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Sensory assessment and acceptability of coated tablets

relationship between

instrumental methods and human data

by

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Abstract

Development of acceptable medicines is central for adherence and effectiveness of treatment. However, the assessment of medicines' acceptability has not yet been standardised. Correlating *in vitro* and *in vivo* acceptability data would facilitate the development of acceptable medicines, but research in this area is limited.

This thesis aims to evaluate and correlate *in vivo* and *in vitro* acceptability data of conventional tablets with a range of coatings. In two randomised studies participants, ranging from pre-school children to older adults, evaluated acceptability of tablets in two aspects: ease-of-swallowing and palatability. Sensory attributes which were statistically related to acceptability were established with high selectivity and specificity, i.e. bitterness, aftertaste, stickiness, slipperiness, and smoothness. Discrepancies found between children and adults responses indicated differences in their perception of tablets and acceptability. Also developed was an array of instrumental methods and results were investigated for links to sensory perception. A linear relationship between tribology and oral sensory perception, specifically for ease-of-swallowing, slipperiness and stickiness, of tablets was found and is described for the first time.

Lastly, a vocabulary describing tablets has been collected and organized into a lexicon, which provides the first step towards the standardisation of sensory testing, as a part of acceptability evaluation.

Impact statement

The importance of studying the acceptability of medicines in the end-user population is endorsed by regulators but there is no standard method of performing these tests. This study is significant in that it establishes the foundations for standardised assessment of acceptability of conventional tablets with the introduction of new *in vivo* and *in vitro* tools. To advance the field, there is a need to better understand the multifactorial nature of acceptability of medicines. For conventional coated tablets, the specific product attributes that drive patient preference, other than size and shape, are unknown. This study generated knowledge of the key acceptability determinants, namely ease of swallowing and oral sensory attributes, of coated tablets in children and adults.

Acceptability of oral medicines may be different in vulnerable populations, like children and older adults.

Firstly, this study identifies the age ranges at which children can swallow 7 mm coated tablets which is critical information for the development of tablet formulations for children. Secondly, differences in sensory perception and tablet acceptability between children and adults have been elucidated which confirms that adults and children are not interchangeable in acceptability testing. These findings highlight the importance of developing age-appropriate medicines, as opposed to manipulating an adult formulation to administer it to children.

Informed by food science, which is far in advance of the pharmaceutical industry for sensory analysis, this study creates a tablet lexicon consisting of 22 terms with their explicit definitions. This lexicon has the potential to reduce ambiguities in the interpretation of the sensory analysis of pharmaceuticals. It can be used in sensory and hedonic evaluation of

product attributes, where the intensity of attributes is scaled and then assessed hedonically. Although the lexicon for tablets is not fully translatable, it is a first step to informing the future sensory analysis of other oral solid dosage forms, e.g. orally dispersible tablets, films, capsules, chewable tablets.

Instrumental methods complement the knowledge of mouthfeel and taste evaluation by allowing exploration of the principles that underpin sensory perception. In this work, a number of instrumental tests provided statistically significant correlations with sensory data. These tests offer the potential to predict acceptability determinants such as the ease of swallowing, slipperiness, stickiness and smoothness of conventional tablets without the need for expensive human panel testing and would therefore have considerable beneficial practical implications. Overall, this study has potential to impact:

Researchers,

- by linking instrumental measurements and sensory perception to increase understanding of processes underlying mouthfeel perception, which then allows to formulate medicines which are "acceptable-by-design";
- by providing a foundation to standardise sensory assessment will enable comparative data to be generated between a range of dosage forms and between research groups

Pharmaceutical industry,

- by providing instrumental methods that can predict sensory attributes which can be incorporated into routine *in vitro* quality testing of final manufactured batches;
- by providing *in vitro* studies to optimise oral formulations to refine and reduce the burden of *in vivo* studies, consequently reduction in the cost of evaluation;
- by manufacturing acceptable-by-design medicines can improve brand profile;

And ultimately patient and their carers,

- as being able to take acceptable medicines benefits patients due to improved adherence and thus better treatment outcomes.

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If you set out on a journey let it be long

a wandering that seems to have no aim groping your way blindly

so you learn the roughness of the earth not only with your eyes but by touch

so you can confront the world with your whole skin

– Zbigniew Herbert, "A Journey"

(Translated by John and Bogdana Carpenter)

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Acronyms and nomenclature

	Acronyms		Nomenclature
API	Active pharmaceutical ingredient	°C	Celsius
AU	Action unit	μ	Coefficient of friction, COF
AUC	Area under the curve	μL	Microlitre
BSE	Back-scattered electrons	μm	Micrometre
CI	Confidence interval	CL%	Coating level (percent weight gain)
COF	Coefficient of friction	cps	Centipoise
CT	Computed tomography	d_s	Sliding distance
DMA	Dynamic mechanical analysis	F	Friction force
DoE	Design of experiments	F_L	Load force
DT	Detection threshold	g	Gram
EMA	European Medicine Agency	k_F	Friction force constant
FACS	Facial Action Coding System	kg	Kilogram
FDA	Food and Drug Administration	k_L	Load force constant
GPA	Generalised Procrustes analysis	k_v	Sliding speed constant
HPLC	High-performance liquid chromatography	L	Litre
HPMC	Hydroxypropyl methylcellulose	M	Torque
IQR	Interquartile range	mL	Millilitre
JND	Just noticeable difference	mPas	Millipascal second
MCC	Microcrystalline cellulose	N	Newton
MCT	Medium chain triglycerides	Pas	Pascal second
MP	Multiparticulate	*q*	Displacement
MWP	Microparticulated whey proteins	R	Radius
ODF	Orally dispersible film	R^2	Coefficient of determination
ODT	Orally dispersible tablet	Ra	Arithmetical mean height measured along a line (roughness parameter)
OR	Odds ratio	r_s	Spearman's rho
OSDF	Solid oral dosage form	Sa	Arithmetical mean height measured within an area (roughness parameter)
PCA	Principal component analysis	U	Mann-Whitney U

PDMS	Polydimethyl siloxane
PEG	Polyethylene glycol
PLS	Partial least squares regression
PRO	Participant reported outcome
PVA	Polyvinyl acetate
ROC	Receiver operating characteristic
RPM	Revolutions per minute
RRO	Researcher reported outcome
SE	Secondary electrons
SEM	Scanning electron microscopy
SRR	Slide roll ratio
T2S	Bitter taste receptor
VAS	Visual analogue scale
WHO	World Health Organisation

v_s	Sliding speed
W	Normal force
Z	Wilcoxon's Z
η	Viscosity
η_{eff}	Effective viscosity
θ	Contact angle, CA
X^2	Pearson Chi square
Ω	Velocity
γ_L	Liquid-gas surface tension
γ_S	Solid-gas surface tension
γ_{SL}	Solid-liquid surface tension
ΔP	Laplace pressure

1 Introduction

1.1 Thesis aims

This thesis combines multidisciplinary knowledge of food science, sensory analysis, and pharmaceutics with the aim to advance understanding of patients' oral perception and acceptability of medicines. Specifically, polymer coatings applied to tablets will be investigated with respect to their taste-masking capability, ease of swallowing and overall behaviour in the mouth. With the help of instrumental methods this thesis attempts to understand the relationship between the textural and tribological properties of coatings during processing in the mouth, and the *in vivo* sensory perception of coated tablets. More specifically, the link between coating constituents and their impact on mouthfeel will be studied.

Aims:

- Develop *in vitro* methods with potential to relate the physical properties of polymer coatings (stickiness, viscosity, and coefficient of friction) to perceived mouthfeel (Chapters 2 and 3).
- Generate data from children and adults on acceptability of coated tablets with a focus on the impact on ease of swallowing, and palatability perception (Chapters 4 and 5).
- Determine correlations between *in vitro* and *in vivo* data on mouthfeel and taste-masking (Chapter 6).
- Explore the vocabulary used to describe coated tablets (Chapter 7).

Purpose of this chapter

This chapter presents a comprehensive review of the topics relevant to the thesis. Firstly, the issue of acceptability of oral medicines is presented and its key determinants are discussed. The concept of improving acceptability of tablets by application of polymer coatings is introduced.

Secondly, the relevant literature concerning instrumental tools used to understand oral perception relevant to acceptability of solid oral dosage forms is discussed together with opportunities for applying these techniques during drug formulation development.

Finally, the principles of acceptability studies in humans are presented, with considerations specific for medicinal products.

1.2 Acceptability of medicines

Acceptability is defined as "the *ability* and *willingness* of a patient to self-administer, and also of any of their lay or professional caregivers, to administer a medicinal product as intended" (European Medicine Agency (EMA), 2017b). It is driven by the characteristics of a medicine as well as the patient. The acceptability of medicines is a predominant factor in adherence to therapy, especially in children. A lack of acceptance can result in medicine refusal (Venables et al., 2015) or discontinuation (Verrotti et al., 2012), and so, have adverse consequences on the therapeutic outcome (Brown and Bussell, 2011). According to reports from Capgemini (2012), medication non-adherence generates annual revenue loss to the pharmaceutical industry of $188 billion in the US, and $564 billion globally. These numbers do not include healthcare costs, such as hospitalisation, emergency department visits, or patient's personal costs (Cutler et al., 2018).

The importance of studying the acceptability of medicines in the end-user population has been endorsed by regulators (FDA, 2002, EMA, 2013, FDA, 2015, EMA, 2017b). However, there is no simple way to measure it. Acceptability is well defined as a term, yet, depending on the target population and dosage form there are multiple factors which affect it (Table 1.1). Such a multitude of factors makes it difficult to choose an appropriate measure of acceptability. The majority of *in vivo* studies focus on the patient's ability to take a dose or medicine's palatability. The importance of broader measurements of acceptability, which encompass all factors relevant to a particular product, was demonstrated in previous studies (Young et al., 2010, Baxter et al., 2014). Baxter et al. (2014) specifically, suggested that evaluation of acceptability should extend beyond palatability, particularly taste, and include for example, mouthfeel, aftertaste, and smell. Furthermore, EMA named a multitude of factors affecting acceptability that need to be considered during product development (Table 1.1) (EMA, 2013, EMA, 2017b). This highlights the complexity of acceptability evaluation in human studies, as distinct from asking a simple yes/no question.

Table 1.1 Factors determining acceptability of solid oral dosage forms in children and older adults. Based on EMA documents (EMA, 2013, EMA, 2017b).

In children	Common	In older adults
	Ability to take	
	• Swallowability (e.g. related to tablet size, shape, coating/waxing, liquid viscosity) • Recommended single dose (e.g. number of tablets, total volume of liquid) • Require chewing	
• Formulation factors that increase risk of choking, chewing, aspiration		• Require sufficient saliva to allow disintegration
	Palatability	
	• Taste • Mouthfeel • Aftertaste • Smell	
• Excessive attractiveness • Ability to mix with food • Appropriateness of food		• Require sufficient saliva

In children	Common	In older adults
	Appearance	
	• Size, shape, colour, embossing	
• Excessive attractiveness		
	Handling/dexterity-related	
	• Shape, size • Container closure system • Administration device • Need of dose manipulation (e.g. opening capsules, measuring liquids, breaking tablets)	
• Dose adjustment		
	Cognitive-related	
	• Complexity of the dosing instructions • Willingness	
• Age of a child		• Readability of inner/outer packaging, labelling
	Logistics-related	
	• Dosing frequency • Duration of treatment • Need for caregiver assistance • Setting(s) where the product is intended to be used	
• Age associated activities (e.g. School)		
	Condition-related	
	• Patient in supine position • Unable to swallow due to illness	

In order to fully assess product acceptability, the gaps in knowledge of the key acceptability determinants need to be identified. Once the product characteristics that reduce or promote acceptability are known, the ultimate goal is to be able to manufacture medicines which are "acceptable-by-design"; confirmation of their acceptability in a targeted population then becomes a formality.

Conventional tablets remain the most common dosage form, due to benefits of low-cost manufacture, high product stability and shelf-life, possibility of high dose loading, dose uniformity, and easy control of release, among others (Jones, 2016). Tablets can be also given to children, providing that the child's age and tablet size are considered (see next section). During formulation development, it important to recognise that children have different needs to adults. Aspects like body size, cognitive abilities, physiological maturity, sensory acuity,

comprehension of the treatment, attitude towards treatment all affect whether the child would be able and willing to take medicine as intended. Extensive reviews on this subject are available: Ernest et al. (2007), Baguley et al. (2011), Liu et al. (2014), Mistry and Batchelor (2016), Drumond et al. (2017), Van Riet-Nales et al. (2017).

1.2.1 Ability to take a dose - tablet swallowing

For conventional tablets, the ability to take a dose is most frequently limited by difficulties in swallowing. Tablet swallowing difficulties are common across all age groups: children, adolescents, adults and older people (Hansen et al., 2007, Marquis et al., 2013, Patel et al., 2015, Mc Gillicuddy et al., 2016). Such difficulties may lead to dose manipulation (e.g. cutting or crushing of tablets) to make it easier to swallow. Schiele et al. (2013) reported that almost 60% of adult patients with swallowing difficulties admitted to manipulating OSDF. Moreover, tablet swallowing problems can result in accidental non-adherence, when the patient cannot swallow their medicines, or intentional non-adherence, because of a fear of choking or discomfort. Missing doses due difficulties in swallowing were reported in 23% of adults (Marquis et al., 2013). The numbers are higher for children, where >50% were reported to be unable to swallow a standard size tablet or capsule (Polaha et al., 2008, in Patel et al., 2015).

In vulnerable populations, the reasons underlying tablet swallowing difficulties differ (Table 1.2). Older adults are especially prone to tablet swallowing difficulties as dysphagia is more prevalent. The incidence of dysphagia is 22% in general population and increases to 68% for nursing home residents (Baijens et al., 2016). Dysphagia can be attributed to physiological changes associated with aging or age-related diseases. In a paediatric population tablet

swallowing issues are related to their smaller body size, less developed swallowing reflexes and lack of experience, among others.

An extensive review by Mistry and Batchelor (2016), identified a child's age and the size of the formulation as the most important factors affecting tablet swallowing ability in the paediatric population. In their review the authors showed increasing ability to swallow 2–7 mm tablets across the age range from neonates to six-year-olds (Figure 1.1A). Jones et al. (2017) explored children's ability to swallow larger OSDFs: 5 mm and 10 mm tablet, and 22 mm capsule. Based on a cohort of in- and out-patient children (3–17-year-old, inpatients n=47 and outpatients n=62) they modelled probability of a tablet to be swallowed based on age (Figure 1.1B). While the value of this model is compromised by the small sample size (and a similar model based on meta-analysis of existing literature would be of interest), these results and the fact that the size of the majority of prescribed paediatric OSDF exceeds 10 mm (Jacobsen et al., 2016) (Figure 1.1C), highlights a discrepancy between size of prescribed OSDF and child's ability to swallow it.

Table 1.2 Factors which might affect swallowing of solid oral medicines in vulnerable populations.

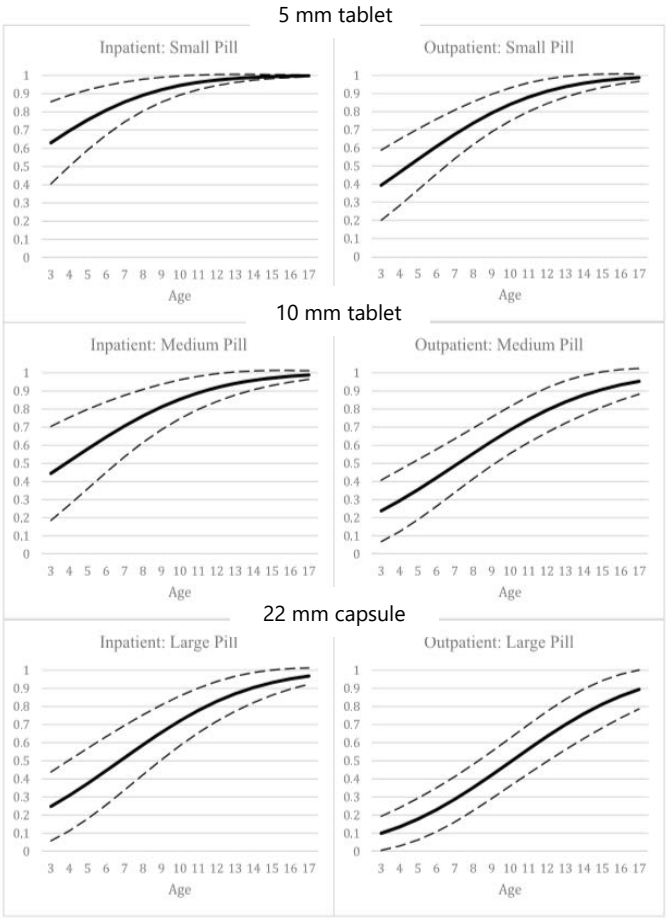
In children	**In older adults**
Less developed swallowing reflexes [1]	Age-related dysphagia
Neophobia [2]	• Deterioration of salivary gland function
Comprehension of the treatment need [3]	• Weakening of the muscles used for swallowing [10]
Smaller body size vs. larger medicine size	• Tooth loss [11]
Lower volume of a swallow [4]	Dysphagia due to age-related diseases
Lack of experience [5]	• Stroke [10]
Discomfort[6]	• Dementia [10]
Psychological reasons	• Parkinson's disease [10]
• Aversive attitude/feelings towards medicines[6]	• Alzheimer's disease [10]
• Fear of choking [7]	Psychological reasons [12]
Age-related diseases	Medication related xerostomia (dry mouth) [11]
• Autism [8]	Bed laying
• Cerebral palsy [9]	
Tooth loss	

[1](Arvedson, 2006), [2](Monnery-Patris et al., 2015), [3](Hommel and Baldassano, 2009), [4](Vaiman et al., 2004), [5](Meltzer et al., 2006), [6](Hansen et al., 2007), [7](Mennella et al., 2015b), [8](Ghuman et al., 2004), [9](Benfer et al., 2017), [10](Baijens et al., 2016), [11](Furuta and Yamashita, 2013), [12](Kelly et al., 2010)

A.

Age (years)	OSDF size	Percent of children who could swallow
Neonates (< 28 days)	2 mm	88.2%
0.5	2 mm	70%
1	4 mm	60%
2	2-3 mm	40-60%
	5 mm	>80%
3	2 mm	50%
	3 mm	53%
	17.6 mm (capsule)	>80%
4	2 mm	75-80%
	7 mm	80%
5	2 mm	100%
	3 mm	85%
6	7 mm	91%

B.



C.

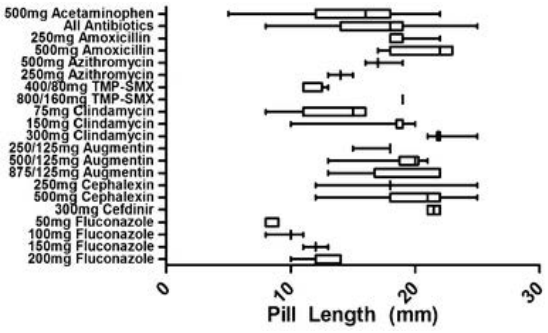


Figure 1.1 Reported evidence of children's ability to swallow OSDFs; A. Literature report adapted from Mistry and Batchelor (2016); B. Probability of swallowing tablets/capsule, by size, age and inpatient/outpatient status; dashed lines represent 95% confidence interval; reprinted from Jones et al. (2017) with permission from SAGE Publications; C. Size variation of common paediatric medicines prescribed in USA; TMP–SMX trimethoprim–sulfamethoxazole; reprinted from Jacobsen et al. (2016) with permission from Springer Nature.

1.2.2 Palatability

Palatability is one of the most important factors that impacts the acceptability of oral formulations in children (Venables et al., 2015) and adults (Baxter et al., 2014). It is known that administering a palatable formulation to children can reduce the difficulties encountered by their carer, as well as improve the day-to-day adherence (Holas et al., 2005).

Palatability is defined as "the overall appreciation of an (oral) medicine by organoleptic properties such as smell, taste, aftertaste and texture (i.e. mouthfeel), and possibly also vision

and sound" (Walsh et al., 2014). As per this definition palatability involves the interaction of a medicine with all the senses; extending from the moment the medicine packaging is opened, and the dosage form releases any aromas, to being picked up by the hand, put in the mouth, and finally swallowed. Within this thesis the palatability of tablets is discussed in terms of their taste and oral perception within the oral cavity (mouthfeel).

1.2.2.1 Taste

An aversive taste impacts upon the palatability of medicines. This is of concern, as poor palatability has been linked to reduced adherence to oral medicines, especially among paediatric patients (Baguley et al., 2011, Mennella et al., 2013). Taste as a barrier to administration of medicines is reported by paediatricians (Milne and Bruss, 2008), parents (Venables et al., 2015), nurses (van der Vossen et al., 2019) and children themselves (Mennella et al., 2015b).

Commonly the word "taste" is used to describe the overall perception of food/medicine in the oral cavity. The definition of taste is limited to five sensations created by chemical interactions between a molecule and a taste bud, i.e. sweet, bitter, umami, sour, and salty. Taste is perceived by the chemosensory gustatory system, which encompasses receptors and channels organised within taste papillae and located mostly on the tongue, but also on oropharynx, larynx, epiglottis, and the upper oesophagus (Jaggupilli et al., 2016). Multiple types of receptor can transduce the same taste. For bitterness, the most troublesome taste in medicine palatability, 25 receptors have been identified (called T2Rs), which bind a variety of molecules. Numerous APIs are known to activate T2Rs, e.g. quinine activates 9 different T2Rs, while paracetamol is selective towards one T2R (Meyerhof et al., 2009, Dagan-Wiener et al.,

2018). The affinity of different APIs to T2Rs, as well as potential to block T2Rs are widely studied as part of the development of more palatable medicines (Bahia et al., 2018). In theory, the discovery of multipotent T2R blockers could be a solution to medicine bitterness. Several bitter-masking compounds are known, yet their effect is not complete, as they do not block all bitterness receptors. As shown by Mennella et al. (2014), their efficiency can differ depending on API, or patient's age.

Historically, the bitter taste of medicines has been masked by incorporating sugar or sweeteners to the chewable tablets, lozenges or liquid formulations, alternatively sugar coating the conventional tablets. This method has two major drawbacks. Formulation of attractive sweet (candy)-like medicine can increase the risk of accidental over dose, particularly in children (Connolly, 2017); adding sweeteners is it is not sufficient for many APIs (Mennella et al., 2015a, Nakamura et al., 2015). Another common method to achieve taste-masking of OSDFs is that used within this thesis i.e. coating of solid oral dosage forms with polymers. In this approach taste-masking is achieved by creating a physical barrier on the tablet surface, which delays API release in the mouth (see section 1.3.1).

1.2.2.2 Mouthfeel

The oral cavity contains some of the most densely innervated tissues in the human body, in terms of peripheral somatosensory system (Haggard and de Boer, 2014). Consequently, the mouth becomes a source of vivid oral sensations, which is of huge importance following administration of any OSDF. These sensations can be regarded pleasant or unpleasant, which then determines acceptability. This section explains the somatosensory principles underlying oral sensations – "mouthfeel", and their importance in medicine acceptability.

Oral sensations can arise from the mouth itself (e.g. perception of dryness, freshness) and from interactions with foreign objects, or both. Thus, the final sensation experienced is an interplay between the state and movements of the mouth as well as the characteristics of the foreign object.

In sensory science, mouthfeel is defined as a physical sensation which is created in the mouth by food or drink (or oral medicine) and is distinct from taste (Mouritsen et al., 2017). It encompasses sensations of touch (received by mechanoreceptors), pain and temperature (both received by nociceptors). Examples of mouthfeel sensations which are relevant for oral medicines include, but are not limited to, hot/cold, astringency, aftertaste, burning sensation, and product texture. Texture and mouthfeel are partially overlapping terms (Figure 1.2), since the texture is a collective term defined as "the sensory and functional manifestation of the structural, mechanical and surface properties of foods detected through the senses of vision, hearing, touch and kinaesthetics" (Szczesniak, 2002).

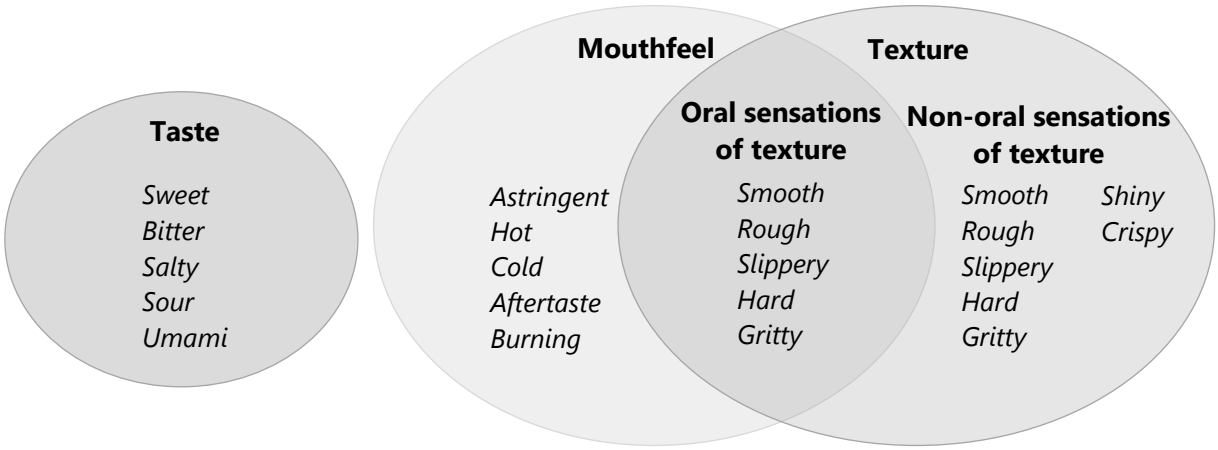


Figure 1.2 Examples of taste, mouthfeel and texture sensations.

Somatosensory receptors project the sensations arising within the mouth, via the trigeminal nerve, to the brain, where they are integrated into an overall perception – mouthfeel. The

processes involved in it are presented in Table 1.3, with a fictional example of the oral perception of multiparticulates (MPs) created for illustrative purposes.

Table 1.3 The hierarchy of processes during somatosensory experience - a theoretical model based on Longo et al. (2010) and Haggard and de Boer (2014).

Hierarchy	**Processing**	**Example** *I've put a spoonful of multiparticulates (MPs) in my mouth*	**Mouthfeel – evaluation of oral sensation**
Somatosensation	• Detection and awareness of individual inputs	*I **feel** touch, I feel pain*	• How your mouth feels *My tongue feels dry, I have less saliva, MPs feel rough and gritty* • Your attitude and emotions towards it *The grittiness is disturbing, I don't like it*
Somatoperception	• Integration of multiple inputs • Identification of the input source (internal/external) • Perception of the body itself • Recognition of the foreign objects and their size	*The feelings come from lots of **small, hard, rough objects** in my mouth, and the sensations increase when they move*	
Somatorepresentation	• Cognitive knowledge about body itself • Conceptualisation what the mouth is like	*I feel it on my **tongue** and between the **teeth;** my mouth feels full of it*	

Mouthfeel can be a reason for preference of one dosage form over another, e.g. tablets over a powder (Baxter et al., 2014), tablets over sprinkles (Young et al., 2010). In some cases, mouthfeel of medicine is so unpleasant that it poses a barrier to administration, in both children (Venables et al., 2015) and adults (Fields et al., 2015). To address this issue, the knowledge on formulation properties which cause unpleasant mouthfeel needs to be expanded. Depending on the type of OSDF, different mouthfeel properties might be key for acceptability. For example, Kimura et al. (2015) demonstrated that roughness reduced acceptability of orally dispersible tablets (ODFs), Scarpa et al. (2018) identified stickiness of orally dispersible films (ODFs) as a key acceptability attribute, and grittiness reduces acceptability of MPs (Lopez et al., 2018b) and chewable tablets (Mishra et al., 2009). It must be recognized that the mouthfeel of the formulations with longer residence time in the

mouth may have larger impact on acceptability, however the principles still apply to all OSDFs. Although still scarce, the body of research on medicines' mouthfeel is growing. To accelerate development of this field, first the sensitivity of oral surfaces to textural differences need to be understood.

In order to perceive either pleasant or unpleasant mouthfeel attributes, i.e. perceptible characteristics (International Organization for Standardization, 2008), a certain threshold of stimuli must be achieved, in analogy to minimal substance concertation required for taste. Oral surfaces are very sensitive to textural differences, and the tongue is more sensitive than any other part of our body (Miles et al., 2018, Furukawa et al., 2019). Literature evidence of sensitivity to mouthfeel is presented in Table 1.4. Research on this subject is more advanced in the fields of neurological or food science when compared to pharmaceutics, therefore here, the evidence and examples gathered are from several fields. It can be seen that dependent on the strength, a stimulus can trigger barely perceptible feelings, or cause discomfort. For roughness, a large spread between a threshold (0.200 μm; detectable stimulus) suprathreshold (>0.51 μm; quantifiable stimulus) and the level that causes a perception of roughness for a particular product (core granules in ODT – 264 μm) can be seen. It is striking, that despite such acute roughness perception, Kimura et al. (2015) found only granules as large as 264 μm to be described as rough. This suggests the importance of a reference product. Once a stimulus, e.g., a steel plate with roughness of 0.200 μm (Linne and Simons, 2017) is compared with no stimuli, smooth steel plate, the acuity of perception can be higher. In their study, Kimura et al. (2015) compared ODTs with and without granules. The reference sample (ODT without granules) had its own level of roughness, while the granules only added to intensity of it, up to the level of discomfort. This shows that the perception of a

pure stimuli differs enormously from that of the final product, where roughness, for example, is just a part of the overall sensory experience.

Understanding the complexity and source of mouthfeel sensations, has potential to drive the development of palatable formulations. During early development of OSDF, it would be beneficial to determine at which level a stimuli, like roughness, is just perceptible, and when it causes discomfort, as accomplished by Kimura et al. (2015) for ODTs with granules.

Table 1.4 Sensitivity of the oral cavity to various tactile stimuli, trigeminal stimuli or mouthfeel perception.

Attribute	Threshold	Reference
Roughness		
• Ra: DT	0.200 µm	(Linne and Simons, 2017)
• Ra: JND	0.023 µm, 0.039 µm	(Linne and Simons, 2017), (Miles et al., 2018)
• Suprathreshold		
moderate stimulus	>0.51 µm	(Linne and Simons, 2017)
strong stimulus	>7.62 µm	(Linne and Simons, 2017)
very strong stimulus	>22.86 µm	(Linne and Simons, 2017)
• Granules*: roughness**	264 µm	(Kimura et al., 2015)
• Granules*: discomfort**	623 µm	(Kimura et al., 2015)
• Core granules* in ODT: roughness**	264 µm	(Kimura et al., 2015)
• Core granules* in ODT: discomfort**	623 µm	(Kimura et al., 2015)
Grittiness		
• MCC in water: size (concentration)	>25 µm (0.2%)	(Imai et al., 1995)
• MCC in water: size (concentration)	>10 µm (0.8%)	(Imai et al., 1995)
• MCC in viscous solution: size (conc.)	>71 µm (0.8%)	(Imai et al., 1995)
• MCC in hard gel: size (conc.)	>26 µm (1.8%)	(Imai et al., 1995)
• MPs in viscous solution: size (amount)	263 µm (1 g)	(Lopez et al., 2016)
• Soft chewable tablet: particle size of drug		
*grittiness not affecting mouthfeel****	75 µm	(Mishra et al., 2009)
*grittiness affecting the taste of chew****	125 µm	(Mishra et al., 2009)
Graininess		
• MCC 50 µm in water	0.4%	(Furukawa et al., 2019)
Viscosity		
• Shear: JND (viscosity difference between samples)	9.33%	(Lv et al., 2017)
• Extensional: JND (viscosity difference between samples)	6.20%	(Lv et al., 2017)
• Xanthan gum solution: JND (increase in conc.)	0.23-fold	(Furukawa et al., 2019)
Pressure (tongue)		
• Force: DT	0.04 g, 0.0044 g	(Furukawa et al., 2019), (Miles et al., 2018)
• Force: JND	0.0017 g	(Miles et al., 2018)
Two-point discrimination		

Attribute	Threshold	Reference
• Tongue: distance	1.8 mm	(Furukawa et al., 2019)
• Upper lip	2.9 mm	(Won et al., 2017)
• Lower lip	3 mm	(Won et al., 2017)
Point-and-edge recognition		
• Letter recognition: size	3.98 mm	(Miles et al., 2018)
Astringency		
• TA	0.212 mM	(Linne and Simons, 2017)
• EGCG	0.770 mM	(Linne and Simons, 2017)
Heat		
• Cold	<32 °C	(Green, 1986)
• Warm	>35 °C	(Green, 1986)
Creaminess		
• Milk: % fat	>1%	(Chojnicka-Paszun et al., 2012)

Ra – average roughness DT – detection threshold; JND – just noticeable difference; ODT – orally dispersible tablet; MCC – microcrystalline cellulose, MPs – multiparticulates (MCC pellets); EGCG – epigallocatechin gallate, TA – tannic acid; * the same spherical granules were tested alone, and after incorporation into ODTs; ** evaluated after spitting out the sample; *** scale description as in publication

1.3 Coatings to improve acceptability

The coating process is a well-established unit operation during the manufacture of tablets. Reasons for applying a coating layer to a final product are manifold and include modification of drug release; protection of API from environmental conditions like light, moisture, air or low pH; aesthetical appearance; brand recognition; improved acceptability, among others. The aspects of acceptability that can be tuned with a coating layer, palatability (taste and mouthfeel) and ease of swallowing, will be discussed here. This thesis discusses polymer-based coatings only as they are most common.

1.3.1 Taste-masking

Masking the aversive taste of an API is key to improving adherence to oral medicines (Al-Shammari et al., 1995, Mennella et al., 2013). Applying a coating layer with taste-masking properties onto a OSDF is the most common technique used to conceal API taste. Several formulation factors which are known to affect taste-masking efficiency of coatings include:

- Coating thickness, also related to shape and size of the dosage form (Römer et al., 2008, Sauer and McGinity, 2009),
- Coating formulation (Joshi and Petereit, 2013),
- Chemistry of the API (Vesey, 2018),
- Use of combination approaches, e.g. addition of flavourings (Pareek and Mohanty, 2001).

A coating creates a physical barrier between the API and the taste buds so that taste receptors are not stimulated. For this method to be effective, the amount of API molecules that are released from the OSDF in the mouth cannot exceed the taste threshold for each particular substance (Yajima et al., 2002). Hence, a requirement for a taste-masking coating is an ability to form a saliva-resistant barrier for the duration of OSDF retention within the oral cavity. One approach is to form a pH-dependent polymer layer (reverse enteric coating), which dissolves in the acidic stomach environment, but remains intact at the neutral pH within the mouth (Table 1.5). Another approach involves water soluble polymers. With the assumption that tablets are intended to only stay briefly in the mouth, the efficiency of taste-masking using water soluble polymers is controlled by the thickness of the coating and rate of dissolution. Coating viscosity can be modified to slow dissolution rates. Alternatively, API release may be modified by the use of coatings composed of both water soluble and insoluble polymers in different ratios. Another approach is to increase the hydrophobicity of the coating, which by having water repelling properties, reduces the dissolution rate.

The efficiency of taste-masking properties *in vitro* (more in section 1.4.4.1) is usually undertaken as a proof of concept of a given technology. The final confirmation is obtained *in vivo* using a human panel (section 1.5).

Table 1.5 Technologies used in pharmaceutical coatings to achieve taste-masking and examples of functional excipients; HPMC – hydroxypropylmethyl cellulose, HEC – hydroxyehtyl cellulose, PVA – Polyvinyl alcohol, PVA-PEG – polyvinylalcohol–polyethylenglycol-copolymer, EC – ethylcellulose.

Technology	Example
pH dependent polymer	Basic butylated methacrylate copolymer (Eudragit® EPO) Hydroxypropylmethyl cellulose phtalate
Water soluble	HPMC, PVA, PVA-PEG
Viscosity modification	Thickeners, e.g. xanthan gum, guar gum, higher molecular grade HPMC
Water insoluble	EC, shellac
Hydrophobicity modification	Polymer (film former) + lipid/wax (hydrophobic)

1.3.2 Mouthfeel enhancement

A coating layer is intended to cover the whole surface of the tablet, thus during administration it is the coating which interacts with the oral surfaces, not the tablet core. While the key textural properties of non-conventional dosage forms including: ODT (Kimura et al., 2015), ODF (Scarpa et al., 2018), or chewable tablets (Mishra et al., 2009) have already been studied to some extent, the mouthfeel of conventional tablets has largely been ignored by researchers. Yet, tablets, and specifically the presence or absence of a coating can affect oral sensations and subsequent acceptability.

The textural properties of tablet coatings that affect acceptability might be likened to those of food where the oral processing is similar. For confectionary, such as sugar-coated candy (e.g. M&Ms®), hard caramel (e.g. Werther's Original®), or mint candy (e.g. Polo®), its surface is known to be critical for consumer acceptance. In particular, smoothness and (low) adhesiveness are expected. Hardness is key when chewing is involved, and brittleness or disintegration in the mouth may be crucial for sweets like mint candy.

In relation to coated tablets, similar textural attributes can have a pronounced impact on mouthfeel perception. Firstly, the coating protects the tablet from quick disintegration in

contact with water, thus allows the tablet to be swallowed intact. Secondly, uncoated tablets can absorb saliva creating a dry feeling, where coatings limit this effect. Furthermore, the roughness of the coating can vary depending on the coating's formulation, thickness and application process. Given the high oral acuity to roughness differences, it can be expected that the tongue would detect even minimal roughness of 'smooth' coated tablets. Some coatings are known to have adhesive properties (Washington, 2001); which can have impact on mouthfeel perception.

It is not only tactile, but also visual impressions of medicines that impact their acceptability. Several studies suggested that coating appearance can affect a consumer's appreciation of the product. It has been known for a long time that "you eat with your eyes". What we see creates an impression of the taste and mouthfeel of the product we are about to try (Michel et al., 2014, Spence et al., 2016). For example, surface defects or roughness of coated tablets can be perceived as a product flaw and decrease the willingness of the consumer to take it (Teckoe, 2017). Extensive research has also investigated the impact of oral medicine colour. Tablet colour alone has been linked with perceived effectiveness (de Craen et al., 1996), associated with emotions (Lechner et al., 2012), and preference. Interestingly, colour preference changes geographically (Lechner et al., 2012) and is gender-related (Smith et al., 2013). The visual impact of OSDFs is beyond the scope of this thesis.

1.3.3 Influence on swallowing

Tablet dimensions (volume, shape) are the main determinants for ease of swallowing with smaller tablets being easier to swallow. Yet, for high dose formulations a reduction in size may not be possible. In such cases, application of a coatings can make swallowing easier for

the patient (Food and Drug Administration, 2015). Multiple studies have confirmed that coating OSDFs can improve the swallowing experience in human volunteers (Uloza et al., 2010, El Edelbi et al., 2015, Mahdi and Maraie, 2015). Measured using video scintigraphy, it has been found that uncoated tablets have a slower oesophageal transit time than coated tablets: swallowed with 30 mL of water 65.2±32.8 and 3.2±0.31 seconds, with 50 mL of water 3.4±0.36 and 2.3±0.18 seconds, respectively (Perkins et al., 2001). Not only was a lack of coating related to an increased risk of oesophageal adhesion during the swallow (Perkins et al., 2001), but also excessive adhesiveness of OSDF surfaces can result in prolonged tablet retention during swallowing (Perkins et al., 1999). Drumond and Stegemann (2018b) reviewed the methodology associated with *in vivo* and *in vitro* assessment of tablet transit and highlighted that coating characteristics like low adhesion and slipperiness are required for an easy to swallow formulation. Other researchers have suggested, that the glossy appearance of a coating can positively affect a patient's perception of the ease of swallowing tablets, as compared with a matte coating or no coating (Yoder et al., 2014). With that in mind, the composition of tablet coatings should be developed to minimize swallowing difficulties and improve patient acceptability. The impact of particular coating ingredients on slipperiness and ease of swallowing is discussed in Chapters 2 and 4.

1.4 Swallowing, taste, texture and mouthfeel – instrumental methods

1.4.1 Oral processing

During swallowing of a tablet, we experience its taste, texture and mouthfeel. This sensory perception develops when the product is manipulated in the mouth and then passed down the oesophagus. Swallowing a tablet involves similar movements, and is potentially subject to

the same sensory perceptions, as oral processing of food. It is, therefore, important to understand this process. The next section will describe oral processing and the *in vitro* techniques used to understand sensory perceptions such as mouthfeel and texture. Further, the forces present during oral processing and the role of saliva will be explained. The concept of oral perception of tablets, and OSDF in general, is novel. Therefore, all principles will be explained in relation to food in order that they can later be applied to tablets.

1.4.1.1 Stages of oral processing

Processing food in the mouth is a complex process. Jaw movements, activity of the tongue and facial muscles, as well as saliva excretion all combine to moisten food and reduce the size of food particles. This results in physico-chemical alterations of food matrix, in order to prepare a food bolus safe for swallowing.

During oral processing the changing properties of food affect sensory perception. Stokes et al. (2013) divided oral processing of solid food into 6 stages (Figure 1.3). Initially, (i, ii) during chewing food is crushed and crispy/crunchy sensations dominate. At this stage, mechanical properties of food dictate the texture perception. As the food particle size reduces (iii) physical surface interactions are manifested by the rubbing of food pieces between the tongue and palate. A relevant technique to replicate this process *in vitro* is tribology, where lubrication and friction are analysed. As the food particles become dispersed in saliva to create a bolus (iv) the viscoelastic properties become more important to describe texture and mouthfeel. The bolus is processed by shearing between oral surfaces, mixing with saliva and enzymatic breakdown, which results in a change in texture and rheology. At the same time, the oral cavity is coated with a film of saliva and residual food, causing lubrication, which

facilitates (v) swallowing. Afterwards, (vi) food residues determine the after-feel. Bolus processing in the mouth can be explained on grounds of rheology and tribology. It needs to be noted that separation of the oral processes in Figure 1.3 is artificial, as the stages overlap in time.

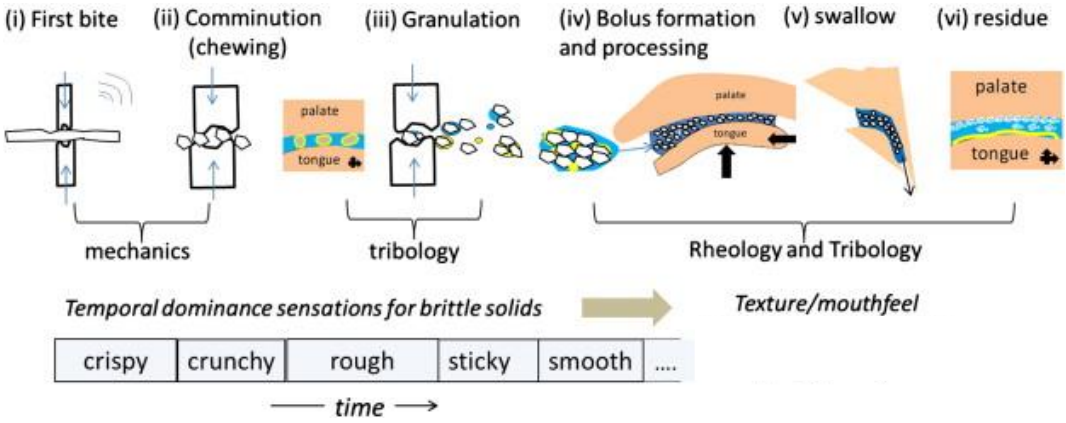


Figure 1.3 Visualisation of the 6 key stages for oral processing of solid food. Reprinted from Stokes et al. (2013) with permission from Elsevier.

1.4.1.2 Forces during oral processing

During the oral processing of food, the forces applied to break down the food into smaller particles include compression/tension, shear, and friction. Forces are not only important to break down food but also because they impact the swallowing mechanism and sensory perception. With this in mind, specific values of the forces present in the mouth have been reported and the attempts made to correlate them with oral sensory perceptions such as texture and mouthfeel.

Compression forces during oral processing range from light pressure, like a tongue touching the teeth, to high loads exerted by teeth during biting (>100 N) (Chen, 2009). The tongue exerts no or minimal forces during rest, and between 0.87 – 3.12 N during a spontaneous swallow (Valentim et al., 2016). Similar values were reported in the review on tongue

biomechanics during swallowing by Ono et al. (2009). (Section 1.4.1.2 further discusses role of compression forces in texture and mouthfeel perception).

Shear forces dominate during bolus transportation around the mouth and during swallowing. There is little consensus in the range of shear rates occurring during oral processing. To date, reported values are either derived from computer simulation or estimation, based on bolus flow, and range from 1 – 1000 s^{-1} (Meng et al., 2005, Gallegos et al., 2012). Sensory researchers have evaluated a range of shear rates based on viscosity measurements in relation to human perception of 'thickness' of liquid products. The most commonly reported value, 50 s^{-1} (Wood, 1968, Steele et al., 2014, He et al., 2016), became the standard for the comparison of thickness of liquids adopted by dysphagia associations from USA and Japan (National Dysphagia Diet Task Force and American Dietetic Association, 2002, Fujitani et al., 2013). Although He et al. (2016) reached a high level of *in vivo-in vitro* correlation (R^2=0.952) using a single value of 50 s^{-1}, other authors have challenged use of a single shear rate value (Ong et al., 2018), as a wider range of shear rates occur during oral processing. Recent studies, which developed mechanical models simulating oral processing (Redfearn and Hanson, 2018) and swallowing (Stading et al., 2019) exerted shear rates below 40 and around 80 s^{-1}, respectively. The former model was employed to imitate disintegration of ODFs, where obtained data were proportional to human data (Scarpa, 2019). The latter has not yet been correlated with human data. In summary, the choice of shear rates most relevant for oral sensory perception is still debatable. (Section 1.4.3.2 further discusses role of shear in texture and mouthfeel perception.)

Friction forces occur whenever one surface moves against another. During oral processing the surfaces of teeth, palate, lips and tongue generate friction between each other and

between food particles. The magnitude of these friction forces depends on tension forces generated by muscle and jaw movements, as well as on the speed of these movements. To illustrate, the speed of tongue movement during a liquid swallow ranges from 2 mm/s to 200 mm/s (Tasko et al., 2002). Frictional interactions between oral surfaces contribute to our perception of food texture and mouthfeel (de Wijk and Prinz, 2005). The intensity of such tactile sensations is modulated by saliva, which wets and lubricates the surfaces involved. (Section 1.4.3.1 further discusses role of friction in texture and mouthfeel perception.)

1.4.1.3 The functions of saliva

The role of saliva in oral food processing is noteworthy. Although saliva consists of 99% water, the ionic and protein components determine its multiple functions (Gittings et al., 2015). Saliva coats and lubricates surfaces in the mouth, specifically teeth and mucosa (Bongaerts et al., 2007b). The salivary coating acts as a protective layer: it reduces shear forces produced during food mastication, defends soft and hard tissues from harmful microorganisms, and during fasting periods and night it prevents the oral mucosa dehydrating and sticking together (Chen and Engelen, 2012).

Saliva plays a vital role in taste and texture perception. Primarily, it helps to disintegrate food particles and disperses them around the mouth enhancing flavour diffusion. It transports compounds to the taste buds on the tongue. The perception of food texture and mouthfeel is also facilitated in the presence of saliva. Saliva modifies the viscosity properties of the food matrix influencing various oral sensations; it can reduce unpleasant feelings of grittiness, dryness, tackiness, mushiness, as well as enhance smoothness, aroma, and tenderness. The importance of saliva in oral processing is most obvious in people suffering from xerostomia

(dry mouth caused by reduced saliva flow). These patients often experience mucosal irritation and reduced pleasure from food consumption (Atkinson et al., 2005). Other studies have shown the negative effect of reduced salivation on overall sensory perception (Logemann et al., 2001) and swallowing (Iwasaki et al., 2016) as a consequence of a defect in lubrication. To date, the relationship between xerostomia and texture perception has not been addressed (Laguna et al., 2017, Muñoz-González et al., 2018).

1.4.1.4 Oral processing in relation to tablets

Specific conditions occur during the oral processing of conventional tablets. Swallowed as a whole, they do not undergo mastication, and oral motions of tablets are limited to sliding on oral surfaces. Lack of chewing also results in lower compression forces and the residence time of medicines in the oral cavity is short. Yet, as a medicine passes through the mouth, it will interact with oral surfaces and be mixed with saliva which impacts oral sensory perception. In this process friction forces and saliva lubrication play a major role. Defining the forces present during oral processing of tablets is crucial to model *in vitro* experiments that relate to sensory perception.

As mentioned above *in vitro* techniques have the potential to measure the characteristics of food in relation to mouthfeel, and we postulate that the same techniques can be applied to oral medicines. The techniques used will be described in the following sections.

1.4.2 Instrumental methods relevant to oral perception

Taste, texture and mouthfeel perception during oral processing of a product are critical to that product's acceptability. When performing sensory studies, human volunteers remain a gold standard method, but researchers are working to develop instrumental methods as

tools to (i) increase understanding of the fundamental mechanisms that cause sensory perception and (ii) build models to predict the sensory experience based on instrumental data. The approaches taken to measure the qualities relevant to oral perception have remained the same for more than half a century. Methods used can be divided into three main approaches (Blair, 1958) (Table 1.6). Fundamental – focuses on well-defined physical characteristics that relate to product oral perception. Empirical – measures parameters which by observation relate to some product property. Imitative – mimics oral processing.

Instrumental methods usually measure a particular taste/texture/mouthfeel attribute by means of one test (e.g. thickness – viscosity), yet they are perceived with multiple senses. Consequently, it is particularly difficult to replicate oral perception using *in vitro* techniques. Currently, the use of a single technique, like tribology, rheology or texture analysis, although very informative, is not sufficient to fully explain sensory perception (Pons and Fiszman, 1996, Chen and Engelen, 2012). Therefore, an array of methods needs to be employed to explore the sensory properties of a product. Key methods, associated with the three different approaches described, will be presented in detail in the following sections. The fundamental and empirical methods described below will be used in the following chapters to characterise coated and uncoated tablets.

