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Defining end-user acceptability attributes of orodispersible films for patient centricity

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Declaration

I, Mariagiovanna Scarpa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Poor acceptability has been associated with low compliance, particularly in special patient populations. Patient acceptability assessment of individual dosage form attributes offers the advantage of providing information to the manufacturer on the strategy to adopt for optimising the dosage form design at an early drug product development stage. The development of *in vitro* methods capable of predicting attribute acceptability based on the quantitative measurement of relevant formulation variables could provide the manufacturer with a decision-supporting toolkit to guide the development of acceptable drug products. However, there is a great need of defining standard methodologies for the assessment of patient acceptability as the current knowledge is fragmented in this field. The orodispersible film (ODF) platform is considered patient-centric, however its attributes have rarely been assessed for acceptability on an individual basis. The aims of this study are to identify key acceptability attributes of the ODF platform by *in vivo* methods, and to develop and optimise *in vitro* methods to predict acceptability. ODF placebo samples differing in specific formulation variables were prepared and the corresponding acceptability attributes were assessed by human panel. Only some attributes differed among samples in the human panel study, and therefore were identified as key acceptability attributes. A series of *in vitro* methods for the prediction of ODF attribute acceptability were developed and optimised, and the same sample set was tested. *In vitro* methods were considered predictive if the measured variable directly or indirectly correlated with the *in vivo* acceptability assessment. Application of the proposed strategy in the acceptability assessment of oral dosage forms was shown, and key acceptability attributes (stickiness, disintegration time) and *in vitro* predictive methods (dynamic mechanical analysis, mechanical oral cavity model) were identified for the ODF platform.

Impact statement

Patient acceptability can significantly affect the safety and efficacy of medicinal treatments. The non-acceptance of a medicinal product could lead to non-adherence or to the manipulation of the dosage form, potentially causing medication errors, and suboptimal treatment effect. Therefore assessing patient acceptability is important to ensure that the medicinal product is taken as intended. The current knowledge on patient acceptability testing is fragmented, and there is no harmonised strategy that defines suitable assessment methods. The adoption of an acceptability assessment strategy to be integrated in the non-clinical phase of the drug product development could drive the formulation design towards the optimisation of highly acceptable medicinal products.

ODFs are acceptable dosage forms, however some attributes such as the perceived stickiness, time to disintegration, thickness and others can influence patient acceptability. The perception of such attributes can be controlled by modifying formulation variables such as the film-forming polymer type and molecular weight.
In the present work an attribute-dependent ODF acceptability assessment strategy was developed and optimised. The strategy involved the identification of key acceptability attributes of the ODF platform, their association with formulation variables that can control attributes' quality, and the development of *in vitro* methods capable of predicting the acceptability of individual key attributes.

In the short term, the implementation of the proposed strategy could benefit the patients by improving the ODF formulation patient acceptability, and the pharmaceutical industry by enabling the implementation of acceptability information into the early stage of the drug product development. The present study was conducted on the young healthy adult population. Based on the data obtained from this

study, the ODF attributes can be tailored to meet the requirements of specific patient groups such as neurodegenerative disease and mental health patients.

In the medium term, future studies aiming at the development of *in vitro* predictive methods for the acceptability of ODF attributes complementary to the tools designed in this study, will enable the complete decision-supporting toolkit that could be implemented in the non-clinical phase. In particular, rheology- or tribology-based *in vitro* methods for the prediction of ODF thickening effect acceptability could be developed. In this way manufacturers would be able to optimise highly acceptable ODF products from an early stage, thus preventing the re-formulation or repurposing of the marketed drug product due to poor patient acceptability.

In the long term, the developed acceptability assessment strategy can be adapted to dosage forms other than ODFs, and it could represent a way to implement the patient acceptability component into the drug product development process.
The integration of the proposed acceptability testing method for ODF will allow exploring different aspects of patient acceptability, and hence contributing to new regulatory guidelines, provided sufficient engagement from the regulatory agencies is obtained, and enabling healthcare professionals to make prescribing decisions based on the appropriateness of medicinal products to patients.

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List of Abbreviations

ADI	Acceptable daily intake
AIDS	Acquired Immune deficiency syndrome
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC	Area under the curve
BATA	Brief animal taste aversion
CMC	Carboxymethylcellulose
DMA	Dynamic mechanical analysis
DS	Degree of substitution
GB	Green-Blue
HCL	Hydrochloric acid
HPMC	Hydroxypropyl methylcellulose
ICH	International Conference on Harmonization
IQR	Interquartile range
ISO	International Organization for Standardization
MAS	Medicine acceptability scale
NAOH	Sodium hydroxide
NOAEL	Non-observed adverse effect level
ODF	Orodispersible film
OLS	Ordinary least squares
ODT	Orodispersible tablet
PIS	Participant information sheet
PMMA	Poly (methyl methacrylate)
PRO	Participant-reported outcome
PSP	Prednisolone sodium phosphate
PVAc	Polyvinyl acetate
PVC	Polyvinyl chloride

PVOH	Poly(vinyl) alcohol
PVP	Polyvinylpyrrolidone
REC	Research Ethics Committee
RG	Red-green
RGB	Red-Green-Blue
RRO	Researcher-reported outcome
SLS	Sodium lauryl sulfate
SSF	Simulated salivary fluid
T_g	Glass transition temperature
VAS	Visual analogue scale

Chapter 1. Introduction

1.1 Patient acceptability

Patient acceptability was defined by the European Medicines Agency as the ability and willingness of a patient to take a medicinal product as intended [1,2]. Depending on the target patient population, or on the specific medical condition of the patient, taking certain medicinal products or treatments might present difficulties. Several patient groups have been identified as frequently experiencing problems related to acceptability, for different reasons.

1.1.1 The paediatric patient acceptability

At first, acceptability issues were identified in the paediatric patient population, mostly because of the limited availability of purposely-developed medicinal products [3]. The ability to take medicines varies greatly with the child's age and physical development [4]. In this respect, the classification of paediatric patients in age groups has been described as a conventional method to identify the most appropriate dosage form and way of administration [4]. Advantages and disadvantages of adopting a specific route of administration or dosage form, and its appropriateness in relation to the child's age were also described. Attributes such as taste, smell, and texture, also called palatability, are likely to influence the paediatric patient's acceptability of orally administered medicines [2]. The shape, and size of the medicinal product may influence the ability to swallow solid dosage forms (swallowability), and is a key factor in determining the paediatric patient acceptability [2,5]. In addition, the required dose (number of tablets, dosing volume, etc.), dosing frequency, and duration of the treatment, the administration device, the primary and secondary packaging, and the actual mode of administration of the medicine are all factors potentially influencing patient acceptability [2]. In addition, factors related to the child's conditions such as the

influence of the illness (presence of any pain or discomfort), the convenience of the parent/caregiver to administer a certain product, and the presence of a disability, or cultural background might also affect acceptability [2,4].

As a result of the raised awareness on the relevance of patient acceptability, the European Medicines Agency issued a guidance document where patient acceptability is considered an integral part of the in the paediatric drug development [2,6]. Currently, there is a great need of appropriate dosage forms for paediatric patients [7], and regulatory agencies have been offering incentives to favour the development of paediatric medicinal products, particularly for the actives included in priority lists [8].

1.1.2 The geriatric patient acceptability

Similarly, geriatric patients might encounter difficulties in taking medications. The demographic trend shows that the percentage of people over 65 years of age is rapidly increasing, and is likely to represent the 24.5% of the total population of developed and developing Countries by 2050 [9], and 30% in the European Union [10]. In turn, this will correspond to an increase in the demand of medicinal products designed to meet the needs of this heterogeneous patient population. Similarities in the acceptability requirements for oral dosage forms were described between the paediatric and geriatric population [11,12]. However, the marked differences in physiological, and pathological conditions between the two patient populations led to the need for a separate acceptability assessment and dedicated strategies for the development of geriatric-centric dosage form development [9,13–16]. Whereas age can represent an indicator for the acceptability requirements of the paediatric patient, the same cannot be assumed for the geriatric patient. Age is considered a poor predictor of the health conditions of the older patient due to the heterogeneity of the population [15]. The number of morbidities and co-morbidities impacting on the physical performances of patients, and the rise in the complexity of drug therapy due to polypharmacy do not

depend on the age of the patient [15]. Clinical conditions including dementia, frailty/disability/sarcopenia, chronic inflammation, sensory impairment, cancer, pain, or a combination of them contribute to the therapeutic needs of the patient [15]. In addition, the psychological and cognitive condition of the patient could either improve or worsen his/her interfacing with, and attitude towards the medicinal product. In turn, specific difficulties and problems with medicine administration could be encountered, particularly if the patient is self-medicating. Among the most common problems with medications faced by the geriatric patient there are those related to the appropriate identification of the right medicinal product due to visual or cognitive impairment issues, the ability to correctly remember the day and time when the medications should be taken, or understanding instructions due to cognitive problems, difficulties in opening the packaging, picking or handling the dosage form due to motor dysfunctions, and difficulties in medicines oral intake due to dysphagia or dry-mouth syndrome conditions [9,11,17,18]. According to the European Medicines Agency, geriatric patient acceptability might be influenced by product characteristics such as the selected route of administration, the site of dermal application (if topical), the product appearance and swallowability, the recommended single dose, dose frequency, treatment duration, and instructions, the packaging characteristics, the selection of medical device (if required), the need of handling the product prior to use, the need of assistance, and the settings where the medicinal product is taken [1]. Under the regulatory perspective, geriatric patient acceptability has been addressed since 1994, with two International Conference on Harmonization (ICH) guidelines [19,20], a Geriatric Medicine Strategy [21], and a concept paper [10,22] that resulted in a draft reflection paper on the pharmaceutical development of medicines for use in the older population [23].

1.1.3 Other patient groups acceptability

Besides children and elderly, other patient populations have specific characteristics and needs that could trigger different acceptability-related issues [24]. Packaging design-related, and dosage form design-related acceptability or preference were analysed in a systematic review conducted in different patient populations [24]. Examples of patient populations with specific needs include long-term cancer survivors, and the cognitive impaired [25], however potentially any patient group affected by a specific pathology or group of pathologies could require a dedicated approach to medicine administration. It would be therefore non-appropriate to develop the entire patient-centric drug product design based on a fixed strategy, as each patient group has a different set of needs and requirements that must be appropriately considered.

1.2 Impact of poorly acceptable medicines on the risks to patients

Patient acceptability was reported to have a significant impact on the adherence to treatment [1,26], on the quality of life of the patient and the caregiver [1], on the institutional or hospital system of medication safety [1], and on the risk vs. benefits profile of the medication [1]. In turn, a good treatment adherence was associated with lower mortality [27,28]. Patient non-compliance has been reported to cause poor treatment outcomes in patients affected by diabetes, epilepsy, AIDS (acquired immunodeficiency syndrome), asthma, tuberculosis, hypertension, and organ transplants [29,30]. Poor compliance has been identified as the main reason for the lack in blood pressure control in patients with hypertension, and therefore, in the increased risk of stroke, myocardial infarction, and renal impairment [30]. In the case of patients affected by infectious diseases, poor adherence is not only dangerous for the subject, but also for other people [30].

1.2.1 Risks associated with the use of non-appropriate medicinal products in children

One of the most significant factors determining poor patient acceptability is represented by the lack of appropriateness of the dosage form. This case has been particularly well documented in paediatric patients. The lack of dosage forms of appropriate strength, shape, taste, smell, or other key acceptability attribute(s) may lead the caregiver to adopt coping techniques such as splitting or crushing tablets, opening capsules, or mixing with foods and liquids [7,31]. The unlicensed or off-label use of medicinal products may result in medication errors, and put at risk the safety of the patient. Potential risks include over/under dosing [31], dose variability [31], problems with the stability of the drug [7], and errors related to the instructions for manipulation [7]. The non-appropriateness of the dosage form could also expose patients to the risk of chocking, aspiration, local irritation, fluid overload, or electrolyte imbalance [32].

1.2.2 Risks associated with the use of non-appropriate medicinal products in older people

Similarly, the use of non-appropriate medicinal products in the geriatric patient population might lead to risks and medication errors. The risk of chocking or aspiration is linked to the administration of tablet and capsules. The use of liquid medications may pose risks associated with errors when measuring the dose, and excipient overload. Uncoated solid formulations may stick to the mucosa in case of scarce salivary flow. Also, safety issues might be associated with the need of tablet breaking, splitting, crumbling, crushing or chewing. The risk of excipients overload could be increased if a patient takes chewable tablets multiple times. Problems with the dissolution of orodispersible tablets can be encountered in case of low salivary rates, and their moisture-protecting packaging might be difficult to open. Under-dosing and sodium

overload could occur with effervescent tablets, whereas capsules might need to be opened in some circumstances [1]. Additional risks are also associated with non-oral dosage forms.

1.3 Patient acceptability of oral dosage forms

The oral route is the most used way of administration in children and elderly [1,11]. Oral dosage forms are available in a variety of forms and shapes, from the monolithic dosage forms such as tablets and capsules, to liquids and multiparticulates.

1.4 Designing patient-centric medicine

The need to formulate medicines capable of meeting the requirements of the target patient population, in order to be perceived as highly-acceptable is increasing. This happened in response of the raise in awareness from the scientific community of the consequences of poorly-acceptable medicines on the success of the medicinal treatment and patient safety. Considerable efforts are being made towards the definition of strategies for the design of patient-centric dosage forms. The patient-centric drug product design differs from the conventional drug product design because the interaction between patient and product, and the consequences of such interaction are considered [25,33]. In particular, effects on the adherence, and medication errors are scrutinised. In this sense, both product-related, and patient-related characteristics must be taken into consideration. As a result, specific design drivers should be identified and used to guide the product design until the best resulting product is achieved. A list of potential design drivers, design inputs, and design outputs were identified by Stegemann and colleagues, and are summarised in Tab. 1.1 [25].

Table 1.1. Summary of Design Drivers, Design Inputs, and related Patient Needs, reported without modifications from Stegemann et al., 2016 [25].

Design drivers	Design Inputs	Design Outputs
Characteristic disease/condition	• Disease-specific expression • Multi- and co-morbidity • Frailty • Disease severity/burden • Disease stage	• Individual drug/drug combination • Individual drug dose accuracy • Dose range • Disease-specific disabilities
Characteristics drug substance/ physiology	• Developmental stage (maturation, declining body functions) • Oro-esophageal and GI transit • Permeability • Fat/water ratio • Drug metabolism and clearance • Homeostasis • Reserves	• Flexible dose adjustment • Appropriate dosage form • Excipient safety/total amount of excipients • Low adverse drug reactions • Low intake/administration frequency
Characteristics drug therapy	• Need for different types of dosage forms • Availability of combination products	• Reimbursement • Dose tracking
Characteristics drug product	• Multiple and polypharmacy • Therapeutic complexity • Prescription guidelines • Different dosage forms • Possibility of product modifications (manipulations) • Range of trademarks	• Simplified regimen • Appropriate dosage form • Drug product identification • Drug product recall • Dosing frequency • Dosing moments • Dispensing, substitution, and re-substitutions • Reimbursement • Dose tracking
Patient characteristics	• Age, gender, socio-emotional development • Mobility (travel) • Perceived wellbeing • Functional limitations (motoric, sensory, cognitive) • Health literacy (disease/therapy understanding) • Dehydration/malnutrition • Motivation • Psychological traits • Remaining life time • Living alone or with others • Daily occupation (work, school) • Social support and interaction • Stress resistance	• Usability/ergonomics • Self-explaining/intuitive use • Drug product information • Product identification • Swallowability • Palatability (taste, smell, texture) • Reminder • Dosing frequency/moments • Least number of units/drug products • Feedback/communication/motivation
Medication management (adherence and administration)	• Intended and non-intended non-adherence • Therapy simplification • Pill boxes and compliance aids • Hoarding • Environment where the medication needs to be prepared and taken • Access/cost	• Identification/differentiation outside packaging • Dosing frequency/moments • In-use stability (e.g., external “Pill box” airport scanning) • Ease of storage • Convenience of use (e.g., specific requirements like before breakfast) • Use discretion

	• Co-medications and changing (generic) prescriptions	• Portability • Food effects • Refill reminders • Harmonized labeling, naming elements, product elements (e.g., packaging), or cue tags
Usability (handling, storage, and disposal)	• Drug product appearance • Drug product shelf life • Drug product storage • Drug product disposal • Drug product packaging • Dose measurement and preparation • Dosing frequency • Need for administration device • Ability to self-administer with ease • Need for help from caregiver • Learned usage/experience	• Handling issues (e.g., round tablets roll off the table) • Ergonomics • Formulations enabling (easier) self-administration • Refrigeration requirements • Stability during use period • Minimize waste (dose form, packaging) • Mechanical stress stability of the product • "Predicted usage" (modification by patient)

The consideration of all the points listed in Tab. 1.1 is a useful strategy for the initial stages of the drug product design process. However, the appropriateness, and acceptability of the final medicinal product cannot be certain without the feedback of the patient. It would therefore be useful to adopt an assessment method for the verification of the end-user acceptability that could directly involve the target patient population [34].

1.4.1 Assessment of patient acceptability

Various published works have focused on assessing the patients acceptability of medicinal products in clinical studies. Methods such as visual analogue scales (VAS) and hedonic facial scales have proven to be reliable for the acceptability assessment of paediatric patients [35]. Other scales and assessment methods have been used to evaluate acceptability in different patient populations [36–39], many of which were implemented from techniques used in the field of food sensory evaluation [35]. The patient acceptability of medicinal products is often limited to the assessment of the formulation aspects of the drug product [39], and the used methods often fail to take into account all the dimensions of patient acceptability [40–42]. Advantages and

disadvantages were also reported when the medicinal product was already being prescribed to the study participants, or when a placebo formulation was administered instead for the purpose of prospecting the acceptability of the final product in pre-marketed formulations [39]. The second case is particularly advantageous during the drug development process. The scientific debate on the suitability of methods for the assessment of patient acceptability has evidenced a fragmented knowledge, and the lack of a harmonised strategy [41].

1.4.2 Applicability of acceptability testing to the drug development life cycle

Regulatory agencies are now encouraging studies to investigate the acceptability of new medicinal products [34]. The collection of acceptability information might find place during the clinical phases of the drug development life cycle (Fig 1.1).

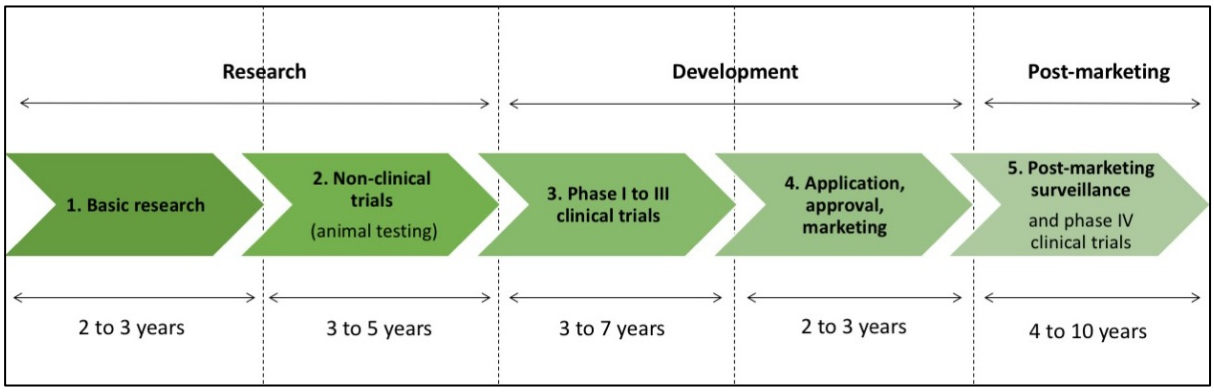


Figure 1.1. Drug development life cycle.

However, before the clinical stage, the drug product must have already been optimised and must have passed the pre-clinical phase tests. If evidence of poor patient acceptability is obtained during the clinical phase, the costs of re-formulating and re-testing the drug product would be too high, and the total development time frame too long.

Therefore, from the drug developer perspective, acquiring information on patient acceptability in the early drug development stage is undoubtedly more convenient. However issues may arise with regards to the costs, time, and safety of a human study conducted during the pre-clinical phase. Unless the corresponding placebo formulation is tested, safety risks associated with the administration of the untested active pharmaceutical ingredient (API) will preclude the authorisation of any human study. In the case of a placebo formulation testing, provided that all the excipients are evaluated as safe for the target patient population, the time required for the study design, the ethical committee authorisation, recruitment, data collection and data analysis might heavily impact on the total span of the drug development process.

Consequently, human testing does not seem to represent a viable solution.

As *in vitro* methods are utilised in the pre-clinical drug development phase to inform on the safety and characteristics of the formulation, so *in vitro* methods could be used in the prediction of patient acceptability.

Increasing efforts are being made towards the development of *in vitro* and animal testing methods that could inform on the patient acceptability of formulations. Animal methods have been extensively studied for the assessment of taste, and a positive correlation between murine and human taste perception has been found [37]. However, technical difficulties have been encountered when attributes other than taste have been assessed using the brief animal taste aversion (BATA) test. *In vitro* dissolution, *in vitro* assays, and biomimetic taste sensing systems, are used for the prediction of the taste of solutions [38]. *In vitro* methods assessing polymer adhesion were also developed [43], and might be used to predict the safety of swallowing of pharmaceutical products.

Although a comprehensive assessment of the overall acceptability of a drug product cannot be obtained, *in vitro* methods represent the most valuable alternative to human testing. In this regard, the formulation variables with the potential to influence patient acceptability must be assessed separately, so that *in vitro* predictive methods to assess the acceptability of each specific attribute can be developed.

1.5 A strategy for the identification of dosage form acceptability attributes

In order to obtain *in vitro* methods capable to guide the drug development process towards an acceptable medicinal product, accurate information on the patient acceptability of the study dosage form should be obtained from the target patient population. Such information should be quantitative, in order to be used for *in vivo/in vitro* correlation studies. Once acceptability information has been obtained, the following stage is to identify appropriate formulation variables that could potentially influence patient acceptability, optimise an *in vitro* quantification method, and verify the correlation of such variable with patient acceptability outcomes. A diagram of the proposed strategy is summarised in Fig. 1.2.

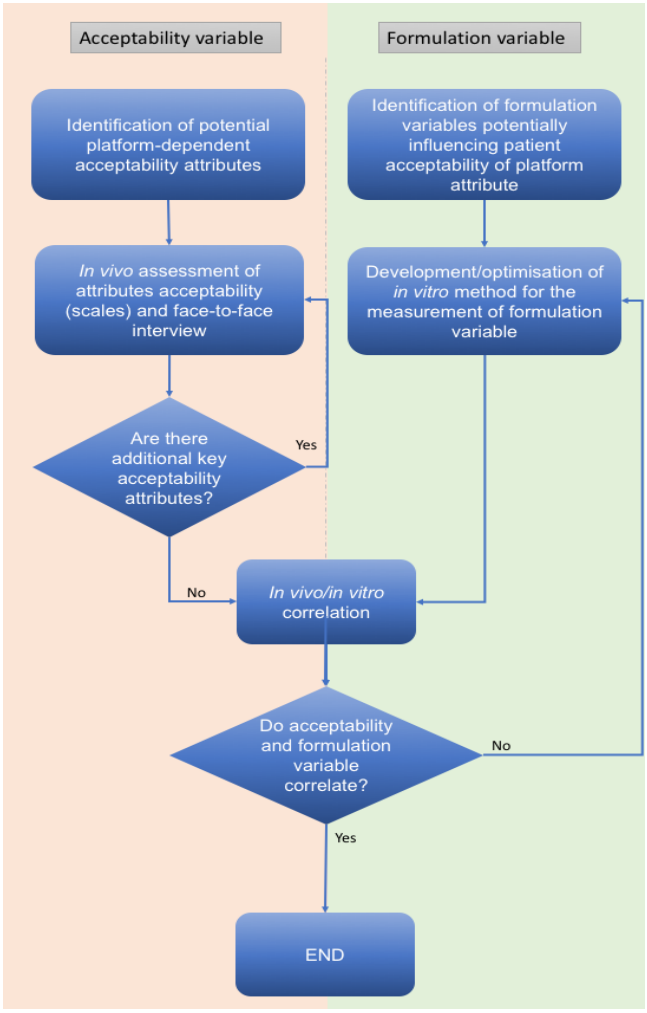


Figure 1.2. Flow chart of strategy for the identification of key acceptability attributes of dosage forms, and development of in vitro decision-supporting tools for the development of acceptable medicinal products.

1.5.1 Identification of dosage form acceptability attributes

No two medicinal products are the same, and depending on the dosage form and the specific characteristics of the formulation being investigated, the attributes influencing the end used acceptability may vary. Therefore the selection of the *in vitro* tools should follow the identification of the attributes that are more likely to affect the end user acceptability. Acceptability attributes of oral dosage forms should be identified based on the intended use of the product, on its intake process, and on its behaviour once inside the mouth (Fig. 1.3).

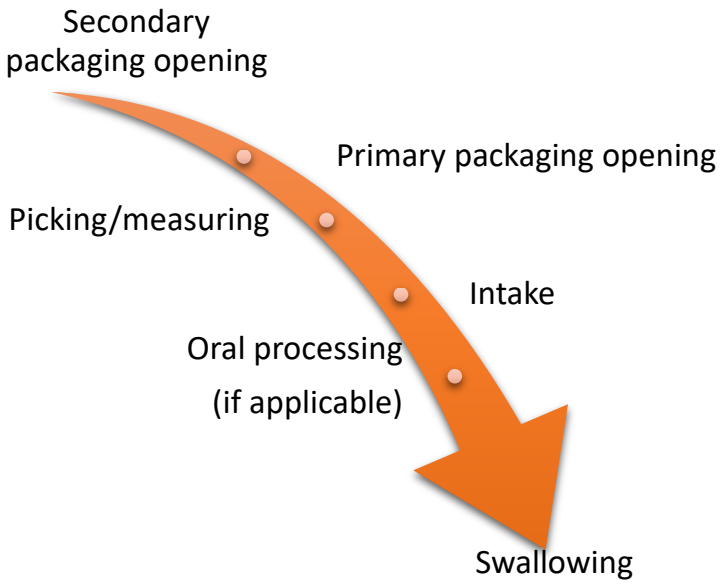


Figure 1.3: Phases of the intake process of oral dosage form.

For example, conventional tablets are removed from the packaging, picked up, brought to the mouth, and directly swallowed with the aid of water, without any oral processing being required. As a consequence attributes such as taste and smell are unlikely to significantly affect the end user acceptability. On the other hand, the size, shape, colour, and swallowability may play a prominent role. Gels and jellies are, on the contrary, very different from tablets. The oral processing required is much more

significant, and attributes such as taste, smell, size, and gumminess may have a more prominent role in determining the end user acceptability. In this respect, a categorisation based on the dosage form platform adopted might serve as guideline to help with the identification of the key acceptability attributes.

1.5.1.1 Identification of dosage form attributes influencing patient acceptability prior to oral intake

Type of packaging, measuring system, and size, shape, colour, thickness, and adhesiveness of dosage forms can greatly affect the patient acceptability during the handling process, particularly for specific patient populations. Usability has been defined as “the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use”, and it has been often used in relation to medical devices and packaging [44–46]. However, usability can also refer to the ability of patients to use medicinal products [24]. In this sense, attributes such as colour could be important for the correct identification of the dosage form, whereas shape, size, thickness, and adhesiveness, among others, could influence the handling of the product.

1.5.1.2 Identification of palatability-related attributes for oral dosage form acceptability testing

In order to describe the attributes of the different dosage forms once placed inside the mouth, the appropriate wording might be borrowed from food science, especially in relation to palatability. Palatability comprises taste, aftertaste, and mouthfeel (e.g. grittiness, texture, cooling, heating) [23,47]. Mouthfeel with reference to medicinal products has been defined as “The sensation from the ingestion, mastication and swallowing of the medicine, all of which are influenced by the physical and chemical

properties of the medicine being administered" [48]. As it was pointed out by Batchelor and co-workers, the mouthfeel of a medicinal product is not studied with the intention to maximise the sensory pleasure, but rather to avoid mouthfeel to represent an acceptability barrier to the patient [48]. Mouthfeel is the result of a combination of other attributes. In food science the vocabulary used to describe the mouthfeel of products is very rich, with different product types having their specific word list. It might be useful to extract the appropriate vocabulary in order to facilitate the description of mouthfeel in medicinal products by focussing on the terms that describe attributes related to rheological and tribological properties. A suggested list of some commonly used attributes used in food science that could also apply to medicinal products is presented in Tab. 1.2.

Table 1.2: Description of palatability attributes.

Palatability attribute	Description	Reference literature (if available)
Adhesion		
Stickiness	Tendency of the sample to induce a sticky sensation on the palate or between the teeth	[49]
Sliminess	Tendency of a viscous liquid to stay in the mouth	[49]
Slipperiness	Tendency of the sample to slip away in the mouth (no grip)	[49]
Filminess	Tendency of the sample to stay behind as a layer in the mouth	[49]
Adhesiveness to palate	Force required to remove product completely from palate, using tongue, after compression of the sample between tongue and palate	[50]
Breakdown		
Initial bite cohesiveness	Amount of deformation undergone by the material before rupture when biting completely through sample by molars	[50]
Fracturability	Force with which the sample ruptures when placed between molars and bitten completely down at a fast rate	[50]
Hardness	Force required to bite completely through sample placed between two molars	[50]

Denseness	Compactness of the cross-section of the sample after biting completely through with molars	[50]
Viscoelasticity		
Firmness	Force required to compress the sample between the tongue and the palate	[51]
Springiness	Force with which the sample returns to its original size/shape after partial compression (without failure) between the tongue and the palate	[50]
Thickness	Thickness of the food in the mouth after the food is compressed via up and down motions of tongue against palate	[52]
Melting	Thinning of the product in the mouth and spreading throughout the mouth	[52]
Degranulation		
Smoothness	Degree in which the food contains granules detected by moving the tongue parallel to palate	[52]
Powderiness	Tendency of the sample to form small particles (e.g. flour)	[49]
Grittiness	A rough feeling in the mouth	[53]
Flow		
Prickliness	A tingling feeling sensed by the tongue, typically associated with slightly carbonated soft drinks	[52]
Thickness	Thickness of the liquid in the mouth after the food is compressed via up and down motions of tongue against palate	[52]

As the dosage form is placed inside the mouth the size and shape could potentially lead to difficulties in the subsequent oral processing. The size of oral dosage forms must be appropriate for the age and physical development of the patient. Also, the presence of sharp edges might cause injuries to the oral mucosa.

1.5.1.2.1 Palatability attributes related to solid dosage form composition

Taste has been defined the most predominant mouthfeel attribute influencing patient compliance and acceptability [54]. Sweetness, sourness and bitterness are at the basis of all the neurochemical information reaching the human sensory system. After integration with the olfactory information coming from the nose, it drives the proneness or recalcitrance of the subject to consume or not the edible product. In pharmaceutical formulations, taste and smell are determined by the type of API and excipients [54]. In the majority of the cases neutral-tasting pharmaceutical excipients are preferred because they do not contribute to the overall taste or smell of the formulation, leaving the taste of the API to be often the only contributor. In case the API exhibits unpleasant taste, the addition of sweetening or flavouring agents, or the implementation of taste-masking technologies is explored [54]. With the purpose of developing *in vitro* methods for the prediction of the palatability of medicinal products, considerable efforts are being made. However due to several reasons, among which the complexity of the human oral sensory system, and the involvement of genetic, and sociodemographic aspects in determining the variability of taste perception and palatability evaluation, and the variety of dosage forms [55], the design and development of an *in vitro* method for the prediction of medicines palatability would require a dedicated project that would deviate from the aims of the present work. Proof-of-concept of the possibility to develop a series of *in vitro* decision-supporting tools to help driving patient-centric medicinal product design can be obtained by analysing other mouthfeel and acceptability attributes. Integration with *in vitro* palatability predictive methods can occur at a later stage, when such methods will be validated for the dosage form platform of interest.

1.5.1.2.2 Palatability attributes related to solid dosage form adhesion

The term “sticky” in relation to food products has been used predominantly for thick and viscous, and less frequently for thin and liquid products [49]. Excessive stickiness could lead to a negative hedonic evaluation of foods, however it is not considered a predominant mouthfeel attribute [49]. In the case of pharmaceutical dosage forms, high stickiness could cover a more predominant role in determining patient acceptability. Some polymers used for tablet coating, capsule shells, orodispersibles, and jellies may have adhesive properties, and could affect the residence time and swallowing process in case the dosage form adheres too strongly to the palate and oesophagus. For this reason mouthfeel attributes associated with adhesion such as sticky, slimy, slippery, powdery, and filmy are worthy to be explored in the context of medicine administration.

1.5.1.2.3 Palatability attributes related to solid dosage form breakdown

In case of chewable tablets or any other dosage form that requires mastication, the breakdown behaviour can trigger specific mouthfeel sensations, towards which attributes such as cohesiveness, fracturability, hardness and denseness play the most prominent role. For example, a chewable tablet must possess sufficient cohesiveness to maintain its compactness, but should not exceed in hardness and denseness so that the patient can process it.

1.5.1.2.4 Palatability attributes related to solid dosage form viscoelasticity and rheology

Some orodispersible dosage forms undergo a disintegration process upon contact with saliva. In this case, the patient might perceive melting of the dosage forms due to the change in their viscoelastic and rheological properties. Moreover all the dosage forms that require oral manipulation can be perceived differently based on their viscous and elastic moduli. Firmness, springiness, thickness, and melting represent some of the terminology used to describe viscoelastic moduli whilst the medicinal product is being processed in the mouth, and they can apply to both solid and semi-solid products.

1.5.1.2.5 Palatability attributes related to solid dosage form degranulation

Upon disintegration, orodispersible tablets tend to break down into small particles. Similarly, multiparticulates such as minitablets, powders and granules can confer mouthfeel associated with the shape, number and size of particles as soon as they are taken into the mouth. In this respect smoothness or powderiness/grittiness attributes could be perceived as potentially uncomfortable. Also, failing to swallow all the particles constituting the required dose might lead to unintentional under-dosing, therefore assessing partial dose loss might be useful in order to assess the ability of the patient to take the medicinal product as intended.

1.5.1.2.6 Palatability attributes related to liquid dosage forms

Effervescent tablets or granules often contain carbonates to make the resulting drink slightly fizzy. Although fizzy drinks are often considered pleasant, in some cases excessive fizziness can result uncomfortable. Attributes such as prickliness could be evaluated in order to assess the related acceptability. Syrups and other drinks might also be subjected to the influence of thickness/viscosity of the liquid.

1.5.1.3 Acceptability attributes studied in conventional and novel dosage forms

In Tab. 1.3 the main oral dosage form acceptability attributes are listed, and references to the literature works where such attributes were analysed were indicated, where available.

Table 1.3. Acceptability attributes of oral dosage forms.

Oral dosage form	Acceptability attribute	Reference literature (if available)
Conventional dosage form		
Capsule	Size	[6]
	Shape	[6]
	Taste/aftertaste (uncoated)	[6]
	Swallowability	[39]
	Colour	
Tablet	Size	[6,11]
	Shape	[6]
	Taste/aftertaste (uncoated)	[6]
	Swallowability	[39]
	Colour	[56]
Powder/granule	Swallowability	[39]
	Grittiness	[57]
	Size	[6]
	Shape	[6]
	Taste	[6]
	Colour	
Liquid	Taste/aftertaste	[6]
	Smell	[6]
	Volume	[6]
	Colour	
	Viscosity	
	Swallowability	[39]
Effervescent tablet/powder	Taste	[58]

	Smell	
	Colour	
	Prickliness	
Novel dosage form		
Soft capsule	Size	
	Shape	
	Colour	
	Hardness/softness	[6]
	Swallowability	[39]
	Resistance to rupture	
Minitablet	Taste (uncoated)	[6]
	Size	[6]
	Shape	[6]
	Colour	
	Number per dose	
	Grittiness	[53]
	Swallowability	[39]
Orodispersible tablet	Taste	[59]
	Size	
	Shape	
	Colour	
	Grittiness	
	Disintegration time	
	Swallowability	[39]
Orodispersible film	Taste	[60]
	Size	[61]
	Colour	
	Shape	
	Thickness	[61]
	Disintegration time	[62] (time measurement)
	Stickiness	
	Stiffness	
	Thickening effect	
	Grittiness	[60]
	Swallowability	[39]
Chewable tablet	Taste	
	Size	
	Colour	
	Shape	
	Hardness	[63]
	Chewiness	
Gel and jelly	Taste	
	Smell	
	Size	
	Colour	
	Shape	
	Gumminess	
	Swallowability	

Some work has been done on the assessment of the patient acceptability of conventional dosage form platforms such as tablets, liquids and capsules, however less information is currently available on novel dosage form platforms.

1.5.1.3.1 Acceptability attributes studied in conventional dosage forms

Swallowability of tablets, capsules, suspensions, powders, liquids, and syrups was assessed and reported in a systematic review [39]. Size, shape, taste, aftertaste, number of units per dose, and colour of conventional tablets and capsules have been assessed for patient acceptability in the paediatric patient population [6,11,56]. Similarly, size, shape, and taste/aftertaste of uncoated multiparticulates, and volume, taste/aftertaste and smell of liquid medicines have been studied [6]. The taste of effervescent tablets has also been studied in children [58].

1.5.1.3.2 Acceptability attributes studied in novel dosage forms

It was reported that novel dosage forms are more acceptable than conventional dosage forms [64]. However studies conducted on multiparticulates evidenced the relevant role played by grittiness on the end user acceptability in adults and children [53]. Taste and mouthfeel were considered more critical acceptability parameters than disintegration time in orodispersible tablets (ODT) [59], however it was acknowledged that all play a key role in acceptability [65]. The swallowability of minitablets, soft capsules, film-coated dispersible tablets, and orodispersible films (ODFs) were assessed and results were presented in a systematic review [39]. Preference of soft vs. chewable tablets has also been reported in children [6]. However, studies conducted on such platforms not always include an exhaustive assessment of the acceptability of all relevant attributes. One of the main reasons for the lack of acceptability information, besides the novelty of the dosage form platform, is the fragmented approach to acceptability testing, and the lack of a standardised methodology. As a result, data are poorly comparable, and often information on specific attributes is missing.

1.5.1.4 Advantages of individual attribute acceptability versus overall acceptability assessment of dosage forms

Criticisms on how the available literature has failed to analyse the complexity of patient acceptability have been raised [40]. This implies that the assessment of the acceptability of single attributes of the formulation platform might further reduce the information related to acceptability aspects other that those formulation-related. However, one of the main advantages of focussing on the acceptability assessment of single attributes of the dosage form platform is that, often, the quality of such attributes can be controlled during the manufacturing process. For example, the grittiness for the minitablet platform correlates with the size (diameter) of the individual unit [53]. Similarly, one or a combination of formulation variables can control other acceptability attributes. This represents a great advantage to manufacturers because acceptability information about a specific attribute can in many cases guide the optimisation process of the formulation being developed. However, work on the correlation between formulation variables and the acceptability of the formulation variables is required, and exploring a potential strategy for doing so is one of the objectives of the present work.

1.5.2 *In vivo* assessment of dosage form acceptability attributes

The *in vivo* assessment of the dosage form platform focussing on the evaluation of single attributes would require human panel participants to take samples differing in the quality of attributes, and rate their acceptability using scales. This method has been adopted in the past, however the goal of the study is to also analyse the correlation between attribute acceptability and formulation variables, hence the evaluation of the intensity of the feeling linked to such attributes should be carried out. In addition, since the initial selection of the acceptability attributes to analyse might leave out some

important aspects, the use of a face-to-face interview will provide more information from the panel participants.

1.5.2.1 Terminology use

Of all the aforementioned oral dosage form acceptability attributes, not all can be easily assessed by the lay person, as it must be taken into consideration that patients are non-trained assessors. Therefore, a simplified terminology should be adopted, yet it should be clear enough to avoid misunderstanding.

1.5.2.2 Assessment modality

Questionnaires/interviews should be appropriately designed for the target patient population to be investigated. For example, electronic questionnaires might be more convenient to use in adults and adolescents as they are more likely to be technology literates, whereas computerised questionnaires might result difficult to use by the older individuals [66]. On the other hand, paper-based questionnaires might be more appropriate for use in the paediatric population, or in other patient populations suffering from cognitive impairment.

1.5.2.3 Acceptability and sensory assessment scales

Acceptability assessment scales should be selected based on the target patient population. For example, children below a certain age might find hedonic scales difficult to use [67], however the ability to use the scales improved if verbal anchoring was provided [68].

Concerning the sensory evaluation methods aimed at assessing the intensity of a stimulus, various scales have been used in the past. Seven- or nine-points scales/ranking systems are often used in food science [69,70], however score point/ranking systems no wider than five points might, once again, result easier to use by non-trained panellists.

1.5.2.4 Participant burden

In every human panel study, participants should never be subjected to difficult/frustrating tasks, long assessment duration, or samples overload. Particularly in the case of patient populations that could already feel debilitated by medical conditions, additional ethical considerations must be made in order to ensure the preservation of patients' safety and wellbeing during and after the assessment session.

1.5.2.5 Independent observation

In some studies involving the acceptability assessment in small children and babies, the parent or carer is responsible for assessing the reaction of the subject to the sample [71,72], since the subject is not able or reliable enough to use scales autonomously [67]. This method could also represent an additional confirmation of the acceptability of the sample, if used in combination to the questionnaire and scales, and if carried out by an independent person.

1.5.2.6 Expected participant-reported outcomes (PROs)

The information obtained from panellists differs depending on the assessment method adopted. Hedonic scales and score point/ranking systems measure quantitative categorical variables, whereas interviews will provide additional qualitative information. In general, all the information obtained from the subject is referred to as participant-reported outcomes (PROs). All the quantitative PROs obtained from the study represent the fixed variable dataset to be used for the assessment of the *in vivo/in vitro* correlation with *in vitro* acceptability-predicting methods.

1.5.3 *In vitro* assessment of dosage form acceptability attributes

1.5.3.1 Identification of formulation variables influencing acceptability

Depending on the analysed dosage form platform, different formulation variables are expected to influence the properties of the medicinal products. For example, the surface area of multiparticulate preparations will determine the amount of API that can be loaded per unit, and therefore, the number of particles required to achieve the full dose [73]. Whereas this is considered an advantage because it confers dose flexibility, a large amount of particles could be perceived as difficult to measure, and uncomfortable to take. Similarly, the type and concentration of a superdisintegrant in an ODT will influence its disintegration [74]. Type and molecular weight of polymers can determine the viscosity of a solution, or the adhesion of a capsule [43]. Formulation variables and related attributes are not only oral dosage form-dependent, but also formulation-dependent parameters, therefore, it is difficult to categorise them. Only the formulator will be sufficiently knowledgeable of its formulation, and will be able to identify the relevant formulation variables. This type of information can be easily

sourced by literature search, or by consulting the manufacturer of the excipients employed. Alternatively, laboratory experiments can help identifying formulation variables and their influence on the final product.

1.5.3.2 Development of *in vitro* methods for the evaluation of acceptability of dosage form attributes

In the simplest case, the quantitative assessment of a formulation variable directly correlates with the qualitative assessment of the corresponding acceptability attribute. Therefore, once a quantitative *in vitro* method for the measurement of the formulation variable is available, the patient acceptability of the corresponding acceptability attribute can be predicted. For example, if the disintegration time of an ODT is identified as a key acceptability attribute, and it is directly correlating with the seconds required for the tablet to disintegrate, then a conventional *in vitro* disintegration time measurement method will also provide information on patient acceptability. Consequently, if the use of a certain concentration of superdisintegrant causes the ODT under development to disintegrate too slowly, the increase of superdisintegrant concentration will probably reduce the disintegration time, and improve patient acceptability.

Sometimes, the acceptability evaluation of an attribute could correlate with a combination of formulation variables. Conversely, more than one acceptability attribute could be determined by the same formulation variable. This is a more complicated case that requires an in-depth investigation on the relationship between variables. After doing so, the integration of two or more *in vitro* methods in one apparatus/measurement session might provide data correlating with the *in vivo* acceptability evaluation.

1.6 The orodispersible film platform

Orodispersible films are stamp-size polymer-made thin wafers that rapidly disintegrate upon contact with saliva immediately after intake. ODFs are relatively recent dosage form platforms and have appeared on the market a decade ago. Commercially available ODF products exist for a range of therapeutic areas, among which there are those for the treatment of Alzheimer's disease (Donepezil – Labtech, Kyukyu Pharmaceuticals, Hexal Pharmaceuticals), emesis (Ondansetron – Monosol, Labtech, Aavishkar), schizophrenia (Olanzapine – Labtech, Hexal Pharmaceuticals), migraine (Zolmitriptan – Monosol, Labtech, NAL Pharma) etc. In Borges et al., 2015, a comprehensive list of registered, marketed, or withdrawn ODF products is presented [75].

1.6.1 ODF manufacturing techniques

ODFs are conventionally manufactured by solvent casting, although less used methods include semisolid casting, and hot melt sheet extrusion [76,77]. The API(s) is/are dissolved or suspended in a solution or feedstock with other excipients, and formulation or processing aids, and then processed into the final product. A typical manufacturing process by solvent casting requires a continuous-coating liner on which the aqueous or non-aqueous casting solution is deposited, levelled, and dried, as thoroughly described in Hoffmann et al., 2011 [78]. The final step requires the cutting of the film matrix into single films of desired size. However, the manufacturing process is still subjected to limitations related to content uniformity, low drug loading [79], dose diversification, and the safety of organic solvents. Other techniques such as hot melt extrusion do not imply the use of solvents [80,81], however other potential disadvantages such as the limited availability of suitable polymers, and the high temperatures may impact on the stability of the API [78]. Novel technologies such as

electrospinning represent potential alternatives to the current manufacturing techniques [82], although issues with the poor mechanical properties of the final product, and the technology scale-up have not yet been resolved.

