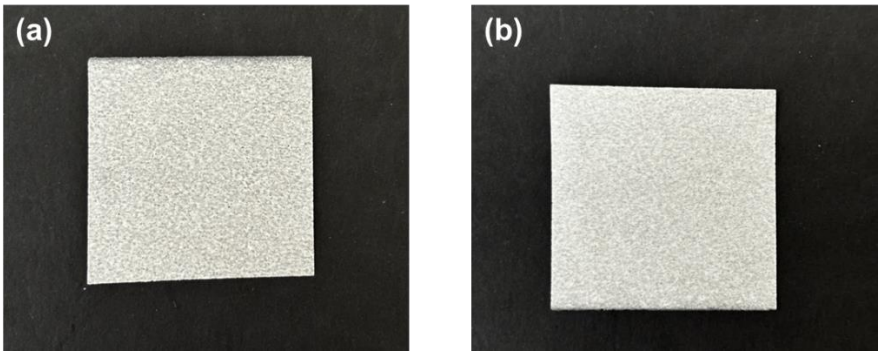

Figure 1: Digital photographs of the upper side (a) and lower side (b) of OrPhyllo™ film cut to a 3 cm x 3 cm square.

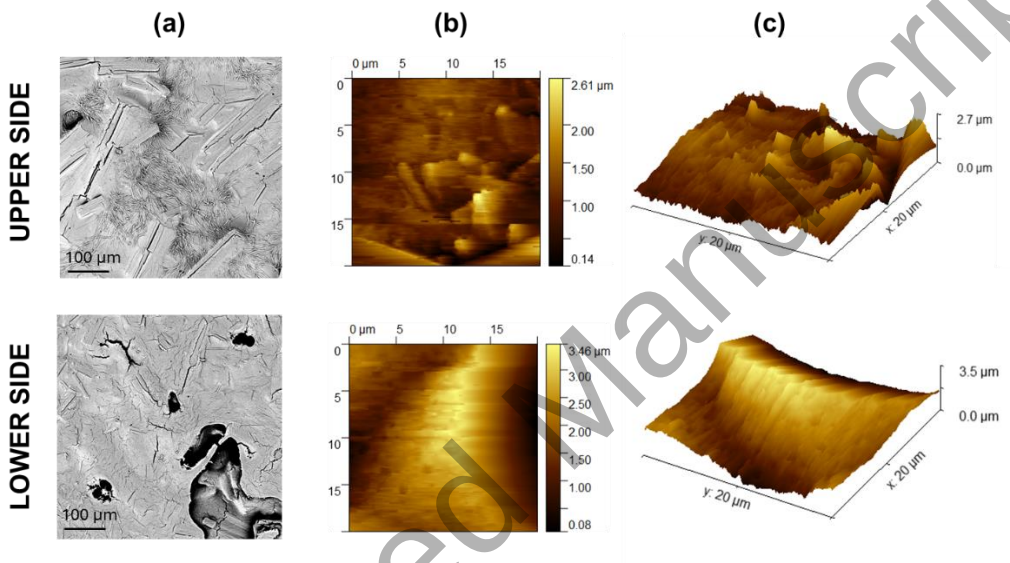

Figure 2: Scanning electron micrographs (a) as well as 2D (b) and 3D (c) AFM topography of upper and lower side of OrPhyllo™ films.