Table 1.6 Three main approaches to in vitro *measurement of product characteristics relevant to oral perception.*

Approach	Fundamental	Empirical	Imitative
Description	Explores the basic principles e.g. answers the question what characteristics of a product define its texture	Measures parameters, often poorly defined, which by observation seem to be related to some sensory quality	Recreates the conditions to which the product is subjected in practice
Advantages	Allows understanding the physical characteristics of a product	Usually simple set up, suitable for routine tests, standardised methodologies (for foods)	In theory, should have the highest correlation with sensory perception
Disadvantages	Test conditions do not always relate to the behaviour of a product during oral processing	Measured qualities that cannot always be defined in clear physical terms	A demanding set up, limited versatility and inter-laboratory reproducibility*; no standardised methodology
Examples	Rheological test -> thickness Tribological test -> smoothness, slipperiness	Texture analysis (e.g. tension test) -> stickiness e-Tongue -> taste intensity	Imitation of swallowing -> ease-of-swallowing Dissolution test -> taste release

* (Bourne, 2002, Zdunek et al., 2011)

1.4.3 Fundamental approaches

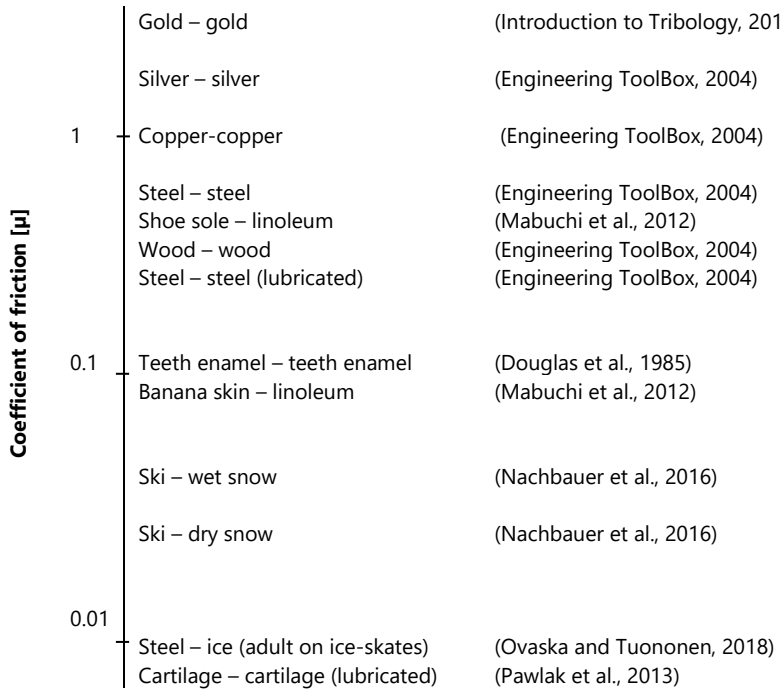
1.4.3.1 Tribology

1.4.3.1.1 Theory

Tribology is a science that deals with the friction, wear, and lubrication of interacting surfaces in relative motion (Merriam-Webster, 2017). Originally, it was applied in mechanical engineering to evaluate friction in engines, wheels, and machinery vulnerable to wear (Nakada, 1994). More recently, it has been applied to understand complex processes during food processing in the mouth (Luengo et al., 1997, Malone et al., 2003). This section describes the basics of tribology in relation to oral applications (called oral tribology). As the use of tribological methods in oral medicines is novel, the principles of oral tribology, presented in this thesis, are based on food applications.

Friction is observed whenever interacting surfaces move against one another, either in dry or lubricated conditions. Tribology quantifies these interactions to give a coefficient of friction (COF, μ). COF is directly proportional to friction force (*F*) and inversely proportional to applied normal force (*W*), $\mu = F/W$. Since friction can only be observed if two surfaces are interacting, COF is considered a constant for given pair of materials. Table 1.7 presents COF values for different materials. Under dry conditions, COF values are usually larger than for lubricated conditions. When two surfaces are lubricated with a fluid (or semi-fluid), the fluid starts to bear the load being applied and isolates the surfaces of the materials under test from one another. This results in fewer interactions between the surfaces and hence a lower COF. Without lubrication, the value of COF depends on the topography of the surfaces.

Table 1.7 Examples of coefficient of friction values for different material pairs (values are given for dry surfaces unless stated otherwise).



1.4.3.1.2 Instruments

A tribometer is an instrument that investigates friction behaviour (changes of COF under different conditions) of a pair of materials. A tribometer consists of two surfaces brought into contact with predetermined force. During a tribological experiment, either one surface is stationary and a second slides onto it, or both surfaces move in relation to one another. A range of tribometers are available, either commercial or bespoke, which vary in the geometry of interacting surfaces, trajectory of movement (e.g. circular, elliptical, linear), surfaces of the components, applied load and speeds. The most common tribometers designed to analyse the frictional and lubricating properties of food are presented in Figure 1.4. The Mini-Traction-Machine (MTM2) is widely used in oral tribology (Figure 1.4 (i)). The particular characteristic of this instrument is the combining of two types of movement sliding and/or rolling, which relates to the movements of the tongue against the teeth and palate. The rotation of the bottom plate constantly supplies fresh sample, thus allowing dynamic observation of friction (e.g. changes of lubricant properties over time) (Vardhanabhuti et al., 2011, Mills, 2012). As an alternative to MTM2, other instruments have been adapted to study friction behaviour. For example, a special attachment to a rheometer (called a tribo-rheology cell) allows measurement of the friction between two surfaces while the top one is rotating (Figure 1.4 (ii)). These cells are popular due to their versatility. Different configurations like ball-on-three plates or three-balls-on-plate provide settings to test many types of products, e.g. milk, cream cheese (Nguyen et al., 2016), chocolate (He et al., 2018), or bread (Kiumarsi et al., 2019). A few research groups have also built bespoke tribometers. These include an optical tribometer cell (OTC) (Figure 1.4 (iii)) or a modified texture analyser (Figure 1.4 (iv)). The former has the unique advantage of real-time observation of the sample with a

microscope. Specifically, it has been used to study shear-induced changes of microstructure of o/w emulsions and microbubble dispersions (Rovers et al., 2016). The latter apparatus consists of a texture analyser in a horizontal position to measure the force needed to pull a sample in a straight line. Due to the demanding set-up and a limited sliding speed range, it has been superseded by tribo-rheology cells (Sarkar and Krop, 2019).

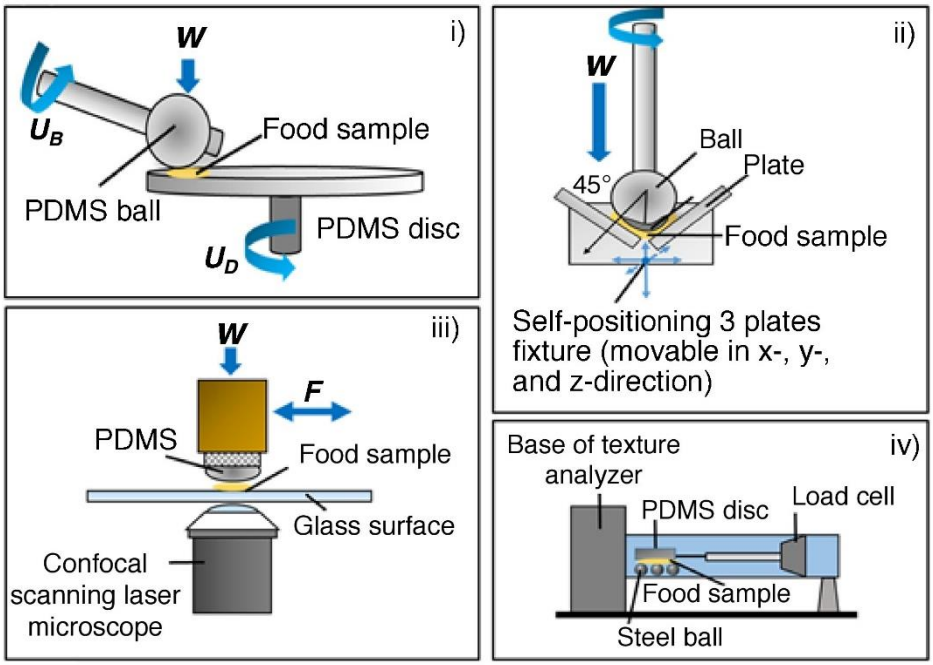


Figure 1.4 Outline of tribology apparatus with precedence in food studies: Mini-Traction-Machine (MTM2) (i), tribo-rheology cell (ii), optical tribometer cell (OTC) (iii), modified texture analyser (iv); adapted from Sarkar and Krop (2019) with permission from Elsevier.

1.4.3.1.3 Lubrication regimes

Lubricants differ in their capability to reduce friction (lubricity). The lubricity of a liquid/semi-liquid depends on the intrinsic properties of the lubricating substance (e.g. viscosity) and the properties of the system (speed of movement, interaction between lubricant and surfaces). To test the lubricity of a liquid/semi-liquid, COF of two lubricated surfaces moving at increasing/decreasing speeds at a constant force is measured. (The surfaces are determined by type of tribometer used.) The resulting data are plotted as a Stribeck curve, where COF (μ)

is a function of sliding speed (v_s) and lubricant viscosity (η). Along the Stribeck curve, three lubrication regimes can be identified: boundary, mixed and hydrodynamic regimes (Figure 1.5). At the lowest speeds (boundary regime) there is no or minimal lubrication between surfaces, and the COF depends on surface properties. As speed increases, in the mixed regime, the lubricant begins to be entrained between surfaces and the surface contact remains only on the larger asperities. As more lubricant is entrapped, friction gradually decreases. Finally, at the highest speeds, both surfaces are separated by a continuous layer of lubricant – this is termed the hydrodynamic regime (also known as elasto-hydrodynamic regime for soft surfaces). At this point, the friction depends on the liquid's lubricity, mostly dictated by its viscosity and overall structure. An illustrative example of the boundary regime is a pair of wet dinner plates, which, when stuck together generate high friction. A mixed regime can be represented by a slipping on a banana skin, when the COF drastically falls with increase of speed. Whereas, the hydrodynamic regime is best represented by skiing on wet snow. When a complete water film separates ski and snow the friction force present is determined by properties of water itself (i.e. viscosity or increase of capillary forces between ski and snow).

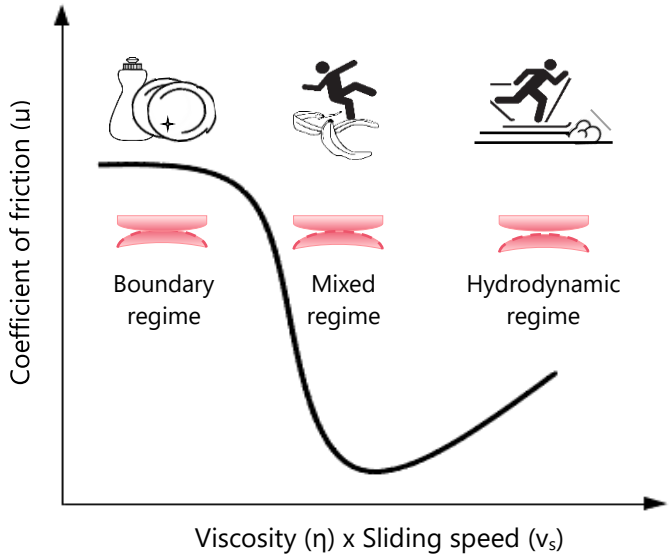


Figure 1.5 Characteristic Stribeck curve representing different lubrication regimes with increasing speed, adapted from: Prakash et al. (2013).

1.4.3.1.4 Mimicking the oral environment for tribology testing

Oral tribology has the potential to link the frictional behaviour and the sensory perception of a product, particularly texture and mouthfeel. A tribological experiment which explains this relationship should mimic the oral environment during oral processing. In this respect, there are several reports that have attempted to recreate mouth-like conditions in tribological tests (Dresselhuis et al., 2007, Zundel et al., 2018). The following section gives an overview of current knowledge on the test parameters relevant to the oral environment, namely surfaces, temperature, lubricant, volume of lubricant, and speed of movement.

Surfaces

Several attempts to mimic oral surfaces to measure friction, mainly a tongue, have been reported in the literature. Three major characteristics were found to be crucial to mimic the tongue surface: (1) roughness (average height of asperities), (2) wetting properties, and (3) mechanical characteristics like elasticity or hardness (Dresselhuis et al., 2008b).

Tongue roughness is attributed to two main types of papillae: filiform and fungiform. The former are most numerous papillae, which have a small, conical shape and are responsible for the sensation of touch. The latter papillae form round structures with a taste bud on their upper surface. Attempts to mimic tongue roughness have been made using artificial materials, such as silicone elastomer or polydimethylsiloxane (PDMS). PDMS, due to its versatility, is a commonly used material to mimic the characteristics of the tongue. For example, it allows tuning of its surface by sanding or moulding in order to form papillae-like projections (Ranc et al., 2006, Bongaerts et al., 2007b). Others have used 3M Transpore™ Surgical Tape with a checkered texture surface, where the surface roughness matches that of the tongue (Nguyen et al., 2016). Achieving an accurate resemblance is difficult due to the variability of the tongue itself.

Furthermore, all oral surfaces are naturally lubricated by saliva, where salivary proteins – mucins – are recognised as instrumental to oral lubrication. The mucin layer on the tongue surface turns an intrinsically hydrophobic tissue into a hydrophilic surface (Dresselhuis et al., 2008b). To mimic the tongue, attempts to render a synthetic surface (PDMS) hydrophilic have been made by oxygen plasma treatment (Bongaerts et al., 2007a) or salivary film coating (Macakova et al., 2011). These methods, however, require relatively complex technology. Alternatively, a mucin layer has also been used to recreate hydrophilic oral surfaces (Drumond and Stegemann, 2019). Porcine mucin was spread and compressed onto carbon adhesive tape, then sprayed with distilled water. Yet, as stated by authors, the layer was depleted rapidly which limited the practicality of the method.

Oral surfaces, like the tongue or palate are softer and more elastic than commonly used artificial surfaces e.g. the Young's modulus (measure of elasticity) of PDMS is 250 times larger

than that of a pig's tongue (Dresselhuis et al., 2008b). Nevertheless, PDMS remains the material of choice due to its adaptability in terms of roughness and wettability.

Although readily available, the disadvantage of artificial surfaces is that they fail to fully mimic oral surfaces, specifically the tongue. To address this, several studies have employed *ex vivo* pig tongue to measure COF (Prinz et al., 2007, Zundel et al., 2018). Such studies represent branch of biotribology, as they use biological samples, or soft tribology, as they use soft surfaces. The good reproducibility of tribological experiments involving porcine tongue tissue has been proved by De Hoog et al. (2006). The authors also highlighted that softness and deformability of tissue affected the contact area depending on applied load. In sum, *ex vivo* tissues seem optimal from a biorelevance point of view, however their softness poses a major challenge to interpretation of COF results (as COF depends on contact area) (Pitenis et al., 2017). Therefore, use of artificial surfaces still predominates in oral tribology.

Lubricant

The mouth cavity is lubricated by constant flow of saliva at rate 0.7mL/min for unstimulated saliva or 1.6 mL/min for stimulated saliva (Shaikh-Omar, 2013), with a mean volume at rest of 0.7 mL (Müller et al., 2010). As saliva dilutes and enzymatically breaks down consumed food, several authors have tried to incorporate human saliva into tribology testing in order to provide more biorelevant conditions. The interaction of food and saliva can be multifold. When mixed together, certain products can either increase, decrease or maintain the lubricity of saliva. For instance, starch breaks down in contact with salivary enzymes, which is observed as a decrease in friction in a tribology test (Morell et al., 2017). In contrast, the presence of human saliva has been found to impair the lubricity of o/w emulsions (with 40% oil content)

(Dresselhuis et al., 2007). Some products do not change their lubricity after mixing with human saliva (i.e. acid milk gel) (Joyner et al., 2014). In this light, saliva effects are important when considering the mouthfeel of food (e.g. dry, astringent feeling caused by red wine; an effect of wine compounds reducing lubricity of saliva (Brossard et al., 2016a)).

Two of the major challenges when using *ex vivo* saliva in tribological studies are obtaining it in large quantities, as well as variability of saliva samples between donors (Gittings et al., 2015). Consequently, substitution with artificial saliva is often reported (Laguna et al., 2017, Torres et al., 2019). However, the results obtained with artificial saliva are disputable as still no fluid is able to accurately simulate the physico-chemical properties of saliva (Chen and Engelen, 2012). This is due to the highly complex and variable composition of human saliva.

Movement

Oral processing engages a range of actions like compression, extension, shearing and sliding. Tribology experiments aim to emulate the shearing and sliding, where two surfaces move against each other. The trajectory of this movement, either reciprocating, sliding, rolling, or rotating, depends on the design of the tribometer (Figure 1.4). Circular rotating/rolling set-ups are advantageous because they allow measurements at a wide range of speeds with a high maximum speed (0–1000 mm/s). This ability, although not biorelevant for oral applications, provides a comprehensive characterisation of a product. In contrast, set-ups with linear reciprocating movements are limited to tests at lower speeds (up to 50 mm/s). However, parallel movement more closely resembles sliding of the tongue over the palate/teeth. Results obtained from different set-ups, are not directly comparable (Campbell

et al., 2017). Yet all tribometer types are used in food research as they allow different insights into the food/liquid behaviour occurring during oral processing.

1.4.3.1.5 Relating oral tribology to mouthfeel of foods

To date, researchers have successfully correlated several mouthfeel attributes like smoothness, roughness, slipperiness, creaminess and astringency with friction. A pioneering study, published in 1977, described several correlations (Kokini et al.). Kokini's model defined smoothness as a function of friction force, and slipperiness as a function of friction and viscous forces. Those principles built a base for further oral tribology studies relating the friction and mouthfeel of food.

More recently, researchers have studied various model foods with tribology to better understand the principles of texture perception. For instance, Malone et al. (2003) tested various concentrations of guar gum solutions (0.05 – 0.6%) and related a slippery mouthfeel with the mixed lubrication regime for entrainment speeds between 10 and 100 mm/s. While Dresselhuis et al. (2008a) reported a link between friction forces and the dry and rough, mouthfeel of an o/w emulsion.

More complex food samples, like vanilla custard desserts, white sauces, or mayonnaises, were investigated by de Wijk and Prinz (2007). They compared instrumental methods to the taste and mouthfeel description from 9 healthy panellists. The authors found a correlation between the oral perception of a creamy and fatty mouthfeel, as well as fatty after-feel and measurements of friction. The same mouthfeel attributes also correlated with other (non-tribological) methods of analysis: infrared reflectance and turbidity. With a combination of all these methods, a prediction of creamy/fatty mouthfeel was possible (using partial least

squares analysis (PLS)). It is worth noting that the prediction of all aspects of mouthfeel is difficult with using a single type of analysis. Others have also related creamy/fatty mouthfeel with fat content (Malone et al., 2003, Chojnicka-Paszun et al., 2012). Another study showed that in emulsions, like mayonnaise, friction correlated not only to fat content, but also to droplet size; the bigger the fat droplet, the higher the coefficient of friction (de Wijk and Prinz, 2005).

Chojnicka-Paszun et al. (2012) compared the oral perception of milk assessed by an expert panel (10 persons) to rheological and tribological measurements. The sensory analysis of homogenised milk (0.6–4% w/w fat) showed that creamy taste and mouthfeel were detected only above a 1% w/w fat content. The intensity of the sensation was positively correlated with fat content. In the boundary regime (below 10 mm/s), the coefficient of friction of samples below 1% fat was independent of fat content. While for milk above 1% fat, friction decreased with increasing fat content, which indicated that fat supported boundary film formation, and so lubrication. The effect was attributed to coalescence of fat droplets on a tribological surface (pig's tongue, glass, Teflon, silicone and neoprene) (Dresselhuis et al., 2008a, Chojnicka-Paszun et al., 2012).

Other researchers have looked at the effect of small particles in foods on their friction and oral perception. Laiho et al. (2017) studied yogurts with whey proteins of various particle sizes (range 27–47 μm). A positive correlation was found between a grainy sensation, size, and COF in tribological analysis (in the mixed lubrication regime between 1–100 mm/s sliding speed). Similar findings were also published by Krzeminski et al. (2014). On the other hand, addition of sharp or rounded particles of various sizes to custard desserts contributed to a rough after

feel of the custard (de Wijk and Prinz, 2005). As reflected in tribological measurements sharper and larger particles resulted in higher COF.

In summary, the study of oral tribology is becoming more common to understand and predict food texture and its perception. Moreover, it helps to analyse the microstructure of food and behaviour of its individual components (e.g. particles or droplets). However, as it is a novel field, the results are limited to certain types of products, so extrapolation to a wider range of food should be done cautiously. Nevertheless, the tribological knowledge gained in food research, provides a premise for the application of tribology to other fields where friction may influence mouthfeel perception i.e. oral medicines.

1.4.3.1.6 Application of tribology in pharmaceutical studies

The tribology research on the texture of food models described earlier set a precedent for its use with oral pharmaceuticals. An advantage of tribology is that its measures can be correlated to certain sensory perceptions. In theory, tribology can be used to screen for favourable textural qualities, and so inform the manufacture of oral formulations with optimised sensory properties.

Oral pharmaceutical formulations create varied sensations in the mouth, some of which have the potential to be studied with tribological methods (Table 1.8). Solid formulations which are swallowed intact (e.g. conventional tablets) create mouthfeel sensations related to the interaction between the tablet and oral surfaces, for instance smoothness or roughness. Theses sensations are affected by the presence of a coating as it creates a physical barrier between the tablet core and oral surfaces and also changes the way the tablet interacts with saliva – to either repel or absorb it. A water-resistant coating may give a feeling of dryness,

while a water-soluble one in contact with saliva may induce slippery or slimy sensations. Additionally, the coating's properties can influence the gliding movement of a tablet through the mouth and oesophagus (as discussed in Section 1.3.3). The glide can be facilitated with a slippery coating, or impeded, if the coating is sticky. Tribological measurements allow the study of interactions between moving surfaces, and hence could be used to explore interactions between tablet and oral surfaces during swallowing. We hypothesise that by measuring slipperiness, tribology can predict the ease of swallowing of a tablet. Furthermore, tribological measurements are sensitive to the hydrophobicity/hydrophilicity of a surface (Bongaerts et al., 2007a) indicating a potential role for tribology to study the mouthfeel of tablets.

Table 1.8 Oral dosage forms and respective sensory attributes which can pose issues during administration; sensory attributes in bold can potentially be explored using tribological methods. (Dosage forms are ordered based on their prevalence in USA (Zhong et al., 2018). Sensory attributes were chosen based on Lawless and Heymann (2010d).

	Oral dosage form	**Sensory attributes (excluding taste and smell)**
Solid	Conventional tablets	dry, **rough**, size, **slippery**, sticky
	Capsules	dry, size, **slippery**
	Lozenge	chewy, hard, soft
	ODT	disintegration time, dry, **gritty, rough,** sticky
	Chewable tablet	hard, **rough**, slimy, soft, sticky
	Powder	chalky, dry, **gritty**
	Effervescent/dispersible tablet	**gritty**, volume
	Granules, Pellets*	amount, dry, **gritty**, **rough**, volume
	ODF*	**disintegration time, gritty, rough**, sticky
	Minitablets*	amount, **gritty**
	Sprinkles*	amount, **gritty**, **rough**
Liquid	Solution	**astringent**, sticky, volume
	Suspension	**gritty**, **mouthcoating** thick, thin, volume
	Syrup	**oily**, **mouthcoating**, thick, thin, volume
	Solid for suspension	**gritty**, powdery, thick, thin
	Solid for solution	thick, thin
*not listed by **(Zhong et al., 2018)**		

The sensory properties of an oral medicine also depend on the size of particles in a formulation, particularly of powders, multiparticulates (granules, sprinkles) or orally

dispersible forms. Large or rough particles may create a grainy/gritty feeling in the mouth, affecting the palatability of medicine. The fact that tribology has already been correlated with the grainy texture of food (Laiho et al., 2017) suggests that translation of these findings to oral medicines is possible.

Liquid formulations may create various mouthfeel sensations such as feeling oily or gritty, leaving an after-taste or coating of the mouth and teeth (Imai et al., 1995, Vickers et al., 2015).

So far, tribology has been successfully applied to differentiate textures of oral infant suspensions (Batchelor et al., 2016); the study showed that lactulose containing medicines decreased friction more than polyol-based ones, which are likely to predict their mouth coating effect.

The variety of textural sensations caused by oral medicines demonstrates the need for a deeper understanding of what is acceptable and unacceptable. Oral tribology is of particular interest as it allows the analysis of a medicine's microstructure and the impact of individual components (e.g. particulates or droplets). Relating tribology to a medicine's characteristics and acceptance would be highly beneficial. Yet, as explained for food examples, prediction of sensory attributes from tribological measurements needs to be done cautiously, due to the complexity of human sensory perception and scarce *in vivo* data.

On the premise that tribology methods reflect the environment within the oral cavity, tribology has the potential to become an essential tool of a formulator. This thesis will describe how tribology has been related, for the first time, with the oral sensory perception of pharmaceutical tablet coatings.

1.4.3.2 Rheology

Rheology is a branch of physics which deals with flow and deformation of matter. It is usually applied to fluid or semi fluid materials. With regards to oral medicines, rheology is primarily used in the assessment of non-solid dosage forms: syrups, suspensions, or gels (beyond the scope of this work). This thesis focuses on coated tablets where rheological tests were used as supplementary measurements to help understand the findings of other methods. Due to the nature of the tests, rheological properties of dispersed coatings were assessed rather than coated tablets; to mimic their dispersion within the oral cavity. The basics of rheology are outlined below.

One of main concepts in rheology is viscosity – resistance of material to deformation due to internal friction. It is measured by applying shear stress to a material. Apparent viscosity, also known as shear viscosity, of a material is defined as:

$$\eta = \frac{\sigma}{\gamma} \qquad \text{(Eq. 1.1)}$$

where, η – apparent viscosity (Pa·s), σ – shear stress (Pa) and γ – shear strain (s^{-1}). There are also other measures of viscosity, like extensional viscosity, where the applied stress is extensional, as opposed to shear.

Viscosity is a fundamental product property, and it affects product behaviour whenever a stress is applied. One effect of viscosity on a product's behaviour has been discussed above (section 1.4.3.1.3), where the flow properties of a liquid impact the lubrication behaviour in thin film tribology tests in the presence of shear stress. Viscosity can also increase the adhesiveness of a product in the presence of extensional stress (refer to section 1.4.4.2).

Rheology is widely applied in formulation engineering in both food and pharmaceutical fields. The rheological properties of a product influence not only the manufacturing processes, but also the sensory experience. Multiple sensory studies of liquid foods have revealed that apparent viscosity can predict the sensation of thickness (Kokini et al., 1977, Steele et al., 2014, He et al., 2016), while extensional viscosity is related to oral perception of stickiness and 'mouthcoating' (He et al., 2016). Apart from textural perception, the viscosity of a liquid product also affects the taste intensity (Cook et al., 2003) and ease of swallowing (Steele et al., 2015).

1.4.3.3 Roughness

The sense of touch is highly relevant in texture perception. During oral processing, tactile perceptions provide information about a product's surface (e.g. roughness) and bulk (e.g. hardness) properties which might be factors that influence how much consumers like the product. Oral surfaces are known to be very sensitive to tactile stimuli. The roughness detection threshold of a tongue has been reported as 0.2 μm (Linne and Simons, 2017), suggesting that anything less than this is regarded as smooth. Also, the tongue's tactile acuity is significantly higher than that of a fingertip. Subjects touching steel plates of known roughness could detect a difference between samples of 0.039 μm with the tongue compared to 0.122 μm with the fingertip (Miles et al., 2018).

Once the roughness detection threshold is known, an estimation of how smooth or rough the surface of a product feels in the mouth can be obtained by an instrumental measure of roughness. Instrumental methods allow both quantitative and qualitative assessment of roughness. Quantitative methods provide a single numerical measure, which allows easy

comparison of products. Qualitative methods visually illustrate roughness to provide a more complete picture. To quantify roughness, two parameters are commonly calculated: profile roughness (Ra – the arithmetical mean height measured along a line to average the peaks and troughs) and surface roughness (Sa – the arithmetical mean height measured within an area). Sa is more commonly used. Sa can be measured by contact and non-contact methods. Where it is essential not to destroy a sample, non-contact methods are preferred, and include microscopy and diffraction methods (such as white light interferometry).

1.4.3.3.1 Interferometry – quantitative method

White light interferometry can accurately measure Sa. A schematic illustration of the interferometer is presented in Figure 1.6. The light beam is split to divide it between a sample and a reference mirror. Then the light diffracted by sample and reflected from the mirror are recombined and sent to the detector. Interference is observed when the optical path of light is the same for both beams. The beam scans the sample as the objective lens is moved up and down to build a 3D map of the surface.

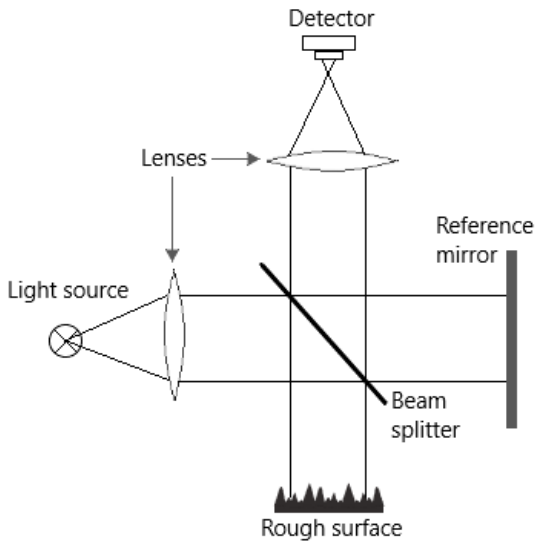


Figure 1.6 Schematic diagram of the interferometer.

1.4.3.3.2 Scanning Electron Microscopy (SEM) – qualitative method

Scanning electron microscopy (SEM) provides information on the topography of the sample surface with fine lateral resolution (≈ 1 nm). It is, therefore, useful for visual inspection of the quality of a surface such as a tablet coating. SEM uses a focused beam of electrons to produce a sample image. The electron beam interacts with atoms in the surface. Then secondary electrons (SE) and back-scattered electrons (BSE) are detected to produce a topographic sample image. The SE signal gives high resolution with large depth of field resembling a 3D image, while the BSE signal provides differentiation between sample materials based on their atomic number.

1.4.3.4 Wetting properties

The surface properties of a material (e.g. wetting properties, hydrophobicity or hydrophilicity) impact its friction behaviour (Kalin and Polajnar, 2013). Thus, studying the wetting properties of a material can be useful to understand slipperiness mechanisms governed by friction.

The wetting ability of a solid by a liquid is quantitatively described by the contact angle (CA), θ. When a water droplet falls onto the surface, an equilibrium between the solid, liquid, and gas is established (for a given pressure and temperature). The CA is defined geometrically as the angle between the three-phases. Optical tensiometers are used to measure CA via a pendant drop or sessile drop technique. In the latter, a known volume of liquid is dropped on a surface and recorded by a camera. The interface tension of a water droplet on a solid surface is fitted to the Young-Laplace model according to equations below (Bonaccurso et al., 2009),

$$\gamma_S - \gamma_{SL} = \gamma_L \cos\theta \qquad \text{Young's equation} \qquad \text{(Eq. 1.2)}$$

$$\Delta P = \frac{2\gamma_L}{R} = \frac{2\gamma_L \sin\theta}{a} \quad \text{(Eq. 1.3)}$$

where γ_S , γ_{SL} , and γ_L are solid-gas, solid-liquid, liquid-gas surface tensions respectively, θ contact angle, ΔP Laplace pressure, R radius of curvature, and a is distance between centre and contact line of droplet (Figure 1.7).

According to Eq. 1.3, a hydrophilic surface has a water contact angle below 90°, while a hydrophobic surface has a contact angle above 90°. Complete wetting is achieved when CA = 0°.

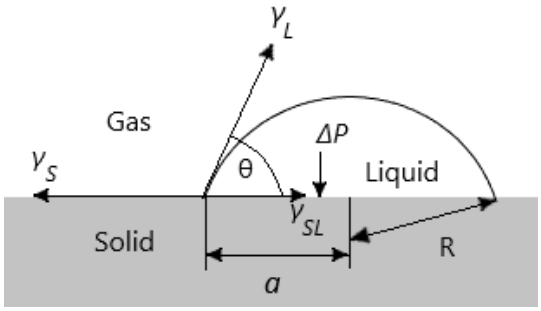


Figure 1.7 Interface surface tension of liquid on solid.

1.4.4 Empirical methods

1.4.4.1 Drug release

Dissolution testing is a widely used method for quality control of OSDFs. It quantifies the amount of drug released in a relevant media (e.g. simulated gastric fluid) for immediate release oral dosage forms. Pharmacopoeias include dissolution testing which mimics stomach or intestinal conditions, yet, there is no official dissolution method to assess taste-masking properties. Based on the principle that taste is perceived only if a bitter molecule can interact with the taste buds on the tongue, quantification of drug molecules released in the oral cavity can indicate whether taste-masking was achieved or not.

Due to a lack of appropriate pharmacopoeial methods for oral dissolution, various dissolution methodologies have been reported and reviewed (Gittings et al., 2014). To mimic oral conditions, parameters including volume, media, temperature, pH, flow, and applied forces should be considered. However, published studies are often biased by the use of inadequate media (with regards to bio-relevance of pH, buffer capacity, osmolarity), and/or quantities exceeding normal human saliva volume (even up to 900 mL), as well as inappropriate time of sampling (minutes, instead of seconds) (Pein et al., 2014). Despite this, many authors have tried to correlate dissolution results and human panel data for taste.

Throughout the literature there is lack of consistency in the threshold limits that relate the level of drug released and effective taste-masking. One recommendation suggested that a formulation which releases less than 10% of API in 5 minutes can be deemed taste-masking (Siewert et al., 2003). Others disagree, stating that taste-masking can only be efficient if the amount of API released in the mouth is lower than its taste threshold (Gittings et al., 2014).

Recently newer dissolution approaches for taste-masked products have emerged with improved bio-relevance. One example is a small volume (≈ 1 mL) flow (1 mL/min) cell (Hoang Thi et al., 2012), which accurately mimics saliva flow and volume *in vivo*. The researchers compared dissolution results with e-tongue measurements of taste generating comparable results. Other groups have developed a dissolution test dedicated to lozenges (Tietz et al., 2018). The unique quality of this model is the addition of an artificial tongue, which imitates pressure and shear forces in the mouth and a tubing system which generates a flow of media mimicking saliva clearance. A further example, Keating et al. (2018) evaluated taste-masking efficiency using a small volume (5 mL) dissolution test in simulated salivary fluid. The authors used the bitterness threshold of the API, as determined with a rat model, as an acceptable

release concentration. The most recently reported dissolution system involved human saliva (Ali et al., 2019). Testing was performed in 1 mL of media, with stirring, but no flow. Compared with a compendial dissolution test (600 mL of phosphate buffer at pH 6.5), the drug release was considerably lower in the new model – 80% vs. 0.02% within 10 minutes, respectively. Their findings highlight the importance of media constitution and volume in the development of dissolution testing for taste-masked products.

1.4.4.2 Adhesive properties

1.4.4.2.1 Theory

The tendency of a product to adhere to a contact surface is known as stickiness or, synonymously, adhesiveness (Adhikari et al., 2001). When food is consumed or an oral medicine taken, its stickiness can be perceived on the tongue, palate, teeth or fingers. Stickiness cannot be measured directly; it is quantified by the force required to separate two surfaces. In sensory research adhesiveness is scaled as: low (tacky), moderate (clingy), high (gooey) and very high (sticky, adhesive). Yet, for instrumental measurements no precise cut-off values for force required to separate two surfaces were assigned to different levels of adhesiveness. Based on sensory science, example of tackiness in OSDFs could be the tackiness of a tablet to a finger or tongue. Whereas adhesiveness can be exemplified by a mucoadhesive tablet adhering to a buccal area. Reasonably, the latter typically requires a greater force and hence energy for surface separation.

Various mechanisms to explain stickiness have been discussed in literature. Measures depend on the type of product being tested and include surface energy, presence of water (moisture) in the system, viscosity, and temperature of the product (Adhikari et al., 2001). Primarily,

adhesiveness depends on the energy of the two materials in contact. High surface energy stimulates sticking, and low does not (this is also one of the reasons why some pharmaceutical powders compress better than others (Fichtner et al., 2008)). Water content also has a high impact on stickiness. When water is present in a material, liquid bridges can build between particles or surfaces. Due to liquid surface tension, liquid bridges increase the tensile strength that holds surfaces together causing stickiness. However, excess of water can decrease this effect. Viscosity also plays a role in stickiness; if the product is viscous, stronger liquid bridges are built resulting in higher adhesive forces (e.g. high viscosity HPMC is used in muco-adhesive tablets, while low viscosity HPMC is used in coatings, where stickiness is not desired). In addition, temperature indirectly influences stickiness because it determines a product's structure and viscosity. In summary, stickiness is a multifactorial characteristic and cannot be predicted with a single parameter like viscosity (Adhikari et al., 2007) or water content (Adhikari et al., 2003). Considering oral medicines, which are complex systems, the stickiness of product is usually a function of several of the factors described above.

1.4.4.2.2 Implications of stickiness in solid oral dosage forms

In context of OSDF, stickiness can be desirable property, e.g. for a mucoadhesive tablet. Whereas for a dosage form intended to be swallowed, excessive stickiness can pose an issue, by slowing the passage of a tablet through the mouth and oesophagus (McCargar et al., 2001). In this sense, stickiness has opposite effects to slipperiness.

While slippery coatings improve the ease of swallowing and allow a coated tablet to pass down the oesophagus faster than uncoated ones (Washington, 2001, Mahdi and Maraie, 2015), a sticky one can prevent smooth tablet passage. The lower the amount of water taken with a dosage form the higher the risk of adhesion (Perkins et al., 2001). The small amount of

liquid in the oesophagus will only moisten the surface of medicine and increase the moisture driven adhesiveness, rather than cause sufficient lubrication to aid transit. Additionally, the pressures within the oesophagus may press the dosage form against the mucosa and cause local dehydration. In the worst case, a solid dosage form can adhere to the mucosa and release the drug in the oesophagus, rather than where intended (i.e. in the lower parts of the gastrointestinal tract), and cause local injury or inflammation (Jaspersen, 2000). Cases of uncoated tablets adhering to the oesophageal mucosa have been reported more frequently than for coated tablets (Perkins et al., 2001). The ingredients in the coating are important and can alter the tablet's tendency to adhere. Where adhesion occurs, it is initiated by gel formation at the interface of the dosage form and mucosa, which then strengthens the adhesion. The most sticky formulations are gelatine capsules, followed by coated tablets (Swisher et al., 1984). Examples of less sticky coating ingredients are cellulose acetate phthalate, shellac, methacrylate copolymer, whereas HPMC and guar gum are stickier. The stickiness of the coating can be manipulated; addition of talc or high molecular grade PEG increases the stickiness whereas addition of sucrose or lipids, like medium chain triglycerides (MCT), reduce it (Washington, 2001, Debeaufort and Voilley, 2009). For many years standard coatings like HPMC, PVA have been regarded as not sticky enough to pose an issue. Yet, growing research on tablet swallowing difficulties (Marquis et al., 2013, Schiele et al., 2013) and case studies reporting tablet arrest in the oesophagus (Jaspersen, 2000, Osmanoglou et al., 2004) have resulted in an increased interest, from coating companies, in the development non-sticky, slippery coatings. To name a few: SheffCoat™ Glide (Kerry), Sepifilm™ White TF (Seppic) and a coating tested in this thesis – Opadry® EZ Swallow (Colorcon).

1.4.4.2.3 Measurement of adhesive properties of solid oral dosage forms

A commonly used instrument to measure adhesive properties is a texture analyser. Although primarily designed for food analysis, it offers multiple uses for the pharmaceutical sector, including coating tack, stickiness of lozenges, or adhesion of mucoadhesive tablets (Smewing, 2015). The texture analyser can control contact force and contact time during measurement which allows an experiment to be designed that is appropriate for many purposes.

Adhesive properties are measured as the force needed to separate two surfaces, usually a probe and the sample. OSDF are tested after wetting to mimic the environment of the oral cavity. When the probe comes into contact with a wet tablet a liquid bridge is built. Upon probe withdrawal this liquid bridge is stretched generating a tensile strength. During the test the force needed to break the liquid bridge is measured. The force/time data, obtained from the instrument, can be converted to tack, work of adhesion, and stringiness as shown in Figure 1.8. The area of the force peak (work of adhesion) is approximated with the trapezoidal rule, as per equation below.

$$\int f(x)dx \approx \sum_{k=1}^{N} \frac{f(x_{k-1})+f(x_k)}{2} \Delta x_k \qquad \text{(Eq. 1.4)}$$

Where $\int f(x)dx$ is the integral of the force curve, Δx_k is the length of the k-th trapezoid subinterval, N is a number of trapezoid intervals.

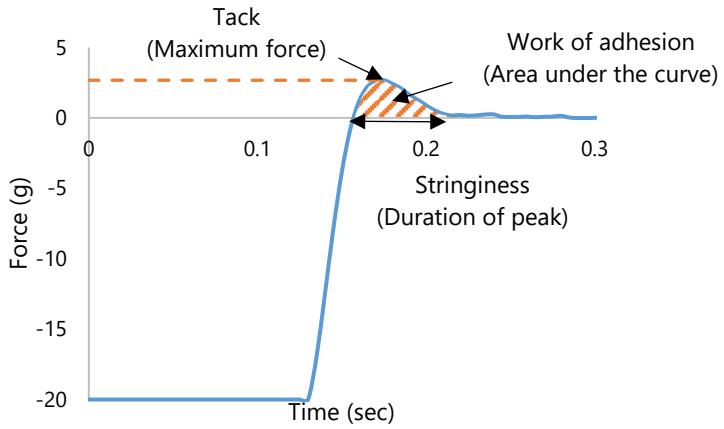


Figure 1.8 Example of force vs. time curve obtained during tack test with depiction of parameters measured.

Several researchers have used a texture analyser to measure the stickiness of oral dosage forms. Scarpa et al. (2018) measured the adhesive force of wetted orally dispersible films. The type and grade of film forming polymer affected the measured adhesive force. The results were obtained with two instruments working on the same principle, but with different testing parameters: texture analyser and dynamic mechanical analysis (DMA). Here, DMA was a more discriminative method. Comparison of the measured adhesive force (DMA) and human perception of sample stickiness showed a positive correlation. (Measurements from the texture analyser were not compared with *in vivo* data). Other researchers have evaluated the stickiness of pastilles (Silva et al., 2017); the authors observed increased adhesiveness when the pastilles were submerged in water, as compared with dry ones. Hence, indicating the importance of wet conditions, relevant for oral processing, during the measurement. A texture analyser has also been employed to evaluate the stickiness of muco-adhesive tablets (Hall et al., 2011) where the authors studied the effect of polymer blend ratios (HPMC:Carbopol) on the adhesive properties of a tablet core.

Instrumental measurement of stickiness needs to be product specific. To characterise the surface adhesion of coated tablets (intended to be swallowed) tackiness should be measured.

This test involves the contact of a probe with a tablet surface and subsequent withdrawal of the probe. The force and time needed to pull back the probe and separate the surfaces is measured. The larger the force, the higher the tackiness. A dry tablet is not expected to be tacky. This is due to the fact that moisture or presence of water are one of the factors determining stickiness (via liquid bridges). To measure the tackiness of coated tablets, the surface should be wetted before testing to mimic the conditions in the oral cavity.

1.4.5 Imitative methods

1.4.5.1 Modelling of swallowing

For the development of OSDF it is beneficial to confirm that they are easy to swallow, specifically, when novel shapes, coatings, forms are designed. Characteristics like a slippery surface or streamlined shape may aid easy swallowing. Several *in vitro* approaches to predict ease of swallowing and/or oesophageal transit of tablets have been reported previously. Some concentrated on a single quality of OSDF (e.g. slipperiness), while others imitated phases of swallowing (e.g. oesophageal transit).

Initial studies concentrated on measuring adhesion, or more accurately, detachment forces between tablets and oral/ oesophageal/ artificial surfaces (Swisher et al., 1984, McCargar et al., 2001, Shakweh et al., 2007, Hall et al., 2011). Results showed that gelatine capsules adhered most strongly to porcine oesophageal mucosa, followed by coated tablets then uncoated tablets which were the least adhesive. However, this model of adhesion was disproved as a prediction of oesophageal transit by human studies that showed faster transit for coated tablets when compared with uncoated or gelatine capsules (Perkins et al., 1999, Perkins et al., 2001).

Later models employed a simple tribological experiment to measure the impact of a coating on the force needed to pull a sample. (Figure 1.9a). Several authors used coating materials in isolation (i.e. separate from the tablet core material). One study tested spin coated glass discs, while another employed melt coated polyethylene discs or cast films stuck onto the same discs (Smart et al., 2015, Drumond and Stegemann, 2019). Whilst the former study reported only detachment force, the latter showed COF values and friction force profiles during the test. Both studies screened a number of materials commonly used for tablet coating: polymers, plasticized polymers and waxes. Similar methods were also employed by companies manufacturing pharmaceutical coatings to test slipperiness of their products (Evonik® and Colorcon®) (Garude et al., 2018, Rajabi-Siahboomi et al., 2018). None of these methodologies were validated using *in vivo* studies.

Recently, more complex models have been built, which mimic the peristalsis of the swallowing process. A three-dimensional model was proposed by Dirven et al. (2017); a soft-robotic machine was designed to transport a bolus in wave-like manner with concurrent pressure measurement (Figure 1.9b). Marconati et al. (2018) suggested another 3D model, where propulsion of the bolus is generated by a roller pushing the sample down a flat membrane (Figure 1.9c). These robotic models offer great variability of force and volume control. While the first machine is still awaiting validation against *in vivo* data, the latter has already been used to imitate swallowing of OSDF (multiparticulates) and the results compared with the sensory assessments of a human panel (Marconati et al., 2019). Both *in vivo* and *in vitro* data indicated that ease of swallowing of a multi-particulate dose depended on size of particles and viscosity of the carrier.

In this thesis a tribological approach to predict ease of swallowing was studied and an attempt to validate it against *in vivo* data was made.

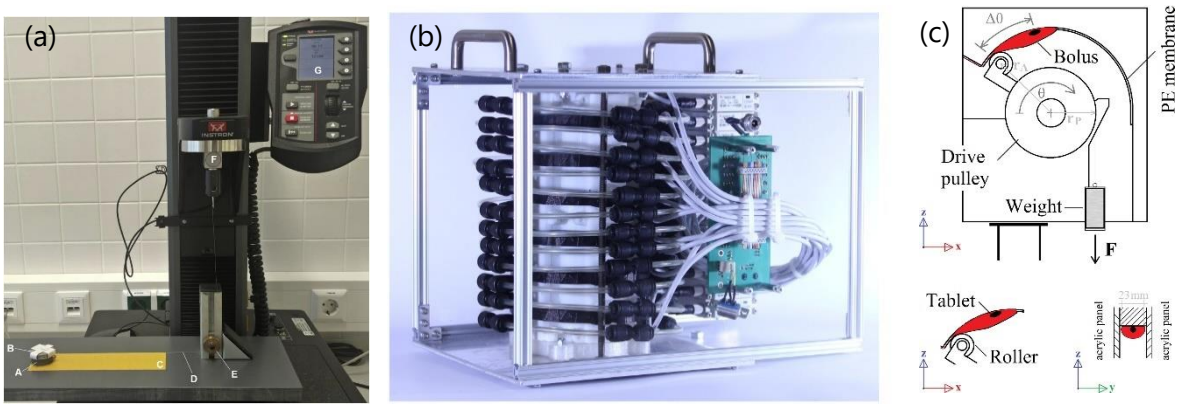


Figure 1.9 Examples of in vitro *models: (a) traction force test to measure tablet slipperiness (Drumond and Stegemann, 2019), (b) soft-robotic propulsion model of oesophageal phase of swallow (Dirven et al., 2017), (c) roller propulsion model of oral phase of swallow (Marconati et al., 2018).*

1.5 Acceptability studies *in vivo*

The *in vivo* methodology to assess acceptability oral medicines is not standardized. Within industry, the lack of standard methodology gave rise to internally developed study approaches or outsourcing of studies, but none of these methods have been validated (Thompson et al., 2013b). Literature reviews have highlighted the issue of multiple non-validated approaches used to assess acceptability of oral dosage forms which aren't comparable (Davies and Tuleu, 2008, Squires et al., 2013, Mistry and Batchelor, 2017a, Ranmal et al., 2018). Although the number of studies is growing, the knowledge is still fragmented and there is presently no harmonized approach (Vallet et al., 2018).

One of the major barriers to developing a standardised approach is the lack of general consensus on the terminology and the measurement endpoint for acceptability. Several terms and methods are used as a surrogate to acceptability like, *'Preference'*, *'Convenience/ease/problems of administration/use'*, *'Palatability'*, *'Satisfaction'*, *'Tolerance'*,

'Medication taking difficulty score', 'Opinion' (Ranmal et al., 2018). Moreover, the measurement criteria and its endpoints very between studies, e.g. *acceptability*, *preference*, *ability to swallow*, *ease of swallowing*, or *problems in administering* (Ranmal et al., 2018).

Therefore, comparison of results between studies in not straightforward. Furthermore, the use of a single acceptability criterion (ability to swallow being the most common), excludes all other dimensions of patient acceptability, such as palatability (Vallet et al., 2018, Walsh et al., 2018).

The patients' acceptance of a product is driven by palatability. There are several reviews on methodologies of palatability assessment for oral pharmaceutical products (Anand et al., 2008, Davies and Tuleu, 2008, Mennella et al., 2013, Squires et al., 2013, Kozarewicz, 2014).

Palatability of oral formulations is usually measured as an overall hedonic response to the product, often measured only as a liking of the taste. In food science, palatability of the product is evaluated as part of broader sensory evaluation, which has a long history since the 1960s (Szczesniak, 1963) and is based on wide range of ASTM standards. There is a need to leverage this knowledge and expertise, and adapt it for sensory studies of oral medicines (Ternik et al., 2018), with the aim to standardize and validate methodologies. Even though, the testing methods from food sciences might not be directly adaptable, many good practices and experiences are relevant to the field of pharmaceutics.