1.6.2 ODF manufacturing parameters

In general, the ODF design process should take into consideration parameters such as the therapeutic target, the target patient population, the product safety, the compatibility between API and excipients, the processability of the excipient mixture, the stability of the final product, its physicochemical and mechanical properties, the drug release profile, and packaging suitability, in addition to patient acceptability. The cost of ODF manufacturing may also be consistent, and it largely depends on the availability and readiness for industrialisation of the manufacturing technologies; on the type of equipment, its cleaning and maintenance costs, and the possibility of scaling up/down; on the critical process parameters, and the process integration, control, and monitoring system; on the possibility of conducting batch or continuous manufacturing; on the throughput capacity, and on the type of packaging. ODF manufacturing is an expensive process, and it often requires considerable investments. Failing to assess any of the manufacturing parameters described above, including the end user acceptability of the final product, could potentially result in insufficient investment returns.

1.6.3 General formulation principles of ODFs

The main constituents of ODFs are polymers. Film-forming polymers are of natural, semi-synthetic, or synthetic origin, and can be used alone or, more commonly, in combination [76,79]. Constituents of the film matrix are polysaccharides, cellulose derivatives, proteins, acrylates, and other polymers [75], that can be available in different grades and molecular weights, thus offering the flexibility necessary to achieve the desired drug loading, mechanical properties, and disintegration time. Film-forming polymers are normally dissolved in the appropriate solvent or mix of solvents in order to be processed, however, the formulation often requires the addition of a plasticiser to achieve satisfactory mechanical properties [83]. Plasticisers are short molecules that insert among the longer polymeric chains, reducing the mechanical cohesion, and thus improving the flexibility of the film [84]. In addition to the plasticiser, other excipients may be required to improve the drug solubility, and the disintegration, the appearance, or the taste of the ODF product. Such excipients include superdisintegrants, colouring, sweetening and flavouring agents, surfactants, saliva stimulating agents, fillers, and, of course, the API(s) [79]. The resulting formulation should meet the requirements for processability, *in vitro* characterisation, and *in vivo* pharmaceutical performance.

1.6.4 Orodispersible films as patient-centric dosage forms

ODFs are generally considered patient-centric dosage forms. Their thin and soft nature, rapid melting, and no requirement of water aid for intake was considered advantageous for those patients being uncooperative, or experiencing difficulties of swallowing [76,77,85]. The delivery of actives through the oral mucosa by ODF administration could provide a fast onset of action [86], that can prove particularly useful in case of emergency circumstances [87] such as anaphylactic shocks,

congestive heart failures, sudden epileptic seizures, breakthrough pain [88]. Various technologies such as inkjet/2D printing, and multilayering were implemented in order to improve dosing precision, to improve the flexibility of the dosage form, and to allow developing fixed-dose combinations [79,89–93]. Moreover, taste-masking technologies can be applied, potentially improving acceptability. Patient acceptability of ODFs has been confirmed in several *in vivo* studies, and in different patient groups. Attributes such as swallowability, palatability, presence of residues in the mouth after intake, grittiness, taste masking, mouth freshening, size, thickness, solubility, disintegration time, ease of administration were assessed [60,61,71,94–97]. In a review paper, Krampe and colleagues considered ODF mouthfeel and texture as key characteristics potentially affecting patient acceptability, and the "gummy" nature of the film product after wetting as potentially contributing to the ODF mouthfeel [77]. However, there is no evidence that the ODF attributes assessed *in vivo* are actually the main contributors to the end-user acceptability, according to patients.

1.6.5 Identification of ODF acceptability attributes

A convenient way to investigate the ODF acceptability attributes might be to consider the phases of ODF intake, as previously suggested (Tab. 1.4).

Table 1.4: ODF acceptability attributes potentially affecting patient acceptability.

ODF acceptability attributes			
Handling phase	**Intake phase**	**Oral processing phase**	**Post-swallowing phase**
Ease of opening (packaging)	Smell	Taste	Presence of viscous residuals
Colour	Size	Thickness	Aftertaste
Size	Shape	Sliminess	Filminess

Thickness	Stiffness	Thickening effect	Astringency/dryness
Stickiness	Adhesiveness to palate (Stickiness)	Disintegration time	

1.6.5.1 Handling phase

ODFs are often highly hygroscopic and the loaded API might be light-sensitive. For this reason, they may require specific packaging that must be moisture-resistance, opaque, compatible with the formulation composition, and, in many cases, child-resistant [87]. The combination of these factors often leads to the adoption of sealed aluminium or composite pouches that may be difficult to open or may require specific opening instructions. If the target patient population for the study product present poor manual dexterity, reduced pinch strength, lowered sight, or cognitive impairment, the *ease of opening* should be explored. Patients with lowered sight might benefit from *coloured* formulations with sufficiently wide film *area*. Similarly, patients with reduced pinch strength or poor manual dexterity might prefer products that are not too *thin*, and which *stickiness* does not interfere with the handling.

1.6.5.2 Intake phase

Immediately before intake, the ODF is at the closest distance from the patient's nose. This is where smell plays an important role in the acceptability of the medicinal product. Upon positioning in the oral cavity, ODFs should possess adequate *size* and *shape* to fit comfortably in the patient's mouth. They should be *soft* and avoid the presence of sharp edges, but *flexibility* should not hinder the correct placement. Moreover the *adhesiveness* should ensure rapid adhesion to palate but not to the lips or teeth, and should not be perceived as uncomfortable.

1.6.5.3 Oral processing phase

After ODFs are placed in the mouth, they uptake saliva and start melting. This is the phase where *taste* begins to be perceived. Also, the *thickness* of the formulation changes rapidly, and if the *disintegration time* is long, a very thick film could result uncomfortable. At this stage the consistency of the ODF also changes, rapidly turning into a viscous fluid. This is when the *sliminess*, and *thickening effect* could become unpleasant. Although the *swallowability* of ODFs has been assessed in few articles, the likelihood of experiencing difficulties to swallow thickened fluids should be low.

1.6.5.4 Post-swallowing phase

The residual thickened liquid remaining in the mouth after swallowing, could mean that part of the dose has not been taken. Therefore, verifying whether there is *residual* formulation after swallowing is advisable.
Other post-swallowing effects, such as the *aftertaste* and *filminess* could become relevant acceptability attributes at this stage. Sometimes the rapid salivary uptake by the ODF polymeric matrix may trigger a sensation of *astringency* or *dryness* in the mouth, that could result uncomfortable.

1.6.6 *In vivo* and *in vitro* assessment of ODF acceptability attributes

As the suggested method for the *in vivo* identification of key acceptability attributes of a dosage form platform has not been fully tested before, the design of a small-sample size, pilot human panel might inform on the reliability of the method, and on the appropriateness of the wording chosen. In this sense, the presence of a negative and a positive control attribute could help verifying and assess the reliability of the sample

population for the evaluation of the acceptability and sensory attributes. Among the proposed acceptability attributes listed in Tab. 1.4, the ease of opening, size, thickness, stickiness, and disintegration time are term of common use, and their meaning in respect to the description of ODF attributes might be more recognised and widely understood compared to more technical terms such as filminess or astringency. Moreover, panel participants could quantify the intensity of the sensory stimulus produced by the stickiness, and by the disintegration time. Such intensity evaluations/quantifications could be used to test their correlation with the formulation variables most likely determining them. In this respect, the disintegration time of an ODF is determined by the type and molecular weight of the film-forming polymer, and could be measured by conventional *in vitro* disintegration time measurement methods such as the petri dish method [98]. The stickiness of ODFs is normally determined by their composition, and in particular, by the type of film-forming polymer used [76]. In turn, *in vitro* methods allowing the quantitative measurement of tack might provide data in correlation with the *in vivo* evaluated intensity and acceptability.

If a toolkit of *in vitro* methods capable of predicting the acceptability of ODF attributes can be developed and verified, such in vitro methodologies could be used during the early drug development phase, and drive the formulation development towards the achievement of a highly acceptable product. The present study represents a feasibility evaluation of the application of the proposed strategy to the ODF platform development.

1.7 Identification of knowledge gaps

Poor patient acceptability has been linked to poor compliance and to risks associated with off-label use, manipulation, and modification of non-appropriate dosage forms. The assessment of patients acceptability is becoming a relevant requirement for drug development, particularly in special patient populations.

There is a lack of a harmonised approach to assess the patient acceptability of medicinal products. Several acceptability assessment methods have been proposed, each exhibiting specific advantages and disadvantages. Assessment methods aimed at evaluating the acceptability of individual oral dosage form attributes possess the advantage of informing on the strategy to drive the optimisation of the drug product by investigating the correlation between attributes' acceptability and formulation variables. In turn, the correlation with formulation variables might serve as guide for the development of *in vitro* methods for the prediction of single attributes' acceptability, thus improving the overall acceptability of the medicinal product.

The strategy for achieving such goal involves an *in vivo*, and an *in vitro* phase, each that must be designed and optimised according to the dosage form platform being analysed. The ODF is considered a patient-friendly platform, and patient acceptability has been assessed in different populations. However, an in-depth study on the acceptability of specific ODF attributes has never been conducted.

Currently such strategy needs to be defined and tested for feasibility.

1.8 Scope of the thesis

The main focus of this thesis was the design of a proof-of-concept study for the implementation of a novel strategy for the end-user acceptability assessment of ODFs. The strategy was developed in the context of a fragmented knowledge on patient medicine acceptability assessment that is currently leading to an unharmonised approach towards the design of assessment methods and data interpretation. The developed strategy is intended to simplify the patient-centric drug product design by providing formulation scientists with a decision-supporting tool at an early drug development stage, and without resorting to pre-clinical studies on human subjects. The strategy consists of an *in vivo* phase where human panel studies were conducted for the identification of key acceptability attributes of the ODF formulation platform; and of an *in vitro* phase, where novel or existing *in vitro* methods were designed or adapted for the prediction of ODF key acceptability attributes on the basis of correlating formulation variables. Some considerations on the obtained results were made with the purpose of further refining the strategy design and to envisage its potential implementation in the design of different formulation platforms and for different target patient populations.

1.9 Thesis aims

The overall aims of this thesis are:

1. To review the current knowledge on patient acceptability assessment methods (chapter 1)

2. To define, test and optimise a strategy for the *in vivo* identification of the key acceptability attributes of the ODF platform (chapters 1, 2, and 5).

3. To define, test and optimise a strategy for the identification, development and optimisation of *in vitro* methods with the potential to predict ODF attribute acceptability (chapters 1, 3 and 4).

Chapter 2. Identification of key acceptability attributes of orodispersible films

This chapter describes the identification of key acceptability attributes of the orodispersible film (ODF) platform by a pilot exploratory human panel carried out on healthy young adults. Potential film-forming polymers for ODF sample preparation were selected based on safety, solution pourability, film-forming, and mechanical properties. Four drug-free single-polymer ODF samples differing in film-forming polymer type, and molecular weight were prepared and presented to volunteers to assess. Four attributes were evaluated both when ODF samples were handled, and taken orally. Sample acceptability was evaluated on a five-point hedonic facial scale, whereas the intensity of the perceived ODF samples stickiness was determined using a four-point score system, and ODF samples disintegration time was measured by stopwatch. A second evaluation of sample acceptability was performed by the researchers using a two-point score system. Among all the attributes assessed, perceived stickiness and perceived disintegration time were found to be key acceptability characteristics of the ODF dosage form platform. The influence of polymer type and molecular weight on the end-user acceptability of perceived stickiness and disintegration time was identified by statistical methods.

Aim:

- To identify key attributes of the ODF platform potentially affecting the end-user acceptability based on a pilot human panel.

Objectives:

- To prepare single-polymer ODF formulations differing in selected formulation variables.
- To assess the suitability of the film-forming polymers by casting solution pourability and film-forming capability assessment.
- To conduct a pilot human panel for the identification of ODF key acceptability attributes.

2.1 Introduction

2.1.1 Existing literature on ODF acceptability

Orodispersible films have been described in the literature as patient-centric dosage forms [11,71,77,87], however concerns remain with regards to the end-user acceptability, especially about appearance, taste, mouthfeel, mucosal irritation and mucoadhesion [77]. Visser suggested that low ODF stickiness was associated with poor patient acceptance in the paediatric population [99], however Hoffmann identified the non-tackiness of ODFs a desirable attribute [78]. According to the European Pharmacopoeia, orodispersible formulations should disintegrate fast, preferably in less than 3 minutes [100]. The pharmacopoeial guideline not only offers the parameters for the definition of orodispersible films, but it also indirectly points to the potential role of disintegration time in ODF acceptability. The existing literature offers fragmented information, and little work has been done on structured studies for the assessment of ODF acceptability.

Moreover, the acceptability of a dosage form might change depending on the needs of specific target populations analysed [11,14,25,101,102].

2.1.2 Attributes of the ODF platform with potential to influence the end-user acceptability

2.1.2.1 Opening of packaging

Due to the limited available literature, the selection of ODF attributes that should be objective of study for their influence on the end-user acceptability cannot be done based on published information. Alternatively, such selection should be based on the consideration of the whole intake process of the dosage form. ODFs are, with some exceptions, packaged in unit dose sealed pouches that need to be opened by the end-user. In order to take the ODF, patients need to be able to open the packaging first. The packaging of medicinal products are designed to be easily opened by the end-user, however they must also prevent non-intended users such as children, to access the medication [25]. In case the end-user is affected by movement disorders, lowered sight, or cognitive problems, he/she can experience difficulties in opening the packaging, seeing or understanding the opening and administration instructions. Such issues have been reported in several published documents, and research papers [17,103,104], mostly in relation to the older patient population. In 2015, Braun-Munker and Ecker adapted the International Organisation for Standardisation (ISO) standard CEN/TS 15945 to assess the ease of opening for blisters [45,105]. The methodology involved the evaluation of three parameters: Efficiency, effectiveness, and satisfaction. Efficiency was defined as the ability of the assessor to acquaint him/herself with the packaging and its opening mechanisms, and then open it within five minutes. Effectiveness was defined as the ability of the assessor to open a second packaging, identical to the previous one, within one minute. Finally, the satisfaction was rated by the assessor using a bipolar five-step scale ranging from -2 (very poor) to +2 (very good) [45]. A similar approach could be used to assess the ease of opening for ODF pouches.

2.1.2.2 ODF intake

After opening, ODFs must be handled by the end-user in order to remove them from the packaging, and take them to the mouth, as prescribed. This process requires eye-hand coordination, processing of the visual inputs, and their translation into a coordinated movement of arms, hands and fingers [106]. In this phase, attributes such as size [71] and thickness of ODFs might play a significant role, especially for special patient populations affected by movement disorders, or lowered sight. ODFs that are too small in size or too thin/thick might make the picking process less easy. Colour [71] and opacity might also play a significant role in the identification of the ODF shape against the background of the packaging, or in determining acceptability. ODF intake instructions usually advise to ensure that the hands of the end-user are dry. Such instructions are specified in order to avoid issues related to the premature moistening of ODFs by the sweat because, in order to undergo disintegration in the mouth, the film-forming polymers, and thus the resulting film, must have hygroscopic properties. Should such moistening occur, the ODF would be likely to become sticky as a result of the initiation of the dissolution process, and interfere with the correct handling.

2.1.2.3 Oral processing

Once placed in the mouth, ODFs are wet by the saliva, and may or may not adhere to the tongue or palate. ODF adherence to the oral mucosa might also be more or less prolonged, and could last until disintegration. Size and thickness of the ODFs might be perceived as more or less comfortable also inside the mouth, and, of course, the duration of the disintegration time might also be perceived as uncomfortable, if prolonged.

The dominant attribute of the disintegrating film, although this has never been studied *in vivo*, is probably the taste [71]. Many published studies focused on the

implementation of taste-masking technologies in ODF formulations, in order to minimise the effects of the unpleasant taste of the active pharmaceutical ingredient (API) [95,107–109]. Taste acceptability depends on many factors: type of API, and addition of sweeteners or flavours to the formulation [110]. Many other ODF attributes could be influencing the end-user acceptability, particularly those in relation to mouthfeel. A specific terminology is often used to describe mouthfeel attributes of food products, and can be adapted to describe mouthfeel attributes of ODFs. However, such terminology might be too specific and poorly understood by non-trained panellists, and therefore not always suitable for the assessment of ODF attribute acceptability by patients or non-trained end-users. Each of the previously described ODF attributes could have a significant impact on the end-user acceptability, however not all of them can be safely tested in an *in vivo* study. In fact, safety concerns might be raised if the size of the tested ODFs causes choking if accidentally aspirated [111]. On the other hand, smaller ODFs might further limit the maximum amount of API that can be administered. Also, because of their adhesive properties, ODFs loaded with APIs cannot be completely spat out until dissolution by the assessors, and some, if not all the API loaded in the film, is therefore absorbed. Thus, safer protocols for the *in vivo* assessment of ODF taste must be optimised before such study can be safely conducted.

An intensity evaluation of the tested ODF attributes should ideally lead to the identification of formulation parameters that can control such attribute intensity. For example, the time to disintegration was suggested to be a function of the chain length of the film-forming polymer used [112,113]. Therefore, by selecting polymers with different molecular weights, a difference in the perceived disintegration time of the resulting ODFs should be observed. A similar example involves the role of different polymeric types [76], and molecular weight [109] in the adhesiveness, and therefore perceived stickiness, of the tested ODFs, based on their mucoadhesive behaviour. Finally, avoiding a biased evaluation by the assessors is also another important factor to consider in the design of an *in vivo* study. Understanding in advance what can bias

the mouthfeel evaluation of ODFs is not an easy task, however there is the risk that coloured vs. plain, clear vs. opaque, sweetened vs. unsweetened, and flavoured vs. unflavoured ODFs might lead assessors to be influenced in the evaluation of other attributes [114,115]. In order to limit the risk of obtaining a biased outcome, and to limit the burden on participants, only a limited number of attributes were studied, and clear, unsweetened, unflavoured, ODFs were used. Moreover, in order to easily identify the manufacturing variables influencing the acceptability attributes analysed, any excipients with the potential to affect attribute perception were excluded from the formulation, leading to the preparation of single-polymer ODFs.

2.1.3 Sensory evaluation methods

The target population studied was composed exclusively of healthy young adults. Hedonic scales have been proven to be good instruments for the acceptability assessment of the organoleptic properties of foods [69], and pharmaceutical products, especially in children [6,35], however they were mostly used for the evaluation of the overall acceptability or palatability, with no evaluation of a set of specific attributes. A score point system defined medicine acceptability scale (MAS) has been also used to assess ODF acceptability in infants and pre-school children [71] that could not reliably express preferences. The intensity of a perceived attribute has been evaluated by using a ranking system [116]. To explore other potential attributes affecting the acceptability of ODFs, a semi-structured interview would allow gathering the personal feedbacks of participants on the administered test ODFs, potentially identifying relevant ODF attributes that were perceived as desired or uncomfortable, and were not evaluated using the scales.

A combination of such scaling systems presented in a plain-worded questionnaire should lead to the optimisation of a method for the assessment of both the end-user acceptability and intensity of specific ODF attributes, and to address the questionnaire

to target populations that can clearly express their preferences, or that may be too young or encountering difficulties in so doing.

2.1.4 Identification of suitable film-forming polymers for ODF *in vivo* testing

Once the characteristics of the test ODFs have been identified, an additional selection step must be taken in order to ensure the safety of the materials used for human testing. In this regard, film-forming polymers must be available as excipient grade suitable for oral consumption, complete with all the safety data on oral toxicity in animals and humans. Participants safety is paramount in *in vivo* studies, and the used materials must be administered in amounts that are well below the acceptable daily intake (ADI), and must avoid causing undesired reactions or side effects. Moreover, given the hypothesis of the potential influence of polymeric type and molecular weight on the acceptability of perceived stickiness and disintegration time, the polymers must be available in a variety of chain lengths. Considering all the restrictions applied for the selection of suitable polymers, the chances of finding polymers capable of forming films by themselves are low. Therefore, a further screening of a range of molecular weight, polymeric concentrations, and casting volumes was necessary.

2.2 Materials and methods

2.2.1 Materials

Four drug-free single-polymer ODF samples were prepared by solvent casting. Poly(vinyl) alcohol (PVOH), and carboxymethylcellulose (CMC), each in two different grades were used. Each PVOH grades had the same degree of hydrolysis (85-89%), but differed in molecular weight, whereas CMC grades differed in molecular weight and degree of substitution (DS). Emprove® PVOH 4-88 (39 kDa), and 40-88 (197 kDa) were purchased from Merck-Millipore (Darmstadt, Germany). Blanose® CMC 12M31P (395 KDa, DS 1.2) and 7HF-PH (725 KDa, DS 0.7) were provided by Ashland (Wilmington, Delaware, U.S.). Metolose® 65SH 1500, and 90SH 4000 hydroxypropyl methylcellulose (HPMC) (Shin-Etsu Chemical Co., Ltd, Chiyoda-ku, Tokyo, Japan), and Kollidon® 30 (30 kDa), 90 (90 kDa) polyvinylpyrrolidone (PVP) (BASF, Ludwigshafen, Germany), were also assessed as film-forming polymers. Sterile water for injection was purchased from Gibco (Grand Island, New York, U.S.).

2.2.2 ODF solution preparation

Polymeric powders or granules were weighted accurately and dissolved in deionised water until a clear solution was obtained. Granules were heated under stirring to either 70 °C or 90 °C depending on the grade. Several concentrations were tested for each polymer type and grade.

2.2.3 Solution pourability assessment

Casting solution viscosity was assessed by testing its pourability performance using a 10 mL disposable syringe (Terumo, New Jersey, US) without needle, according to a modified version of the pourability test [117]. Polymeric solutions were put into the syringe and gently poured into a beaker. The pourability performance was evaluated by assigning pourability criteria corresponding to:

a) Appears as a solid, does not pour
b) Viscous liquid, pours very slowly
c) Fluid, pours readily

Solutions marked with a) were discarded, whereas solutions marked with b) or c) were further evaluated for film-forming capability.

2.2.4 ODF sample preparation by solvent casting

Selected solutions were used for ODF sample preparation by solvent casting [118]. A 15 x15 cm polyvinyl chloride sheet (PVC) (Tierrafilm - Nac Industrial, London, U.K.) was positioned on the plane of a hot plate (IKA Labotechnik, Staufen, Germany) that was previously levelled carefully. A silicone ring with an 8 cm internal diameter (Shenzhen Yimeifen Technology, Guangdong, China) was placed in contact with the PVC sheet, and a weight was added in order to eliminate any gaps between the ring and the sheet. A solution volume of 7.5 mL or 15 mL was measured using a 10 mL syringe without needle, and poured onto the acetate sheet, and inside the silicone mould, and carefully spread to the whole area of the silicone ring. The film was left to dry at 50 °C. The formed film was then peeled off the acetate sheet and stored until use. Depending on the following use, manufacturing and storage conditions changed

accordingly. For laboratory-based experiments, films were wrapped in aluminium foil, and stored in a desiccator maintained at low relative humidity with phosphorous pentoxide (Sigma-Aldrich, Gillingham, U.K.), at room temperature for at least one week. Then, films were equilibrated at room humidity for two hours before testing. For human panel test samples, solutions and films were prepared in a class II clean room, using purposely dedicated sterile or food-compatible materials, and with operators wearing appropriate food manufacturing clothing. Dry films were vacuum sealed and stored in a dedicated container at room temperature until two hours before the assessment.

2.2.5 Film-forming capability assessment

The film-forming capability of polymers was assessed by visual inspection, and evaluated based on several criteria. Factors such as brittleness, adhesion to the substrate, homogeneity, existence of lumps, and ease of peeling were also assessed. A positive or negative evaluation (+ or -) was given for each characteristic inspected, and only the films receiving positive evaluation in all criteria were selected for the following studies.

2.2.6 ODF thickness measurement

The thickness of the ODF samples was measured in five different locations, as shown in Fig. 2.1, using a thickness gauge (Mercer Ltd, Manchester, U.K.). The method was adapted from Liew and colleagues [60].

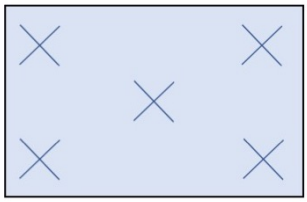


Figure 2.1: ODF thickness measurement areas.

2.2.7 Pilot human panel on healthy young adults

2.2.7.1 ODF acceptability study

A pilot single centre, single blind, crossover human panel study was designed in three sessions, each taking place in a different day, in order to gain insight into the reliability of the method. Volunteers who accepted to participate in the study were asked to attend all the three sessions.

The study was approved by the University College London (UCL) Research Ethics Committee (REC ID 8249/001) on 10th October 2016. All the relevant information on study design, safety data of all the excipient used for the preparation of the samples, manufacturing process and storage, target participant cohort, recruitment process, and assessment conditions was provided in the REC application (Appendix 1).

Authorisation for personal data collection, handling, and storage was granted by the UCL Data Protection Office (Data Registration Number: Z6364106/2016/08/68), and conducted in compliance with the Data Protection Act 1998. Participants were informed on how their data were handled, and on how the results of their assessment were analysed, presented, and distributed. A Participant Information Sheet (PIS) containing all the details of the study, including eligibility criteria, composition and safety information of the ODF samples, and assessment tasks, was provided to each participant (Appendix 1), and any question or concern was addressed promptly. Before

the study, the details of the assessment were explained verbally, and a consent form was signed by each participant.

2.2.7.2 Study participants and inclusion/exclusion criteria

The sample size was selected based on the work published by Thyssen and colleagues [119]. The panel described in Thyssen's work involved a sensory attribute assessment of a pharmaceutical dosage form on a five-point step scale [119]. Male or female volunteers able to speak and understand English were included in the present study. Volunteers who had received dental care in the 15 days preceding the study, anaesthetics into the mouth in the 24 hours preceding the study, or volunteers taking medicines altering salivation, with any known hypersensitivity to excipients, or affected by sensory disorders of the mouth were excluded from the study.

2.2.7.3 Study design

The design of the study is summarised in Figure 2.2. In each session, participants received four single-polymer, coded ODF samples, (composition and coding shown in Tab. 2.6) presented in a randomised sequence [36].

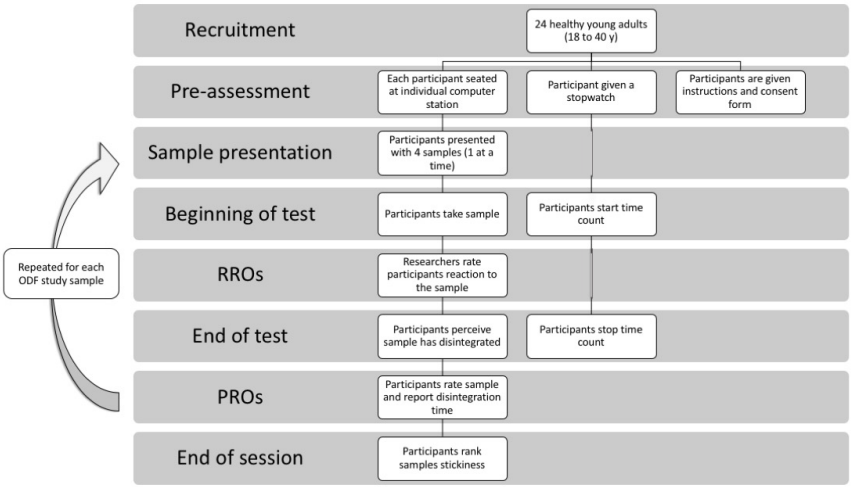


Figure 2.2: Flow chart of pilot human panel study (Figure from Scarpa et al., 2018) [120].

Participants were instructed to take the sample, place it on top of their tongue, and immediately start the stopwatch that they were provided with before the start of the study. They were asked to stop the stopwatch as soon as they perceived that the sample film had completely dissolved.

2.2.7.4 Data collection

During sample assessment, a researcher took note of the participants' intake performance and their reaction to the sample on a two-point medicine acceptability scale (MAS) [121], following the criteria listed in Tab. 2.1. The researcher's feedback was regarded as Researcher-Reported Outcomes (RROs).

Table 2.1: Researcher-Reported Outcomes (RROs) of sample intake performance, and participants reaction to sample on MAS scale.

Points	Facial expression outcome	Jaw movement outcome	Sample intake outcome
0	Signs of distress (grimacing, squinting eyes, etc…)	More than 3, or repeated chews, or observed tongue movements	Sample spit out completely

1	No facial expression	1 to 3 chews until swallow	Sample spit out with partial loss
2	Positive face or other signs of approval	No jaw movements until swallow	Sample swallowed without loss

After the film sample had completely dissolved in the mouth, participants were asked to answer a questionnaire, and to rate their comfort/discomfort with respect to attributes such as perceived size, perceived thickness, and perceived stickiness on sample handling, and perceived size, thickness, stickiness, and disintegration time on sample intake using a five-point hedonic facial scale [6,69] (Tab. 2.2).

Table 2.2: Five-point hedonic scale, and corresponding word anchors used for PRO evaluation.

Facial scale					
Corresponding word scale	Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable

Participants were also asked to answer a multiple choice question on whether the sample disintegration time was less than one minute, between one and three minutes, or more than three minutes. After the assessment of all four samples, participants were asked to rank the ODFs from the least to the most sticky. Participants' comfort/discomfort, perceived stickiness intensity ranking, and perceived disintegration time assessment were considered Participant-Reported Outcomes (PROs).

A semi-structured interview was conducted after the assessment of each sample. Questions are listed in Tab. 2.3.

Table 2.3: Semi-structured interview conducted after each sample's assessment.

	Semi-structured interview
Q1	Is there anything you would like to change in this sample?
Q2	If so, what would it be?

2.2.7.5 Data analysis

RRO were assigned on three items, each one that could receive a score from 0 (least acceptable) to 2 (most acceptable). The median scores, and interquartile range (IQR) assigned to each of the three items by all the twenty-four participants were calculated for each sample, and in each session. For each participant, the scores assigned to each of the three items were then summed together, and the total median MAS score, and IQR of all participants was calculated for each sample and in each session [71]. Sample comfort/discomfort PROs were converted into numerical values (1 = extremely uncomfortable; 2 = somewhat uncomfortable; 3 = neither comfortable nor uncomfortable; 4 = somewhat comfortable; 5 = extremely comfortable) [70], and treated as ordinal variables. The median PRO values, and IQR assigned by the twenty-four participants were calculated for each analysed attribute, and for each session. Samples with a median PRO value above 3 were considered acceptable [35]. Results of the multiple choice question on samples disintegration time were analysed by frequency for each session. The stickiness ranking exercise was also interpreted by assigning numerical values (1 = least sticky, 4 = most sticky), and by analysing them as ordinal variables [116].

Results of the semi-structured interview were analysed by counting the number of participants giving the same answer.

If samples received significantly different median acceptability scores (PROs and RROs) for a specific ODF attribute, such attribute was considered key for its potential influence on the end-user acceptability.

To evaluate the overall end-user acceptability of the test samples, the willingness of the participants to take the sample was interpreted based on all the median PROs obtained for all attributes, and the median RROs assigned on facial expression, and the ability to take the sample was interpreted based on the median total scores of the jaw movements, and intake performance RROs.

2.2.7.6 Statistical analysis

Differences among sample scores were analysed using the Friedman's test for the analysis of variance followed by Dunn's post hoc test for multiple comparisons (Prism 7, GraphPad Software Inc., La Jolla, CA, U.S.) [122]. Sample-related effects were analysed using Spearman's rank correlation coefficient (dumb variables were assigned for polymer types and molecular weights).

2.3 Results and discussion

2.3.1 Selection of film-forming polymers

2.3.1.1 Selection criteria for polymers

Polymers most frequently used for oral film preparation were identified by literature search [76,78,87,98,111,123–125]. Only the polymers meeting the following criteria were selected to enable the human panel study, and tested for solution pourability and film-forming capability:

- Availability of a range of specified molecular weights
- Availability of full toxicity data for short-term, and long-term animal and human studies, and specification of non-observed adverse effect levels (NOAEL), and acceptable daily intake (ADI) values
- Availability of excipient-grade raw materials

PVOH, CMC, HPMC, and PVP met the above criteria, and were assessed for solution pourability.

2.3.1.2 Solution pourability assessment

All polymer solutions were prepared using a range of different concentrations that were either found in the literature, or recommended by the manufacturer. Solution concentrations and pourability results are summarised in Tab. 2.4.

Table 2.4: Pourability test of polymeric solutions. Solutions were evaluated either a) appears as a solid, does not pour; b) viscous liquid, pours very slowly; or c) fluid, pours readily.

Polymer	Molecular weight/grade	Concentration (w/v)	Pourability
PVOH	39 KDa	1%	c
		2.5%	c
		5%	c
		7%	c
	197 kDa	1%	c
		2.5%	c
		5%	b
		7%	b
CMC	395 kDa	0.5%	c
		1%	c
		2%	b
	725 kDa	0.5%	c
		1%	b
		2%	a
HPMC	65SH	2%	c
		4%	c
	90SH	2%	c
		4%	b
PVP	30 kDa	2%	c
		5%	c
	90 kDa	2%	c
		5%	b

For the purpose of solvent casting ODF manufacturing in a non-industrial setup, only solutions appearing as solids, and therefore identified as non-pourable from the syringe, were excluded from film-forming capability testing.

2.3.1.3 Film-forming capability

The results of film-forming capability assessment are summarised in Tab. 2.5. Of all the polymers and grades tested, only PVOH, and CMC could form films with acceptable flexibility, homogeneity, and ease of peeling, and adhesion to substrate, however only at the concentration of 1% w/v. Lower and higher concentrations resulted in films that were poorly elastic and brittle. HPMC 65SH, at a concentration of 4% w/v formed a homogeneous, flexible film as opposed to other HPMC grades and concentrations, where the formation of lumps was often observed. However, the drying time of 4% HPMC 65S was much longer than that of other polymers, and less suitable for experimental testing. Moreover, only one HPMC grade was found to possess film-forming capability, therefore, the comparison with different molecular weights/grades was not possible. PVP 90 kDa 5% produced a film that was difficult to peel off due to the high adhesion of the polymer to the PVC sheet. Other PVP molecular weights and concentrations resulted in brittle films.

Table 2.5: Film-forming capability of selected polymers and molecular weight/grades. Films were assigned + where the characteristic assessed was acceptable, and - where not acceptable (b = brittle; a = strong adhesion to the substrate).

Polymer	Molecular weight/grade*	Concentration (w/v)	Flexibility	Homogeneity	Ease of peeling
PVOH	39 KDa	1%	-	+	- (b)
		2.5%	-	+	- (b)
		5%	+	+	+
		7%	+	-	+
	197 kDa	1%	-	+	+
		2.5%	+	+	+
		5%	+	+	+
		7%	-	-	+
CMC	395 kDa	0.5%	-	-	-
		1%	+	+	+
		2%	-	+	-
	725 kDa	0.5%	-	+	-
		1%	+	+	+
HPMC	65SH	2%	+	-	- (b)
		4%	+	+	+
	90SH	2%	+	-	- (b)
		4%	-	-	- (b)
PVP	30 kDa	2%	-	-	- (b)
		5%	-	-	- (b)
	90 kDa	2%	-	+	- (b)
		5%	+	+	- (a)

* HPMC molecular weight was not specified by the manufacturer, however, each grade is associated with a specific solution viscosity. In turn, solution viscosity depends on polymeric molecular weight, which is controlled during manufacturing.

2.3.2 Thickness

The thickness of single-polymer ODF samples is reported in Table 2.6. PVOH, HPMC, and PVP-based films had average thickness values ranging between 69 and 77 μm, whereas CMC-based samples had a thickness comprised between 35 and 44 μm.

Table 2.6: Thickness values of the polymeric films prepared with polymers selected for film-forming capability (n = 3). Results are expressed as mean and standard deviation.

	Molecular weight/grade*	Concentration (w/v)	Thickness (μm)
PVOH	39 KDa	5%	75.95 ± 4.62
	197 kDa	5%	76.55 ± 6.82
CMC	395 kDa	1%	34.26 ± 9.42
	725 kDa	1%	30.05 ±10.02
HPMC	65SH	4%	69.41 ± 6.98
PVP	90 KDa	5%	75.83 ± 3.47

2.3.3 Exploratory pilot study on the mouthfeel evaluation of ODF

2.3.3.1 ODF sample composition for human panel

Based on the film capability assessment of the single-polymer ODFs, PVOH, and CMC-based films were selected for *in vivo* evaluation. The composition and coding of the four samples is summarised in Tab. 2.7.

Table 2.7: Coding and composition of ODF samples selected for in vivo studies.

	P1	P2	C1	C2
PVOH	(39 kDa) 5%	(197 kDa) 5%	-	-
CMC	-	-	(395 kDa) 1%	(725 kDa) 1%
Solvent	water	water	water	water

Casting volume (mL)	7.5	7.5	15	15
Thickness (μm)	74.4 ± 2.3	76.8 ± 6.4	24.2 ± 2.7	25.1 ± 4.3

2.3.3.2 Demographics

Twenty-four healthy young adults aged between 18 and 35 years took part to the study. Participants were divided in two groups, each taking the assessment in different days. Each participant assessed the same set of samples in a different order in three assessment days. Demographic data are summarised in Tab 2.8. Participants' mean age of was 25.5, the 37.5% of participants were male, and 62.5% were female.

Table 2.8: Demographic characteristics of study participants.

Group	N	Age (Mean ± SD)	Gender %
Group 1	9	28.78 ± 4.66	M = 44.5% F = 55.5%
Group 2	15	23.53 ± 4.56	M = 33.4% F = 66.6%
Total	24	25.5 ± 5.19	M = 37.5% F = 62.5%

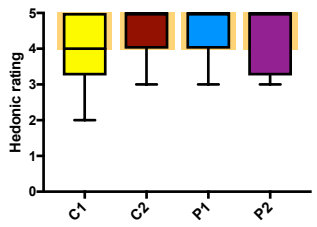
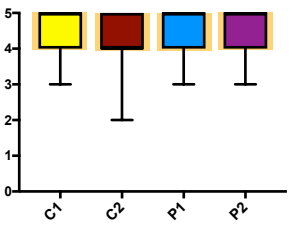
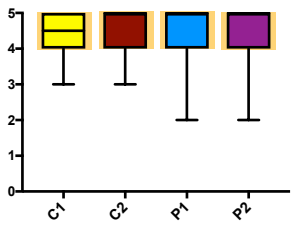
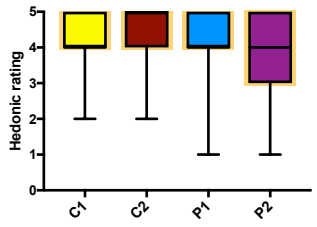
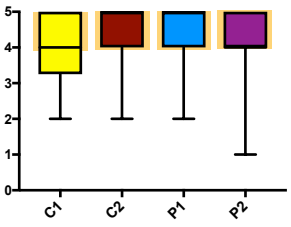
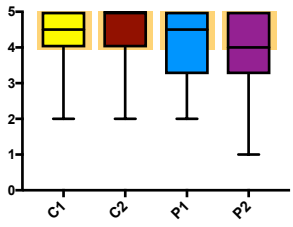
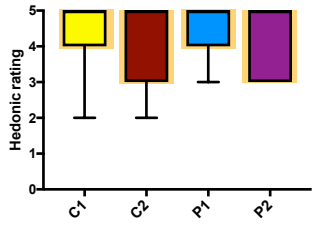
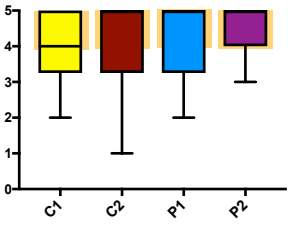
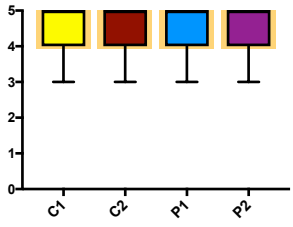
2.3.3.3 Participant Reported Outcomes

During and after the study, participants did not report any adverse reaction related to samples intake or discomfort. The PRO and RRO median values and IQR relative to the four analysed samples and collected during the three sessions are summarised in Tab. 2.8, and Fig. 2.3. Statistically significant differences between samples and among sessions are tabulated in Tab. 2.9.

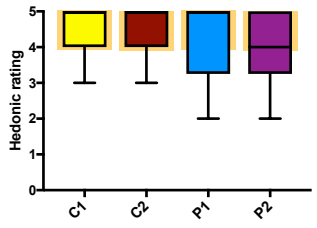
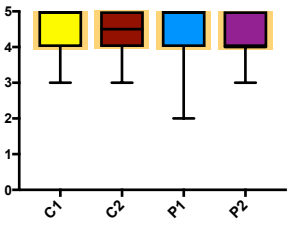
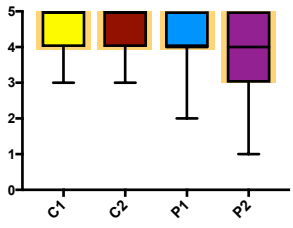
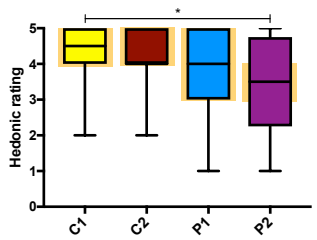
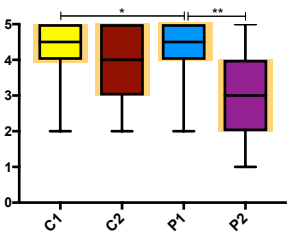
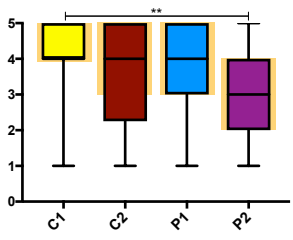
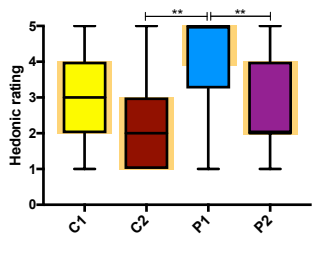
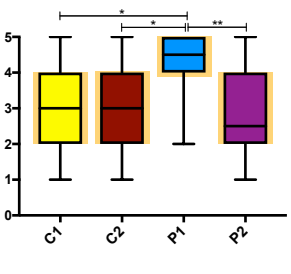
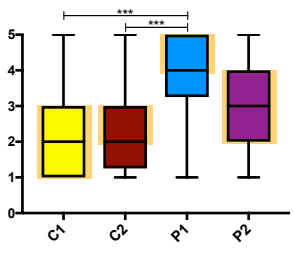
Table 2.9: PRO and RRO median and IQR values for each sample presented by attribute.