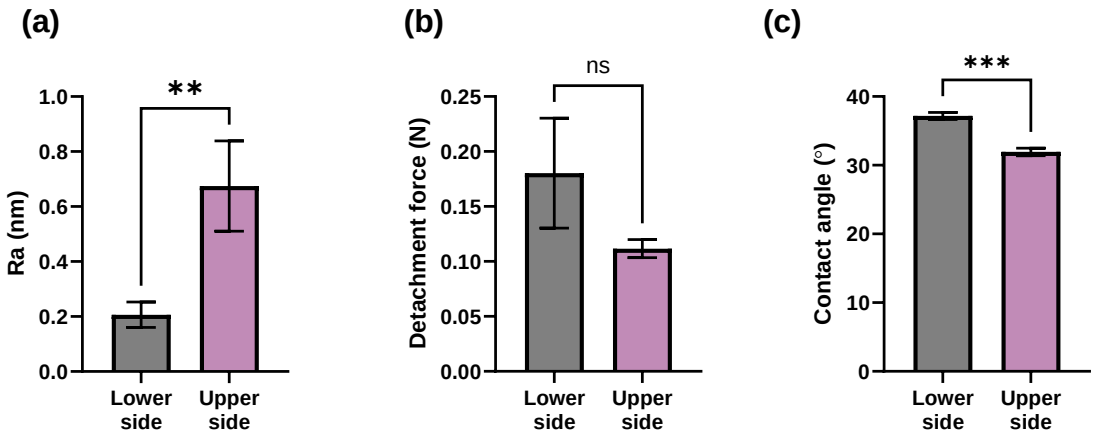

Figure 3: Summary of surface analysis properties for the lower and upper sides of the OrPhyllo™. Surface roughness (a), mucoadhesion (b) and contact angle (c) measurements were performed on the lower and upper sides of the OrPhyllo™. Data are presented as mean ± S.D. (n=3). An unpaired two-tailed t-test was performed, and statistical significance was annotated as: ns (p-value >0.05), ** (p-value ≤0.01), *** (p-value ≤0.001).