1.5.1 Considerations for human studies of oral pharmaceuticals

1.5.1.1 Study design and setting

Acceptability studies include clinical trials, when they involve patients (Verrotti et al., 2012) or healthy volunteers (Thompson et al., 2013a) and medicinal products, as well as other types of

study, e.g. sensory evaluation of placebo formulations in healthy volunteers. Studies can be run as part of the drug development process, a post-marketing survey, or as a standalone investigation. The setting for the conduct of acceptability studies is important. It will depend on study design but should provide a safe space for the patient/participants and the infrastructure to conduct the study. Examples include homes, nursing homes, pharmacies, hospital, clinics, health centres, public spaces, sensory laboratories.

1.5.1.2 Population

Acceptability studies can be undertaken during formulation design or once a final dosage form have been developed. In the early development stages, adult sensory panels are recommended (Thompson et al., 2015), especially for novel, not yet marketed dosage forms. At this point, key acceptability issues can be identified and resolved. Acceptability studies of a final product involve end-users. For medicinal products this is usually patients, whose sensory perception might be affected by their medical condition, current medication, co-morbidities, or disabilities. Due to their health status, acceptability in patients can differ from that in healthy volunteers, which needs to be considered in acceptability evaluation.

Paediatric formulations require acceptability studies in children. The challenge here is the great variability in anatomical, physiological, and cognitive development within the paediatric population. In addition, sensory sensitivity as well as the liking of taste and textures differ within age-groups (Kälviäinen et al., 2000, Schwartz et al., 2009, Mennella et al., 2014). The appropriateness of a formulation cannot, therefore, be assessed for the whole group but needs to be subdivided into different age groups (EMA, 2013). The use of an adult panel is often complementary but while they may give and indicator of acceptability, they cannot

replace or be used instead of paediatric panels, at least not until there is more complete knowledge on age-differences in sensory perception.

In contrast, in food sensory studies a trained panel of healthy adults (panel size, n=10–12) is usually employed to gather sensory information of the product, and consumers (panel size, n=50–100 of regular consumers) are used for hedonic testing (Lawless and Heymann, 2010a). This approach is not always feasible for pharmaceuticals. Firstly, there is a limited number of companies that provide a professional service of panellists trained for oral pharmaceuticals (e.g. Senopsys, USA; SLR Pharma, Ireland). Secondly, identification of regular users of medicines is not be possible for novel/orphan products.

1.5.1.3 Methods and tools

The major methodological consideration for acceptability assessment is the study population. When designing a study for children, the choice of methodology will depend on the age of the population of interest. For the studies involving babies and toddlers, the participant does not have the skills to autonomously use the assessment tools (Guinard, 2000), thus the parent, investigator or both, are required to interpret non-verbal reactions to the sample (Klingmann et al., 2015, Blume et al., 2018). It is recognized, that from the age of three a child can vocalize their opinions and use simple scales to compare a limited number of products (Guinard, 2000). Abilities improve with age, and for teenagers (>12yrs) the complexity of tasks during the study can be similar to that of adults (Guinard, 2000). Since attention span is limited in some children, the study length should be short to minimise participant burden and maintain their interest.

The study tasks should not cause excessive burden to the participant, particularly considering their age and health condition. Also, the terminology and the assessment tools used need to be understood by the participant (Ranmal et al., 2018). Specifically, in children, due to limited language comprehension, the tools selected require age-appropriate vocabulary, where possible lay definitions or examples should be given. Performing a study with elements of a game minimizes the impact of language, increases its attractiveness and can increase a child's involvement in the task (Mennella and Beauchamp, 2008). Use of visualisations – icons, emojis can be helpful for children to express their opinions (Laureati and Pagliarini, 2018), for example the tools can be presented in an attractive form, e.g. by use of simple facial scales (Figure 1.10) (Thompson et al., 2015). Moreover, because children tend to give affirmative answers, forced-choice questions should be asked to provide discrimination between samples (Engen, 1982). For adults, the tasks can be language based, and scales can have more increments than for children.

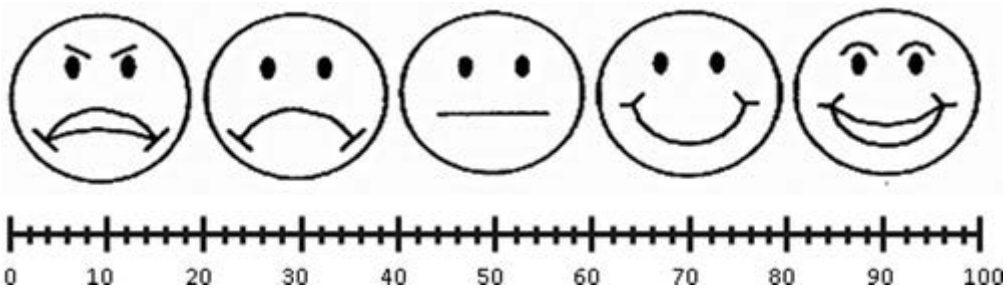


Figure 1.10 Example of five-point facial hedonic scale with a correlated 100-point visual analogue scale (VAS), reprinted from Thompson et al. (2015) with permission of SAGE Publications.

Among the tools used to assess acceptability, the following are most prevalent (Ternik et al., 2018, Ranmal et al., 2018):

- Reported by participant:
    - Questionnaire/survey
    - Rank order/preferential method

    - Binary questions
    - Scaling methods (visual analogue scale – VAS, hedonic facial scales, separate or combined)
    - Verbal response (descriptive methods)
- Reported by researcher
    - Observation
    - Observation of negative facial response based on Facial Action Coding System (FACS)

The VAS and facial hedonic scale are the most commonly used in paediatric populations (Mistry and Batchelor, 2017b), while in adults – questionnaires with a various quantitative (e.g., 1–10) or descriptive scales (Drumond et al., 2017, Ranmal et al., 2018) are more common. An attempt to standardize VAS and 5-point facial hedonic scales has been undertaken in a large population of children between 2–17 years old using a range of products (total 57, most commonly paracetamol, ibuprofen, prednisolone, co-amoxiclav, amoxicillin and clarithromycin) to measure participants liking of the product (palatability aspect of acceptability) (Mistry et al., 2018). Both scales gave a good correlation of responses between each other and proved to be reliable scaling methods in children, which indicates that they can be used interchangeably. Younger children, below 10 years old, tend to use the extreme ends of scales, confirming a need to adapt the complexity of the scale used to the child's age. In their study Mistry et al. (2018), also found that outcomes based on researcher observations of a child's behaviour accurately measure the ability of the child to take the medicine as intended, but not the palatability (Mistry et al., 2018).

1.5.1.4 Acceptability criteria

The acceptability criteria for medicines are significantly different from other products. For example, with food the aim is to create a product that gives sensory pleasure. While for oral medicines, the requirement is for the product to be taken without a barrier to administration, not as a source of enjoyment. This highlights a difference between taste/mouthfeel acceptance and preference versus palatability. For a medicine, the product needs to be sufficiently palatable to be acceptable but does not have to be pleasant, it could for example be neutral.

In order to measure acceptability, the endpoint for the method used needs to be defined. An agreement of 80% of the sample population that the product is acceptable is generally considered sufficient (Mistry and Batchelor, 2017b). Using this principle, binary questions or when scaling methods can be used to measure the endpoint. Whereas binary (yes/no) questions are simple to interpret, scaling methods require acceptability cut-off values to be statistically determined but give a greater depth of information. The majority of current reports lack consistency in the definition of endpoints on scales as well as scientific and statistical justification for a given number (Mistry and Batchelor, 2017b). A good example of a defined endpoint has been reported by Mistry et al. (2018). They demonstrated a cut-off for acceptability of taste on a 100 mm VAS as <70 mm (where 0 was *I really liked it*), and on a 5-point hedonic scale – score of ≤3 (neutral or positive face). Similarly Kimura et al. (2015) established a cut-off VAS score for rough mouthfeel and overall palatability of ODTs; different values were obtained for feelings of roughness and of discomfort. As the threshold of perception of roughness and level of its acceptability differed, this demonstrates the need for clear definitions of acceptability endpoints.

General criticism on how assessment methods fail to evaluate the multimodality of medicine acceptability have been raised (Vallet et al., 2018). Excepting the two aforementioned studies, assessment of overall acceptability fails to distinguish the particular liked or disliked characteristics of a product. It is advantageous therefore, to measure the acceptability of an individual attribute as well as overall acceptability. Such data on individual attributes enables determination of whether a particular taste or mouthfeel sensation reduces or improves overall acceptability. This builds scientific evidence for further studies to measure the most relevant attributes and a basis for what is and is not acceptable with a formulation. For example, inclusion of multiple variables, allows the researcher to distinguish positive (overall palatability, sweetness, disintegration time) and negative (bitterness, voluminous residue) attributes of ODTs (Uchida et al., 2013). This knowledge can then be transferred onto new products being developed and substantially increase acceptability by improving all problematic product characteristics.

1.6 Importance of identifying the knowledge gaps

The importance of studying the acceptability of medicines in the end-user population has been endorsed by regulators (EMA, FDA). Although the number of undertaken and reported acceptability studies is growing, knowledge in this area is still fragmented and there is presently no harmonized approach. Broader measurements of acceptability, which encompass all factors relevant to a particular product, as distinct from a yes/no question, have been recognised as important.

Studies that identify key acceptability attributes and correlate them with formulation properties can benefit the drug development. Once correlations are established, *in vitro*

methods could be used as a screening tool at an early stage of the development process to drive optimisation of the drug product. Early optimisation of acceptability brings great advantage to the pharmaceutical industry. Ensuring acceptability prior to a clinical study reduces the costs of re-formulating and associated development time. From the patient perspective, receiving medicines with proven acceptability has the potential to reduce the risk of discomfort associated with their therapy and improve quality of life.

Identification of the main acceptability determinants and bridging the *in vitro* and *in vivo* data are necessary to speed up the development of acceptable medicines for all populations.

2 Instrumental methods – Tribology

Purpose of this chapter

This chapter explores the potential of tribology to assess the slipperiness of tablet coatings. The chapter is separated into two sections: surface tribology and thin film tribology, where individual methodologies were developed and used to characterise coated tablets.

2.1 Surface tribology

2.1.1 Introduction

The process of swallowing tablets involves passage through the oral cavity and oesophagus. As most solid oral medicines are swallowed as a whole hard unit, the slipperiness of the dosage form becomes an important factor as it can assist swallowing. Slipperiness is related to the resistance to motion when sliding over an oro-oesophageal surface (Seo et al., 2007). A tablet which has low resistance to movement should be easy to swallow. Several strategies have been suggested by industry and academia to modify a tablet surface to make it more slippery. Firstly, addition of certain excipients to a coating formulation, e.g. polysaccharide and medium chain triglycerides (MCT) (Opadry® EZ Swallow, Colorcon), HPMC co-processed with hydrophobic plasticiser (SheffCoat™ Glide, Kerry), magnesium stearate (Sepifilm™ White TF, Seppic), or xanthan gum (Mahdi and Maraie, 2015). Secondly, application of a secondary coating *in situ* (Medcoat®, Med Coat AB), where a patient applies a soft gelatine coating onto a tablet by pushing the tablet through a gelatine membrane directly before administration. And lastly, co-administration of a solid dosage form with a slippery gel (Gloup™, Mundipharma Pty Limited) or liquid (Med-Easy™ Liquid Swallowing Aid, FAGRON UK LTD). The most convenient solution for the patient is to receive the medicinal product

pre-designed to be slippery (i.e. the first strategy), rather than use a multi-stage administration process.

In order to verify, whether a tablet is slippery, several *in vitro* tools have been developed (as discussed in Chapter 1.4.5). In this thesis, an alternative method has been developed using tribology. As discussed in Chapter 1, tribology is currently used in food research to characterise product texture. Specifically, tribology measures the coefficient of friction (COF, μ), which is inversely related to slipperiness, and so relevant to human perception of "slippery" (Pradal and Stokes, 2016).

On the premise of the principles set out in Chapter 1.4.3.1.6, this thesis describes the assessment of tablet coating slipperiness using tribological methods. In an approach intended to emulate the movement of a tablet across the oral surfaces during swallowing, the proposed method evaluates the friction between a model surface and a coated tablet immersed in water.

2.1.2 Materials and methods

2.1.2.1 Formulations

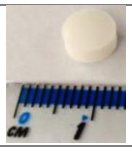
2.1.2.1.1 Preparation of tablet cores

Three types of tablet core were used: convex oval, 19 x 9 x 7 mm, and convex round, in 7 x 3 mm and 7.5 x 2.5 mm diameter.

Oval cores were supplied by VerGo Pharma Research Laboratories Pvt. Ltd., and comprised lactose, starch, microcrystalline cellulose, and magnesium stearate. Round 7.5 mm cores were supplied by Chrysalis Health & Beauty Ltd., and comprised quinine sulfate, microcrystalline cellulose, calcium carbonate DC, magnesium stearate, and silicone dioxide. Preliminary tests

were also performed with in-house manufactured 7 mm round cores composed of 2.5% (w/w) quinine sulfate (Sigma-Aldrich, USA) and directly compressed powder (Firmapress, Oxfordshire, UK), which comprised microcrystalline cellulose, magnesium stearate, silica dioxide and di-calcium phosphate. In-house tablets were compressed using a MiniPress single punch tablet press, type MII, (Riva S.A, Argentina) with average force of 15 kN. Details of all cores are given in Table 2.1.

Table 2.1 Characteristics of tablet cores used in the study. Target limits are given in brackets.

	Oval 19 mm cores (VerGo Pharma)	**Round 7.5 mm cores (Chrysalis)**	**Round 7 mm cores (in-house made)**
Picture			
Notation	T_A	T_B	T_C
Average mass	951 mg (950 mg ± 5%)	186 mg (200 mg ± 5%)	212 mg (200 mg ± 5%)
Disintegration time	1 minute 53 seconds (< 15 minutes)	1 minute 53 seconds (< 15 minutes)	1 minute 14 seconds (< 15 minutes)
Hardness*	125 N (> 50N)	113 N (> 50N)	81 N (> 50N)
Friability**	0.1% (< 1%)	0.03% (< 1%)	0.1% (< 1%)

* Measured as a force needed to break a tablet using a hardness tester (Copley, UK), n = 10.
** Measured as a weight loss of 6.5g of tablets after 100 rotation cycles using friability tester (Copley, UK).

2.1.2.1.2 Preparation of tablet coatings

The following materials were used to prepare the coatings: HPMC 5 (Biogrund GmbH, Germany), Eudragit® EPO readymix (Evonik, Germany), glycerol (Sigma-Aldrich, USA), talc (Scientific Laboratory Supplies Ltd, UK), titanium dioxide (Fisher Scientific, UK), xanthan gum (Sigma-Aldrich, USA), Lubritab® (JRS PHARMA, Germany), Capmul® MCM (ABITEC Corporation, USA), Surelease® (Colorcon, USA), Opadry® 03F (Colorcon, USA), Opadry® EZ Swallow white (Colorcon, USA), Opadry® EZ Swallow clear (Colorcon, USA).

Table 2.2 lists the composition of the tablet coatings used. The set of coatings from 1 to 3 was applied only onto T_A cores. Coatings from 4 to 8 were applied onto two types of core, T_B and T_C.

The T_A and T_B tablet cores were coated by the manufacturer. The in-house tablet cores (T_C) were coated in the following manner. Firstly, the coating solution was prepared, according to manufacturer instructions, by adding ingredients to a water vortex, starting with the polymer, plasticiser, and then other ingredients as specified. The coating solution was mixed with a propeller stirrer for 45 minutes. Secondly, the coating solution was sprayed onto a batch of tablets (15 g) using a Caleva Mini Coater 2 (Dorset, UK) under the following conditions: pump 1.6 rpm, fan 16 m/s, agitation 15.2 Hz and temperature 60°C. The coating level was controlled by weighing the batch of tablets until 4% weight gain was achieved. Coating level (*CL%*) is defined by:

$$Coating\ level: CL\% = \frac{m_1 - m_0}{m_0} \times 100 \quad \text{(Eq. 2.1)}$$

where, m_0 is mass of uncoated tablets, and m_1 – mass of coated tablets.

2.1.2.1.3 Equipment

The tribology experiments were performed using a rheometer with a tribo-rheology cell (modified three balls-on-plate) (Discovery HR-2, TA Instruments, USA). The setting for tablet COF measurement is depicted in Figure 2.1. The instrument measures the friction and wear of two surfaces in sliding contact. The design of the instrument defines the parameters of contact: angle, surface area, and path of movement. The instrument used in this thesis measured changes in COF in a rotational movement between two parallel surfaces, under

lubricated conditions. The probe was equipped with a beam coupling that self-aligned the two surfaces under test to ensure uniform contact and axial force distribution.

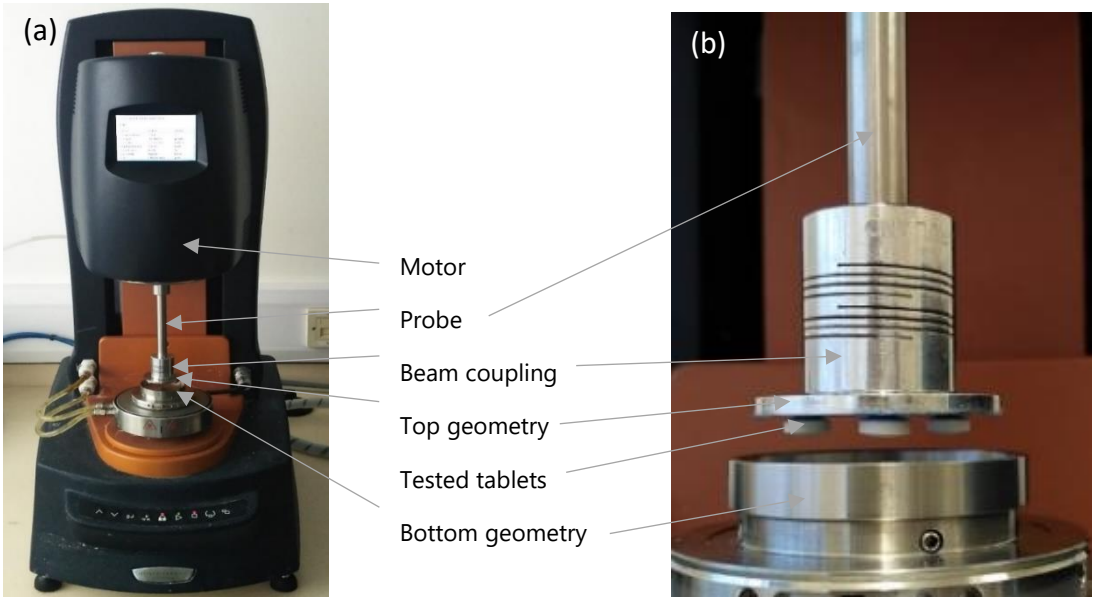


Figure 2.1 Tribo-rheo cell for Discovery HR-2 rheometer; (a) overview of the instrument, (b) geometry setting for experiment using tablets.

During the experiment, the equipment controlled: torque, velocity, displacement and normal (axial) force. Tribological variables were calculated according to the equations below:

$$Coefficient\ of\ friction: \mu = \frac{F}{W} \quad \text{(Eq. 2.1)}$$

$$Friction\ force: F = k_F \times M \quad \text{(Eq. 2.2)}$$

$$Load\ force: F_L = k_L \times W \quad \text{(Eq. 2.3)}$$

$$Sliding\ speed: v_S = k_v \times \Omega \quad \text{(Eq. 2.4)}$$

$$Sliding\ distance: d_S = k_v \times q \quad \text{(Eq. 2.5)}$$

Where, F stands for friction force, k_F – friction force constant, M – torque, F_L – load force, k_L – load force constant, W – normal force, v_s – sliding speed, k_v – sliding speed constant, Ω – velocity, d_s – sliding distance, q – displacement, and μ – coefficient of friction. If the load force is perpendicular to bottom plate, $F_L = W$.

Table 2.2 List of formulations used in the study.

Formulation		T_A*	T_ACoat-1*	T_ACoat-2*	T_ACoat-3	T_B/T_C	T_B/T_C Coat-4	T_B/T_C Coat-5	T_B/T_C Coat-6	T_B/T_C Coat-7	T_B/T_C Coat-8
Tablet core		oval	oval	oval	oval	round	round	round	round	round	round
Final coating level (w/w)		**0%**	**3%**	**3%**	**3+1%****	**0%**	**4%**	**4%**	**4%**	**4%**	**4%**
Coating solution ingredients	HPMC 5	0	-	-	-	0	10%	2.25%	10%	-	2%
	Eudragit® EPO readymix	0	-	-	-	0	-	-	-	15%	-
	Glycerol	0	-	-	-	0	2%	-	2%	-	0.2%
	Talc	0	-	-	-	0	-	1%	1%	-	1%
	Titanium dioxide	0	-	-	-	0	-	1%	1%	1%	1%
	Xanthan gum	0	-	-	-	0	-	-	0.3%	-	-
	Lubritab®	0	-	-	-	0	-	7.5%	-	-	-
	Capmul® MCM	0	-	-	-	0	-	2%	-	-	-
	Surelease®	0	-	-	-	0	-	-	-	-	8g solid (32g liquid)
	Opadry® 03F mix[#]	0	15%	-	-	0	-	-	-	-	-
	Opadry® EZ Swallow clear mix [##]	0	-	-	8%	0	-	-	-	-	-
	Opadry® EZ Swallow white mix [###]	0	-	15%	15%	0	-	-	-	-	-
	Water	0	q.s. to 100%	q.s. to 100%	q.s. to 100%	0	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

* formulations used for method development; ** final product comprised 3% (w/w) of Opadry® EZ Swallow white mix coat and 1% (w/w) of Opadry® EZ Swallow clear mix;
[#] list of ingredients: HPMC, titanium dioxide, polyethylene glycol; [##] HPMC, talc, polysaccharide, maltodextrin, medium chain triglycerides, polyvinyl alcohol; [###] same as Opadry® EZ Swallow clear mix plus titanium dioxide

2.1.2.2 Method development for the measurement of tablet slipperiness

Measurements of static and dynamic coefficients of friction were performed to evaluate (i) the slipperiness of tablet samples and also (ii) the mechanical durability of the coating under lubricated, shear conditions. The experiment attempted to imitate the oro-oesophageal passage of a tablet. Varying force and surface settings were evaluated in order to develop the most robust and differentiating method.

2.1.2.2.1 Instrument setting

COF measurement of the tablet samples was performed using the tribo-rheology cell. The instrument was adapted for the tablet coating measurement by modification of the contact surfaces. A three-point contact geometry was chosen to provide a stable conformation during testing. Top geometry: three tablets (a minimum number to obtain stable geometry) were mounted on the flat top plate with cyanoacrylate glue; a reproducible positioning was ensured using a custom 3D-printed mould. Bottom geometry: a 10 mL steel cup filled with 4mL lubricant (distilled water) was used to provide wet conditions during the experiment. Various materials were placed at the bottom of the cup to test different surfaces.

2.1.2.2.2 Test parameters

Prior to the experiment the top and bottom surfaces were brought into contact and a pre-set load was applied. Lubricant, distilled water, was added at t = 0 s. The top surface (with attached tablets) rotated with increasing speed from 0.001 to 1 rad/s. The low initial speed was set to allow observation of static friction. Changes of COF in time were recorded at a rate of one data point per second. Each experiment was performed in quadruplicate. Further parameters of the test are shown in Table 2.3; the choice of variable factors is explained in the next subsection.

Table 2.3 Parameters of static and dynamic coefficient of friction measurement.

Parameter	Value
Fixed parameters	
Sliding speed ramp	0.001 – 1 rad/s
Sampling	1 pt/s
Test duration	100 sec
Distilled water volume	4 mL
Temperature	25 °C
Variable factors	
Load force	1 N 2 N* 3 N
Bottom surface	Transpore™ surgical tape (3M™)* Tegaderm™ hydrocolloid thin dressing (3M™) Stainless steel Silicone rubber

* Parameters chosen based on the method development experiments.

2.1.2.2.3 Full factorial design

Full factorial design $3^1 4^1$ was used during method development. In this design 2 factors were evaluated, at 3 or 4 levels, resulting in 12 trials. The load force and the counter surface were selected as independent variables. For this study, forces relevant to the force exerted by the tongue during swallowing (0.87-3.12 N, as discussed in Chapter 1.4.1.2) were represented: 1 N, 2 N, and 3 N.

Four different surfaces were examined in order to determine which one provided the most reproducible and discriminative results. However, the ability to mimic oral surfaces was also considered (as discussed in Chapter 1.4.3.1.4). Silicone rubber has a precedence of usage in oral mimicking tests as its Young's modulus is close to that of the tongue (Ranc et al., 2006) (Table 2.4). Inclusion of Transpore™ Surgical Tape to the study was based on its previous uses to mimic tongue surface (Nguyen et al., 2016). Transpore™ is a porous plastic tape, hence simulates the roughness of tongue papillae. Tegaderm™ Hydrocolloid Thin Dressing was suggested as a novel surface (no previous reports of its use in oral tribology). As hydrocolloid dressings are conformable to skin, they have potential to mimic oral surfaces.

Several brands of readily available dressings were evaluated (data not shown). Tegaderm™ was chosen as during hydration it becomes rough, pliable and hydrophilic, and hence reflects the tongue's surface. A further benefit of this surface is that the tablet sample comes directly into contact with a moist surface. Steel was included into the study for comparison purposes, although it is not a relevant material to represent oral surfaces due to its hardness. Characteristics of the bottom surface materials as well as details of their preparation for the experiments are presented in Table 2.4.

2.1.2.2.4 Method development

In the first set of experiments the impact of load force on coefficient of friction was investigated using one type of sample only (T_ACoat-1, chosen as an HMPC-based standard commercial coating). In the second set of experiments, the capability of bottom surface to discriminate between friction behaviour of the tablets was examined. Three formulations, which were expected to show biggest differences, were tested: T_ACoat-1, T_ACoat-2 (slippery commercial coating) and T_A (uncoated). Once the method was developed, all tablet samples listed in Table 2.2 were tested using optimised force and bottom surface setting.

Table 2.4 Characteristics of bottom surface materials used during method development in comparison to a tongue.

Material	Image	Young's modulus	Roughness (Sa)*	Affinity for water**	Surface preparation
Stainless steel		189 – 210 GPa (Granta Design Database, 2003)	0.4 µm	Hydrophobic	▪ 3 minutes sonicate in isopropanol ▪ 3 minutes sonicate in distilled water ▪ dry
Silicone rubber		7 MPa (Mills, 2012)	0.5 µm	Hydrophobic	▪ 3 minutes sonicate in isopropanol ▪ 3 minutes sonicate in distilled water ▪ dry
Transpore™		N/A	37.1 µm	Hydrophobic	▪ stick onto a clean steel cup
Tegaderm™		N/A	9.0 µm	Dry: Hydrophilic After 1h hydration: Hydrophillic	▪ stick onto a clean steel cup using double sided tape ▪ hydrate in distilled water for 1 hour ▪ drain excess water
Tongue as a reference		Relaxed 12 kPa Tensed 123 kPa (Funami, 2016)	65.0 µm (Uemori et al., 2012) 89.5 µm (Wang et al., 2019)	Dry: hydrophobic Wet with saliva: hydrophilic (Dresselhuis et al., 2008c)	N/A

*Sa values were measured with white light interferometer (MicroXAM, KLA Tencor, UK) and analysed using MapVUE AE software.
** Based on the contact angle between water droplet and the surface: hydrophobic >90°, hydrophilic <90°; measured using Theta Optical Tensiometer (Biolin Scientific, Sweden), n=4.
N/A – not available

2.1.3 Results and discussion

2.1.3.1 Developmental experiments – tablet slipperiness

2.1.3.1.1 Effect of axial force

During tablet slipperiness testing the load force varied unexpectedly from the pre-set value. Hence, load force data was screened post-test. Taking into account instrument sensitivity (±0.1 N per specification), only the data points collected when the load force was within ±10% of the set value were included in the analysis. The percentage of data points that lay outside the allowable force limits is reported in Table 2.5. Plots of load force and COF vs. time for all tested surfaces at 1 N, 2 N and 3 N are shown in Figure 2.2 and Figure 2.3.

Comparison of the three load force settings showed that the force was better stabilised (with less variability) at higher loads (Figure 2.2). Yet, the shape of COF vs. time plot was not affected by the force setting (Figure 2.3). Additionally, the higher the force used, the deeper the indentation and wear of the bottom surface; no wear was observed on the steel surface. Therefore, the force of 2 N was selected as this gave low force variability with lower surface wear than the 3 N setting.

Table 2.5 Experiment characteristics evaluated during method development for tablet slipperiness measurement.

Test	Surface	Set force [N]	% of points outside force limits* (whole test)	% of points outside force limits* (first 50 sec)	SD [N] (RSD %) (first 50 sec)	Detection of static friction	Detection of differences between samples
1	Transpore™	1	63	36	± 0.02 (2.9)	Yes	NA
2	Transpore™	2	44	5	± 0.04 (2.2)	Yes	Yes
3	Transpore™	3	20	10	± 0.09 (3.3)	Yes	NA
4	Tegaderm™	1	78	56	± 0.07 (9.0)	Yes	NA
5	Tegaderm™	2	48	20	± 0.12 (6.9)	Yes	No
6	Tegaderm™	3	12	10	± 0.08 (2.8)	Yes	NA
7	Silicone rubber	1	49	44	± 0.14 (14.0)	No	NA
8	Silicone rubber	2	20	7	± 0.09 (4.6)	No	No
9	Silicone rubber	3	10	0	± 0.07 (2.4)	No	NA
10	Steel	1	11	1	± 0.02 (1.7)	No	NA
11	Steel	2	23	3	± 0.05 (2.9)	Yes	No
12	Steel	3	5	2	± 0.05 (1.8)	No	NA

* ±10% of pre-set force value

NA – not assessed

$$RSD = \frac{SD}{\bar{x}} \times 100$$

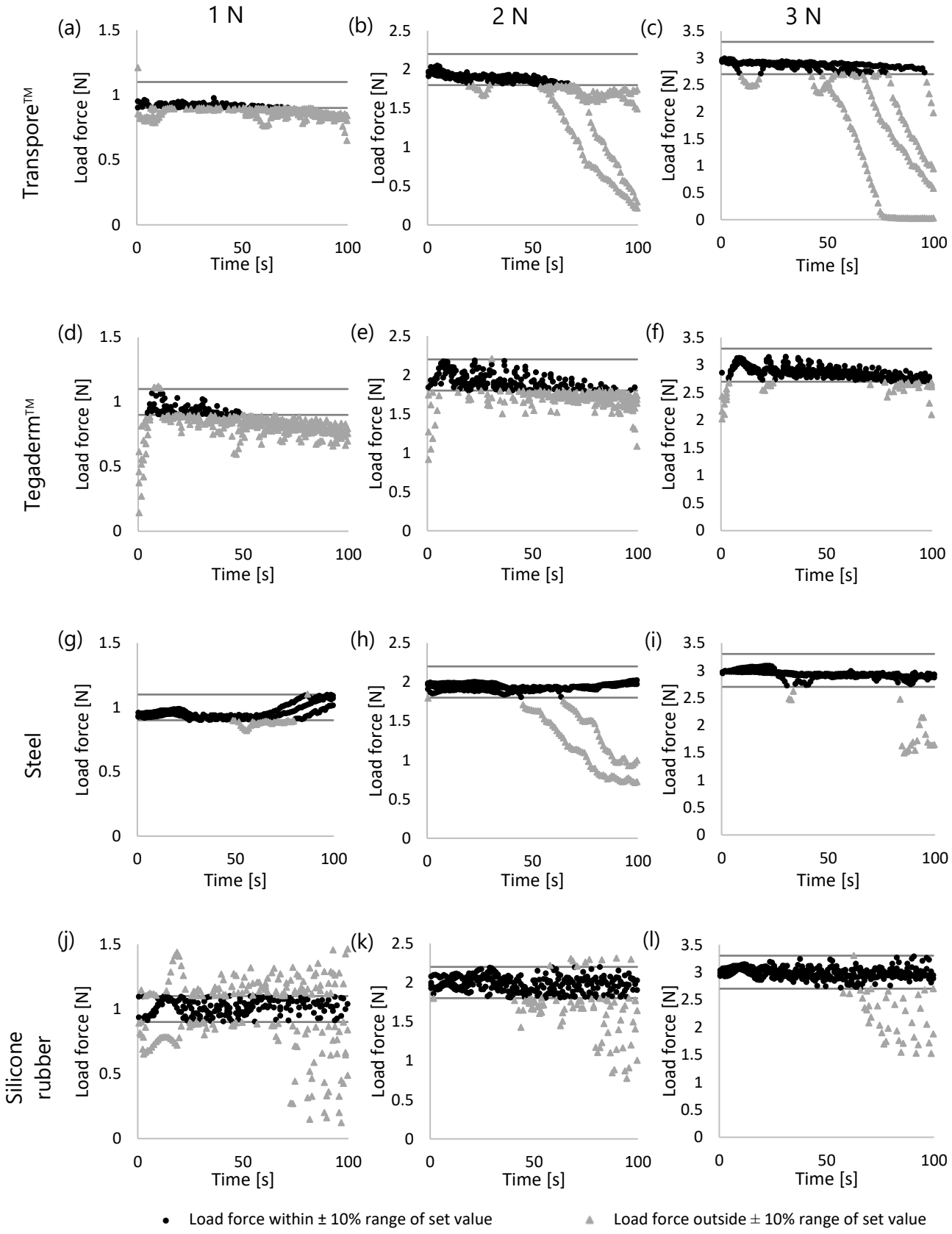


Figure 2.2 Comparison of load force stability during method development experiments on four surfaces: Transpore™ (a, b, and c), Tegaderm™ (d, e, and f), steel (g, h and j), and silicone rubber (j, k, and l); sample: T_ACoat-1, n=4. Data points with load force within/outside set value are distinguished.

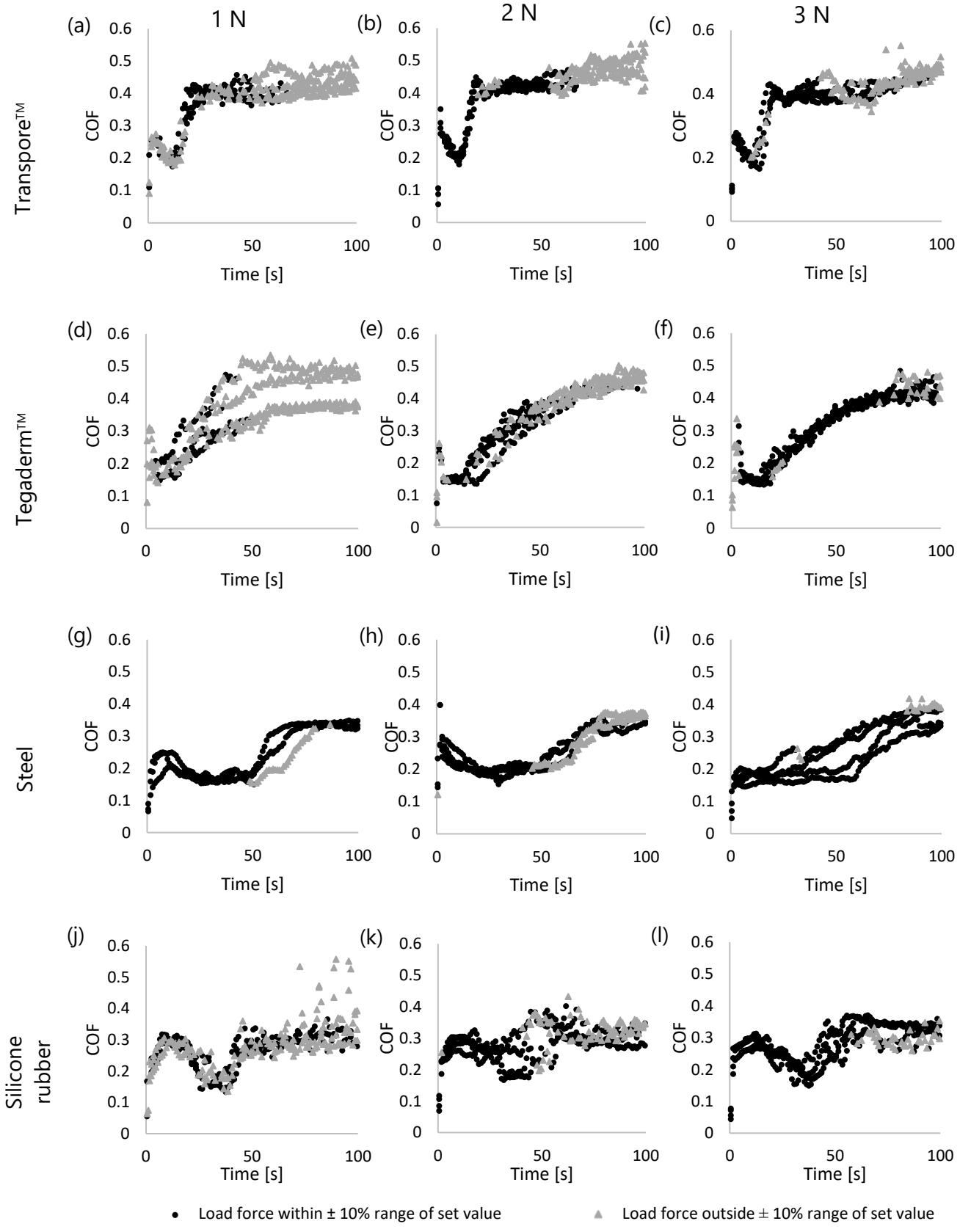


Figure 2.3 Comparison of coefficient of friction (COF) during method development experiments on four surfaces: Transpore™ (a, b, and c), Tegaderm™ (d, e, and f), steel (g, h and j), and silicone rubber (j, k, and l); sample: T_ACoat-1, n=4. Data points with load force within/outside set value are distinguished.

2.1.3.1.2 Effect of bottom plate surface

Of the four tribological surfaces used, one was stiff (steel) and the other three were elastic. The force was better maintained using the stiff contact surface than with elastic ones. The stiffness of the surface influenced how the surface responded to the load applied. This arises from the fact that for elastic surfaces the contact area is load dependent (Pitenis et al., 2017). Hence, the stiff surface (higher Young's modulus) maintained the contact area, while elastic ones (lower Young's modulus) deformed under the load. These deformations increased the contact area and friction (Figure 2.4). Additionally, the elasticity of the bottom surface may cause temporal variations in the contact area. Therefore, the steel measurements resulted in the lowest force variation (Table 2.5). The highest variation was observed for Tegaderm™, as it was the most elastic substrate used. During the test this material was gradually indented, which was also reflected by the additional time that the instrument needed to achieve the set force (Figure 2.2 d-f). For several samples an unexpected drop in load force was observed at the end of measurement period (Figure 2.2 b, c and h). For these samples, tablet inspection after the test indicated that tablet fracture was the cause of declining force trail.

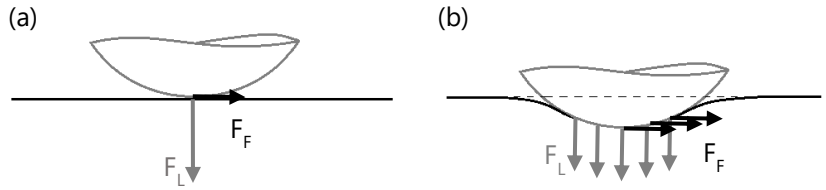


Figure 2.4 A diagram of contact between solid-solid (e.g. where steel was the bottom plate) (a), and solid-soft tribopair (e.g. where Tegaderm™ was the bottom plate) (b), indicating direction of load force (F_L) and friction force (F_F).

Friction behaviour was also affected by the choice of tribological surface. Published literature report several factors that have a major impact: surface modulus (Dresselhuis et al., 2008b), roughness (Krzeminski et al., 2012), and hydrophobicity (Bongaerts et al., 2007a). In general,

softer, rougher, and hydrophobic surfaces yield higher friction. This finding was consistent with the results presented in this thesis. For example, for materials with similar roughness, slightly higher friction was observed for softer silicone vs. hard steel (Figure 2.3 (g-i) vs. (j-l)). While rougher Tegaderm™ or Transpore™ resulted in higher COF than for the other two surfaces. Interestingly, for Tegaderm™, although hydrophilic, a reduction of friction was not clearly observed, possibly due to the fact that roughness and softness had a greater impact on COF than hydrophilicity.

The surface characteristics highly influenced the shape of the COF curve. The shape of the curve was consistent for each bottom surface, regardless of the load force (Figure 2.3). On the COF vs. time curve two characteristic regions could be distinguished: static friction region (I), dynamic friction region (II). The latter was further split into a slip region (IIA) and a high friction region (IIB) (Figure 2.5a). In the static friction region (I), the instrument detected the friction force required to initiate movement. (The experiments carried out on silicone and steel did not detect static friction, probably due to smoothness of surface). Once the tablet started moving, the friction reduced (IIA). The presence of lubricant in the system (distilled water) caused hydration of the tablet and tablet coating, which can alter lubrication and further decrease COF. In hydrated conditions, a decrease in COF could occur in a dual fashion: by formation of a hydrocolloid suspension[1] (Riedl et al., 2000, Garrec and Norton, 2012), and by deposition of slip enhancing particles at the contact surface (Stokes et al., 2011). Eventually, the interaction of the tablet and the bottom surface led to wear of the coating. Lack of coating at the contact area resulted in higher COF (IIB), at this point the rough surface of tablet core directly interacts with bottom surface.

[1] Hydrocolloids at low concentrations decrease surface tension, which in result decreases the coefficient of friction

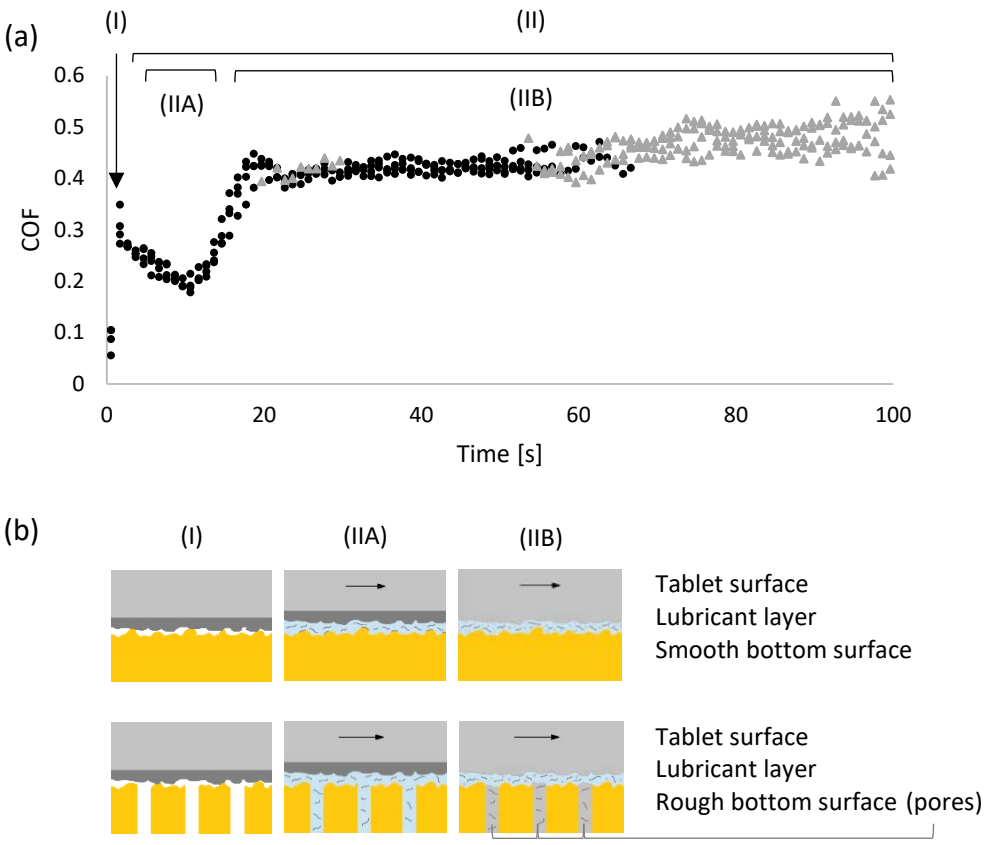


Figure 2.5 Depiction of static (I) and dynamic (II) friction regions on COF vs. time plot; (IIB) slip region and (IIB) high friction region (a); hypothetical mechanism of coating wear on a smooth and a rough (porous) surface (b).

It was observed that the progression of coating wear was dependent on the bottom surface roughness. Smoother surfaces (steel and silicone) resulted in slower wear of the coating, and the lubricating effect of the coatings lasted longer. The pores present on the rougher surfaces led to faster wear of the coating and deposition of worn material in the pores. A hypothetical mechanism is presented in Figure 2.5b.

A critical feature of a useful tribological experiment is the ability to detect differences between samples. To determine this ability three samples were used: uncoated tablet (T_A), T_ACoat-1 and T_ACoat-2 coated tablets. Samples T_ACoat-1 and T_ACoat-2 were chosen based on the composition difference; both were based on HPMC polymer, while T_ACoat-2 included additionally a hydrocolloid gum to enhance slipperiness. On all surfaces, apart from silicone rubber, the experiment showed that both coatings improved lubricating behaviour of the

tablet surface (T_ACoat-1 and T_ACoat-2) as compared to uncoated tablet (Figure 2.6). Yet, only the Transpore™ surface showed a difference between T_ACoat-1 and T_ACoat-2. On this surface, T_ACoat-2 was shown to be the most slippery (as expected) and resulted in a lower COF.

Analysis of these results showed that Transpore™ was the only surface which fulfilled test parameter requirements for force stability, detection of static friction and differentiation of the friction behaviour between tablets. Hence it was the tribological surface of choice for further experimentation.

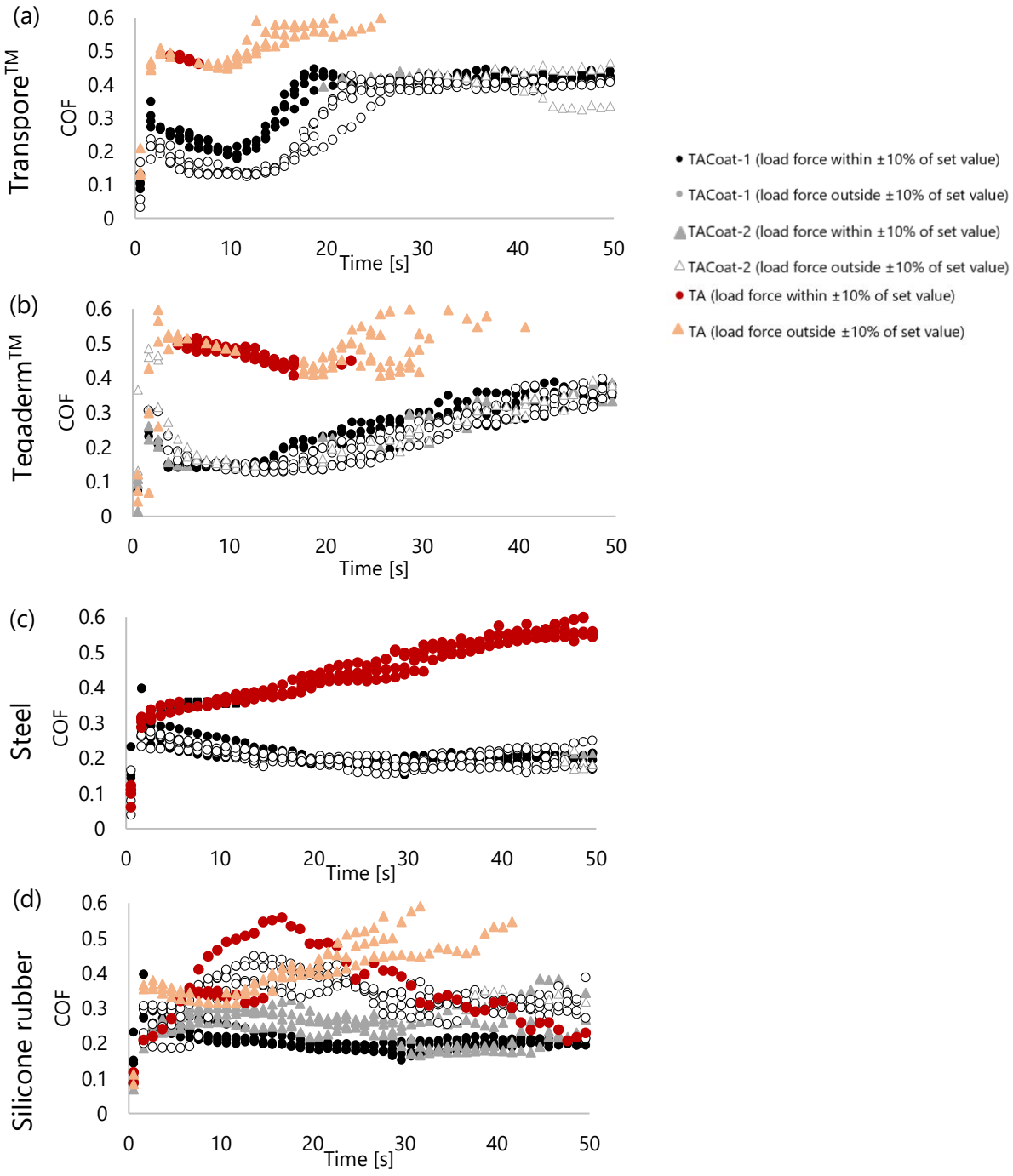


Figure 2.6 Coefficient of friction (COF) vs. time on four surfaces Transpore™ (a), Tegaderm™ (b), steel (c), and silicone rubber (d); samples: T_ACoat-1, T_ACoat-2 coated tablet and T_A uncoated tablet; n = 4; data points with load force within/outside force setting (2N) are distinguished.

2.1.3.2 Friction behaviour of tablet samples

The friction behaviour of oval tablets (T_A – T_ACoat-1–3) and round tablets (T_B – T_BCoat-4–8 and T_C – T_CCoat-4–8) were analysed (details in Table 2.2). The shape and size were dictated by the prerequisites of the two clinical studies described in the following chapters (T_A – refer to Chapter 4, T_B – refer to Chapter 5). For the oval (T_A) tablets the tests were performed with the samples provided by VerGo Pharma. A preliminary study with round in-house made (T_C) tablets was used to confirm the choice for samples for a clinical study. Then the friction tests were repeated to include tablets (T_B) made for clinical study by Chrysalis.