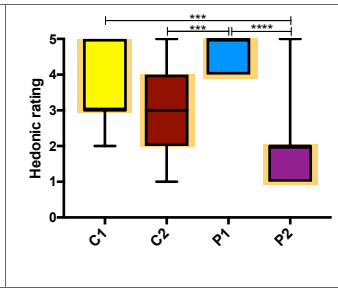
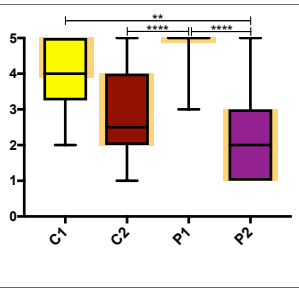
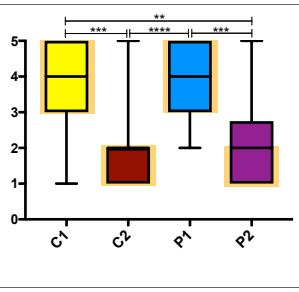
PROs												
	P1			P2			C1			C2		
	S1	**S2**	**S3**	**S1**	**S2**	**S3**	**S1**	**S2**	**S3**	**S1**	**S2**	**S3**
	Attributes perceived on handling											
Size	5 (1)	5 (1)	5 (1)	5 (1.75)	5 (1)	5 (1)	4 (1.75)	5 (1)	4.5 (1)	5 (1)	4 (1)	5 (1)
Thickness	4 (1)	5 (1)	4.5 (1.75)	4 (2)	4 (1)	4 (1.75)	4 (1)	4 (1.75)	4.5 (1)	5 (1)	5 (1)	5 (1)
Stickiness	5 (1)	5 (1.75)	5 (1)	5 (2)	5 (1)	5 (1)	5 (1)	4 (1.75)	5 (1)	5 (2)	5 (1.75)	5 (1)
	Attributes perceived on intake											
Size	5 (1.75)	5 (1)	4 (1)	4 (1.75)	4 (1)	4 (2)	5 (1)	5 (1)	5 (1)	5 (1)	4.5 (1)	5 (1)
Thickness	4 (2)	4.5 (1)	4 (2)	3.5 (2.5)	3 (2)	3 (2)	4.5 (1)	4.5 (1)	4 (1)	4 (1)	4 (1)	4 (2)
Stickiness	5 (1.75)	4.5 (1)	4 (1.75)	2 (2)	2.5 (2)	3 (2)	3 (2)	3 (2)	2 (2)	2 (2)	3 (2)	2 (1.75)
Disintegration time	5 (1)	5 (0)	4 (2)	2 (1)	2 (2)	2 (1.75)	3 (2)	4 (1.75)	4 (2)	3 (2)	2.5 (2)	2 (1)
	Attribute intensity											
Stickiness	1 (1)	1 (1)	1 (1.75)	3 (2)	3 (1.75)	2.5 (2)	3 (2)	2.5 (1)	3 (1)	3 (2)	3 (1)	3 (2)
RROs												
	P1			P2			C1			C2		
	S1	**S2**	**S3**	**S1**	**S2**	**S3**	**S1**	**S2**	**S3**	**S1**	**S2**	**S3**
Facial expression	1 (1)	1 (1)	1 (1)	1 (1)	1 (0.25)	1 (1)	1 (0)	1 (0)	1 (0.25)	1 (1)	1 (0)	1 (1)
Jaw movements	1 (1.25)	1.5 (2)	1 (1)	0 (0)	0 (0)	0 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (2)	0 (0)
Sample intake	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
RRO total	4 (1)	4 (1)	4 (1)	3 (1)	3 (0.75)	3 (2)	4 (2)	4 (1)	3.5 (1)	3.5 (1)	4 (2)	3 (1.75)

Attributes perceived on handling PROs

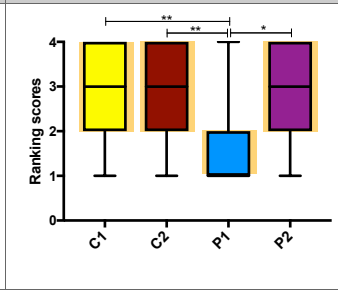
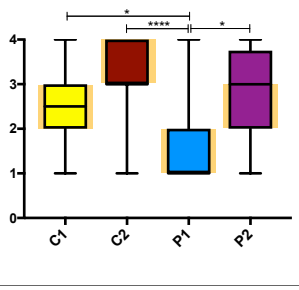
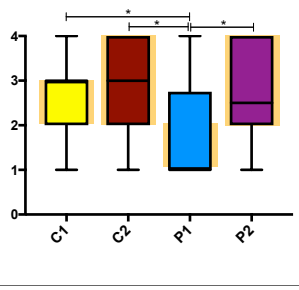
	Session 1	Session 2	Session 3
Size			
Thickness			
Stickiness			

Attributes perceived on intake PROs

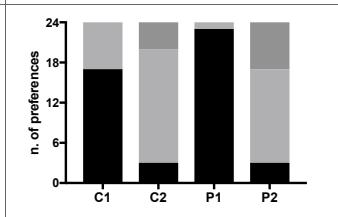
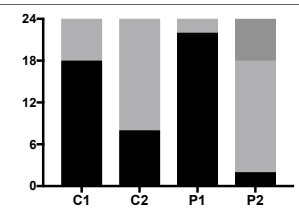
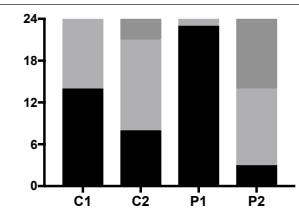
	Session 1	Session 2	Session 3
Size			
Thickness			
Stickiness			

Disintegra-tion time			

Perceived stickiness intensity PROs

	Session 1	Session 2	Session 3
Stickiness			

Perceived disintegration time (stopwatch) PROs

	Session 1	Session 2	Session 3
Disintegration time			

RROs

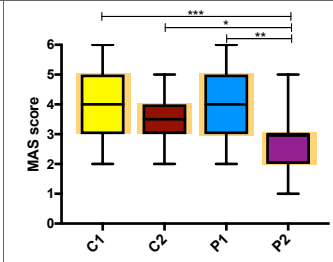
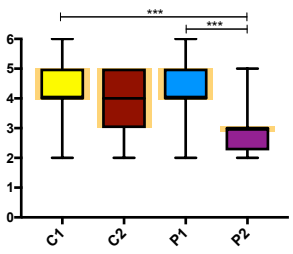
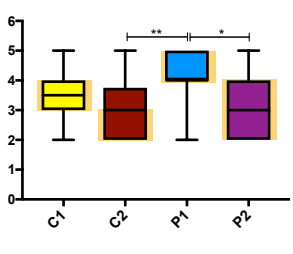
	Session 1	Session 2	Session 3
MAS			

Figure 2.3: Box and whiskers plot of PROs and RROs presented by ODF sample and session. The line in the middle indicates the median, yellow rectangles represent 95% confidence interval, lower and upper

margins of the boxes represent the 25th and 75th percentile, and bars indicate the maximum and minimum values. Statistical differences between samples are indicated by the horizontal bars, and p-values are represented by the asterisks.

Table 2.10: Statistical differences between samples and among sessions of PROs and RROs.

PROs									
	Session 1			Session 2			Session 3		
	Perceived ODF size								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	-	-	-	-	-	-	-	-	-
P2		-	-		-	-	-	-	-
C1			-			-	-	-	-
	Perceived ODF thickness								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	-	-	-	p<0.05	-	-	p<0.01	-	-
P2		p<0.05	-		p<0.05	-		-	-
C1			-			-			-
	Perceived ODF stickiness								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	p<0.01	-	p<0.01	p<0.01	p<0.05	p<0.05	-	p<0.001	p<0.001
P2		-	-		-	-		-	-
C1			-			-			-
	Perceived ODF disintegration time								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	p<0.0001	-	p<0.01	p<0.0001	-	p<0.0001	p<0.001	-	p<0.001
P2		p<0.01	-		p<0.01	-		p<0.001	-
C1			-			-			p<0.001
	Perceived ODF stickiness intensity								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	p<0.05	p<0.01	p<0.01	p<0.05	p<0.05	p<0.0001	p<0.05	p<0.05	p<0.05
P2		-	-		-	-		-	-
C1			-			-			-
	RROs								
	P2	**C1**	**C2**	**P2**	**C1**	**C2**	**P2**	**C1**	**C2**
P1	p<0.01	-	-	p<0.001	-	-	p<0.05	p<0.01	-
P2		p<0.001	p<0.05		p<0.001	-		-	-
C1			-			-			-

2.3.3.3.1 Attributes perceived on handling

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 between ODF samples (Tab. 2.9, Fig. 2.3).

2.3.3.3.2 Negative control attribute: perceived ODF size on intake

The size perceived on intake (Tab. 2.9, Fig. 2.3) was evaluated between somewhat comfortable, and extremely comfortable by participants, with no significant differences among samples (Tab. 2.10). The size of all the test ODF samples was 6 cm^2, and was kept constant in all samples. This attribute was therefore treated as a negative control to evaluate the reliability of the test method, and to confirm that the magnitude of the stimulus perceived by participants was fairly constant for identical administered stimuli.

2.3.3.3.3 Positive control attribute: perceived ODF thickness on intake

The ODF sample thickness perceived on intake was evaluated between somewhat comfortable to extremely comfortable in all samples except for sample P2, which was evaluated between neither comfortable nor uncomfortable and somewhat comfortable (Tab 2.9, Fig. 2.3). Significant differences were found between samples C1 and P2, only in the first and second session (Tab. 2.10).

There was a difference in actual thickness between the CMC-based ODF samples (approximately 20 μm), and PVOH-based ODF (approximately 70 μm) samples, with C1 being the thinnest, and P2 the thickest. Therefore, a difference in thickness perceived

between such samples was expected. However, due to the in-house ODF manufacturing method, the actual thickness of the samples for human panel was subjected to inhomogeneity, potentially explaining differences in perceived thickness such as those reported for samples P1 and P2 in session 2 and 3 (Tab. 2.10). Moreover, the differences in perceived thickness among samples were not reported in all the sessions, further confirming the potential role played by the inhomogeneity of samples thickness.

Results of the semi-structured interview also evidenced the different perception in thickness between samples made of the two polymeric species reported by participants (Tab 2.11). An average of 5.0, and 8.7 participants complained about the high thickness of samples P1 and P2 respectively, whereas 5.3, and 2.7 participants on average reported that the thickness of samples C1 and C2 needed improvement, but for the opposite reason. This observation was often associated with reports of high levels of stiffness for samples P1 and P2, but not for C1 and C2. Therefore, observed sample characteristics such as high stiffness, high thickness, and inhomogeneity might have been all reflected in the perceived thickness PRO. Overall, the perceived thickness of the four ODF samples was considered between somewhat comfortable and extremely comfortable except for sample P2, however a difference in the perceived thickness among the two polymeric species was identified in the semi-structured interview. These findings suggested that the perceived thickness was probably not the most appropriate attribute to be used as positive control under the current manufacturing method, as its comfort/discomfort did not correspond with the actual thickness of the samples. An improvement in the manufacturing conditions might reduce variability or a different acceptability attribute should be chosen as positive control for the *in vivo* method.

2.3.3.3.4 Perceived ODF stickiness on intake

With regards to the stickiness perceived in the mouth sample P1 was evaluated between somewhat comfortable and extremely comfortable. Samples C1, C2, and P2 were considered between neither comfortable nor uncomfortable, and somewhat uncomfortable (Tab. 2.9; Fig. 2.3). Significant differences were found between C1 and P1, between C2 and P1, and between P1 and P2 (Tab. 2.10).

Only the difference between C2 and P1 was reported by participants in all the three sessions, and was therefore considered a robust outcome.

The most sticky sample in terms of intensity was C2, followed by C1, P2, and P1 (Tab. 2.9, Fig. 2.3). Significant differences were found between C1 and P1, between C2 and P1, and between P1 and P2 (Tab. 2.10).

Perceived stickiness PROs were further confirmed by the semi-structured interview, where between 12 and 19 participants pointed the need for improvement with regards to the stickiness of samples P2, C1, and C2, and between 2 and 4 participants for sample P1 (Tab. 2.11).

The resulting PROs on ODF sample perceived stickiness suggested that the higher was the perceived stickiness of the sample, the lower was its acceptability score, with the exception of sample C1, which acceptability varied among sessions. However, an average of 14 or 15 participants per session indicated that the stickiness of C1 required improvement, further pointing to the sample's low acceptability.

The stickiness perceived in the mouth is also described as mucoadhesion in the literature [126–128], and its mechanisms are mediated by various theories [128], but no conclusive research to elucidate the mucoadhesive interaction has been conducted. It appears that mucoadhesion phenomena are mostly mediated by surface and interfacial properties [126,128], and are less likely to be influenced by the inhomogeneity of polymer concentration in the ODF volume compared to other ODF attributes.

Adhesion to the oral cavity surface is a desired and essential attribute for buccal films in order to favour the permeability of the API through the oral mucosa, to the point that its adhesive properties are often evaluated *in vitro* [127–133]. ODF or oral films not necessarily exhibit adhesive properties, and the strength of the adhesion is potentially linked to the molecular weight range of the film-forming polymer used [76]. The impact of adhesion on the ODF end-user acceptability has not been thoroughly explored. In a study conducted by Visser and colleagues, the poor adhesion of ODFs to the tongue or palate was associated with poor acceptance in adults [99]. The present study showed, on the contrary, that low stickiness was associated with high acceptability in the adult population, although due to the limited number of tested samples, a conclusive correlation could not be ruled out. Nevertheless, the very different methodology, and testing ODFs samples could potentially explain the different results obtained in the two studies.

Because the perception of ODF stickiness differed among the tested samples in the present study, such attribute could potentially influence on the end-user acceptability.

2.3.3.3.5 Perceived ODF disintegration time

The disintegration time of the test ODF samples was considered between neither comfortable nor uncomfortable 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 (Tab. 2.9; Fig. 2.3). Significant differences were found between C1 and C2, C1 and P2, C2 and P1, and P1 and P2 (Tab. 2.10).

All the differences among samples were found in all the three sessions with the exception of C1 vs. C2, suggesting that also the perceived disintegration time has the potential to influence the end-user acceptability.

Sample P1 was reported to disintegrate in less than 1 minute by participants in sixty-eight tests, between 1 and 3 minutes in four tests, and more than 3 minutes in zero tests

(Fig. 2.3). C1 disintegrated in less than 1 minute in fourty-nine tests, between 1 and 3 minutes in twenty-three tests, and more than 3 minutes in zero tests. C2 disintegrated in less than 1 minute in nineteen tests, between 1 and 3 minutes in fourty-six tests, and more than 3 minutes in seven tests. P2 disintegrated in less than 1 minute in eight tests, between 1 and 3 minutes in fourty tests, and in more than 3 minutes in twenty-four tests. Around twelve participants reported the need to improve the disintegration time of samples P2 and C2, while only three participants reported so for sample C1, and none for sample P1 (Tab. 2.11). Taken together, all PROs collected on disintegration time suggested that the shorter the disintegration time, the higher its acceptability, and that low-molecular weight polymeric films were considered more acceptable than their high-molecular weight counterparts.

Disintegration time is a key attribute to the ODF platform performance. ODF disintegration time is often measured *in vitro* for quality assurance purposes, and it is mentioned in the European Pharmacopoeia as the identification criterion of orodispersible formulations [100]. Few literature works evaluated the disintegration of oral dosage forms *in vivo* [119,134–137], and almost exclusively in terms of quantitative rather than qualitative terms. The disintegration time of ODFs should ideally be shorter than 3 minutes [100]. Links between the oral processing time of foods and the intensity/dominance of other attributes such as flavour, stickiness, grittiness, and its dependence on the physicochemical properties of the food was reviewed extensively by Foster and colleagues [138]. The disintegration/dissolution time of solid dosage forms was indicated as critical acceptability attribute in the paediatric population [6], however little is known about the direct relationship between processing time and palatability of medicines in the oral cavity.

2.3.3.4 Semi-structured interview

Additional ODF attributes emerged from the participants' feedback obtained by semi-structured interview (Tab. 2.11). ODF taste is notoriously known to affect the end-user acceptability, especially in the paediatric patient population [6,78]. Ideal ODF film-forming polymers are supposed to have a neutral taste that does not contribute to the overall mouthfeel. Surprisingly, the taste of the CMC-based ODF samples was reported to require improvement, although no API or flavours were added to the formulation. Also the CMC-based ODF samples were reported to have a "drying" effect on the tongue, and to thicken the participants saliva during dissolution. Such characteristics agreed well with the reported water retention, and thickening characteristics of CMC [139]. Other characteristics of the test ODF samples that were pointed by participants were the tendency of almost all samples to form aggregates or lumps during disintegration, and their inhomogeneity. In particular, inhomogeneity was referenced to the tendency of one part of sample P2 to dissolve faster than the rest, confirming the thickness inhomogeneity issues arising due to in-house manufacturing process.

Table 2.11: Semi-structured interview results expressed as number of participants who gave the same answer.

Participants comments	**P1**			**P2**			**C1**			**C2**		
Session	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Stiffness needs improvement (sharp edges)	6	7	5	5	5	5	-	-	-	-	-	-
Disintegration time needs improvement	-	-	-	9	12	14	4	2	4	10	11	11
Taste needs improvement	2	2	-	1	1	6	6	6	4	5	3	3
Stickiness needs improvement	4	3	2	14	12	12	14	15	15	18	13	19
Thickness needs improvement	6	5	4	11	8	7	6	7	3	3	2	3

Size needs improvement	2	1	-	1	-	1	1	1	-	1	-	-
It has a thickening effect on saliva	-	-	-	-	2	3	7	4	5	9	8	3
Brittleness needs improvement	-	-	-	-	-	-	2	1	2	-	2	-
Tendency to fold/form lumps	-	4	4	5	5	8	1	2	1	8	5	11
Inhomogeneity (one part dissolved faster)	-	1	2	6	5	3	2	-	1	1	-	1
It dries the mouth	-	-	-	-	-	1	1	1	2	2	2	4
It feels rough	-	-	-	-	-	-	-	-	-	-	1	-
Shape needs improvement	-	1	-	1	1	-	-	-	-	-	-	-

2.3.3.5 Researcher Reported Outcomes and overall acceptability

RROs and MAS median values are reported in Tab. 2.9, and graphed in Fig. 2.3.

The maximum total MAS score per sample was 6. The highest total MAS scores of 4 was assigned to sample P1, followed by C1, C2, and P2. Friedman's and Dunn's multiple comparisons tests on total MAS scores showed significant differences in acceptability between C1 and P2, between C2 and P2, between P1 and P2, and between C2 and P1 (Tab. 2.10). Only the difference between P1 and P2 was significant in all the three sessions. Almost all samples received the maximum score (2) for sample intake performance, indicating that participants did not encounter any difficulty in taking the samples as instructed. With regard to the facial expression, a score of 1 was assigned to all samples with little variability, whereas the jaw movements determined the difference in MAS scores between the analysed samples. Overall, sample P1 was deemed the most acceptable, with the highest MAS score, and highest PROs scores, whereas P2 received the lowest PRO and RRO scores. Sample C2 also received low PROs with regards to perceived stickiness and disintegration time acceptability, but

higher MAS scores, whereas C1 was the most variable in terms of acceptability assessment.

2.3.3.6 Identification of polymer type, and molecular weight effects on perceived stickiness and perceived disintegration time

The Spearman r correlation coefficient was calculated in order to identify any polymer type or molecular weight effect on the perceived stickiness in the mouth, perceived disintegration time, and perceived stickiness intensity PROs. Results divided by session are reported in Tab. 2.12.

Table 2.12: Spearman correlation coefficients of polymer type and polymeric molecular weight with perceived stickiness, perceived stickiness intensity, and perceived disintegration time PROs (n = 96).

PRO	**Effect**	**Session**		
		S1	S2	S3
Perceived stickiness	Polymer type	+0.284 (p<0.01)	+0.223 (p<0.05)	+0.394 (p<0.0001)
	Molecular weight	-0.365 (p<0.001)	-0.302 (p<0.01)	-0.200 (n.s.)
Perceived stickiness intensity	Polymer type	-0.354 (p<0.001)	-0.242 (p<0.05)	-0.205 (p<0.05)
	Molecular weight	+0.354 (p<0.001)	+0.326 (p=0.001)	+0.242 (p<0.05)
Perceived disintegration time	Polymer type	-0.071 (n.s.)	+0.086 (n.s.)	+0.047 (n.s.)
	Molecular weight	**-0.635 (p<0.0001)**	**-0.623 (p<0.0001)**	**-0.607 (p<0.0001)**

The type of polymer used to prepare the test ODF samples showed a weak positive monotonic correlation with the reported perceived stickiness acceptability, and stickiness intensity PROs, and no monotonic correlation with the perceived disintegration time PROs, with very low probability that the correlation exists. The polymeric molecular

weight showed a weak negative and positive monotonic correlation with perceived stickiness acceptability, and stickiness intensity respectively, and a strong negative monotonic correlation with the perceived molecular weight PROs. The correlation between polymer dissolution and molecular weight has been reported in the literature [140]. Phenomena such as polymeric chain disentanglement, availability of substitution groups to hydrogen bonding, and swelling properties of the polymers might have determined such correlation [141,142]. The weaker correlation between molecular weight and perceived stickiness acceptability, and intensity suggested the influence of other manufacturing variables or attributes.

The Friedman's test conducted on PROs assigned by participants to the same attribute showed that there was no significant difference between the three sessions. A difference between sessions 2 and 3 ($p < 0.05$) was found in the evaluation of the perceived disintegration time acceptability of sample P1. It must be noted that the lack of significant difference between sessions must not be taken as an indication of the reliability of the method.

2.4 Conclusions

Four excipient-grade polymers available in different molecular weights were used to prepare casting solutions at different concentrations, and tested for solution pourability. Out of 22 solutions, 21 were also assessed for film-forming capability. Of those, only PVOH (39 kDa, and 197 kDa), CMC (395 kDa, and 725 kDa), HPMC 65 SH, and PVP 90 kDa solutions produced films with acceptable flexibility, homogeneity and ease of peeling. HPMC, and PVP were excluded from further analyses due to the lack of possible comparison between different molecular weights, therefore two CMC-based ODF samples were tested, together with two PVOH-based ODF samples, for *in vivo* acceptability. A single-blind, single centre, exploratory pilot human panel was conducted on twenty-four young healthy adults. Participants evaluated the acceptability of several

ODF attributes by taking orally the four single-polymer ODF samples, and by answering a computerised questionnaire and participating in a semi-structured interview. The sample perceived thickness, perceived stickiness in the mouth, and the perceived sample disintegration time received different acceptability scores in dependence of the sample analysed, and were considered attributes having the potential to influence the end-user acceptability of ODFs. Questionnaire results suggested that the perceived stickiness acceptability could be inversely correlated with the perceived stickiness intensity assessed by participants. Similarly, the perceived disintegration time acceptability seemed to show inverse correlation with the disintegration time measured by stopwatch. The acceptability assessment made by participants on the four samples was further confirmed by the researchers' evaluation of the participants' reaction to the sample, and intake performance. From the semi-structured interview, other potential attributes with influence on the end-user acceptability were identified. Among them, the thickening effect on saliva, the tendency to form lumps during disintegration, and, expectedly, the taste. A strong negative correlation was found between the molecular weight of the film-forming polymer and the acceptability of the disintegration time. A weak negative correlation was found between polymeric molecular weight and the perceived stickiness acceptability, and a weak positive correlation between molecular weight and perceived stickiness intensity. Although it was not possible to assess the reliability of the method due to limited dataset, no significant differences on the overall acceptability scores assigned were found among panel sessions. Future work will entail the identification and optimisation of *in vitro* methods capable of predicting the acceptability of perceived stickiness and disintegration time of ODF acceptability.

** Part of the data presented in chapter 2 has been published in Scarpa et al., 2018* [120].

Chapter 3. *In vitro* methodology assessment for the acceptability testing of orodispersible film attributes

This chapter describes the assessment of existing *in vitro* methods for their predictive capability towards the end-user acceptability of orodispersible films (ODFs). Texture analysis and dynamic mechanical analysis were assessed to quantify *in vitro* adhesive characteristics and predict perceived stickiness of ODF samples. Petri dish method, drop method, and a mechanical oral cavity model were assessed for the *in vitro* quantification, and prediction of the acceptability of perceived ODF sample disintegration time. The *in vitro/in vivo* correlation of the data obtained informed on the potential of the *in vitro* methods to serve as a decision-supporting tool for the design of ODF formulations with regards to the optimisation of perceived stickiness and perceived disintegration time. Strengths and limitations of the assessed methods are also discussed.

Aims:

- To explore the predictive capability of existing or adapted *in vitro* methodologies for key ODF acceptability attributes based on human panel data.
- To develop new *in vitro* methodologies for the prediction of key ODF acceptability attributes.

Objectives:

- To test a set of ODF samples differing in *in vivo*-perceived stickiness by texture analysis.
- To test a set of ODF samples differing in *in vivo*-perceived disintegration time by petri dish and drop methods.
- To adapt a mechanical oral cavity model and dynamic mechanical analyser for the assessment of ODF disintegration and tack respectively, and to optimise a novel method.

3.1 Introduction

The human panel to assess the end-user acceptability allowed the identification of ODF perceived stickiness and disintegration time as key acceptability attributes. *In vitro* methods capable of predicting the end-user acceptability of key ODF attributes should bring together the ability to quantify the intensity of perceived stickiness or perceived time to disintegration, and offer an outcome measure that correlates with the acceptability scores measured *in vivo*.

3.1.1 *In vitro* analysis of ODF perceived stickiness

3.1.1.1 The six theories of mucoadhesion

In order to assess the perceived stickiness od ODFs, the test samples needed to be formulated with polymers with different degrees of adhesiveness [76].

The stickiness perceived by participants of the human panel study was referred to the tendency of the ODF sample to adhere to the hard palate. Such adhesive behaviour is likely to be mediated by the adhesive properties of the film-forming polymers used for ODF sample preparation [143]. The adhesion of a material to biological tissues is defined as bioadhesion, whereas adhesion to mucosal tissue is regarded as mucoadhesion [126]. Several theories proposed to explain the underlying causes of mucoadhesive phenomena, and a combination of such theories could actually govern mucoadhesion, depending on the adhesive system analysed. There are six theories of mucoadhesion. The *electronic theory* applies when there is a transfer of electrons across the adhesion surface of two materials. The transfer occurs because of the difference in electronic structure between materials, resulting in the formation of an electric double layer at the interface, and therefore to attractive forces [126]. The *wetting theory* applies to the ability

of liquids to spontaneously spread onto a surface. This phenomenon is regarded as a prerequisite for the formation of an adhesive bond [126]. The *adsorption theory* describes the adhesive bond formation as a consequence of hydrogen bonds or van der Waals forces between surfaces [126]. The *diffusion theory* describes adhesion as a phenomenon mediated by the interdiffusion of polymeric chains and mucins, high-molecular weight glycoproteins present on mucosal surfaces [126]. The *mechanical interlocking theory* suggests that mucoadhesion may occur because of interlocking mechanisms between a liquid, and the irregularities of the mucosal surface [126]. Finally, the *fracture theory* uses the measurement of the force applied to detach two surfaces as indication of the adhesive bond [126]. This is the most used theory to explain adhesion occurring between surfaces. Every theory can be validated or disqualified for the specific system analysed by using specific methodologies. For example, the wetting theory can be tested by measuring the contact angle of the adhesive material, if the last exposes a solid surface. The mechanical interlocking theory can be tested by measuring the roughness of the adherent surface, if the adhesive is in a liquid form. However, not all theories can be applied to every system.

3.1.1.2 Hypothesis on mucoadhesive mechanisms involved in hard palate/ODF adhesion

Before the selection of the experimental methods to test, it is important to build a hypothesis based on the characteristics of the adhesive bond between ODF and hard palate occurring *in vivo*. The human hard palate is covered by a keratinized epithelium constituting a masticatory mucosal surface of approximately 0.2 mm thickness [144]. The superficial layer of the hard palate mucosa is characterised by a stratified squamous epithelium composed of dead cells rich in cytoskeletal elements, where keratin can constitute up to 85% of the total protein content [145]. Both acidic and basic or neutral keratin variants are expressed in hard palate keratinocytes [145], making difficult to

estimate the net surface charge of the palate. Little information is available on the surface roughness of the hard palate epithelium, however tongue surface roughness was reported to be high [146]. Moreover, a low salivary flow rate, and a limited presence of salivary proteins were noticed on the hard palate in comparison with other oral surfaces [147]. Surface and electrochemical properties of the palate surface can provide basic information on which mucoadhesion theory is more likely to explain the adhesive phenomena observed in ODF samples, and consequently, which techniques/methods to use for the assessment of ODF adhesion. In particular, mechanical interlocking is unlikely to be involved in the adhesive bond between ODF and palate because the participants to the human panel reported that films tended to adhere to the palate instead of the rougher surface of the tongue [71,148]. If mechanical interlocking was involved, ODFs would have probably adhered to the tongue instead. The diffusion theory is also unlikely to be responsible for ODF/palate adhesion because of the reduced salivary protein concentration, probably including mucins, on the palate surface compared to other regions of the oral cavity [147]. In some cases, despite the hypothesis of the involvement of a specific mucoadhesion theory could not be rejected, the method to test such hypothesis could not be applied to the analysed system. The measurement of water contact angle might have provided information on the tendency of a hydrophilic liquid medium such as saliva or mucus to adhere to the ODF surface, and therefore to mediate adhesion according to the wetting theory. However, the highly hydrophilic nature of the ODF samples, made impossible to obtain a stable image of the contact angle formed by the liquid drop deposited onto the film surface. Remaining plausible theories that could explain the observed ODF adhesion are therefore the fracture, electronic, and adsorption theories. Fracture theory was tested first.

3.1.1.3 Fracture theory and testing methods

The most used theory in mucoadhesive phenomena is the fracture theory [126,149]. It is based on the mechanical measurement of the force required to separate two surfaces after adhesion occurs [126,150]. The force (Sm) is expressed as the normalisation by the adhesive area ($A0$) of the maximum detachment force (Fm) measured in a test for resistance to rupture [128], in accordance with Equation 3.1.

Equation 3.1:

$$Sm = \frac{Fm}{A0}$$

The adhesive force Sm, can be linked to the fracture energy, and Young's modulus measured by rheological methods [128], however multiple-component systems can be more complicated to analyse this way. Considering that the observed ODF adhesion to the palate is a two-component system, a simple tensile testing-type method might be more suitable to provide a descriptor of ODF adhesive properties.

Various *in vitro* methods have been used to test mucoadhesion. *In vitro/ex vivo* tensile testing methods constituting of compressed disks of porcine mucins [151], excised porcine mucosa [150], or rat intestinal mucus [152], and a universal tensile tester or a texture analyser were employed. Other methods aimed to measure the shear strength of a parallel polymer/mucus sample [153]. Both perpendicular and shear stresses are likely to be applied to the ODF sample in the oral cavity. Non-*ex vivo* methods for the measurement of perpendicular force will be assessed first, in order to maintain the testing conditions as simple as possible, and avoid variability potentially introduced by the utilisation of animal tissue.

3.1.2 *In vitro* analysis of ODF perceived disintegration time

Disintegration time is defined by the United States Pharmacopoeia as “the state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core” [154], and such definition also applies to orodispersible films. However, ODFs become soft and impalpable very quickly after hydration due to their polymeric nature. Hence, it might be complicated to identify an appropriate definition of disintegrated status for ODFs, and consequently, to determine a disintegration endpoint [155], and acceptability criteria.

The perceived disintegration time was quantitatively and qualitatively evaluated by participants of the human panel study. Both time to disintegration and acceptability of the disintegration time were assessed. Whereas the disintegration time is easy to quantify, and can be measured using a stopwatch, its acceptability may not depend on time alone, and might be difficult to predict. However, *in vivo* disintegration time measurement and acceptability scores seemed to show a certain degree of proportionality. Therefore, a simple method for the measurement of disintegration time might also provide information on its acceptability in ODF samples. There is a good availability of *in vitro* methods for the quantitative measurement of disintegration time. According to the European Pharmacopoeia guidelines, orodispersible formulations such as films, should disintegrate in less than 180s, and any suitable method can be used to test the disintegration time [100]. Campbell and co-authors highlighted the importance of assessing disintegration in a system mimicking physiological conditions as closely as possible, in order to achieve proportionality between *in vitro* and *in vivo* rates [156]. Since no method is currently specified, several research groups have presented biorelevant methods [98,107,157–159] for disintegration testing of solid dosage forms. Such apparatuses, however, enable the measurement of disintegration time based on the ODF sample’s interaction with the disintegration medium, and applies mechanical stresses that do not reflect those applied in *in vivo* conditions. First, two “conventional”

in vitro methods were chosen for disintegration time testing, and assessed for *in vivo/in vitro* correlation. Petri dish and drop methods differ between each other in volume of disintegration medium, and presence or absence of mechanical stress applied to the sample [107].

3.1.2.1 Adaptation of in vitro mechanical oral cavity model for the assessment of ODF disintegration time

In order to assess the disintegration time of ODF samples by application of a mechanical stress mimicking the *in vivo* condition more closely than in the petri dish method, an oral cavity model previously developed by the University College London Department of Mechanical Engineering was adapted and tested. The model was originally intended for the study of the flow properties

of thickening agents during the swallowing process, and its design is shown in Fig. 3.1 [160].

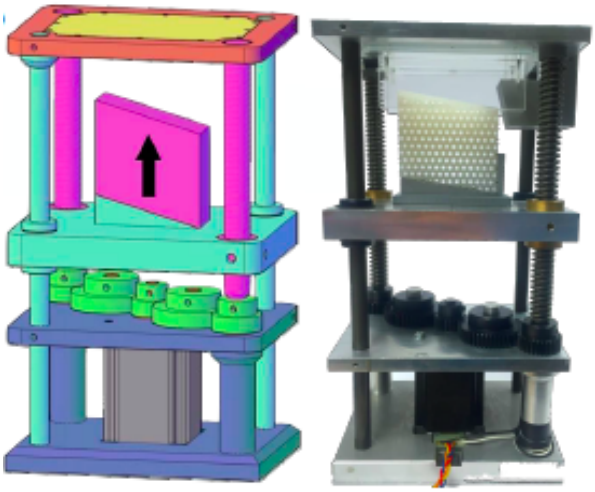


Figure 3.1: Design of the mechanical oral cavity model (figure from Redfearn and Hanson, 2017). [161]

As both dimensions and mechanical characteristics of the materials of the artificial mouth reflect the *in vivo* characteristics of the oral cavity, the model could be adapted to the study of the disintegration behaviour of ODFs. The device is composed of two fixed and

one mobile metallic plates capable of travelling upwards on four threaded rods by tailspin movement. A piece of moulded silicone with specific dimensions is accommodated on top of the mobile plate and secured to it. On full compression, the silicone tongue completely adheres to an upper acrylic plate (parallel to the mobile metal plate) representing the hard palate, and applies a specific pressure at different points on the sagittal axis. The pressure can therefore be regulated by adjusting the position of the mobile plate. Motion control is regulated manually by an Arduino Uno microcontroller equipped with buttons, a rotary knob, and a digital display, or electronically, by a compression cycle program purposely created using Matlab (MathWorks, Natick, MA, USA).

3.2 Materials and methods

3.2.1 ODF samples

Unless specified otherwise, four drug-free single-polymer ODF samples were prepared in house by solvent casting as described in chapter 1. Listerine PocketPacks® breath strips was purchased from Johnson & Johnson (New Brunswick, New Jersey, U.S.). The simulated salivary fluid was composed of potassium dihydrogen phosphate (Fisher Scientific, Loughborough, Leics, UK), EMSURE ® sodium chloride (Merck-Millipore, Darmstadt, Germany), calcium chloride (Merck-Millipore, Darmstadt, Germany), and sodium hydroxide (Fisher Scientific, Loughborough, Leics, UK).

3.2.2 Tack measurement of ODF samples by texture analysis

ODF sample tack was measured by texture analysis by adaptation of a previously optimised method [162,163]. A TA.XT Plus (Stable Microsystems Ltd., Godalming, Surrey, U.K.) equipped with a 30 Kg load cell, and a 6 mm cylindrical poly(methyl methacrylate) (PMMA) probe was used. ODF samples were cut to a 1 x 1 cm^2 area, and attached to a microscope slide (Thermo Scientific, Braunschweig, Germany) with non-conductive double-sided adhesive tape (SPI supplies, West Chester, Pennsylvania, U.S.). The microscope slide was then placed beneath the probe, and 200 μL of pre-warmed distilled water (37°C) was deposited on top of the test ODF sample. The probe was set to lower at a speed of 0.4 mm/s, and to apply a force of 2.308 N for 12 s. The retraction speed was 1 mm/s. Data were analysed using Exponent software (Exponent v6, Stable Microsystems Ltd., Godalming, Surrey, U.K.).

3.2.3 Tack measurement of ODF samples by DMA

The adhesive force profile of ODF samples was measured using a Q800 Dynamic Mechanical Analyser (DMA) (TA Instruments Delaware, US) operating in controlled force mode. A set of 15 mm diameter steel compression clamps were installed and the instrument calibrated. ODF samples were cut to 15 mm diameter discs, and attached to the lower disk of the compression clamps using a non-conductive double-sided adhesive tape (SPI supplies, West Chester, Pennsylvania, U.S.). The clamps were kept separated by applying a negative force of -0.8 N until the equilibration temperature of 37 °C was reached. 0.45 mL of pre-warmed deionised water was deposited on top of the ODF sample surface, as shown in Fig. 3.2.

Figure 3.2: ODF adhesive force measurement experimental setup.

The clamps were brought to contact by applying a force of +2.649 N (compression = 0.015 MPa), and then immediately withdrawn by ramping the force at -25 N/min to -8 N. The data obtained were analysed using Universal Analysis 2000 v.4.5A (TA Instruments Waters LLC, Delaware, US) software by plotting the static force and displacement signals vs. time. The adhesive force value was taken at the intersection between the ordinate of the onset point of the displacement ramp and the static force curve. An example of resulting plot is shown in Fig. 3.3.

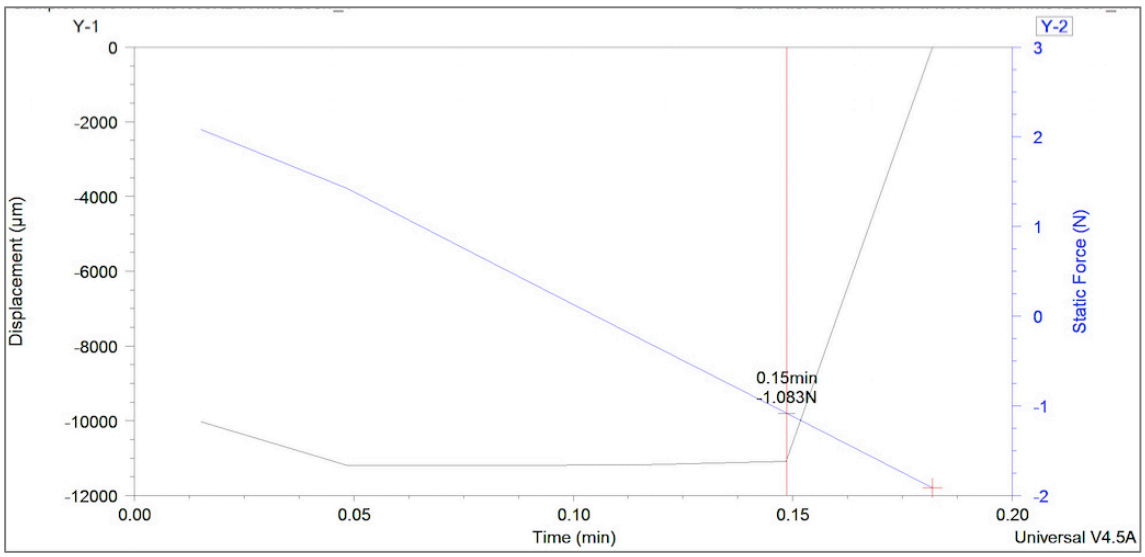


Figure 3.3: Example of a sample's adhesive force calculation on the displacement and static force vs. time plot.

The adhesive force measurement was taken after 10s, 60s, 120s, and 180s from drop deposition.

3.2.4 Measurement of the disintegration time of ODF samples by petri dish and drop methods

For the petri dish method, ODF samples were cut to 3 x 2 cm rectangles and placed in a 9 cm petri dish in a 37 °C water bath under gentle shaking (70 rpm). Pre-warmed distilled water or simulated salivary fluid (SSF) [164] (2 mL) was deposited on top of the film [107] and the time to disintegration was taken when the film was observed breaking from the viewing area [155]. For the drop method, a piece of ODF sample was secured between two metallic plates with a semi-circular hole on one side, in order for part of the film surface to be exposed on both sides. The sandwich was positioned at 1 cm height and parallel to the ground. A drop of 200 μL [107] pre-warmed (37 °C) water or SSF was deposited on the upper surface of the film, and time was taken until the drop formed a hole, and fell down, as shown in Fig. 3.4.

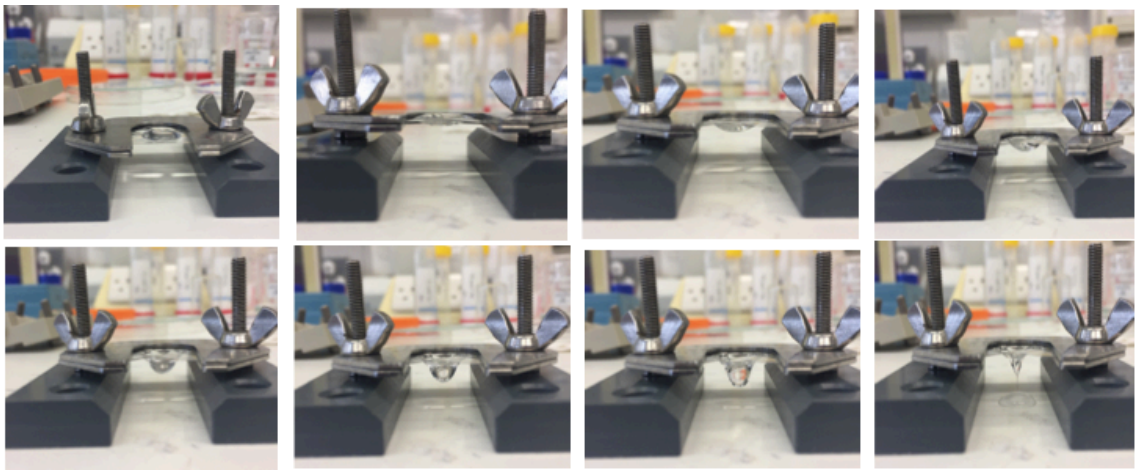


Figure 3.4: Example of disintegration time measured by drop method.

3.2.5 Measurement of the disintegration time of ODF samples by mechanical oral cavity model

3.2.5.1 ODF sample composition for disintegration assessment by oral cavity model

Four single-polymer orodispersible films were prepared by solvent casting following the method described in chapter 1. Two carboxymethylcellulose (CMC) (395 and 725 KDa), and two poly(vinyl) alcohol (PVOH) (31 and 197 KDa) solutions were prepared as described in chapter 1. A 1% v/v red food colouring agent (Waitrose Ltd, UK) was added to the polymeric solutions before casting. Listerine® strips (Johnson & Johnson Inc., Skillman, NJ, U.S.) were also analysed.

3.2.5.2 Adaptation of the experimental conditions for disintegration time measurement

A swallowing frequency of one compression every 60.8 s. was initially calculated using the equation developed by Rudney and Larson [165]. However, a faster cycle was later adopted in order to avoid system overload. The compression cycle and inter-compression lag, were set by modifying the existing Matlab code to 660 ms, and 2,000 ms respectively. A compression distance of 16.5 cm was calculated in order to apply a pressure of 30 kPa at the median section of the artificial palate [166]. The artificial oral cavity internal volume was 12 mL prior to compression, and 0 mL on full compression. A Canon (Sony RX100M4) camera recording at 25 fps was installed above the artificial palate facing downwards so that the framing included the whole surface of the silicone tongue on full compression. Controlled lighting conditions were applied.

Each test ODF sample was positioned on the surface of the silicone tongue as shown in Figure 3.5.

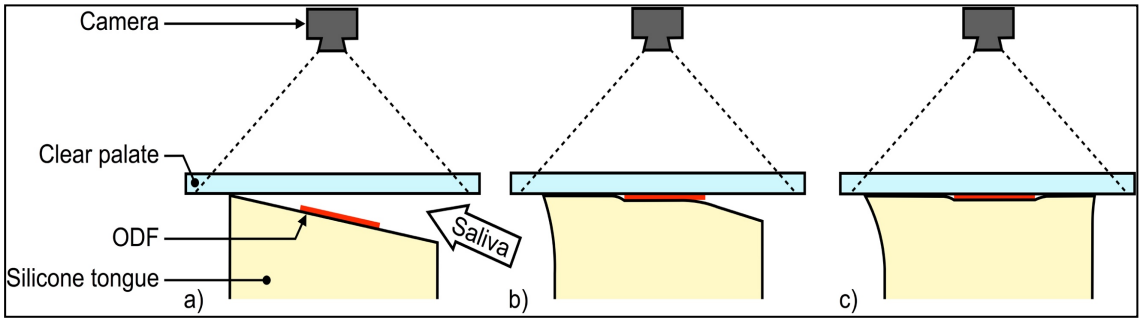


Figure 3.5: ODF sample position in the oral cavity model (figure from Redfearn et al., 2019) [167].

Recording was started and compression cycle sequence initiated. After the first compression, simulated salivary fluid (composition in Tab. 3.1) [168] was sprayed in the artificial oral cavity, and the procedure was repeated every two compressions, in order to achieve a simulated salivary flow rate of 1.5 mL/min [169]. Upon film disintegration, the device was switched off and the recording stopped.

Table 3.1: Artificial salivary fluid (SSF) composition according to Guhmann et al., 2012.

Component	Concentration
Potassium dihydrogen phosphate	12 mM
Sodium chloride	40 mM
Calcium chloride	1.5 mM
Sodium hydroxide	To pH 7.4
Demineralised water	To 1 L

3.2.5.3 Video data analysis

The obtained video file was then analysed using a program developed in Matlab environment (MathWorks, Natick, MA, USA). A video frame was extracted after exactly 2320 ms. from the beginning of every compression cycle (Fig. 3.6). This was to ensure that the extracted frame corresponded to the film's most distant position from the palate.

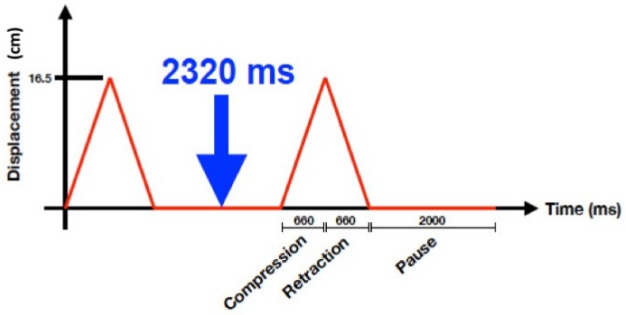


Figure 3.6: Compression and retraction cycle of the oral cavity model.

The number of frames extracted depended on the length of the video. A "crop" function allowed selecting the area corresponding to the silicon tongue from the first extracted frame. Then, the area corresponding to the ODF sample was selected using a second "crop" function (Fig. 3.7).

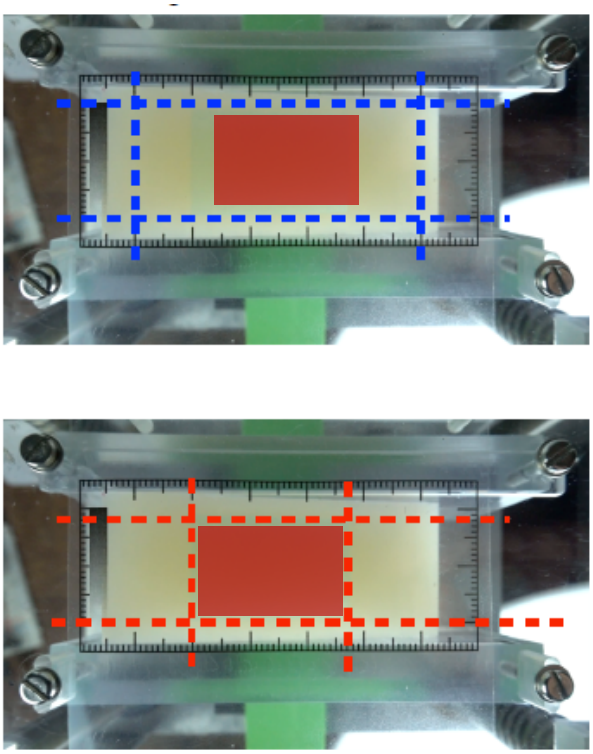


Figure 3.7: Crop function for background and sample area selection of the oral cavity model video analysis method.