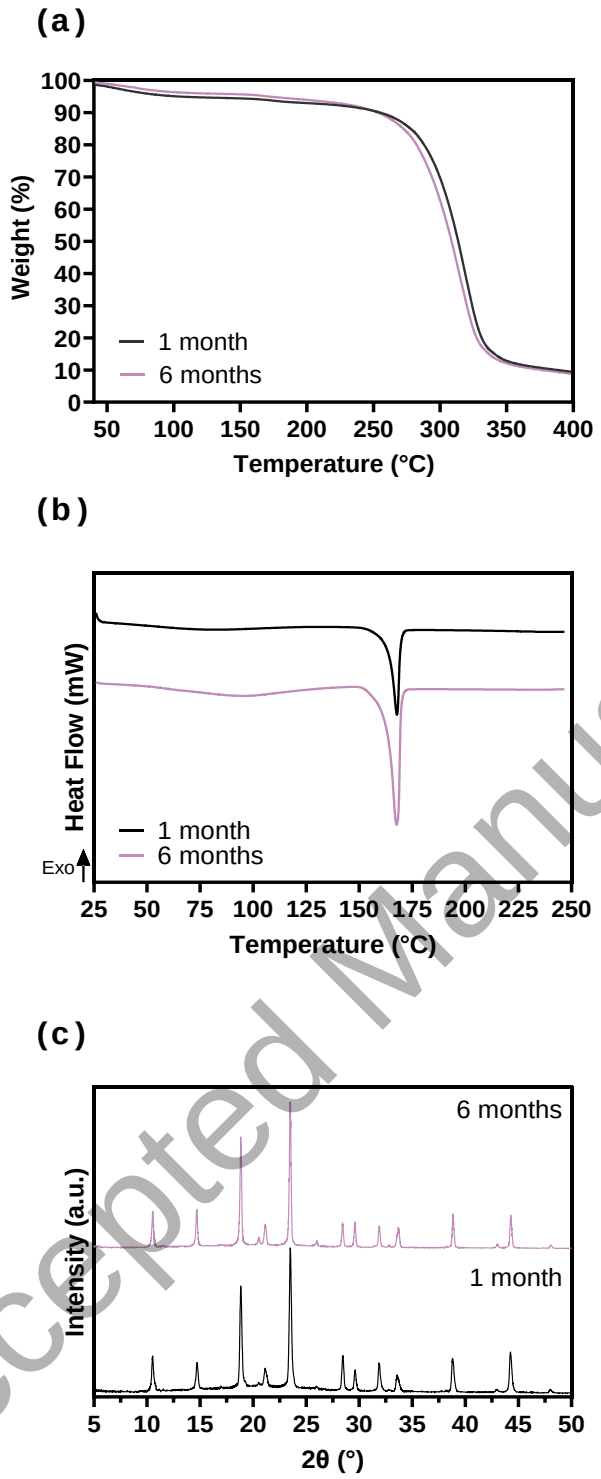

Figure 4: Thermogravimetric analysis (a), differential scanning calorimetry (b) and X-ray diffraction (c) analysis of OrPhyllo^{TM} films one month (black) and 6 months (pink) after storing at room temperature.

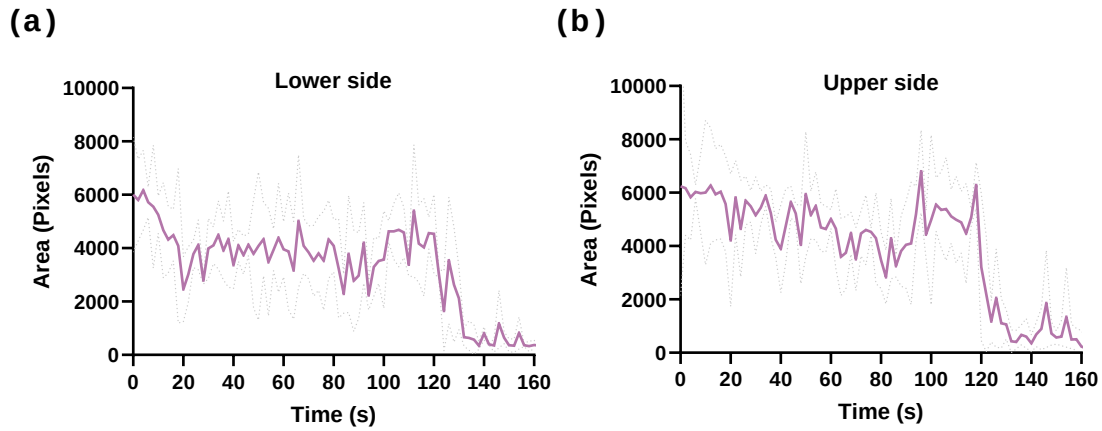

Figure 5: Oral cavity model (OCM) disintegration test performed by placing the lower side (a) and upper side (b) of placebo OrPhyllo™ films on the silicone tongue.