2.1.3.2.1 Results T_A - T_ACoat-1-3 – tablets provided by VerGo (Figure 2.7)

The first batch of tablets consisted of coatings chosen by Colorcon® and manufactured by VerGo Pharma; T_ACoat-1 being the commercially available HPMC-based coating (Opadry® 03F white), T_ACoat-2 (Opadry® EZ Swallow white) and T_ACoat-3 (Opadry® EZ Swallow white and clear) being experimental formulations with enhanced slipperiness. T_A was used as an uncoated tablet reference.

For the formulations T_ACoat-2 and T_ACoat-3, when compared with T_ACoat-1, a lower static friction (region I), as well as lower dynamic friction (IIA region) were obtained (Figure 2.7). Plus, the low friction in IIA region lasted longer for coatings with enhanced slipperiness (T_ACoat-2, T_ACoat-3). Compared with T_ACoat-2, T_ACoat-3 had an additional topcoat layer of experimental coating (1% w/w). This thicker coating contributed to a slightly longer IIA region, but not to lower COF values. The enhanced lubrication of T_ACoat-2 and T_ACoat-3 was attributed to the polysaccharide and middle chain triglycerides (MCT) present in the formulation (see Table 2.2). The polysaccharides enhanced lubrication through both adsorbing to hydrophobic surfaces and viscosity modification (see section 1.4.3.1.3) (Stokes

et al., 2011). The additional slipperiness effect might also be due to presence of MCT which is oily.

The lack of coating resulted in higher COF of formulation T_A. Most of the data points of load force lay outside ±10% of set value, leading to credible COF determination for only the initial few seconds of the test. (Thus, data presented for T_A included all data points collected.) It is possible that poor force reproducibility was due to fast disintegration of the tablet. The uncoated tablets (T_A) rapidly absorbed water and disintegrated preventing the tribometer from maintaining the applied force.

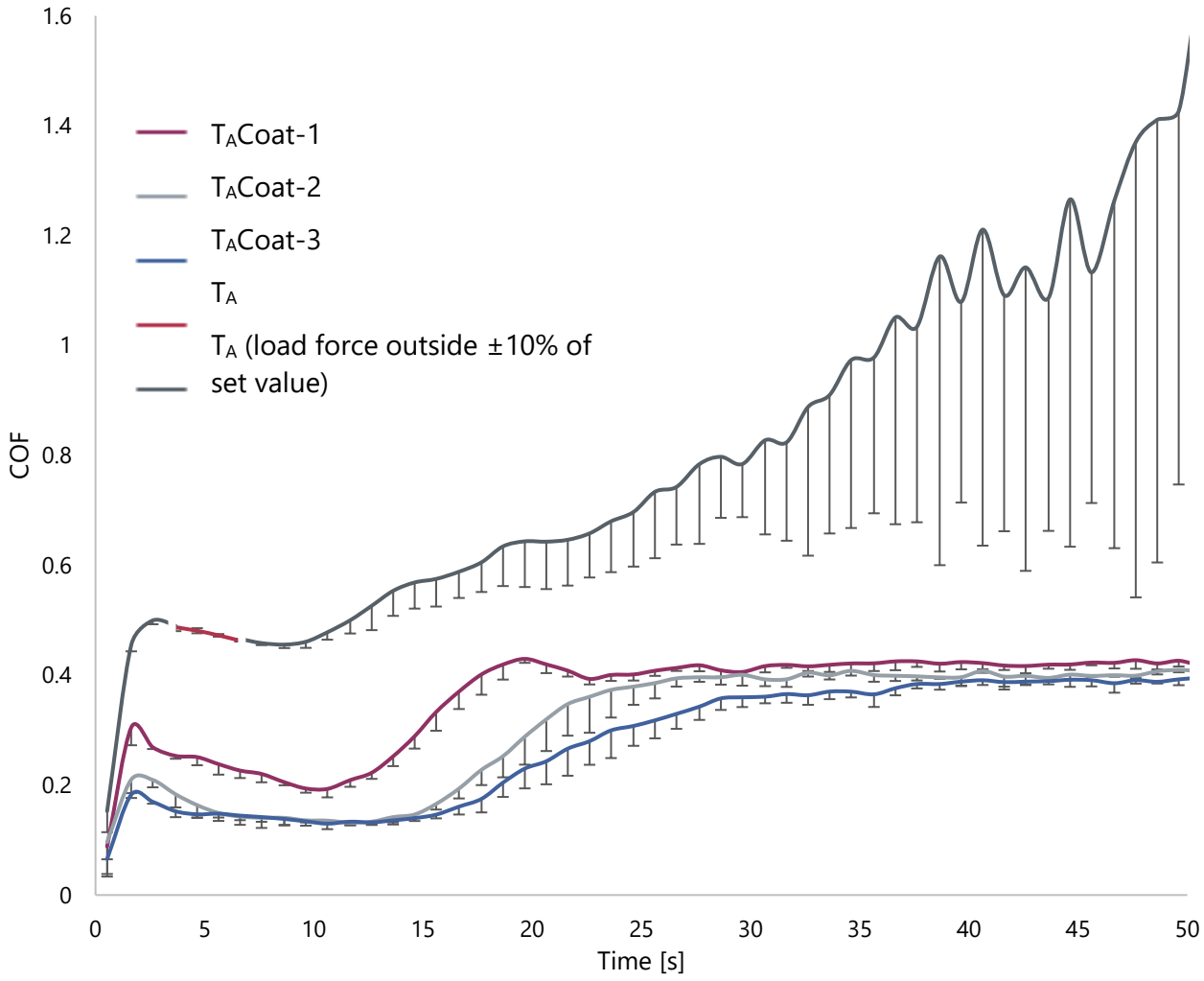


Figure 2.7 Friction behaviour of tablet cores provided by VerGo Pharma on a Transpore™ surface; T_ACoat-1 – T_ACoat-3 – coated tablets, T_A – uncoated tablet; load force within ±10% range of set value (2N) (unless stated otherwise);note that data for uncoated tablets consists of two lines; error bars represent standard deviation, only negative error bars are shown for clarity.

2.1.3.2.2 Preliminary results T_C – T_CCoat-4–8 – in-house made tablets (Figure 2.8)

The second batch of tablets consisted of a standard reference tablet coating (T_CCoat-4), two coating systems that were expected to have improved slipperiness (T_CCoat-5 and T_CCoat-6) and two coating systems that were chosen based on their taste-masking properties (T_CCoat-7 and T_CCoat-8).

The reference coating formulation (T_CCoat-4) comprised water soluble polymer (HPMC) and glycerol. In the COF vs. time plot the static and dynamic friction regions could be identified (Figure 2.8). For T_CCoat-4 the static friction was the highest observed of all six coated formulations. The low friction region was attributed to the presence of HPMC and glycerol. At low concentrations, HPMC forms a colloid in water which enhances lubrication hence its use in lubricating eye drops (Fonn, 2014). In this formulation glycerol was used as a plasticiser, yet its lubricating properties might also have contributed to the reduction of friction (Shi et al., 2014). After the coating had worn off the value of COF increased (region IIB).

Lipid coatings are commonly found as naturally occurring lubricants in circumstances where reduced friction is important e.g. snakeskin, human cartilage (Jahn et al., 2016). Thus, the lipid-based coating formulation, T_CCoat-5, was expected to provide good lubrication. In contrast with tablets coated with other formulations, tablets with the lipid-based coating maintained low friction for whole length of the test. Even after the coating had worn off the residual amount of coating (on the tablet and dispersed in the water) could still provide lubrication once separated from the tablet. The effect is likely to be due to lipid droplets being deposited in the contact area.

Coating formulation T_CCoat-6 comprised HPMC and xanthan gum. As explained for T_ACoat-2 and T_ACoat-3, polysaccharides, such as guar gum, enhance lubrication through both adsorbing on hydrophobic surfaces and viscosity modification. Likewise, the presence of xanthan gum increased the viscosity of the coating, as compared with T_CCoat-4 (data available in Chapter 3, Table 3.2). This viscosity aided lubricant entrainment and retention within the contact area (a phenomena observed for viscous colloids (de Vicente et al., 2006, Stokes et al., 2011)). As a result, static friction was easier overcome and lower initial (0-5 sec) COF values were observed.

Whilst the first three formulations (T_CCoat-4, -5, -6) consisted of water-soluble polymers, T_CCoat-7 and T_CCoat-8 were based on the water insoluble polymers basic butylated methacrylate copolymer, and ethyl cellulose, respectively. For these samples, the shape of the COF vs. time curve did not include the characteristic regions, (I, IIA, and IIB, Figure 2.5a) mentioned previously. At the beginning of COF vs. time plots an increase in COF was observed. This is likely to be due to the hydrophobic character of the polymers impeding surface lubrication with water. Unlike soluble polymer coatings, insoluble polymer coatings break up under shear forces and water pressure. The insoluble coating particles are entrained into the contact area, further increasing COF values. As a result, the COF for these samples was comparable, or higher, than for the uncoated tablet (T_C).

2.1.3.2.3 Results T_B – T_BCoat4-8 – tablets provided by Chrysalis (Figure 2.8)

Following on from preliminary friction results of the tablets manufactured in-house, tablets prepared by Chrysalis with the same coatings by were analysed under the same conditions, in order to compare the effect of core on COF. For the tablets provided by Chrysalis the

shape of COF vs. time curves was found to be similar regardless the coating type (Figure 2.8). Curves T_BCoat-4, T_BCoat-6 and T_BCoat-8 overlapped to large extent.

On the premise that the coating governs the friction behaviour of the whole tablet, it was expected that data from tablets manufactured in-house and by Chrysalis would provide good agreement. Yet, comparison of these data showed that the same coatings when applied to different tablet cores produce different friction patterns (Figure 2.8). The coating on Chrysalis tablets wore off more quickly when compared to in-house tablets. Furthermore, in the IIB region all Chrysalis tablets demonstrated similar COF values. While for tablets manufactured in-house, the effect of the coating on COF was visible for the duration of the test.

These findings suggest that the coatings, specifically at 4% (w/w) coating level, did not fully mask the friction properties of the tablet core. There are several core tablet characteristics that we hypothesise could contribute to this phenomenon:

- Core size, shape and curvature – as these properties determine contact area;
- Core porosity – as it impacts the rate and volume of lubricant absorbed;
- Core disintegration time – as a rapid disintegration might speed up coating wear;
- Core blend particle size – as larger particles might increase surface roughness and thus speed up coating wear;
- Core alignment on the plate during the test – as the tablets were affixed to the plate using a 3D printed template, slight size difference might cause misalignment.

In summary, the tablet core had major impact on how the coating wore off and how effective the lubricating properties of the coating were.

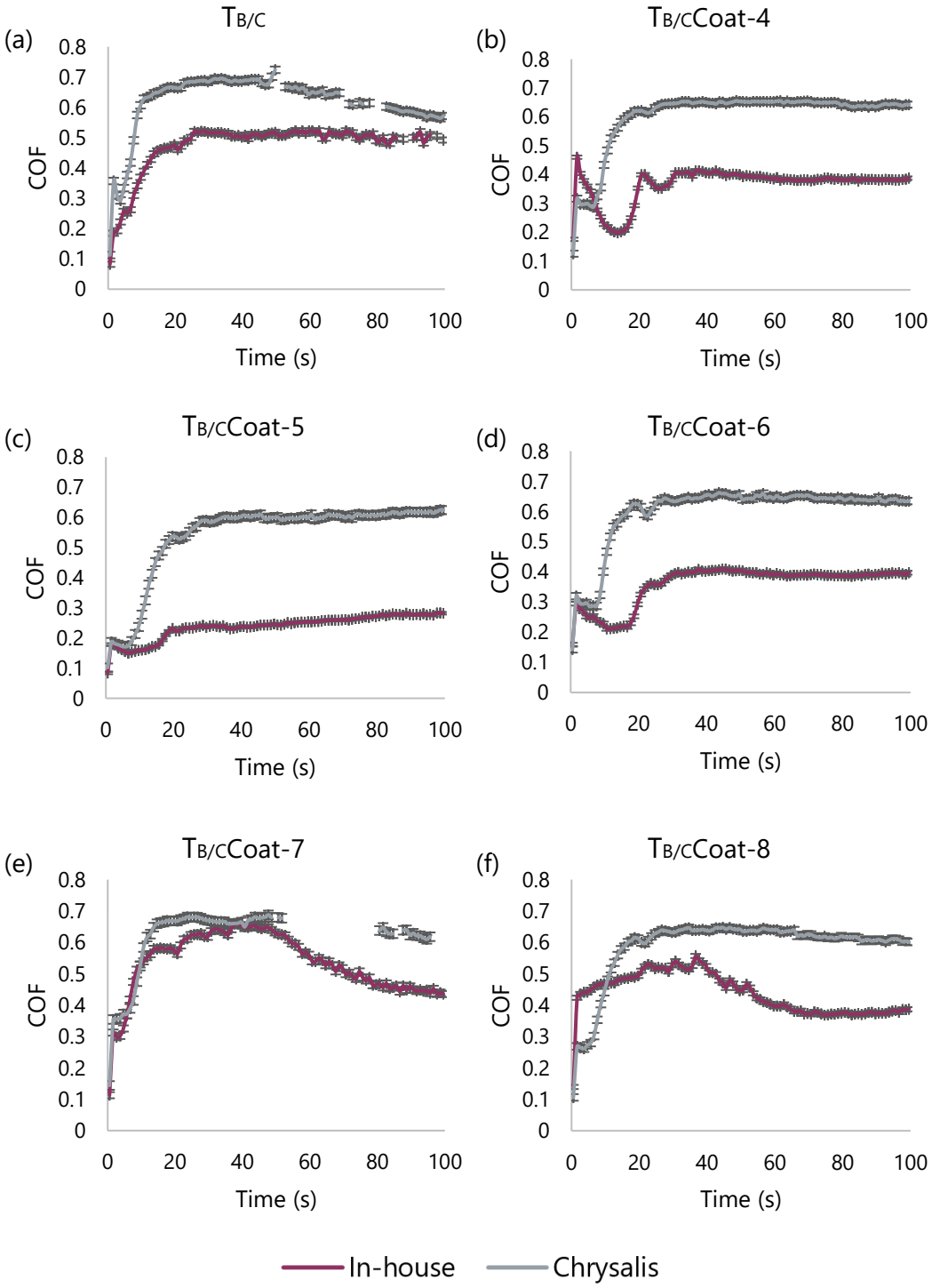


Figure 2.8 Friction behaviour of in-house made tablet cores and tablet cores provided by Chrysalis; $T_{B/C}$Coat-4 – $T_{B/C}$Coat-8 – coated tablets, $T_{B/C}$ – uncoated tablet; load force within ±10% range of set value (2 N).

2.1.3.3 Discussion in relation to previous studies

The efficiency of tablet passage through the surfaces of the oral cavity and along the oesophagus is in part governed by tablet slipperiness and adhesion to the mucosa.

The work presented in this chapter explores the friction behaviour of coated and uncoated tablets. In terms of a methodological approach, the work resembles the experiments of Drumond and Stegemann (2019) where a static and dynamic friction force of coated plastic discs was observed during the test. Whilst previous studies used plastic disks coated with various polymers, disregarding the influence of tablet core, here behaviour of the whole tablet was considered. The tablet core has an influence on the oesophageal transit, as core shape determines the size of the contact area with mucosa. This study shows that it is not only the size of the tablet core which could have an influence. The core properties of the tablet had a major influence on the *in vitro* friction behaviour. In this study the coating level (4%) was similar to that commonly used in industry and generally employed for aesthetics and recognisability. A rapid disintegration was observed which suggested that a thin coating allowed faster water uptake. Therefore, the oral and oesophageal surfaces could potentially be exposed to contact with a tablet core, not just the coating. This finding suggests that, the duration of friction measurement should be extended until tablet coatings wear off so as to include COF measurement of the tablet core. To date, no publication has been identified which examines the friction behaviour of different tablet cores or the impact of the core on friction of a tablet coating.

The results reported in the thesis corroborate previously published reports which demonstrate that the choice of the film-forming polymer used in a coating has a major influence on slip behaviour (Drumond and Stegemann, 2019). HPMC, employed in this study,

is a widely used tablet coating material mainly due to its excellent film-forming properties. In addition, this polymer also has adhesive characteristics meaning that it is also used as a coating for in buccal tablets (e.g. Loramyc®, miconazole) which need to adhere to the oral mucosa for drug delivery. Where adhesiveness is not a desirable property, modification of the coating formulation is necessary. While the addition of plasticisers to HPMC coating formulations was not effective in reducing adhesiveness (Smart et al., 2015), the results presented in this thesis showed a decreased friction force when polysaccharides and MCT were incorporated into the coating formulation (T_ACoat-2, T_ACoat-3, and T_BCoat-6). This concept was tested *in vivo* (see Chapter 4).

A range of published *in vitro* methods used to predict swallowing focus on oesophageal transit (Dirven et al., 2017, Drumond and Stegemann, 2019). The experiments presented in these publications were designed to reflect movement in a single direction and lubricant flow across a sample surface representing the oesophageal mucosa. In contrast, the set-up presented in this thesis, was designed to mimic the oral cavity, where a tablet sample was immersed in liquid, and the contact surface represented the tongue rather than the smooth oesophagus.

2.1.3.4 Method limitations

The developed method allowed observation of tablet (and tablet coating) friction behaviour under shear and load forces. This method is limited in bio-relevance by several factors: oral surfaces, mechanical swallowing action and lubricating solutions. Oral surfaces cannot be mimicked directly, this model uses a surface intended to mimic the tongue and not any of the surrounding mucosa. In addition, the surface chosen was limited by the parameters of the experiment. Mechanical swallowing action cannot be replicated using a tribometer, as

the instrument used allowed circular rather than linear movement. Distilled water is fully not representative of human saliva as an oral lubricant. Lastly, the properties of the tablet samples – shape and size – were dictated by the clinical study design. Thus, impact of the physical tablet attributes was not fully investigated and would be of interest for future studies.

2.1.3.5 Implications of the findings

The main aim of this study was to develop a tribology method to measure slipperiness of tablet coatings with the potential to correlate the findings with sensory analysis. In the method development section, it was demonstrated that discrimination of the tablets with different coatings was achievable, provided that the study design considers force and surface properties of the system. Further experiments have shown that a wider range of coatings could be successfully characterised with the proposed method.

Importantly, comparison of two different tablet cores, of same shape and size, with the same coatings showed different friction patterns leading us to conclude that the tablet core has a major impact on coating wear and the effectiveness the its lubricating properties. This outcome suggests that the same coating, when applied on different tablet cores cannot be compared *in vitro*. Plus, in order to measure the friction properties of a coated dosage form, both the coating and the final tablet core formulation needs to be considered. Also, the optimal coating thickness should be considered as a potential factor that may impact ease of swallowing.

Alternatively, the properties of the coating can be measured in isolation from the core, where the lubricity of coating ingredients can be better understood. Such a method is presented and evaluated in the following part of the Chapter (2.2).

2.1.4 Conclusions

Oral tribology is a developing discipline used to study texture and mouthfeel of products that come in contact with the oral cavity (e.g. food, oral medicines, oral care). The rationale of using tribology to explore mechanisms underlying oral perception lies in the fact that it provides information on friction and lubrication behaviour between oral surfaces which is one of the major mechanisms dominating perception of food texture. Interaction of a sample with the tongue, teeth and palate creates sensory perception informed by a sample's surface properties, its roughness/smoothness, stickiness/slipperiness.

In this chapter tribology was used to measure the coefficient of friction of a tablet's surface. The method was found to be useful to discriminate and explain the lubrication behaviour of coated tablets. The results obtained compared the forces needed to move a tablet against a rough wet surface. Yet, as shown in the method development section, analysis of friction requires a considered choice of experimental parameters and extensive testing. In particular, this is because solid oral dosage forms require different methods from those used with food and liquid pharmaceuticals.

The impact of these findings needs to be further assessed by comparison with *in vivo* testing, where the difference in perceived slipperiness can be related to measured friction. What this means in clinical practice is reported in Chapter 6 where this *in vitro* model and resulting data are related to the sensory perception and experience associated with the swallowing process of the same samples in human volunteers.

2.2 Thin film tribology

2.2.1 Introduction

In the field of sensory research two approaches have been taken to measure product slipperiness: direct measurement of the sample surface as described in first part of this Chapter (2.1) and thin film measurements using liquid samples. This part of chapter will focus on thin film tribology as a measure of lubrication properties.

Thin film tribology is a method which measures friction between two surfaces immersed in a lubricant. As the surfaces are brought into contact with a fixed load, no lubricant is present at the contact area. When movement begins the lubricant becomes entrained within the contact area and creates a thin layer – 'thin film' – between the surfaces. The presence of this thin film and its lubricant properties impact the friction properties of whole system.

Thin film tribology has been found as useful to study the slippery texture of food and personal care products. Its principles were introduced in Chapter 1.4.3.1.3. In brief, the properties of the lubricant are tested by measuring the coefficient of friction (COF) at a range of relative speeds at a constant load force. The results are plotted as a Stribeck curve (COF plotted against sliding speed multiplied by effective viscosity), which usually depicts three characteristic lubrication regimes: boundary, mixed and hydrodynamic.

Several studies have found a correlation between the sensory perception of slipperiness and thin film tribological measurement (Malone et al., 2003, Krop et al., 2019). Where an *in vitro in vivo* correlation has been found, it has been in the mixed lubrication regime. The first reported relationship described by Kokini (1987) investigated the slipperiness of food and showed that there was an inverse relationship between the COF and slipperiness (Eq. 2.7). Yet, it is not clear which regime was under test.

$$Slipperiness \propto \frac{1}{Viscous\ force + \mu W} \quad \text{(Eq. 2.7)}$$

where, W - normal force, μ - coefficient of friction.

In a more recent study Malone et al. (2003) investigated slipperiness of model hydrocolloid solutions at various sliding speeds and also found an inverse relationship between human and instrumental data between 10 and 100 mm/s (mixed regime). A similar relationship in the mixed regime was later found with polysaccharide model solutions (Chojnicka-Paszun et al., 2014). Other research has evaluated the sensory properties of aqueous hydrogels (Krop et al., 2019) and found a tribology-sensory relationship for a 'slippery' perception in the mixed lubrication regime (50 mm/s). Opposite to another studies, Krop et al. (2019) found a direct, rather than inverse, relationship. However, the authors advised caution when interpreting data, due to poor agreement within the testing panel responses and the unexpected direct correlation. Overall, the general consensus within published literature agrees that the mixed regime of lubrication is most relevant for studying slipperiness.

On the premise of abovementioned studies, the assessment of tablet coating slipperiness was undertaken and is reported in this thesis. To date, no other studies have investigated this topic using thin film tribology. It is proposed that the method described will be able to evaluate the friction of a dispersed coating (as a lubricant) using a thin film model. The method used intended to imitate the *in vivo* environment. Tablet coatings were tested as films dispersed in water. Isolation of the coating allowed the properties of the individual coatings to be investigated without the influence of the tablet core. Dispersion of the coating in water was intended to mimic the dissolution of the coating in the mouth.

2.2.2 Materials and methods

2.2.2.1 Formulations

2.2.2.1.1 Preparation of dispersions from the coating films

The coating formulations used in this study were the same as those listed in Chapter 2.1 Table 2.2. In total, eight coating formulations were tested.

The list of materials used for preparation of coatings is given in Chapter 2.1 section 2.1.2.

Firstly, coating solutions were prepared as described in section 2.1.2. Secondly, coating solutions were sprayed onto an acetate sheet with spray gun (Caleva Mini Coater 2, Dorset, UK), with continuous drying at 60°C, until a 200 µm thick film was achieved. The coating film was then cured at 40°C for 2h. Finally, the coating film was dispersed in deionized water to a concentration of 5 mg/mL and its tribological properties were tested the next day to ensure the dispersed polymer was fully hydrated. The concentration of coating matches the one that can be achieved when the tablet coating dissolves/disperses in the mouth (calculated as a mass of coating on a tablet divided by average volume of saliva at rest). The samples of dispersed coatings are referred to as Coat-1_{dis}, Coat-2_{dis}, Coat-3_{dis}, etc. to distinguish from the tablet samples, described in the previous part of the chapter.

2.2.2.2 Equipment

Tribology experiments were performed using a rheometer with tribology attachment (Discovery HR-2, TA Instruments, USA) using 3-balls-on a plate geometry (Figure 2.9). Various materials were placed at the bottom of the cup to test different surfaces.

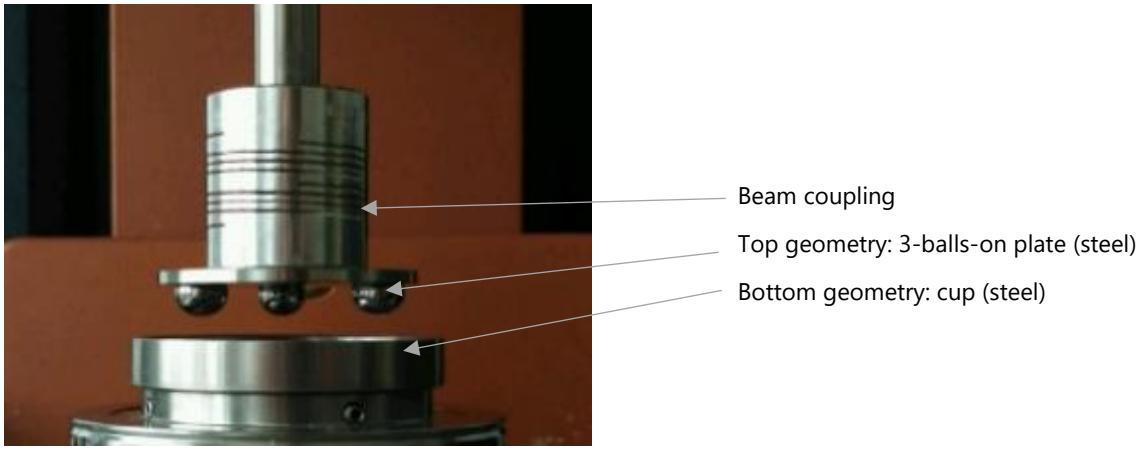


Figure 2.9 Tribo-Rheometry accessory: 3-balls-on-plate geometry setting for experiment using coating dispersions; the bottom surface can be modified by placing material to be tested on the bottom of the cup.

2.2.2.3 Method development for measurement of the lubricating properties of a dispersed coating

Coating dispersions were evaluated for their lubricating properties using thin film tribology. Three normal force settings and three different bottom surfaces were investigated in order to develop the most robust and differentiating method.

2.2.2.3.1 Test parameters

The thin film method measured the friction between two surfaces: the top one which rotated, and the bottom one which remained stationary. Dispersed coatings were used as the lubricant of interest. COF vs. sliding speed curves (μ versus v_s) were obtained in 6 consecutive sweeps, with the sliding speed first increasing, and then decreasing in a stepwise logarithmic mode. Due to variability, the first curve was discarded. The variations of the first sweep are explained by the time needed for a good deposition of lubricant on the surfaces. Further methodological parameters are listed in Table 2.6.

Analogous to Chapter 2.1, a full factorial design $3^1 3^1$ was used during method development. In this design 2 factors were evaluated, at 3 levels, resulting in 9 experimental trials to determine optimal test conditions. The load force and the bottom surface were selected as

independent variables. Development experiments were performed in single repetition and the results were obtained within an average of 5 sweeps (the first of the 6 sweeps was discarded). Then data was plotted as a Stribeck curve.

2.2.2.3.2 Tested samples

Firstly, the bottom surface (as listed in Table 2.6) was stuck with double sided tape to the bottom of the cup. Then 4 mL of dispersed coating at a concentration 5 mg/mL (used as a lubricant) was added to the cup. After a pre-set load force was applied, the top geometry rotated with ascending and descending sliding speeds. The following samples were used for development experiments: Coat-1_{dis} (HMPC-based), Coat-2_{dis} (HPMC + polysaccharide gum + MCT based), and corn syrup. These coatings were chosen because they were expected to show the biggest differences when tested. The corn syrup was tested as a model Newtonian fluid with precedence of use in soft tribology (de Vicente et al., 2006). Once the method was developed, further experiments were carried out with all samples listed in Table 2.7 and pictured in Figure 2.10.

Table 2.6 Parameters of the coefficient of friction measurement to obtain a Stribeck curve.

Parameter	**Value**
Fixed parameters	
Sliding speeds	0.001 – 10 rad/s
Logarithmic sampling	5 points per decade
Sample volume	4 mL (concentration 5mg/mL)
Temperature	25 °C
Variable factors	
Load force	1 N* 2 N 3 N
Bottom surface (placed in the steel cup)	silicone rubber Transpore™ surgical tape (3M™) Tegaderm™ hydrocolloid thin dressing (3M™)*

* Parameters chosen based on the method development experiments.

Table 2.7 List of samples used in thin film tribology measurements.

Formulation	Type	Structure in water	Concentration	η_{eff}[mPa s]*
Coat-1_{dis}	Standard commercial coating	Hydrocolloid dispersion	5 mg/mL	1.13
Coat-2_{dis}	Slippery commercial coating	Hydrocolloid emulsion	5 mg/mL	1.67
Coat-3_{dis}	Slippery commercial coating	Hydrocolloid emulsion	5 mg/mL	1.60
Coat-4_{dis}	Standard reference coating	Hydrocolloid dispersion	5 mg/mL	1.11
Coat-5_{dis}	Lipid-based coating	Thin emulsion	5 mg/mL	0.82
Coat-6_{dis}	Slippery coating	Hydrocolloid dispersion	5 mg/mL	1.59
Coat-7_{dis}	pH dependent coating	Thin dispersion	5 mg/mL	0.98
Coat-8_{dis}	Insoluble–soluble polymer coating	Thin dispersion	5 mg/mL	0.81
Distilled water	Reference Newtonian fluid	N/A	N/A	0.76
Corn syrup	Reference Newtonian fluid	Thick solution	90%	407.6

*Effective viscosity = minimum viscosity value at 25°C measured at high shear rates (>100 s^{-1}) (full method given in Chapter 3.3.1)

Figure 2.10 Dispersed coatings at a concentration 5 mg/mL.

2.2.2.3.3 Plotting Stribeck curves

Thin film measurements provided data as a function of COF vs. sliding speed (μ versus v_s). Combination of the sliding speed with lubrication parameters, i.e. lubricant effective viscosity (η_{eff}), gave a Stribeck curve (μ versus $v_s\,\eta_{eff}$) which allowed better comparison between measurements.

Effective viscosity (η_{eff}) represents the viscosity of the sample under test at the contact area during the COF measurement. As η_{eff} cannot be directly measured, an estimate is usually used, based on the following reasoning:

- When the sample enters the space between top and bottom geometry it is sheared by top geometry rotation.
- Only a thin layer of sample is entrained into the contact area, because there is very small gap between the top and bottom geometries.
- As a result, high shear rates are present at the contact area.

Shear rate is inversely proportional to the distance between surfaces, $\gamma = \frac{v}{h}$.

Following de Vicente et al. (2005), to gain an estimate of the effective viscosity in tribological contact, the minimal value of viscosity (η_{min}) at high shear (>100 s^{-1}) should be used. In this thesis, the viscosity of dispersed coatings was measured at shear rates up to 1000 s^{-1} (TA Discovery HR-2 Rheometer) and a single effective viscosity ($\eta_{eff} = \eta_{min}$) was chosen for each sample (Table 2.7).

All data presented in this chapter is plotted as Stribeck curves.

2.2.3 Results and discussion

2.2.3.1 Developmental experiments – thin film measurement

Three force settings and three surfaces (Table 2.6) were analysed to determine which combination gave a well-defined Stribeck curve and allowed differentiation between the lubricants.

2.2.3.1.1 Effect of force

During thin film measurements, for all surfaces a low force variation was observed (relative standard deviation, RSD< 5%). The measurement setting allowed an equilibration time for

each sampling point ensuring that the force was stabilized (±0.1N) throughout the experiment. Therefore, the hardness of the surface had no major impact on the force stability. Nonetheless, the data points collected were screened, and only points with load force within ±10% of the set value were included for analysis. RSD and the percentage of data points that lay outside the allowable force limits are reported in Table 2.8. The Stribeck curves obtained with all tested surfaces at 1 N, 2 N and 3 N are presented in Figure 2.11. As can be seen, the shape of the Stribeck curve was similar for all load force settings. Visual inspection of the bottom surfaces after the test revealed that a load force ≥2 N resulted in visible wear of the surface. Thus, a 1 N load force was chosen for further studies.

Table 2.8 Factors evaluated for tablet Stribeck curve measurement - method development.

Test	Surface	Set force [N]	% of points outside force limits	SD [N] (RSD %)	Detection of differences between samples
1	Transpore™	1	0	± 0.04 (3.9)	No
2	Transpore™	2	0	± 0.03 (1.3)	NA
3	Transpore™	3	1	± 0.02 (0.8)	NA
4	Tegaderm™	1	17.1	± 0.05 (4.7)	Yes
5	Tegaderm™	2	8.6	± 0.08 (3.8)	NA
6	Tegaderm™	3	1	± 0.07 (2.3)	NA
7	Silicone rubber	1	0	± 0.03 (3.0)	No
8	Silicone rubber	2	0	± 0.02 (0.9)	NA
9	Silicone rubber	3	0	± 0.03 (1.0)	NA

NA – not assessed

2.2.3.1.2 Effect of surface

Figure 2.11 illustrates the lubrication behaviour of the Coat-1_{dis} sample (5 mg/mL) on the three bottom surfaces under test. Each bottom surface resulted in a different curve shape. Only Tegaderm™ resulted in a well-defined Stribeck curve with hydrodynamic, mixed and boundary lubrication regimes. For Transpore™/silicone rubber and 3-balls set-up, a full Stribeck curve could not be obtained. This is likely due to particular wetting properties of the lubricant or surface roughness. Such observations have also been reported previously (de Vicente et al., 2005, Bongaerts et al., 2007a). In the case of the silicone rubber surface, the

Stribeck curve was within the boundary ($v_s\eta \leq 10^{-4}$ N/m) and mixed ($v_s\eta \geq 10^{-4}$ N/m) regime (Figure 2.11 g-i). It may be argued that the hydrodynamic regime could only be reached at higher sliding speeds when the lubricant could carry the load. For Transpore™ tape, only the boundary regime was obtained.

The lubrication properties of Coat-1_{dis}, Coat-2_{dis} and corn syrup were tested in three set ups to identify the surface which allowed the behaviour of the samples to be distinguished from one another. The clearest definition of Stribeck curve, as well as best differentiation between samples, was obtained using Tegaderm™ (Figure 2.12). On this surface there was a clear shift of mixed regime to lower speeds, along with low boundary COF values observed for Coat-2_{dis}. Also, for Coat-1_{dis} shift of mixed regime to lower speeds was noted.

The shape of the Stribeck curve is controlled by the properties of the system. In the boundary regime at low speeds, COF is highly dependent on surface roughness with a smoother surface giving lower friction (Yakubov et al., 2015) (Figure 2.12 a, c). This was not true for the rough and elastic Tegaderm™ surface. As discussed in section 2.1.3.1.2, a more elastic surface increases contact area, hence a higher boundary friction is observed. When speed increases, the lubricant is entrained within the contact area, in a so-called mixed regime. In this regime, COF decreased at lower speeds for the more hydrophilic surface, Tegaderm™. This is explained by the hydrophilic surface being favourably wetted by the aqueous lubricant (as compared with hydrophobic surface) (Stokes et al., 2013). At higher speeds, when the lubricant fully supports the load, a hydrodynamic regime was observed for Tegaderm™ only. In this region COF depends on the viscosity and bulk properties of the lubricant (Bongaerts et al., 2007a). In concordance with this fact, the increase in COF was faster for corn syrup than Coat-1_{dis} on the Tegaderm™ surface, (Figure 2.12c).

In a Stribeck curve a hysteresis may be observed when the composition of lubricant in the contact area differs between the ascending and descending sweep (e.g. more particles are present in the contact area during the ascending sweep) (Garrec et al., 2012). To accommodate the hysteresis phenomenon, COF values were averaged separately for increasing/decreasing speed sweeps and plotted as shown in Figure 2.12. Particularly for the silicone rubber surface, hysteresis was observed for the dispersed coating samples (Coat-1_{dis} and Coat-2_{dis}). A higher COF was observed with decreasing sliding speed in the mixed regime with little difference at higher and lower speeds. This phenomenon indicates a structural change within the lubricant, and can be explained by dynamic entrapment of water insoluble solid particles into the contact area (Yakubov et al., 2015). In other words, more particles are present in the contact area during the ascending than the descending sweep result in higher COF values in the mixed regime. As expected, no hysteresis was observed for corn syrup – a Newtonian solution. Hysteresis was observed on the smooth surface of silicone rubber only. It is likely, that the porous structure of other surfaces allowed sedimentation of particles into the pores, and consequently removed them from the contact area leaving friction unaffected.

Analysis of lubrication behaviour under various loads and on different surfaces informed the choice of test parameters used in the following sections of this thesis. Based on the most clearly defined Stribeck curve shape and lowest surface wear the Tegaderm™ surface and 1N load were chosen.

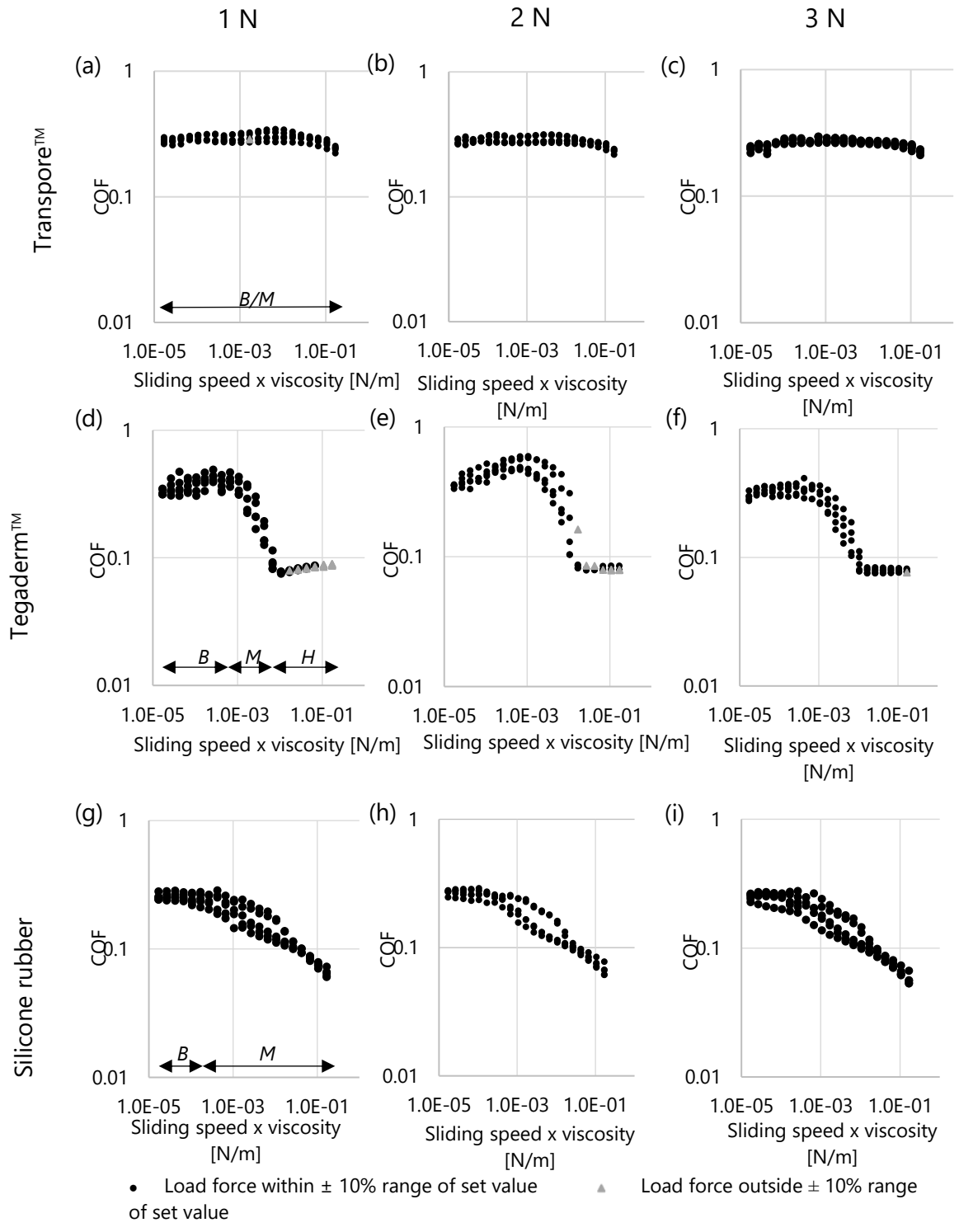


Figure 2.11 Stribeck curves obtained during method development experiments for Transpore™ (a, b, and c), Tegaderm™ (d, e, and f), and silicone rubber (g, h and i) surfaces; sample: Coat-1$_{dis}$. Lubrication regimes are depicted: B – boundary, M – mixed, H – hydrodynamic.

2.2.3.2 Lubricating properties of dispersed coatings

Conventional tablets are supposed to be taken with water; thus, it was used as a dispersion liquid for the coatings to observe their capacity to alter the lubricant properties of water.

Figure 2.13 shows the Stribeck curves obtained for distilled water (as a control) and samples Coat-1_{dis} – Coat-8_{dis} at a concentration of 5 mg/mL using the Tegaderm® bottom surface at 1N load force. For distilled water, a boundary regime was obtained at $v_s\eta \leq 10^{-3}$ N/m. The unusual COF increase as a function of sliding speed observed in this regime has also been reported previously for rough surfaces (Bongaerts et al., 2007a). This phenomenon was attributed to either (i) deformability of substrate or (ii) increase in shear stress with increase of sliding speed (Cassin et al., 2001, Yakubov et al., 2015).

Water is a poor lubricant as a water film is easily disrupted, impeding a full film lubrication. This disadvantage may be overcome by viscosity modification. As shown in Figure 2.13 all coatings enhance lubrication as compared with water. Their lubrication behaviour is discussed below according to the structure the dispersed coatings formed in water (Table 2.7).

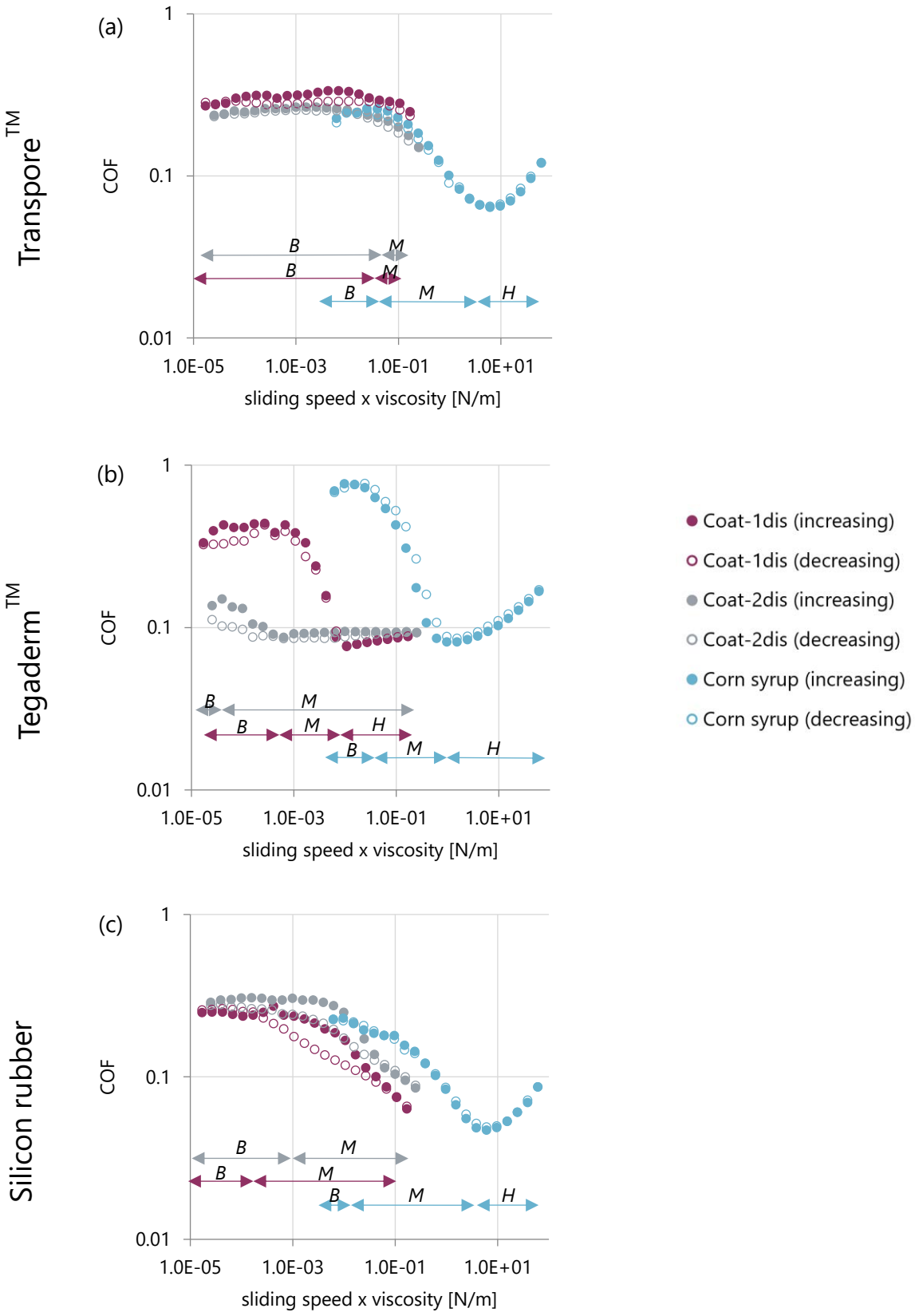


Figure 2.12 Stribeck curves on three surfaces Transpore™ (a), Tegaderm™ (b), and silicone rubber (c); samples: Coat-1$_{dis}$, Coat-2$_{dis}$, corn syrup at 1N load force; data points collected during sweeps with increasing/decreasing sliding speed are distinguished. Lubrication regimes are depicted: B – boundary, M – mixed, H – hydrodynamic.

2.2.3.2.1 Lubrication behaviour of viscosity modified dispersions

Polymers, like HPMC or the gums used in this thesis, enhance the viscoelastic properties of aqueous solutions. This increase in viscosity and elasticity encourages lubricant entrainment into the contact area and favours lubricant retention (as discussed in Chapter 2.1.3.2). Formulations Coat-1_{dis}, Coat-4_{dis} (both HPMC-based) and Coat-6_{dis} (HPMC + xanthan gum based) are examples where even a low concentration of polymer considerably improved lubrication (i.e. a much lower COF for the mixed and/or hydrodynamic regime). The improvement of lubrication in the mixed regime has been reported previously for polymers in aqueous solutions which exhibit viscoelastic behaviour (de Vicente et al., 2005). The lubricity increased with increasing polymer concentration. Much alike in this chapter, where Coat-6_{dis} showed lower COF than Coat-4_{dis}. This was due to addition of xanthan gum – a high-molecular-weight polymer, used as a thickening agent in the food and pharmaceutical industry.

Viscosity enhanced lubrication was also observed in Coat-2_{dis} and Coat-3_{dis}. These coating formulations are based on HPMC, hydrocolloid and include also medium-chain triglycerides (MCT), and thus will be discussed in the next section.

2.2.3.2.2 Lubrication behaviour of emulsion-based formulations

Oil in water (o/w) emulsions exhibit a reduction in friction determined mainly by deposition of oil droplets on the surfaces (Dresselhuis et al., 2008c). As more oil droplets adhere and spread on the surface, they coalesce forming a film. In this thesis, two types of lipids were present in coating formulations. Coat-2_{dis}, Coat-3_{dis} comprised MCT, Coat-5_{dis} contained hydrogenated cottonseed oil. When dispersed in water both lipids formed o/w emulsion. For these three formulations, low COF values were observed even at low speeds (Figure 2.13),

with negligible differences between shapes of Stribeck Curve. None of the emulsion-based coatings showed the increase in COF with increasing sliding speed characteristic of the hydrodynamic regime. Thus, under tested conditions lubrication was in the boundary and/or mixed regime.

It is possible that the sample preparation method (dispersion of film coating in water) in this study resulted in an unstable emulsion which enhanced lubrication due to increased oil deposition. This is likely to also be the case *in vivo* when the coating dissolves in the mouth. Research has shown that less stable emulsions better lubricate hydrophobic surfaces, as they are more likely to coalesce (Dresselhuis et al., 2007).

2.2.3.2.3 Effect of large water insoluble particles on lubrication

Two formulations Coat-7_{dis}, Coat-8_{dis} were composed of water insoluble polymers (basic butylated methacrylate copolymer and ethyl cellulose, respectively). In contact with water, these film coatings break-up into large solid flake-like particles which yield a more complex dependence of friction on sliding speed. When particles were present in the lubricant, their shape and size were crucial, as only particles small enough can be constantly entrained into a contact area. Although larger particles are generally excluded from the measurement, they may still occasionally be entrained. It is likely, that such behaviour was observed for Coat-8_{dis} based on the large standard deviation of COF and flat shape of particles (Figure 2.13 h, Figure 2.10). At higher speeds, the value of COF decreased, as at these speeds the particles were not able to enter the contact area.

In contrast, a study introducing a suspension of glass spheres (mean diameter 9 µm) into tribological contact (Yakubov et al., 2015), produced a decrease boundary friction as an effect of 'ball-bearing' behaviour. However, this is only observed when particles in the

contact area are spherical with a regular shape unlike the flake-like particles observed with the break-up of the insoluble films described above. What is more, the samples Coat-7_{dis} and -8_{dis} had a lower viscosity when compared with the hydrocolloid-based samples discussed earlier (Table 2.7). As such, lubricity was impaired, which was observed as a shift in the mixed regime towards higher speeds.