The program calculated the intensity of the three Red (R) Green (G), and Blue (B) colour channels for each pixel, and extracted the highest and second highest intensity channel (RG for the analysed ODF samples, and GB for Listerine®) from the selected film area (Fig. 3.8 a,b). A manual thresholding was conducted in order to exclude any pixels belonging to the selected background (tongue) area from the ODF area calculation. Subsequently, the R and G signals were summed together and the result subtracted from the background signal intensities for each extracted frame (Fig. 3.8 c). The resulting values were plotted against time. The data was then normalised based on the resulting RG values of the first extracted frame (at time 0) and smoothed (Fig. 3.8 d).

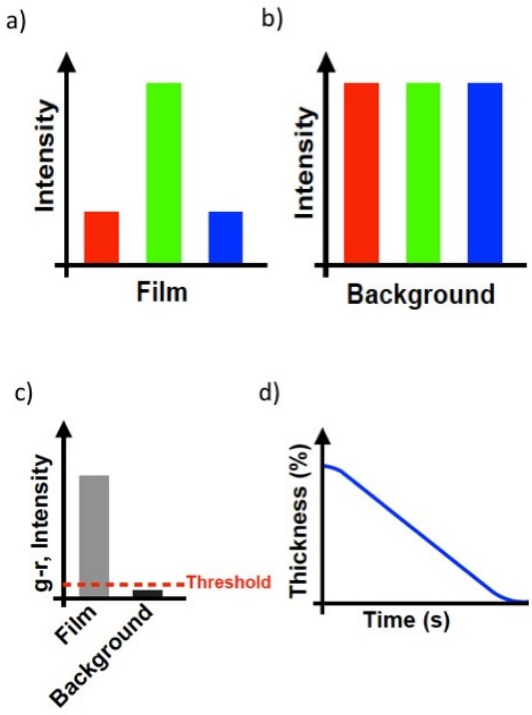


Figure 3.8: Example of frame sample signal calculation (a,b,c), and normalisation (d) of the oral cavity model video analysis method.

An alternative method for data analysis was also developed. Instead of selecting the two highest signal channels from the film area of the extracted frames, the computer program considered all the three RGB channels intensities for comparison with the background. This method was named “Difference” method, as opposed to the method previously described that was named “Red-Green” method.

3.2.5.4 Thickness calibration

The signal intensity was measured on a strip of ODF samples with varying thickness using the two methods. The real film thickness was measured using a microcaliper and plotted against the signal intensity obtained by the computer program. This calibration was then used to predict the thickness of the strip image using the two video data analysis methods described before. Therefore, the ODF sample disintegration data represented the film volume (ODF area multiplied by ODF thickness) compared to the

first extracted frame, when the film had not started to disintegrate. The resulting disintegration curves represented the % of the ODF initial volume over time, and indicated its progressive volume reduction.

3.3 Results and discussion

3.3.1 Tack assessment of ODF samples

3.3.1.1 Adhesive force measurement of ODF samples by texture analysis

The adhesive force profiles of the ODF samples are represented in Fig. 3.9.

Samples P1 and P2 reached their maximum adhesive force values of 0.430 ± 0.005 N/mm^2 and 0.478 ± 0.063 N/mm^2 respectively after 10s of hydration time. Then it decreased in both samples to 0.200 N/mm^2 and 0.290 N/mm^2 respectively at 60s, and stabilised around these values. The adhesive force of sample C1 was 0.157 ± 0.006 N/mm^2 after 10 s, and maintained stable adhesion until 240s. Sample C2 reached a similar value (0.105 ± 0.001 N/mm^2) at 10s and maintained it to 240s.

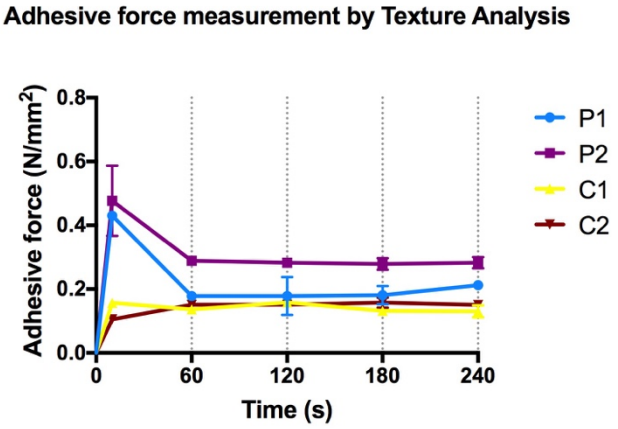


Figure 3.9: Adhesive force profile of the four tested ODF samples by texture analysis (n = 3).

The two PVOH-based films maintained adhesive force values always above 0.180 N/mm^2, whereas CMC-based samples showed adhesive force always below 0.200 N/mm^2. The Kruskal-Wallis test 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 ($p < 0.05$). The texture analyser showed discriminative capability towards different polymer types after the first 10s of hydration, but not afterwards. It was not discriminative towards different polymeric molecular weights or degrees of substitution. The adhesive properties of partially hydrolysed PVOH are well known, and the polymer is widely utilised in the adhesives industry [170]. CMC is mainly used as a thickener in the food industry [171], however it has been used in pharmaceutical preparations as a disintegrant, stabilising, suspending, emulsifying, gel-forming, and viscosity-regulating agent [172]. Bioadhesive applications of PVOH and CMC were also explored due to their high biocompatibility, and their abundance in hydroxyl and carboxylic groups respectively [76,143], therefore a certain level of adhesion of the polymeric ODF samples was expected. Differences in adhesive behaviour between polymeric adhesives differing in molecular weight were described by Weiss [173]. The effect of polymeric molecular weight of PVOH on its adhesion to different materials was described [174], and so was the effect of CMC molecular weight and degree of substitution on adhesion to $Li_4Ti_5O_{12}$ anodes [175]. Consequently, it was reasonable to expect a difference in adhesive behaviour between different molecular weight-polymeric films, when measured by *in vitro* methods showing potential predictive power. Different perceived stickiness intensities of ODF samples were also reported by human volunteers, especially in correlation with PVOH molecular weight. The missing correlation between sample type/molecular weight and adhesive properties of polymers measured by texture analysis might be attributable to the material properties of the cylindrical probe utilised. PVOH was reported to adhere and adsorb to PMMA [176,177], and CMC was also observed to influence the adhesion of polyisobuthylene to PMMA [178], however the influence of polymeric molecular weight, and any differences in

adhesive force strength between the two polymer types were not reported in the literature.

3.3.1.2 Adhesive force measurement of ODF samples by DMA

The developed DMA method allowed measuring the maximum force required to detach the hydrated film from a stainless steel plate as a description of the tack properties of the polymeric species analysed. The adhesive force was measured at different time points in order to obtain a profile of the adhesive behaviour of each film over time. The adhesive force profile of the four ODF samples, and Listerine® is shown in Fig. 3.10.

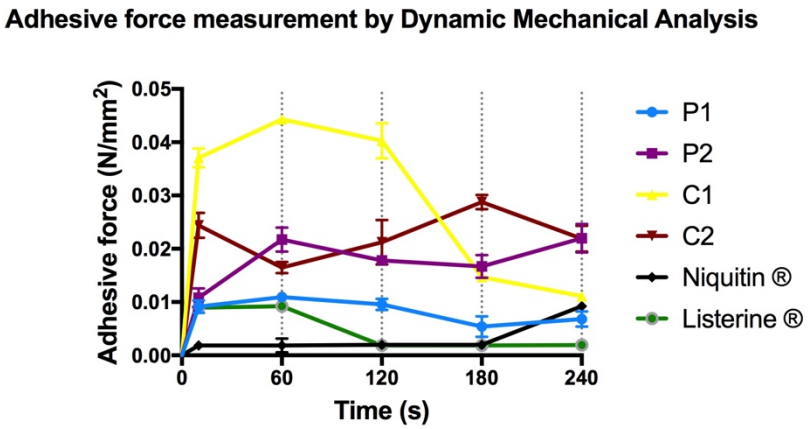


Figure 3.10: Adhesive force profile of the four tested ODF samples, Listerine (R) and Niquitin (R) films analysed by DMA (n = 3). Figure from Scarpa et al., 2018 [120].

The adhesive force profiles of the four placebo ODFs and commercial films differed between samples and over time. The highest adhesive force value was exhibited by the low molecular weight CMC sample (395 KDa – C1), which increased to 0.0370 ± 0.0010 N/mm^2 at 10s, reached a maximum peak of 0.0443 ± 0.0003 N/mm^2 after 60s, and dropped to 0.0147 ± 0.0002 N/mm^2 at 180s. Listerine® had the lowest adhesive force values, that reached 0.0089 ± 0.0001 at 10s, decreased to 0.0019 ± 0.0000 N/mm^2 at 120s, and stabilised around similar values until 180s. The low molecular weight PVOH

sample (39 KDa - P1) increased its adhesive force to 0.0091 ± 0.0007 N/mm^2 at 10s, and maintained similar values until 180s, when it dropped to 0.0054 ± 0.0011 N/mm^2. The high molecular weight PVOH-based film (197 KDa – P2), reached 0.0108 ± 0.0010 N/mm^2 at 10s, increased to 0.0217 ± 0.0013 N/mm^2 at 60s, and then it decreased to 0.0167 ± 0.0012 N/mm^2 at 180s. The high molecular weight CMC-based sample (725 KDa – C2) increased its adhesive force to 0.0244 ± 0.0013 N/mm^2 at 10s, then it decreased to 0.0165 ± 0.0006 N/mm^2 at 60s, increased to 0.0212 ± 0.0024 N/mm^2 at 120s, and decreased again to 0.0288 ± 0.0007 N/mm^2 at 180s. Listerine® is a commercially available healthcare breath freshener strip product in the form of ODF, that was estimated to be used by 8.86 million Americans within one month in 2018 (Census data and Simmons National Consumer Survey) [179], and hence selected for comparison purposes in the study. When tested for tack, Listerine® showed the lowest adhesive force profile compared with all the other samples analysed. The role of water as solvent in the adhesion process observed is fundamental, as dry films did not adhere to the metallic plate. Polymeric molecular weight may also affect adhesion, especially in relation to the mobility of the polymeric chains, and thus influence their ability to diffuse, adsorb, improve surface wetting, and form electrically charged double layers [143]. This might explain the difference between the adhesive force profiles observed in PVOH-based samples differing in molecular weight. The adhesive force values of sample C1 increased during the first 120s, and then decreased considerably until 180s. The specific CMC polymers used in the experiment have different degrees of substitution (DS), and different molecular weights (DS 0.7 for 725 KDa, and DS 1.2 for 395 KDa). A high DS means that more carboxylic groups are present in the molecule [180]. Carboxylic groups are involved in the bioadhesive properties of CMC, alongside hydroxylic groups [143], and might also determine the cohesive properties of the molecule [181], potentially explain the higher tack exhibited by sample C1 compared to sample C2, in spite of its lower molecular weight. A cohesive dominance effect was suggested to be responsible for the adhesive properties of thick polymeric coatings made of polyelectrolyte

multilayers mediated by disentanglement processes [182], and an increase in cohesion as a result of CMC addition to foods [183] and biomass pellets [184] was also reported. However, the DS of CMC added to low-fat frankfurters was not observed to influence the cohesiveness of the product [185]. Moreover, CMC molecular weight and DS were found to influence its adhesion to $Li_4Ti_5O_{12}$ anodes, but in an inverse relationship compared to the adhesion behaviour to stainless steel observed in the present study [175]. Therefore, it is difficult to determine whether the adhesive behaviour of high-DS sample C1 could be attributed to strong cohesive forces between the polymeric chains that subsequently failed after the first two minutes of hydration. Also, it is not clear as to whether the inverse adhesive force relationship observed by Lee and co-workers [175] can be attributed to the specific binding material ($Li_4Ti_5O_{12}$ anodes or stainless steel) or to other reasons. A high degree of polymeric chain packing was reported for high molecular weight PMMA films by Linossier and colleagues [142]. In turn, chain packing was responsible for the limited access of binding sites for water. Considering the involvement of water in wet adhesion phenomena, and if the same chain packing process occurs in high molecular weight CMC films, then the lower adhesion of sample C2 compared to sample C1 could be explained by the limited interaction of water molecules and C=O groups, thus causing reduced tack. The strong affinity of C=O groups for water could also potentially explain the similarity in adhesive force values between samples P2 and C2, despite their difference in molecular weights. Highly packed long polymeric CMC chains might hide water binding sites compared to shorter PVOH chains, therefore resulting in the reduced tack of sample C2. Chain entanglement mechanisms may also play a role in the observed phenomenon [186]. Considering the different nature of PVOH and CMC, it is reasonable to hypothesise that the entanglement/disentanglement behaviour of the two polymeric species during a dissolution process might differ as well, potentially affecting the adhesive properties observed *in vitro*. Furthermore, surface properties might be involved in the adhesive bond occurring between polymers and metallic plates. Stainless steel materials are known to form a protective chromium oxide layer on their surface [187]. Chromium oxide surfaces can be further functionalised by coating using materials

containing specific functional groups [187]. Depending on the type and functionalisation of the steel, the surface energy changes as well. For example, the Lifschitz/Van der Waals polar part of freshly polished (grade AISI 304) stainless steel surface energy measured by contact angle was higher (38-39) than its basic (2.1 – 7.2), and acidic (0) parts [188], meaning that the surface is more likely to chemically interact with polar materials. The type and grade of stainless steel of the DMA metallic plates might differ from that analysed by Hedberg and colleagues, however, a potential hypothesis explaining the adhesive bond observed between ODF samples and DMA clamps might involve the formation of polar interactions between the -OH, and -COOH groups of the polymers, and the stainless steel surface. However, other mechanisms related to the molecular structure or other physicochemical properties of the polymer might be involved in the adhesion mechanism between ODFs and DMA plates, hence the type of DMA equipment (e.g. material used for DMA plates) should be considered.

3.3.1.3 *In vivo/in vitro* correlation of ODF samples tack assessment

Texture analysis did not evidence differences in the adhesive properties of different molecular weight polymeric films, whereas the dynamic mechanical analysis did. Considering that a molecular weight effect for PVOH samples was also observed *in vivo*, the texture analyser did not show promising predictive capability with respect to adhesive properties of ODF samples, as the DMA did. The low perceived stickiness intensity reported by human volunteers was reflected in the low adhesive force profile of sample P1 analysed by DMA. However, DMA data interpretation for *in vitro/in vivo* correlation purposes is complicated by the fact that adhesive force changes of ODF samples are studied over time, making them difficult to compare to numerical scores assigned by panel participants. The identification of a specific reference time point for *in vivo/in vitro* data comparison is also not advisable, as the stickiness perception depends on the time

the ODF resides in the oral cavity, and therefore, on its disintegration time. A different approach to DMA data interpretation must then be adopted.

3.3.2 Disintegration time assessment of ODF samples

3.3.2.1 Disintegration time measurement of ODF samples by petri dish and drop methods

The disintegration of samples C1, P1, P2 and Listerine® measured by petri dish method was much faster than sample C2 (Tab. 3.2). Only the difference in disintegration time between samples C2 and P1 was significant ($p<0.05$). Measurements carried out by drop method seemed to slightly overestimate the disintegration time of PVOH-based samples, and to overestimate that of CMC-based films, and Listerine® compared to the petri dish method. There was no significant difference in disintegration time measured in water or SSF (data not shown). The molecular weight of the film-forming polymer seemed to influence the disintegration time of the ODF samples, as opposed to what was reported by Chan, Hao, and Heng in 1999 for low-hydrolysis degree PVOH [189]. On the other hand, a correlation between molecular size of CMC and drug release by erosion or matrix relaxation mechanisms was found for other orally disintegrating dosage forms [190]. Moreover, the type of film-forming polymer also seemed to influence the disintegration of ODF samples, probably due to the presence of COOH groups. Strong hydrogen bonding is likely to occur between carboxylic groups and water, however, long polymeric chains may lead to high molecular packing, and therefore, to a limited availability of binding sites [142], potentially explaining the slower disintegration time of sample C2 compared to sample C1.

Table 3.2: Average disintegration time of ODF samples measured by petri dish and drop methods. Results are expressed in seconds (n = 3).

Sample	P1	P2	C1	C2	Listerine®
Petri dish method	7.2 ± 0.8	55.8 ± 2.8	25.4 ± 0.2	262.0 ± 11.2	12.9 ± 0.6
Drop method	14.6 ± 1.0	113.3 ± 20.0	19.3 ± 3.0	202.6 ± 10.9	14.9 ± 0.3

3.3.2.2 Disintegration time measurement of ODF samples by oral cavity model

An oral cavity model previously developed by the UCL Department of Mechanical Engineering was adapted for the *in vitro* assessment of ODF disintegration.

3.3.2.2.1 Correlation between video signal intensity and ODF thickness

The two video data analysis methods were compared and the method giving the least data deviation from the fitted curve was selected. The best curve fitting of the calculated vs. measured thickness data corresponded to an exponential curve for both the methods analysed (Fig. 3.11).

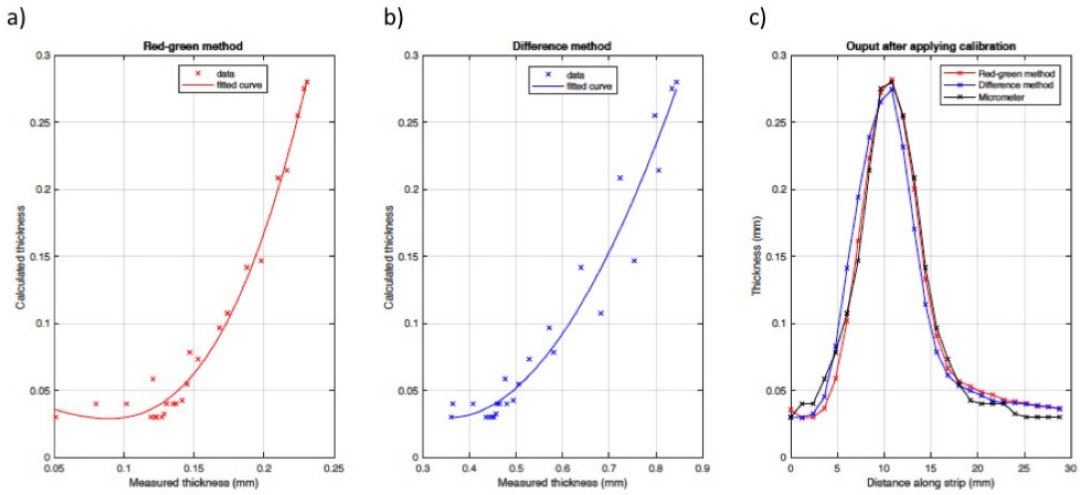


Figure 3.11: Measured vs. calculated thickness curve fitting for a) RG method, b) Difference method, c) both methods in the oral cavity model video analysis (courtesy of Dr Andrew Redfearn).

In the RG method, the largest data deviation was observed for real film thickness values between 50 to 150 μm, however, for higher film thickness values, the data dispersion reduced (Fig. 3.11 a). In the Difference method, on the other hand, the data deviation was significant in all the real thickness range (Fig. 3.11 b). This difference was also observable when the calculated thickness with both methods, and the real thickness measured by micrometer were plotted against the distance along the film strip (Fig. 3.11 c). The deviation from the real thickness (black line), and the Difference method (blue line) was more pronounced across the whole length of the strip, whereas the RG method predicted thickness values closer to the real thickness, especially in the central part of the strip. The purpose of the analysis was to predict the disintegration time and observe the disintegration behaviour of ODF, therefore an accurate detection of the film thickness and, consequently, of the calculated film volume was a key requirement. This observation provided the rationale for the selection of the RG method to analyse the video data of ODF disintegration time.

3.3.2.2.2 Disintegration time measurement of ODF samples by mechanical oral cavity model

The disintegration of four red-coloured single-polymer ODFs and a Listerine ® strips was measured. The data representing the percent of film volume reduction over time is shown in Fig. 3.12.

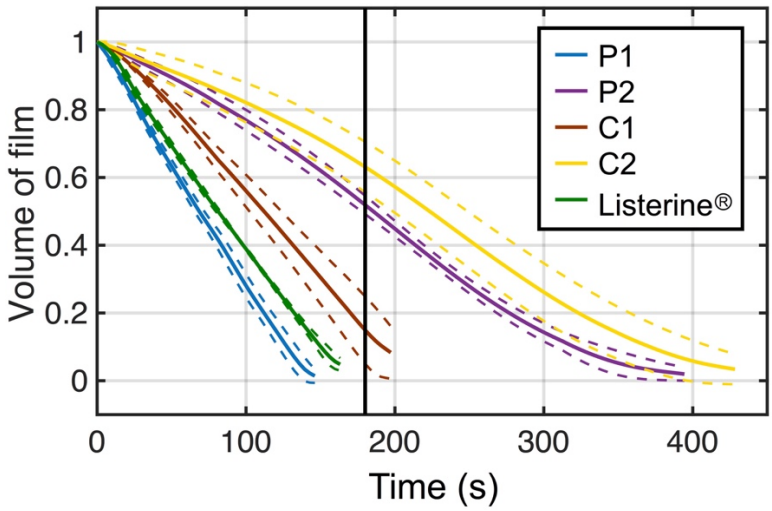


Figure 3.12: Percent volume reduction at 180s of ODF samples (n = 3). Standard deviation is represented by the dashed lines (figure from Redfearn et al., 2019) [167].

The method presented and tested in this work was able to measure film volume (relative to initial volume) for five different ODF formulations, including a commercial film, during mechanical and chemical degradation. A clear difference between characteristic volume reduction curves for each ODF sample was found. During the disintegration process all ODF samples tested adhered to the acrylic palate after the first compression cycle.

The European Pharmacopoeia indicates a cut-off disintegration time of 3 min. for a dosage form to be considered orodispersible [100]. Therefore, 180s was selected as a reference time to compare the analysed formulations. Sample P1, and Listerine® reached complete disintegration in less than 3 min., whilst the % volume reduction of the other films at 180s was approximately 90%, 50%, and 39% for samples C1, P2, and C2 respectively. The low molecular weight polymeric films disintegrated faster than the high

molecular weight polymeric films within the same polymer species, with P1 being the fastest dissolving film, and the C2 being the slowest. The molecular weight of PVOH was reported not to influence its solubility at low hydrolysation degrees [189], however other authors reported the molecular weight influence on the disintegration of other polymeric species [112,113]. In the present study, a molecular weight effect was observed within ODF samples made of the same polymeric species, and that could depend on the higher entanglement density present between high-molecular weight polymeric chains. Interestingly, the curve fitting of the film volume vs. time plot was linear for samples P1 and Listerine®, and became non-linear as the polymeric molecular weight increased. The presence of the two non-linear regions of the sigmoid curves could be explained by the disentanglement behaviour of the polymeric chains in solution. Also, the different curve fitting might depend on the interaction between water molecules and the substitution groups in the two polymeric species analysed [142]. According to Linossier and colleagues, a hydration lag was observed in PMMA films having the same thickness, but different molecular weight. This was attributed to the limited bonding sites accessibility due to high chain packing in high molecular weight polymers. If the same reasoning can be applied to CMC and PVOH polymers, this could explain the lag in hydration, and therefore in the consequent erosion process observed in the higher molecular weight ODF samples, and corresponding to the non-linear region of the curve at the beginning of the experiment. The low-molecular weight CMC film disintegrated faster than the high-molecular weight PVOH film, despite their difference in molecular weight. This could have occurred because, at pH 7.4, carboxyl groups are ionised whereas hydroxyl groups are not. Therefore, as CMC has carboxyl substitution groups, we could expect it to exhibit negative charges that can favour dissolution. The non-linear region at the end of the disintegration curve might be explained by the interfacial interaction between films and the acrylic plate. Adhesive behaviour between ODF sample and the PMMA rigid surface was observed during the experiment. This adhesion could have determined a temporary limitation of the polymeric chains mobility, and therefore prevent water molecules to access hydrogen bonding sites to untangle the

polymeric matrix. In support of this observation, absorption phenomena, and potentially bonding between PVOH and PMMA was reported in the literature [176,177]. In addition to erosion processes mediated by hydration mechanisms, the recurrent compression applied to the samples by the oral cavity model may have favoured the elimination of the solubilised polymeric chains by pushing the SSF out of the posterior side of the artificial oral cavity.

3.3.2.2.3 Disintegration behavior of ODF samples

The oral cavity model not only provided information on the disintegration rate of the test ODF samples, but also on their disintegration behaviour over time (Fig. 3.13).

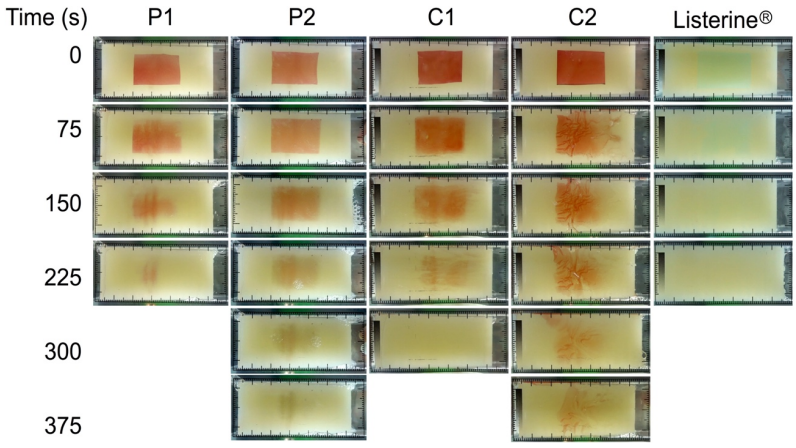


Figure 3.13: Extracted frames of the dissolving ODF samples at different time points (figure from Redfearn et al., 2019) [167].

It was possible to appreciate the tendency of the PVOH-based films to break into pieces as opposed to the proneness of CMC-based films to a more homogeneous breakdown pattern by forming a thickened fluid during their dissolution. CMC is widely used as a thickener in many pharmaceutical and food preparations due to its excellent water retention properties. Water solubility of CMC is a function of its degree of substitution, with higher degrees of substitution, corresponding to more carboxylic groups per

monomer, exhibiting higher solubility [191]. Moreover, low DS CMC was associated with the thixotropic behaviour of the molecule in solution [191]. The different disintegration patterns were observed in the two CMC-based ODF samples as a result of their different DS. Also, if the polymeric solubility is increased by the presence of C=O groups, this could explain the different disintegration behaviour observed between the C=O containing CMC-based and non-C=O containing PVOH-based films. The breakdown behaviour of Listerine® was similar to that of the CMC-based films, although its disintegration time was much faster. Listerine® strips do not contain CMC, however other polysaccharides such as pullulan, carrageenan, locust bean gum, and xanthan gum are present in the list of excipients. As the specific characteristics of the polymers used in Listerine® are not specified, it was difficult to understand the relationship between attributes such as polymeric molecular weight with the strips disintegration time and behaviour. However, similarities in the molecular structures such as the presence of repeated monosaccharide units, might have determined the similar breakdown behaviour observed between CMC and Listerine® samples.

3.3.2.3 *In vivo/in vitro* correlation of ODF samples disintegration time assessment

The disintegration time measured by petri dish and drop methods reflected the disintegration time duration reported by panel volunteers, with the exception of a slight overestimation for sample C2. Only in the petri dish method, the disintegration time of sample P2 was slightly underestimated compared to *in vivo* data. The discrepancy between *in vitro/in vivo* results might depend on the different nature and intensity of mechanical stresses applied to the samples compared to *in vivo* conditions, besides the relatively limited volume of disintegration medium used in the experiment, which was considered biorelevant [124]. This provided the rationale for attempting the design of a new disintegration apparatus integrating the concept of a different type of mechanical

stress applied to the sample, in order to mimic more closely the natural conditions of the human oral cavity.

The disintegration data obtained by artificial oral cavity model tended to overestimate the disintegration time measured by other *in vitro* methods, and *in vivo*. In the *in vivo* study, the disintegration time of all samples analysed was reported to be much faster, with P1, and C1 disintegrating in less than 1 min., and P2, and C2 disintegrating between 1 and 3 mins (Fig. 2.6). A potential explanation for the observed difference could lie, once again, in the type of mechanical stress to which samples are exposed during the experiment in the oral cavity model. In fact, the oral cavity model was designed to apply a recurrent perpendicular pressure to the film sample [160,192]. The perpendicular pressure has been proven a relevant component in the design of oral cavity models aimed at investigating the breakdown and bolus formation of foods in bulk food samples [192], however in the case of thin films, like the ones analysed in the present study, friction forces could represent a more significant stress component in mimicking human oral function [193,194]. Therefore, future studies will be aimed at investigating the role of friction in the breakdown and degradation of ODFs in the mouth, and to upgrading the oral cavity model with the capability of reproducing both the force components. The ODF sample volume reduction rate ordered from the fastest to the slowest-dissolving film was P1 > Listerine ® > C1 > P2 > C2, in agreement with the disintegration times ordered from fastest to slowest measured by drop method. In the petri dish method, however, Listerine ® dissolved faster than P1. The disintegration time of sample P1 was the only one that was considered acceptable by panel participants (Fig. 2.3) in the ODF acceptability study, whereas Listerine ® was not tested *in vivo*. This might suggest that the feeling of a solid or a viscous liquid present in the mouth for too long might be related to the discomfort expressed by the panel participants *in vivo*. Such discomfort might originate from the inconsistency between the absence of particles and the perception of a solid/highly viscous object in the mouth. In normal circumstances (solid food) the chewing and salivation processes are aided by the tongue to achieve a specific particle size [192], and bolus viscosity before swallowing. When the food takes too long to

achieve the target viscosity, it can trigger an uncomfortable feeling. Moreover, the adhesion of the ODFs to the palate, further interferes with the ability to break the film structure into pieces. The real time cut-off beyond which an ODF is considered uncomfortable might not correspond to 180s *in vivo*, however, this disintegration time could be adopted as a convention to predict uncomfortable disintegration time *in vitro*, making the oral cavity model a potential tool for the *in vitro* prediction of the end user acceptability of ODF disintegration time in the healthy young adult population.

The qualitative evaluation of ODF disintegration evidenced the different behaviour of PVOH- and CMC-based films, with CMC films forming a thickened fluid. This observation corroborates the feedback of the panel participants, who reported in a semi-structured interview that the two CMC-based films had a marked thickening effect on the saliva.

3.4 Conclusions

Two *in vitro* methods were assessed for ODF tack measurement, and three *in vitro* methods were used for the measurement of ODF disintegration time. DMA showed promise as a descriptive method for the quantitative and qualitative evaluation of the adhesive properties of ODFs, and as a predictive methodology for the assessment of ODF tack. However, the nature of the adhesive interaction between polymeric film and the stainless steel surface of the DMA clamps needs to be further elucidated. The accurate selection of an extended series of test ODF samples might inform on the underlying adhesion theory behind the observed phenomenon. Also, a new data interpretation approach must be adopted in order to enable *in vitro/in vivo* comparison between DMA adhesive force profiles and perceived stickiness intensity and acceptability scores assigned by volunteers.

All the *in vitro* techniques explored for the measurement of ODF disintegration time showed discriminative power for both polymer type and polymeric molecular weight of the ODF samples analysed. The disintegration time of ODF samples measured by petri

dish and drop methods correlated better than the disintegration time obtained by oral cavity model with human panel data, however the order in which the ODF samples reached complete disintegration was maintained in both *in vitro* methods. Further optimisation of the mechanical oral cavity model is therefore required in order to achieve a better predictive power over disintegration time measurement. On the other hand, a new concept of ODF disintegration characterisation was presented. Instead of measuring the time to disintegration only, the mechanical oral cavity model made possible for the first time to explore the concept of ODF volume reduction over time, as an indication of ODF disintegration behaviour. This analysis holds potential to provide information to better understand ODF dissolution mediated by erosion mechanisms.

** Part of the data presented in chapter 3 has been published in Scarpa et al., 2018* [120].

Chapter 4. Mechanisms involved in the ODF tack quantification by Dynamic Mechanical Analysis

The following chapter describes a new approach to the data analysis of the *in vitro* tack measurement of orodispersible films (ODFs) as a method to predict the acceptability of ODF perceived stickiness. In order to understand the mechanisms involved in the physicochemical interaction between ODF and dynamic mechanical analysis (DMA) plates, an extended range of ODF samples differing in their composition such as molecular weight, charge, hydrophobicity of the polymer, and addition of active pharmaceutical ingredient (API) and excipients, were tested. Placebo, and drug-loaded ODF formulations were optimised by mechanical properties prior to the tack test. The results of the *in vitro* study provided useful information on the physicochemical interaction potentially mediating the adhesive bond responsible for the measured tack, and on the mucoadhesion theories potentially involved.

Aims:

- To optimise a data analysis method of the tack results obtained by DMA to achieve the prediction of *in vivo* perceived ODF stickiness
- To analyse an extended set of ODF samples by DMA in order to elucidate the adhesion mechanisms involved in the ODF tack quantification

Objectives

- To consider the contribution of disintegration time to the perception of ODF stickiness in the data interpretation of the DMA analysis conducted in chapter 2
- To formulate ODFs with different pharmaceutical (excipients, API) and chemical (charge, polarity) properties to investigate the adhesion mechanisms between ODFs and DMA plates.

4.1 Introduction

The fracture theory of mucoadhesion provided a potential, although partial explanation of the nature of the adhesive bond forming between ODFs and human palate. One of the most used experimental methods based on the fracture theory for the measurement of bulk adhesion was adopted. A DMA method was optimised according to the principles of fracture theory testing, and proved to represent a good methodology for the measurement of ODF tack. As ODFs dissolve in the mouth, and change their physical properties, ODF sample tack was measured at several time points for each sample. The resulting data allowed the identification of an adhesive force profile that described how ODF tack changed over time (chapter 3). However, the goal of the present study was to identify an *in vitro* method that could predict the end-user acceptability of the perceived ODF stickiness. In this respect, the adhesive force profile taken as it was, could not provide information on acceptability. In order to investigate the correlation between tack data and acceptability of the perceived ODF stickiness, the selection of a specific time point on the adhesive force profile would not be ideal.

4.1.1 The contribution of residence time to the oral perception of stickiness

In a study conducted by Hutchings and colleagues on food processing, several volunteers were presented with samples of whole and blended cashew nuts. Volunteers were asked to chew, and rate the stickiness intensity of the samples over time on a 9 points score system [195]. Hutchings found that the stickiness intensity of whole cashew samples rose over time and was rated less intense, on average, than the blended cashew samples. In addition, the total duration of the assessment (mastication time) was significantly shorter for blended cashews. Based on Hutchings' data, an existing relationship seems to exist between stickiness perception, degree of oral processing, and processing time. In broad terms, the perception of the physical and rheological

properties of foods changes over time, and the perception of food texture, and palatability should be always assessed in relation to time [138]. In particular, the adhesiveness of foods changes over time during mastication [196]. Very likely, ODFs are no exception to this rule, and disintegration time might play a significant role in the perception of ODF stickiness *in vivo*. For this reason, ODF disintegration time was introduced as a variable in the calculation of perceived ODF stickiness acceptability.

4.1.2 Other mucoadhesion theories potentially involved in the adhesion between ODF and DMA plates

The fracture theory might not be the only theory of mucoadhesion explaining the ODF adhesion phenomenon. The impossibility to carry out some testing method to verify some mucoadhesion theories (e.g. wetting theory) was discussed in chapter 3. Other mucoadhesion theories can be excluded from influencing the ODF/DMA plates system. For example, the diffusion theory describes how the adhesive bond forms because of the interdiffusion and interaction of molecular chains between two surfaces [126]. Unless intentionally functionalised, the surface of stainless steel does not normally have long molecular chains attached to its surface, therefore making the interdiffusion process impossible. There might be a certain degree of diffusion of the polymeric chains on the ODF side, however the type of interaction with the metallic plate must be different. Also, mechanical interlocking mechanisms are unlikely to be involved, as the surface of the stainless steel plates is very smooth and non-porous. Differences in the electronic structure of the two surfaces may play a role in the adhesive bond formation, as could the formation of hydrogen bonds and van der Waal's forces. Therefore, the electronic and adsorption theories are worth exploring.

4.1.3 Testing of the adsorption and electronic theories in the DMA system

Since no experimental methods have been specified for the testing of the adsorption and electronic theories, a method was designed and implemented. In order to understand what type of chemical bonds/interactions were involved in the ODF/DMA plate adhesion phenomenon, polymeric films with different molecular weights, charges, polar properties, excipients, and amounts of loaded drug were tested.

4.1.3.1 Assessment of potential chemical bonds involved in ODF samples adhesion

A set of two polymeric species, each in two molecular weight variants were tested in chapter 3, in order to assess the suitability of the DMA and other methods for tack measurement, and end-user acceptability prediction. Such set of polymeric ODF samples suggested that a potential correlation between ODF tack and polymeric molecular weight existed. A confirmation of such finding could suggest that the strength of the adhesive bond increases with the length of the polymeric chain, and could therefore be dependent on the type and number of substitution groups specific to the polymeric species analysed. In turn, this could mean that there is a cohesive component involved in the adhesive bond, which strength could depend on the number of substitution groups interacting with each other [197], assuming that the number of substitution groups interfacing with the metallic plate is the same, regardless of the chain length. If only one substitution group is present in the polymeric species, it would theoretically be possible to understand the contribution of such group in both intermolecular and interfacial forces. An ideal polymer for such test would be the poly(vinyl) alcohol (PVOH) because of its availability in a range of molecular weight at the same degree of substitution, and because of the presence of hydroxyl groups only.

4.1.3.2 Assessment of the role of polymeric charge in ODF samples adhesion

In order to assess the role of charged molecules in ODF adhesion, two polymers of opposite charges should be tested. Several polymers are known to be positively charged, however their solubilisation could be challenging, and their film-forming capability is not always good. Eudragit E PO® is a good film-forming, cationic polymer that is soluble in acidic solutions, and is often used as coating and taste masking agent (manufacturer recommendations). It was therefore chosen as a positively-charged polymer, after full ionisation was induced. Carboxymethylcellulose is a negatively-charged derivative of cellulose, however its net charge depends on the solution it is dissolved in. Fully ionised carboxymethylcellulose (CMC) can be obtained by appropriately increasing the pH of the solution. A direct comparison between negatively-charged CMC, and positively-charged Eudragit E PO® ODF samples could further inform on the contribution of polymeric charge on ODF adhesion.

4.1.3.3 Assessment of the role of polymeric polar properties in ODF samples adhesion

Hydrophobic polymers can also be used as film-forming agents to load poorly soluble drugs in the ODF platform [198]. Testing a hydrophobic polymer, in comparison with a hydrophilic polymer could provide useful information as to whether hydrophobic interactions contribute to the adhesive bond. However, the addition of hydrophilic excipients is required for the film to form [198]. Therefore, the comparison could only be performed between ODF samples having the same composition, but differing in the presence or absence of the hydrophobic component. Kollicoat SR 30D® is a suspension of polyvinyl acetate (PVAc), polyvinylpyrrolidone (PVP), and sodium lauryl sulfate (SLS) that is frequently used for tablet coating (manufacturer instructions). If combined with a

PVOH polymeric solution, a film could be obtained, and compared with a second film only containing PVOH, PVP, and SLS.

4.1.3.4 Effect of the addition of excipients and drug on ODF samples adhesion

Poly(vinyl) alcohol proved to be a good film-forming polymer, and received different acceptability feedback from panel participants based on types differing in their polymeric molecular weight. Low molecular weight films were considered highly acceptable, whereas high molecular weight films received negative acceptability scores. Films made with both high, and low molecular weight PVOH can be optimised as placebo, and drug-loaded formulations by adding increasing concentrations of a model active pharmaceutical ingredient (API), in order to see how the additions have an effect on ODF tack. The optimisation of the formulations should be done in order to ensure acceptable mechanical properties, so that the films are capable to withstand the stresses related to manufacturing and handling.

4.2 Materials and methods

4.2.1 Materials

EMPROVE® PVOH 8-88 (83 kDa), and 18-88 (130 kDa), glycerol and sucralose were purchased from Merck Millipore (Darmstadt, Germany). Eudragit E PO® was provided by Evonik (Essen, Germany), whereas Kollicoat SR 30D®, and SLS (PVP 30 kDa) were kindly donated by BASF (Ludwigshafen, Germany). 4-Hydroxy-2,5-dimethyl-3(2H)-furanone (strawberry furanone), and glycerol were purchased from Sigma (Gillingham,

Dorset, UK). The composition of the simulated salivary fluid (SSF) is summarised in Tab. 3.1.

4.2.2 ODF sample preparation

An extended set of ODF samples were prepared by solvent casting. The formulation composition of samples is summarised in Tab. 4.1.

Table 4.1: ODF sample composition for tack analysis.

Sample code	P1	P3	P4	P2	E1	C1	C2	C3	H1	H2
PVOH	(39 kDa) 5%	(83 kDa) 5%	(130 kDa) 5%	(197 kDa) 5%	-	-	-	-	(39 kDa) 5%	(39 kDa) 5%
Eudragit® E PO	-	-	-	-	(150 kDa) 3.66%	-	-	-	-	-
CMC	-	-	-	-	-	(395 kDa) 1%	(725 kDa) 1%	(395 kDa) 1%	-	-
PVP	-	-	-	-	-	-	-	-	(30 kDa) 0.9%	(30 kDa) 0.9%
SLS	-	-	-	-	-	-	-	-	0.10%	0.10%
PVAc	-	-	-	-	-	-	-	-	9%	-
Glycerol (v/v)	-	-	-	-	-	-	-	-	-	-
Sucralose	-	-	-	-	-	-	-	-	-	-
4-Hydroxy-2,5-dimethyl-3(2H)-furanone	-	-	-	-	-	-	-	-	-	-
PSP (mg/film)	-	-	-	-	-	-	-	-	-	-
Solvent	water	water	water	water	water (8.46%) + hydrochloric acid (91.54 %)	water	water	water (77.12%) + sodium hydroxide (22.8%)	water	water
Casting volume (mL)	7.5	7.5	7.5	7.5	7.5	15	15	15	7.5	7.5

Table 4.1: (Continued).

Sample code	F1	F2	F3	F4	F5	F6	F7	F8
PVOH	(197 kDa) 5%	(197 kDa) 5%	(197 kDa) 5%	(30 kDa) 5%	(30 kDa) 5%	(30 kDa) 5%	(197 kDa) 5%	(197 kDa) 5%
Eudragit® E PO	-	-	-	-	-	-	-	-
CMC	-	-	-	-	-	-	-	-
PVP	(30 kDa) 1.26%	(30 kDa) 1.26%	-	(30 kDa) 0.63%	(30 kDa) 0.63%	(30 kDa) 0.63%	(30 kDa) 1.26%	(30 kDa) 1.26%
SLS	-	-	-	-	-	-	-	-
PVAc	-	-	-	-	-	-	-	-
Glycerol (v/v)	0.25%	0.25%	0.25%	0.25%	0.30%	0.30%	0.25%	0.25%
Sucralose	0.10%	-	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
4-Hydroxy-2,5-dimethyl-3(2H)-furanone	0.10%	-	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
PSP (mg/film)	-	-	-	-	1	5	1	5
Solvent	water	water	water	water	water	water	water	Water
Casting volume (mL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

PVOH-based samples with molecular weights 39 and 197 kDa were re-analysed by DMA, and compared with two intermediate molecular weights (83, and 130 kDa) to better understand the influence of molecular weight on ODF tack.

Fully-ionised positively-, and negatively-charged polymers were also analysed by DMA, in comparison with high- and low-molecular weight CMC films in order to understand the role of charged molecules in the adhesive bond. Eudragit® E PO is a cationic copolymer that can be solubilised in acidic solvents [199,200], whereas CMC is negatively charged, and it is not fully-ionised in water, however an increase in ionisation can be obtained in alkaline solvents [201]. To carry out a comparison, the same number of positive and negative charges per film area should be obtained. The number of charges per clamp area was approximately estimated by calculating the mass of polymer present on the clamp area, and then by dividing the polymeric mass by the molecular weight of the repeating unit (and the result multiplied by the degree of substitution (DS) for CMC [202]), in order to obtain the total number of moles of charges/clamp area. Then, the corresponding number of moles of acid or base were calculated in order to obtain full ionization of the charged substitution groups, and the corresponding volume of hydrochloric acid (HCl) or sodium hydroxide (NaOH) was added to the solvent.

To understand whether hydrophobic interactions also played a role in the adhesive bond between film and DMA clamp, two film formulations differing only in the presence of the hydrophobic polymer PVAc [203] were prepared.

The influence of a loaded drug on the tack of a fully optimised formulation was assessed by testing both high- and low-molecular weight PVOH formulations in their placebo version, and after the incorporation of 1, and 5 mg of the model drug Prednisolone Sodium Phosphate (PSP). Full-composition formulations were optimised by mechanical properties before being tested by DMA.

Taste, smell, and other attributes can have a significant influence on the perception of other mouthfeel characteristics [115]. Therefore, to assess whether the *in vivo* perceived stickiness of formulations containing sweetener and flavour, differed from

that of films mainly composed of polymers, ODF formulations F1, F2, and F3 (Tab. 4.1) were compared *in vitro* and *in vivo* for perceived stickiness acceptability.