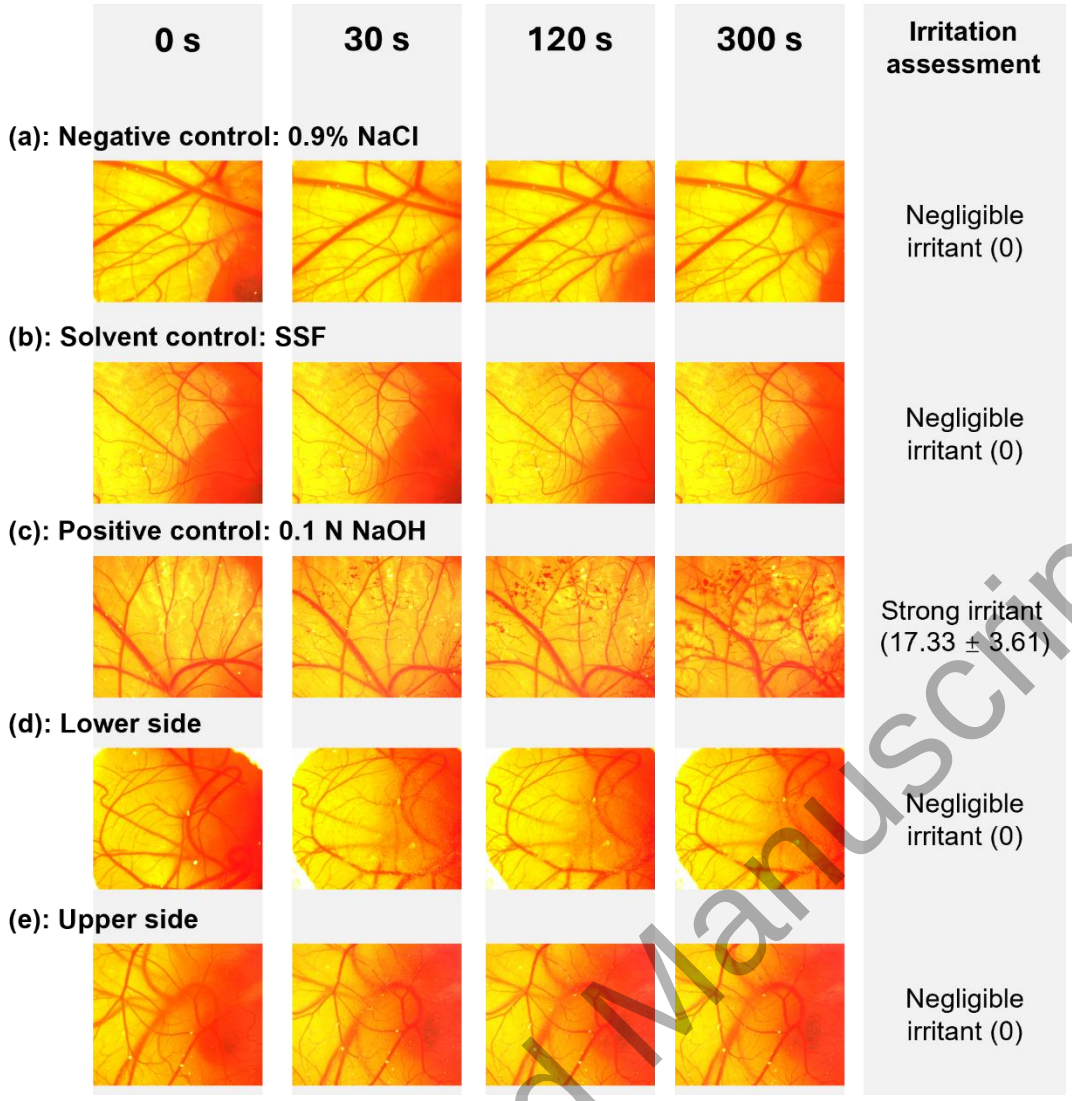

Figure 6: Vascular responses of CAM surface at each timepoint following application of a) negative control (0.9% NaCl), b) solvent control (SSF), c) positive control (0.1 N NaOH) as well as d) the lower side and e) the upper side of the film. Under irritation assessment, the cumulative score for the severity of irritation potential is in brackets on the right-hand side of the figure.