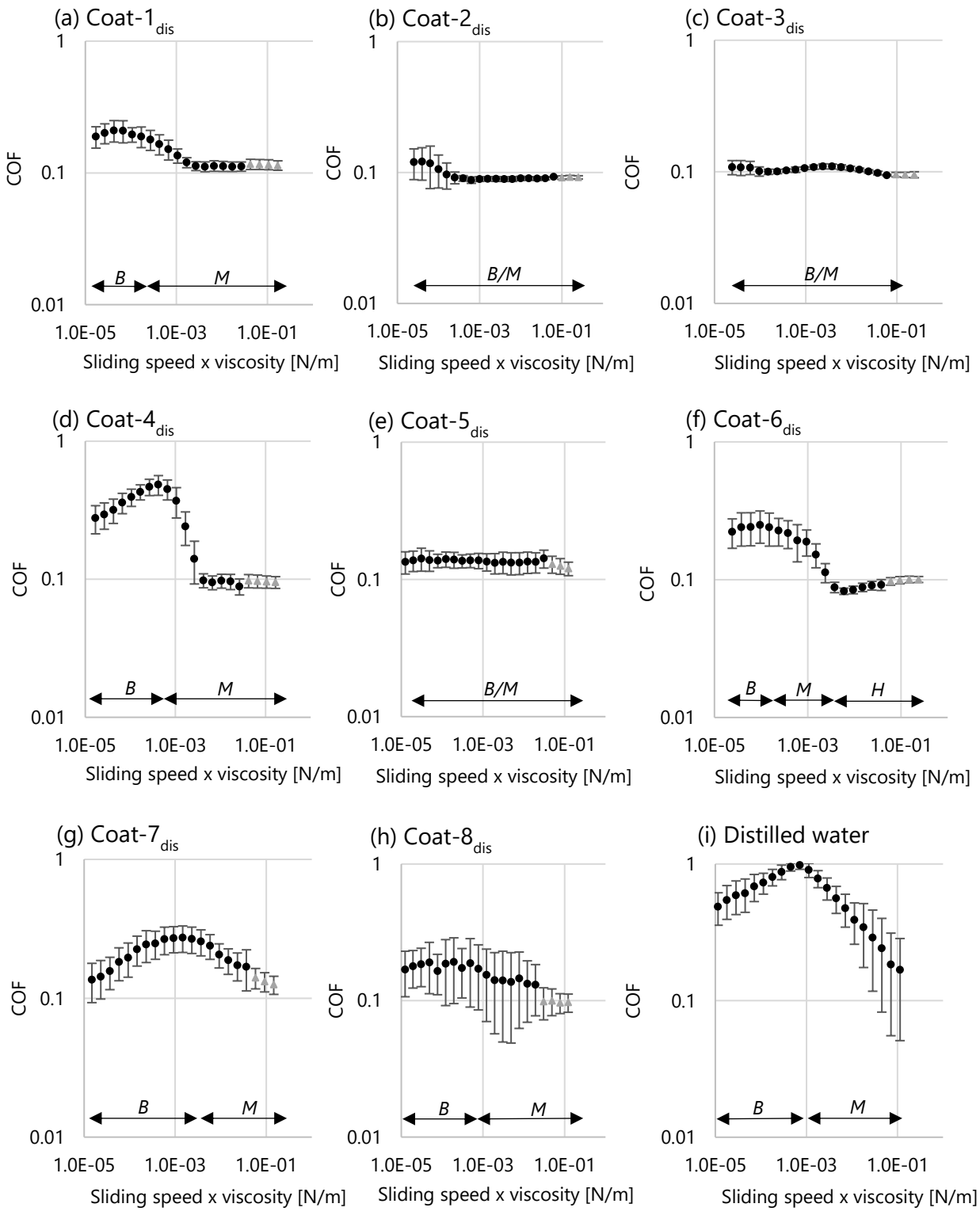


Figure 2.13 Friction behaviour of coating dispersions Coat-1_{dis} – Coat-8_{dis} and distilled water at Tegaderm™ bottom surface and 1N load force. Lubrication regimes are depicted: B – boundary, M – mixed, H – hydrodynamic.

2.2.3.3 Relation to sensory perception

Medicine texture is an important attribute which influences consumers' acceptance of medicines. To date texture analysis based on mechanical and rheological properties have been widely studied in the context of oral processing of food. In the case of a solid medicine, in particular coated tablets, these methods are not sufficient to explain mouthfeel properties. In the mouth tablets are not chewed but swallowed whole. Thus, the oral surfaces come into contact with the solid coated (or uncoated) tablet surface. This contact is modulated by a thin film of saliva or water with which the medicine was taken. Consequently, the texture characteristics of coatings and tablets cannot be analysed as a bulk property but as a thin film interaction and supports tribology as a reasonable method of assessment.

As presented in this chapter, tablet coatings can be composed of soluble or insoluble in water materials. For soluble ones, the thin film between the tablet and oral surfaces is composed of partially dissolved coating. For insoluble materials, the carrying fluid is mostly water, but as this study showed, insoluble coatings may release flake-like insoluble particles under stresses like those found in the mouth.

The *in vivo* perception of slipperiness has previously been correlated with tribological lubrication in the boundary and mixed regime (Malone et al., 2003, Prakash et al., 2013). The experiments of Malone et al. (2003) found a correlation for sliding speeds between 10 and 100 mm/s. However, this speed range is not relevant for our study. Firstly, at such high speeds COF values were similar for all of the samples. Secondly, some samples entered the mixed regime below 1 mm/s ($\approx v_s\eta_{eff} \leq 10^{-3}$ N/m), suggesting that correlation is more likely at lower speeds.

In this study, water was used as a dispersion media for tablet coatings. The choice of water was justified in two ways. Firstly, water is the liquid of choice to take solid medicines with and, secondly that presence of other media might have changed the observed lubrication behaviours. The choice of liquid used to take a tablet has major impact on ease of swallowing and mouthfeel. Milk, for example, as an emulsion, may reduce friction. Thickened liquids can aid swallowing because they are more cohesive, hence their use for people with dysphagia (Cichero, 2013, Barnett and Parmar, 2016). On the other hand, the liquid taken with a tablet might affect its sensory properties. Specifically, changes in texture and flavour perception have been reported for samples of different viscosity (Ong, 2017). In the context of the work presented in this thesis, it would be of future interest to test the behaviour of tablets in different liquids/semisolids taken with medications, for example: juice, milk, tea, apple puree, or yogurt, as well as artificial or human saliva (note that human saliva consists of 99% water (Humphrey and Williamson, 2001)).

2.2.3.4 Relation to surface tribology (Chapter 2.1)

In general, thin film tribology revealed that emulsions decreased boundary friction, while the presence of insoluble particles in dispersion impeded lubrication. These results coincided with the friction measurement of tablet samples presented in section 2.1.3.2. Both methods confirmed the superior lubricating properties of coatings that incorporated lipid ingredients. However, thin film methods provided better discrimination between the coatings when compared to whole tablets in section 2.1.3.2.

Thin film tribology allowed a deeper understanding of the lubrication properties of coatings without interfering factors (i.e. properties of tablet core). Indeed, thin film tribology is widely used in food science in order to understand the mechanisms that influence texture

perception. Published reviews of oral tribology-sensory relationships indicate that the majority of studies employing this method use model foods with precisely designed formulations (Prakash et al., 2013, Pradal and Stokes, 2016, Sarkar and Krop, 2019), where the impact of the slightest formulation change can be analysed and understood. Thin film tribology explains the fundamental properties of food that underlie texture perception. For example, it offers the opportunity to analyse interactions at microstructure level: oil droplet coalescence under shear (observed with confocal microscope) (Dresselhuis et al., 2008b), or reaction between tannins and saliva (Brossard et al., 2016b) (responsible for astringent feeling in mouth). In this thesis, the use of a thin film method, effectively allowed discrimination between the majority of samples (only emulsion-based formulations yielded the same shape of Stribeck curves).

In contrast, surface tribology testing was an empirical method that intended to mimic tablet movement in the mouth. This method enabled a quick test of final product and comparison between coated and uncoated samples. However, as an empirical method, the results are difficult to analyse. Firstly, because there is no established reference standard relating friction values to acceptable levels of tablet slipperiness only comparative studies are possible. Secondly, as discussed in Chapter 2.1, while inclusion of the tablet core may provide a more realistic picture, it can also obscure the mechanisms governing lubrications.

Comparison of two different coating formulations Coat-4 and Coat-6 provided an example that illustrates the different applicability of both methods. Coat-4 and Coat-6 are both HPMC-based, while Coat-6 had a small addition of xanthan gum. Using thin film tribology, the difference in friction behaviour was detected by lower boundary friction of Coat-6_{dis}. However, when T_ACoat-4 and T_ACoat-6 coated tablets were tested, the impact of viscosity in

reducing friction was detected with in-house tablet cores, but for Chrysalis cores the samples exhibited the same friction pattern. The tablet core hindered differentiation between coatings. While this example demonstrates the high sensitivity of thin film tribology to lubricant differences, it also shows that multiple factors can affect surface tribology and alter the results. On the other hand, given that surface tribology mirrors real-life by measuring the effect of tablet core and coating together, it is possible that the difference between Coat-4 and Coat-6, when applied onto a tablet core, is not detectable *in vivo* and therefore not relevant in terms of sensory perception (i.e. the sensory experience associated with both tablets would be the same). The study to correlate the tribological findings from the tested tablets with *in vivo* sensory analysis is discussed in Chapter 6.

2.2.3.5 Method limitations

The developed method measured lubrication properties of dispersed coatings. The method required preparation of the coatings in isolation of the tablet, therefore, the test condition did not reflect circumstances present during coated tablet ingestion. Furthermore, the test excluded the impact of saliva on friction, which may have an impact on oral lubrication (Bongaerts et al., 2007b).

2.2.3.6 Implications of the findings

The main aim of this study was to develop an *in vitro* method to measure the slipperiness of tablet coatings with a potential to correlate the findings with sensory analysis. Method development demonstrated that the lubricant properties of dispersed coatings could be measured using thin film tribology and significant differences were observed dependent on the coating formulation. These findings suggest that different tablet coatings may provide

different levels of lubrication when placed in the wet oral environment, but this needs to be confirmed with *in vivo* testing.

Further, the same fluid produced different lubrication behaviour when the bottom surface was changed during testing, thus reinforcing the view that lubrication is based on the entire system, not only the fluid phase. Applying this principle to practice, it is likely therefore that the same tablet with the same coating may be perceived differently by different patients. For instance, people with dry mouth syndrome or rougher morphology of the tongue might require a coated tablet with higher slipperiness. This implies that when testing lubrication of the coatings *in vitro*, it would be valuable to mimic the most unfavourable conditions, i.e. not only the tongue of a healthy patient, but also that of a dry mouth. Similar, may be valid for lubrication testing *in vivo*.

Comparison of the two methods, surface and thin film tribology, suggest they have different potential applications. Testing coated tablets in their entirety is likely to yield results more comparable to the human perception of slipperiness but the sensitivity of thin film measurements to small differences in formulation make it of use in coating development.

2.2.4 Conclusions

Oral tribology is an emerging discipline for texture and mouthfeel studies. The rationale of using thin film tribology lies in the fact that it provides information on lubrication behaviour between oral surfaces which is one of the mechanisms dominating the perception of food texture. Interaction of a sample with the tongue, teeth and palate informs its surface properties – its roughness/smoothness, stickiness/slipperiness. Current literature provides a solid background to apply thin film tribology as a tool relating mouthfeel attributes (smoothness, roughness, and slipperiness) to lubrication properties of food samples. In this

chapter the potential to assess tablet coating slipperiness with thin film tribology was discussed.

Lubrication was evaluated in various experimental set-ups. It was found that besides viscosity and composition of the fluid, surface hydrophilicity and roughness played an important factor in lubrication. Hence, lubrication should be assessed as a system property. What is more, comparison of lubricant properties requires a set-up, which allows a well-defined Stribeck curve to be obtained. To achieve it, a pragmatic choice of testing conditions (e.g. surface) is required.

Finally, thin film tribology was found to detect small differences in the lubricant properties of dispersed tablet coating samples. The differences found in lubricant properties could be related to the tablet coating formulation. Hence, thin film tribology has the potential to be is a powerful tool to build a physically reasonable hypotheses for the friction or lubricating behaviour of dispersed tablet coatings in the mouth.

3 *In vitro* direct and indirect assessment of tablet texture and taste

Purpose of this chapter

This chapter applies instrumental methods to directly and indirectly assess tablet texture and taste. The former approach has a close link to the texture as perceived by humans. The latter focuses on fundamental physicochemical properties of tablets. A wide range of methods was used to understand which tablet properties might underlie or explain particular sensory attribute (e.g. if viscosity properties impact an attribute of stickiness).

3.1 Introduction

With the realisation that an oral medicines' palatability impacts its acceptance, increased attention has focussed on the evaluation of taste and texture. Both aspects have been recognised as a barrier to medicine administration in children and adults (Gee and Hagemann, 2007, Venables et al., 2015). The specific properties of oral medicine texture that affect the sensory perception are not clear. To know the basis underlying the textural attributes of a product, its fundamental properties need to be understood. By analogy with food sciences, if creaminess of yogurt is a desirable attribute then a food engineer would need to understand the formulation properties that enhance creaminess. Whereas, if the stickiness (tendency to adhere to a contact surface) of a pharmaceutical tablet is undesirable, the factors contributing to it must be analysed and understood.

The concept of texture can be considered as an interaction between human senses and the mechanical properties of product (Corey and Finney, 1970, cited in Szczesniak, 1973). In this sense, instrumental methods cannot measure it, but only relate a tested parameter to an

attribute perceived by a human. Nevertheless, instrumental methods widely complement the knowledge of texture and taste evaluation. Instrumental measures have a potential to (i) increase understanding of the fundamental mechanisms that cause sensory perception and (ii) build models to predict the sensory experience based on instrumental data. The texture of oral medicines encompasses a complex group of physical properties, hence an array of methods needs to be employed to explore the sensory properties of a product (Szczesniak, 2002). While perception of taste is based on chemical stimulation of taste buds; the intensity of taste depends on the concentration and type of stimulus. The evaluation of taste and/or taste-masking is an important aspect of the overall perception of the tablet. In this chapter, the texture and taste analysis of coated and uncoated tablets will be evaluated using the following approaches (as described in section 1.4.2):

- Fundamental – rheology, roughness, wetting properties;
- Empirical – adhesive properties;
- Imitative – drug release.

Roughness and adhesive properties can be classified as direct measures of texture, while others are indirect measures of texture. Drug release studies do not relate to the textural aspects of tablets, but measure of taste-masking efficiency of tablet coatings which influence taste perception.

3.2 Materials

In the work presented in this chapter two batches of tablets were used: oval T_A and round T_B, both prepared by a contracted manufacturer. The short description is given in Table 3.1. For full quantitative details on the composition refer to Chapter 2, methods section (Table 2.2).

Table 3.1 List of formulations used in the study.

Formulation	Sample description	Coating ingredients	Tablet core shape	Final coating level (w/w)*
T_A	Uncoated	-	oval	0%
T_ACoat-1	Standard commercial	Opadry® 03F mix (HPMC-based)	oval	3%
T_ACoat-2	Slippery commercial	Opadry® EZ Swallow white (HPMC-based + guar gum and MCT)	oval	3%
T_ACoat-3	Slippery commercial	Opadry® EZ Swallow white Opadry® EZ Swallow clear (HPMC-based + guar gum and MCT)	oval	3% + 1%
T_B	Uncoated	-	round	0%
T_BCoat-4	Standard reference	HPMC 5, glycerol	round	4%
T_BCoat-5	Lipid-based	Lubritab®, Capmul® MCM, HPMC 5, talc, titanium dioxide	round	4%
T_BCoat-6	Slippery	HPMC 5, xanthan gum, glycerol, talc, titanium dioxide	round	4%
T_BCoat-7	pH dependent	Eudragit EPO readymix, titanium dioxide	round	4%
T_BCoat-8	Insoluble – soluble polymer	HPMC 5, Surelease®, glycerol, talc, titanium dioxide	round	4%

*as declared by manufacturer
HPMC - hydroxypropyl methylcellulose
MCT – medium chain triglycerides

3.3 Methods

3.3.1 Rheology

The TA Discovery HR-2 Rheometer was used to measure the viscosity of dispersed coatings at concentration 5 mg/mL. A 40 mm parallel plate geometry was used with a 1 mm gap. Viscosity data was collected in six consecutive logarithmic sweeps at shear rates increasing and decreasing from 0.01 to 1000 s^{-1}. Testing temperature: 25°C; sample volume: 1.25 mL. Samples were analysed in quadruplicate. The following samples were measured: Coat-1_{dis} - Coat-$8_{dis,}$ (film coatings dispersed in distilled water, same as used in Chapter 2.2), distilled water and corn syrup.

3.3.2 Roughness

3.3.2.1 Interferometry – quantitative method

A white light interferometric microscope (MicroXAM, KLA Tencor, UK) was used to map and quantify the surface roughness (Sa) of tablets. Images were acquired using a 10X objective lens. For each sample, four 862 x 641 µm regions from the top side of a tablet were imaged. The data collected was processed and analysed using MapVUE AE software (version 2.27.1, KLA Tencor, UK). Image processing was performed to remove artefacts (noise and spikes) (Baryshev et al., 2013). Then, using the interpolate function, void pixels were filled in. Finally, polynomial plane correction was applied to account for tablet curvature.

Tablets were imaged dry and after a wetting treatment, which involved rinsing the tablet surface with 0.5 mL of water and drying it with compressed air before measurement.

3.3.2.2 Scanning Electron Microscopy (SEM) – qualitative method

Whole tablet samples as well as tablet cross-sections were used for SEM. Samples were mounted onto stubs with conductive carbon tape, and then platinum sputter coated for imaging. The surface topography was imaged using a Hitachi TM3030Plus benchtop SEM (Hitachi High Technologies, USA) in secondary electron mode with a beam voltage of 5 kV. Cross-section samples were studied at 15kV. Based on cross-section images, the average thickness of coatings was measured using Image J software. Coating thickness was measured at 10 locations across the longer edge of two tablets and averaged.

3.3.3 Wetting properties

Interfacial tension between tablet surface and water was measured using a Theta optical tensiometer (Biolin Scientific, Sweden). A drop of distilled water, 4 µL, was deposited on the flat surface of the tablet sample using a Hamilton syringe. The side-view profile of the water drop was recorded with a high-speed camera at 22 frames per second for 20 seconds. The images were analysed with a Young Laplace model using OneAttension software (Biolin Scientific, Sweden) to obtain the contact angle (CA, θ) values between tablet surface and drop. Measurements were performed in quadruplicate and the average reported.

Observation of the equilibrium state between the water droplet and tablet surface was not possible. The interaction of the tablet sample surface with the water (i.e. dissolution of coating or penetration of the droplet through the coating into the tablet) caused constant changes of CA value. Thus, CA values were compared at several time points for each tablet sample to track CA change in time.

3.3.4 Adhesive properties

The adhesive properties of coated and uncoated tablet samples was characterized using a TA.XT plus texture analyser (Stable Micro Systems Ltd, UK), equipped with a 5 kg load cell, a 0.635 cm diameter spherical stainless steel probe (P/0.25S) and a confectionery holder (Figure 3.1). The testing method was adapted from Scarpa et al. (2018). A tablet was immobilized in the holder and positioned under the probe. A 500 µL volume of distilled water was dispensed onto the tablet surface using a pipette. The probe was advanced vertically onto the sample at 1 mm/s until a 20 g compression force was reached. The compression was held for 1 second, and then the probe was withdrawn at 2 mm/s. The test was performed in quadruplicate (using a fresh tablet for each measurement). Further

parameters used in the test included: trigger force 5 g, room temperature. There was a lag time of 7 seconds between wetting the tablet and tack measurement, due to the measurement technique.

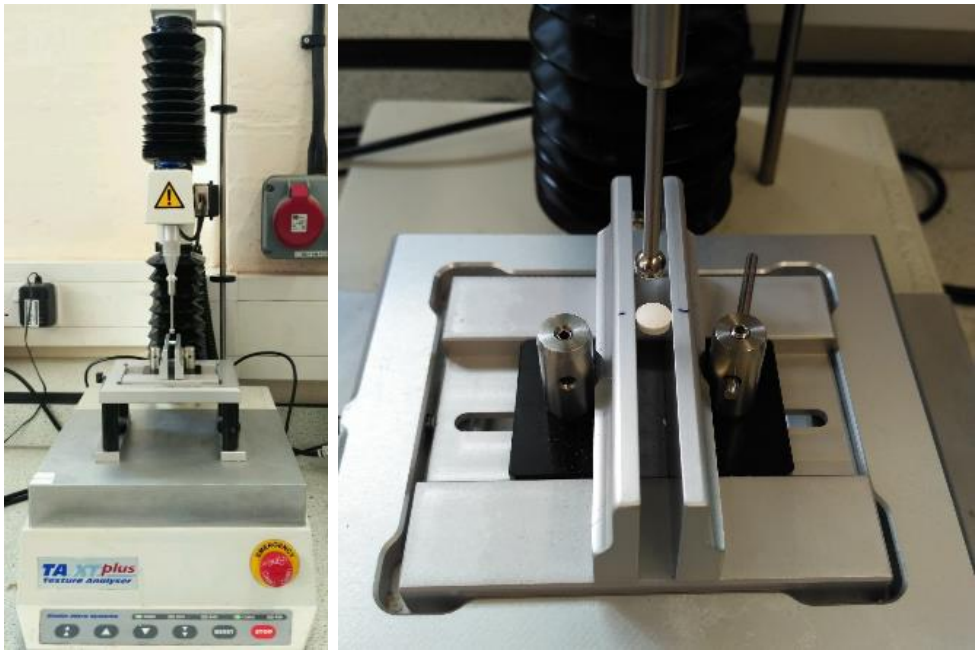


Figure 3.1 Texture analyser TA.XT plus (left); setting of a tablet sample in a confectionery holder and a spherical probe (right).

3.3.5 Drug release study

Dissolution studies were performed using a USP II tester with a small volume (100 mL) adapted vessel (Copley DIS 6000). T_A tablets did not contain any quinine sulfate therefore drug release was only performed on T_B and T_BCoat4–8 tablets. One tablet was added to 25 mL of distilled water, at 37°C, and stirred at 50 rpm. An aliquot of 1 mL was withdrawn after: 2, 5, 10, 15, 30, 45, 60 minutes, and replaced with 1 mL of fresh media. Dissolution was carried out in quadruplicate. Quinine sulfate release was quantified using HPLC.

HPLC analysis was performed using Agilent 12600 Infinity (Germany), and R18 column (XSelect® CSH™, diameter 4.6 mm x 150 mm, particle size 3.5 µm). Mobile phase 0.1M ammonium acetate:acetonitrile:methanol (50:10:40) (adjusted to pH 3 with perchloric acid), flow 1 mL/min, injection volume 50 µL, wavelength 330 nm, run-time 4 minutes. The system

was purged and equilibrated with mobile phase for 30 minutes before experiments. Calibration was conducted with a series of six quinine sulfate solutions (0 – 0.4 mg/mL) (prepared in triplicate). Quinine sulfate contains a natural impurity – dihydroquinine sulfate; when analysing the drug content, both compounds where taken into account.

3.4 Results

3.4.1 Rheology

Viscosity data from tested tablet samples is presented in Table 3.2. To allow comparison between samples, a 50 s^{-1}shear rate regarded as representative of within the oral cavity (Chapter 1.4.1.2), was used as a benchmark. The highest viscosity was observed for samples containing thickening polymers (guar gum – Coat-2_{dis}, Coat-3_{dis}, or xanthan gum – Coat-6_{dis}). The thinnest dispersions were lipid-based (Coat-6_{dis}) and insoluble – soluble polymer formulation (Coat-8_{dis}). Additionally, for each sample the minimum viscosity at high shear rates (≥100 s^{-1}) is given in Table 3.2 (η_{min}), as these values are relevant for tribological testing (refer to Chapter 2.2).

Table 3.2 Viscosity of dispersed coating formulations and reference liquids at 25°C at a range of shear rates.

Formulation	Sample description	Concentration	η_0 [mPa s]	η_{50} [mPa s]	η_{1000} [mPa s]	η_{min} [mPa s]
Coat-1_{dis}	Basic commercial	5 mg/mL	1559	1.20	2.80	1.13
Coat-2_{dis}	Slippery commercial	5 mg/mL	337	1.70	3.25	1.67
Coat-3_{dis}	Slippery commercial	5 mg/mL	670	1.82	3.02	1.60
Coat-4_{dis}	Basic reference	5 mg/mL	1109	1.17	2.65	1.11
Coat-5_{dis}	Lipid-based	5 mg/mL	605	0.83	2.33	0.82
Coat-6_{dis}	Slippery	5 mg/mL	1413	1.78	3.05	1.59
Coat-7_{dis}	pH dependent	5 mg/mL	526	1.05	2.25	0.98
Coat-8_{dis}	Insoluble – soluble polymer	5 mg/mL	958	0.80	2.40	0.81
Distilled water	Reference	-	202	0.76	2.52	0.76
Corn syrup	Reference	90%	588	613.9	407.6	407.6

3.4.2 Roughness

The roughness of samples was quantified using an interferometer (Table 3.3) and visualised using SEM imaging (Table 3.4). For the T_A batch, all dry coated tablets were smoother (Sa <1.8 µm) than the dry uncoated ones (Sa = 5.25 µm). These results were further reinforced by SEM imaging which, when compared to the uncoated tablet core, showed the coating covered core surface cracks and unevenness (Table 3.4). Whereas for the T_B batch, differences between coated and uncoated tablets were less pronounced. One explanation is the smoother surface of the uncoated tablet core. Another, is the patchy surface of the coatings which contained HMPC (T_BCoat-4, -6, -8), which may be attributed to suboptimal coating conditions (e.g. flow rate, spraying air pressure and temperature) (Ruotsalainen et al., 2003).

Roughness measurement for both dry and wetted then dried samples permitted a better description of the interaction of the tablet surface with water. Uncoated tablets T_A and T_B absorbed the water which resulted in a significant increase in Sa (Table 3.3, Dry vs. wetted & dried tablets). The surfaces of T_ACoat-1, T_ACoat-3, T_BCoat-6, and T_BCoat-8 were smoother after being wetted and dried (Figure 3.2). These were the coatings, which underwent partial dissolution, but still protected the core from contact with water. In contrast, T_BCoat-7 sample absorbed the water with no dissolution and so showed increased Sa after wetting. Fast water penetration into this sample can be attributed to cracks on the coating surface (visible on SEM image (Table 3.4)) which allowed water permeation.

Table 3.3 Surface roughness, Sa, interferometer measurements of the dry and wet tablet surface with x10 objective lens

	Surface Roughness, Sa (µm)		**t-test (p value)**	
Sample	Dry	Wetted & dried	Dry vs. wetted & dried	Dry uncoated vs. dry coated
T_A	5.25 ± 0.63	12.8 ± 1.96	<0.01	-
T_ACoat-1	1.55 ± 0.13	0.38 ± 0.04	<0.01	<0.001
T_ACoat-2	1.72 ± 0.47	2.34 ± 0.40	0.12	<0.001
T_ACoat-3	1.41 ± 0.19	0.73 ± 0.07	<0.01	<0.001
T_B	2.67 ± 0.63	11.01 ± 2.64	<0.01	-
T_BCoat-4	3.88 ± 0.36	3.04 ± 0.85	0.14	<0.05
T_BCoat-5	1.43 ± 0.19	2.48 ± 0.78	0.07	<0.05
T_BCoat-6	3.1 ± 0.39	1.94 ± 0.30	<0.01	0.30
T_BCoat-7	2.19 ± 0.13	7.29 ± 1.02	<0.01	0.22
T_BCoat-8	3.93 ± 0.39	2.69 ± 0.82	<0.05	<0.05

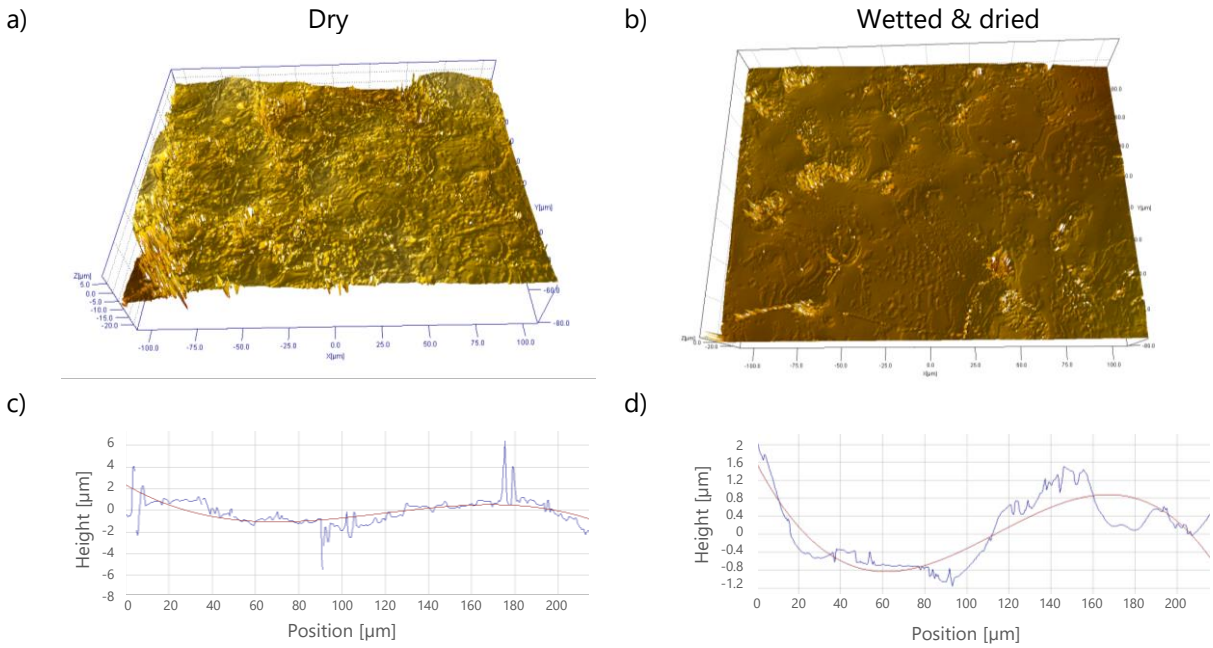
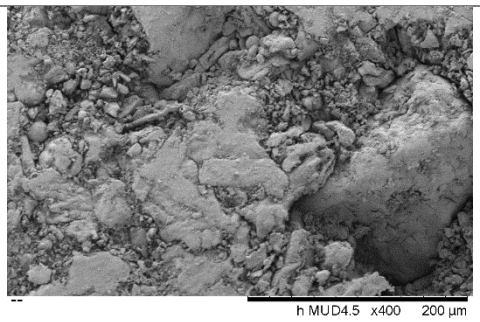
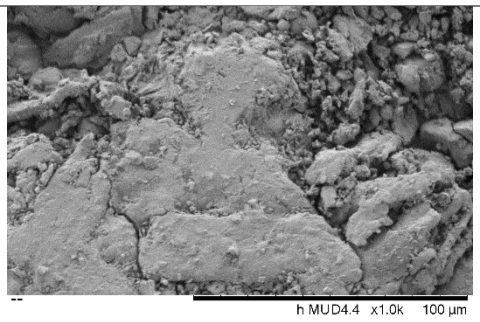
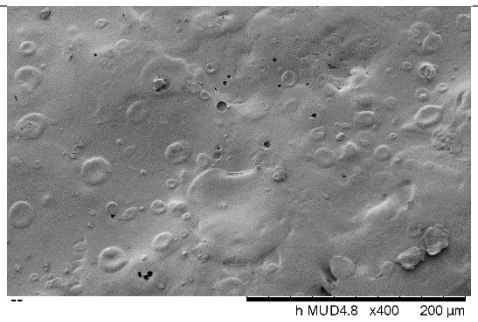
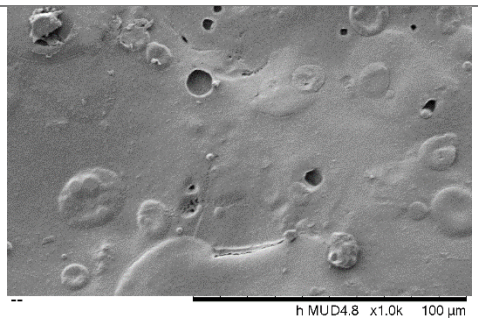
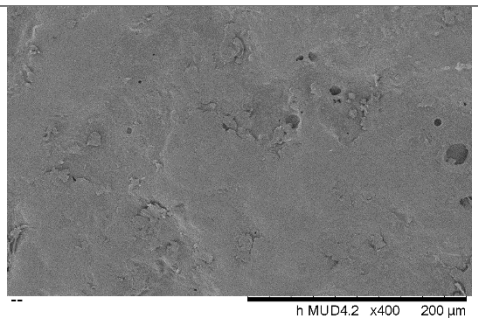
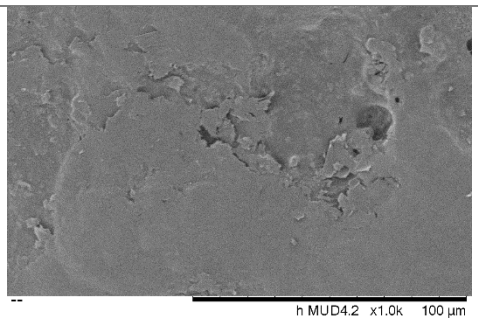
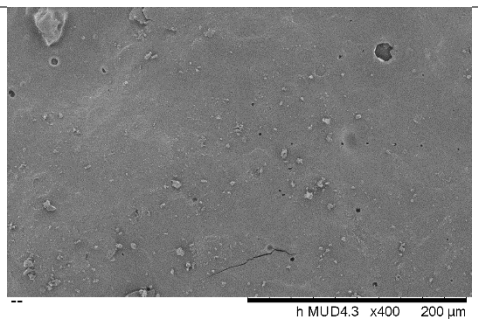
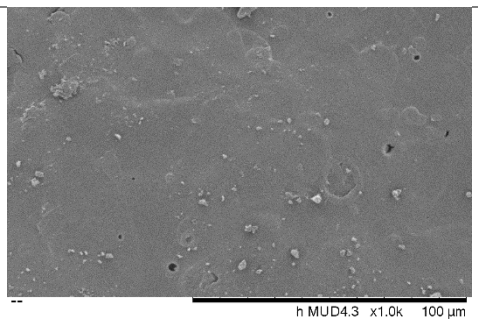
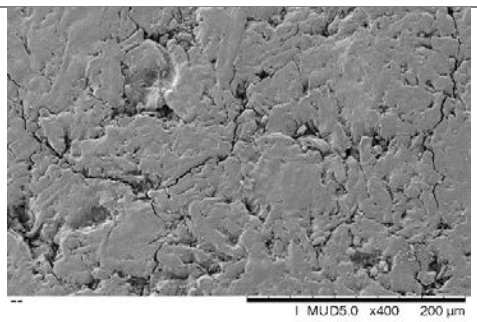
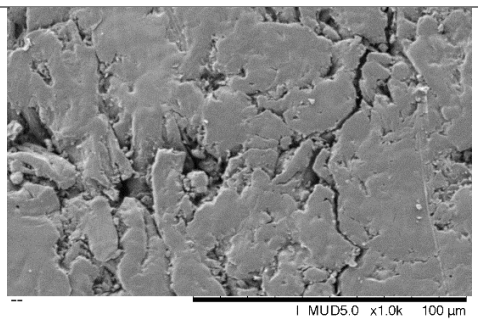
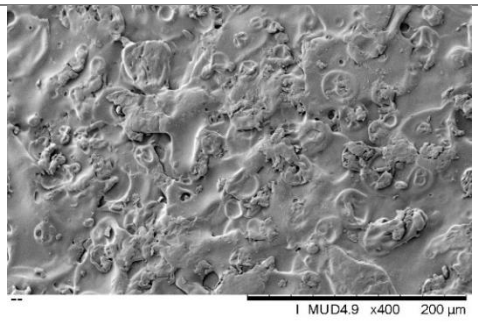
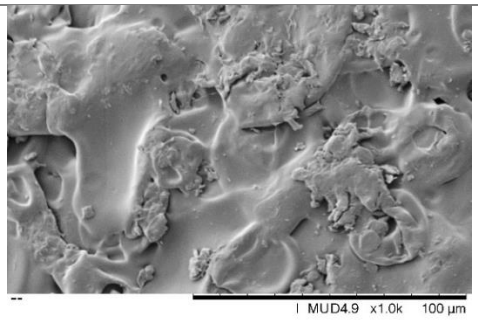
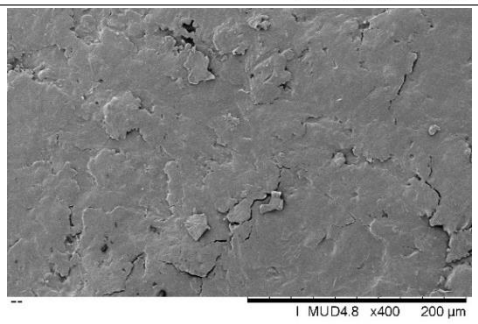
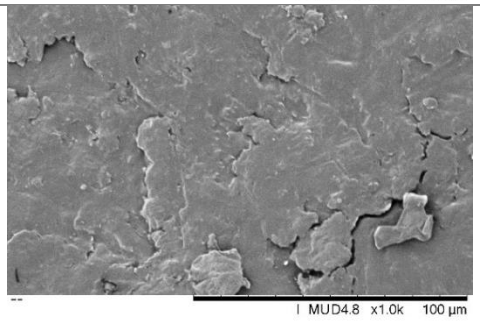
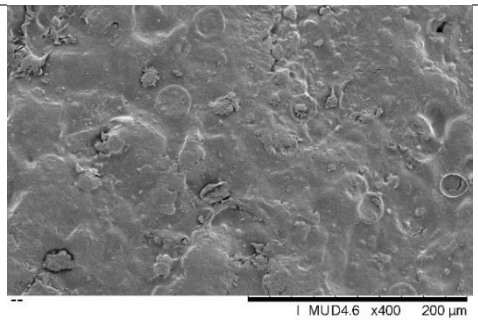
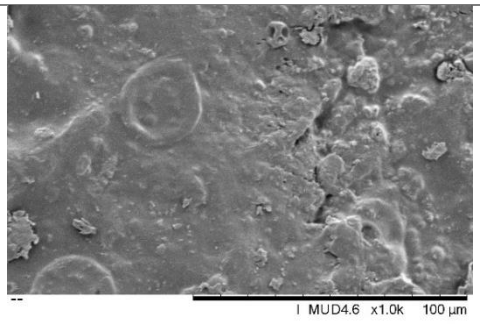
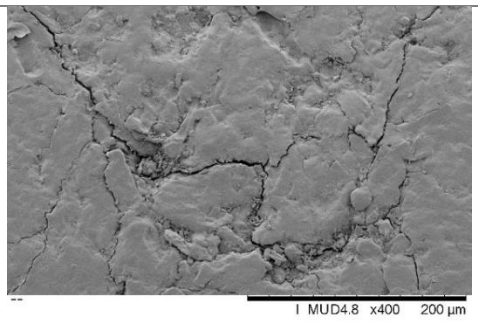
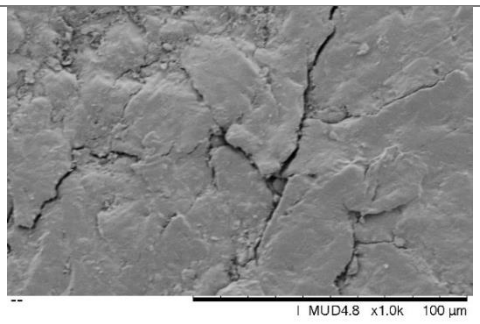
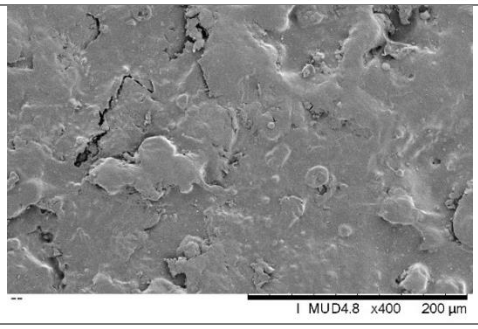
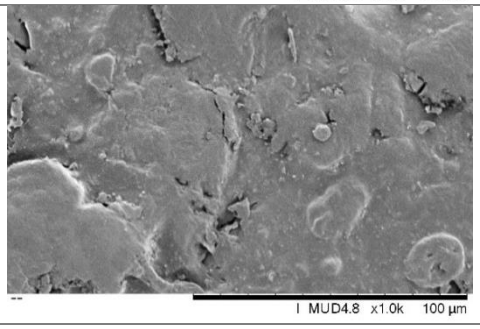


Figure 3.2 Example of 3D map of T_ACoat-3 surface sample: dry (a), wetted & dried (b) tablet; cross-section profile of T_ACoat-3 surface roughness: dry (c), wetted & dried (d) tablet (note different Y-axis).

Table 3.4 SEM images of coated and uncoated tablets.

Sample / Magnification	x400	x1000
T_A		
T_ACoat-1		
T_ACoat-2		
T_ACoat-3		
T_B		

Sample / Magnification	x400	x1000
T_BCoat-4		
T_BCoat-5		
T_BCoat-6		
T_BCoat-7		
T_BCoat-8		

SEM images of tablet cross-sections revealed that the coating on the T_A tablet cores was almost 10 times thicker than on the T_B ones (Table 3.5, Figure 3.3). This finding does not support a 4% w/w coating level for batch T_B as requested from the contract manufacturer (i.e. the coating on T_B cores was thinner than expected). The study design was dependent on coating level and hence an additional tablet batch (T_C – tablets) was prepared and coated in-house to the required level and cross-sectional images taken. A coating thickness of greater than 30 µm for all T_C coated tablets, further supported the conclusion that batch T_B had a thinner coating than expected (see further discussion in section 3.5.1).

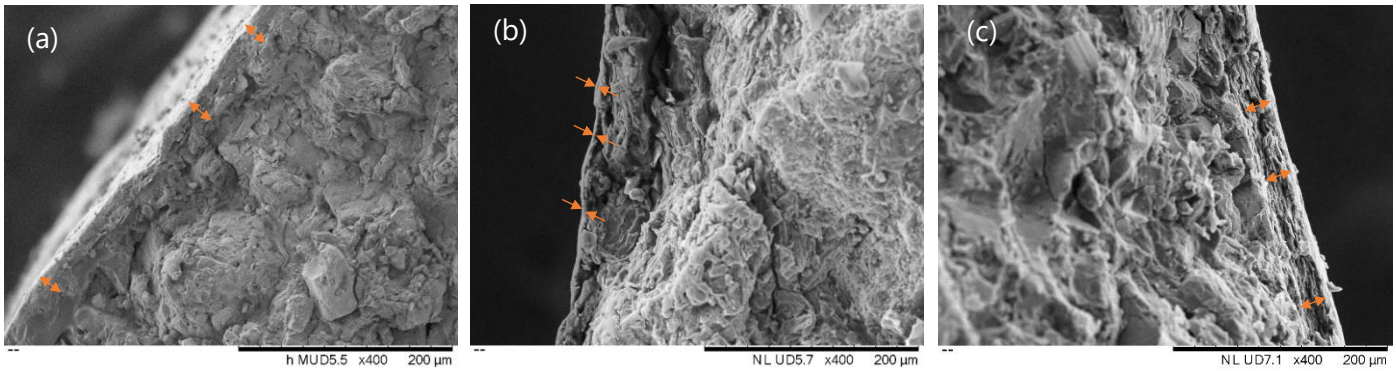


Figure 3.3 SEM image of tablet cross-section: (a) T_ACoat-2, (b) T_BCoat-6, (c) T_CCoat-5. Arrows indicate points for coating thickness measurement.

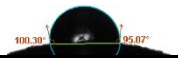
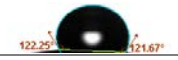
Table 3.5 Coating thickness of coated T_A and T_B tablets measured using Image J based on SEM images at magnification x400.

Sample	Coating Thickness (µm)
T_ACoat-1	31.0 ± 5.0
T_ACoat-2	22.4 ± 2.5
T_ACoat-3	31.4 ± 3.8
T_BCoat-4	3.6 ± 0.8
T_BCoat-5	3.3 ± 0.5
T_BCoat-6	3.6 ± 1.1
T_BCoat-7	2.9 ± 0.5
T_BCoat-8	2.6 ± 0.6

3.4.3 Wetting properties

Contact angle (CA) measurements showed a change in the CA, between a drop of water and tablet surface, with time. The magnitude of this change was dependent on the tablet core as well as the coating formulation, as illustrated in Table 3.6. Uncoated tablets T_A and T_B displayed very different wetting properties. Deposition of a drop onto T_A led to complete wetting and penetration through the coating into the tablet core within less than 1 second. In contrast, the T_B surface was more hydrophilic (initial CA above 90°) and showed slower drop penetration. The drop readily penetrated uncoated tablets, but coated tablets had a higher resistance to wetting, i.e. could sustain a drop on their surface for longer. Samples T_ACoat-1, -2, -3 and T_BCoat-5, -6 maintained the drop on the surface without allowing penetration into the tablet core for >10 seconds. Other tablet samples showed a faster decrease of CA indicating faster penetration. As expected, based on coating formulation, T_BCoat-5 and -7 showed highest initial CA values relating to the hydrophobic nature the coating ingredients.

Table 3.6 Changes of CA values over time for tablet samples (note the different time frame for uncoated/coated tablets). CA values represent the average of four measurements, images show the sequence of a single measurement.

Uncoated	**0 s**	**0.5 s**	**1 s**	**1.5 s**	**2 s**
T_A	29°	16°	0°	0°	0°
					
T_B	100°	85°	75°	70°	65°
					
Coated	**0 s**	**1 s**	**5 s**	**10 s**	**15 s**
T_ACoat-1	57°	57°	55°	54°	54°
					
T_ACoat-2	68°	63°	59°	57°	56°
					
T_ACoat-3	56°	49°	47°	46°	46°
					
T_BCoat-4	90°	84°	78°	70°	62°
					
T_BCoat-5	113°	115°	111°	105°	96°
					
T_BCoat-6	81°	80°	78°	75°	72°
					
T_BCoat-7	138°	126°	99°	72°	65°
T_BCoat-8	97°	89°	74°	51°	35°

3.4.4 Adhesive properties

The adhesive properties (i.e. tack, stringiness, and work of adhesion) of the coated/uncoated tablets were measured in wet conditions (tablet wetted with 500 µL of water). The test aimed to mimic the situation when a tablet is taken with water. In contact with water the coating partially dissolves which affects the adhesive properties.

Results for batch T_A revealed that tablet coatings have a significant impact on the adhesive properties of the tablet surface (Figure 3.4a). Each coated sample displayed lower adhesive properties than the uncoated tablet for all parameters evaluated. As expected, T_ACoat-2 and -3 showed similar results, due to the same composition of these coating formulations. Both these coatings yielded lower values than T_ACoat-1.

In contrast, the samples from batch T_B revealed that the coating had a negligible effect on adhesive properties when compared with the uncoated tablet (Figure 3.4b). The only exception was sample T_BCoat-6 which was more adhesive based on AUC values.

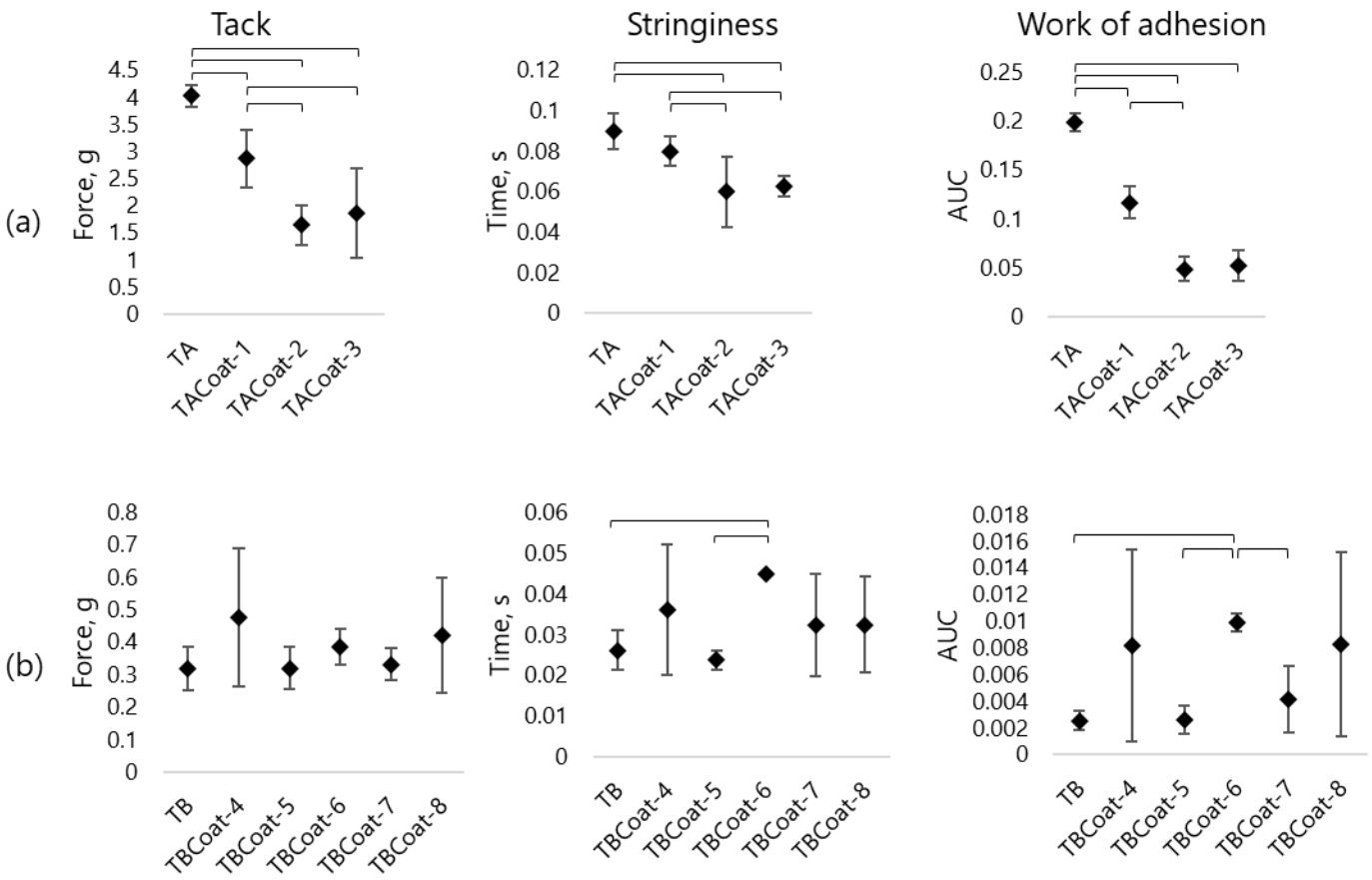


Figure 3.4 Tack, stringiness, and work of adhesion for tablet samples, (a) T_A batch and (b) T_B batch, brackets indicate significant difference (t-test, $p<0.05$), n=4, error bars represent standard deviation.