4.2.3 Optimisation of the ODF sample formulation by mechanical properties

ODF sample tensile strength, elongation at break, and Young's modulus were measured using an Instron Universal Tester 5567 (Instron Ltd., Wycombe, UK), equipped with a 500 N load cell, and 1 kN capacity pneumatic grips. The ODF sample was cut to a specific type 3 dumbbell shape according to the international Standard EN ISO 37, and EN ISO 527 [204,205], with the following dimensions: overall length, 50 mm; length of the narrow portion, 16 mm; width of the wide ends, 8.5 mm; width of the narrow portion 4 mm [206]. The thickness of each sample was measured by microcaliper (Mahr Plc., Milton Keynes, UK), and entered as measurement parameter. Samples were positioned so that the distance between the grips was 16 mm (Figure 4.1), and the experiment was carried out by applying an uniaxial stress at a crosshead speed of 50 mm/min [207].

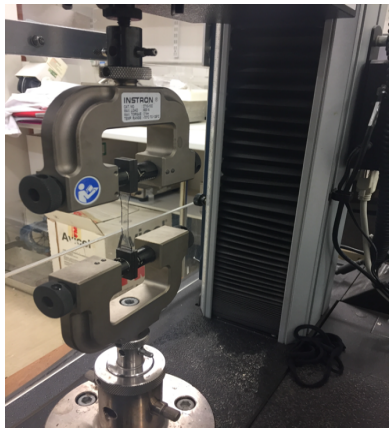


Figure 4.1: Sample positioning between the tension grips of the universal testing instrument.

A stress versus strain curve (Figure 4.2 a), and resulting parameters were visualised using Bluehill software v. 3 (Instron Ltd., Wycombe, UK).

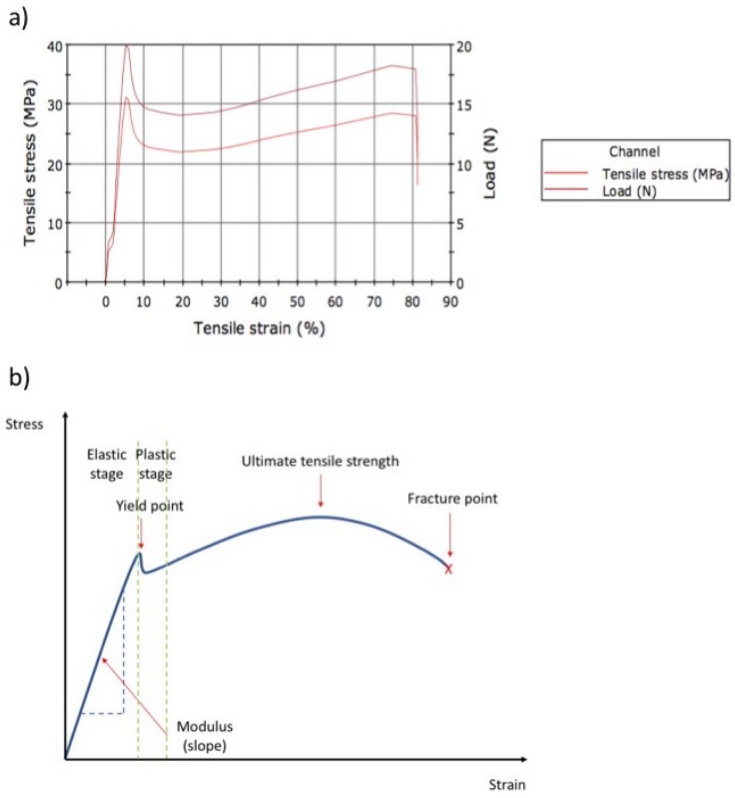


Figure 4.2: Example of a stress vs. strain curve obtained by testing a PVOH 197 kDa ODF sample (a). Interpretation of the stress/strain curve (b).

Tensile strength is the maximum tensile stress recorded at the sample breaking point [204,205] (Fig. 4.2 a,b). It is calculated with Equation 4.1 [78], where F_{max} is the maximum load applied, and A is the cross-sectional area of the film. The elongation at break is the change in sample length, or deformation, at the breaking point expressed in percentage, and it is calculated using Equation 4.2 [78], where ΔL is the difference between the initial and final length of the sample, and L_0 the initial length. The Young's modulus is an indication of the elasticity of the sample, and corresponds to the slope of the linear region of the stress/strain curve [78] (Fig. 4.3 b), and it is obtained by resolving Equation 4.3, where F is the force applied at corresponding strain, and ε is the strain.

Equation 4.1

$$Tensile\ strength\ (\sigma_B) = \frac{F_{max}}{A}$$

Equation 4.2

$$\%\ Elongation\ (\varepsilon_B) = \frac{\Delta L}{L_0} \times 100$$

Equation 4.3

$$Young's\ modulus\ (E) = \frac{F}{A} \times \frac{1}{\varepsilon}$$

4.2.4 *In vitro* tack assessment of ODF samples by DMA analysis

ODF sample tack was analysed using the same method described in chapter 3, with a slight modification. The liquid medium with which ODF samples were hydrated prior to tack measurement was a simulated salivary fluid (SSF), which composition was also described in chapter 3. Also, the adhesive force was measured more frequently at 10s, 30s, 60s, 90s, 120s, and 180s.

4.2.4.1 Analysis of data obtained from DMA-measured ODF samples adhesive force profiles for the calculation of the Area Under the Curve (AUC)

The adhesive force profiles of the four PVOH- and CMC-based single-polymer ODF samples could not be directly compared with *in vivo* data on perceived stickiness acceptability collected by human panel, as *in vitro* adhesive force was measured for the duration of the adhesive interaction between 0 and 240 seconds. Therefore, the Area Under the Curve (AUC) for adhesive force vs. time figure was calculated based on the disintegration time measured *in vitro* by drop method. X-axis values for AUC calculation were approximated to the closest time point assessed in the DMA experiment. For

instance, in the case of sample C1, the *in vitro*-measured disintegration time was 52 seconds, and hence the AUC was calculated between 0 and 60 s on the x axis (Fig.4.3).

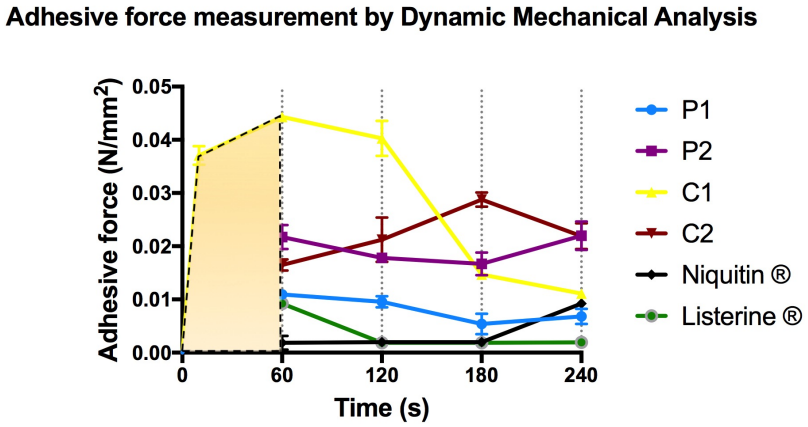


Figure 4.3: Example of AUC calculation of ODF samples. Integration was calculated for x values between 0 and the disintegration time measured in vitro by drop method (yellow area).

4.2.5 *In vitro* disintegration time assessment of ODF samples by drop method

The drop method was identified in chapter 3 as the most suitable *in vitro* method to measure ODF disintegration time, because the resulting data collected for samples P1, P2, C1, and C2 were the closest to the *in vivo* measurement compared to other *in vitro* methods. Therefore, the same experimental protocol was maintained with the only difference being the use of SSF instead of deionised water as disintegration medium.

4.2.6 Data analysis

Datasets were analysed using GraphPad Prism 7 (GraphPad Software Inc., La Jolla, US.). AUC was calculated using the approximated trapezoid rule. A One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test was conducted in order to identify statistically significant differences among sample AUCs.

Other normally distributed, continuous datasets were analysed using one-way ANOVA followed by Tukey's post hoc test. Linear regression was performed using the ordinary least squares method.

4.3 Results and discussion

4.3.1 Formulation optimisation of ODF samples by mechanical properties

Poly(vinyl) alcohol 197 kDa, and 39 kDa were respectively selected based on previously obtained *in vivo*, and *in vitro* data as examples of poorly-, and highly-acceptable film-forming polymers, and developed into full ODF formulations in order to understand how the addition of excipients, and different concentrations of API, influenced the *in vitro* predicted stickiness acceptability, and *in vivo* perceived stickiness acceptability (only placebo formulations were tested *in vivo*). Mechanical properties are very often measured as a quality control parameter when a new ODF formulation is developed [208], and are key quality discriminative parameter in the industrial setting ensuring that the ODF product is able to withstand mechanical stresses. The concentrations of the excipients were optimised based on the ODF sample mechanical properties, in order to satisfy the acceptable ranges specified by Visser et al., 2015, and Borges et al., 2016 [207,209] (Tab. 4.2).

Table 4.2: Acceptable ranges of ODF mechanical properties published by Visser et al., 2015, and Borges et al., 2016.

Mechanical property	Visser et al., 2015	Borges et al., 2016
Tensile strength (MPa)	>2	15-35
Elongation at break (%)	>10	5-40
Young's modulus (MPa)	<550	100-1500

4.3.1.1 Thickness measurement of ODF samples

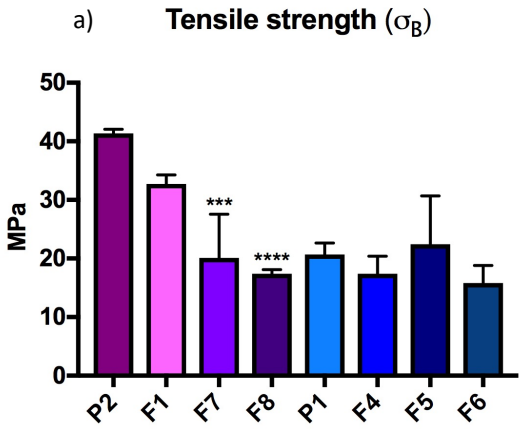
The thickness of the optimised formulations did not significantly differ between samples, and it maintained values between 90 and 105 μm. Single-polymer ODF samples had a thickness of 76-77 μm. Results are summarised in Tab. 4.3

Table 4.3: Thickness of single-polymer PVOH ODF samples, and optimised formulations (n = 3).

Sample	Thickness (μm)
P2	76.33 ± 6.63
F1	91.92 ± 3.61
F7	90 ± 3.99
F8	92 ± 5.97
P1	77.5 ± 2.36
F4	105 ± 7.56
F5	98.33 ± 4.49
F6	97.33 ± 7.43

4.3.1.2 Tensile strength

Tensile strength, elongation at break, and Young's modulus of ODF samples are presented in Figure 4.4 a, b, and c.



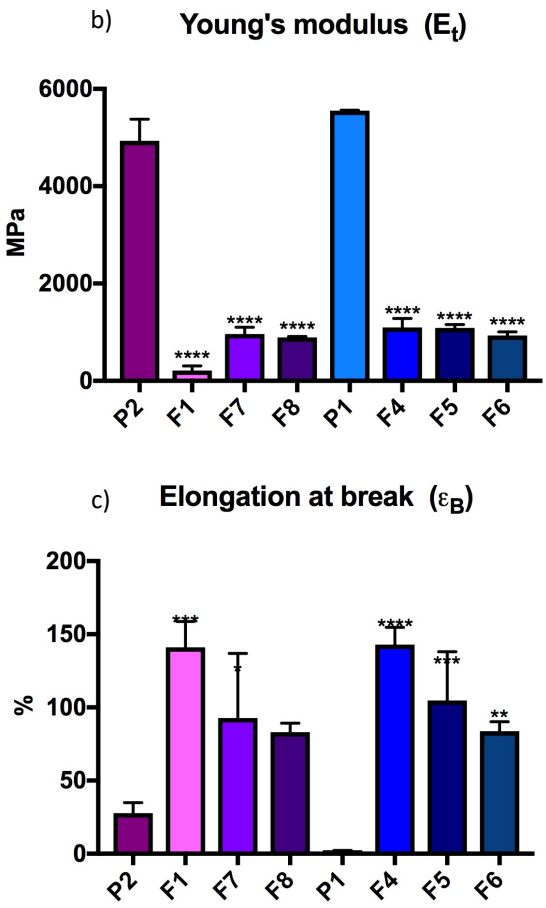


Figure 4.4: Tensile strength (a), Young's modulus (b), and elongation at break (c) of the optimised ODF formulations are compared with single-polymer ODFs (n = 3). Asterisks refer to statistical significance in comparison with the correspondent single-polymer ODF (F1, F7, F8 compared with P2; F4, F5, F6 compared with P1).

The highest tensile strength values were exhibited by the high-molecular weight single polymer PVOH (P2), followed by F1, with 41.36 ± 0.41 MPa, and 32.72 ± 0.89 MPa respectively. The lowest value of 15.82 ± 1.72 MPa belonged to sample F6. The tensile strength is an indicator of the robustness of the film in response to mechanical tensile stresses. P2 and P1, corresponding to high- and low-molecular weight single polymer PVOH films, differed considerably in tensile strength ($p<0.001$), suggesting that increasing molecular weight of the film-forming polymer can confer higher resistance to load. This behaviour has been observed by Nunes and colleagues, who explained that for molecular weights higher than 10^5 Da, the polymeric chains showed enough entanglement to exhibit a rubbery behaviour, therefore acquiring resistance to load [210] compared to lower molecular weights, however, the glass transition temperature (T_g) of

PVOH ranges between 70 and 90 °C. Significant differences were found between P2, and samples F7 ($p<0.001$) and F8 ($p<0.0001$), whereas no significant difference was observed with sample F1. The lack of difference in tensile strength between samples P2 and F1 suggests that the addition of plasticiser, known for its ability to lower the tensile strength of films [211,212], did not have a significant effect, or its influence was likely mitigated by other excipients, most likely of polymeric nature. On the contrary, the addition of PSP decreased significantly the tensile strength in a concentration-dependent way, in accordance to what observed by Visser [61]. There was no significant difference between P1, and F4, F5 or F6. The addition of excipients, and API seemed to have little effect on the tensile strength of the low-molecular weight PVOH samples. This might be due to the low-molecular weight of the film-forming polymer and the already poor ability of its chains to entangle with each other [210]. Visser, and Borges both published ranges of acceptable mechanical properties for orodispersible films [207,209] (Tab. 4.2), based on a quality-by-design study in the first case, and on measurements conducted on commercial products in the second. According to the tensile strength values reported in Borges et al., 2016, only sample P2 was outside the acceptable range, whereas all samples' tensile strength would be acceptable according to Visser et al., 2015. The value ranges reported in the two articles refer to marketed ODF formulations, including one or a blend of film-forming polymers, plasticiser(s), API(s), and possibly other excipients. It is therefore acceptable for the tensile strength of sample P2 to fall outside the acceptable limits. It is possible to affirm that all the placebo and drug-loaded formulations were successfully optimised according to tensile strength.

4.3.1.3 Young's modulus

The Young's modulus of single-polymer ODF samples was very high, indicating non-ideal elastic properties. The highest modulus of 5,551.0 ± 5.4 MPa was measured in sample P1, and the lowest modulus of 213.6 ± 54.2 MPa in sample F1. A considerable

difference was noticeable between single-polymer, and optimised samples, indicating that the addition of excipients, particularly the plasticiser, decreased the Young's modulus and improved elasticity [212]. Significant differences were observed between F1, and F7, F8, suggesting that PSP slightly increased the modulus, in accordance with the effect of PSP observed on different ODF formulations [61]. However, PSP loading seemed to have no influence on the Young's modulus of optimised formulations prepared from low-molecular weight PVOH. The Young's modulus is a measure of the recoverable deformation of a material, indicating the ability to re-gain the original shape after a stress is applied [213]. This property is tightly dependent on the properties of the material analysed, and does not necessarily correlate with other mechanical properties [210]. However, it depends on the flexibility of the polymeric atoms to move in dependence on the bonds with other atoms, and the empty space available around them [214]. As long as polymeric chains are prevented to slide past each other, and do not break bonds, the polymeric structure will recover its shape [214]. In this respect, the molecular interaction between long or short polymeric chains, and plasticiser and API, and the order in which the excipients were added to the mixture could have determined the difference observed between samples F1 and F4. In support of this finding, glycerol added to PVOH was reported to reduce the interactions between polymeric chains [212]. According to the mechanical property ranges specified by Borges (Tab. 4.2), all the moduli of the optimised formulations were acceptable, whereas those of single-polymer ODF samples were not. On the contrary, only the Young's modulus of formulation F1 would be acceptable if the more restrictive parameters reported by Visser were considered.

4.3.1.4 Elongation at break

A % elongation at break of 142.89 ± 6.89% was reached by sample F4, and it was the largest deformation detected among the analysed samples. The smallest deformation of 1.667 ± 0.33% was exhibited by sample P1. The % elongation of single-polymer films was very small, indicating brittleness, and poor resistance to deformation. Significant differences in elongation at break were found between F1 and P2 ($p<0.001$), between F7 and P2 ($p<0.05$), and between F4 and P1 ($p<0.0001$), F5 and P1 ($p<0.001$), and F6 and P1 ($p<0.01$). The % elongation at break is calculated from the strain at which a material breaks [215], and represents the ability of the material to resist changes without cracking, with high % values corresponding to highly deforming materials. The addition of excipients increased considerably the elongation of optimised formulations [212] in comparison with the single-polymer films, as opposed to the drug loaded formulations, where the addition of API that decreased the deformation [61] in a concentration-dependent manner. An anti-plasticising effect of drug-loaded API was reported by Buanz and colleagues [216]. The % elongation at break of none of the ODF formulations, except P2 would be acceptable according to Borges, whereas the deformations of all samples except P1 would be considered acceptable according to Visser.

4.3.1.5 Comparison with literature data

Solvent-cast PVOH films (DS 95.5%) 10% (w/v) were reported to have a tensile strength of 20 MPa, a % elongation of 300%, and a Young's modulus of 2,000 MPa [217]. A 150 μm thick, 10% w/v PVOH (133 kDa, DS 98%) film was reported to have a tensile stress of 105 MPa, a % elongation at break of approximately 100%, and a Young's modulus of 2,500 MPa [218]. A 78 kDa 5% (w/w) PVOH film (DS 87-89%) was reported to have a tensile strength of 14 MPa, and a % elongation at break of approximately 210% [219].

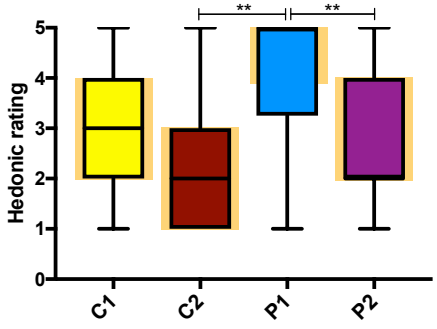
Mechanical properties data found in the literature differed from those exhibited by the tested PVOH-based formulations. A potential explanation could involve the lower concentrations, thickness, and potentially different polymeric molecular weights used in the present study compared to those used in the other literature works. In particular, the elongation at break and Young's modulus of samples P1 and P2 appeared outside the range reported in the literature data. This difference might be attributed to the lack of plasticising effect, which have prevented brittleness, and improved the elastic deformation component.

4.3.2 Tack assessment of ODF samples by DMA analysis

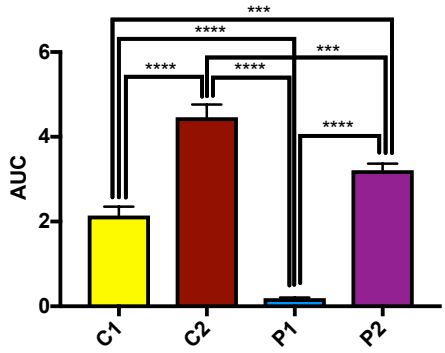
4.3.2.1 ODF samples AUC calculation and *in vivo/in vitro* correlation with perceived stickiness acceptability data

The calculation of the AUC led to the identification of a correlation with *in vivo* perceived stickiness acceptability scores assigned by pilot human panel participants. Results are shown in Fig. 4.5.

a) **Perceived stickiness acceptability measured *in vivo* - session 1**



b) **AUC calculated on adhesive force profiles measured by DMA**



c) **AUC / *in vivo*-measured perceived stickiness correlation**

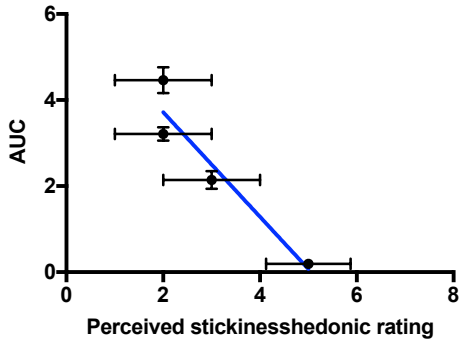


Figure 4.5: AUC values of four single-polymer ODF samples (a) (n = 3), compared with in vivo perceived stickiness PROs (b) (session 1), and linear regression of the two datasets (c). (R2=0.903; PRO data are from three sessions).

AUC values were calculated for the four single-polymer ODF samples. Statistically significant differences were identified between all samples (Fig. 4.5 a). An inverse correlation seemed to relate the hedonic rating on perceived stickiness reported by pilot human panel participants with the calculated AUC values. The higher the acceptability scores, the lower the AUC values (Fig. 4.5 a,b,c). The highest acceptability assigned to sample P1 also had the lowest AUC (5 $\pm$ 0.87, and 0.19 $\pm$ 0.12 respectively), whereas the lowest acceptability scores were assigned to samples P2 and C2 (2 $\pm$ 1.00), and the AUC values were 3.21 $\pm$ 0.92, and 4.46 $\pm$ 0.59 respectively. In this case the reliability of the linear regression model for the identification of an inverse correlation must be taken with care for two main reasons: the number of samples analysed was very little, and the two datasets were very different in nature, with the PROs scores being a categorical ordinal variable, and the AUC a continuous variable with residues not perfectly normally

distributed. Although this has not been identified as a precluding factor for using the Ordinary Least Squares (OLS) method to calculate linear regression [220], there are conflicting opinions on the topic. However, the preliminary regression analysis on the four single-polymer ODF samples paved the way towards a more extensive analysis that includes a higher number of samples. The identification of a correlation between perceived stickiness acceptability scores and AUC values also confirms the potential influence of disintegration time on the perception of ODF stickiness, as previously hypothesised.

4.3.2.2 Tack assessment of an extended set of ODF samples by DMA analysis

The extended set of samples was tested by DMA analysis in the same experimental conditions that were described in chapter 3, with the only different factor being the use of SSF instead of deionised water.

4.3.2.2.1 Effect of PVOH molecular weight on ODF samples tack

First, single-polymer, PVOH-based ODF samples were tested, in order to better understand the molecular weight effect on ODF tack. Results are presented in Figure 4.6.

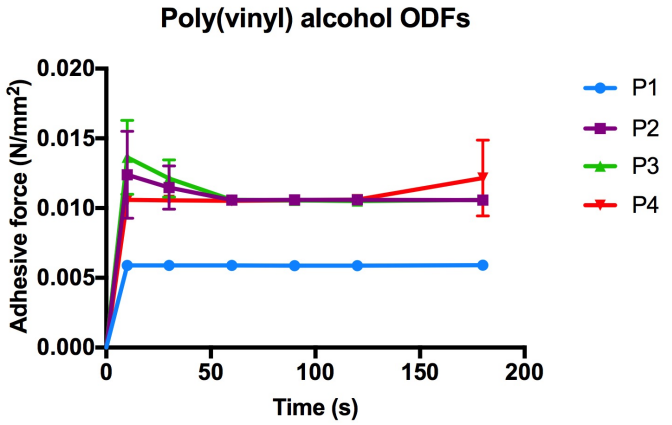


Figure 4.6: Adhesive force profile of PVOH 39 kDa (P1), 78 kDa (P3), 139 kDa (P4), and 197 kDa (P2) single-polymer ODF samples (n = 3).

The adhesive force of sample P1 in SSF immediately increased to 0.0058 ± 0.0005 N/mm^2 after 10s of hydration, and maintained the same values until the end of the assessment. Samples P2 and P3 increased to higher values at 10s (0.0123 ± 0.0003 N/mm^2, and 0.0136 ± 0.0005 N/mm^2 respectively), decreasing slightly to 0.0106 ± 0.0004 N/mm^2, and 0.0106 ± 0.0005 N/mm^2 from 60s until the end of the experiment. Sample P4 reached an adhesive force of 0.0106 ± 0.0002 N/mm^2, and maintained similar values until 180s. From the results obtained it appeared that the molecular weight of PVOH only influenced ODF tack above a certain threshold, while for molecular weights lower than 78 kDa, the force of the adhesive bond was relatively limited. A linear correlation between polymeric molecular weight and adhesion was reported by Gurney and colleagues, who assessed adhesion between styrene-butadiene copolymers, in wet conditions, and for contact times shorter than 10s [221], however, there is no information about a linear relationship existing between molecular weight and adhesion in PVOH. A difference in adhesive force values was also detected when samples P1, and P2 were tested in deionised water, however in that case, the values were consistently higher, potentially indicating that the presence of salts dissolved in the hydration medium could lower adhesion between polymer and steel plate [222].

4.3.2.2.2 Effect of polymeric charge on ODF samples tack

A fully-ionised Eudragit E PO ® positively-charged, a fully-ionised CMC negatively-charged, and high and low-molecular weight CMC ODF samples were tested in order to assess the involvement of charges in the adhesive bond between ODFs and DMA plates. Adhesive force profiles are plotted in Figure 4.7.

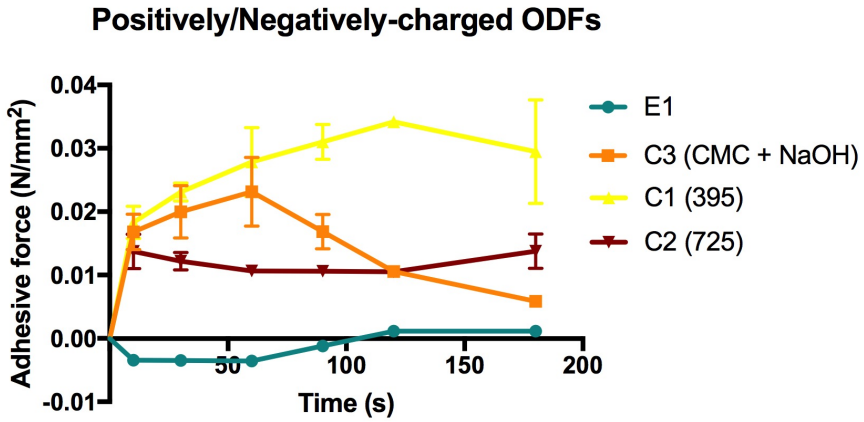


Figure 4.7: Adhesive force profiles of ionised Eudragit E PO (R) (E1), low-molecular weight CMC (C1), high-molecular weight CMC (C2), and fully-ionised, low-molecular weight CMC (C3) ODFs (n = 3).

The adhesive force of Eudragit ® film was characterised by an almost repulsive force, reaching negative values until 100s. Higher adhesive force values were exhibited by both fully-ionised CMC (max. adhesive force 0.0231 ± 0.0002 N/mm^2), and low-molecular weight CMC (max. adhesive force 0.0342 ± 0.0003 N/mm^2), with a decrease of the fully-ionised CMC adhesive bond strength after 60s of hydration. Takehara and Fukuzaki explored the adsorption behaviour of charged and unionised pectin on untreated and treated stainless steel [223]. They discovered that stainless steel treatment incrementing the availability of basic hydroxyl groups on the steel surface, favoured the adsorption of unionised pectin by bonding with pectin polar groups (-COOH, and -OH). They also found that the degree of ionisation of pectin influenced its affinity for the steel surface. The adsorption of ionised pectin molecules to the stainless steel surface was predominantly mediated by the formation of ion pairs at the contact

region, however, adsorption was pH dependent. At higher pH, ionised pectin molecules tended to develop intermolecular repulsive forces, preventing the formation of intermolecular hydrogen bonds, and thus the formation of compacted structures able to adhere to stainless steel by both adhesive and cohesive mechanisms [223]. The lack in cohesion might have negatively affected the strength of the adhesive bond. A similar event might have taken place in the present study. The low-molecular weight CMC was more free to establish hydrogen bonds with the stainless steel clamp, whereas its fully-ionised counterpart might have initially established ion pairs, in addition to the available hydrogen bonds. When the film began disintegrating, and the charged molecules became free to move in a high-pH environment, the more prominent repulsion between charges of the fully-ionised CMC and the consequent weakening of intermolecular cohesion might have caused the observed decrease in adhesive strength. It must be noticed how the standard error of the low-molecular weight CMC film adhesive force widens considerably at 180s. A potential explanation for this could be that the SSF used in the experiment has a pH of 7.4. This could mean that, as soon as the SSF gets in contact with CMC carboxyl groups, the lasts ionise, and the film decreases in cohesion, and thus in tack, due to the mechanisms previously explained. Moreover, the difference in adhesive force profiles between high- and low-molecular weight CMC films that was observed during the first DMA study (chapter 3) was confirmed, with an overall reduction of adhesive force values, and a delay in the peak adhesive force in sample C1. This difference could be attributed to the presence of dissolved salts in the SSF utilised.

4.3.2.2.3 Effect of hydrophobic polymers on ODF samples tack

Two ODF samples, one with, and one without the presence of the hydrophobic polymer PVAc were assessed by DMA. Adhesive force profiles are reported in figure 4.8.

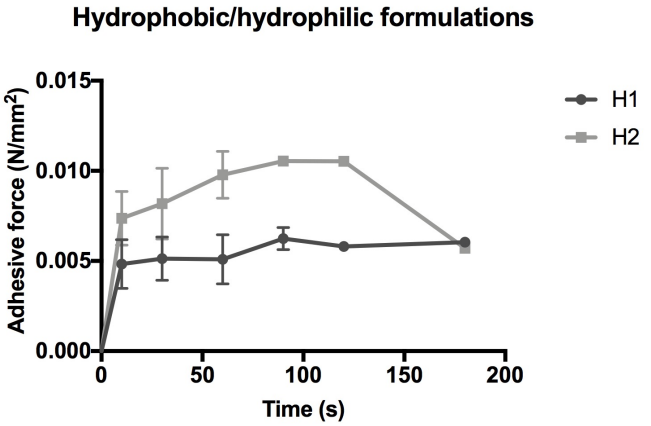


Figure 4.8: Adhesive force profiles of ODF sample containing PVAc (H1), and ODF sample without PVAc (H2) (n = 3).

The two ODF formulations differed only in the presence of PVAc. The adhesive force of both films tended to slightly increase over time, and to decrease at initial values at 180s. However, consistently higher adhesive force values were exhibited by the hydrophilic film, suggesting that the presence of hydrophobic excipients weakened the adhesive bond between films and steel plate. Stainless steel is considered hydrophilic, with contact angles of approximately 90° [224]. It is no surprise, then that hydrophobic interactions are unlikely to be involved in the adhesive bond between ODFs and DMA plates. It is therefore possible that the hydrophobic component of sample H1 had contributed to decreased adhesion by reducing the area of the hydrophilic polymer available to form hydrogen bonds with the stainless steel surface.

4.3.2.2.4 Effect of excipients on ODF samples tack

No significant difference was observed when the adhesive force profile of a placebo optimised formulation containing a combination of two polymers, plasticiser, sweetener, and flavour was compared with that of the same formulation deprived of sweetener and flavour, or deprived of part of the polymeric component (Fig. 4.9).

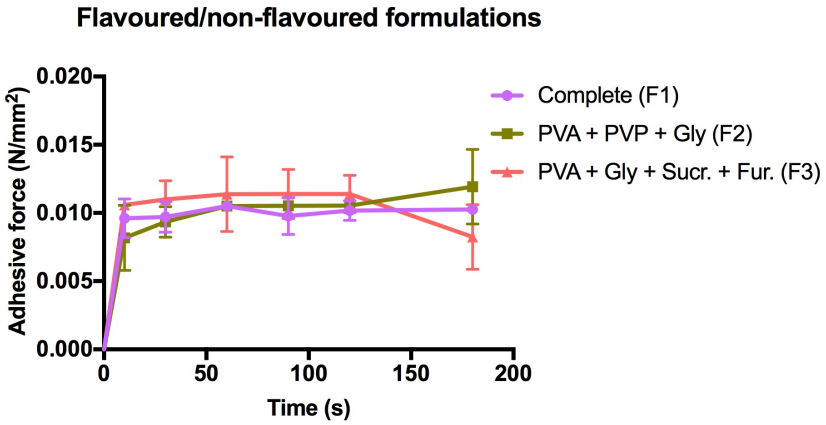


Figure 4.9: Adhesive force profile of PVOH (high m.w.) optimised formulation (F1), polymers and plasticiser ODF sample (F2), PVOH, plasticiser, sweetener, and flavour ODF sample (F3) (n = 3).

The adhesive force values of all three samples were in the range of 0.010 N/mm^2, and did not change significantly for the whole experiment. The adhesion profile was also consistent with that of the single-polymer ODF samples prepared with high-molecular weight PVOH (P2) (Fig. 4.6). The rationale behind this experiment was to assess whether any difference in adhesion behaviour was observable *in vitro* among the three samples, and if the presence or absence of palatability-enhancing excipients such as sweetener and flavour could influence the perception of ODF stickiness in *in vivo* experiments. The relevant results will be given in chapter 5.

4.3.2.2.5 Effect of drug loading on ODF samples tack

Optimised placebo formulations were compared with correspondent formulations drug-loaded with 1mg or 5mg PSP. The formulations were optimised from the highly-acceptable film-forming polymer (PVOH 39 kDa), and the poorly acceptable film-forming polymer (PVOH 197 kDa), based on the participant-reported outcomes (PROs) obtained from the pilot human panel. Adhesive force profiles are presented in Fig. 4.10.

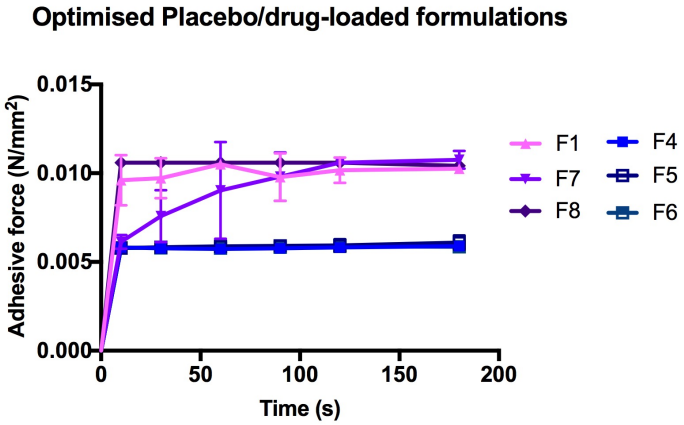


Figure 4.10: Adhesive force profile of PVOH 197 kDa placebo formulation (F1), and drug-loaded with 1mg (F7), and 5mg (F8) PSP; and adhesive force profile of PVOH 39 kDa placebo formulation (F4), and drug-loaded with 1mg (F5), and 5mg (F6) PSP (n = 3).

The adhesive force values of both the formulation families did not change significantly over time, and were consistent with the profiles of the corresponding single-polymer ODF samples (Fig. 4.6). Only sample F7 seemed to deviate from the adhesive force profile of samples F1, and F8, with values increasing more slowly over time. However difference with F1, and F8 were not significant. The addition of excipients (samples F1 and F4), and of increasing concentrations of API did not seem to affect the tack of ODF samples in any way, underlining the relevance of the appropriate selection of the main film-forming polymer for the development of highly-acceptable ODF products.

4.3.3 *In vitro* assessment of ODF samples disintegration time

The disintegration time of the analysed ODF samples was assessed by drop method. Results are summarised in table 4.11.

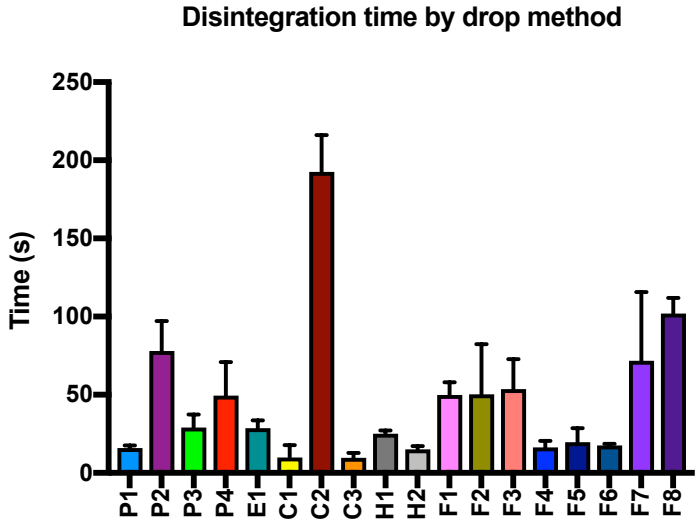


Figure 4.11: In vitro ODF samples disintegration time measured by drop method (n = 3).

The *in vitro* disintegration time of the single-polymer PVOH-based ODF samples increased according to molecular weight, however only the difference between P1 and P2 was statistically significant ($p<0.01$), and both disintegration times were similar to those reported in chapter 3. Sample E1 quickly broke where the drop was located, however the SSF did not form a round-shaped hole as it did for other samples. A potential explanation for this behaviour could reside in the insolubility of Eudragit E PO ® at high pH. Probably, the SSF (pH 7.4) was able to dissolve the film only until the pH of the film was sufficiently concentrated, allowing just the time to break the surface in its weakest points. As soon as the SSF neutralised the pH, Eudragit E PO ® was no longer solubilised, and the erosion process was halted. Samples C1 and C2 differed considerably in disintegration time ($p<0.0001$), and even though the disintegration time of sample C2 was similar to that reported in chapter 3, sample C1 disintegrated slightly faster. Sample C3 disintegrated almost as fast as sample C1, which was expected

since the two ODF samples were made with the same polymer. Sample H1 disintegrated in 25.1 ± 1.3 s, however the drop could fall because the surface of the film was broken in correspondence of the drop without the typical round-shaped erosion front formation. Such observation could be explained by the formation of areas of the ODF surface more concentrated in hydrophilic polymer, and functioning as "tunnels" for the passage of liquids. Thus, instead of the concentric progression in surface erosion typical of hydrophilic polymers, a cut through the surface was observed instead. H2 disintegrated faster than H1, thanks to the lack of hydrophobic polymer. F2 disintegrated much slower than F1, and F3, however the difference in disintegration time was significant only against sample F3 ($p<0.01$). It appeared that the presence of polyvinylpyrrolidone (PVP) and absence of sucralose and furanone had the effect of prolonging F2 disintegration time. No significant difference was observed between F1, F7, and F8, and between F4, F5, and F6, indicating that the addition of API did not affect the disintegration time.

4.4 Conclusions

The calculation of the AUC represented a quantitative predictive method to estimate the perceived stickiness acceptability of ODFs. A linear correlation was found between AUC and acceptability scores assigned by participants to four single-polymer ODF samples assessed *in vivo* and *in vitro* in chapter 2 and 3 respectively. An extended set of ODF samples were formulated, and some of them optimised by mechanical properties before their adhesive force profiles were studied by DMA. The molecular weight of the film-forming polymer, as well as the addition of the model drug prednisolone sodium phosphate (PSP) affected the tensile strength and elongation at break of ODF samples, however only the addition of excipients and PSP influenced the Young's modulus. With regards to the type of interactions contributing to the adhesive bond forming between ODF samples and the stainless steel plate of the DMA

equipment, hydrophobic interactions were excluded, and negatively and positively-charged polymers were found to inhibit, or even impairing adhesion. The addition of increasing concentrations of PSP did not influence the strength of the adhesive bond, although the molecular weight of PVOH seemed to determine the tack of the ODF sample, regardless the presence of other excipients. This suggested that, by appropriately selecting the film-forming polymer, it might be possible to determine the stickiness acceptability of the final ODF product. There was no linear relationship between PVOH molecular weight and ODF tack, but rather a threshold-dependent mechanism, where below a certain molecular weight (39 kDa), the adhesion of ODFs is limited. Disintegration time of the analysed ODF samples was measured by the drop method, in order to serve as parameter for the calculation of the AUC. As expected, the disintegration time of PVOH samples increased according to the polymeric molecular weight. A marked difference between high, and low-molecular weight partially-ionised CMC samples was confirmed from the previous *in vitro* study, whereas fully-ionised polymers disintegrated relatively fast. The hydrophobic component caused the sample to become insoluble, as opposed to its hydrophilic counterpart. The addition of API only influenced the disintegration time of ODF samples based on high-molecular weight PVOH, but not those based on low-molecular weight polymer. The addition of plasticiser, sweetener, and flavour tended to shorten the disintegration time of ODF samples. Considered together, all the DMA study pointed to the importance of polar interactions in the adhesion between ODFs and DMA plates, confirming that the adsorption theory, in addition to the fracture theory, is one of the adhesion mechanisms more likely to describe the observed ODF tack phenomenon. Phenomena explained by the electronic theory seemed, on the other hand, to have a limited influence on the bonding between negatively-charged fully-ionised CMC, and metallic plate, and no influence at all in the case of positively-charged polymers. In order to confirm that the calculation of AUC from DMA adhesive force profiles can in fact predict *in vivo* perceived stickiness acceptability, some samples that were tested *in vitro* will be assessed *in vivo* by a second human panel. Unfortunately, some key ODF samples

such as those made from fully-ionised positively, and negatively-charged polymers were characterised by an extreme pH, making them not suitable for human consumption. Thus, such samples cannot be further analysed *in vivo* by a human panel. However, differences in adhesive characteristics between DMA and human mouth will be assessed, with regards to the role of polar interactions, hydrophobic interactions, and the effect of excipients in the perception of stickiness, in chapter 5.

Chapter 5. Assessment of the *in vitro/in vivo* correlation of ODF perceived stickiness acceptability

This chapter describes the *in vitro/in vivo* correlation between the area under the curve (AUC) values calculated from the tack data previously collected on an extended set of orodispersible films (ODF) samples, and the perceived stickiness Participant-Reported Outcomes (PROs) obtained by a second human panel. The extended set of samples tested included single-polymer films made with four poly(vinyl) alcohol (PVOH) molecular weights, one sample with the hydrophobic polymer polyvinyl acetate (PVAc), and one having the same composition except PVAc. Furthermore, an optimised placebo ODF formulation, and its corresponding high polymer/excipients ratio, and low polymer/excipients ratio were tested. Healthy adults were recruited and were asked to assess ODF samples perceived size, perceived thickening effect, perceived thickness, perceived stickiness, and perceived disintegration time. The same study design was maintained from the pilot human study in chapter 2, whereas the intensity of the ODF sample perceived thickening effect, and perceived ODF sample stickiness intensity was measured on a five-point score system. *In vivo/in vivo* correlation was calculated between the comfort/discomfort, and intensity PROs of the perceived thickening effect and perceived stickiness attributes. The AUC of the tested samples was calculated from the tack data previously collected by DMA, and using the disintegration time measured *in vitro* by drop method. Subsequently, the *in vitro/in vivo* correlation with the perceived stickiness PROs was calculated. The correlation resulted non-linear, and the PROs from other attributes, and from the semi-structured interview suggested the existence of a potential influence of other ODF attributes on stickiness perception. The utilisation of *in vitro*-measured disintegration time by drop method for the calculation of AUC values showed an underestimation of the latest, indicating that a more accurate *in vitro* disintegration time method needs to be optimised.

Aims:

- To confirm *in vitro/in vivo* correlation between predicted and perceived ODF disintegration time and stickiness acceptability.
- To identify the influence of other acceptability attributes in the perception of ODF stickiness

Objective:

- To conduct a second human panel to evaluate *in vivo* the acceptability attributes of the extended set of ODF samples previously assessed *in vitro* in chapter 4.

5.1 Introduction

5.1.1 Selection of ODF samples for *in vivo* assessment by a second human panel

In the previous chapter, a correlation was found between the AUC calculated from the samples' adhesive force profile measured over time, and the perceived stickiness PROs of the pilot human panel. The number of samples tested was limited, and in order to explore the adhesion mechanisms involved in the DMA experiment, purposely-formulated ODF samples needed to be analysed. Four different molecular weights of PVOH, a fully-ionised carboxymethylcellulose (CMC), and Eudragit E PO®-based ODF samples were analysed for tack by DMA. In addition, the tack of an ODF sample containing the hydrophobic polymer PVAc and its corresponding formulation without PVAc, of two complete ODF formulation loaded with different concentrations of prednisolone sodium phosphate (PSP), and of a complete ODF formulation with and with different polymer-to-excipient ratios was also analysed *in vitro*. In this chapter some of the samples that were assessed for adhesive force by DMA are also selected

for acceptability assessment in a second human panel, in order to confirm whether an *in vivo/in vitro* correlation exists between the calculated AUC and PROs for ODF perceived stickiness. Due to safety reasons, some of the samples analysed by DMA could not be assessed *in vivo*, preventing from formulating a hypothesis on the mucoadhesion theories most likely to contribute to the adhesion between ODFs and human palate. Due to the extreme pH and the presence of corrosive material, the fully-ionised positively, and negatively-charged ODF samples were not given to the panel participants. CMC-based ODF samples were also not given to participants because they were already tested in the pilot human panel, and thus they would have represented an unnecessary burden. Due to the presence of an active pharmaceutical ingredient, also the drug-loaded ODF formulations were not given to participants.
The remaining samples eligible for *in vivo* administration corresponded to the four single-polymer PVOH-based samples, the two samples with and without a hydrophobic polymeric component, and the optimised high-molecular weight PVOH samples containing all the excipients, or with a high or low polymer-to-excipients ratio.