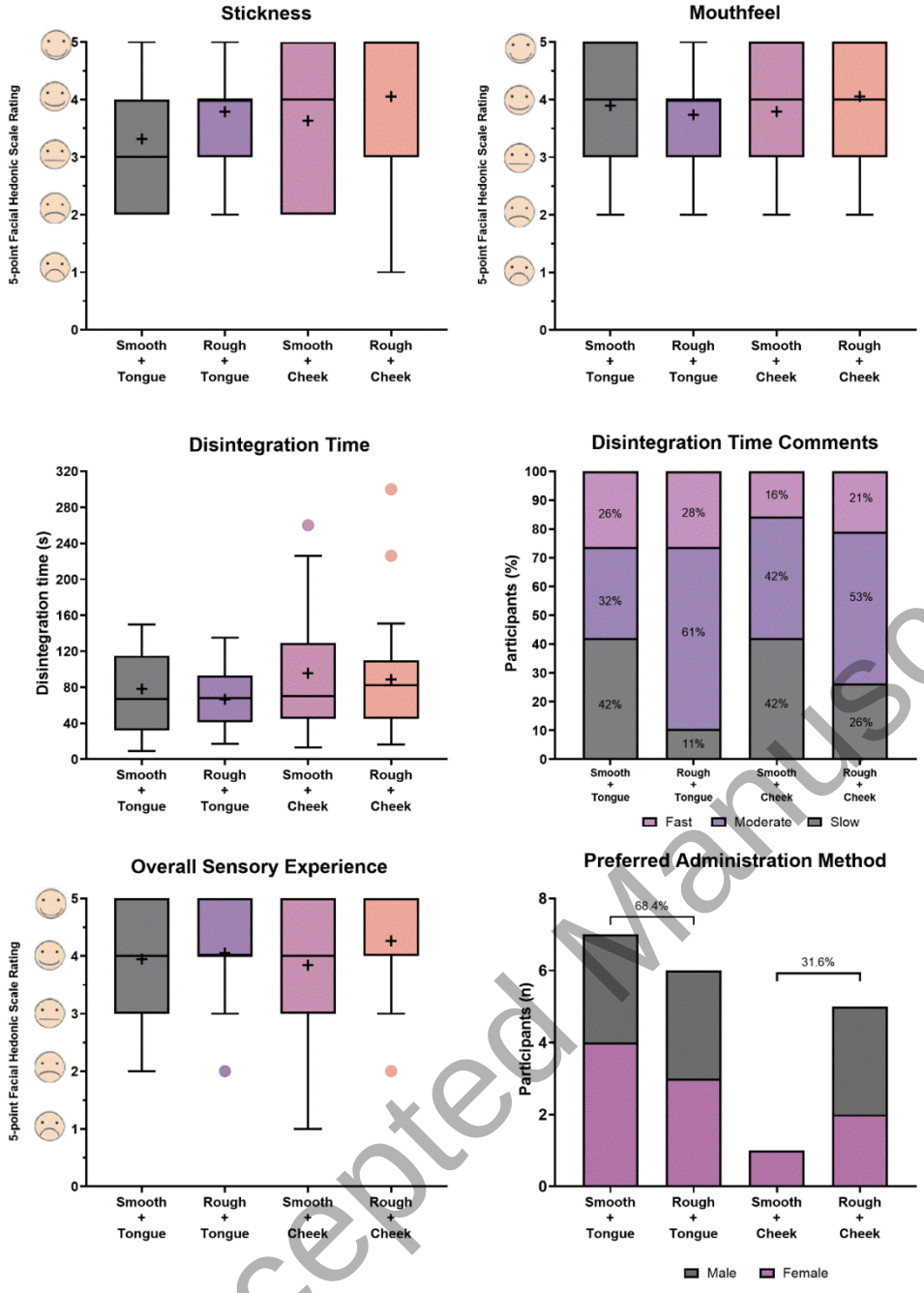

Figure 7: Sensory evaluation results across four drug administration methods. (a) Box plot illustrating the stickiness ratings for films applied to the tongue and cheek with either the smooth or rough side against the mucosal surface. The central line shows the median, the red triangle indicates the sample mean, and the blue diamond indicates outliers. The box limits indicate the 25th and 75th percentiles and the whiskers extend 1.5 times the interquartile range. (b) Box plot displaying the mouthfeel ratings under the same conditions as (a). (c) Box plot depicting the time required for films to disintegrate, measured in seconds, with the films placed on the tongue or cheek and with the smooth or rough side applied. (d) Categorical analysis of participants' comments with disintegration time, categorized as fast, moderate, or slow across different administration methods. (e) Box plot summarizing the overall sensory experience ratings for the other administration methods. (f) The bar chart illustrates the distribution of participants' preferences for four different administration methods, separated by gender.