3.4.5 Drug release study

Drug release was calculated based on the area of HPLC peaks using a calibration curve (f(x) = 31887x + 124.95; R^2 = 0.9996). An example chromatogram with peaks for quinine sulfate and dihydroquinine sulfate is shown in Figure 3.5.

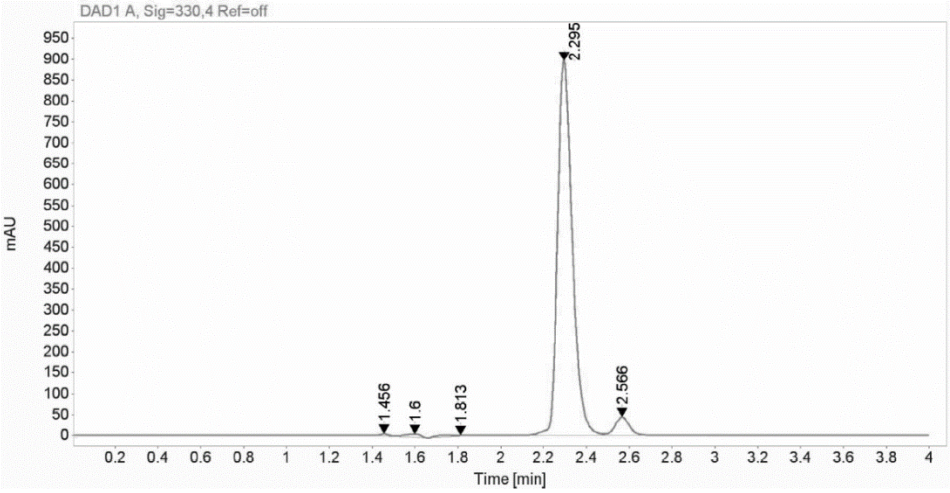


Figure 3.5 HPLC chromatogram of quinine sulfate (retention time, RT = 2.295 s) and dihydroquinine sulfate (RT = 2.566 s); sample T_BCoat-6, sampling time 15 minutes.

Figure 3.6 presents drug release in distilled water. The release from all formulations was very similar, suggesting coatings had a negligible effect. Only T_BCoat-4 showed slight delay in the release.

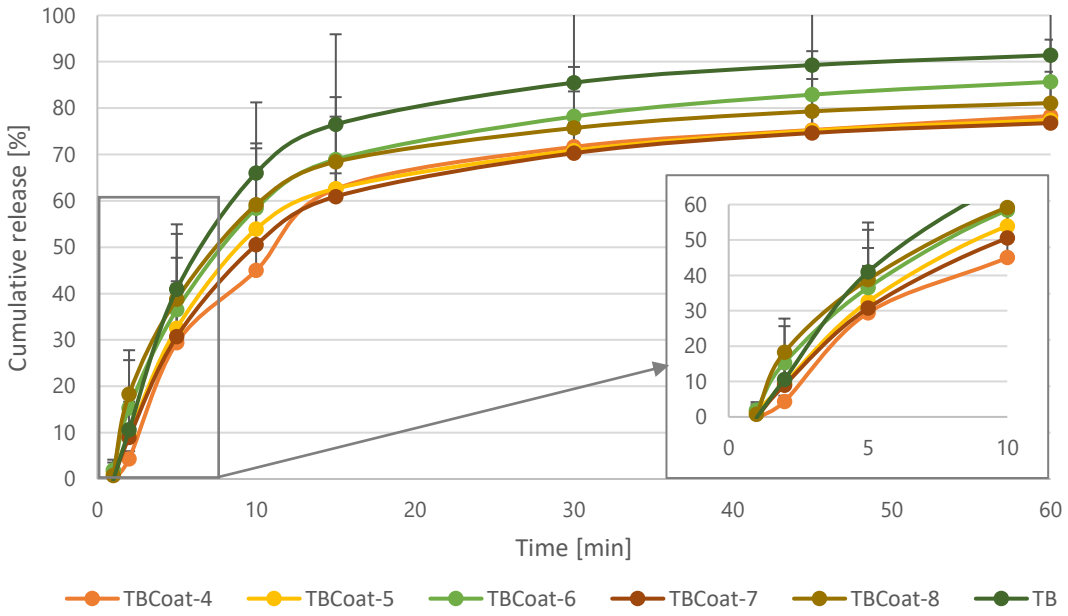


Figure 3.6 Cumulative drug release (quinine sulfate and dihydroquinine sulfate) for coated and uncoated tablets (n = 4); error bars represent standard deviation.

3.5 Discussion

3.5.1 Significance of the coating thickness

The thickness of the tablet coating layer is critical for its intended function. Typically, the thicker the coating, the lower its permeability. Among other properties, this can result in slower drug release or better taste-masking (Sauer and McGinity, 2009, Joshi and Petereit, 2013).

Cross-section SEM imaging of tablets enabled direct measurement of the thickness of the coating layer (Table 3.5). It was expected that batches T_A and T_B, would have similar coating thicknesses, as both tablets had comparative coating level, 3-4% weight gain, as reported by the manufacturer. However, the thickness of coatings for T_B batch was lower than expected. Different coating thicknesses for T_A and T_B prevented direct comparison between the tablet batches. Moreover, the thin coating layer was insufficient to form a complete barrier on

the core for batch T_B. The impact of coating thickness on specific measurements is discussed in next sections, where relevant.

The measurement of coating thickness is crucial for quality control, yet not all the methods used are fully reliable. Currently, the most often used measurement of coating level involves calculating the increase in mass of the coated batch (weight gain) at the end of the coating process (this method was also used in this thesis). Calculation of weight gain can be imprecise when several parameters are not recognised, namely the tablet moisture content prior to and after the coating process, moisture loss during coating, and mechanical abrasion of the tablets during the coating process. In addition, using this method the determination of the end of coating process, i.e. when the intended coating level is achieved, is difficult. As presented in this thesis, SEM imaging is a reliable method of coating thickness measurement, but it has low throughput, is time-consuming and not feasible as a method of batch-to-batch quality control.

The most practical method is in-line coating thickness measurement. For example, terahertz pulsed imaging (reliable > 50 μm coating thickness), optical coherence tomography (> 20 μm) (Lin et al., 2017), near-infrared spectroscopy (Römer et al., 2008) or visual inspection by high-speed camera (reliable < 20 μm) (Podrekar et al., 2019). Yet, these methods are still very new and not widely employed. All in all, whichever method is employed, the optimal thickness of the coating needs to be ensured as it can affect its functionality.

3.5.2 Coating properties relevant for taste-masking

One of the functionalities that coatings may provide is taste-masking, which is achieved by creating physical barrier between the tablet core containing unpalatable API and taste buds.

To confirm taste-masking properties, dissolution testing was performed to show the lag time in drug release, typically <10% release in 5 minutes (Siewert et al., 2003). Although, it may be argued that the amount of drug release should relate to the taste threshold for each API (Gittings et al., 2014).

In this thesis, the dissolution method used to assess quinine release from tablets was limited in its ability to mimic the oral environment, e.g. non-continuous sampling time and large dissolution volume (25 mL). The test revealed fast dissolution and only marginal differences in release between coated and uncoated tablets (T_B). The marginal differences in release can be attributed to limitations of the dissolution test. Yet, the fast quinine release was a consequence of thin coating (layer thickness of ~3 µm, as visualized by SEM) and the high solubility of quinine as a model drug. Coating thickness is crucial parameter influencing taste-masking functionality. As shown by Pearnchob et al. (2003) the thicker the coating layer, the longer the delay in taste onset (tested *in vivo*). A reliable coating barrier requires a minimum thickness of 10 µm (Joshi and Petereit, 2013). Based on coating thickness and dissolution data, none of the coatings on T_B tablets achieved effective taste-masking. Presumably, the tablets with thicker coating (T_C) would show a lag in drug release but this was not tested as these tablets were not used later in the *in vivo* studies and hence were not a batch of interest.

Along with coating thickness, measuring the contact angle of a water drop on the coating over time can indirectly indicate its taste-masking properties. The time needed for the drop to penetrate into the core is observed, which indirectly provides a measure of coating durability in wet conditions. The coating provides a physical barrier which isolates drug molecules in the tablet core from the taste buds on the tongue. If the drop penetrates

quickly, it suggests that the coating failed to provide this physical barrier sufficient for taste-masking.

Coating properties affect the penetration and rate of the movement of water molecules through the film (Joshi and Petereit, 2013). A hydrophobic coating will impede water penetration into a tablet. A previous study found that inclusion of hydrophobic molecules in a tablet coating delayed drug release (Hiew et al., 2019). Although their study used sustained release coatings, similar behaviour is expected for immediate release coatings. Thus, hydrophobic coatings, due to slower dissolution, could provide a better physical barrier with improved taste-masking properties.

The discussion above is only valid when optimal coating thickness is achieved. Based on affinity to water, the most hydrophobic coatings used in this thesis (T_B-Coat-5 and -7) should sustain the water drop on their surface the longest. Yet, this was not observed. As shown in Table 3.6, the coated tablet T_A-Coat-1–3 sustained the water droplets on their surface, while for samples T_B-Coat-4–8 the droplet quickly penetrated into the tablet core. The effect was clearly associated with the difference in coating thickness (~30 µm vs. ~3 µm). This explains why most hydrophobic coatings (T_B-Coat-5 and -7) did not sustain a drop on their surface. Additionally, the faster water penetration for T_B-Coat-7 and -8 was attributed to the cracks visible by SEM on the coating surface (Table 3.4). The coatings, which did not present with cracks visible by SEM, were characterised by slower water absorption.

The findings discussed show that a simple test like measuring the wettability of coatings can provide information valuable for a formulator. Resistance of coatings to penetration of a drop of water can be used as an indicator of its quality, e.g. completeness of the coating cover and lack of cracks. Additionally, the evaluation of coating hydrophobicity seems

a promising as a way to control the rate of drug dissolution, and hence taste-masking, in the oral cavity.

3.5.3 Coating properties relevant for oral perception and swallowing

3.5.3.1 Roughness

Given the tongue's low detection threshold for rough surfaces (Sa 0.2 μm, (Linne and Simons, 2017)), surface roughness is highly likely to be a factor which influences the acceptance and 'liking' of a tablet. The roughness of all tablet samples tested in this thesis exceeded these Sa values, indicating that humans might detect differences in roughness between the different tablets. In the mouth, tablets are wetted with saliva and water hence the Sa value of a wetted sample is likely to be more relevant for oral perception. Wetting uncoated tablets increased Sa due to water absorption, whereas some of the coated tablets (e.g. T_ACoat-1) displayed a smoother surface after wetting (Table 3.3). This smoothing effect was attributed to polymer dissolution, which evened the rough surface of the dry tablet (visible as patches on SEM images (Table 3.4)).

3.5.3.2 Adhesive properties

Tablet stickiness can be desirable when a buccal tablet intended to adhere to oral mucosa is formulated. Yet, if a tablet is intended to be swallowed, stickiness can impede oesophageal transport or even cause tablet lodging (McCargar et al., 2001, Perkins et al., 2001). Two mechanisms of unintended tablet adhesion to oro-oesophageal surfaces are known. Uncoated samples tend to absorb the water which leads to dehydration of oral mucosa and tablet sticking. While for coated tablets, a partial dissolution of coating can cause the formation of a concentrated gel, which, if sticky, causes tablet adhesion to the mucosa

(Reynolds, 1996, in McCargar et al., 2001). Application of a non-sticky coating can prevent both.

Several factors contribute to product stickiness, among others: presence of water, product composition and viscosity (Adhikari et al., 2001). Tablets, when ingested, become wet in the mouth. Therefore, their adhesive properties should be assessed in wet conditions. In this chapter the adhesive properties of a wet coating were measured using a texture analyser. A similar method to those previously reported was used to assess the stickiness of different oral dosage forms – orally dispersible films and mucoadhesive tablets (Hall et al., 2011, Scarpa et al., 2018).

The adhesive properties for the two batches of tablets tested (T_A and T_B) are not directly comparable (see different Y scales, Figure 3.4). In the main, this is due to differences in coating thickness between the batches. As discussed previously, the coatings for the T_B batch were very thin (Table 3.5) and thus did not provide a good physical barrier from the core (observed by SEM and also as a quick absorption of water droplet deposited on the surface (Table 3.6)). When tablets were wetted before measuring adhesive properties, there was simply more coating material on T_A than T_B tablets, which could interact with water and create a sticky dispersion on the surface. Where thicker coating was present, a more viscous dispersion on the tablet surface was created, and thus the higher tablet stickiness was recorded (Figure 3.4).

Regardless of coating thickness, the results presented in this thesis indicate that the adhesive properties of tablet coatings are formulation related. For example, formulation T_ACoat-1, showed the highest tack from all T_A coated tablets (Figure 3.4). This was due to the fact that T_ACoat-1 was based solely on HPMC polymer, which is known to have a sticky, adhesive

nature (Washington, 2001). Whereas, the samples T_ACoat-2 and -3, composed of HPMC and MCT had significantly lower tack. This effect was attributed to MCT, which as a lipid, has the capability to reduce surface stickiness (Debeaufort and Voilley, 2009). In a similar manner, a lipid-based sample from batch T_B (T_BCoat-5) showed the lowest adhesive properties.

It is known that sample viscosity can cause stickiness (Adhikari et al., 2001). Based on the results presented in this chapter, more viscous coatings had higher stringiness, a greater AUC and are, therefore, likely to be perceived as more sticky (Table 3.2, Figure 3.4). Yet, viscosity is not the only factor that affects adhesiveness, its effects can be mitigated by presence of lipid triglycerides, e.g. in the coating formulations T_ACoat-2 and -3 containing MCT.

3.5.3.3 Wetting properties

The contact angle between tablet and water provides information about the wetting properties of the surface. A surface with a low contact angle is easily wetted (i.e. it is hydrophilic). The wetting properties of a tablet surface are likely to influence tablet behaviour in the oral environment and during swallowing. This links back to the thin film tribology measurements described in Chapter 2.2, where the more hydrophilic surfaces became slippery at lower speeds than hydrophobic surfaces (i.e. showed shift of Stribeck curve in the mixed regime towards lower speeds). On the other hand, when whole tablets were tested (Chapter 2.1), the wetting properties were not the main determinant of friction. These findings seem contradictory but can be explained by different mechanisms of lubrication. For Stribeck curve measurement, hydrophilicity aids surface wetting and does not affect the value of friction. For tablet friction testing, affinity to water was not the main factor influencing the COF value, rather, it was the composition of lubricant – e.g. presence of lipids.

What this means in practise, is that the hydrophilicity of the oro-oesophageal surfaces would aid tablet passage, but the wetting properties of the coating may not be key to predicting how easy it is to swallow a tablet. Further observation showed fast penetration of the water drop for uncoated tablets and some coated tablets from batch (T_B). This suggests that in physiological conditions these tablets may dry the oral/oesophageal surfaces thus preventing an easy swallow and potentially causing discomfort, particularly for patients with an already dry mouth.

3.5.4 Reasons for development of instrumental methods

The exploration of tablet samples described in this chapter was aimed at widening the known spectrum of texture attributes relating to the perception of coatings. In particular, the roughness, adhesive and wetting properties of tablets were evaluated, and significant differences were found. For example, surface roughness differed between coated and uncoated samples, and coating formulation affected adhesive properties of the tablet. Providing that human senses are usually more sensitive to textures than an instrument, it may be hypothesised that a sensory evaluation would also detect these differences.

Instrumental measurement of texture brings a benefit of fast, low cost and reproducible testing. Also, due to ethical considerations instrumental testing are favoured as a screening method, which can reduce number of samples used in human testing.

Literature provides examples where early *in vitro* testing has allowed formulation of a product with improved sensory attributes for the benefit of patients. One example is the development of a commercial coating which facilitates swallowing tablets (Opadry® EZ Swallow, Colorcon). *In vitro* testing which related to its perceived slipperiness were used as a means of choosing a formulation with the most potential to be slippery in humans (To et

al., 2017). A different example is that of thickeners for patients with dysphagia. Thickeners are a food product with the special medical purpose of thickening fluids for patients with dysphagia to facilitate swallowing of the fluid. Therefore, the rheological properties of potential thickeners should to be analysed to provide a functional product (Torres et al., 2019).

Any instrumental method used to assess a product texture should be validated and correlated with human sensory evaluation to be applicable in practice. Where a correlation is found one can deduce what is actually perceived in the mouth and/or how to design a product with desired qualities. Correlating *in vivo* and *in vitro* methods of texture measurement is challenging. One reason is the poor definition of what is measured by instrumental empirical methods. Besides that, instrumental devices measure only some aspects of what is perceived by all senses when assessing texture. Ultimately, only a human can perceive and integrate the overall sensory experience.

The history of *in vitro* taste-masking assessment of ODFS is a good example of how challenging creating an instrumental method can be. For this purpose multiple methods have been already used, an extensive review was published by Gittings et al. (2014), and new methods are continuously emerging (Keating et al., 2018, Ali et al., 2019). The effort of many researchers on development process illustrates that instrumental methods are highly useful for formulator but challenging to create.

3.6 Conclusions

In this chapter several instrumental methods were used to directly and indirectly assess tablet and coated tablets' texture and taste. The measurements were able to discriminate between differences in properties like roughness, stickiness, and wettability. The presence

and type of coating affected all of these properties. In general, compared with uncoated tablets, the coated tablet surfaces were smoother and had higher resistance to wetting, i.e. could sustain a drop of water rather than let it penetrate into the core. These characteristics could have a positive effect on oral perception and swallowing. A tablet which absorbs water is more likely to lodge during oro-oesophageal passage and the adhesive properties of a coating are also likely to impact ease of tablet swallowing. The findings in this thesis related particular coating characteristics with higher stickiness – coating thickness and coating viscosity. While the presence of lipids was associated with lower stickiness. Coating thickness was found to be crucial to the interpretation of data. In particular, low coating thickness explained why coatings on quinine tablets (T_B) failed to provide a sufficient taste-masking effect. Ensuring adequate coating thickness in a reliable way should form a part of the manufacturing process.

The instrumental methods used in this chapter increased understanding of the tablet properties that might be related to oral perception and swallowing. Ultimately, all methods should be correlated with sensory evaluation performed with human subjects. The reader is referred to Chapter 6 to find out how the findings described in this chapter relate to human data.

4 Ease of swallowing and sensory evaluation of large tablets in adults

The work described in this chapter has been previously published:

Hofmanová, J. K., Rajabi-Siahboomi, A., Haque, S., Mason, J., Teckoe, J., To, D. and Batchelor, H. K. (2019) 'Developing methodology to evaluate the oral sensory features of pharmaceutical tablet coatings', *International Journal of Pharmaceutics*, 562, pp. 212-217.

4.1 Introduction

Consideration of patient acceptability of medicines is fundamental in the development of pharmaceutical dosage forms (Liu et al., 2014). For any oral formulation, ease of swallowing is an important determinant of patient acceptability both in children and adults. It is affected by both the medicinal product's features (e.g. dosage size, shape, slipperiness of the coating), and the patient's ability (physiological and/or psychological) to swallow (EMA, 2017b). This chapter explores the effect of coatings on the ease of swallowing tablets.

Application of a film layer coating onto a tablet can improve the ease of swallowing in two ways. Firstly, by inhibiting disintegration of the tablet in the mouth, as a coating assists swallowing by keeping the tablet intact. Secondly, the film layer can enhance the gliding properties of the tablet surface during swallowing i.e. provide a slippery layer within the oral cavity to aid swallowing (Mahdi and Maraie, 2015). Multiple studies have confirmed that coating an OSDF can improve the swallowing experience in human volunteers (Uloza et al., 2010, El Edelbi et al., 2015, Mahdi and Maraie, 2015).

The palatability of an OSDF is mainly affected by taste, texture and mouthfeel (Schiele et al., 2013, Fields et al., 2015, Liu et al., 2016a). An unpleasant taste is known to reduce patient

adherence in paediatric (Venables et al., 2015) and adult (Schiele et al., 2013) populations. Similarily, a feeling of roughness negatively correlates with overall palatability of orally dispersible tablets (Kimura et al., 2015). Yet, there is limited data available on which texture/mouthfeel attributes have the largest impact on the acceptance of OSDF, in particular conventional tablets.

The study presented in this chapter used a crossover, single centre design to assess the ease of swallowing and sensory perception of the mouthfeel of large placebo tablets in healthy adults. The main assessment tool for this study was a visual analogue scale (VAS) used for previous clinical studies involving OSDF (Kimura et al., 2015, Hayakawa et al., 2016). VAS provides continuous data suitable for statistical analysis and enables detection of small differences between samples (Villanueva et al., 2005). Additionally, VAS data allows exploration of the relationships between mouthfeel attributes and overall hedonic judgement (Lopez et al., 2016). Data collected in this study will inform the development of coatings which optimise acceptability of tablets.

4.2 Aims of the study

The aim of this study was to investigate the ease of swallowing and oral sensory properties of tablet coatings applied to placebo tablets in comparison to an uncoated tablet.

Primary aims

1) Identify the ease of swallowing of tablets with a range of coatings compared to uncoated tablets.

2) Evaluate the attributes of mouthfeel and palatability of tablets with a range of coatings compared to uncoated tablets.

Secondary aims

1) Examine the influence of the coating on time to swallow and amount of water used to swallow tablets.

2) Identify whether there is a correlation between a participant's history of tablet swallowing difficulties and ease of swallowing coated and uncoated tablets.

3) Investigate which coating formulation factors influence the acceptance (and preference) of the tablets.

4.3 Materials and methodology

4.3.1 Design

A cross-over single centre study design was used to investigate the oral perception of placebo tablets with commercial coatings in comparison to uncoated placebo tablets. The ease of swallowing and palatability ratings of the randomised tablets were assessed by healthy adult volunteers using visual analogue scales (VAS).

This study was financially supported by Colorcon and their coatings were evaluated within the study.

4.3.2 Ethical approval

Ethical approval for the study was obtained from the Ethical Review Committee of the University of Birmingham (ERN_17-0883 (17-1074); RG_17-152).

4.3.3 Participants

Adults between 18 and 75 years were recruited to the study. The number of participants required was determined on the basis of the effect size needed to find a difference between two tablet scores on the VAS. To detect a 10 mm point difference on the VAS in a one-tail test ($p<0.05$) with power = 0.8, the number of participants required would be 38.

Participants were recruited from the University of Birmingham and associated groups and networks of the research team via advertisements placed on relevant noticeboards and within newsletters. Volunteering participants were asked to self-assess eligibility for the study according to exclusion criteria listed: smokers, illnesses that compromise taste or smell, dental care within 2 weeks of the study date, lactose intolerance, and inability to swallow a tablet. An older population (≥55 years) was targeted in order to represent a population known to have a higher incidence of swallowing disorders (Baijens et al., 2016, Moody et al., 2017).

Each participant received a Participant information sheet (Appendix A) a minimum of 24 hours prior to the study. Before the study began the all participants gave written informed consent (Appendix B).

4.3.4 Materials

The study used placebo tablets with or without the coatings listed in Table 4.1. Large oblong tablets, 19x9x7mm, were selected for this study to match the tablet features most likely to cause swallowing problems (Schiele et al., 2013). The coated and uncoated placebo tablets were supplied by VerGo Pharma Research Laboratories Ltd. (Verna Salcette, Goa, India) with a statement of fitness for human consumption. Tablets were manufactured using a direct compression method of a mix comprising, lactose monohydrate (69%), microcrystalline cellulose (15%), starch 1500® (partially pregelatinised maize starch, 15%), colloidal silica (0.5%) and magnesium stearate (0.5%), then aqueous-based film coatings were sprayed onto cores as per Table 4.1.

Table 4.1 Details of tablet coatings used on placebo tablets within this study.

Formulation	Sample description	Coating ingredients	Tablet core shape	Final coating level (w/w)*
T_A	Uncoated	-	oval	0%
T_ACoat-1	Standard commercial	Opadry® 03F mix (HPMC-based)	oval	3%
T_ACoat-2	Slippery commercial	Opadry® EZ Swallow white (HPMC-based + guar gum and MCT)	oval	3%
T_ACoat-3	Slippery commercial	Opadry® EZ Swallow white Opadry® EZ Swallow clear (HPMC-based + guar gum and MCT)	oval	3% + 1%

*as declared by manufacturer
HPMC – hydroxypropyl methylcellulose
MCT – medium chain triglycerides

4.3.5 Procedure

The study was conducted on University of Birmingham premises, in an allocated room, at different times of the day (morning, lunchtime, afternoon) to allow flexibility for participants.

Initially participants completed a background questionnaire to collect demographic data, i.e. age range and gender, as well as information on any previous problems with swallowing of tablets (Appendix C). The study activity was timetabled for 1.5 hours and consisted of two parts: assessment of (i) ease of swallowing and (ii) palatability of placebo tablets. In each part, all participants were presented with four tablets in their respective order according to prior randomisation. The tablets were randomised, using the RANDBETWEEN function in MS Excel, to all possible sequences to reduce carry-over effects and sequential bias. This method ensured receipt of balanced averaged group data (Lawless and Heymann, 2010b).

The randomisation process was separated for parts (i) and (ii). Before each tablet was assessed, participants were given a palate cleanser of drinking spring water at room temperature followed by a piece of lightly salted cracker (Jacob's, or Schar gluten free) then drinking water again (Lucak and Delwiche, 2009).

4.3.5.1 Part (i) – Ease of swallowing

During part (i) participants were asked to swallow one tablet at a time in their usual manner. While unlimited access to drinking water was provided to aid swallowing, no suggestion on the method or amount of water to take was given. The amount of water taken by each participant was measured as a difference in the mass of the cup of water provided before and after swallowing each tablet (ρ_{h2o} was assumed to be 1 g/mL). Participants rated how easy the tablet was to swallow using a 100 mm VAS with anchor phrases as shown in Figure 4.1. For each tablet, participants recorded the time taken to swallow using stopwatches with a precision of ±1 second. Additionally, participants were asked to report whether they felt that the tablet became stuck whilst in the mouth or during the swallow. After all four samples were taken, participants ranked them using an ordinal scale (1-4) from easiest to hardest to swallow, and assessed each tablet for acceptability as a Yes/No question (Appendix C).

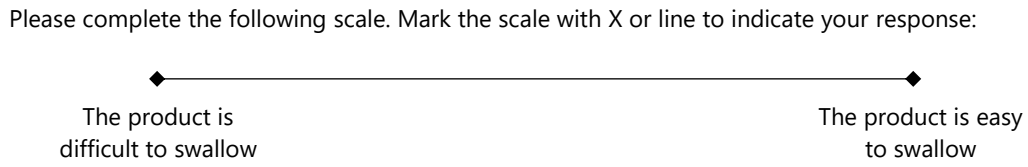


Figure 4.1 Example of 100 mm unmarked visual analogue scale (VAS) used in this study.

4.3.5.2 Part (ii) – Palatability

During part (ii) participants were instructed to hold the tablet in their mouth for minimum of 10 seconds and feel its surface with their tongue. Tablets were then spat out or swallowed depending on participant preference. The participant was then asked to evaluate the tablet for roughness, adhesiveness, slipperiness, and palatability using a VAS; exact questions and anchor phrases given on VAS scales are listed in Table 4.2 (Appendix C). Upon completion of the study, the participants were given a £30 voucher as compensation for their time.

Table 4.2 Sensory questions and end anchor phrases used during palatability part (ii).

VAS	Head question	Anchor phrase
Roughness	Immediately upon administration to the mouth, how does the tablet surface feel on the tongue?	Rough - Smooth
Adhesiveness	Does the tablet stick to the palate?	Tablet is very sticky - Doesn't stick at all
Slipperiness	Does the tablet resist movement?	Stays in place - Slips easily
Palatability	How does the tablet taste?	Unpleasant - Pleasant

4.3.6 Data analysis

4.3.6.1 Exclusion of participant's data

A decision on whether participant's data should be excluded was based on non-adherence to the protocol and analysis of data outliers. One participant's data was excluded from analysis because they were non-adherent to the protocol i.e., they did not undertake palate cleansing between samples. The same participant also generated multiple data outliers (defined as values more than 1.5 IQR's = 1.5 times bigger than interquartile value). The data from 83 participants were analysed (Figure 4.2).

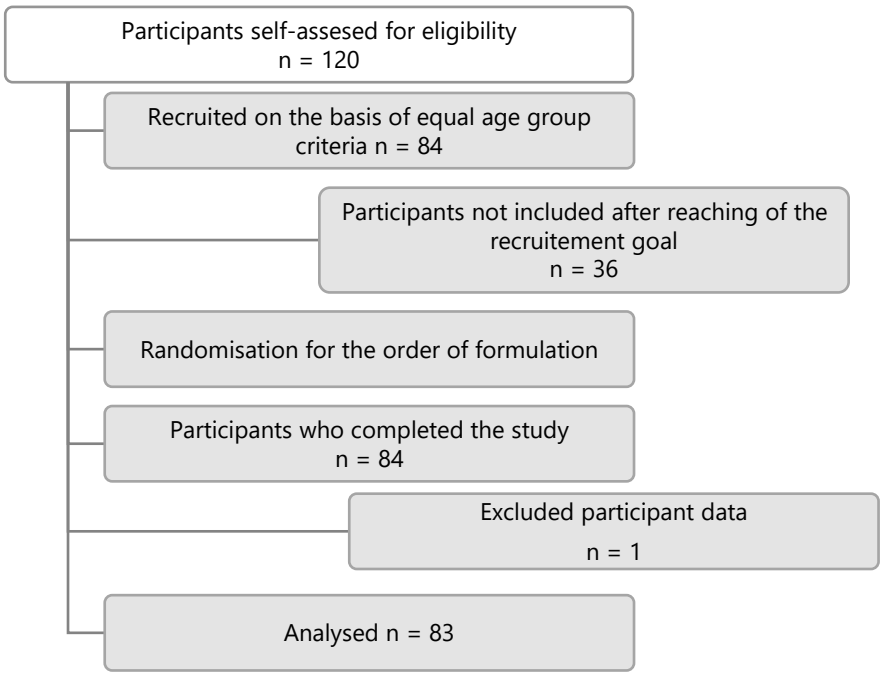


Figure 4.2 Participant flow diagram.

4.3.6.2 Missing data

Missing data represented 0.8% (39/5066) of all data points in this study. Several factors influenced whether data was recorded or not. The main reasons for missing data were technical issues with the participant handling a stopwatch meant that some data was not collected, and information not being disclosed by the participant. Missing data was disregarded, and all other data was included in subsequent analysis.

4.3.6.3 Statistical analysis

Statistical analysis was conducted to explore differences between samples, and also the relationship between demographic data and participants' responses. For all tests the level of significance $p<0.05$ was used, unless stated otherwise. Prior to analysis the data was inspected for normality of distribution (Shapiro-Wilk test). Participant marks on VAS were translated into scores from 0 to 100 (a 0 score referring to negative quality and 100 to positive quality). The comparison of samples was done using non-parametrical tests for related samples, as data was not normally distributed. The order in which tablet samples were taken may have influenced findings due to carry-over and training effects. Thus, a comparison Friedman's ANOVA test was used to screen data for sequential effects. Further, to compare sample scores between each other (pairwise) Wilcoxon's signed rank test was performed. Whenever pairwise comparison was performed, Bonferroni correction of p level was used to account for repeated testing effects; e.g. to perform a comparison of 3 samples (e.g. A, B, C), 3 pairwise tests a performed (e.g. A vs. B, B vs. C and A vs. C), thus the p value was divided by 3 (0.05/3=0.016667). Additional measures assessed correlations between numerical parameters (e.g. VAS scores) by calculating Spearman's correlation coefficient (r_s).

Further, the relationship between demographic data and participants' responses was examined. The correlation of categorical data was tested with the Pearson Chi-Square test (χ^2). To compare participants' responses within different populations the Mann-Whitney U test was used. Additionally, the probability of the tablet arrest (feeling of tablet getting stuck during swallow) depending on the tablet sample taken was evaluated as an odds ratio with 95% confidence intervals.

To analyse the effect of age, participants were divided into 2 groups: ≤54 and ≥55 years old, and are hereafter referred to as the younger group and the older group. Narrower age groups were not analysed, due to the fact that smaller groups would decrease the power of analysis and have a lower discriminating power.

Finally, a Mann-Whitney U test was employed to determine the association between acceptability of the tablet sample and numerical parameter (e.g. VAS scores, time to swallow). Furthermore, for each parameter that related to product acceptability the cut-off value was determined. This was performed using Receiver Operating Characteristic (ROC) analysis.

Statistical analysis was performed using SPSS statistical software version 24 (IBM Corp.).

4.4 Results

4.4.1 Participant demographics

The study included 84 healthy adult participants, ranging in age from 18 to 75 years. Analysis was performed on data from 83 participants. One participant was excluded, as explained in the methods section. Participant demographics are presented in Table 4.3. Of the participants included for analysis, forty-nine (49/83, 59%) were female, about half (42/83, 51%) were over 55 years old, over a quarter (22/83, 26.5%) reported previously experiencing

swallowing difficulties when taking tablets. More than half of the cohort reported taking oral solid medicines on daily basis (48/83, 57.8%).

Table 4.3 Participant demographic data.

Number of participants (n=83)	Frequency	Percent [%]
Gender		
Male	34	41.0
Female	49	59.0
Age (years)		
<24	10	12.0
25-34	13	15.7
35-44	11	13.3
45-54	7	8.4
55-64	10	12.0
>65	32	38.6
Problems with swallowing tablets previously		
No	60	72.2
Yes	22	26.5
Missing*	1	1.2
History of taking medicines		
None daily	34	41.0
Between 1-3 daily	32	38.5
4 or more daily	16	19.3
Missing*	1	1.2

*Participant did not answer the question

4.4.2 Ease of swallowing assessment

Prior to data analysis it was verified that the assumption of normality was violated for numerical data (Shapiro-Wilk test, $p<0.05$) and that sequence effects did not influence the VAS scores of the participants (Friedman's ANOVA test, $p>0.05$).

Median VAS results showed that all coated tablets were reported as easier to swallow than uncoated (median 85-87 mm vs. 66 mm), χ^2 (3) = 52.545, $p<0.001$. As illustrated in Figure 4.3, the differences between the different coated tablets were minor, and not statistically significant (χ^2 (2) = 4.315, $p=0.116$). More apparent differences were found with ranked data for ease of swallowing, which ordered the tablet samples as follows T_ACoat-3 > T_ACoat-2 > T_ACoat-1 > T_A. The majority of participants selected a coated tablet as their first choice,

T_ACoat-3 (31/82, 37.8%), T_ACoat-2 (21/82, 25.6%), and T_ACoat-1 (18/82, 22.0%). Only 14.6% (13/82) of subjects ranked the uncoated tablet as the easiest to swallow, while for 64.6% (53/82) it was their last choice. One participant did not perform the ranking task.

Participants drank from 0 mL to 125 mL of water with a single tablet. The median volume consumed was smaller for coated tablets, 28.8 mL when compared to the uncoated one 35.9 mL (χ^2 (3) = 20.678, $p<0.001$). The time to swallow the tablet, from putting it in the mouth until the feeling of a complete swallow, ranged from 1 to 49 seconds, with uncoated tablets requiring a longer time than uncoated ones (χ^2 (3) = 14.855 $p<0.01$). No difference was found between different coated tablets.

Participants recorded the tablet arrest when they felt that tablet was stuck in the mouth or throat during swallowing. This was reported as positive (i.e. a yes response to a yes/no question) for one in five of the tested tablets (20.5%, 68/332). Unsurprisingly, 41% (34/83) of participants reported the tablet arrest incident to be with the uncoated tablets, whereas only 14% (34/249) reported it for coated tablets (OR 0.229, CI 0.130-0.404). The ease of swallowing VAS and rank order were negatively correlated with the event of tablet arrest ($U = 2119$, $p<0.001$, and $U = 3111$, $p<0.001$, respectively). Moreover, in the event of tablet arrest participants tended to drink more water and take more time to swallow the tablet ($Z (1) = -2.349$, $p<0.05$, and $Z (1) = -4.160$, $p<0.001$, respectively).

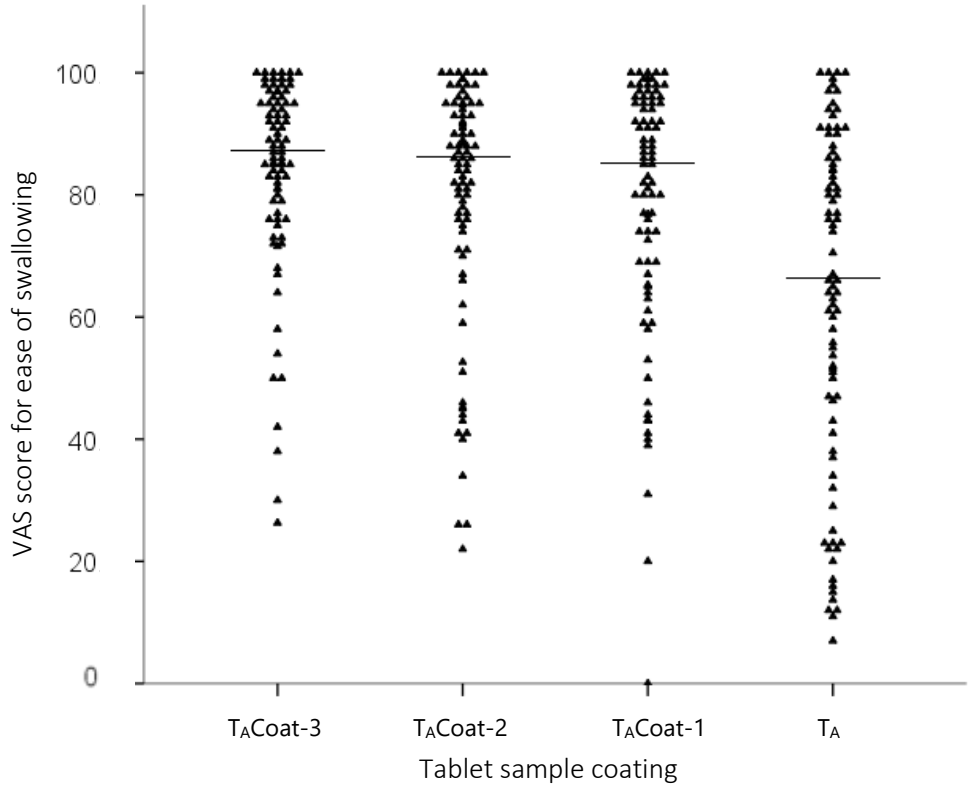


Figure 4.3 Ease of swallowing VAS scores for all tablet samples; each ▲ represents one participant, line depicts median score (n=83).

The Spearman's correlation coefficient (r_s) was calculated for all four variables for all 332 tablet samples (Table 4.4). No pair of parameters provided a large association (effect size >0.5). The biggest value of Spearman's rho was found for ease of swallowing and rank (0.475).

Table 4.4 Spearman's correlation coefficient (r_s) for part (i) parameters; only significant values of at least medium effect size (>0.3) are presented; (n=332).

Parameter	Volume of water	Time to swallow	Rank
Ease of swallowing	<0.3*	0.352*	0.475*
Volume of water		0.396*	<0.3*
Time to swallow			<0.3*

*p<0.01

4.4.3 Mouthfeel and palatability assessment

Mouthfeel and palatability were assessed by the participants using VAS. Median scores are presented in Figure 4.4. The uncoated tablet was found to be statistically different in all four of the mouthfeel attributes being investigated: roughness, adhesiveness, slipperiness and

palatability (Wilcoxon's test, $p<0.01$). Participants were not always able to discern differences between the different coated tablets. The median roughness of T_ACoat-3 coated tablets differed statistically from that of those coated with T_ACoat-1, but not T_ACoat-2 (median VAS 86.3, 82, and 85, respectively); a similar relationship was found for palatability (median VAS 60, 54, and 54, respectively). With regard to adhesiveness, participants assessed the T_ACoat-1 coated tablets as stickier than both T_ACoat-2 and T_ACoat-3 coated tablets (median VAS 76, 91, and 91, respectively). The only attribute that allowed all the different coated tablets to be distinguished from one another was slipperiness (median VAS 77, 82, 88 for T_ACoat-1, -2 and -3, respectively).

The Spearman's correlation coefficients (r_s) for mouthfeel attributes and palatability were calculated (n = 332) (Table 4.5). The largest effect size was observed for following attributes: roughness, adhesiveness and slipperiness.

- The smoother the sample, the more slippery
- The rougher the sample, the more sticky
- The more slippery the sample, the less sticky

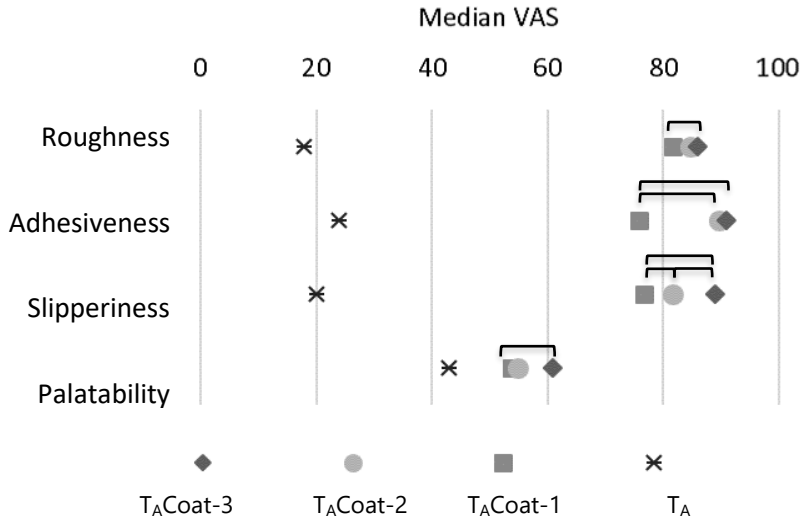


Figure 4.4 Comparison of the four tablet samples in the mouthfeel test (score 0 means negative quality, 100 positive quality). Brackets indicate statistical significance ($p<0.0167$).

Table 4.5 Spearman's correlation coefficient (r_s) for part (ii) parameters; only significant values of at least medium effect size (>0.3) are presented; (n=332).

Parameter	Adhesiveness	Slipperiness	Palatability
Roughness	-0.596*	0.742*	0.320*
Adhesiveness		-0.728*	-0.331*
Slipperiness			0.387*

*p<0.01

4.4.4 Relation between participant demographics and collected data

Demographic analysis of the study population found several trends, e.g. in ease of swallowing and perceived palatability, which are presented below.

4.4.4.1 History of issues with swallowing tablets

This study recruited only participants who reported no *current* issues in ability to swallow a tablet. Thus, people with major swallowing difficulties were excluded from the study.

Within the study population 26.8% (22/83) reported *previous* issues with swallowing tablets. Most commonly, participants stated that the reason for their difficulties was the tablet size (Table 4.6). In general, participants who reported previous problems with swallowing tablets scored the tablet samples in this study as more difficult to swallow than participants who did not declare any issues (based on VAS, U = 8633.5, p<0.05).

Table 4.6 Reported reasons for previous difficulties with swallowing tablets.

	Frequency*	Percentage of study population (n=83)	Percentage of participants with previous tablet swallowing issues (n=22)
Size of tablet	18	21.69	81.82
Taste of tablet	5	6.02	22.73
Texture of tablet	6	7.23	27.27
Aftertaste	9	10.84	40.91
Dry mouth	6	7.23	27.27
Other	1**	1.20	4.55
Total	38		

* Multiple answers were possible, ** shape

4.4.4.2 Age

A Pearson Chi-Square test showed that younger (≤54 years old) participants reported problems with swallowing tablets more often than older ones (≥55 years old) (χ^2 (1) = 4.530, $p<0.05$) (Table 4.7). While older participants typically take more tablets on a daily basis (χ^2 (2) = 10.473, $p<0.001$) (Table 4.7), there was no correlation with the number of tablets taken and occurrence of previous issues in swallowing tablets for this study population (χ^2 (2) = 0.955, $p = 0.620$).

The process of swallowing the tablet sample was analysed in the context of age. Younger participants reported swallowing the tablet faster (median 6 s vs. 7.5 s), but needed more water (median 34.2 mL and 26.4 mL, respectively) compared to the older participants (Table 4.7). Instances where no water at all was used to swallow a tablet sample occurred most often amongst the older group (10 observations (10/168, 6.0%) vs. 4 observations (4/164, 2.4%)).

It is known that ageing reduces the sensitivity of senses (Kremer et al., 2007). Based on this premise, VAS (palatability part (ii)) scores between the younger and older group were compared for ability to distinguish between different tablet samples. Both age groups could differentiate the coated tablets from the uncoated one. Albeit, the older group, showed lower sensitivity to differences between coated samples. With mouthfeel parameters, the older population could only differentiate between the roughness of T_ACoat-3 and T_ACoat-2 coated tablet sample. In contrast, younger participants could not only detect more differences, but also discriminate between the tablet samples on the basis of slipperiness: T_ACoat-3 > T_ACoat-2 > T_ACoat-1 > Uncoated (T_A).

4.4.4.3 Gender

Participant reports of previous issues in swallowing tablets were not found to be gender related (χ^2 (1) = 0.004, p=0.951). Neither, the time nor volume of water needed to swallow the tablet correlated with gender. Females are acknowledged to have more acute senses, which was proven with varying sensory stimuli for taste, texture, and smell (Michon et al., 2009). Indeed, in this study we found that females were better able to differentiate between the tablets than males. For example, unlike males, females could differentiate the level of stickiness between coated samples (Friedman ANOVA test, $p<0.001$). Furthermore, males gave similar palatability scores for all the samples (Wilcoxon's test, $p>0.0167$), while females rated the uncoated tablet significantly less pleasant than coated ones (Wilcoxon's test, $p<0.0167$). In other words, females tended to rate the uncoated tablet as less palatable than males (median 36 vs. 50; U = 545, $p<0.01$). The scores given for roughness and slipperiness were not different between genders. In sum, gender influenced adhesiveness sensitivity and palatability perception.

Table 4.7 Statistical data used to evaluate the relationship between participant demographics and collected data.

Hypothesis	Data			Statistical test and significance
Problems with swallowing tablets were reported more often among younger participants	*Percent of cases* Younger (< 55y): 37.5% (15/40) Older (≥ 55y) : 16.7% (7/42)			χ^2 = 4.53 (p<0.05)
Volume of water taken with sample is age related	*Median volume of water:* Younger (< 55y): 34 mL Older (≥ 55y): 26 mL			Mann-Whitney U = 9950.5 (p<0.001)
Older participants take more medicines daily	*Percent of participants who take >4 medicines daily* Younger (< 55y): 5.0% (2/40) Older (≥ 55y): 33.3% (14/42)			χ^2 = 10.473 (p<0.005)
Older people take more time to swallow the tablet	*Median time taken to swallow the tablet:* Younger (< 55y): 6 s Older (≥ 55y): 7 s			Mann-Whitney U = 9711.0 (p<0.001)
Participants who take more medicines daily do not perceive coated tablets as significantly easier to swallow	*Mean VAS score of ease of swallowing:*	*Coated tablet*	*Uncoated tablet*	
	Participants who take no medicines daily (n=34)	87.5	71.5	Mann-Whitney U = 1140.5 (p<0.005)
	Participants who take between 1-3 medicines daily (n=32)	84	52.84	Mann-Whitney U = 632 (p<0.005)
	Participants who take >4 medicines daily (n=16)	91	80.5	Mann-Whitney U = 328 (p=0.384)

4.4.5 Determinants of tablet acceptability

The acceptability of tablet samples was established with a yes/no question. Coated tablets were reported as acceptable by almost all participants (T_ACoat-3 96%, 80/83; T_ACoat-2 93%, 77/83; and T_ACoat-1 95% 79/83), as opposed to uncoated tablets (66%, 55/83). This information on acceptability was used to determine an association to the numerical parameters used in parts (i) and (ii) of the study (listed in Table 4.8). The Mann-Whitney U test indicated the parameters for which acceptable and unacceptable tablets were scored differently. For each parameter a cut-off value was established by ROC (Receiver operating characteristic) analysis (Table 4.8). For instance, for the ease of swallowing the VAS value of 60 divides acceptable and unacceptable samples on the basis of the VAS score given.

The parameters with the most sensitive and specific cut-off values were ease of swallowing and rank.

Table 4.8 Results of Mann-Whitney U test for influence of parameter on acceptability, and the sensitivity and specificity of the cut-off (n=83).

Parameter	Mann-Whitney U	P value	Cut-off	Sensitivity	Specificity
Ease of swallowing (0 = difficult)	153.5	0.001	60	0.88	0.82
Volume of water (mL)	214	0.018	40	0.64	0.64
Time to swallow (sec)	263.5	0.186	-	-	-
Rank (1 = best)	71.5	0.000	3	0.81	1
Roughness (0 = rough)	145	0.017	70	0.65	0.75
Adhesiveness (0 = sticky)	136	0.011	20	0.89	0.63
Slipperiness (0 = not slippery)	149	0.020	30	0.80	0.63
Palatability (0 = not pleasant)	258	0.522	-	-	-

4.5 Discussion

4.5.1 Coating related factors

The assessment of ease of swallowing indicated that addition of a coating onto a tablet significantly helps to swallow the tablet when compared to an uncoated one. Further, the coated tablets tended to get stuck less often and required less water to take. This result can be interpreted based on the interplay between the product surface and the oral/oesophageal lining. Two different explanations can be postulated for uncoated and coated tablet samples. Upon placement in the mouth, the uncoated tablet absorbed saliva which impeded lubrication and made swallowing more difficult. Whereas for coated tablets, the coating layer inhibited water uptake, thereby maintaining lubrication. Also, in contact with water the HPMC polymer within the coating hydrated and dissolved, thus creating a slippery 'gel' layer on the surface of the tablet which further reduced the friction. This characteristic is intrinsic for hydrophilic polymers.