5.1.2 Selection of ODF attributes to be investigated based on the results of the pilot human panel

From the results of the pilot human panel conducted on 24 healthy adult volunteers, key ODF acceptability attributes, and manufacturing variables influencing the end-user acceptability were identified. The main attributes potentially influencing the end-user acceptability were tested for acceptability, and intensity where possible, by using a five-point hedonic facial scale, and a four-point ranking system respectively. The acceptability of the perceived ODF thickness, perceived stickiness, and perceived disintegration time varied among the four samples, and were therefore identified as potentially influencing attributes. The same attributes were investigated in the second human panel on a different set of samples. Perceived size was also analysed as a

negative control attribute. More information on ODF attributes affecting acceptability was collected by means of a semi-structured interview conducted at the end of each sample assessment. In addition to samples perceived thickness, stickiness, and disintegration time, attributes such as taste, a “drying”, or thickening effect on saliva, stiffness, brittleness, tendency to fold/form lumps, and sample thickness inhomogeneity were reported by participants as requiring improvement. Samples’ thickness inhomogeneity could have been related to the in-house manufacturing method lacking of a levelling knife, while the tendency to fold and form lumps could have been an intrinsic characteristic of polymeric thin films, and the result of ODF manipulation in the mouth. On the other hand, the stiffness, the brittleness, the drying and thickening effects could represent relevant attributes for their potential to influence the end-user acceptability. The drying effect was not specifically investigated in this chapter because of the small number of volunteers who reported it in the pilot panel interview. The perceived thickening effect was investigated for its comfort/discomfort and intensity in the second human panel, although from the pilot semi-structured interview, only CMC-based samples seemed to receive reports of such effect. Perceived thickening effect was investigated in the second panel, despite the absence of CMC-based ODF samples, because the use of other film-forming polymers or the addition of excipients to PVOH-based formulations could have contributed to such mouthfeel attribute. Similarly, the perceived ODF stiffness seemed to only affect PVOH-based samples. Perceived ODF stiffness is an attribute directly related to the mechanical properties of a material [225], rather than to its physicochemical properties. Assuming that fully optimised formulations accessing the market should meet certain standards in terms of mechanical properties, it is probable that their perceived stiffness should also be optimised. As a consequence, perceived stiffness was not specifically assessed in the second panel. In order to obtain more information on the tested ODF samples, a semi-structured interview was carried out in a similar structure as that used in the pilot human panel.

5.1.3 Expected findings from the selected set of ODF samples

The *in vitro/in vivo* correlation for the comfort/discomfort response, and the intensity of the perceived thickening effect and perceived stickiness, and perceived disintegration time should inform whether a direct correlation exists between the two variables or if there is an influence of other parameters/attributes.

An important outcome expected from the second human panel would be the verification of whether an *in vitro/in vivo* correlation exists between the calculated AUC values, and PROs on ODF sample perceived stickiness. The AUC values will be calculated using the adhesive force profiles measured by dynamic mechanical analysis (DMA), and the disintegration time measured *in vitro* by drop method.

Another potential source of information regards the suitability of existing *in vitro* methods for the measurement of ODF disintegration time, and consequently, for the calculation of AUC without the need of obtaining human data. The drop method proved to be the best methodology to accurately measure ODF disintegration time *in vitro* of the four samples analysed in chapter 2. The same method was used to calculate the AUC values of the extended set of samples in the present chapter. AUC values obtained with samples disintegration time measured by drop method will be compared with the AUC values obtained from the real disintegration time measured *in vivo* in order to evaluate the suitability of the drop method for AUC calculation.

Due to the limitations in the number of ODF samples that can be tested *in vivo*, it is likely that the role of positive or negative charges in the adhesion between ODF and human palate will not be investigated. Instead, the role of hydrophobic interactions are aimed to be investigated.

Finally, the influence of flavouring and sweetening agents added to the ODF formulation on the perception of stickiness and overall acceptability will be assessed [226,227].

5.2 Methods

5.2.1 Human panel on healthy young adults

5.2.1.1 ODF acceptability study

A second single-centre, single-blind human panel was conducted on healthy young adults. The study was conducted in a single session, as no substantial difference in PROs was observed between the three sessions in the pilot human panel (chapter 2). However, samples containing sweetener and flavour, and unsweetened, unflavoured samples were presented to participants in separate days. Therefore, participants were asked to attend both days. The study was approved by the University College London Research Ethics Committee (REC ID 8249/002) on 29th November 2016 (Annex 2). Data collection, handling, and storage were conducted in accordance with the Data Protection Act 1998, after permission was obtained by the University College London Data Protection Office (Data Registration Number: Z6364106/2016/10/51). Volunteers were informed about the study details and potential hazard/risks involved by receiving the Participant Information Sheet (PIS), and, verbally, immediately before the study. Informed consent was signed by all participants prior to the assessment (Annex 2).

5.2.1.2 Sample size, and inclusion/exclusion criteria

Healthy volunteers aged between 20 and 49 years (median age 25 years) were recruited. Of 24 participants recruited, 18 were females, and 6 were males. The sample size was estimated by nomogram-assisted calculation based on the data obtained from the pilot human panel, according to the method described by Jones and

co-workers [228]. The sample size for a 95% confidence level and a power of 0.9 was estimated to be between 20 and 24 participants (depending on the item assessed). A power level of 0.9 was selected to ensure avoidance of type II error considering that the study:

- Did not involve any drug-related safety trial or evaluation of efficiency of a medical-related screening method. Hence the selected power level could exclude the most restrictive parameters such as 0.95 or 0.99.
- The statistical tests used were non-parametric, therefore the power level should have been increased compared to parametric analyses.

It was concluded that a sample size of 24 was sufficient for the parameters specified. Inclusion/exclusion criteria were maintained identical from the pilot human study. Male and female volunteers able to understand and speak English could take part to the study. Volunteers were excluded if they had received dental care in the 15 days preceding the study, or anaesthetics into the mouth in the 24 hours preceding the study. Also, volunteers taking medicines altering salivation, or with any known hypersensitivity to excipients, or affected by sensory disorders of the mouth were excluded.

5.2.1.3 Study design and data collection

The study design, and flow chart were maintained similar to those of the pilot human panel, with slight modifications to the questionnaire. Each participant received six ODF samples in the first session (P1, P2, P3, P4, H1, and H2), and three in the second session (F1, F2, and F3) in a randomised order (Tab. 5.1). Comfort/discomfort assessment was carried out by participants for attributes such as size perceived in the mouth, thickness perceived in the mouth, stickiness perceived in the mouth, perceived

disintegration time, and thickening effect perceived on saliva, on a five-point hedonic facial scale, and data was collected as PROs. The intensity of the perceived stickiness, and thickening effect were evaluated by participants on a five-point scale ranging from non-sticky/thickened to extremely sticky/thickened. A multiple choice question was used to ask participants whether the ODF sample disintegrated in less than one minute, between one and three minutes, or in more than three minutes, however participants were also required to report the precise disintegration time as it appeared on the stopwatch display. Researcher-Reported Outcomes (RROs) were obtained by researchers using the same method and score point system adopted for the pilot human panel (chapter 2). Briefly, during sample intake, researchers assessed the facial expression, jaw movements, and intake performance of the participants, on a 2-point score system. A semi-structured interview after the assessment of each sample was carried out, and the same questions of the pilot human panel were asked. In addition, participants were asked about their willingness to take the assessed sample every day, if it was a medicine.

Table 5.1: Codes and composition of ODF samples for human panel study.

Sample code	P1	P3	P4	P2	H1	H2	F1	F2	F3
PVOH	(39 kDa) 5%	(83 kDa) 5%	(130 kDa) 5%	(197 kDa) 5%	(39 kDa) 5%	(39 kDa) 5%	(197 kDa) 5%	(197 kDa) 5%	(197 kDa) 5%
Eudragit® E PO	-	-	-	-	-	-	-	-	-
CMC	-	-	-	-	-	-	-	-	-
PVP	-	-	-	-	(30 kDa) 0.9%	(30 kDa) 0.9%	(30 kDa) 1.26%	(30 kDa) 1.26%	-
SLS	-	-	-	-	0.10%	0.10%	-	-	-
PVAc	-	-	-	-	9%	-	-	-	-
Glycerol (v/v)	-	-	-	-	-	-	0.25%	0.25%	0.25%
Sucralose	-	-	-	-	-	-	0.10%	-	0.10%
4-Hydroxy-2,5-dimethyl-3(2H)-furanone	-	-	-	-	-	-	0.10%	-	0.10%
PSP (mg/film)	-	-	-	-	-	-	-	-	-
Solvent	water	water	water	water	water	water	water	water	water
Casting volume (mL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

5.2.1.4 Data and statistical analysis

Hedonic scale, and Medicines Acceptability Scale (MAS) data were converted, and analysed as in the pilot human panel with the exception of the ODF perceived stickiness, and thickening effect intensity evaluation. The intensity of the perceived ODF sample stickiness, and thickening effect were converted into numerical values with non-sticky/thickened = 1, and extremely sticky/thickened = 5, and analysed as categorical ordinal variables (Tab. 5.2).

Table 5.2: Five-point score system used for the in vivo assessment of the perceived thickening effect intensity, and perceived stickiness intensity of ODF samples.

Word scale for perceived thickening effect intensity	**Not thickened**	**Slightly thickened**	**Moderately thickened**	**Strongly thickened**	**Extremely thickened**
Word scale for perceived stickiness intensity	Non-sticky	Slightly sticky	Moderately sticky	Strongly sticky	Extremely sticky
Corresponding assigned score	**5**	**4**	**3**	**2**	**1**

The actual disintegration time was treated as continuous variable. The yes/no answer about the willingness of participants to take the ODF sample every day was analysed as frequency distribution. Friedman's test followed by Dunn's multiple comparisons post hoc test (Prism 7, GraphPad Software Inc., La Jolla, US.) was used to calculate differences between samples for categorical variables, whereas one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test was used to assess differences among samples (Prism 7, GraphPad Software Inc., La Jolla, US.).

5.2.2 Data analysis for *in vivo/in vitro*, and *in vivo/in vivo* correlation

AUC values were calculated from the DMA data obtained in chapter 4, and analysed using the same method. *In vitro/in vivo* correlation, and *in vivo/in vivo* correlation were assessed by linear regression calculation using the ordinary least squares method, and by Spearman r correlation coefficient (Prism 7, GraphPad Software Inc., La Jolla, US.).

5.3 Results and discussion

5.3.1 Human panel on the mouthfeel evaluation of ODF

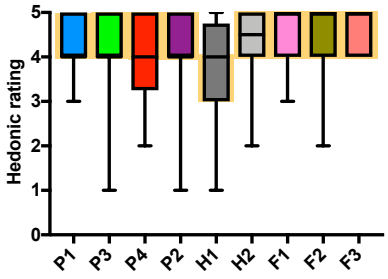
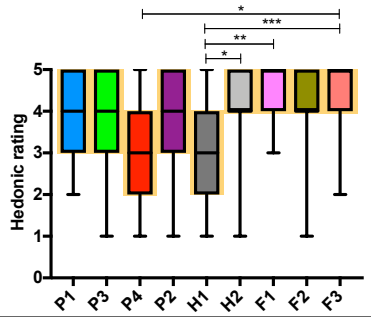
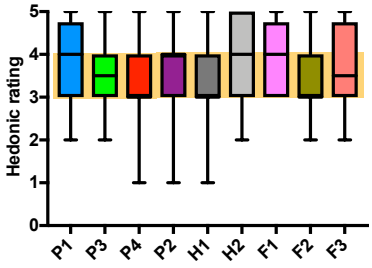
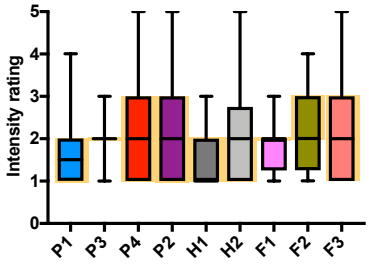
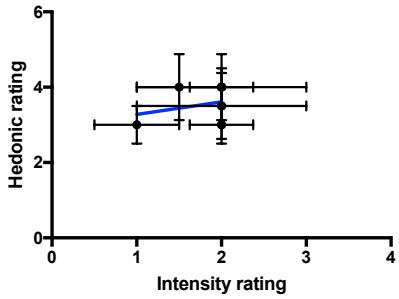
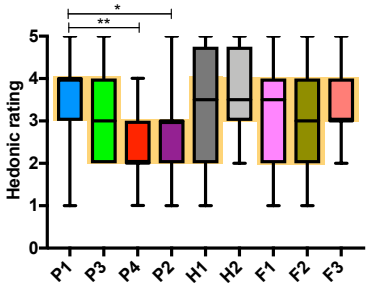
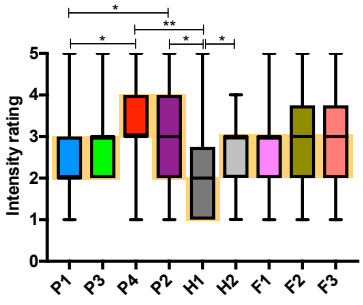
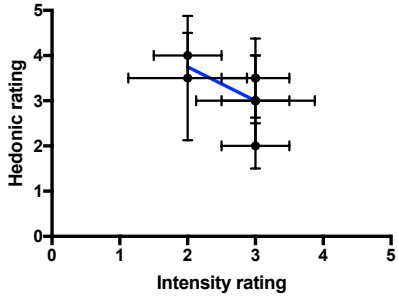
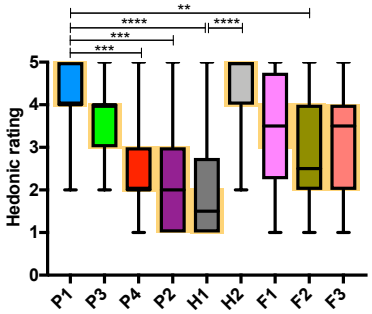
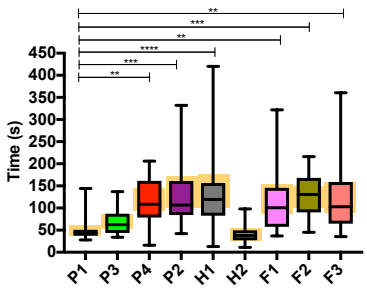
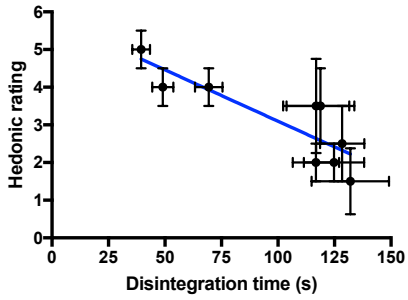
A second human panel was conducted on 24 young healthy volunteers with the purpose of verifying the predictive capability of the DMA method on perceived ODF stickiness, and to assess the effect of palatability-enhancing excipients on stickiness and other mouthfeel attributes' perception. During and after this human panel study, no discomfort or adverse reactions were reported. Results are summarised in Tab. 5.3, and Fig. 5.1.

Table 5.3: PRO and RRO median and IQR values for each ODF sample presented by attribute (n = 24).

	PROs								
	P1	**P3**	**P4**	**P2**	**H1**	**H2**	**F1**	**F2**	**F3**
	Attributes perceived on intake								
Size	4 (1)	4 (1)	4 (1.75)	4 (1)	4 (1.75)	4.5 (1)	4 (1.75)	5 (1)	5 (1)
Thickness	4 (2)	4 (2)	3 (2)	4 (2)	3 (2)	4 (1)	5 (1)	4 (1)	5 (1)
Thickening effect	4 (1.75)	3.5 (1)	3 (1)	4 (1)	3 (1)	4 (2)	4 (1.75)	3 (1)	3.5 (1.75)
Stickiness	4 (1)	3 (2)	2 (1)	3 (1)	3.5 (2.75)	3.5 (1.75)	3.5 (2)	3 (2)	3 (1)
Disintegration time	4 (1)	4 (1)	2 (1)	2 (2)	1.5 (1.75)	5 (1)	3.5 (2.5)	2.5 (2)	3.5 (2)
	Attribute intensity								
Thickening effect	1.5 (1)	2 (0)	2 (2)	2 (2)	1 (1)	2 (1.75)	2 (0.75)	2 (1.75)	2 (2)

Stickiness	2 (1)	3 (1)	3 (1)	3 (2)	2 (1.75)	3 (1)	3 (1)	3 (1.75)	3 (1.75)
RROs									
	P1	**P3**	**P4**	**P2**	**H1**	**H2**	**F1**	**F2**	**F3**
Facial expression	1 (0)	1 (0)	1 (0.75)	1 (0)	0 (1)	1 (0)	1 (0)	1 (0)	1 (0.75)
Jaw movements	2 (2)	1 (1)	1 (1)	1 (1.75)	0 (0)	2 (1)	1 (2)	1 (2)	1 (1.75)
Sample intake	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
RRO total	5 (2)	4 (2)	3.5 (1)	4 (1.75)	2 (1)	4.5 (1)	4 (1.75)	4 (2)	4.5 (1)

Attributes perceived on intake PROs

	Comfort/discomfort	Intensity	Correlation
Size			
Thickness			
Thickening effect			
Stickiness			
Disintegration time			

RROs

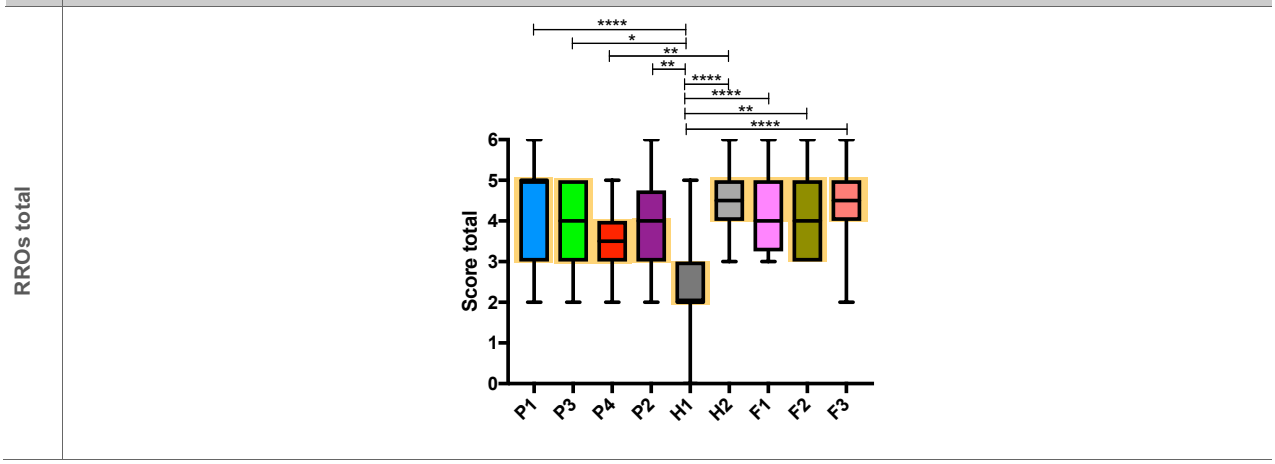


Figure 5.1: Box and whisker plot of PROs and RROs presented by ODF sample and by attribute. The horizontal line in the middle of the boxes indicates the median, Yellow rectangles behind the boxes represent 95% confidence intervals, lower and upper margins of the boxes represent the 25th and 75th percentile, and bars indicate the maximum and minimum values. Statistical differences between samples are indicated by the top horizontal bars, and p-values are represented by the asterisks. A hedonic rating of 3 and above on 5-points scales was considered acceptable according to Mistry et al., 2017 [6]. In correlation graphs vertical and horizontal bars are indicated. For categorical variables, bars correspond to the interquartile range, whereas for continuous variables, bars represent the standard deviation.

5.3.1.1 Perceived size and perceived thickening effect of ODF samples

As expected, the control attribute represented by the perceived ODF size was evaluated between somewhat comfortable, and extremely comfortable in all samples by the majority of participants, with no significant differences among sample PROs (Tab. 5.3; Fig. 5.1).

In the case of the ODF thickening effect and its perceived intensity, no significant difference was reported among samples (Tab. 5.3; Fig. 5.1). This result was not surprising, as none of the administered ODF samples was made with polymers with known thickening effect. A poor correlation was found between the perceived thickening effect comfort/discomfort, and the thickening effect intensity PROs

(R^2=0.06452; r=0.122, n.s.), most likely due to the lack of thickening effect variability among the analysed samples (Fig. 5.1).

5.3.1.2 Perceived thickness of ODF samples

Participants reported differences in the acceptability scores of the ODF thickness, particularly between sample H1, and other ODF samples (Tab. 5.3; Fig. 5.1). Sample H1 was characterised by the presence of PVAc, a hydrophobic polymer that was combined with the other hydrophilic excipients by means of an emulsifying agent (sodium lauryl sulfate – SLS). After the drying process, the obtained film resulted of a high, non-uniform thickness, and had a very brittle consistency. Moreover, once placed in the mouth, sample H1 resided for a long time without thinning. Therefore, the perception of a highly thick sample reported by participants is reasonable for sample H1. No significant difference was found between the thickness acceptability scores of samples F1, F2, and F3, indicating that the presence or absence of sweetener and favour did not alter participants' thickness perception.

5.3.1.3 Perceived stickiness of ODF samples

PROs on perceived stickiness are summarised in Tab. 5.3, and in Fig. 5.1. Sample P1 was reported to be a highly acceptable ODF with a low perceived stickiness intensity, receiving a median acceptability score of 4, and a median stickiness intensity score of 2. Significant differences were found with samples P4 ($p<0.01$), and P2 ($p<0.05$) in both perceived stickiness acceptability, and intensity ($p<0.05$), whereas no significant difference was observed with sample P3. A low median stickiness intensity score (2) was reported for sample H1, significantly different from sample P4 ($p<0.01$), P2 ($p<0.05$), and H2 ($p<0.05$).

A high acceptability score for sample P1 compared to sample P2, corresponding to low, and high stickiness intensity scores respectively, were also reported by the participants of the pilot human panel, confirming the relationship between the tack of high-and low-molecular weight PVOH polymers. However, from the results of the second human panel, such relationship turned out to be non-linear, with sample P2 (197 kDa) receiving higher median acceptability scores than sample P4 (130 kDa), although the difference was non-significant.

Interestingly, the stickiness acceptability, and stickiness intensity scores of samples F1, F2, and F3 were very similar, indicating that the presence of palatability-enhancing excipients had no effect on the stickiness perception.

There was a poor correlation between the perceived stickiness acceptability and intensity PROs (Fig. 5.3 c). The absence of a direct correlation suggests that the evaluation of the ODF perceived stickiness acceptability does not depend exclusively on the intensity of the stimulus, confirming previous findings (chapter 2). Most likely, other sensory attributes might be determining the samples end-user acceptability.

5.3.1.4 Perceived stickiness intensity as indicator of in vivo ODF tack

In the absence of a quantitative method to evaluate the strength of ODF adhesion to the human palate, the perceived stickiness intensity represents the best indicator of the *in vivo* ODF tack. In this respect, a low stickiness intensity was reported for samples P1, and H1, whereas the rest of the samples were evaluated moderately sticky. The threshold of 39 kDa as the PVOH molecular weight determining lower tack, in comparison to the higher-molecular weight polymeric counterparts was confirmed. The stickiness intensity of sample H1 was evaluated as lower than that of sample H2, again confirming the *in vitro* data. Finally, samples F1, F2, and F3 had similar perceived stickiness intensity, also reflecting the adhesive force profiles measured by DMA. As a result, it can be hypothesised that hydrophobic interactions are likely not involved in the

ODF adhesion in both the *in vitro* and *in vivo* systems. On the other hand, it cannot be excluded that polar interactions might be mediating the adhesive bond between ODFs, and both DMA plates and human palate.

5.3.1.5 Perceived disintegration time of ODF samples

Perceived disintegration time was assessed by participants, and its comfort/discomfort and real time as appeared on the stopwatch display were reported (Tab. 5.3; Fig 5.1). Similarly to the pilot human panel, an inverse correlation between perceived disintegration time acceptability and span was observed. The perceived disintegration time of sample H2 was considered extremely comfortable, whereas the disintegration time of samples P1 and F1 were evaluated between somewhat comfortable and extremely comfortable. Differences between sample P1, and P4 ($p<0.001$) and P2 ($p<0.001$) were confirmed by statistical analyses, and so was the difference with H1 ($p<0.0001$), and F2 ($p<0.01$), confirming the poor acceptability of samples P4, P2, and H1 with regards to the perceived disintegration time. There also was a significant difference in disintegration time acceptability between H1, and H2 ($p<0.0001$). A decrease in disintegration time acceptability was expected from P1, to P2 as a similar evaluation was reported in the pilot human panel. As disintegration time is supposed to be influenced by PVOH molecular weight, also the difference between P1, and P4 was foreseen, however, so was the difference between P1, and P3, which was, instead, non-significant. Differences in acceptability between H1 and H2 was also not surprising because the presence in sample H1 of PVAc, a polymer which is insoluble in saliva, was characterised by a long permanence in the mouth, and could have made the formulation uncomfortable. Sample F2 was composed by two polymeric species and a plasticiser, and did not contain any sweeteners or flavours. On the contrary, samples F1, and F3 did contain such excipients, which seemed to have shortened the perceived disintegration time, and made it more acceptable. The perceived disintegration time acceptability

seemed to show some correlation with the real disintegration time measured by stopwatch (R^2 = 0.7217; Spearman r = -0.8355, p<0.01) (Fig. 5.1). The linearity of the correlation improved if the set of flavoured samples was excluded from the calculation (R^2 = 0.9647), potentially indicating either the influence of taste in the acceptability of ODF disintegration time, or the different evaluation made by participants in the two assessment days.

5.3.1.6 Researcher-Reported Outcomes

The RROs were calculated as previously described in chapter 2, and results are summarised in Tab. 5.3, and Fig. 5.1

Facial expression RROs did not evidence much variability among the samples, except for H1, which induced signs of distress in many of the participants. The same sample also had to be chewed, probably due to its insolubility. Samples P1 and H2 did not induce jaw movements, and also corresponded to samples characterised by a fast disintegration time. All other samples required 1 to 3 chews, or observed tongue movements before they were swallowed, however the IQR was wide, indicating a certain degree of variability. No sample loss was reported in any of the samples. Overall, samples that received the highest RROs were P1, H2, and F3, which were also characterised by either a fast disintegration time, or the presence of sweetener and flavour, and a reduced polymeric component. In general, participants did not encounter any difficulties hindering their ability to take the sample.

5.3.1.7 Semi-structured interview

Like in the pilot human panel, a semi-structured interview was conducted in order to learn more about the participants' experience. Answers are summarised in Tab 5.4.

Table 5.4: Semi-structured interview results expressed as number of participants who gave the same answer.

Participant comment	P1	P3	P4	P2	H1	H2	F1	F2	F3
Stiffness needs improvement (sharp edges)	8	3	4	2	3	-	-	1	-
Disintegration time needs improvement	1	2	8	7	9	3	5	8	8
Taste needs improvement	5	5	3	2	10	13	4	6	4
Stickiness needs improvement	1	9	9	9	8	3	5	7	5
Thickness needs improvement	1	1	3	4	1	2	2	3	4
Size needs improvement	2	-	1	1	-	-	-	-	-
It has a thickening effect on saliva	-	3	2	-	-	1	-	-	1
Brittleness needs improvement	1	-	-	-	2	1	-	-	1
Tendency to fold/form lumps	1	1	2	-	2	1	2	3	1
Inhomogeneity (one part dissolved faster)	-	1	-	1	-	1	-	1	-
It dries the mouth	-	-	1	-	-	1	-	-	-
It feels rough	-	-	-	-	-	-	-	-	-
Shape needs improvement	1	-	-	-	-	-	-	-	-
Add colour	1	1	-	-	1	1	-	-	-
If feels like plastic	1	1		1	2	1			
Sweetness needs adjustment	-	-	-	-	-	-	4	-	2

High levels of stiffness and the presence of sharp edges were reported for samples P1, P2, P3, and P4, indicating that single-polymer ODF samples based on PVOH needed improvement in that direction. High stiffness was also reported by three participants for sample H1, which tended to lose its flexibility upon drying. Sample F2 was indicated as being stiff by one participant only. Compared to sample F1 and F3, F2 was characterised by the highest polymer/excipient ratio, probably reducing the flexibility of the resulting ODF.

A shortening in disintegration time was required for samples P4 and P2, H1, F1, F2, and F3, as also confirmed by the perceived disintegration time acceptability (Fig. 5.1). P4 and P2 corresponded to the highest molecular weight PVOH-based ODF sample, H1 contained a part of hydrophobic insoluble polymer, and F1, F2, and F3 had high-molecular weight PVOH as main film-forming polymer. All these samples, with the exception of H1, were also characterised by the longest disintegration time measured *in vitro* (Fig. 4.11 – Chapter 4). Fewer participants also indicated P1, P3, and H2 as samples requiring improvement with respect to disintegration time, however this result was not supported by *in vitro* disintegration data (Fig. 4.11 – Chapter 4), nor by other *in vivo* acceptability data (Fig. 5.1).

Taste was a critical aspect addressed by panel participants. Sample H1, and H2 were reported having a bad taste by the majority of participants, and this could have been caused by the presence of SLS in both samples. In this respect, some complaints of "bitter aftertaste" were made. Taste was not considered acceptable, although by fewer participants, also for the PVOH-based sample, especially for P1, and P3. Surprisingly, four participants did not particularly like the taste of samples F1, and F3, indicating that they were too sweet, or too intensely flavoured, whereas F3 had no sweetener nor flavour, therefore an improvement in taste was deemed desirable by six participants.

High stickiness levels were reported in samples P2, P3, P4, H1, F1, F2, and F3. Samples P2, P3, P4, F2, and F3 were associated with relatively low perceived stickiness acceptability (Fig. 5.1), whereas samples H1, and F1 received higher stickiness acceptability scores. There was a discrepancy between participants' acceptability

scores, and their comments in the semi-structured interview for H1, and F1. With regards to sample H1, some comments indicated that the sample was indeed sticky in nature, but as it reminded participants of the consistency of a “candy”, it was deemed tolerable. In the case of sample F1, no additional comment helped to identify the reason for the different feedback.

A desirable thickness improvement was suggested by a relatively low number of participants, with four people indicating samples P2, and F3 as “too thick”. Sample P2 was considered thick also in the semi-structured interview conducted during the pilot human panel (Tab. 2.8 – Chapter 2). Participants commented that sample F3 became thick upon hydration with saliva, whereas samples containing a higher polymeric fraction did not. The *in vivo* perceived thickness was evaluated less comfortable for samples P4, and H1 (Fig. 5.1), which did not receive any comments in the semi-structured interview. The size of samples P1, P4, and P2 was considered unsuitable to two, and one participants respectively. It was also reported that this corresponded to the presence of sharp edges, therefore a reduction in size was proposed as potential solution. This could then explain the overall high acceptability of the ODF sample size obtained from the questionnaire (Fig. 5.1). Only the single-polymer PVOH-based samples received such comment.

A thickening effect on saliva was indicated in samples P2, and P3 by two and three participants respectively, and by one participant for samples H2, and F3. Higher thickening effect intensity was reported for samples P2, P3, P4, H2, F1, F2, and F3, however only samples P4, H1, and F2 received lower, though non-significantly, acceptability scores (Fig. 5.1). The many inconsistencies in the evaluation of ODF sample thickening effect between hedonic scale evaluations, and interview suggested either the existence of a problem with how the questionnaire was phrased or explained to participants, or the influence of other factors in the perception of such attribute. On the other hand, the low number of participants who reported issues with the perceived thickening effect of samples in the semi-structured interview might justify the non-significance of the differences in intensity and acceptability scores. The thickening effect

might have negatively influenced the perceived stickiness acceptability score of sample P4 considering that the perceived stickiness intensity scores of P2, P3, and P4 were very similar to each other, however this did not happen for samples H2, and F3.

Brittleness was reported for samples P1, H1, H2, and F3, probably for a combination of short polymeric chains, and lack of plasticiser in samples P1, H1, and H2, and for the low polymer/excipient ratio in sample F3.

The tendency to fold or form lumps was a widespread characteristic among the analysed ODF samples. All samples except P2 had at least one participant reporting this issue, which could be linked to the nature of PVOH.

Very few participants reported the necessity for improvement in thickness homogeneity, drying effect, roughness, and shape.

The addition of colour was suggested as improvement for the difficulty to visualise and picking samples P1, P3, and H2. Instead, sample H1 was easy to see and pick up, but its appearance was cloudy and the addition of a colouring agent was seen as an improvement.

The feeling of a plastic material in the mouth was reported for samples P1, P2, P3, H1, and H2, and it could be explained by the absence of excipients intended to improve the mechanical properties of ODFs.

Finally, the excessive sweetness of samples F1, and F3 resulted uncomfortable to participants, and it pointed out that the concentration of sweetener recommended by the manufacturer not always corresponds to acceptable palatability, especially if in combination with other excipients.

During the interview, participants were asked if they were willing to take the ODF sample every day, if it was a medicinal product (Fig. 5.2).

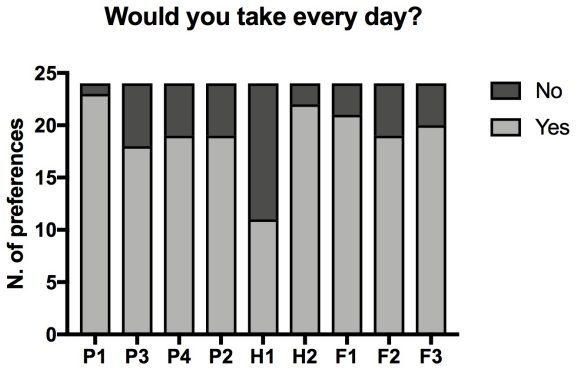


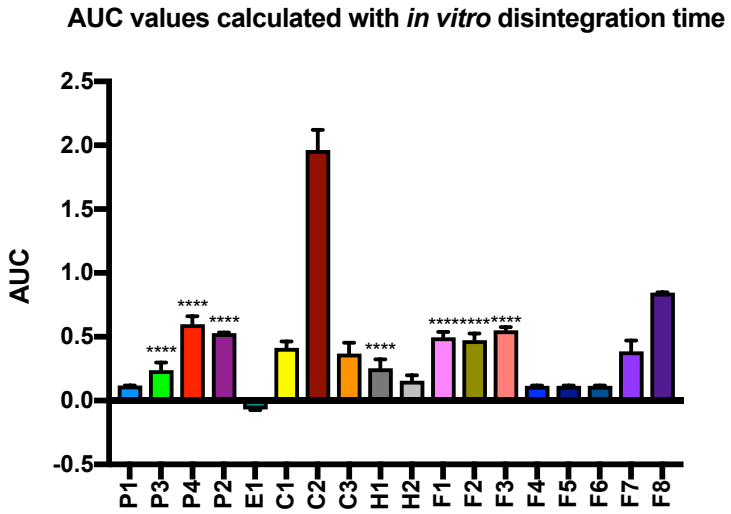
Figure 5.2: Willingness to take the ODF sample every day (n = 24).

Less than half participants were willing to take sample H1 every day, whereas the large majority of them were willing to take sample P1. Among the single-polymer PVOH-based samples P3, which had a lower molecular weight, a faster disintegration, and the same stickiness as samples P2, and P4, was considered to be taken daily by seventeen participants, and P2, and P4 by eighteen. Twenty-two participants would take the completely hydrophilic sample H2 daily. Twenty-one, nineteen, and twenty participants respectively were willing to take samples F1, F2 and F3 every day, indicating that, in the adult population, the addition of sweeteners and flavours had a limited influence on the overall willingness to take ODFs, whereas other attributes seemed to have a more prominent effect. Overall, all the samples analysed with the exception of sample H1 would be taken every day, and without improvements by the majority of participants. This was also reflected in a total RRO score higher than 3, except in sample H1, and by perceived disintegration time acceptability scores higher than 2, whereas perceived stickiness acceptability scores were higher than 2 in all samples. This result suggests that the perceived disintegration time might have a prominent role in the willingness of end-users to take ODFs as medicines on a daily basis.

5.3.2 AUC calculation and *in vitro/in vivo* correlation of ODF samples perceived stickiness acceptability

The AUC values for each sample were calculated as previously described in chapter 4. AUCs were therefore calculated using the disintegration time measured *in vitro* by drop method (Fig. 5.3 a), and differences with the AUC calculated using *in vivo* measured disintegration time (Fig. 5.4) were evaluated where possible. Disintegration times for AUC calculation were approximated to the closest time point at which ODF sample tack was measured in the DMA analysis.

a)



b)

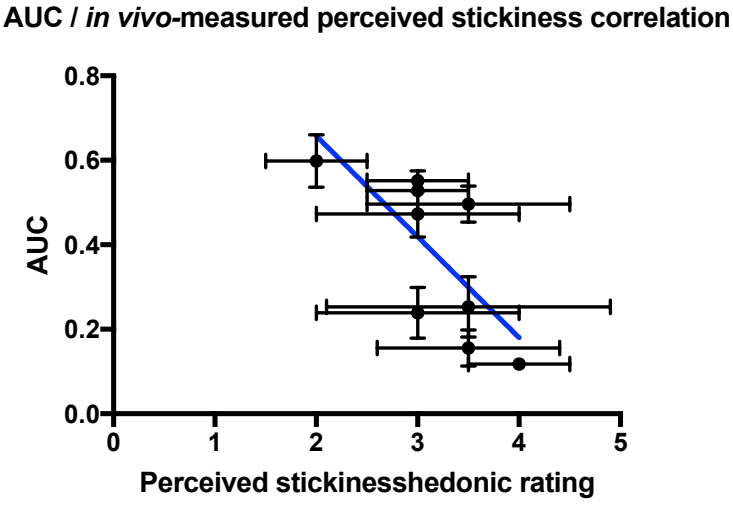


Figure 5.3: AUC calculated using the disintegration time measured by drop method (a) (n = 3), and correlation between AUC and perceived stickiness acceptability PROs (b). (R2 = 0.5151). Asterisks indicate

significantly different disintegration time compared with the corresponding in vivo disintegration time measured by participants. Vertical bars indicate standard deviation, whereas horizontal bars indicate the interquartile range.

The AUC measured with *in vitro* disintegration data confirmed the existence of a certain degree of correlation with the perceived stickiness PROs (Fig.5.6 b), with low AUC values corresponding to high perceived acceptability scores. Nevertheless, the relationship between the two variables was not perfectly linear.

5.3.2.1 Non-linearity due to data collection methods

This could be due to two factors, also representing the major weaknesses of the developed method:

- The number of response categories panel participants were required to choose among, in order to express their comfort/discomfort were few (5 points). In this respect, the utilisation of a 6 or 9 points hedonic scale, or a Visual Analogue Scale (VAS) for the assessment of ODF perceived stickiness could have resulted in a more accurate correlation with *in vitro* measurement. On the other hand, because the end-user population was not composed of trained panellists, panel participants might have encountered difficulties in using such scales, and results would have probably been too disperse.

- The disintegration times used for the calculation of the AUC were rounded to the closest time point used to measure sample tack in the DMA analysis. This was done for purely practical reasons, in order to avoid the tack assessment of too many time points. By increasing the number of time points for tack assessment, the AUC values would probably correlate better with the perceived stickiness acceptability PROs.

Considering that the purpose of the method was to predict whether the formulation being developed would receive a positive acceptability feedback by the end-users, such degree of approximation could be considered acceptable. A good correlation was found in samples P1, P3, P4, and P2, indicating that linearity is maintained if ODFs are made of a single film-forming polymer. It is important to point out that the difference in perceived stickiness acceptability between samples P4, and P2 was non-significant, and the variability in the acceptability scores of sample P3, and P4 was wide. As a consequence, also the apparent inconsistency between AUC and perceived stickiness acceptability score of sample P3 might be non-significant. Sample H1 was also close to the resulting regression line. Low AUC values were found in sample H2, which was considered somewhat comfortable by participants. Also in the case of sample F1, F2, and F3 the AUC values were higher than expected compared to their acceptability assessment.

Another potential cause of the poor linear correlation, could reside in the evaluation being carried out in two different days. Although in the pilot human panel, the evaluation of the four samples seemed to not differ among the three sessions, in the second human panel, the type of samples assessed differed between the assessment days. This might have caused a shift in the PROs because participants had different sets of samples to compare among. Reference samples have been used in some published works on the sensory evaluation of dosage forms, in order to provide a comparator for panellists [53,229]. If the reference sample changes, it is very likely that the outcome will be affected.

5.3.2.2 Non-linearity due to the influence of other mouthfeel attributes

The perceived disintegration time of ODFs is one of the parameters upon which the AUC is calculated, and it is one of the main contributors to the perception of ODF stickiness, as it was discussed before (chapter 4).

The thickness of samples P4, and H1 was evaluated less acceptable than the other samples, although this data was inconsistent with the participants comments in the semi-structured interview. This might have contributed to further lower the perceived stickiness acceptability of sample P4, and to increase the AUC compared with other single-polymer ODF samples. During the interview, the highest number of participants (four) received comments related to the need to improve the thickness of samples P2, and F3.

P4, H1, F2 had a poorer acceptability with regards to thickening effect, however it was difficult to determine whether the thickening effect was influencing the acceptability of the perceived stickiness.

Samples H1 and H2, were indicated in the semi-structured interview as having a poor taste.

Many participants reported that sample H1 struggled to dissolve, factor that should have negatively affected the perceived stickiness acceptability as reported in the previous study (chapter 4). Both poor taste and long disintegration time could have affected the stickiness perception of sample H1. Despite this, participants also admitted that the texture of sample H1 was familiar, and reminded them of candies, which might justify why the acceptability scores did correlated with the AUC. Another factor potentially contributing to the correlation between datasets for sample H1, could have been the lower perceived stickiness intensity. On the contrary, the poor taste of sample H2 was not compensated by a familiar consistency/texture, and might have resulted in poor acceptability with regards to stickiness. This might explain how the acceptability of H1 was as expected despite its difficult disintegration, and the acceptability of H2 was lower than expected.

With regards to sample F1, F2, and F3, there is the possibility that the presence of glycerol, which has a plasticising and sweetening effect, in the formulation might have

positively influenced not only the *in vivo* perception of stickiness acceptability, but also that of stickiness intensity.

Different ODF attributes can have positive or negative effect on the perceived stickiness acceptability. A hypothesis on the potential relationship is summarised in Tab. 5.5.

Table 5.5: Hypothesis on the potential effect of ODF attributes on perceived stickiness acceptability. (positive correlation =⇑; negative correlation = ⇓).

	Perceived disintegration time	**Perceived thickness**	**Perceived thickening effect**	**Perceived good taste**	**Perceived poor taste**
Effect on perceived stickiness acceptability	⇓	⇓	⇓	⇑	⇓

It was clear that several ODF attributes influenced participants' perception of ODF stickiness, and therefore of its acceptability, however determining the dominance of one attribute over another, was not possible with the current dataset. To this end, a more detailed study to establish which sensory attribute is dominant, such as that described by Pineau et al., 2009 should be adapted to the set of attributes analysed, and carried out [230].

5.3.2.3 Non-linearity due to the material properties of the *in vitro* equipment

A second reason that could explain why the *in vitro/in vivo* correlation of samples AUC with human panel data was not linear could lie in the differences in materials between the DMA and the human mouth. The oral mucosa is characterised by an external layer of keratin, and by the presence of multiple protein species on its surface and solubilised

in saliva. The surface properties of the DMA stainless steel plate might exhibit some similarities with the human hard palate, therefore explaining the correlation between AUC, and the PROs on perceived stickiness of the first set of samples analysed. However, the absence of negatively-charged surface mucins might have prevented the Eudragit E PO® film from adhering, in contrast with what was observed when chitosan was used as mucoadhesive polymer [126]. Due to the extreme pH of the positively, and negatively-charged ODF samples, it was not possible to have a comparison between *in vitro* and *in vivo* stickiness evaluation. Differences in the materials of the DMA and human mouth could also be responsible for the inconsistency between perceived stickiness acceptability and AUC values of sample H1.

5.3.3 ODF samples perceived stickiness acceptability *in vivo/in vitro* correlation with AUC values calculated using *in vivo*-measured disintegration time

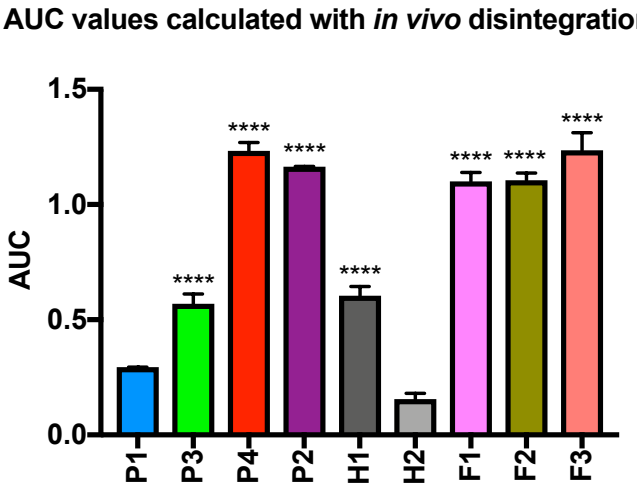


Figure 5.4: AUC calculated using the disintegration time measured in vivo by panel participants (n = 24). Asterisks represent statistically significant differences with the corresponding AUC values calculated using in vitro data.

Not all samples were tested by human panel, hence it was not always possible to obtain *in vivo* data on the perceived disintegration time.

Significantly higher values were found in the majority of the samples when the AUC was calculated with disintegration time measured *in vivo* (Fig. 5.4), except for samples H2, and P1, where the AUC was similar. This was an indication that the drop method was not the most suitable methodology for the measurement of *in vitro* disintegration time, and that other methods are required to accurately predict ODF perceived disintegration time.

5.4 Conclusions

A second human panel conducted on 24 healthy young adults on a set of nine samples was conducted. The acceptability of perceived size, and perceived thickening effect of the analysed ODF samples did not differ significantly among samples, although this could not always find confirmation in the outcomes of the semi-structured interview. The acceptability of the perceived thickness, perceived stickiness, and perceived disintegration time, on the other hand, varied among samples. With regards to the perceived stickiness acceptability, the molecular weight of the single-polymer ODFs seemed to confirm its influence, as previously identified by DMA, with the exception of sample P4. In this respect, the additional influence of other attributes might have occurred. Despite the difference in the perceived stickiness intensity between samples H1, and H2, there was no significant difference in their perceived stickiness acceptability. The acceptability of the perceived disintegration time was higher for lower-molecular weight single-polymer PVOH samples. A very low perceived disintegration time acceptability of sample H1 in comparison with sample H2 was noticeable, as well as a lower acceptability of the formulation with a high polymer-to-excipients ratio. A linear relationship between perceived disintegration time acceptability and real disintegration time measured *in vivo* was found, and the correlation was better if flavoured samples were excluded. RROs evidenced a high overall sample acceptability with the exception of sample H1. The results of the semi-structured interview showed for the first time the potential influence of attributes such

as colour, sweetness, and a “plastic” feeling on the acceptability of ODFs. Not all the feedbacks given by participants in the semi-structured interview agreed with the PROs given for the corresponding attributes on the five-point scale, although the number of participants suggesting sample improvement in the semi-structured interview was much smaller. All samples analysed would be taken by participants every day, except for sample H1, in agreement with the RROs. Overall, attributes including the perceived disintegration time, perceived thickness, perceived thickening effect, and perceived taste were found to have a potential positive or negative influence on the perception of ODF stickiness. Samples AUCs were calculated using both the disintegration time measured *in vitro* by drop method, and that reported by the panel participants. The AUC values calculated with *in vitro*-measured disintegration time were much lower than those calculated with the *in vivo*-measured disintegration time, however the method showed predictive capability of ODF perceived stickiness acceptability. The *in vitro/in vivo* correlation between the calculated AUC and the perceived stickiness PROs was non-linear, possibly due to the data collection method, to the influence of other mouthfeel attributes on stickiness perception, or to the material properties of the *in vitro* equipment.

Chapter 6. General discussion, conclusions and future work

In the present work, key acceptability attributes of the orodispersible film (ODF) platform contributing to the end-user acceptability were identified, and an *in vitro* method for the prediction of the perceived ODF stickiness acceptability was developed and evaluated. In this chapter, the experimental results, methodology strengths and limitations, and potential implications of the integration of the proposed strategy into the early drug development stage will be discussed. Future work involving further method optimisation and development will be described.

6.1 Review of experimental results and methodology

The assessment strategy for the oral dosage form attributes acceptability assessment was developed and tested for the first time, and it was proposed as an example to guide the acceptability assessment of all oral dosage forms. It is composed of various phases, each requiring a different methodology.

6.1.1 Adoption of a new terminology use for the description of ODF attributes

The very first step was represented by the identification of the most appropriate terminology for the description of oral dosage form acceptability attributes. In this approach, some of the terms used in the sensory evaluation of food were adapted to the assessment of oral dosage forms. This represents an advantage as it enabled the unambiguous description of the sensory aspects of relevant attributes of the dosage form analysed. On the other hand, a limitation of the adoption of such terminology is related to the knowledge and ease of use by the lay person. For thorough sensory analysis of orally administered medicinal products a partial training to the target patient

population sample participating in acceptability assessment studies might add value. Such training does not need to be extensive, however it should provide panel participants with the sufficient knowledge and proficiency to ensure that all the sensory features of the sample contributing to the end-user acceptability are evaluated.

6.1.2 Rationale behind the acceptability assessment of the ODF platform

ODFs are considered patient-friendly dosage forms for a number of reasons. Proof of the high patient acceptability of ODFs has been provided in several literature works. Testing a new method for the assessment of patient acceptability on a dosage form platform that is already considered highly acceptable represents a “stress-test” for method robustness. If the method allows the identification of poorly acceptable attributes in a dosage form that is generally considered highly acceptable, it is likely that it will be able to work even better for dosage forms which patient acceptability is questioned.

A potential pitfall of the method regards the fact that, although the acceptability of one or more attributes was considered poor, it did not significantly affect the willingness of the panel participants to take the ODF samples even every day, if it was a medicinal product, in the study population. This observation rebounds to the debate raised by the scientific community about the difference between medicine acceptability and preference [24]. Patient acceptability is supposed to have a significant impact on the adherence and success of the medicinal treatment, whereas preference is more related to the sensory satisfaction of a medicinal product. Where the first is an important aspect related to the safety and quality of life of an individual, the second does not represent a barrier, as sensory unpleasant products can be taken anyway when the benefits of the therapeutic effects exceed the sensory displeasure for the medicinal product. However, the boundaries between the two concepts are weak, since small children or uncooperative patients, not always can be easily convinced to take a

poorly tasting medicinal product. Therefore, depending on the target population, the acceptability criteria can change, and should be assessed. Thus, the poor acceptability of ODF attributes found in the healthy young adult population might not have the same impact on overall patient acceptability as in other patient populations, however the developed method proved to be capable of detecting it.

6.1.3 Selection of ODF attributes for acceptability assessment

ODF attributes were identified following consideration of the whole intake process, and the most appropriate ones were selected for pilot testing *in vivo*. Ease of packaging opening, ODF size, thickness, and stickiness perceived by the panel participants on handling, and size, thickness, stickiness, and disintegration time perceived during intake were evaluated for acceptability and, in some cases, intensity of the stimuli. The acceptability assessment of attributes perceived on handling did not differ among samples, whereas novel acceptability information was obtained from the packaging usability, and from the assessment of ODF attributes perceived during intake. The attribute selection process allowed the identification of some of the key acceptability attributes of the ODF platform. Other attributes such as taste and smell had a significant influence on the ODF end-user acceptability, however they were excluded from the study as they would require a dedicated project. A second set of mouthfeel attributes were not analysed because of the limitations related to terminology use by the panel participants, although they were identified, during the attribute identification process, as potentially influencing patient acceptability. Overall, the key acceptability attributes identification strategy led to the pre-selection of many relevant aspects of the dosage form for acceptability assessment. However, there is always the possibility that some relevant attributes were missed. In this sense, tools like face-to-face interview proved to facilitate the identification of additional relevant acceptability attributes directly from the end-user population.

6.1.4 Importance of conducting an *in vivo* acceptability assessment

With respect to the identification of ODF acceptability attributes, the initial selection of the attributes to test for the ODF platform had left out some potentially relevant ones, which were reported by the same participants during the semi-structured interview. Although this can be seen as a limitation to the method employed, it also confirms how, without the direct feedback of the end-user, it is difficult to predict the acceptability of a medicinal product, and it underlines the need of appropriate methods for acceptability testing.

6.1.5 Selection of the healthy young adult population for optimising the *in vivo* acceptability assessment method

A small sample of the healthy young adult population was recruited for both the human panel studies carried out in this project. Such population was recruited because it was suitable not only for collecting acceptability data, but also to test the reliability of the method. It is reasonable to think that healthy adults are not likely to experience difficulties with ODF intake. Surprisingly, poor acceptability was detected in the perceived stickiness and disintegration time of some samples, potentially affecting the willingness of the participant to take the sample, if it was a medicinal product. Patient groups above or below certain age ranges, or affected by various pathological conditions are more likely to experiencing difficulties to handle and take ODFs due to poor manual dexterity, lowered sight, cognitive impairment, reduced saliva production, and other conditions.

6.1.6 Questionnaire design for *in vivo* acceptability assessment

Information on the acceptability of individual ODF attributes was obtained by designing a questionnaire and an assessment protocol containing multiple scales and assessment modalities. This was done with the purpose of gathering as much information as possible, using the most versatile and appropriate approach that could be suitable for different study populations. Populations ranging from small children/neonates to the elderly were considered in the study design. Aspects such as the ability to use the assessment scales, the distribution of the data collected, the potential involvement or contribution of a third party (researchers or parent/carer), participant safety, the number of samples analysed, number of sessions, and the type and difficulty of the tasks were all carefully considered and integrated into the study design. For example, the use of a five-point scale was preferred to seven- or nine-point scales, as non-trained panellists might have difficulties evaluating sensory attributes using too many response categories, despite hedonic scales with more than four points were found to perform better with regards to discriminating power [231]. Similarly, hedonic facial scales were considered easier to use by children or other patient groups, therefore they were preferred to other types of scales.

6.1.7 Selection of polymeric type and grade for ODF sample preparation, and limitations of the in-house ODF sample manufacturing method

Some difficulties encountered before ODF sample preparation included the poor availability of polymers in different molecular weights, capable of yielding films with good mechanical properties (sometimes the mechanical properties had to be overlooked in favour of data collection). Also, limitations related to the poor manufacturability of some polymeric solutions were identified. Thickness inhomogeneity issues of the test ODF samples were encountered due to the in-house

manufacturing method adopted for film casting, whereas industrial-scale manufacturing methods should considerably reduce thickness variability.

The advantage of testing single-polymer ODF samples for initial method validation was represented by the possibility to study individual formulation variables such as polymer type or molecular weight.

6.1.8 Selection of ODF samples for *in vivo* and *in vitro* acceptability assessment

The selection of ODF samples to test in the first part of the project (chapters 2 and 3) was carried out with the purpose of assessing whether formulation variables such as film-forming polymer type and molecular weight influenced the acceptability of different ODF attributes. Therefore, single-polymer ODF samples prepared with different polymer types, and molecular weights were tested. After a preliminary selection process involving the safety assessment for human intake, manufacturability assessment of the polymeric solutions, and film-forming capability assessment, two polymers in two different molecular weight variants were tested. A correlation was found between the *in vivo* acceptability assessment of ODF perceived stickiness, and the AUC calculated from the *in vitro* adhesive force measurement of the tested ODF samples. Then, an extended set of samples was prepared in order to elucidate the characteristics of the adhesion mechanisms responsible for the sample adhesion measured with the developed *in vitro* method, and for the stickiness perceived *in vivo*. Poly(vinyl) alcohol (PVOH) was available in a wide range of molecular weights, and it was suitable for further understanding the effect of polymeric molecular weight on ODF *in vitro*-measured tack and *in vivo*-measured perceived stickiness. More molecular weight variants of carboxymethylcellulose (CMC) were difficult to find, however the possibility to fully ionise CMC to obtain a negatively-charged ODF sample was possible, and a comparison with a fully ionised positively-charged Eudragit E PO®

ODF sample was carried out *in vitro*. This led to understand the role played by opposite ODF charges on the measured tack. Unfortunately, this set of samples could not be tested *in vivo* due to safety concerns. The testing of ODF samples with and without a hydrophobic polymeric component confirmed that hydrophobic elements reduce ODF tack *in vivo* and *in vitro*, but not the *in vivo* perceived stickiness acceptability. The formulation optimisation by addition of other excipients and active pharmaceutical ingredient (API) did not seem to substantially affect the ODF sample tack, which was determined by the film-forming polymer. Of the optimised formulations, only the placebo sweetened/flavoured or non-sweetened/non-flavoured ones could also be tested *in vivo*.

6.1.9 The participant group can influence the identified acceptability attributes in human panel studies

The ability to swallow ODFs has been previously defined as acceptability attribute for infants and children [71]. In the present study, the swallowability of ODF was not reported as an acceptability barrier by healthy young adults. This suggests how the perception of an ODF acceptability attribute was affected by the study population.

6.1.10 Identification of ODF formulation variables influencing the key acceptability attributes

The formulation variables with potential to influence patient acceptability were identified based on the key acceptability attribute identified, and the physics behind how the ODF interacts with the human body to trigger the corresponding sensory effect. For example, the disintegration time is perceived based on the time required for the ODF matrix to dissolve. In turn, the time to dissolution of a polymeric network is mediated by hydration and polymeric chain disentanglement processes in a liquid environment.

Shorter polymeric chains have a lower entanglement density than long polymeric chains. Therefore, the molecular weight of the film-forming polymer is likely to determine the disintegration time of the ODF product. These conclusions were drawn based on literature study, and some aspects related to the influence of other formulation variables on the studied ODF attribute might have been missed. However, the goal of proving the correlation between formulation variable and corresponding attribute acceptability was achieved, confirming the validity of the method.

6.1.11 Identification and optimisation of *in vitro* methods for the assessment of ODF acceptability attributes

In the simple cases, existing *in vitro* assessment methods for the measurement of ODF attributes were used or adapted for the prediction of ODF attributes acceptability. However, if an existing assessment method was not available, a novel one was developed. The assessment method was based on the principles governing the physical mechanisms mediating the interaction between the ODF sample and the human body, and triggering the corresponding sensation. For example, ODF perceived stickiness is elicited by the adhesive properties of the ODF sample onto the palate of the individual, upon hydration with saliva (tack). This process is also known as mucoadhesion, and six theories have been proposed to explain such phenomenon. Depending on the mucoadhesion theory considered, different testing methods can measure the related physical property potentially involved in the phenomenon. Several tack measurement methods are used to measure mucoadhesion *in vitro*. However, the simplest method that more closely recreates the conditions of the human oral cavity consisted in the adhesive force measurement of a hydrated ODF sample after compression. Because *in vitro* methods are not the exact reproduction of the human oral cavity physiological conditions, differences between the two systems might have determined the non-linear correlation between *in vitro*-predicted and the *in vivo*-

evaluated perceived stickiness acceptability. However, the exclusion of some mucoadhesion theories, and the testing of others have led to a better understanding of the physical and chemical mechanisms governing ODF tack, and probably the oral stickiness perception in general. Such goal was also obtained by testing the appropriate set of ODF samples, as discussed in section 6.1.8.

6.1.12 Perception dominance of ODF attributes

The influence of the perceived ODF disintegration time on the perception of ODF stickiness was identified from the results of the pilot human panel. This finding guided the optimisation of the dynamic mechanical analysis (DMA) method for the prediction of the *in vivo* acceptability by including ODF disintegration time in the calculation of the area under the curve (AUC). This passage was important as it led to obtain a more accurate acceptability prediction. It also pointed to the possibility that several ODF acceptability attributes may influence the perception of other ODF acceptability attributes, which further complicated the optimisation of *in vitro* acceptability predictive methods. Literature works proved that the temporal dominance of a sensory attribute in foods can change over time [230]. There is the possibility that a similar phenomenon occurs in the perception of ODFs attributes, where further studies need to be conducted. The overall acceptability of ODF is therefore the result of an interplay between a limited set of sensory attributes that can represent the main acceptability predictors. In addition to ODF perceived stickiness and disintegration time, taste is very likely to be one of them. Therefore, the development and optimisation of *in vitro* methods predicting the acceptability of all the identified key ODF acceptability attributes should provide a sufficiently accurate prediction of the overall end-user acceptability with regards to formulation-related aspects.

6.1.13 Appropriateness of the DMA method for the prediction of ODF stickiness acceptability

The *in vivo/in vitro* correlation between the AUC calculated by DMA, and the perceived stickiness participant-reported outcomes (PROs) resulted monotonic but non-linear. Non-linearity could be due to the used data collection methods, to the influence of other ODF attributes on the panel participants' stickiness perception, or to the material properties of the DMA equipment. Although further optimisation of the *in vitro* method is required, an indication of the acceptability of an ODF formulation could already be obtained.

6.1.14 Appropriateness of the oral cavity model for the prediction of ODF disintegration time acceptability

The oral cavity model proved to be a promising experimental method for the *in vitro* prediction of the acceptability of the perceived disintegration time. However, the compression stress applied to the ODF samples did not seem to be sufficient to accurately measure the disintegration time. With the purpose of predicting the acceptability of ODF disintegration time, the oral cavity model allowed the identification of the ODF samples that were considered comfortable from those that were considered uncomfortable by the human panel participants. The difference was consistent with the shape of the ODF volume reduction vs. time curves obtained from the oral cavity model analysis. An extended set of purposely-designed ODF samples could confirm the relationship between ODF disintegration time acceptability PROs, and sample disintegration curve. The integration of both compression and shear stresses in the same equipment might lead to a more accurate measurement of the *in vitro* disintegration time.

6.2 Future work

The present work provided data of the initial experimental steps taken towards the development and optimisation of a new strategy for the assessment of the patient acceptability of the ODF formulation platform. When successfully optimised, such strategy might lead to the provision of *in vitro* decision-supporting tools for the prediction of the end-user acceptability that can be implemented in the early drug development process. In order to achieve such goal more research work and optimisation are required.

- The new terminology adopted for the description of ODF acceptability attributes should be further refined, or a method for the training of panel participants should be designed. Such method could involve a short briefing before the assessment session in which the definition of the sensory attribute is given and examples are made. A Q&A session could also be useful to ensure panel participants have understood the description and are able to evaluate the attribute.
- Provided that panel participants could be effectively trained to use the appropriate terminology for the assessment of ODF acceptability attributes, an extended range of attributes with the potential to affect patient acceptability should be tested, in order to obtain a comprehensive overview of the ODF platform acceptability, and to identify more key formulation variables.
- Human panel testing of ODFs should also be carried out in different populations, particularly in those potentially benefitting from the use of such dosage form platform. In this respect, children, elderly, and patients affected by dry mouth syndrome should be prioritised.
- Particular attention should be given to the scaling system used to assess ODF attribute acceptability. The selection of the appropriate scales was carried out based on the target patient population assessing ODF acceptability. However,

the expression of comfort/discomfort by five-point scales/score systems might be one of the factors causing the non-linearity of the correlation between AUC values and PROs on the perceived stickiness acceptability. Therefore, a revision of the selection of the scaling system in ODF attribute acceptability assessment should depend on the confirmation that *in vivo/in vitro* correlation linearity in ODF perceived stickiness is the correct description of the relationship between the two variables, and the hypothesis that scaling systems with more than five points can improve correlation linearity, and still be comfortably used by the population assessed.

- More formulation variables, and a wider set of samples should be tested with the currently developed method to further drive the optimisation of the DMA method, and the development of new *in vitro* acceptability-predicting methods. In this respect, more polymer types with different molecular weight and grades could be tested. Formulation variables other than film-forming polymer type and molecular weight could be influencing ODF attributes. The adoption of a factorial design approach might be beneficial in this sense.
- The developed DMA method for the *in vitro* prediction of ODF perceived stickiness acceptability should be further optimised, particularly with regards to the integration of the influence of other attributes in the calculation of the AUC. This implies that the predictive system should move from a two-dimensional (integration of ODF tack and disintegration time), to a multi-dimensional one, and be able to work with limited datasets.
- The developed *in vitro* oral cavity model for the acceptability assessment of the perceived ODF disintegration time should be further tested with additional ODF samples in order to confirm the relationship between ODF volume reduction vs. time curve and perceived disintegration time PROs. Moreover, the method could be implemented with the ability to apply shear stresses to the sample, thus potentially improving the accuracy of the sample disintegration time measurement.

- Finally, when the whole strategy will be optimised and validated, it could be assessed for suitability for the acceptability prediction of other dosage forms.

6.3 Conclusions

The increasing need to gather information on patient acceptability has prompted the scientific community to propose a range of assessment methods. A harmonised approach has, however, not yet been achieved. The acceptability assessment of oral dosage form acceptability attributes was proposed in this work as a novel strategy to help the manufacturers to optimise the drug product at an early development stage. The strategy has been designed and optimised around ODFs, example of a "challenging" dosage form known for its patient-centric design. The study led to the identification of key ODF acceptability attributes influencing patient acceptability, and guided the development of *in vitro* methods for the prediction of ODF attribute acceptability. Although both the developed *in vivo* and *in vitro* methods will require further optimisation, the concept of an acceptability assessment of oral dosage form individual attributes has been proven feasible. When appropriately optimised, and adapted for other pharmaceutical dosage forms, such a strategy can provide a set of *in vitro* methods for the prediction of individual dosage form attribute acceptability. Such a set of *in vitro* methods represents a decision-supporting toolkit that can be implemented in the pre-clinical formulation development phase, potentially facilitating the development of highly-acceptable medicinal products, and minimising post-marketing risks. Translated into benefits for the patient, the present work is expected to promote the engagement of the patients in the design of highly-acceptable medicinal products, thus providing manufacturers with a real-world feedback, and consequently bringing about significant improvements in the patients' quality of life.

Research publications

Journal articles

Scarpa M, Stegemann S, Hsiao WK, Pichler H, Gaisford S, Bresciani M, Paudel A, Orlu M. 2017. *Orodispersible films: Towards drug delivery in special populations.* International Journal of Pharmaceutics; 523(1):327-335.

Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit AW, Orlu M. 2017. *Patient acceptability of 3D printed medicines.* International Journal of Pharmaceutics; 530(1-2):71-78.

Scarpa M, Paudel A, Kloprogge F, Hsiao WK, Bresciani M, Gaisford S, Orlu M. 2018. *Key acceptability attributes of orodispersible films.* European Journal of Pharmaceutics and Biopharmaceutics; 125:131-140.

Redfearn A, Scarpa M, Orlu M, Hanson B. 2019. *In vitro oral cavity model for screening the disintegration behaviour of orodispersible films: a bespoke design.* Journal of Pharmaceutical Sciences; Accepted manuscript.

Oral presentations

Scarpa M, Paudel A, Hsiao WK, Bresciani M, Kloprogge F, Gaisford S, Orlu M. *What makes orodisperible films patient-centric dosage forms? Identifying critical acceptability attributes.* 9th EuPFI Conference: 'Formulating better medicines for children', September 2017, Warsaw, Poland.

Poster presentations

Scarpa M, Paudel A, Hsiao WK, Bresciani M, Kloprogge F, Gaisford S, Orlu M. *What makes orodisperible films patient-centric dosage forms? Identifying critical acceptability attributes.* 9th EuPFI Conference: 'Formulating better medicines for children', September 2017, Warsaw, Poland.

Goyanes A, Kamlow W, Scarpa M, Gaisford S, Basit AW, Orlu M. *Acceptability of 3D printed tablets (printlets) based on shape and size.* 8th APS International PharmSci Conference, September 2017, Hatfield, United Kingdom.

Goyanes A, Kamlow M, Scarpa M, Gaisford S, Basit AW, Orlu M. *Patient acceptability of 3D printed tablets (printlets) based on the shape and size.* AAPS PharmSci 360 Annual Meeting, November 2017, San Diego, California, United States.

Scarpa M, Redfearn A, Hanson B, Orlu M. *Novel approach to disintegration testing of orodispersible films: In vitro oral cavity simulator.* 10th EuPFI Conference: 'Formulating better medicines for children', September 2018, London, United Kingdom.
Awarder 'best poster presentation' in London (UK), September 13, 2018.

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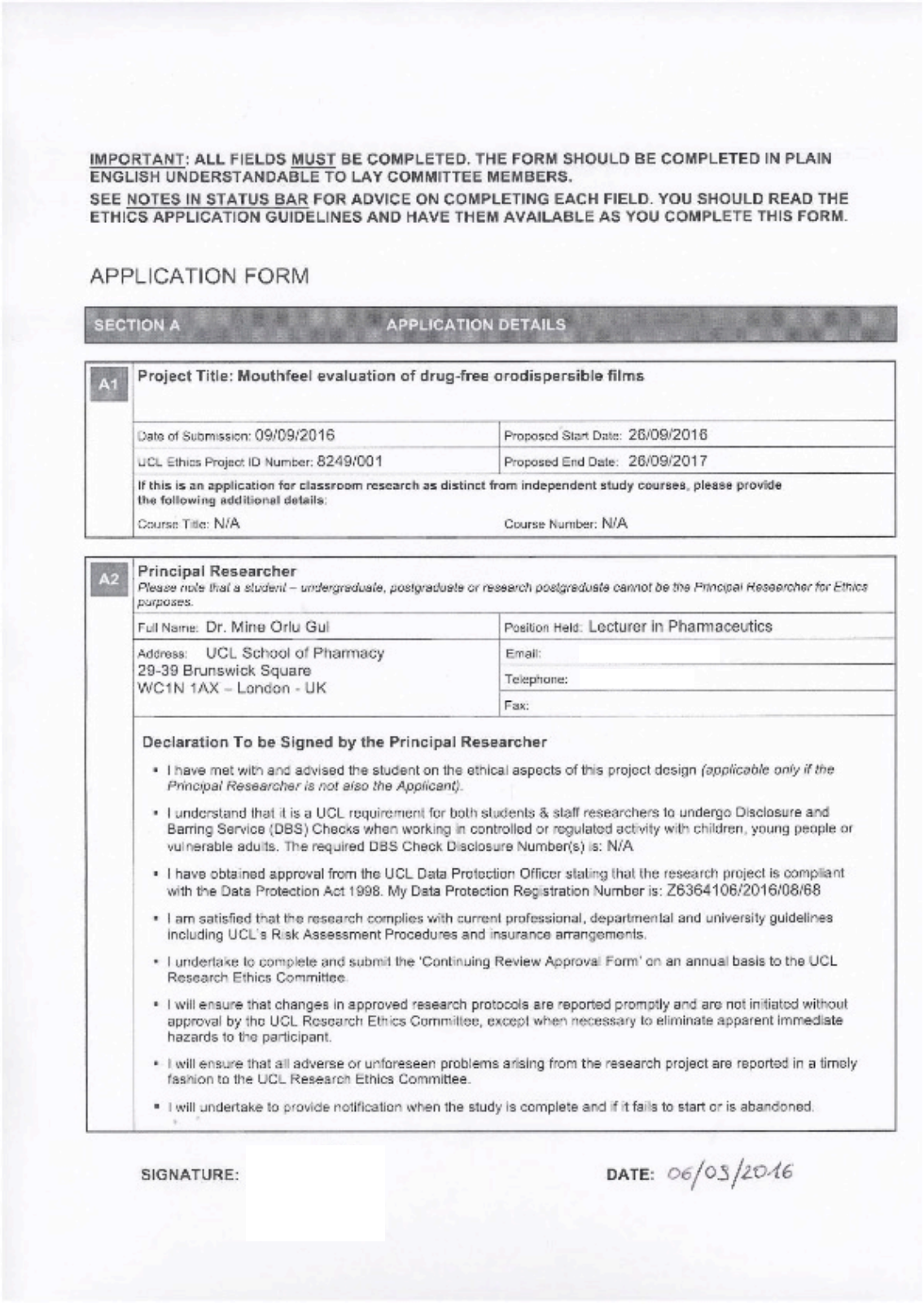
Annexes

Annex 1: REC application related to study presented in chapter 2

Annex 2: REC application related to study presented in chapter 5

1. REC application related to study presented in chapter 2



IMPORTANT: ALL FIELDS MUST BE COMPLETED. THE FORM SHOULD BE COMPLETED IN PLAIN ENGLISH UNDERSTANDABLE TO LAY COMMITTEE MEMBERS.

SEE NOTES IN STATUS BAR FOR ADVICE ON COMPLETING EACH FIELD. YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.

APPLICATION FORM

SECTION A APPLICATION DETAILS

A1 **Project Title: Mouthfeel evaluation of drug-free orodispersible films**

Date of Submission: 09/09/2016	Proposed Start Date: 26/09/2016
UCL Ethics Project ID Number: 8249/001	Proposed End Date: 26/09/2017

If this is an application for classroom research as distinct from independent study courses, please provide the following additional details:

Course Title: N/A Course Number: N/A

A2 **Principal Researcher**

Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.

Full Name: Dr. Mine Orlu Gul	Position Held: Lecturer in Pharmaceutics
Address: UCL School of Pharmacy 29-39 Brunswick Square WC1N 1AX – London - UK	Email: Telephone: Fax:

Declaration To be Signed by the Principal Researcher

- I have met with and advised the student on the ethical aspects of this project design *(applicable only if the Principal Researcher is not also the Applicant).*
- I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: N/A
- I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the Data Protection Act 1998. My Data Protection Registration Number is: Z6364106/2016/08/68
- I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements.
- I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee.
- I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate hazards to the participant.
- I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee.
- I will undertake to provide notification when the study is complete and if it fails to start or is abandoned.

SIGNATURE: **DATE:** 06/03/2016

A3 **Applicant(s) Details** *(if Applicant is not the Principal Researcher e.g. student details):*

Full Name: Mariagiovanna Scarpa	
Position Held: PhD student	
Address: UCL School of Pharmacy 29-39 Brunswick Square WC1N 1AX – London - UK	Email: Telephone: Fax: N/A
Full Name: N/A	
Position Held: N/A	
Address: N/A	Email: N/A Telephone: N/A Fax: N/A

A4 **Sponsor/ Other Organisations Involved and Funding**

a) **Sponsor:** ☒ **UCL** ☐ **Other institution**
If your project is sponsored by an institution other than UCL please provide details: N/A

b) **Other Organisations**: If your study involves another organisation, please provide details. *Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request.* N/A

c) **Funding:** What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? *If study is funded solely by UCL this should be stated, the section should not be left blank.* UCL

A5 **Signature of Head of Department [or Chair of the Departmental Ethics Committee]**
(This must not be the same signature as the Principal Researcher)

A. I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it.

I am satisfied that *[please highlight as appropriate]*:

(1) Data Protection registration:

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

(2) a risk assessment:

- **has been satisfactorily completed**
- **has been initiated**

(3) appropriate insurance arrangements are in place and appropriate sponsorship [funding] has been approved and is in place to complete the study. ☒ **Yes** ☐ **No**

(4) a Disclosure and Barring Service check(s):

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

Links to details of UCL's policies on the above can be found at: http://ethics.grad.ucl.ac.uk/procedures.php

****If any of the above checks are not required please clarify why below.**

The study does not involve children under 18 years of age or vulnerable adults

B. Having read the 'criteria of minimal risk' as defined on page 3 of our Guidelines at: http://ethics.grad.ucl.ac.uk/forms/guidelines.pdf I recommend that this application should be considered by the Chair of the UCL REC ☐ Yes ☒ No

PRINT NAME: Duncan Craig

SIGNATURE: **DATE:** 07/09/2016

SECTION B DETAILS OF THE PROJECT

B1 **Please provide a brief summary of the project in simple prose outlining the intended value of the project, giving necessary scientific background** *(max 500 words)*.

The non-acceptance of a medicine due to issues concerning ability or willingness to take it can have detrimental consequences on treatment outcomes if the medicine is not taken as prescribed. Mouthfeel and other organoleptic properties of the orally administered dosage form that can potentially affect acceptability are becoming relevant issues for patient compliance with prescribed medicines, especially in special populations (Liu et al. 2014). Orodispersible films (ODF) are stamp-size polymer-made wafers exhibiting promising patient-friendly features. ODF can trigger specific mouthfeel and handling experiences (Krampe et al. 2015), that could either have a positive or negative impact on patient compliance. To study how ODF can offer strategic characteristics to meet the needs of specific patient populations, the overall acceptability of the dosage form to young healthy volunteers must be first assessed. Our aim is to assess how different aspects of ODF mouthfeel and handling affect patient acceptability.

The film-forming polymer determines specific characteristics of the final product depending on its nature and molecular weight (Mw). Drug-free orodispersible films made of Polyvinyl Alcohol (PVOH) or Polyvinylpyrrolidone (PVP) with different molecular weight ranges will be assessed (PVOH Mw 13 – 23,000; PVOH Mw 164 - 184,000; PVP Mw 2 – 3,000; PVP Mw 44 – 54,000). Among the ODF characteristics, stickiness on handling, size, thickness, stickiness in the mouth, and disintegration time will be assessed.

The aim of this study is to conduct an sensory analysis in human volunteers to assess:

- The acceptability of size, thickness, stickiness and disintegration time
- The impact of polymeric molecular weight on the perception of ODF stickiness and disintegration time.

B2 **Briefly characterise in simple prose the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken** *(max 500 words).*

Type: Single blind, crossover, single centre study (Annex 1 – flow diagram).

Duration: 2 hours per day for 3 repeated sessions.

Food: No spicy food should be taken from 30 minutes before investigation.

Inclusion criteria: Healthy male or female adults, able to understand and speak English. We will attempt to recruit an equal number of male and female subjects.

Exclusion criteria: Recent dental care up to 15 days before the tests and any known excipient allergies. Medicinal treatments altering saliva production. Sensory disorders affecting the mouth or local anaesthetics into the mouth within 24 hours of the study.

Sample preparation:

Samples will be prepared under strict quality measures in a dedicated class II clean room under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621; Sejal Ranmal 2074443) and according to standard operating procedures that have been approved by the PI and the departmental safety officer; Annex 3 – Standard Operating Procedures). Excipients and sterile water for injection will be GMP compliant, and meeting the Ph. Eur specifications for human oral administration.

Experimental protocol:

Participants will be asked to place the whole sample in their mouth, start the stopwatch, allow the sample to dissolve completely, stop the stopwatch, and swallow the sample. Participants will be alerted of the possibility to reject one or more samples if they don't feel confident to swallow the sample safely. Immediately after sample ingestion, they will rate the sample properties using a computerised questionnaire (Qualtrics) with categorical scales and multiple choice questions (Annex 4 - data collection form). Participants will have free access to water to aid swallowing and/or rinse their palate. At the same time, the researcher will rate the participant's facial expression, jaw movements, and swallowing of the film using a modified version of the Medicines Acceptability Scale (MAS). At the end of the session, volunteers will be invited to participate in a brief semi-structured interview (10 mins).

The assessment will be divided in three repeated sessions of approximately 2h each. In each session, participants will receive a total of four placebo ODF (3 x 2 cm – 60 to 100 μm thick) film samples. An interval of 10 minutes will be respected between samples. ODF samples will be numbered with a random three-digit code.

Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).

B3 **Where will the study take place (please provide name of institution/department)?**
If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998?

UCL School of Pharmacy, in the pharmacy practice dispensary. Participants will be seated at individual computer stations and screened off from other volunteers.

Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test).

B4 **Have collaborating departments whose resources will be needed been informed and agreed to participate?**
Attach any relevant correspondence.

N/A

B5 **How will the results be disseminated, including communication of results with research participants?**

Upon recruitment, participants will be assigned an individual, anonymous code only accessible by the researchers. If they wish so, participants can request to visualise the results of their performance after the study. Once completed, the results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations.

A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. As the results are collected anonymously, participant confidentiality will be maintained when results are disseminated.

B6 **Please outline any ethical issues that might arise from the proposed study and how they are be addressed.** *Please note that all research projects have some ethical considerations so do not leave this section blank.*

Confidentiality: This study will not be very intrusive since minimum personal details (contact details, age and gender) will be recorded. Confidentiality will not be breeched as once participants will be recruited, they will be assigned a code only accessible by the researchers. Once completed, the results of the study may be reported and disseminated in anonymous form.

Participant burden: The study will require each participant to attend sensory evaluation sessions for approximately 2h on each assessment day (2h 10 min in the last session only). There is a potential for participants to suffer from temporary oral discomfort if the taste, aftertaste or mouthfeel of the sample is aversive. In some cases, sample size or misplacement may cause the film to accidentally trigger chocking reflex though this is rare. This does not represent any hazard as the film samples are very thin, soft and flexible, and their maximum disintegration time is 60 seconds. Even in case of aspiration, the film will keep dissolving as previously wet by the participant's saliva and will turn into a completely liquid form. Furthermore, the small size of the films prevents any risk of airway obstruction. If any participant shows high discomfort, the assessment will be immediately stopped.

Adverse effects: The time of contact with the sample depends on the disintegration time and film forming polymer. In any case, this will not exceed 90 seconds. The formulation in dissolved form will be swallowed by the participant. All the formulations are placebos (no drug content), and excipients are selected on the basis of their safety and only when already in use in authorised dosage forms. Participants who are aware of any allergic reaction to any of the components will be excluded from the study.

Concentrations for Poly(vinyl) alcohol (PVOH):

Poly(vinyl) alcohol (PVOH) (CAS no. 9002-89-5) is a synthetic polymer used in a wide range of industrial, commercial, medical and food applications. The acute oral toxicity of PVOH is very low, with LD50s in the range of 15-20 g/kg. Orally administered PVOH is very poorly absorbed from the gastrointestinal tract. PVOH does not accumulate in the body when administered orally. PVOH is not mutagenic or clastogenic. No-Observed-Adverse-Effect-Level (NOAELs) of orally administered PVOH in male and female rats were 5000 mg/kg body weight/day in the 90-day dietary study and 5000 mg/kg body weight/day in the two-generation reproduction study (DeMerlis and Schoneker, 2003). In 2003, PVOH received notification as Generally Recognised As Safe (GRAS) by the Food and Drug Administration (FDA). The assignment of a permanent Acceptable Daily Intake (ADI) of 50 mg/kg body weight/day by the Joint FAO/WHO Expert Committee on Food Additives was conferred in June 2003 (FDA-WHO).

Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the ADI would correspond to 3,500 mg/day (3.5 g/day). Each orodispersible film (area 6 cm^2), contains 31 mg of PVOH. Each participant receives maximum 2 samples. Therefore, the total daily intake of PVOH would be 62 mg/day (Males: 0.91 mg/kg/day; Females: 1.06 mg/kg/day), way below the ADI values stated by FDA.

Concentration of Polyvinylpyrrolidone (PVP):

The acute oral toxicity of PVP (CAS no. 9003-39-8) is very low, with LD50 between 15 and 20 g/kg (40 g/kg in rats) (Scheffner, 1955; BASF, 1958). Orally administered PVP is poorly absorbed from the

gastrointestinal tract and quickly eliminated. PVP of varying molecular weights was reported not to pass the blood-brain as well as the placental barriers (Ravin et al.,1952). The $T_{1/2}$ for the elimination of povidone in the average molecular weight range of 40 000 has been reported to be as low as 12 hours and as high as 72 hours. FSCJ (Food Safety Commission of Japan) concluded that PVP is of no concern for genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity and reproductive and developmental toxicity, on the basis of the available toxicological data. PVP is among the inactive ingredients in FDA approved drugs database (FDA, 2010). PVP acceptable daily intake for man (ADI) was fixed at 25 mg/kg body weight by the Joint FAO/WHO Expert Committee on Food Additives in 1966 and 1973 (FDA-WHO). Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the ADI would correspond to 1,700 mg/day (1.7 g/day), and 1,450 mg/day (1.45 g/day) respectively.
Each orodispersible film (area 6 cm^2), contains 31 mg of PVP. Each participant receives maximum 2 samples. Therefore, the total daily intake of PVOH would be 62 mg/day (Males: 0.91 mg/kg/day; Females: 1.07 mg/kg/day), way below the ADI values stated by FDA.

In the case of any adverse events, first aid will be sought as necessary and the study will be stopped. Dr. Catherine Tuleu is a First aider at work (St John's Ambulance). For complaints, the supervisor or a third party (not directly involved in research team) Ms. Joanna O'Brien (Institute Manager) can be contacted for further advice.

The research team has previous experience in taste assessment studies using the "swirl and spit" method. The principal investigator has considerable experience of conducting and supervising such studies using volunteer panels including the following published/presented research:

School of Pharmacy REC/A/09/68 - Orlu-Gul M, Fisco G, Parmar D, Gill H, Tuleu C. A new reconstitutable oral paediatric hydrocortisone solution containing hydroxypropyl-β-cyclodextrin. Drug Dev Ind Pharm. 2013;39(7):1028-36;

UCL REC 4612/003 - Soto J, Ranmal S, Gondongwe X, Olanipekun F, Marbay J, Orlu Gul M and Tuleu C. Amlodipine in Paediatrics and Geriatrics: palatability issues. 5th European Paediatric Formulation Initiative Conference-Formulating Better Medicines for Children, 18-19 September 2013, Barcelona, Spain.

SECTION C DETAILS OF PARTICIPANTS

C1 **Participants to be studied**

C1a. Number of volunteers:	24
Upper age limit:	65
Lower age limit:	18

C1b. Please justify the age range and sample size:

Any healthy adults (staff and students) working at UCL. Age range should exclude any vulnerable groups. We will attempt to recruit an equal number of male and female subjects. This sample size is within the range used in previous human taste panel pilot palatability studies and large enough to apply appropriate statistical analysis.

C2 **If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the UK Data Protection Act 1998.**

N/A

C3 **Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship?** ☐ **Yes** ☒ **No**

How will you ensure that participants in these groups are competent to give consent to take part in this study? *If you have relevant correspondence, please attach it.*

N/A

C4 **Will payment or any other incentive, such as gift service or free services, be made to any research participant?**

☒ **Yes** ☐ **No**

If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.

Participants will be paid £10 in cash for volunteering. This will be paid from the GL account of the applicant. Before and during any part of the study, participants will have the option to withdraw if they wish.

Please justify the payment/other incentive you intend to offer.

This is a thank you gesture for the time committed to the project.

C5 **Recruitment**

(i) Describe how potential participants will be identified:

Potential participants will be students and staff members of UCL School of Pharmacy (healthy adults aged 18 to 65 years), and these will be the only persons invited to participate in this study.

(ii) Describe how potential participants will be approached:

An email (annex 2) will be circulated using the UCL School of Pharmacy Staff and Students mailing lists to advertise the study. Potential participants interested in taking part in the study will be invited to contact the research team directly using the contact details included in the email. Members of the research team who will be responsible for recruitment will be postgraduate students only. Staff members in the position of influencing in any way the decision of participants in taking part to the study will not be involved in the recruitment process.

(iii) Describe how participants will be recruited:

Potential participants who contact the research team will be provided with the information sheet. They will until one week before the study to evaluate whether to take part, and will be invited to ask questions or obtain further information if they wish. Once decision has been made, participants will contact the research team to confirm their participation and select suitable dates and times. Prior to the session, a member of the research team will verbally explain the study and take informed consent from the participant.

Attach recruitment emails/adverts/webpages. A data protection disclaimer should be included in the text of such literature.

C6

Will the participants participate on a fully voluntary basis? ☒ Yes ☐ No

Will UCL students be involved as participants in the research project? ☒ Yes ☐ No

If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.

Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?

Granting this information will be included in the invitation email, information sheet and consent form, all participants will be reminded in any suitable occasion that their participation is completely optional and will not affect in any way their studies/ relationships with the academic environment.

C7

CONSENT

Please describe the process you will use when seeking and obtaining consent.

The attached form will be used to obtain written informed consent from the recruited participants on the day of the study. Participants are expected to sign the consent form only after having read and understood the information sheet previously provided, and after having asked any questions they may have to the research team. On the day of the study, members of the research team will be available to further provide information before the consent form will be signed. The form will be provided in two copies to be signed. One will be kept by the participant and another will be retained by the research team.

A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.

In cases where it is not proposed to obtain the participants informed consent, please explain why below.

N/A

C8

Will any form of deception be used that raises ethical issues? If so, please explain.

No

C9

Will you provide a full debriefing at the end of the data collection phase? ☒ Yes ☐ No

If 'No', please explain why below.

N/A

C10

Information Sheets And Consent Forms

A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.

UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE

Mouthfeel evaluation of drug-free orodispersible films

Participant Information Sheet

You will be provided with a copy of this information sheet.

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 8249/001

Principal Investigator: Dr. Mine Orlu Gul
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 77535968
Email:

We would like to invite you to participate in this research project. Taking part is voluntary; it is up to you to decide whether or not to take part, and choosing not to will not disadvantage you in any way. If you do decide to take part, you will still be free to withdraw at any time without the need to give a reason.

Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish. Please feel free to ask us if there is anything that is not clear or you would like more information.

Details of the Study

What is the purpose and aim of this project?

The ability to take medicines according to their instructions is key to the success of a medical treatment. Orodispersible films (ODFs) are considered "more acceptable" dosage forms, especially to certain patient groups (E.g. children, older patients, etc…). However, some characteristics of ODFs may affect the ability or willingness to take them as recommended. There is a great need to understand which characteristics of ODFs make them preferable or unpleasant/unacceptable. This study is expected to provide us with valuable information to develop more acceptable ODF.

Drug-free films will be given to you to test. These are thin transparent films that quickly dissolve with saliva. The ingredients (Polyvinyl alcohol and Polyvinylpyrrolidone) are two pharmaceutical excipients that are widely used in tablets and food.

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 65 years to take part.

If you have any allergies to excipients, or if you have had any dental care or specific medicinal treatments (see list below) during the 15 days before the tests, then unfortunately you will be unable to take part.

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL. You will be asked to commit to three sessions of 2 hours each. If you decide to take part, you will

be asked to take four drug-free orodispersible films. We will ask you to place them in your mouth, wait until they dissolve completely and then swallow. Meanwhile, you will be asked to take the time in which films dissolve in your mouth using a stopwatch. We will then ask you to rate various sensory aspects each time on a scale (size, thickness, etc.), and to tell us more about your experience in a quick face-to-face interview (10 minutes).

You will be allowed to reject ANY of the samples at any point of the study if you don't feel comfortable to take it.

Are there any risks involved?

The films being tested only contain polyvinyl alcohol (PVOH) and polyvinylpyrrolidone (PVP). These are two perfectly safe pharmaceutical excipients already used in many marketed formulations. If you experience any unpleasant reaction, you must alert a member of the team and we will stop the study immediately. The researchers are trained in First Aid and medical doctors will be present to assess the situation. If necessary, we will also contact emergency services. PVOH and PVP are very safe compounds, so we do not anticipate that you will experience any side effects.

If the samples you are given have a poor taste or texture, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples and vomit, however this is extremely rare. Nevertheless, films dissolve rapidly, which minimises the potential for adverse effects, and can be spit out at any time. Further a minimum delay of 10 minutes will be respected between each test film.

Who will know that I took part, and what happens after?

Only members of the research team will know that you took part and have access to the results. Confidentiality will be maintained during the study and after it has finished. If the study is published or presented to a wider audience, your anonymity will be respected through anonymisation procedures. All data will be collected and stored in accordance with the Data Protection Act 1998.