Prior research suggests that the slipperiness of a tablet coating is formulation dependent. As reported by Mahdi and Maraie (2015), the addition of a slippery polysaccharide (xanthan

gum) into the Kollidon IR (hydrophilic polymer) coating reduced the time to swallow a coated tablet, as compared with plain Kollidon IR coating. Yet, in our study addition of a polysaccharide to a coating (T_ACoat-3 and -2 vs. T_ACoat-1) did not ease or speed up swallowing. The discrepancy might be explained by the fact that the participants in Mahdi's trial swallowed the tablets without water, which could contribute to better discrimination of samples.

Based on the VAS results for mouthfeel and palatability, uncoated tablets were found to be inferior in all respects to the coated ones and were described as rough, sticky and not slippery. The coated tablets yielded opposite responses: smooth, not sticky and slippery. These considerable VAS score differences can be explained in terms of the sensations produced by the tablet surface, i.e. the hydrated layer of polymer coating versus the tablet core for uncoated tablet samples.

Although little statistical difference in VAS scores was observed amongst the three coated tablets, several observations are of interest. Firstly, coatings containing the polysaccharide guar gum, T_ACoat-3 and T_ACoat-2 formulations, were more slippery due to the glide-enhancing property of this gum. Secondly, both T_ACoat-3 and -2 were less sticky than the T_ACoat-1. This was due to the fact that T_ACoat-1 coating is based solely on HPMC, a polymer known to have adhesive properties (Drumond and Stegemann, 2018a). While, for both T_ACoat-3 and -2 adhesiveness was reduced by medium chain triglycerides in the formulation (Debeaufort and Voilley, 2009). Finally, the perceived roughness of all coated tablet samples was almost identical. The roughness of coated tablets is highly dependent on the polymer type within the coating formulation and coating conditions (% solids and spray rate) (Bharadia and Pandya, 2014). All coatings used in this study were based on the same

polymer (HPMC) and prepared under similar conditions resulting, as expected, in similar roughness.

The presence of a tablet coating reduced the volume of water needed to swallow the tablet, with the median volume of 26.4 mL taken with coated and 34.2 mL with uncoated tablets. Generally, all participants used a smaller volume of water to swallow each tablet sample than recommended, i.e. a full glass of 250mL (Tamboli et al., 2010). Study set up may have influenced the volumes of water participants used. Participants knew they would be taking multiple tablets in sequence and hence may have minimised the amount of water they consumed. However, other studies also report small quantities of liquid being used to swallow tablets or capsules – on average 115 mL out of 150 mL provided (Fuchs, 2009). These authors noted that participants taking uncoated tablets used less water than those who took coated ones, which is the opposite of the findings from this thesis. However, the published data was not controlled for the tablet size, which might have changed the interpretation of results. Another research group demonstrated that using a lower volume of water (30 mL vs. 50 mL) increased the oesophageal transit time of a tablet (Perkins et al., 2001). They also reported faster transit for coated than uncoated tablets. The slower transit of uncoated tablet explains why the participants in our study might need more water to feel that uncoated tablet was completely swallowed.

4.5.2 Participant related factors

In line with previous studies which have found that 37.4% and 13.4%, respectively (Marquis et al., 2013, Schiele et al., 2013) of the general adult population have experienced tablet swallowing difficulties, 26.8% (22/83) of our study population had previously experienced problems with swallowing tablets. In agreement with published reports (Overgaard et al., 2001, Marquis et al., 2013, Schiele et al., 2013, Liu et al., 2016a), the most common cause of

problems with tablet swallowing reported in this study was the tablet size. Other formulation factors that were linked to swallowing difficulties associated with medicines included size (74.6%), surface (70.5%), shape (43.5%), and flavour (22.1%) (Schiele et al., 2013). While Marquis et al. (2013) also mention that a sticky coating and unpalatability can also cause swallowing problems.

The age of the participant was found to affect the experience of taking tablets. In this study older participants (>55 years) were the group of interest due to a greater occurrence of dysphagia or dry mouth issues (Strachan and Greener, 2005). It was, therefore, expected that in this population swallowing issues would occur more frequently. On the contrary, the older group in this study reported difficulties with swallowing tablets less often and also used less water to take the tablet samples than younger participants (Table 4.7). As the number of medicines taken daily positively correlated with participant age ($p<0.001$) (Table 4.7), these findings could be attributed to experience in swallowing a range of OSDFs. Alternatively, the recruitment process (healthy participants) may have naturally excluded patients with serious swallowing problems.

Compared to the younger group, older participants took more time to swallow the tablet samples. However, the swallowing time reported may have been due to difficulties with using a stopwatch or dexterity problems, rather than the slowness of swallowing itself. The most accurate, yet more costly, way to analyse the speed of swallowing would be the measurement of time of sample transit in the oesophagus via video scintigraphy or computed tomography (CT) scanning. Published literature confirms that the duration of swallow is longer in older adults when analysed by CT scanning (Pongpipatpaiboon et al., 2018). Based on video scintigraphy, median oesophageal transit time varied between coated

and uncoated tablets (Perkins et al., 2001). Authors reported a transit time between 2 and 3 seconds for oval (5.7×11.5 mm) coated and, 3 to 4 seconds for round (9.5 mm) uncoated tablets. This aligns with our results where median time from putting tablet to the mouth until complete swallow was also longer for coated tablets. Within their study, Perkins et al. (2001) reported that in 4% of observations the oesophageal transit time was >20 seconds, which was regarded as oesophageal adhesion and occurred only for uncoated tablets. Surprisingly, none of the participants were aware of the tablet being lodged in their oesophagus. In our study, the tested tablets were much bigger (oblong, 19x9x7mm), therefore instances of the tablet being stuck were reported more often (20.5% overall, 41% uncoated, 14% coated tablets), suggesting a role for tablet size in a perception of a complete swallow.

Apart from the process of swallowing, the perception of tablet mouthfeel was also affected by age. Participants of 55 years and older were less sensitive to textural tablet sample differences. This relationship has also been described in several other studies. Sensitivity to touch starts to decrease in ones 40s for both oral as well as skin perception (Sehlstedt et al., 2016, Park, 2017). Thus to study older population most sensory studies recruit participants above 55 years (Ikebe et al., 2007) or 65 years old (Vandenberghe-Descamps et al., 2017) as sensory sensitivity decreases more with age. For example, a study comparing food samples with different flavour concentrations and textural changes showed that older people (>60 years) needed a larger increase in stimuli to perceive the same difference as young people (Kremer et al., 2007). The rationale behind the decrease in sensory sensitivity is explained by Boyce and Shone (2006). They attribute it to age-related deterioration of sensory function, and also to reduction of saliva production, and multiple medical conditions. Additionally, tactile perception in the mouth is highly influenced by oral health and dental status, which is often impaired in an older population (Vandenberghe-Descamps et al., 2017). In this light, it

may be argued that within our study the texture differences between coated tablets may be too small for detection by older adults.

Participants' perception of tablets differed between genders; we found that females were more sensitive to different textures than males. This finding aligns with published literature which reports that women not only have more acute senses, e.g. a greater ability to differentiate textures with their tongue (Michon et al., 2009), they are also are more often supertasters (having a superior taste identification), have more taste buds (Bartoshuk et al., 1994), and a more developed olfactory centre in the brain (Oliveira-Pinto et al., 2014). This all contributes to females dominating in trained sensory panels (Raithatha, 2016) and, as sensory evaluation always involves all the senses, helps to explain the findings of this study.

Tablet swallowing is known to be a skill which can be taught, even to children (Meltzer et al., 2006). This suggests that practise can decrease swallowing difficulties regardless of tablet shape, size and other properties. Indeed, in our study the subgroup of participants taking 4 of more medicines daily did not report swallowing enhancement of coated tablets over the uncoated ones (Table 4.7). It is possible that these participants were more practiced in the swallowing process for OSDFs, and hence the uncoated tablets did not cause any difficulties.

4.5.3 Defining acceptability

The generally acknowledged definition of acceptability describes it as "the ability and willingness of a patient and their caregiver to administer a medicinal product as intended" (European Medicine Agency (EMA), 2017b). The definition does not indicate which attributes of medicine are most important for the user. This study identifies parameters associated with acceptability of coated tablets based on the participant responses. Ease of swallowing was found to be a highly sensitive and specific measure i.e. an ease of swallowing cut-off can

accurately separate acceptable from unacceptable tablets. The high sensitivity of the ease of swallowing measure is likely to be related to the large size of the tablets used in this study. Smaller tablets, being easier to swallow whether coated or uncoated, may well not have shown the same degree of sensitivity in this measure. This is supported by previous studies, which found that in the case of single OSDF (tablets or capsules) the size is generally agreed to be a main determinant of ability to swallow across all age groups: children, adults and elderly (Schiele et al., 2013, Liu et al., 2016a, Mistry and Batchelor, 2016). In our study the large tablets were deliberately chosen to render more discrimination between samples which are more difficult to swallow.

Among the mouthfeel parameters measured, adhesiveness was found to be most related to acceptability. The adhesiveness cut-off of <20 (where 0 = sticky) indicates that while highly sticky tablets were unacceptable, some stickiness was acceptable. Adhesiveness can hinder mouth clearance and slow transit of a tablet down the throat hence requiring more effort to swallow (Vickers et al., 2015). In addition, there is a potential that the perception of a sticky surface may increase the fear of a tablet getting stuck on the way down which might, in turn, influence the perceived ease of swallowing and acceptability. As expected, therefore, slipperiness (as an opposite of adhesiveness) was also attributed to acceptability as a desired quality. Finally, the roughness of the tablet was a surface property rather than an irritant or painful stimulus, which could cause any discomfort. Looking more closely at the tablet scores, it can be seen that the roughness of all three coated samples was very similar and above the cut-off of 70, while data points for uncoated tablets were below 70 (Figure 4.4, 0 – rough, 100 – smooth). This suggests that all coated samples would be perceived as smooth, which was a desired and acceptable attribute to participants. This implies the importance of tablet coatings on surface quality.

The palatability of an oral medicine is widely discussed as fundamental for a patient with links to acceptability (Mistry and Batchelor, 2016). Remarkably, in this study palatability was not associated with acceptability, suggesting that palatability has a limited ability to explicitly predict tablet preferences. This finding can be attributed to the fact that, in the case of an oral medicinal product, the desired palatability includes "neutral taste" or "generally acceptable taste" (EMA, 2013). This means that a medicine does not necessarily need to be a tasty product, rather one "not disturbing" taste. This naturally expands the range of products that can be found as acceptable. In our study the tablets used were placebos, thus based on the excipient formulation the tablets and coatings had a neutral taste, which may explain the palatability of the tested tablet samples did not drive acceptability.

In a review discussing acceptability of oral paediatric medicines, Mistry and Batchelor (2016) expressed the need to better understand the acceptability of medicines and formulation factors that affects it. This would benefit both pharmaceutical industry and patients. To achieve this goal the determination of acceptability as described in this chapter can be of a value. VAS based assessment techniques may provide: firstly, an insight into what drives the acceptability, and secondly a quantitative evaluation tool.

4.6 Conclusions

The aim of this study was to investigate the ease of swallowing and oral sensory properties of coated vs. uncoated tablets, as well as determine how mouthfeel can affect acceptability. The presence of the coating was proved to enhance ease of swallowing and improve the mouthfeel sensation, with sample T_ACoat-3 being superior to others in all the attributes. The coated tablets were perceived as smooth, slippery, not sticky and pleasant, whereas uncoated ones were described by opposing attributes. This infers that the oral sensory

properties of tablets can be assessed by VAS. Additional measures, such as time to swallow and the amount of water used to swallow, were lower for coated tablets and correlated with ease of swallowing, but only with medium effect size.

This study found that several participant related factors affected swallowing and sensory experience. Firstly, participants who reported previous problems with swallowing tablets scored the tablets in this study as more difficult to swallow than participants who did not declare any issues. Secondly, older participants reported that they took more medicines and were found to use less water than younger participants when swallowing tablets, suggesting a training effect. Moreover, both gender and age were related to sensitivity of the participant to discriminate between the different mouthfeel of samples, with females and younger participants being more sensitive.

This study showed that sensory properties can be related to acceptability with high selectivity and specificity. Each mouthfeel attribute can be defined as acceptable or not for a particular tablet sample. Currently, because acceptability is mostly assessed as an overall quality of a product, being able to break down its assessment to more specific tablet attributes can be useful for product development. The cut-off values obtained are applicable only to this set of tablet samples. However, expanding this methodology to include different types of OSDF has the potential to allow the assignation of specific VAS scale references to attributes, and then use VAS with acceptability cut-offs as standards for the testing of different/new OSDF in the future.

The sensory assessment findings of the study presented in this chapter have been developed further (see Chapter 5) to include an evaluation of the impact of taste on perception of mouthfeel.

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5 MASCoT study - Mouthfeel, Acceptability and Ease of Swallowing of Coated small Tablets in children and adults

5.1 Introduction

Currently, there is much emphasis on the development of paediatric dosage forms which would allow easy and convenient dosing. For a long time, the "gold standard" for child-friendly medicines was oral liquids with a dose measured using a spoon or syringe. However, liquid dosage forms are often compromised by chemical, physical and microbiological instability; and also pose palatability issues. A recent paradigm shift has seen a move from liquids to small solid dosage forms for paediatric oral medication. Just 10 years ago, for infants below 2 years old the EMA recommended only liquid dosage forms, whereas in their newest paediatric guidelines there are no age-limiting recommendation for solid medicines in children (EMA, 2006, EMA, 2013).

Small tablets offer an alternative oral dosage form with benefits of stability, easy dosage adjustment and simple taste-masking options. It is widely accepted that 6 years is the general age at which tablets are considered suitable for children (EMA, 2006). There is evidence that children can swallow smaller tablets. Previous studies have shown that >80% of four-year-olds and 91% of seven-year-olds are able to swallow 7 mm tablets (Kokki et al., 2000, Meltzer et al., 2006), which is a smaller sized tablet than that usually prescribed for children (Chapter 1.2.1 (Jacobsen et al., 2016)).

A key barrier in developing acceptable and age-appropriate tablets is the lack of knowledge of what is acceptable, and what tablet features are preferred by children. In this sense, the acceptability of small tablets has not been fully established in children. Previous studies

on acceptability have used placebo dosage forms, where palatability (taste-masking and mouthfeel) were not represented (Kokki et al., 2000, Meltzer et al., 2006). Furthermore, the impact of coatings on the mouthfeel and swallowing experience associated with tablets has not been explored in children. To assess impact of taste (taste-masking) on sensory perception, without exposing participants to API, standard taste flavours can be used, like quinine for bitterness. Low bitterness threshold of quinine (Soto et al., 2018), allows it to be used in minimal concentrations, way below therapeutic effects (FDA, 2018).

The design of this study is based upon the recommendations made by Mistry and Batchelor (2017a), and is also informed by a review on 'Sensory and consumer testing with children' (Guinard, 2000) and other relevant literature.

Previously, the ability to swallow a tablet has been used as an indicator of its acceptability, especially in infants and young children who cannot verbally express their opinion (Klingmann et al., 2015, Sznitowska et al., 2015). In the work presented in this thesis, acceptability has been primarily measured as per the definition, by assessing ability to swallow a tablet. However, as the simple ability to swallow a tablet is not fully representative of the patients' experience, this work uses additional methods, such as facial feature observation, to scrutinise the experience. Observation of facial features has proved to be useful as an indicator of food preferences in children, and can be used to assess the hedonic and/or aversive reaction to foods, i.e. level of acceptance (Berridge, 2000). Mistry and Batchelor (2017a) suggested that facial feature observation could be a useful tool to assess medicine acceptability which could be used in addition to other methods. Facial expressions are coded using a Facial Action Coding System, which is widely used, standardised, anatomically based system, where each facial movement is coded as an action unit (AU)

(Ekman, 2005). The system can be used as a tool to recognise emotions (Kring and Sloan, 2007).

In this study, the acceptability of small tablets was assessed with participant reported taste, mouthfeel and hedonic perception of the tablet, along with researcher reported success of taking the sample and negative facial expressions. Collected data was analysed to determine key attributes for the acceptability of tablets in children; adults were used as a comparator population.

5.1.1 Aims of the study

Primary aims

1. Determine the acceptability of a single small (7.5 mm) placebo tablet, given with water as the only carrier, in children (aged 4–12 years) and adults.
2. Use sensory evaluation tools to evaluate the mouthfeel attributes of a single small (7.5 mm) placebo tablet.
3. Determine the impact of coating on mouthfeel.
4. Measure the taste-masking efficacy of tablet coatings on small (7.5 mm) placebo tablets containing quinine.

Secondary aims

1. Identify the coating factors that promote the perception of an acceptable mouthfeel.
2. Identify the barriers to acceptance of small (7.5 mm) placebo tablets in children and adults.

5.2 Materials and methodology

5.2.1 Design

A cross-over single centre study design was proposed to investigate the oral perception of quinine-containing tablets with five different coatings. The study was conducted in two

cohorts: A – healthy children, and B – healthy adults. Within each cohort participants evaluated coated tablets in three parts: assessment of (i) ease of swallowing, (ii) palatability, and (iii) onset of bitterness.

5.2.2 Ethical approval

Ethical approval for the study was obtained from the Ethical Review Committee of the University of Birmingham (ERN_18-1782A).

5.2.3 Participants

Children between 4–12 years old and adults between 18–75 years old participated in the study. Sample size was determined on the basis of the effect size needed to find a difference between two tablets on a 5-point scale. To detect a one point difference on a 5-point scale in a two-tail test ($p<0.05$) with power of 0.8, a sample of 38 would be required (number of evaluations of each tablet) (Soper, 2019). A minimum of 38 adults and 95 children volunteers were required, taking into account the number of tablets received during study: total of 11 for adults, and 5 for children. Children received less tablets, due to lower cognitive abilities and attention span.

Adult participants were recruited from the University of Birmingham and from groups and networks associated with the research team. This was done via advertisements placed on relevant noticeboards and within newsletters. Child participants were recruited using the same channels plus through STEM outreach links and personal contacts. The following exclusion criteria were applied: reported allergy/hypersensitivity to quinine, smokers, illnesses that compromise taste or smell, lactose intolerance, and swallowing impairment. Adult volunteers were asked to self-assess eligibility for the study while for child volunteers,

eligibility was assessed by the child's legal guardian. On the day of the study eligibility was confirmed by a researcher.

Each participant/their legal guardian received a participant information sheet (Appendix E) a minimum of 24 hours prior to the study. On the study date the aims of the research were explained verbally to participants. Participants were then given the opportunity to ask any questions. Before the study began, all participants/their legal guardians gave written informed consent (Appendix F) and child participants gave verbal assent.

5.2.4 Materials

The study used round 7.5 mm tablets containing 2.5% (w/w) quinine sulfate which is known to have a bitter flavour. Tablets were coated with five different coatings to weight gain 4% as stated by contracted manufacturer (actual coating thickness ~3 µm, see Chapter 3.4.2). The details of the tablet coatings are listed in Table 5.1 (for quantitative composition refer to Chapter 2, Table 2.2). The samples were supplied with a statement of fitness for human consumption by Chrysalis Health & Beauty Ltd (Nottingham, UK).

Table 5.1 Details of tablet coatings used on quinine tablets used within this study

Formulation	Sample description	Coating ingredients	Tablet core shape	Final coating level (w/w)*
T_BCoat-4	Standard reference	HPMC 5, glycerol	round	4%
T_BCoat-5	Lipid-based	Lubritab®, Capmul® MCM, HPMC 5, talc, titanium dioxide	round	4%
T_BCoat-6	Slippery	HPMC 5, xanthan gum, glycerol, talc, titanium dioxide	round	4%
T_BCoat-7	pH dependent	Eudragit EPO readymix, titanium dioxide	round	4%
T_BCoat-8	Insoluble – soluble polymer	HPMC 5, Surelease®, glycerol, talc, titanium dioxide	round	4%

*as declared by manufacturer
HPMC – hydroxypropyl methylcellulose

5.2.5 Methods

5.2.5.1 Cohort A – Children

The study was conducted on the premises of the ThinkTank Science Museum (Birmingham, UK) in a dedicated room. Research data was gathered with groups of participants (between 4–7 children) in sessions run over six days, three times a day to allow flexibility to the participants.

Following consent, demographic information was collected including age, gender, ethnicity, as well as previous problems with swallowing of tablets (Appendix G). The study activity was timetabled for 40 minutes and consisted of three parts: assessment of (i) ease of swallowing, (ii) palatability, and (iii) onset of bitterness of quinine tablets (Table 5.2). In parts (i) and (ii) all participants were presented with two tablets, in part (iii) one tablet (5 tablets in total). For each part the tablets were chosen randomly. Randomisation procedures ensured that each of the five tablets were assessed by a similar number of participants. The tablets were presented in all possible combinations to reduce carry-over effects and sequential bias. Additionally, before each tablet sample participants were given a palate cleanser. This included room temperature spring drinking water, followed by a piece of lightly salted cracker (Jacob's, or Schar gluten free) and spring drinking water again.

During the ease of swallowing assessment part (i) participants were asked to swallow one tablet at a time in their usual manner. Unlimited access to drinking water was provided; no suggestion on the method or amount of water to take was given. Participants rated how easy the tablet was to swallow using a 5-point facial scale (scale – Figure 5.1; study flow – Table 5.2). After both samples were taken, participants wrote down their preferred sample.
The amount of water taken was measured as the difference in the mass of the cup of water before and after swallowing the tablet ($\rho_{H2O} \approx 1$g/mL). Researchers observed and recorded

the success of the sample administration (tablet swallowed/spat out/refused) and any verbal comments made by participants about the tablet. Researchers also recorded the facial expressions of participants on a tick chart. For this study, six negative facial expressions were selected from FACS system: lips pressed together (AU 24), nose wrinkling (AU 9), eyes squeezed shut (AU 6+43), brows pulled together and lowered (AU 4), head shake (AU 84) (Appendix G). The action units chosen were based on similar (food and medicine) studies which used the same tools (Zeinstra et al., 2009, Lopez et al., 2018b).

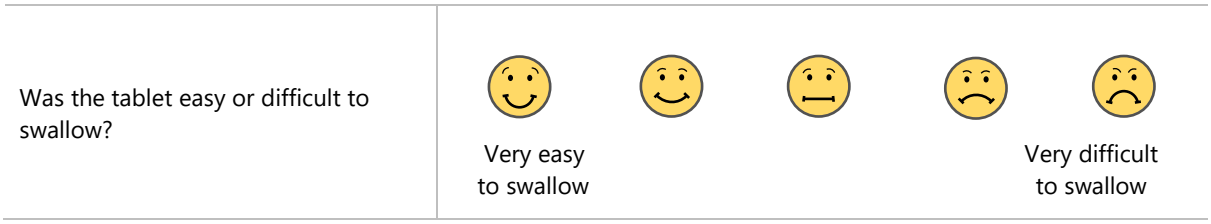

Figure 5.1 Example of a 5-point facial scale

During the palatability assessment part (ii) participants were instructed to put the tablet in their mouth, feel its surface with their tongue for 5 seconds, then spit it out. As the participants undertook this process, researchers observed and recorded participant facial expressions and any verbal comments they made about the tablet. Participants evaluated the sample bitterness, stickiness, smoothness, slipperiness, and aftertaste (pleasant/unpleasant) on 5-point facial scale (Table 5.2). Finally, the participants expressed their overall liking of the tablet sample on 5-point facial scale. After both tablet samples were taken, participants wrote down their preferred tablet sample.

In the third part, participants assessed the onset of bitterness (iii). The time the participant placed the tablet in their mouth (t_0) to the point that they reported a bitter taste was recorded with a stopwatch by the participant. When the child was too young to use the stopwatch, the researcher operated the stopwatch and recorded the onset of bitterness

as verbally expressed by the child. The tablet sample was then spat out and participants assessed their liking of the tablet sample taste using a 5-point facial scale.

At the end of the study, participants were offered juice, crackers and fruit of their choice to minimise any unpleasant taste they might have experienced as a result of the study. An example of setting for a child participant is shown in Figure 5.2A.

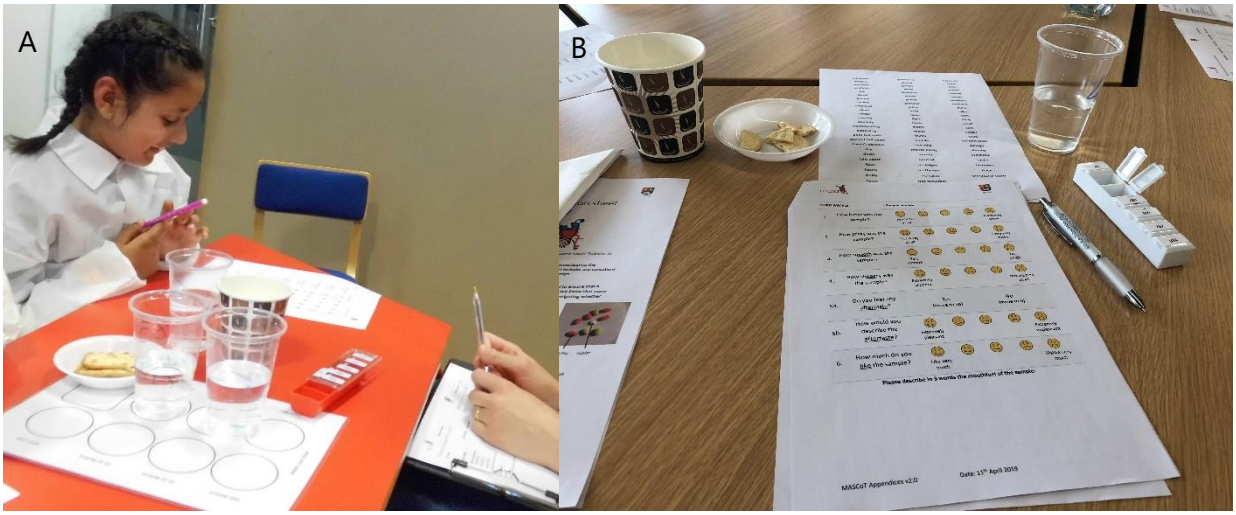

Figure 5.2 Child participant during a palatability part (ii) of the study (picture obtained with a written parental consent of picture taking and publishing) (A); table set up for an adult participant (B).

5.2.5.2 Cohort B – Adults

The study was performed at the premises of the University of Birmingham using dedicated room. The study was conducted at different times of a day to suit participants.

To begin, participants completed a background questionnaire on their demographics, as per cohort A. The study activity was timetabled for 90 minutes and consisted the same three parts as in cohort A (Table 5.2). In total, all participants received 11 tablets in a randomized order (5 tablets for ease of swallowing (part (i)), 5 tablets for palatability (part (ii)), and 1 tablet for onset of bitterness (part (iii))). Tablets were presented in the respective order according to a prior randomization. Before each sample participants were given a palate cleanser, as per cohort A.

The flow and details of the study activity was the same as for the children's study (Table 5.2). Adults used the same assessment tools as children. With the exception that, the adult participant palatability assessment included extra space for additional written (free text) comments about each tablet sample. An example of setting for an adult participant is shown in Figure 5.2B.

Table 5.2 Study flow and assessment tools used for both cohort A (children) and B (adults); number of tablet samples received is reported as children (adults); PROs - participant reported outcomes, RROs - researcher reported outcomes.

	Acceptability		**Taste-masking effect**
	PROs	RROs	PROs
Part (i) Ease of swallowing 2 (5) samples	**Ability to take** ‣ Ease of swallowing *5-point scale* **Hedonic** ‣ Preference test	**Ability to take** ‣ Success of taking the sample *The child swallowed/ spat out/ refused to take a tablet* ‣ Amount of water used *Volume* **Hedonic** ‣ Record of negative facial expressions *Tick chart*	
Part (ii) palatability 2 (5) samples	**Taste intensity** ‣ Bitterness *5-point scale* **Mouthfeel** ‣ Stickiness ‣ Smoothness ‣Slipperiness *5-point scale* **Hedonic** ‣ Liking ‣ Appreciation of aftertaste *5-point scale* ‣ Preference test	**Hedonic** ‣ Record of negative facial expressions *Tick chart*	**Taste intensity** ‣ Bitterness *5-point scale*
Part (iii) onset of bitterness 1 (1) sample			**Taste onset** ‣ Onset of bitterness *Time* **Hedonic** ‣ Liking of bitterness *5-point scale*

5.2.6 Data analysis

5.2.6.1 Exclusion of participant data

Participant data was excluded was based on non-adherence to the protocol and analysis of data outliers (defined as values more than 1.5 IQR's = 1.5 times bigger than interquartile value). No child participant was non-adherent or found to generate multiple outlying responses (over 5 outliers per participant).

All adult participants were adherent to the protocol and no-one generated multiple data outliers. Thus, no adult data was excluded (Figure 5.3).

Each participant had the right to withdraw from the study at any time. For cohort A (children), there were 3 cases of discontinuation based on a child's withdrawal. Two participants decided to withdraw after first or second tablet in the ease of swallowing part (participant #59 – 7-year-old, #63 – 4-year-old, respectively) and one participant withdrew after part (ii), palatability (#74 – 4-year-old). Data collected up to the point of withdrawal was included in the analysis. No adults withdrew.

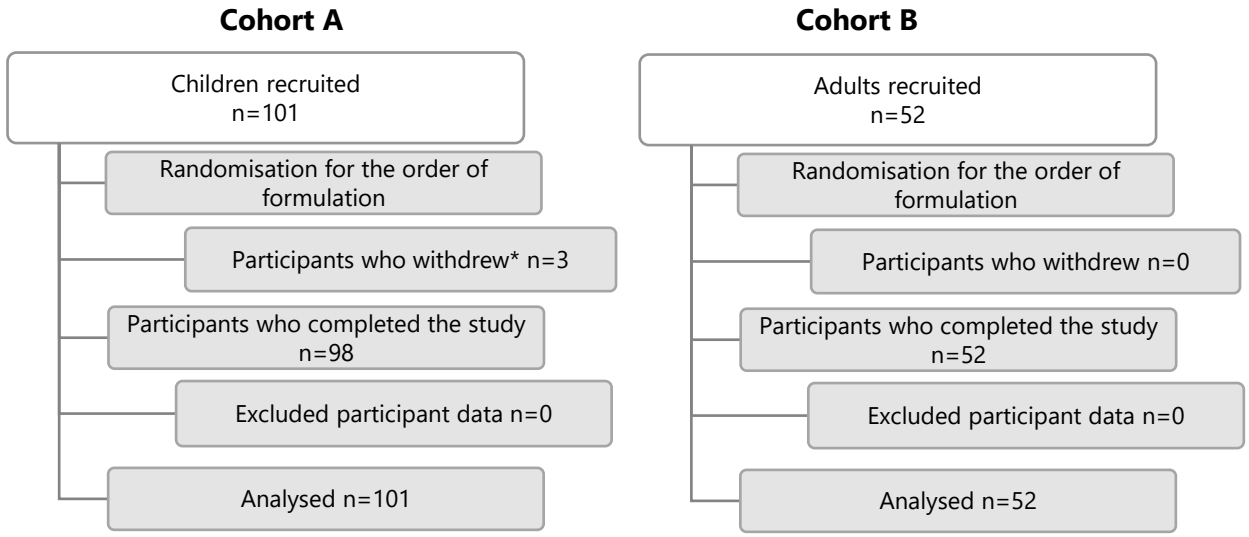

*Figure 5.3 Children and adults: Flow diagram showing the numbers of the participants included in the study; * the data collected up to the point of participant withdrawal was included in the analysis.*

5.2.6.2 Missing data

Missing data represented 0.7% (49/7127) of all data points in the adult cohort, and 1.0% (57/5858) in the children cohort. The main reasons for missing data were unrecorded data (i.e. due to technical issues with handling a stopwatch), information not disclosed by participant, illegible handwriting. The missing data was disregarded, and all other data was included in analysis.

5.2.6.3 Statistical analysis

Statistical analysis was conducted to explore differences between tablet samples, and also the relationship between demographic data and participants' responses. For all tests the level of significance $p<0.05$ was used, unless stated otherwise. Prior to analysis the data was inspected for normality of distribution (Shapiro-Wilk test). Participant marks on 5-point facial scale were translated into scores from 1 to 5 (where a score of 1 referred to a negative quality – sad face; and 5 to positive quality – happy face). Comparison of samples was done using non-parametric tests, as data was not normally distributed (Shapiro-Wilk, $p<0.05$). The order in which tablet samples were taken may have influenced findings due to carry-over and training effects. Thus, a comparison Friedman's ANOVA test was used to screen data for sequential effects.

For related tablet samples (i.e. one participant assessing several tablet samples for the same parameter) Wilcoxon's signed rank test (pairwise) was performed in order to compare different tablet sample scores for the same parameter. Whenever pairwise comparison was performed, Bonferroni correction of p level was used to account for repeated testing effects. When independent samples were analysed (e.g. for part (iii), onset of bitterness), the Kruskal Wallis H test was used. Moreover, correlations between numerical parameters were assessed

(e.g. facial scale scores, volume of water used) by calculating Spearman's correlation coefficient (r_s).

Further, the relationship between demographic data and participants' responses was examined. The correlation of categorical data was tested with the Pearson Chi-Square test ($\chi 2$). To compare participants' responses within different populations the Mann-Whitney U test was used.

To analyse the effect of age, children participants were divided into 3 groups: 4–6, 7–9, and 10–12-year-olds. Narrower age groups were not analysed, since smaller groups would decrease the power of analysis, i.e. have a lower discriminating power. Adults were not subdivided into smaller age groups.

Finally, for both study populations, a Mann-Whitney U test was employed to determine the association between overall tablet liking of the tablet sample and numerical parameter (e.g. scores on a 5-point facial scale). The effect size was calculated to establish the strength of this association. Furthermore, for each parameter that related to tablet sample overall liking, the cut-off value was determined. This was performed using Receiver Operating Characteristic (ROC) analysis.

Statistical analysis was performed using SPSS statistical software version 26 (IBM Corp.).

5.3 Results

5.3.1 Participant demographics

The study included 101 children and 52 adult participants in the age range 4–12, and 18–75 years, respectively. Participant demographics are presented in Table 5.3.

Table 5.3 Children and adults: Participant data collected in a background questionnaire.

	Children (n=101)		**Adults (n=52)**	
Number of participants	Frequency	Percent [%]	Frequency	Percent [%]
Gender				
Male	56	55.4	19	36.5
Female	45	44.6	33	63.5
Age (years)				
4-6	28	27.7		
7-9	40	39.6		
10-12	33	32.7		
<24			11	21.2
25-34			29	55.8
35-44			5	9.6
45-54			5	9.6
55-64			1	1.9
>65			1	1.9
Ethnicity				
Arabic	1	1.0	2	3.8
Asian	18	17.8	6	11.6
Black	0	0	2	3.8
British	6	5.9	2	3.8
Mixed	17	16.8	4	7.7
White	52	51.6	34	65.5
Missing*	7	6.9	2	3.8
Problems with swallowing tablets previously				
No	84	83.2	46	88.5
Yes	14	13.8	6	11.5
Missing*	3	3.0	0	0

*Participant did not answer the question

5.3.2 Ease of swallowing assessment

It was confirmed that the sequence of taking the sample did not affect the ease of swallowing score, in both adults and children (Friedman's ANOVA, p=0.755, and p=0.307, respectively).

The vast majority of adults scored all the tablet samples as easy to swallow, median equalled 5 for all samples ($\chi 2$ (4) = 3.646, p=0.456) (Figure 5.4). The volume of water taken to swallow did not differ between the tablets ($\chi 2$ (4) = 1.955, p=0.744). All but one adult (#63) managed to completely swallow all the presented tablets. The adult participant (#63) was unable to swallow any of the five tablet samples. They had previously identified themselves as

generally unable to swallow tablets in the pre-study questionnaire and scored all tablets samples as difficult to swallow.

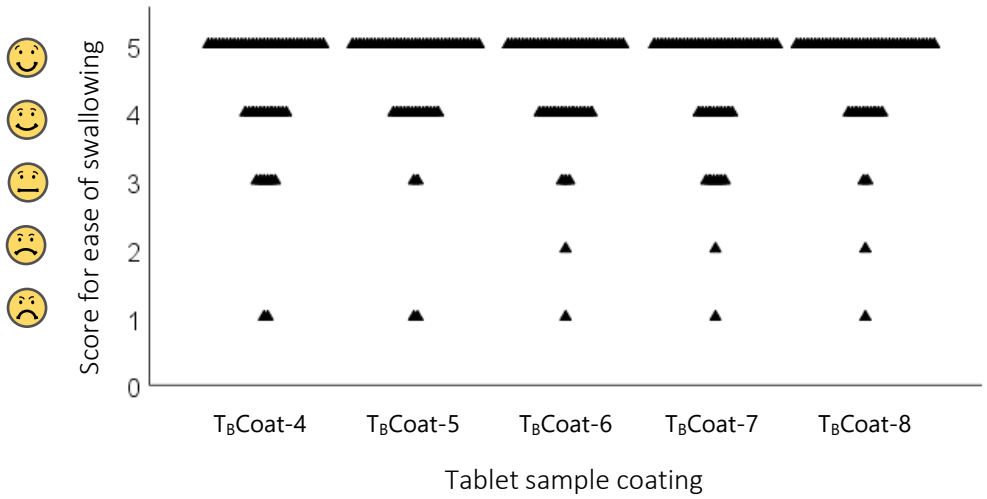

Figure 5.4 Adults: Ease of swallowing scores for all tablet samples; each ▲ represents one tablet, (n=260). Note that a score of 5 meant that the tablet was easy to swallow.

Sixty-three (62.4%, 63/101) children managed to swallow at least one tablet. The success of tablet swallowing (completely swallowed vs. spat out) was age related ($\chi 2$ (2) = 27.977, $p<0.001$), with 35.7%, 66% and 84.4% of 4–6, 7–9 and 10–12-year-olds, respectively, completely swallowing at least one tablet. Boys were more likely to swallow the tablet than girls ($\chi 2$ (1) = 6.960, $p<0.008$) with an odds ratio of 2.2 (CI 1.22–3.97). The type of coating did not relate to the success of swallowing the tablet ($\chi 2$ (4) = 2.627, $p=0.622$).

Participants recorded incidences of tablet arrest defined as when they felt that the tablet was stuck in their mouth or throat during swallowing. This was reported by 7 children, with one of them reporting it for >1 tablet (4.2%, 8/189 of all tablets; 6.4%, 7/110 of the tablets that were swallowed). Incidents of tablet arrest and were not related to the gender nor age ($\chi 2$, $p>0.05$) of the child. For adults, tablet arrest was reported by 16 participants, with 5 reporting its occurrence for >1 tablet (9.3%, 24/259 of all tablets). In the adult population,

the ease of swallowing score was negatively correlated with the event of tablet arrest (U = 686, p<0.001). No such relationship was found for children (p>0.05).

Children who managed to completely swallow the tablet tended to give higher scores for ease of swallowing than those who spat out the sample (Figure 5.5) (U = 275, p<0.001). Those who refused to take a tablet did not provide a score for ease of swallowing. For children no difference between ease of swallowing was found between the different tablet samples (Kruskal Wallis H=4.237, p=0.375), even when the data was controlled by success of swallowing (sample refused, completely swallowed, spat out).

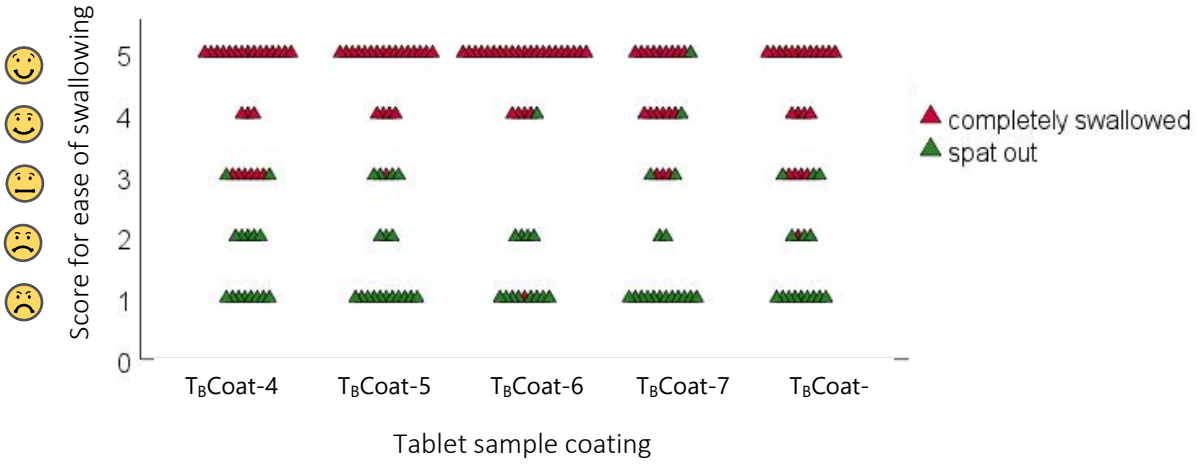

Figure 5.5 Children: Ease of swallowing scores for all tablet samples; children who refused to take the tablet did not give a score; each ▲ represents one tablet, (n=189).

The Spearman's correlation coefficient (r_s) was calculated for ease of swallowing and volume of water used. No significant correlation was found for adult data (p=0.815) nor for children data (p=0.896).

5.3.3 Palatability assessment

In general, the sequence in which the tablet samples were taken did not affect the mouthfeel or palatability scores, in both adults and children (Friedman's ANOVA, p>0.05). Yet, some sequence effects were found for the assessment of stickiness in children. Out of two tablet

samples presented for mouthfeel assessment, children tended to rate the second tablet sample as stickier than the first one (Wilcoxon test, $p<0.05$).

The median scores for all mouthfeel attributes are given in Figure 5.6 and Table 5.4.

The tablets which received the highest scores in both populations were T_BCoat-5 and T_BCoat-6, while the lowest scores were given for T_BCoat-7. Table 5.4 lists the statistical differences found between different tablet samples and specifies the tablet samples for which there was a variation in score between the children and adult population.

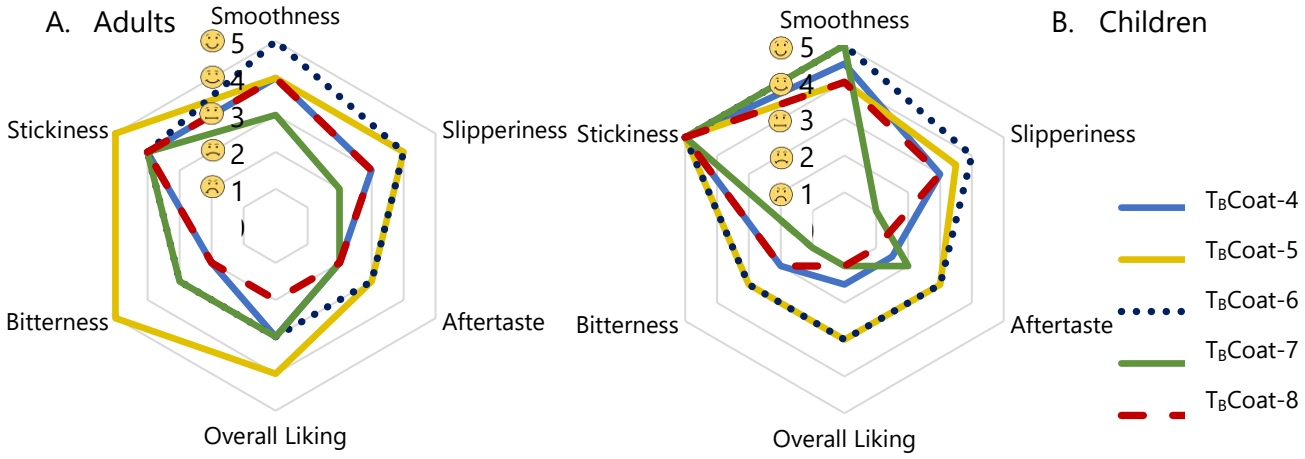

Figure 5.6 Children and adults: Comparison of the five tablet samples in the palatability test – median values for each question are given (score 1 means negative quality, 5 positive quality); A. adults (n=260); B. Children (n=202).

Table 5.4 Children and adults: Comparison of the median scores in the mouthfeel test (score 1 means negative quality, 5 positive quality).

Median		**T_BCoat-4**	**T_BCoat-5**	**T_BCoat-6**	**T_BCoat-7**	**T_BCoat-8**	Friedman's ANOVA
Bitterness	Children	2*	3*	3	2	2	NA
	Adults	2 [a]	5 [b]	3 [c]	3 [a, c]	2 [a]	<0.001
Mann-Whitney U		NS	<0.05	NS	<0.05	NS	
Stickiness	Children	5	5*	5	5	5	NA
	Adults	4 [a]	5 [b]	4 [a]	4 [a]	4 [a]	<0.001
Mann-Whitney U		<0.05	NS	<0.05	<0.01	<0.01	
Smoothness	Children	4.5	4	5	5	4	NA
	Adults	4 [a, b]	4 [a, c]	5 [c]	3 [d]	4 [b]	<0.001
Mann-Whitney U		NS	NS	NS	<0.001	<0.05	
Slipperiness	Children	3	3.5	4	1	3	NA
	Adults	3 [a, d]	4 [a, b]	4 [a, b]	2 [c]	3 [c, d]	<0.001
Mann-Whitney U		NS	NS	NS	NS	NS	

Median		**T_BCoat-4**	**T_BCoat-5**	**T_BCoat-6**	**T_BCoat-7**	**T_BCoat-8**	Friedman's ANOVA
Aftertaste	Children	1.5	3	3	2	1	NA
	Adults	2 [a, b]	3 [a]	3 [a, b]	2 [a, b]	2 [b]	<0.05
Mann-Whitney U		<0.05	NS	NS	<0.05	<0.01	
Overall Liking	Children	1.5*	3	3	1*	1	NA
	Adults	3 [a, b]	4 [c]	3 [a, c]	3 [b, d]	2 [d]	0.000
Mann-Whitney U		<0.01	<0.01	NS	<0.05	<0.05	

a-d, tablet samples which do not share a letter are statistically different; based on adults scores (Wilcoxon test, $p<0.005$ (after Bonferroni correction))

* tablets samples which carry an asterisk are statistically different from the other four samples; based on children scores) (Wilcoxon test, $p<0.05$)

NS – not statistically significant; NA – not assessed

Researchers recorded negative facial expressions as an indicator of a participant's aversion to the tablet sample. The most commonly observed facial expression was 'lips pressed together' (observed in 24.8%, 50/202 of tablets tested in children, and 11.5%, 30/260 of tablets tested in adults). This was followed by 'wrinkling nose' (19.8% and 13.8%), 'brows pulled together and lowered' (10.4% and 12.7%), 'voice disgust' (17.3% and 3.1%), 'eyes squeezed shut' (14.4% and 5.0%) and 'head shake' (15.8% and 1.9%), respectively. Children expressed negative facial expressions more often than adults, which suggests lower acceptability of the tablet for children and/or social conditioning in adults. The sum of negative facial expressions was also indicative of the most and least disliked sample. Among children, the most disliked was T_BCoat-7 (72 recorded negative expressions), and least disliked T_BCoat-6 (35 negative expressions). For adults, both T_BCoat-4 and T_BCoat-8 were most disliked (34 negative expressions), and T_BCoat-5 most liked (7 negative expressions).

Spearman's correlation coefficient (r_s) for all attributes was calculated based on adult (n = 260) (Table 5.5) and children reponses (n=202) (Table 5.6). Based on adult responses the largest effect size was observed for following correlations:

- The more bitter the sample, the less liked
- The more unpleasant the aftertaste, the less liked

- The smoother the sample, the more slippery
- The more bitter the sample, the more unpleasant the aftertaste

Table 5.5 Adults: Spearman's correlation coefficient (rs) for palatability part (ii) parameters; only significant values of at least medium effect size (>0.3) are presented; values with large effect size (>0.5) are shown in bold (n=260).

Parameter	Stickiness	Smoothness	Slipperiness	Aftertaste	Overall Liking	Negative facial expressions***
Bitterness	<0.3**	0.307**	<0.3**	**0.668****	**0.778****	-0.453**
Stickiness		0.448**	0.415**	<0.3*	<0.3**	NS
Smoothness			**0.624****	<0.3**	0.422**	-<0.3**
Slipperiness				NS	0.372**	NS
Aftertaste					**0.714****	-0.345**
Overall Liking						-0.440**

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level; *** minus sign expresses negative direction of the correlation; NS – not significant

Table 5.6 Children: Spearman's correlation coefficient (rs) for palatability part (ii) parameters; only significant values of at least medium effect size (>0.3) are presented; values with large effect size (>0.5) are shown in bold (n=202).

Parameter	Stickiness	Smoothness	Slipperiness	Aftertaste	Overall Liking	Negative facial expressions***
Bitterness	NS	<0.3**	<0.3**	0.485**	**0.629****	-.0386**
Stickiness		0.309**	NS	NS	NS	-<0.3**
Smoothness			<0.3*	<0.3*	<0.3**	-<0.3*
Slipperiness				<0.3*	<0.3*	NS
Aftertaste					**0.555****	-0.312**
Overall Liking						-0.470**

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level; *** minus sign expresses negative direction of the correlation; NS – not significant

5.3.4 Onset of bitterness assessment

The time to onset of bitterness for all tablet samples ranged from 1 to 830 seconds and 1 to 112 seconds in children and adults, respectively; both maximum values were extreme outliers (3 x IQR). For all the tablet samples, the minimal recorded onset of bitterness was between 1–3 seconds. The liking of the taste and time to onset of bitterness were similar for all tablet sample types; no difference was found between the children or adult responses (Table 5.7).

Table 5.7 Children and adults: Median onset of bitterness and liking of the taste of the tablet during part (iii) of the study.