If you would like to know the results of the study once it has finished, please feel free to contact us using the details overleaf, as we'd be happy to share these with you.

Who can I contact for more information?

Please contact the research team, using the details overleaf, if you would like to take part, or have any questions about the study.

If you would like to discuss it with someone outside of the research team, please contact

Ms Joanna O'Brien
Institute Manager
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel:
Email:

Thank you for taking the time to read this information sheet

- Medications preventing your eligibility to participate to the study (Scully CBE, 2003):

  Anticholinergic drugs
  Tricyclics antidepressants
  Muscarinic receptor antagonists for treatment
  of overactive bladder
  Alpha receptor antagonists for treatment of urinary retention

Antipsychotics such as phenothiazines
Diuretics
Antihistamines
Sympathomimetic drugs
Antihypertensive agents
Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)
Appetite suppressants
Decongestants and cold cures'
Bronchodilators
Skeletal muscle relaxants
Antimigraine agents
Benzodiazepines, hypnotics, opioids and drugs of abuse
H 2 antagonists and proton pump inhibitors
Cytotoxic drugs
Retinoids
Anti-HIV drugs such as dideoxyinosine (DDI) and protease inhibitors
Cytokines

When you have completed your Information Sheet, please DELETE the advice section below from your application form before submitting it to the Committee.

Details of Study MUST include the following:

- Aims of the research and possible benefits.
- Who you are recruiting
- What will happen if the participant agrees to take part (when, where, how long etc)
- Any risks (e.g. need for disclosure of information to a third party, possibility for distress)
- Possible benefits (it is good practice to offer participants a copy of the final report)
- Arrangements for ensuring anonymity and confidentiality (see optional statements below for examples). To ensure compliance with the Data Protection Act participants must be informed of what information will be held about them and who will have access to it (this relates to information that is identifiable or could potentially be linked back to an individual.)

Statements which researchers MIGHT also include as appropriate:

- A decision to withdraw at any time, or decision not to take part, will not affect the standard of care/education you receive.
- If you agree to take part you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not be re-contacted.
- You may withdraw your data from the project at any time up until it is transcribed for use in the final report (*insert date)*.
- Recorded interviews will be transcribed (written up) and the tape will then be wiped clear.
- If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form.
- Submission of a completed questionnaire implies consent to participate.
- As participation is anonymous it will not be possible for us to withdraw your data once you have returned your questionnaire.
- What if I have further questions, or if something goes wrong? If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact UCL using the details below for further advice and information:
  Student researchers: Insert the name and full UCL contact address and number of your supervisor.
  *Staff researchers: Please insert the following: The Chair, *Insert full address details for the UCL Research Ethics Committee, ethics@ucl.ac.uk

Informed Consent Form for in Research Studies

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: **Mouthfeel evaluation of drug-free orodispersible films**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 8249/001

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- Agree that my data, after it has been fully anonymised, can be shared with other researchers *[to satisfy Research Council funded projects as Research Councils have changed their guidance regarding data sharing]*

Signed: Date:

When you have completed your Informed Consent Form, please DELETE the advice section below from your application form before submitting it to the Committee.

Statements which researchers MIGHT include as appropriate:

- I understand that my participation will be taped/video recorded and I consent to use of this material as part of the project.
- I understand that I must not take part if
- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies.
- I understand that the information I have submitted will be published as a report and I will be sent a copy. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- I understand that I am being paid for my assistance in this research and that some of my personal details will be passed to UCL Finance for administration purposes.
- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.

This is not an exhaustive list and you should consider whether you need to amend any of these statements or design different ones that are more applicable to your research.

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SECTION D DETAILS OF RISKS AND BENEFITS TO THE RESEARCHER AND THE RESEARCHED

D1 **Have UCL's Risk Assessment Procedures been followed?** ☒ **Yes** ☐ **No**

If **No**, please explain.

N/A

D2 **Does UCL's insurer need to be notified about your project before insurance cover can be provided?** ☐ **Yes** ☒ **No**

The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.

If **Yes**, please provide confirmation that the appropriate insurance cover has been agreed. *Please attach your UCL insurance registration form and any related correspondence.*

N/A

D3 **Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).**

This project hold little risk to the research which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.

D4 **Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research?** ☒ **Yes** ☐ **No**

If **Yes**, please describe the nature of the risk or stress and how you will minimise and monitor it.

The procedures may cause temporary physical discomfort (exposure to unpleasant taste or general mouthfeel) during assessment if the test samples texture, taste or aftertaste is aversive. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, a delay of at least 10 minutes will be respected between each tested sample. Before and after each test sample, subjects can rinse their mouth with water until they can no longer perceive the previous sample. The participants will be provided with necessary instruction on properly testing the samples. Risk will be continuously monitored by asking participants how they feel between sample administrations. If participant report any distress, they will be excluded from the study. If some participants show high discomfort to texture or taste, the study will be immediately stopped.

D5 **Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?**

No

If **Yes,** please explain how you will deal with this.

N/A

D6 **Please describe any expected benefits to the participant.**

Participants will receive no direct benefits by taking part to this study. They may receive indirect benefit through contribution to patient care improvement regarding the acceptability of patient-centric formulations.

D7 **Specify whether the following procedures are involved:**

Any invasive procedure(s) ☐ **Yes** ☒ **No**

Physical contact ☐ **Yes** ☒ **No**

Any procedure(s) that may cause mental distress ☐ **Yes** ☒ **No**

Please state briefly any precautions being taken to protect the health and safety of the research participants.

The study is divided in three sessions and the number of samples is kept to a minimum in each session to minimise fatigue and discomfort. Before and after each test sample, subjects will rinse their mouth with water and will have free access to water during the study. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the study will be immediately stopped.

D8 **Does the research involve the use of drugs?** ☐ **Yes** ☒ **No**

If **Yes**, please name the drug/product and its intended use in the research and then complete Appendix I

N/A

Does the project involve the use of genetically modified materials? ☐ **Yes** ☒ **No**

If **Yes**, has approval from the Genetic Modification Safety Committee been obtained for work? ☐ Yes ☐ No

If **Yes**, please quote the Genetic Modification Reference Number: N/A

D9	Will any non-ionising radiation be used on the research participant(s)? ☐ Yes ☒ No If **Yes**, please complete Appendix II.

D10	Are you using a medical device in the UK that is CE-marked and is being used within its product indication? ☐ Yes ☒ No If **Yes**, please complete Appendix III.

CHECKLIST

Please submit ether 12 copies (1 original + 11 double sided photocopies) of your completed application form for full committee review or 3 copies (1 original + 2 double sided copies) for chair's action, together with the appropriate supporting documentation from the list below to the UCL Research Ethics Committee Administrator. You should also submit your application form electronically to the Administrator at: ethics@ucl.ac.uk

Documents to be Attached to Application Form (if applicable)	Ticked if attached	Tick if not relevant
Section B: Details of the Project		
• Questionnaire(s) / Psychological Tests	☒	☐
• Relevant correspondence relating to involvement of collaborating department/s and agreed participation in the research.	☐	☒
Section C: Details of Participants		
• Parental/guardian consent form for research involving participants under 18	☐	☒
• Participant/s information sheet	☒	☐
• Participant/s consent form/s	☒	☐
• Advertisement	☒	☐
Section D: Details of Risks and Benefits to the Researcher and the Researched		
• Insurance registration form and related correspondence	☐	☒
Appendix I: Research Involving the Use of Drugs		
• Relevant correspondence relating to agreed arrangements for dispensing with the pharmacy	☐	☒
• Written confirmation from the manufacturer that the drug/substance has has been manufactured to GMP	☐	☒
• Proposed volunteer contract	☐	☒
• Full declaration of financial or direct interest	☐	☒
• Copies of certificates: CTA etc…	☐	☒
Appendix II: Use of Non-Ionising Radiation		
Appendix III: Use Medical Devices		

2. REC application related to study presented in chapter 5

IMPORTANT: ALL FIELDS MUST BE COMPLETED. THE FORM SHOULD BE COMPLETED IN PLAIN ENGLISH UNDERSTANDABLE TO LAY COMMITTEE MEMBERS.

SEE NOTES IN STATUS BAR FOR ADVICE ON COMPLETING EACH FIELD. YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.

APPLICATION FORM

SECTION A — APPLICATION DETAILS

A1

Project Title: Mouthfeel evaluation of drug-free orodispersible films - 2

Date of Submission: 11/11/2016	Proposed Start Date: 28/11/2016
UCL Ethics Project ID Number: 6249/002	Proposed End Date: 28/11/2017

If this is an application for classroom research as distinct from independent study courses, please provide the following additional details:

Course Title: N/A Course Number: N/A

A2

Principal Researcher

Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.

Full Name: Dr. Mine Orlu Gul	Position Held: Lecturer in Pharmaceutics
Address: UCL School of Pharmacy 29-39 Brunswick Square WC1N 1AX – London - UK	Email: Telephone: Fax:

Declaration To be Signed by the Principal Researcher

- I have met with and advised the student on the ethical aspects of this project design *(applicable only if the Principal Researcher is not also the Applicant).*
- I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: N/A

I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the Data Protection Act 1998. My Data Protection Registration Number is: Z6364106/2016/10/51

- I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements.
- I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee.
- I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate hazards to the participant.
- I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee.
- I will undertake to provide notification when the study is complete and if it fails to start or is abandoned.

SIGNATURE: **DATE:**

A3 **Applicant(s) Details** *(if Applicant is not the Principal Researcher e.g. student details):*

Full Name: Mariagiovanna Scarpa	
Position Held: PhD student	
Address: UCL School of Pharmacy 29-39 Brunswick Square WC1N 1AX – London - UK	Email: Telephone Fax: N/A
Full Name: N/A	
Position Held: N/A	
Address: N/A	Email: N/A Telephone: N/A Fax: N/A

A4 **Sponsor/ Other Organisations Involved and Funding**

a) **Sponsor:** ☒ **UCL** ☐ **Other institution**
If your project is sponsored by an institution other than UCL please provide details: N/A

b) **Other Organisations**: If your study involves another organisation, please provide details. *Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request.* N/A

c) **Funding:** What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? *If study is funded solely by UCL this should be stated, the section should not be left blank.* UCL

A5 **Signature of Head of Department [or Chair of the Departmental Ethics Committee]**
(This must not be the same signature as the Principal Researcher)

A. I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it.

I am satisfied that *[please highlight as appropriate]*:

(1) Data Protection registration:

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

(2) a risk assessment:

- **has been satisfactorily completed**
- **has been initiated**

(3) appropriate insurance arrangements are in place and appropriate sponsorship [funding] has been approved and is in place to complete the study. ☒ **Yes** ☐ **No**

(4) a Disclosure and Barring Service check(s):

- **has been satisfactorily completed**
- **has been initiated**
- **is not required**

Links to details of UCL's policies on the above can be found at: http://ethics.grad.ucl.ac.uk/procedures.php

****If any of the above checks are not required please clarify why below.**

The study does not involve children under 18 years of age or vulnerable adults

B. Having read the 'criteria of minimal risk' as defined on page 3 of our Guidelines at: http://ethics.grad.ucl.ac.uk/forms/guidelines.pdf I recommend that this application should be considered by the Chair of the UCL REC ☐ Yes ☒ No

PRINT NAME: Duncan Craig

DATE: 3 Nov 2016

SIGNATURE:

SECTION B DETAILS OF THE PROJECT

B1 **Please provide a brief summary of the project in simple prose outlining the intended value of the project, giving necessary scientific background** *(max 500 words)*.

The non-acceptance of a medicine due to issues concerning ability or willingness to take it can have detrimental consequences on treatment outcomes if the medicine is not taken as prescribed. Mouthfeel and other organoleptic properties of the orally administered dosage form that can potentially affect acceptability are becoming relevant issues for patient compliance with prescribed medicines, especially in special populations (Liu et al. 2014). Orodispersible films (ODF) are stamp-size polymer-made wafers exhibiting promising patient-friendly features. ODF can trigger specific mouthfeel and handling experiences (Krampe et al. 2015), that could either have a positive or negative impact on patient compliance. To study how ODF can offer strategic characteristics to meet the needs of specific patient populations, the overall acceptability of the dosage form to young healthy volunteers must be first assessed. Our aim is to assess how different aspects of ODF mouthfeel and handling affect patient acceptability.

The nature of the film-forming polymer determines main characteristics of the final product. However, other ingredients can be added in order to improve the film manufacturability, texture and taste. Some commonly added ingredients include other polymers, plasticisers, surfactants, and taste modifiers. The first application submitted (REC ID n. 8249/001) aims to investigate how different aspects of ODF mouthfeel and handling affect patient acceptability. In this study we would like to investigate whether combinations of different ingredients can further affect the organoleptic characteristics of ODF.

Drug-free orodispersible films made of Polyvinyl Alcohol (PVOH) or Carboxymethyl cellulose (CMC) combined with another polymer (polyvinylpyrrolidone – PVP), plasticiser (glycerol), and sweetener (sucralose) will be assessed. Among the ODF characteristics, stickiness on handling, size, thickness, stickiness in the mouth, and disintegration time will be assessed.

The aim of this study is to conduct a sensory analysis in human volunteers to assess:

- The impact of the addition of other polymers, plasticiser and sweetener to the backbone film-

	forming polymer on the perception of ODF stickiness and disintegration time.

B2	**Briefly characterise in simple prose the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken** *(max 500 words).*

Type: Single blind, crossover, single centre study (Annex 1 – flow diagram).

Duration: 3 hours per day for 3 repeated sessions.

Food: No spicy food should be taken from 30 minutes before investigation.

Inclusion criteria: Healthy male or female adults, able to understand and speak English. We will attempt to recruit an equal number of male and female subjects.

Exclusion criteria: Recent dental care up to 15 days before the tests and any known excipient allergies. Medicinal treatments altering saliva production. Sensory disorders affecting the mouth or local anaesthetics into the mouth within 24 hours of the study.

Sample preparation:

Samples will be prepared under strict quality measures in a dedicated class II clean room under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621; Sejal Ranmal 2074443; Alexander Keeley 2204242) and according to standard operating procedures that have been approved by the PI and the departmental safety officer; Annex 3 – Standard Operating Procedures). Excipients and sterile water for injection will be GMP compliant, and meeting the Ph. Eur specifications for human oral administration.

Experimental protocol:

Participants will be asked to place the whole sample in their mouth, start the stopwatch, allow the sample to dissolve completely, stop the stopwatch, and swallow the sample. Participants will be alerted of the possibility to reject one or more samples if they don't feel confident to swallow the sample safely. Immediately after sample ingestion, they will rate the sample properties using a computerised questionnaire (Qualtrics) with categorical scales and multiple choice questions (Annex 4 - data collection form). Participants will have free access to water to aid swallowing and/or rinse their palate. At the same time, the researcher will rate the participant's facial expression, jaw movements, and swallowing of the film using a modified version of the Medicines Acceptability Scale (MAS). At the end of each sample assessment, volunteers will be invited to participate in a brief semi-structured interview (10 mins).

The assessment will be divided in three repeated sessions of approximately 3h each. In each session, participants will receive a total of seven placebo ODF (3 x 2 cm – 60 to 100 μm thick) film samples. An interval of 10 minutes will be respected between samples. ODF samples will be numbered with a random three-digit code.

Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).

B3	**Where will the study take place (please provide name of institution/department)?** If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998? UCL School of Pharmacy, in the pharmacy practice dispensary. Participants will be seated at individual computer stations and screened off from other volunteers. Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test).

B4	**Have collaborating departments whose resources will be needed been informed and agreed to participate?** *Attach any relevant correspondence.* N/A

B5	**How will the results be disseminated, including communication of results with research participants?** Upon recruitment, participants will be assigned an individual, anonymous code only accessible by the researchers. If they wish so, participants can request to visualise the results of their performance after the study. Once completed, the results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations. A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. As the results are collected anonymously, participant confidentiality will be maintained when results are disseminated.

B6	**Please outline any ethical issues that might arise from the proposed study and how they are be addressed.** *Please note that all research projects have some ethical considerations so do not leave this section blank.* Confidentiality: This study will not be very intrusive since minimum personal details (contact details, age and gender) will be recorded. Confidentiality will not be breeched as once participants will be recruited, they will be assigned a code only accessible by the researchers. Once completed, the results of the study may be reported and disseminated in anonymous form. Participant burden: The study will require each participant to attend sensory evaluation sessions for approximately 3h on each assessment day. There is a potential for participants to suffer from temporary oral discomfort if the taste, aftertaste or mouthfeel of the sample is aversive. In some cases, sample size or misplacement may cause the film to accidentally trigger chocking reflex though this is rare. This does not represent any hazard as the film samples are very thin, soft and flexible, and their maximum disintegration time is 60 seconds. Even in case of aspiration, the film will keep dissolving as previously wet by the participant's saliva and will turn into a completely liquid form. Furthermore, the small size of the films prevents any risk of airway obstruction. If any participant shows high discomfort, the assessment will be immediately stopped. Adverse effects: The time of contact with the sample depends on the disintegration time and film forming polymer. In any case, this will not exceed 90 seconds. The formulation in dissolved form will be swallowed by the participant. All the formulations are placebos (no drug content), and excipients are selected on the basis of their safety and only when already in use in dosage forms authorised by regulatory bodies. Participants who are aware of any allergic reaction to any of the components will be excluded from the study. Poly(vinyl) alcohol (PVOH) safety information: Poly(vinyl) alcohol (PVOH) (CAS no. 9002-89-5) is a synthetic polymer used in a wide range of industrial, commercial, medical and food applications. PVOH has been used in US Food and Drug Administration approved drug product for oral administration as listed in electronic Medicines Compendium (eMC) https://www.medicines.org.uk/emc/medicine/28020#EXCIPIENTS

PVOH is contained as inactive ingredient in Setofilm® orodispersible films (license holder: Norgine BV). The product contains ondansetron as active ingredient and used as preventive of nausea/vomiting. Polyvinyl alcohol is used as inactive ingredient in the product. Setofilm® is commercially available in 2 x 2 cm films. Thickness of the product has not been specified but in the range of the sample films of our study.

The acute oral toxicity of PVOH is very low, with LD50s in the range of 15-20 g/kg. Orally administered PVOH is very poorly absorbed from the gastrointestinal tract. PVOH does not accumulate in the body when administered orally. PVOH is not mutagenic or clastogenic. No-Observed-Adverse-Effect-Level (NOAELs) of orally administered PVOH in male and female rats were 5000 mg/kg body weight/day in the 90-day dietary study and 5000 mg/kg body weight/day in the two-generation reproduction study (DeMerlis and Schoneker, 2003). In 2003, PVOH received notification as Generally Recognised As Safe (GRAS) by the Food and Drug Administration (FDA). The assignment of a permanent Acceptable Daily Intake (ADI) of 50 mg/kg body weight/day by the Joint FAO/WHO Expert Committee on Food Additives was conferred in June 2003 (FDA-WHO).

PVOH exposure levels:

Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the ADI would correspond to 3,500 mg/day (3.5 g/day). Each orodispersible film (area 6 cm^2), contains maximum 31 mg of PVOH. Each participant receives maximum 4 samples. Therefore, the total daily intake of PVOH would be 124 mg/day (Males: 1.82 mg/kg/day; Females: 2.14 mg/kg/day), way below the ADI values stated by FDA.

Carboxymethyl cellulose (CMC) safety information:

Carboxymethylcellulose (CMC) (CAS n. 9004-32-4) is a cellulose derivative widely used in foods (E number E466 – Food Standards Agency (https://www.food.gov.uk/science/additives/enumberlist). as a thickener and emulsion stabiliser (e.g. ice creams). It is also used in pharmaceuticals as thickening agent. CMC has been used in Food and Drug Administration approved drug product for oral administration as listed in the FDA Inactive Ingredients Database (http://www.fda.gov/) . CMC is also contained in the marketed orodispersible film formulation Onsolis® (License holder: Meda Pharmaceuticals) as inactive ingredient (https://www.drugs.com/cdi/onsolis-soluble-film.html) . Onsolis® contains Fentanyl as active ingredient and used as narcotic analgesic to decrease pain. Size and thickness of the product are not specified.
Further information about the CMC safety data is as follows: The LD50 for CMC acute oral toxicity in Rat is 27,000 mg/Kg. CMC is generally recognised as safe by the Food and Drug Administration (FDA) (http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm261244.htm) and is neither degraded nor absorbed by the human body after ingestion. No mortality, clinical signs of toxicity, or adverse toxicological effects on haematology or serum chemistry parameters, feed consumption, or ophthalmologic examinations were noted in any treatment group. The same study was also conducted on pregnant rats with no signs of maternal, foetal or embryo toxicity. The ADI values in humans are "not specified", however, doses as high as 30 g orally administered to men for 7 days were well tolerated by the subjects (Ziegelmayer et al., 1951). Eleven patients received 10 g of Na-CMC daily for six months without complaint, but in seven further cases the dose had to be reduced owing to abdominal discomfort. No haematological changes were observed (Brick, 1952). No acute or chronic toxicity, short or long-term carcinogenity, genotoxicity or teratogenicity were observed. Carboxymethylcellulose nomenclature: Carboxymethylcellulose (CMC) will be also referred to as Sodium Carboxymethylcellulose (Na-CMC) as sodium combines with CMC in saline solutions and during the manufacturing process.

CMC exposure levels:

Each participant will receive maximum 4 orodispersible films made of CMC which is equivalent to maximum 45.84 mg of CMC intake in total. This corresponds to 0.67 and 0.79 mg/Kg/day in males and female participants respectively. Exposure concentrations remain way below the NOAEL values found in rats , and below the laxative effect observed in humans. *Freeman et al., 2003* (https://www.ncbi.nlm.nih.gov/pubmed/12851148) reported No-Observed-Adverse-Effect-Level (NOAEL) at 3,922 and 4,712 mg/Kg/day in males and female rats respectively, after 90 days of treatment with 50,000 ppm Ac-Di-Sol® (CMC – FMC BioPolymer). A laxative effect was observed in men at doses as low as 5 g/person/day (Ref. WHO food additive series n.6 http://www.inchem.org/documents/jecfa/jecmono/v26je08.htm).

Polyvinylpyrrolidone (PVP) safety information:

PVP has been used in US Food and Drug Administration approved drug product for oral administration as listed in DailyMed
https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=37352
PVP is contained as inactive ingredient in Benadryl® strips (license holder: Johnson & Johnson). The product contains Diphenyhydramine HCL as active ingredient and used for temporary relief of symptoms due to hay fever or other upper respiratory allergies. Polyvinylpyrrolidone is used as inactive ingredient in the product. Benadryl® is commercially available in size 4.2 cm. Thickness of the product has not been specified but in the range of the sample films of our study.
The acute oral toxicity of PVP (CAS no. 9003-39-8) is very low, with LD50 between 15 and 20 g/kg (40 g/kg in rats) (Scheffner, 1955; BASF, 1958). Orally administered PVP is poorly absorbed from the gastrointestinal tract and quickly eliminated. PVP of varying molecular weights was reported not to pass the blood-brain as well as the placental barriers (Ravin et al.,1952). The $T_{1/2}$ for the elimination of povidone in the average molecular weight range of 40 000 has been reported to be as low as 12 hours and as high as 72 hours. FSCJ (Food Safety Commission of Japan) concluded that PVP is of no concern for genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity and reproductive and developmental toxicity, on the basis of the available toxicological data. PVP is among the inactive ingredients in FDA approved drugs database (FDA, 2010). PVP acceptable daily intake for man (ADI) was fixed at 25 mg/kg body weight by the Joint FAO/WHO Expert Committee on Food Additives in 1966 and 1973 (FDA-WHO).

PVP exposure levels:

Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the ADI would correspond to 1,700 mg/day (1.7 g/day), and 1,450 mg/day (1.45 g/day) respectively.
Each orodispersible film (area 6 cm^2), contains 31 mg of PVP. Each participant receives maximum 2 samples. Therefore, the maximum total daily intake of PVP would be maximum 62 mg/day (Males: 0.91 mg/kg/day; Females: 1.07 mg/kg/day), way below the ADI values stated by FDA.

Glycerol safety data:

Glycerol occurs naturally in varied combined forms as a simple, mixed or complex glyceride in association with fatty acids, carbohydrates, phosphate or amino acid in the human body. It is a sweet non-toxic compound widely used as sweetener and humectant in the food and pharmaceutical industry. As a food additive glycerol is labeled as E number E422 (https://www.food.gov.uk/science/additives/enumberlist). Glycerol has been used in Food and Drug Administration approved drug product for oral administration as listed in the FDA Inactive Ingredients Database (http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm). Glycerol is also contained in the marketed orodispersible film formulation Tornetis® (License holder: Sandoz) as inactive ingredient (https://www.drugs.com/uk/tornetis-50-mg-orodispersible-film-leaflet.html). Tornetis® contains Sildenafil Citrate as active ingredient and used to treat erectile dysfunctions. Tornetis® orodispersible film is available in three strengths: 25 mg (size 14 x 25 mm); 50 mg (size 28 x 25 mm); and 75 mg (size 42 x 25 mm). The thickness is not specified.

Further information about glycerol safety data is as follows: The acute oral toxicity of Glycerol (CAS no. 56-81-5) is very low, with LD50 between 17.2 and 27.5 mg/kg in rats (Smyth et al., Atlas Co. 1961). Orally administered glycerol is readily metabolised and deposited as glycogen in the liver (Catron and Lewis, 1929), or provides a direct energy source. In addition, long-term studies are available to show that synthetically derived glycerols are biologically similar to naturally derived glycerol.
Glycerol is of no concern for genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity and reproductive and developmental toxicity, on the basis of the available toxicological data. Fourteen (10 male, 4 female) graduate students ingested 110 g of 95% glycerol in 3 divided doses with their food daily for a period of 50 days. Preceding and following this period were 10 day control periods. Uric acid excretion and basal metabolism were not significantly affected, nor were there changes in red and white blood cell counts or hemoglobin level during the test period. No adverse effects were reported (Johnson, 1933).
Glycerol acceptable daily intake for man (ADI) is not specified by the Joint FAO/WHO Expert Committee on Food Additives in 1966 and 1973 (FDA-WHO)
(http://www.inchem.org/documents/jecfa/jecmono/v10je06.htm).

Glycerol exposure levels:

Each participant will take maximum 4 glycerol-containing films. This corresponds to maximum 128 mg of

glycerol. Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the maximum total intake of glycerol will be 1.88 and 2.21 mg/Kg/day.

Sucralose safety information:

Sucralose is an artificial sweetener and sugar substitute labelled under E number E955 (https://www.food.gov.uk/science/additives/enumberlist). Its proposed uses include soft drinks, sugar substitute preparations, desserts, chewing gums, baking mixes, and salad dressings. Sucralose has been used in Food and Drug Administration approved drug product for oral administration as listed in the FDA Inactive Ingredients Database (http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm). Sucralose is also contained in the marketed orodispersible film formulation Donepezil® (License holder: Sandoz) as inactive ingredient (https://www.drugs.com/uk/donepezil-5-mg-orodipersible-film-leaflet.html). Donepezil® contains donepezil hydrochloride as active ingredient and used for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. Donepezil® orodispersible film is available in two strengths: 5 mg (size 3 cm^2); 10 mg (size 6 cm^2). The thickness is not specified.

Further information about sucralose safety data is as follows: The acute oral toxicity of sucralose (CAS no. 56038-13-2) is very low, with No-Observed-Effect-Levels (NOEL) of more than 10,000 mg/kg in rats (http://ec.europa.eu/food/fs/sc/scf/out68_en.pdf). Orally administered sucralose is poorly absorbed by the human body (only 8-22%), and quickly excreted in urine without metabolisation. The European Scientific Committee for Food (SCF) concluded that accumulation after repeated doses is unlikely to happen in man. Sucralose is of no concern for genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity and reproductive and developmental toxicity, on the basis of the available toxicological data. There is the possibility of a small effect on glucose homeostasis in subjects with non-insulin-dependent and insulin-dependent diabetes assuming 667 mg of sucralose/day for 6 months. However, the SCF committee has concluded that if any such effect occurred, it would be so small as to be clinically insignificant. Sucralose acceptable daily intake for man (ADI) has been established at 0-15 mg/kg/day (http://ec.europa.eu/food/fs/sc/scf/out68_en.pdf) specified by the SCF in 2000.

Sucralose exposure levels:

Each participant will take maximum 2 sucralose-containing films. This corresponds to maximum 46 mg of sucralose. Considering the average weight of participants (young adults) to be around 68 kg (males) and 58 kg (females) (Source: British National Formulary), the maximum total intake of sucralose will be 0.68 and 0.79 mg/Kg/day.

In the case of any adverse events, first aid will be sought as necessary and the study will be stopped. Dr. Catherine Tuleu is a First aider at work (St John's Ambulance). For complaints, the supervisor or a third party (not directly involved in research team) Ms. Joanna O'Brien (Institute Manager) can be contacted for further advice.

The research team has previous experience in taste assessment studies using the "swirl and spit" method. The principal investigator has considerable experience of conducting and supervising such studies using volunteer panels including the following published/presented research:

School of Pharmacy REC/A/09/68 - Orlu-Gul M, Fisco G, Parmar D, Gill H, Tuleu C. A new reconstitutable oral paediatric hydrocortisone solution containing hydroxypropyl-β-cyclodextrin. Drug Dev Ind Pharm. 2013;39(7):1028-36;

UCL REC 4612/003 - Soto J, Ranmal S, Gondongwe X, Olanipekun F, Marbay J, Orlu Gul M and Tuleu C. Amlodipine in Paediatrics and Geriatrics: palatability issues. 5th European Paediatric Formulation Initiative Conference-Formulating Better Medicines for Children, 18-19 September 2013, Barcelona, Spain.

SECTION C	DETAILS OF PARTICIPANTS

C1	**Participants to be studied**

C1a. Number of volunteers:	24
Upper age limit:	65
Lower age limit:	18

C1b. Please justify the age range and sample size:

Any healthy adults (staff and students) working at UCL. Age range should exclude any vulnerable groups. We will attempt to recruit an equal number of male and female subjects. There are no regulatory specifications on the recommended sample size for sensory evaluation of pharmaceutical products. We have selected the sample size based on similar peer-reviewed papers on sensory evaluation of medicines as listed below.

In Aibani, Bajaj and Sing, 2013 (https://www.researchgate.net/publication/236066338_In_vivo_evaluation_of_taste_masking_for_developed_chewable_and_orodispersible_tablets_in_humans_and_rats), 6 volunteers aged between 23 and 26 years were selected for the taste assessment of taste-masked chewable and orodispersible tablets.

In Rudnitskaya et al., 2013, (https://www.researchgate.net/publication/236066338_In_vivo_evaluation_of_taste_masking_for_developed_chewable_and_orodispersible_tablets_in_humans_and_rats), 15 panelists (average 45 years) were recruited to assess the bitterness of pharmaceuticals.

In Lopez et al., 2016 (https://www.ncbi.nlm.nih.gov/pubmed/27402099), sensory evaluation study was carried out (in our research group), 30 adult volunteers were recruited for the assessment of grittiness of multiparticulates.

Overall, we have proposed to recruit 24 participants. This sample size is within the range used in previous human panel palatability studies with non-trained participants at UCL School of Pharmacy (UCL REC 4612/003, School of Pharmacy REC/A/09/68) and it is appropriate to apply statistics. Study samples will be evaluated by participants on a 5-point facial hedonic scale. Each facial hedonic scale point will be translated into numerical values so that a statistical analysis similar to the one used in Lopez et al., 2016 will be applied. In addition, the study design will allow us to collect further information about the outcomes as a semi-structured interview scheduled at the end of every sample assessment. The proposed sample size (n=24) will enable us to investigate the study outcomes including the difference in the perception of participants for placebo ODFs formulated with various types of pharmaceutical grade film forming excipients. The obtained information will impact the formulation development in terms of optimising the composition of the ODF and improve patient acceptability.

C2 **If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the UK Data Protection Act 1998.**

N/A

C3 **Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship?** ☐ **Yes** ☒ **No**

How will you ensure that participants in these groups are competent to give consent to take part in this study? *If you have relevant correspondence, please attach it.*

N/A

C4 **Will payment or any other incentive, such as gift service or free services, be made to any research participant?**

☒ **Yes** ☐ **No**

If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.

Participants will be paid £10 in cash for volunteering. This will be paid from the GL account of the applicant. Before and during any part of the study, participants will have the option to withdraw if they wish.

Please justify the payment/other incentive you intend to offer.

This is a thank you gesture for the time committed to the project.

C5 **Recruitment**

(i) Describe how potential participants will be identified:

Potential participants will be students and staff members of UCL School of Pharmacy (healthy adults aged 18 to 65 years), and these will be the only persons invited to participate in this study.

(ii) Describe how potential participants will be approached:

An email (annex 2) will be circulated using the UCL School of Pharmacy Staff and Students mailing lists to advertise the study. Potential participants interested in taking part in the study will be invited to contact the research team directly using the contact details included in the email. Members of the research team who will be responsible for recruitment will be postgraduate students only. Staff members in the position of influencing in any way the decision of participants in taking part to the study will not be involved in the recruitment process.

(iii) Describe how participants will be recruited:

Potential participants who contact the research team will be provided with the information sheet. They will until one week before the study to evaluate whether to take part, and will be invited to ask questions or obtain further information if they wish. Once decision has been made, participants will contact the research team to confirm their participation and select suitable dates and times. Prior to the session, a member of the research team will verbally explain the study and take informed consent from the participant.

Attach recruitment emails/adverts/webpages. A data protection disclaimer should be included in the text of such literature.

C6 **Will the participants participate on a fully voluntary basis?** ☒ **Yes** ☐ **No**

Will UCL students be involved as participants in the research project? ☒ **Yes** ☐ **No**

If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.

Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?

Granting this information will be included in the invitation email, information sheet and consent form, all participants will be reminded in any suitable occasion that their participation is completely optional and will not affect in any way their studies/ relationships with the academic environment.

C7 **CONSENT**

Please describe the process you will use when seeking and obtaining consent.

The attached form will be used to obtain written informed consent from the recruited participants on the day of the study. Participants are expected to sign the consent form only after having read and understood the information sheet previously provided, and after having asked any questions they may have to the research team. On the day of the study, members of the research team will be available to further provide information before the consent form will be signed. The form will be provided in two copies to be signed. One will be kept by the participant and another will be retained by the research team.

A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.

In cases where it is not proposed to obtain the participants informed consent, please explain why below.

N/A

C8 **Will any form of deception be used that raises ethical issues? If so, please explain.**

No

C9 **Will you provide a full debriefing at the end of the data collection phase?** ☒ **Yes** ☐ **No**

If 'No', please explain why below.

N/A

C10 **Information Sheets And Consent Forms**

A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.

UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE

Mouthfeel evaluation of drug-free orodispersible films

Participant Information Sheet

You will be provided with a copy of this information sheet.

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 8249/002

Principal Investigator: Dr. Mine Orlu Gul
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London. WC1N 1AX
Tel:
Email:

We would like to invite you to participate in this research project. Taking part is voluntary; it is up to you to decide whether or not to take part, and choosing not to will not disadvantage you in any way. If you do decide to take part, you will still be free to withdraw at any time without the need to give a reason.

Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish. Please feel free to ask us if there is anything that is not clear or you would like more information.

Details of the Study

What is the purpose and aim of this project?

The ability to take medicines according to their instructions is key to the success of a medical treatment. Orodispersible films (ODFs) are considered "more acceptable" dosage forms, especially to certain patient groups (E.g. children, older patients, etc…). However, some characteristics of ODFs may affect the ability or willingness to take them as recommended. There is a great need to understand which characteristics of ODFs make them preferable or unpleasant/unacceptable. This study is expected to provide us with valuable information to develop more acceptable ODF.

Drug-free films will be given to you to test. These are thin transparent films that quickly dissolve with saliva. Films are made from ingredients that are pharmaceutical excipients widely used in marketed orodispersible films, tablets and foods. You may already know some commercially available ODF containing these excipients such as Setofilm® (Norgine) containing polyvinyl alcohol, Onsolis® (Meda Pharmaceuticals) containing carboxymethylcellulose, and Benadryl® (Johnson & Johnson) containing polyvinylpyrrolidone. Furthermore, Carboxymethylcellulose, glycerol and sucralose are widely used thickener, humectant, and sweeteners in foods under the E number E466, E422, and E955 respectively.

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 65 years to take part.

If you have any allergies to excipients, or if you have had any dental care or specific medicinal treatments (see list below) during the 15 days before the tests, then unfortunately you will be unable to take part.

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL. You will be asked to commit to three sessions of 3 hours each. If you decide to take part, you will be asked to take four drug-free orodispersible films. We will ask you to place them in your mouth, wait until they dissolve completely and then swallow. Meanwhile, you will be asked to take the time in which films dissolve in your mouth using a stopwatch. We will then ask you to rate various sensory aspects each time on a scale (size, thickness, etc.), and to tell us more about your experience in a quick face-to-face interview (10 minutes).

You will be allowed to reject ANY of the samples at any point of the study if you don't feel comfortable to take it.

Are there any risks involved?

The films being tested contain polyvinyl alcohol (PVOH), carboxymethylcellulose (CMC), polyvinylpyrrolidone (PVP), glycerol and sucralose. These are perfectly safe pharmaceutical excipients already used in many marketed formulations. If you experience any unpleasant reaction, you must alert a member of the team and we will stop the study immediately. The researchers are trained in First Aid. If necessary, we will also contact emergency services. All the excipients used in this study are very safe compounds, so we do not anticipate that you will experience any side effects.

If the samples you are given have a poor taste or texture, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples and vomit, however this is extremely rare. Nevertheless, films dissolve rapidly, which minimises the potential for adverse effects, and can be spit out at any time. Further a minimum delay of 10 minutes will be respected between each test film.

Who will know that I took part, and what happens after?

Only members of the research team will know that you took part and have access to the results. Confidentiality will be maintained during the study and after it has finished. If the study is published or presented to a wider audience, your anonymity will be respected through anonymisation procedures. All data will be collected and stored in accordance with the Data Protection Act 1998.

If you would like to know the results of the study once it has finished, please feel free to contact us using the details overleaf, as we'd be happy to share these with you.

Who can I contact for more information?

Please contact the research team, using the details overleaf, if you would like to take part, or have any questions about the study.

If you would like to discuss it with someone outside of the research team, please contact

Ms Joanna O'Brien
Institute Manager
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel:
Email:

Thank you for taking the time to read this information sheet

- Medications preventing your eligibility to participate to the study (Scully CBE, 2003):

  Anticholinergic drugs

Tricyclics antidepressants
Muscarinic receptor antagonists for treatment of overactive bladder
Alpha receptor antagonists for treatment of urinary retention
Antipsychotics such as phenothiazines
Diuretics
Antihistamines
Sympathomimetic drugs
Antihypertensive agents
Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)
Appetite suppressants
Decongestants and cold cures'
Bronchodilators
Skeletal muscle relaxants
Antimigraine agents
Benzodiazepines, hypnotics, opioids and drugs of abuse
H 2 antagonists and proton pump inhibitors
Cytotoxic drugs
Retinoids
Anti-HIV drugs such as dideoxyinosine (DDI) and protease inhibitors
Cytokines

When you have completed your Information Sheet, please DELETE the advice section below from your application form before submitting it to the Committee.

Details of Study MUST include the following:

- Aims of the research and possible benefits.
- Who you are recruiting
- What will happen if the participant agrees to take part (when, where, how long etc)
- Any risks (e.g. need for disclosure of information to a third party, possibility for distress)
- Possible benefits (it is good practice to offer participants a copy of the final report)
- Arrangements for ensuring anonymity and confidentiality (see optional statements below for examples). To ensure compliance with the Data Protection Act participants must be informed of what information will be held about them and who will have access to it (this relates to information that is identifiable or could potentially be linked back to an individual.)

Statements which researchers MIGHT also include as appropriate:

- A decision to withdraw at any time, or decision not to take part, will not affect the standard of care/education you receive.
- If you agree to take part you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not be re-contacted.
- You may withdraw your data from the project at any time up until it is transcribed for use in the final report (*insert date)*.
- Recorded interviews will be transcribed (written up) and the tape will then be wiped clear.
- If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form.
- Submission of a completed questionnaire implies consent to participate.
- As participation is anonymous it will not be possible for us to withdraw your data once you have returned your questionnaire.
- What if I have further questions, or if something goes wrong? If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact UCL using the details below for further advice and information:
  Student researchers: Insert the name and full UCL contact address and number of your supervisor.
  *Staff researchers: Please insert the following: The Chair, *Insert full address details for the UCL Research Ethics Committee, ethics@ucl.ac.uk

Informed Consent Form for in Research Studies

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: **Mouthfeel evaluation of drug-free orodispersible films**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 8249/002

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- Agree that my data, after it has been fully anonymised, can be shared with other researchers *[to satisfy Research Council funded projects as Research Councils have changed their guidance regarding data sharing]*

Printed name:

Signed: Date:

When you have completed your Informed Consent Form, please DELETE the advice section below from your application form before submitting it to the Committee.

Statements which researchers MIGHT include as appropriate:

- I understand that my participation will be taped/video recorded and I consent to use of this material as part of the project.
- I understand that I must not take part if
- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies.
- I understand that the information I have submitted will be published as a report and I will be sent a copy. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- I understand that I am being paid for my assistance in this research and that some of my personal details will be passed to UCL Finance for administration purposes.
- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.

This is not an exhaustive list and you should consider whether you need to amend any of these statements or design different ones that are more applicable to your research.

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SECTION D DETAILS OF RISKS AND BENEFITS TO THE RESEARCHER AND THE RESEARCHED

D1 **Have UCL's Risk Assessment Procedures been followed?** ☒ **Yes** ☐ **No**

If **No**, please explain.

N/A

D2 **Does UCL's insurer need to be notified about your project before insurance cover can be provided?** ☐ **Yes** ☒ **No**

The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.

If **Yes**, please provide confirmation that the appropriate insurance cover has been agreed. *Please attach your UCL insurance registration form and any related correspondence.*

N/A

D3 **Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).**

This project hold little risk to the research which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.

D4 **Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research?** ☒ **Yes** ☐ **No**

If **Yes**, please describe the nature of the risk or stress and how you will minimise and monitor it.

The procedures may cause temporary physical discomfort (exposure to unpleasant taste or general mouthfeel) during assessment if the test samples texture, taste or aftertaste is aversive. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, a delay of at least 10 minutes will be respected between each tested sample. Before and after each test sample, subjects can rinse their mouth with water until they can no longer perceive the previous sample. The participants will be provided with necessary instruction on properly testing the samples. Risk will be continuously monitored by asking participants how they feel between sample administrations. If participant report any distress, they will be excluded from the study. If some participants show high discomfort to texture or taste, the study will be immediately stopped.

D5 **Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?**

No

If **Yes,** please explain how you will deal with this.

N/A

D6 **Please describe any expected benefits to the participant.**

Participants will receive no direct benefits by taking part to this study. They may receive indirect benefit through contribution to patient care improvement regarding the acceptability of patient-centric formulations.

D7 **Specify whether the following procedures are involved:**

Any invasive procedure(s) ☐ **Yes** ☒ **No**

Physical contact ☐ **Yes** ☒ **No**

Any procedure(s) that may cause mental distress ☐ **Yes** ☒ **No**

Please state briefly any precautions being taken to protect the health and safety of the research participants.

The study is divided in three sessions and the number of samples is kept to a minimum in each session to minimise fatigue and discomfort. Before and after each test sample, subjects will rinse their mouth with water and will have free access to water during the study. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the study will be immediately stopped.

D8 **Does the research involve the use of drugs?** ☐ **Yes** ☒ **No**

If **Yes**, please name the drug/product and its intended use in the research and then complete Appendix I

N/A

Does the project involve the use of genetically modified materials? ☐ **Yes** ☒ **No**

If **Yes**, has approval from the Genetic Modification Safety Committee been obtained for work? ☐ Yes ☐ No

If **Yes**, please quote the Genetic Modification Reference Number: N/A

D9	**Will any non-ionising radiation be used on the research participant(s)?** ☐ **Yes** ☒ **No** If **Yes**, please complete Appendix II.

D10	**Are you using a medical device in the UK that is CE-marked and is being used within its product indication?** ☐**Yes** ☒ **No** If **Yes**, please complete Appendix III.

CHECKLIST

Please submit ether 12 copies (1 original + 11 double sided photocopies) of your completed application form for full committee review or 3 copies (1 original + 2 double sided copies) for chair's action, together with the appropriate supporting documentation from the list below to the UCL Research Ethics Committee Administrator. You should also submit your application form electronically to the Administrator at: ethics@ucl.ac.uk

Documents to be Attached to Application Form (if applicable)	Ticked if attached	Tick if not relevant
Section B: Details of the Project		
• Questionnaire(s) / Psychological Tests	☒	☐
• Relevant correspondence relating to involvement of collaborating department/s and agreed participation in the research.	☐	☒
Section C: Details of Participants		
• Parental/guardian consent form for research involving participants under 18	☐	☒
• Participant/s information sheet	☒	☐
• Participant/s consent form/s	☒	☐
• Advertisement	☒	☐
Section D: Details of Risks and Benefits to the Researcher and the Researched		
• Insurance registration form and related correspondence	☐	☒
Appendix I: Research Involving the Use of Drugs		
• Relevant correspondence relating to agreed arrangements for dispensing with the pharmacy	☐	☒
• Written confirmation from the manufacturer that the drug/substance has has been manufactured to GMP	☐	☒
• Proposed volunteer contract	☐	☒
• Full declaration of financial or direct interest	☐	☒
• Copies of certificates: CTA etc…	☐	☒
Appendix II: Use of Non-Ionising Radiation		
Appendix III: Use Medical Devices		