Median		**T_BCoat-4**	**T_BCoat-5**	**T_BCoat-6**	**T_BCoat-7**	**T_BCoat-8**	Kruskal Wallis H
Onset of Bitterness	Children	13	8	10	5.5	6	NS
	Adults	6 [a]	6 [a]	11 [a]	5 [a]	6 [a]	NS
Mann-Whitney U		0.05	NS	NS	NS	NS	
Liking of the taste	Children	2	2	2	3	2	NS
	Adults	2 [a]	2 [a]	2 [a]	2 [a]	3 [a]	NS
Mann-Whitney U		NS	NS	NS	NS	NS	

a, tablet samples which do not share a letter are statistically different (Wilcoxon test, $p<0.005$ (after Bonferroni correction))
NS – not statistically significant

5.3.5 Relation between participant demographics and collected data

5.3.5.1 History of issues with swallowing tablets

Within the study population, 13.8% (14/101) of children 11.5% (6/52) of adults reported *previous* issues with swallowing tablets (Table 5.8). The numbers of children reporting a previous issue in swallowing a tablet are likely to be low due to lack of exposure to or experience of tablet swallowing. This means that the reports of previous issues in this population may not be representative of the actual number who might experience tablet swallowing issues. In addition, a lack of need to take tablets might be the reason why problems with swallowing tablets were reported more often among older children compared to younger children (Table 5.9).

Most commonly, participants (or the child's legal guardian) stated that the reason for their difficulties was the tablet size (Table 5.8). Other reasons listed by parents included: *memory of being sick after medicine, the idea of swallowing a tablet without chewing, [being] scared of doing it,* as well as *[a child] has autism, so in general bad experience [with tablets].* Similar to children, adults reported the size of the tablet as a reason for difficulties in tablet swallowing.

No association between reported previous problems with swallowing tablets and score of ease of swallowing was found for either children or adults (Mann-Whitney U, $p>0.05$).

Table 5.8 Children and adults: Reported reasons for previous difficulties with swallowing tablets; legal guardians were answering the questions for the child in their care.

Children (adults)	Frequency*	Percentage of study population n=101 (n=52)	Percentage of participants with previous tablet swallowing issues
Size of tablet	12 (5)	11.88 (9.62)	85.71 (83.3)
Taste of tablet	5 (1)	4.95 (1.92)	35.71 (16.67)
Texture of tablet	3 (1)	2.97 (1.92)	21.43 (16.67)
Aftertaste	3 (0)	2.97 (0)	21.43 (0)
Dry mouth	0 (0)	0 (0)	0 (0)
Other	5 (2)	4.95 (3.85)	35.71 (33.33)
Total	28 (9)		

* Multiple answers were possible

5.3.5.2 Age

Age-related associations were only analysed for the children population (Cohort A).

The youngest children (4–6-year-olds) found swallowing tablets more difficult, based on the 5-point scale (Mann-Whitney U, $p<0.01$), with median scores of 2, 4, and 5 for 4–6, 7–9, and 10–12-year-olds respectively. Younger children were found to use less water to take a tablet (Table 5.9). During part (ii), palatability, no relation between children's age and the score given was found.

5.3.5.2.1 Children vs. adults

Significantly fewer children managed to swallow a 7.5 mm tablet than adults (62.4% vs. 98.1%). Yet, both children and adults were found to use the same volumes of water to swallow the tablet, 23 mL and 21 mL (median), respectively ($U= 21116.5$; $p >0.05$).

When the scores given by children and adults during the part (ii), palatability, were compared, both populations scored the tablets similarly for only one attribute i.e. slipperiness (Table 5.9). The perception of other attributes differed; adults reported tablets to be less bitter, stickier, and less smooth than children. Adults also gave higher hedonic scores, i.e. overall liking and appreciation of aftertaste, than children. This was supported by anecdotal comments expressed by child participants. The majority of comments made by

children concerned the taste of the tablets, e.g. *very bitter, tasteless, tasted weird,* or expressed negative hedonic opinion, e.g. *disgusting, ugh, 'thumbs down*'.

5.3.5.3 Gender

5.3.5.3.1 Females vs. Males

In agreement with the findings from Chapter 4, reports of previous issues in swallowing tablets were not found to be gender related (χ^2 (1) = 0.030, p=0.862). However, unlike the study presented in Chapter 4, the volume of water needed to swallow the tablet was associated with gender, with females using more water (Table 5.9). Females had a higher taste sensitivity and scored the samples as more bitter than males (Table 5.9). This was also expressed in the lower hedonic scores given and greater incidence of negative facial expressions recorded for females. Moreover, females were found to be more sensitive to mouthfeel characteristics of the tablet samples. Unlike males, females could differentiate between the tablet samples for both stickiness and smoothness (based on number of tablet sample pairs differentiated in the Wilcoxon test). Sample discrimination for other mouthfeel parameters (slipperiness and aftertaste) was not different between genders.

5.3.5.3.2 Girls vs. Boys

The children population in this study (cohort A) was evenly split across both age range and gender ($\chi^2(2)$ = 4.976; p>0.05). Within the ease of swallowing part (i), girls found tablet swallowing more difficult than boys (U = 3338; p<0.001). During the palatability part (ii), all the attributes were scored similarly by both girls and boys (Mann-Whitney U; p >0.05). Several gender differences which were found in adults, were not significant between girls and boys, i.e. perceived bitterness intensity, overall liking, expression of negative face expressions and water taken with a tablet.

Table 5.9 Statistical data used to evaluate relationship between participant demographics and collected data; hypotheses in bold showed statistical significance; A – adults, Ch – children, F – female, M – male, G – girls, B – boys.

Hypothesis	Data	Statistical test and significance
	Taste assessment	
Children are more sensitive to bitterness than adults	*Bitterness median (mean):* A: 2 (2.53) Ch: 2 (2.35)	Mann-Whitney U = 22165.5 **(p<0.01)**
Females are more sensitive to bitterness than males	*Bitterness median (mean):* F: 2 (2.42) M: 2 (2.75)	Mann-Whitney U = 6118.5 **(p<0.005)**
Girls are more sensitive to bitterness than boys	*Bitterness median (mean):* G: 2 (2.45) B: 2 (2.28)	Mann-Whitney U = 4619 (p=0.612)
Children are more sensitive to bitterness than females	*Bitterness median (mean):* F; 2 (2.81) Ch: 2 (2.69)	Mann-Whitney U = 15164.5 (p=0.228)
	Mouthfeel assessment	
The difference in perception of mouthfeel attributes between children and adults	*Stickiness median (mean):* A: 4 (3.76) Ch: 5 (4.34) *Smoothness median (mean):* A: 4 (3.61) Ch: 4.5 (4.09) *Slipperiness median (mean):* A: 3 (2.99) Ch: 3 (2.99)	Mann-Whitney U = 18717 **(p<0.001)** Mann-Whitney U = 20837 **(p<0.001)** Mann-Whitney U = 23734.5 (p=0.192)
Difference in perception of mouthfeel attributes between females and males	*Stickiness median (mean):* F: 4 (3.96) M: 4 (3.67) *Smoothness median (mean):* F: 4 (3.74) M: 4 (3.68) *Slipperiness median (mean):* F: 3 (3.08) M: 3 (3.09)	Mann-Whitney U = 6777 (p=0.068) Mann-Whitney U = 7453 (p=0.546) Mann-Whitney U = 7770 (p=0.972)
Girls are more sensitive to mouthfeel differences than boys	*Stickiness median (mean):* G: 5 (4.40) B: 5 (4.30) *Smoothness median (mean):* G: 5 (4.04) B: 4 (3.95) *Slipperiness median (mean):* G: 3 (2.82) B: 3 (3.00)	Mann-Whitney U = 4684 (p=0.825) Mann-Whitney U = 4460 (p=0.486) Mann-Whitney U = 4475.5 (p=0.462)
	Hedonic assessment	
Adults gave higher hedonic scores to the tablets than children	*Liking median (mean):* A: 3 (2.60) Ch: 2 (2.18) *Aftertaste (pleasantness) median (mean):* A: 2 (2.37) Ch: 2 (2.14)	Mann-Whitney U = 17345.5 **(p<0.001)** Mann-Whitney U = 8821.5 **(p<0.01)**

Hypothesis	Data	Statistical test and significance
Males gave higher hedonic scores to the tablets than females	*Liking median (mean):* F: 2 (2.51) M: 3 (2.80) *Aftertaste (pleasantness) median (mean):* F: 2 (2.33) M: 2 (2.51)	Mann-Whitney U = 5811 **(p<0.01)** Mann-Whitney U = 3149.5 (p=0.200)
Boys gave higher hedonic scores to the tablets than girls	*Liking median (mean):* G: 2 (2.20) B: 2 (2.18) *Aftertaste (pleasantness) median (mean):* G: 2 (2.25) B: 2 (2.06)	Mann-Whitney U = 1783 (p=0.602) Mann-Whitney U = 3876 (p=0.097)
Children gave higher hedonic scores to the tablets than females	*Liking median (mean):* F: 2 (2.28) Ch: 2 (2.42) *Aftertaste (pleasantness) median (mean):* F: 2 (2.33) Ch: 2 (2.15)	Mann-Whitney U = 11873.5 **(p<0.001)** Mann-Whitney U = 6142,5 **(p<0.05)**
Females showed more negative expressions	Sum of occurrences: F: 106 M: 19	Mann-Whitney U = 5905 **(p<0.001)**
Girls showed more negative expressions	Sum of occurrences: G: 54 B: 61	Mann-Whitney U = 4401.5 (p=0.275)
	Miscellaneous	
Problems with swallowing tablets were reported more often among older children	*Percent of cases* 4-6y: 4.0% (2/50) 7-9y: 15.0% (12/80) 10-12y: 21.2% (14/66)	χ^2 (2) = 6.939 **(p<0.05)**
Volume of water taken with sample is age related	*Median volume of water:* 4-6y: 17 mL 7-9y: 28 mL 10-12y: 26 mL	Kruskal Wallis H = 6.208 **(p<0.05)**
Females needed more water to swallow a tablet (adults)	*Volume median (mean):* F: 24.5 (28.9) mL M: 16.5 (20.8) mL	Mann-Whitney U = 4513.5 **(p<0.001)**

5.3.6 Determinants of tablet acceptability – liking

The acceptability of tablet samples was established on the basis of the liking scores given within the palatability part (ii). This was decided on the premise that the participant would be willing to take a tablet which is liked, rather than a disliked one. Two potential thresholds were compared:

- A sample which scored 4 or 5 (positive features) on the liking facial scale is regarded as acceptably liked;
- A sample which scored 3 or 4 or 5 (neutral plus positive features) on the liking facial scale is regarded as acceptably liked.

Both thresholds were compared to see which one yielded the bigger effect size, i.e. which one better explained the relationship between different attributes and liking. The Mann-Whitney U test indicated that the second threshold yielded a larger effect size (data for the first threshold not shown, data for second threshold shown in Table 5.10). For each parameter a cut-off value was established by ROC analysis. The parameters with the most sensitive and specific cut-off values were bitterness and aftertaste (for both children and adult data). Based on children data the stickiness did not determine the liking of the sample. The cut-off for negative facial expressions had low practical value because its sensitivity was close to zero.

In addition, a relationship between the presence of aftertaste (yes/no) and liking was established. Tablets where an aftertaste was reported were disliked by both children ($\chi 2$ (1) = 8.653, $p<0.01$) and adults ($\chi 2$ (1) = 43.408, $p<0.001$).

Table 5.10 Adults and children: Results of Mann-Whitney U test for influence of the mouthfeel parameter on liking (disliked = score 1 or 2; liked = score 3, 4, or 5), and the sensitivity and specificity of the cut-off (n=260 adults, n=202 children).

Parameter	Mann-Whitney U	P value	Effect size	Cut-off	Sensitivity	Specificity
Adults						
Bitterness (1= bitter)	1646	0.000	0.66	2	0.79	0.87
Stickiness (1 = sticky)	5390	0.001	0.21	3	0.75	0.78
Smoothness (1 = rough)	4326.5	0.000	0.34	3	0.72	0.61
Slipperiness (1 = not slippery)	4906	0.000	0.26	3	0.52	0.77
Aftertaste (1 = not pleasant)	969	0.000	0.68	2	0.78	0.89
Negative facial expressions	4224	0.000	0.43	1	0.03	0.69
Children						
Bitterness (1= bitter)	1757	0.000	0.52	2	0.77	0.71
Stickiness (1 = sticky)	4120.5	0.478	0.05	-	-	-
Smoothness (1 = rough)	3269	0.003	0.22	4	0.59	0.31
Slipperiness (1 = not slippery)	3619.5	0.044	0.15	3	0.49	0.70
Aftertaste (1 = not pleasant)	562.5	0.000	0.88	2	0.68	0.86
Negative facial expressions	2242.5	0.000	0.44	2	0.07	0.76

5.4 Discussion

5.4.1 Acceptability – measure of participant's ability to take a dose

Tablet acceptability, defined as the ability of the participant to take the sample, was measured as a number of participants who completely swallowed the tablet. Among adults 98.1% (51/52) swallowed the tablet, while among children only 62.4% (63/101). The succes of swallowing was age dependent, where only 35.7% of 4–6-year-olds managed to swallow the tablet. Based on this outcome, a 7.5 mm round tablet cannot be deemed acceptable in the youngest participants with the study population. The percentage of children succesfully swallowing tablets in this study (MASCoT) was lower than reported in the literature. Previous research in children between 1–9 years old who were administered a ketroprofen tablet (7 mm, round) by their parent to relieve the pain after surgical removal of the adenoids, showed that 80% (418/555) managed to swallow the tablet without problems (Kokki et al., 2000). They also found difficulties in tablet administation more often for children younger than 48 months than the older ones. Another study reported that 91% of children between 6–11 years old could swallow a 7 mm round, wax coated, tasteless tablet (Meltzer et al., 2006). In these studies a higher tablet swallowing success rate could be attributed to the additional means undertaken to help the children to take a tablet: the subjects were trained how to swallow the tablet, offered a special pill cup, and also offered pain-relief or money as an incentive. The study of Meltzer et al. (2006) as well as other studies (Ghuman et al., 2004, Kaplan et al., 2010) prove that children are able to learn how to successfully swallow tablets. In this light, the lower swallowing success may have been predicted in the study described in this chapter, as children were asked to swallow without any training or instructions.

In contrast to previous studies on ease of swallowing of tablets in children, the tablets used in the MASCoT study contained a bitter flavour. The bitterness of the tablet was taste-masked with different coatings, which in the results provided tablets of differing bitterness intensity. We hypothesised that the tablet's aversive taste may negatively impact upon the success of swallowing the sample. Yet, based on Mann-Whitney U test the type of coating on the tablet swallowed did not relate to its swallowing success ($p=0.644$). This suggests that the success of swallowing per se does not depend on the tablet taste. However, if a bitter dose were to be given repeatedly, the taste may pose palatability issues and reduce adherence.

5.4.2 Acceptability – measure of sample palatability

It is key for a medicine to be palatable in order to be acceptable. In the pharmaceutical field, palatability is often assessed as a liked/disliked quality without a full understanding of specific product attributes that drive participant preference. Possible determinants of palatability (taste and mouthfeel) for coated tablets were analysed in this chapter. Palatability of tablet samples was rated on 5-point scales as measure of overall liking (like/dislike). The most pronounced determinant of a participant's liking of the tablet sample was taste. For children and adults, the greater the perceived intensity of bitterness, the more the tablet sample was disliked (Table 5.5, Table 5.6). Sensitivity to bitterness was age- and gender-related. Both children and females, the more bitter they rated the tablets, the higher the tendency to score tablets as less liked. When children were compared females, no difference in bitterness scores was found but children disliked the tablet samples more than females (Table 5.9). This finding suggests that females can give a reliable approximation of the children's perception of bitterness.

Based on palatability scores of children as well as adults the most liked samples (liking score 3, 4 or 5) were also characterised as less bitter, smoother, and more slippery. We hypothesise that the liking score reported for a tablet was not just a function of taste (bitterness), but a combined effect of multiple attributes. This was confirmed by calculating the association effect size between liking and other attributes based on Mann-Whitney U test (Table 5.10). As expected, the largest effect sizes (>0.5) were seen for aftertaste and bitterness in both children and adult populations. While the effect sizes for smoothness and slipperiness were smaller, they still show that these attributes influence how much a tablet is liked (i.e. its palatability). For both children and adults, the attribute with the least effect on liking (palatability) of the tablets was stickiness, which can be explained by small differences in stickiness between the samples (see instrumental measurement of stickiness in Chapter 3.4.4). The aforementioned associations emphasise the impact of mouthfeel on palatability, as distinct from palatability being only a function of taste.

Unlike in pharmaceutics, mouthfeel/texture preference has been widely studied in food sciences (Kälviäinen et al., 2000, Jeltema et al., 2015). Food texture is known to drive the consumer's choice of product. Furthermore, the tactile sensitivity and hedonic responses of children and young adults to various food textures have been correlated with picky eating (Nederkoorn et al., 2015, Nederkoorn et al., 2019). By relating the findings from food science to oral medicines, it may be argued that sensitivity to textures will also impact upon the palatability of oral medicines.

For oral medicines, the studies which relate a specific mouthfeel attribute and palatability/liking are scarce. A possible reason for the low precedence of such studies might be put down to the different administration mode, residence time in the mouth and oral

processing of various types of OSDFs. In order to find the key mouthfeel attributes, which determine OSDF palatability, and so its acceptability, multiple testing methods may be required. Several mouthfeel attributes were indicated in the literature as important for palatability/acceptability; these include: grittiness (ODT) (Lopez et al., 2016), stickiness (ODF) (Scarpa et al., 2018), volume of residue (ODT) (Casian et al., 2018), and rough mouthfeel (ODT) (Kimura et al., 2015). The study presented in this chapter (MASCoT) adds to this list by showing a direct correlation between palatability and aftertaste, smoothness and slipperiness of conventional coated tablets. Further studies are required to generate a definitive list of mouthfeel attributes critical to acceptability of OSDFs.

5.4.3 Sensory perception of coated tablets

The way people perceive and appreciate taste changes with age (Forestell and Mennella, 2015). Thus, a child's perspective and opinions about medicines needs to be discussed separately to adults. Within this study children scored the taste and hedonic attributes of tablets differently to adults (Table 5.9). In agreement with previous studies (Mennella and Bobowski, 2015), children were more sensitive to bitterness (i.e. gave lower scores on 5-point scale, where 1 = extremely bitter). Moreover, children tended to give lower hedonic scores than adults (5-point liking scale, where 1 = dislike very much). This was supported by anecdotal comments expressed by children participants. These findings agree with the fact that both sensitivity and appreciation of taste stimuli changes with time – children are more sensitive to bitterness and have more aversive reaction to it (Nu et al., 1996, Mennella et al., 2014), whereas adults develop a certain tolerance to bitter taste with age (Drewnowski et al., 2001) (for example by repeated exposure to coffee or tonic water). The taste perception of oral medicines was studied by Mennella et al. (2014), who found that bitterness blockers

were less effective in children than adults. The differences in taste sensitivity have important implications for the development of oral medicines. A formulation with an acceptable taste for adults may not be acceptable to children. As a consequence, adults' sensory assessment cannot be directly translated to a paediatric population, therefore adults are not a suitable substitute of children in the sensory evaluation of paediatric medicines. These findings highlight the importance of developing medicines specifically for children, as opposed to manipulating an adult formulation to administer it to children.

Apart from taste, texture perception and preferences also change with age (Song et al., 2016). Based on the mouthfeel scores, children in this study rated samples as smoother and less sticky than adults rated them (Table 5.9). A better discrimination between tablet samples was achieved using adults' data (Table 5.4). There was less variability in the data from adults than children suggesting that adults can more reliably discriminate between samples. In addition, scaling might be a more difficult task for children; as children tend to use extreme ends of the scale (Mistry et al., 2018).

As texture preferences can differ between age groups (Lukasewycz and Mennella, 2012), the relation between mouthfeel parameters and overall liking of the tablets was analysed separately for children and adults (Table 5.10). All mouthfeel parameters could be used to indicate how much an adult participant liked a tablet. This was not true for children, where all attributes but stickiness were proven to be indicative of tablet liking. In children, stickiness of all the tablet samples was scored similarly (mode 5 = not sticky at all). Data from children and adults resulted in different cut-off values for smoothness: 4 and 3, respectively. Cut-off value of 4 indicated that only samples scored by children as very smooth (score 5) were

regarded as liked, while for adults' samples that scored 4 and 5 were equally liked. This discrepancy illustrates the difference in textural preferences between two populations.

5.4.4 Determination of taste-masking properties of the coatings

Tablet coating taste-masking effect was measured in two ways. Firstly, by measurement of bitterness intensity (part (ii)). Secondly, by observing the onset of bitterness (part (iii)). Based on the bitterness intensity, significant differences between samples were found (Table 5.4). The adults rated the bitterness of samples slightly differently than children (Table 5.4), yet the results of both groups agreed on the two least bitter samples, i.e. T_BCoat-5 and T_BCoat-6.

Differences in the perceived bitterness intensity between samples could be related to the formulation of coatings. As all tablet cores contained the same amount of quinine flavouring, the bitterness could be inhibited only by a taste-masking coating. For the two least bitter samples, T_BCoat-5 and T_BCoat-6, taste-masking was achieved using different approaches. Formulation T_BCoat-5 comprised lipids, which, because they are hydrophobic, inhibited water penetration into the tablet core, and so constrained the diffusion of quinine molecules from the tablet core to the taste buds. In the case of T_BCoat-6, taste-masking was achieved due to the increased viscosity of the coating attributable to xanthan gum which slowed coating dissolution. In comparison, the standard formulation without viscosity modifying ingredients, T_BCoat-4, was perceived as more bitter than T_BCoat-6. The tablets samples perceived as most bitter (T_BCoat-7 and T_BCoat-8) had coatings based on water insoluble polymers, and as such, were expected to inhibit water penetration into the core and subsequent quinine diffusion to the taste buds. Although similar coating formulations have previously been shown to be effective in taste-masking (Hughes et al., 2016, Drašković et al., 2017), here taste-masking was not achieved. This may be explained by the results

presented in Chapter 3.4.2, where the coatings on T_BCoat-7 and T_BCoat-8 tablets were found to be cracked and therefore incapable of providing a complete protective layer. Insoluble coatings are less flexible, and so more prone to cracks, than soluble ones; thus, they may require a thicker layer to provide a taste-masking effect. A discussion of the characterisation of the physical properties of coatings which can impact taste-masking properties can be found in Chapter 3.5.2.

Apart from assessing the bitterness intensity of the tablet samples, participants also measured the time to onset of bitterness. Based on these results, no statistical difference was found between samples (Table 5.7). For all the tablet samples, the minimal recorded onset of bitterness was 1–3 seconds, with a median time below 13 seconds (for both children and adults), which indicates no substantial lag time. According to previous studies, for effective taste-masking, a sufficient time of no perceivable bitterness after a tablet is placed in the mouth is 30 seconds (Drašković et al., 2017, EMA, 2017a). Hence, none of the coatings used in this study provided effective taste-masking. The lack of taste-masking efficacy is likely to be explained by the thickness of the coating. Thin coatings may not create a barrier good enough to delay release of API (ref to Chapter 3.5.2). It could be argued that a 30 second rule for effective taste-masking is excessive, as the time for a tablet to pass through the mouth is usually shorter. However, it is important to note that a time to swallow a tablet, from putting it in the mouth until the feeling of a complete swallow (as reported in Chapter 4.4.2) ranges from 1 to 49 seconds. This indicates that some people need longer that 30 seconds to swallow a tablet. Taking into account that the bitterness receptors are located not only in the oral cavity, but also in the oesophagus (Chapter 1.2.2.1), the taste-masking effect should, therefore, last for the time necessary for the tablet to pass through whole oro-oesophageal tract.

During the onset of bitterness test, some participants generated extreme outlier data, i.e. one adult (112 seconds) and five children (ranging from 210 to 830 seconds). Such long onset of bitterness times coupled with ratings of "not bitter at all" (score 5) from the same participants in the study's palatability part (ii) can be explained by variability in human bitter taste sensitivity, rather than tablet sample factors. The variability in bitterness perception has been strongly related to a bitter taste receptor gene, TAS2R38. An allele of this gene responsible for bitterness-insensitivity was present in ~30% of population, referred to as non-tasters, and related to taste preferences (Mennella et al., 2015b, Cont et al., 2019). This suggests that some non-tasters could also be present in this study. Previous research suggests that the race/ethnicity does not affect the genotype (Wooding et al., 2004, Mennella et al., 2010), yet in this study four out of five children who showed low bitterness sensitivity were of Asian origin. Interestingly, one of the five was white, but with diagnosed autism which is known to be associated with senses which are over- or under-sensitive (Chistol et al., 2018). The adult demonstrating a low sensitivity to bitterness was of mixed ethnicity.

In summary, the measure of bitterness intensity was more discriminative than the time to onset of bitterness. The onset of bitterness test showed that none of the tablet coatings was effectively taste-masking the bitterness associated with the tablet core, and eventually all the samples tasted bitter.

5.4.5 Study limitations

There are some limitations to this study. Firstly, the provided tablet samples had a thinner coating thickness than expected (see Chapter 3.4.2). Secondly, there was no reference for maximum and minimum intensity of attributes, which did leave the scales more open to an

individual's interpretation. The limitation of the palatability evaluation method was the short assessment time (5 seconds), which might not be representative if the patient requires more than 5 seconds to swallow a tablet.

5.5 Conclusions

Within the MASCoT study the acceptability of 7.5 mm round tablets with five different coatings was investigated in children and adults. The ability of the participant to swallow the tablet was independent of the applied coating. The tablets were successfully swallowed by the vast majority of children 7 years and older (74%) and adults (98%). The ability to take this tablet in children between 4–6 years old was low (35.7%), which indicates low acceptability in this age group.

The study found that the type of coating affected the intensity of perceived bitterness of tablet, indicating difference in coatings to effectively mask the taste. Although none of the coatings were taste-masking for at least 30 seconds, the intensity of perceived tablet bitterness differed between samples, with T_BCoat-5 (lipid-based coating) and T_BCoat-6 (HPMC coating with addition of xanthan gum as a viscosity modifier) being least bitter. The poor taste-masking properties were explained by the low thickness of the applied coatings.

Additionally, this study showed that sensory properties can be related to palatability, showing its multifactorial nature. Not only bitterness of the tablets, but also mouthfeel was found to determine whether the tablet is liked, or disliked. The overall trend in palatability was similar between children and adults. In both populations, low bitterness, high smoothness, high slipperiness, and pleasant aftertaste had positive impact on overall palatability. Yet, the scores given by children differed from the adults. Children perceived

the tablets as more bitter, smoother, less sticky, and less liked. This suggests that adults' palatability scores cannot be directly translated to a paediatric population.

This study broadens the knowledge of the acceptability and palatability of small coated tablets in children and adults. The findings highlight the difference in bitterness and hedonic perception of tablets between populations. Moreover, the results show direct correlation between palatability and aftertaste, smoothness, and slipperiness of conventional coated tablets, which emphasizes the need to analyse medicine palatability as a multifactorial attribute, rather than a simple hedonic parameter.

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6 Mouthfeel of tablets: correlations between sensory evaluation and instrumental methods

6.1 Introduction

6.1.1 Lessons from food science

The reasons to seek correlations between mouthfeel attributes and instrumental data lies in their potential to: (i) be a tool for quality control, (ii) predict consumer preference (iii) understand processes underlying mouthfeel perception, as well as (iv) replace human panels for sensory evaluation and consequently reduce the costs of evaluation (Szczesniak, 1987). To achieve a correlation the food industry provide a high number of standards for both sensory and instrumental methods (International Organization for Standardization). In pharmaceutical industry no standards for sensory methods exist, leading to researchers undertaking various in-house approaches. Refinement, development and harmonization of sensory methodologies within pharmaceutical field has also been advocated for pharmaceutical products (Ternik et al., 2018).

One of the challenges in correlating sensory with instrumental texture measurements is the temporal character of textural sensations (Ningtyas et al., 2019). As food is moistened by saliva and masticated, its properties change, which needs to be acknowledged in an instrumental technique. Another issue encountered when establishing *in vivo/in vitro* correlations is the multimodal nature of mouthfeel. Some sensory perceptions are straightforward (e.g. thickness as function of viscosity (He et al., 2016)), while others are triggered by a combination of attributes (e.g. creaminess combines viscosity, taste, smoothness and thickness (Prakash et al., 2013)). To develop an understanding of the complexity of multimodal attributes, knowledge is built by establishing individual

correlations. To achieve this, the food industry has used 'model' foods/products. These are simplified products where each formulation variable can be tuned. For example, a range of o/w emulsions with particles (microparticulated whey proteins, MWP) at different concentrations (Liu et al., 2016b) has been used to study the effect of oil and MWP content on sensory and instrumental properties. Model products reduce number of variables, and so allow more robust conclusions and correlations to be drawn.

From a statistical point of view, the majority of correlations in food sciences are based on linear regression or agreement in rank order of sensory assessment and instrumentally obtained values (Szczesniak, 1987, Sarkar and Krop, 2019). Such correlations build an understanding of the processes underlying mouthfeel perception. Once the complexity of a sensory perception is known, multifactorial analysis can be applied (Szczesniak, 1987). By encompassing an array of factors which affect sensory perception, multifactorial analysis provides more meaningful results and predictive capacity. Examples of multifactorial analyses used in food studies include principal component analysis (PCA) or partial least squares (PLS) regression, and generalised Procrustes analysis (GPA) (Chung et al., 2003).

The range of correlations established to date for food products and model foods as well as the mechanistic explanations for these correlations are a good starting point for the development of correlations for oral medicines.

6.1.2 Establishing correlations for oral pharmaceuticals

The need to bridge *in vivo* and *in vitro* palatability data for oral medicines has recently been acknowledged and advocated (Ternik et al., 2018). Once links are established, this knowledge can be leveraged to build predictive models. For taste perception of ODSFs correlations with *in vitro* data have already been established for several methods (e.g. e-Tongue (Uchida et al.,

2003, Nakamura et al., 2015) or BATA rat studies (Soto et al., 2018)). In terms of mouthfeel correlations, the research is limited.

In a literature review on *in vitro/in vivo* methods of mouthfeel assessment Asiri, Hofmanová and Batchelor (under preparation) found only 2 studies which showed explicit correlation, and 4 studies which related formulation properties with perceived mouthfeel (Table 6.1). Considering the statistical methods used to analyse these relationships, the majority of studies did not use predictive tools, but simply compared the differences observed between *in vivo* and *in vitro* data.

The work of Casian et al. (2018) stands out as an exemplar of a study where researchers built a regression model to predict *in vivo* ODTs perception using the PLS method. Model input was based on (i) formulation characteristics (like filler ratio or granule size), (ii) multiple parameters obtained via texture analysis test, and (iii) sensory data. The model was build using a set of ODTs selected by design of experiments (DoE) and validated with marketed ODT formulations. This robust approach allowed prediction of *in vivo* volume of residue and total palatability of ODTs. The statistical approach undertaken in the study and high data input into the model highlight the complexity of palatability/mouthfeel predictions.

In this chapter, the data from previous chapters are linked together. The results of two sensory studies, ease of swallowing sensory study (Chapter 4) and the MASCoT study (Chapter 5) are explored to find correlations with the results from instrumental experiments. Tribological data was taken from Chapter 2; while data on viscosity, wetting properties, adhesiveness and coating thickness from Chapter 3.

Table 6.1 Statistical methods used to analyse the relationship between in vivo *mouthfeel data and* in vitro *measures/formulation properties; ODT – orally disintegrating tablet, ODF – orally disintegrating film, MPs – multiparticulates, DoE – design of experiments.*

Dosage form	Sensory attribute	*In vitro* measure/ Formulation property	Statistical method	Type of analysis	Reference
ODT	Residual volume, palatability	Texture analysis profile (data from load vs time plot and array of selected parameters) + formulation DoE	Multivariate analysis: principal component analysis (PCA) and partial least squares (PLS) regression	Predictive	(Casian et al., 2018)
ODF	Stickiness	Dynamic mechanical analysis (the area under the adhesive force curve corrected for disintegration time)	Friedman analysis of variance followed by Dunn's post hoc test, relationship based on the order of scores	Comparative	(Scarpa et al., 2018)
ODT, granules	Roughness, palatability (after spitting out)	Core granule size	t-test with post-hoc Bonferroni correction; relation based on the rank order of scores	Comparative	(Kimura et al., 2015)
Chewing gum	Chewability	Gum weight	t-test, relationship based on the rank order of scores	Comparative	(Paradkar et al., 2016)
	Softness	Different Types of softening agents	t-test, relationship based on the rank order of scores	Comparative	
MPs	Grittiness	MPs size and amount	Multiple linear regression analysis	Predictive	(Lopez et al., 2016)
Administration media for MPs	Mouthfeel, ease of swallowing, grittiness, residue in mouth	Viscosity, MPs size	Kruskal Wallis H one-way analysis of variance followed by Dunn's test, relationship based on the rank order of scores	Comparative	(Lopez et al., 2018a)

6.1.3 Aims of this chapter

1. Find and explain correlations between sensory attributes and instrumental measurements of coated and uncoated tablets.
2. Employ multifactorial analysis to determine which sensory attributes contribute to the distinction between the tablets and how they relate to the palatability.

6.2 Materials and methods

6.2.1 Formulations

In the work presented in this chapter, data from two batches of tablets were used: oval T_A and round T_B, both prepared by a contracted manufacturer to allow human evaluation. A brief description of the tablets is given in Table 6.2. For full quantitative details on the composition refer to Chapter 2 methods section (Table 2.2).

Table 6.2 List of formulations used in the study.

Formulation	Sample description	Coating ingredients	Tablet core	Final coating level (w/w)*
T_A	Uncoated	-	oval	0%
T_ACoat-1	Standard commercial	Opadry® 03F mix (HPMC-based)	oval	3%
T_ACoat-2	Slippery commercial	Opadry® EZ Swallow white (HPMC-based + guar gum and MCT)	oval	3%
T_ACoat-3	Slippery commercial	Opadry® EZ Swallow white Opadry® EZ Swallow clear (HPMC-based + guar gum and MCT)	oval	3% + 1%
T_BCoat-4	Standard reference	HPMC 5, glycerol	round	4%
T_BCoat-5	Lipid-based	Lubritab®, Capmul® MCM, HPMC 5, talcum, titanium dioxide	round	4%
T_BCoat-6	Slippery	HPMC 5, xanthan gum, glycerol, talcum, titanium dioxide	round	4%
T_BCoat-7	pH dependent	Eudragit EPO readymix, titanium dioxide	round	4%
T_BCoat-8	Insoluble – soluble polymer	HPMC 5, Surelease®, glycerol, talcum, titanium dioxide	round	4%

*as declared by manufacturer
HPMC – hydroxypropyl methylcellulose
MCT – medium chain triglycerides

6.2.2 Data collection

Table 6.3 lists sensory and instrumental variables analysed in this chapter. The *in vitro* data was obtained during instrumental analysis as described in Chapter 2 and 3 using all the tablets. The *in vivo* data was obtained during two human studies, described in Chapter 4 and 5, using two different sets of tablets T_A and T_B, respectively. The sensory variables varied between studies, as indicated in Table 6.3; the study described in Chapter 4 is referred to as the 1st and the one in Chapter 5 as the 2nd study.

The data generated in tribology tests (Chapter 2.1 and 2.2) included multiple data points collected for the length of experiments. For tablet friction tests, the three time points with the biggest difference between the samples were used in the analysis. For thin film tribological testing, correlations were sought across the whole range of sliding speeds. The highest correlation found in a boundary (COF_B) and mixed (COF_M) regime were reported.

Table 6.3 Sensory and formulation variables analysed in this chapter.

Study	Sensory variables	Symbol	*In vitro* variables
1st, 2nd	Ease of swallowing	COF_{static}	Static tablet friction at beginning of test
1st, 2nd	Volume of water used	COF_{10}	Tablet friction at t=10 sec
1st	Time to swallow	COF_{30}	Tablet friction at t=15 sec
1st, 2nd	Stickiness	COF_B	Boundary friction of dissolved coating
1st, 2nd	Slipperiness	COF_M	Mixed friction of dissolved coating
1st, 2nd	Smoothness	η_{50}	Viscosity of dissolved coating at shear rate 50 s^{-1}
1st	Palatability	η_{min}	Minimum viscosity of dissolved coating at high shear (>100 s^{-1})
1st	Rank	Sa_{dry}	Surface roughness of dry tablet
2nd	Bitterness	$Sa_{wetted\ and\ dried}$	Surface roughness of wetted and dried tablet
2nd	Aftertaste (scale)	CAt_0	Contact angle at t_0
2nd	Liking	CAt_{max}	Contact angle at t_{max}
2nd	Sum of negative facial expressions	T	Tack
		S	Stringiness
		AUC	Work of adhesion
		d	Coating thickness

6.2.3 Data analysis

In vivo data was collected using two types of scales: VAS (1st study) and 5-point facial scale (2nd). To enable combined analysis, participant's scores on 5-point facial scales were

recalculated to match responses on 100 mm VAS. Values from 0 to 100 were assigned in increments of 25 to respective points on the 5-point scale. Participants' scores for palatability (1st study) and liking (2nd) were combined into a single variable.

6.2.3.1 Pearson correlation coefficient and linear regression

To assess the strength and direction of correlation between each pair of *in vitro* and *in vivo* variables, Pearson correlation coefficient (Pearson's R) was performed. Pearson's R measures the linear correlation and is expressed as r value between -1 and 1. A value of 1 indicates total positive, −1 total negative linear correlation, and 0, no linear correlation. The average for each *in vitro* and *in vivo* variable was calculated and used in the correlation. Data analysis was carried out using SPSS statistical software version 26 (IBM Corp.). For all correlations, linear regressions were calculated; where a linear regression reached R^2 value >0.8, the data was plotted and the linearity equation reported.

6.2.3.2 Principal component analysis

Principal component analysis (PCA) was used to evaluate which sensory attributes had most discriminating power, which caused clustering of tablets, and to evaluate which attribute related to tablet palatability. In contrast to the analysis carried out in Chapters 4 and 5, where the determinants of tablet acceptability were established for type of tablet, for PCA the data from both studies were combined. PCA was performed using the sensory attributes evaluated in both studies. Data from each individual evaluation of each tablet sample was input into the analysis (a total of 997 observations).

PCA is a statistical procedure applied to multivariate data to reduce the original variables into a lower number of uncorrelated variables called principal components. The first principal component is assigned to account for the largest variability in the data, and the second

captures the next largest variability. The first two principal components form a plane onto which the data are visualised. Data analysis was carried out using XLstat version 2019.4.1 (Addinsoft). Prior to performing PCA, the adequacy of the data for PCA analysis was confirmed using the Kaiser-Meyer-Olkin Measure of Sampling Adequacy test in SPSS.

6.3 Results

The level of correlation between data, presented as Pearson's R value, is shown in Table 6.4. The plots of correlations with very strong association (R^2>0.8) are shown in Figure 6.1.
The highest number of correlations was found for tribological data. The COF_{30} of tested tablets correlated strongly with ease of swallowing and slipperiness, while COF at earlier times during the test, for example 10 seconds, correlated with stickiness. Correlation of COF with both, stickiness and slipperiness, was expected, as these two attributes also were correlated with each other (Chapter 4.4.3 and 5.3.3). Contact angle at t=max was associated with volume of water consumed and bitterness. The correlation between stickiness and AUC was expected, yet not observed for the whole data set Figure 6.1. Notably, when data from T_A and T_B tablets were analysed separately, the link was stronger for batch T_A than T_B (R^2 equalled 0.9298 and 0.1940, respectively).

Table 6.4 Pearson's R values for correlations between sensory and in vitro *variables; data for the sensory attributes in bold where obtained in both sensory studies; correlations in blue are plotted on the Figure 6.1.*

	COF_{static}	COF_{10}	COF_{30}	COF_{B}	COF_{M}	η_{50}	η_{min}	Sa_{dry}	$Sa_{wet\&dry}$	CAt_{0}	CAt_{max}	T	S	AUC	d
Ease of swallowing	-0.766*	-0.810**	-0.944**	NS	NS	NS	NS	0.870**	0.736*	NS	NS	NS	NS	NS	0.776*
Volume of water used	NS	NS	NS	NS	NS	0.783*	0.783*	NS	NS	-0.712*	-0.948**	0.803**	0.694**	0.807**	NS
Time to swallow	NS	0.678*	NS	NS	NS	NS	NS	NS	NS	0.776*	NS	-0.880**	-0.912**	-0.796*	-0.725*
Stickiness	0.763*	0.928**	0.862**	NS	0.757*	NS	NS	0.826**	NS	NS	NS	NS	NS	NS	-0.754*
Slipperiness	-0.824**	-0.866**	-0.945**	NS	-0.831*	NS	NS	-0.754*	-0.836**	NS	NS	NS	NS	NS	0.777*
Smoothness	-0.796*	NS	-0.742*	NS	-0.841**	-0.901**	-0.901**	-0.714*	-0.947**	NS	0.815**	NS	NS	NS	NS
Palatability/Liking	NS	-0.860**	-0.679*	NS	-0.756*	NS	NS	-0.680*	NS	NS	NS	NS	NS	NS	NA
Rank	NS	0.964*	0.973*	NS	NS	NS	NS	NS	NS	-0.972*	NS	NS	NS	NS	NS
Bitterness	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.911*	NS	NS	NS	NS
Aftertaste (scale)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Sum of negative facial expressions	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

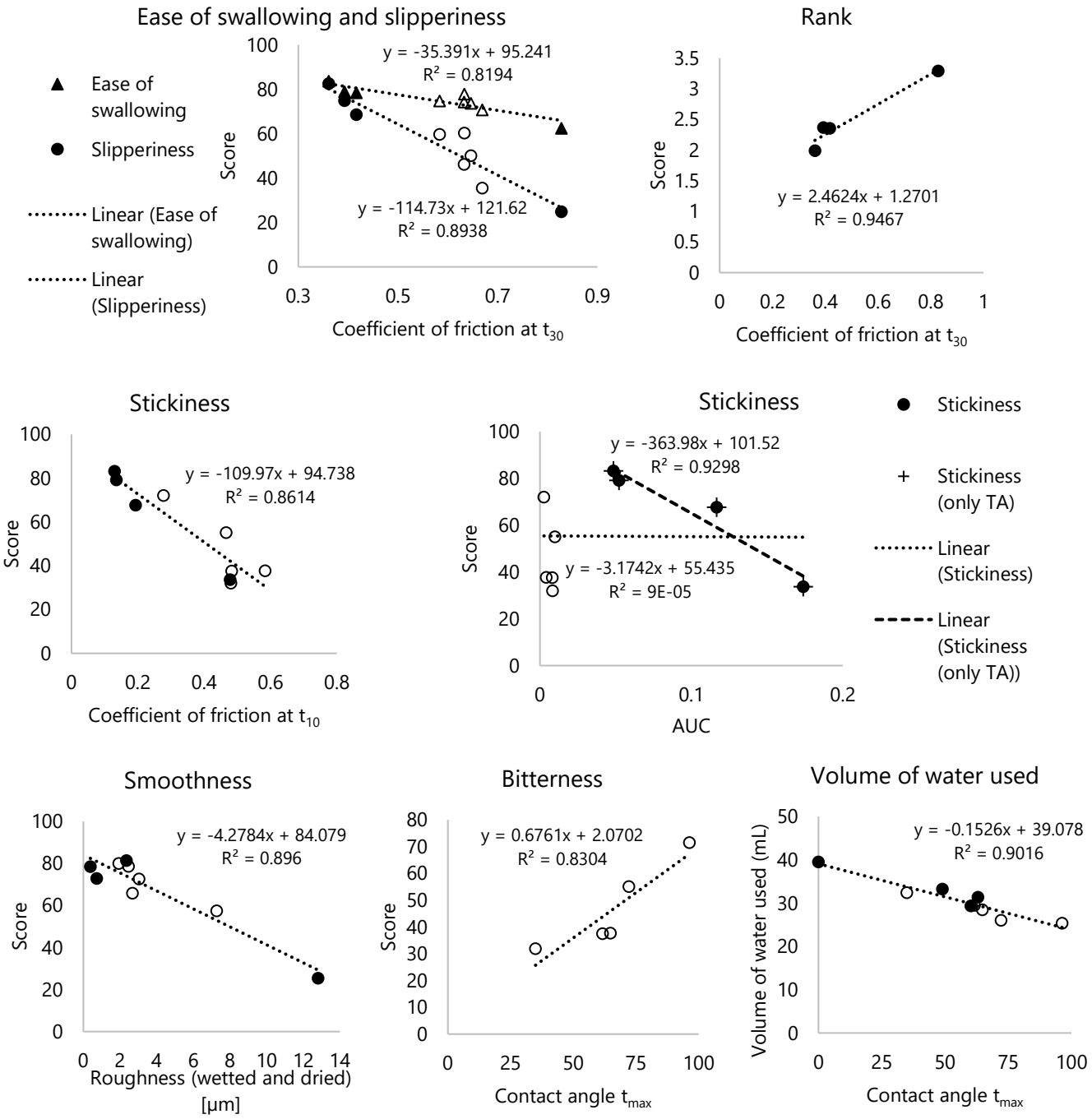

Figure 6.1 Linear regression between sensory (Y-axis) and instrumental (X-axis) data; ●, ▲ – average scores for T_A tablets; ○, Δ – average scores for T_B tablets; correlation is given for both batches combined unless stated otherwise.

PCA

Sensory attributes were analysed with PCA to determine which had most discriminating power and caused clustering of tablets (based on the data from both studies). The PCA model was fitted using 2 principal components, which cumulatively explained 92.45% of

the variability between tablet samples. To identify the attributes that were responsible for the clustering of the tablet samples, data was presented in a biplot (Figure 6.2). The biplot simultaneously represents the variables (sensory attributes; a loading plot) and observations (tablet scores; a score plot) in the PCA space. The first component (F1) explained 71.19% of the data variability, which was due to the attributes with the highest discriminating power: smoothness, slipperiness, stickiness, and ease of swallowing. The second component (F2) clustered the samples based on liking/palatability and volume of water used to take a tablet. The projections of each variable on the loading plot are interpreted with consideration of both clustering and the distance from the centre of the plot. The clustering provides information about the correlation between variables. The distance from the centre indicates the influence of the variable on the principal component.

Distance between samples indicates dissimilarity, while extent of the ellipse overlap indicates similarity. The uncoated T_A tablet was located the furthest from other samples indicating large sensory differences between them. Tablets associated with high palatability, T_ACoat-2, -3 and -1, were located in top right quadrant. They received higher scores for slipperiness, ease of swallowing, low stickiness (a high score indicated low stickiness).

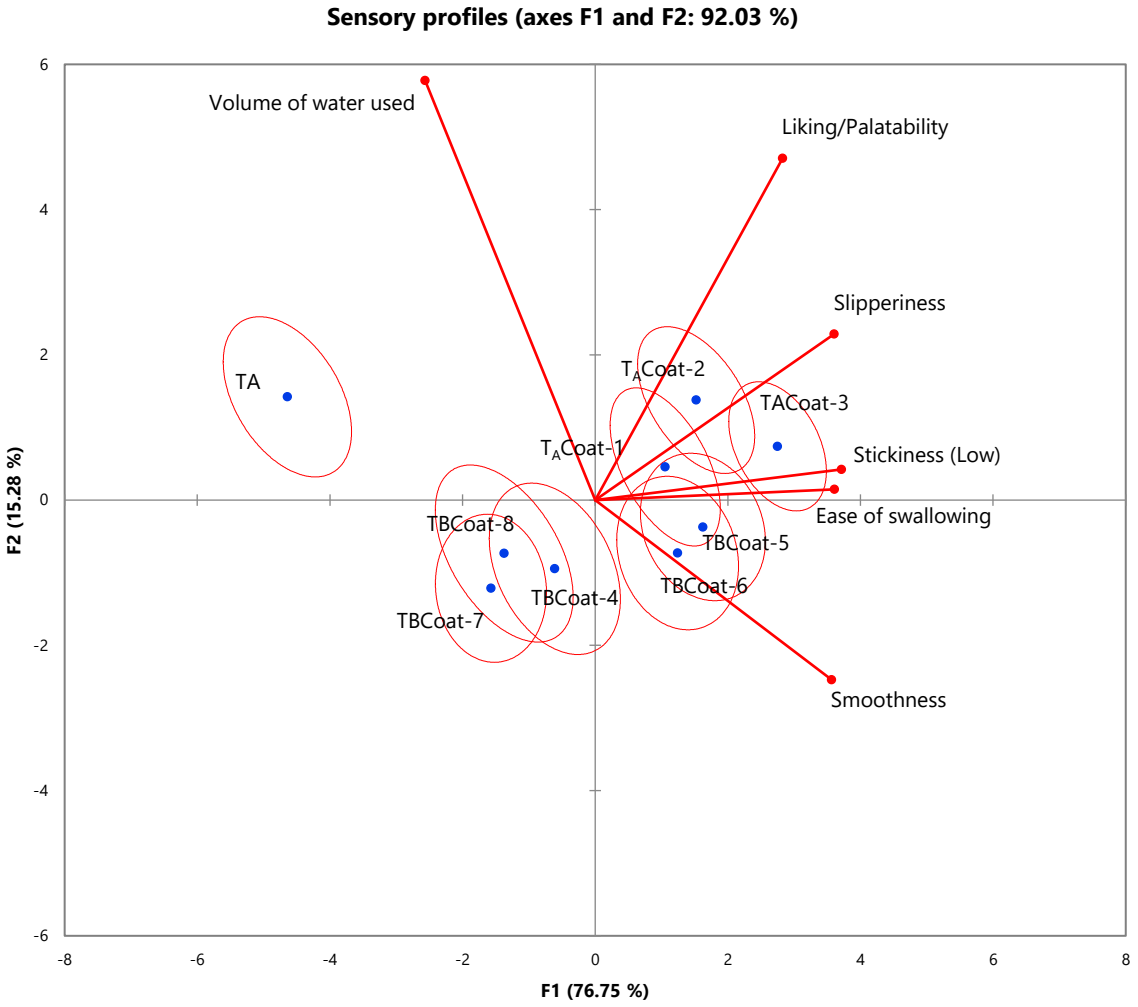

Figure 6.2 PCA biplot; F1 – first principal component, F2 – second principal component, blue dots – central point of scores for each tablet, ellipse – area of 95% confidence for each tablet sample, red dots – projections for variables.

6.4 Discussion

6.4.1 Explanation of the *in vivo – in vitro* correlations

In order to establish meaningful *in vivo – in vitro* correlations one needs to examine the logical link between the two variables being compared. As, statistical methods do not consider the context of the experiment, the results need to be interpreted to avoid erroneous conclusions. For example, the correlation between perceived smoothness and measured roughness was expected and found (R^2=0.896). However, bitterness was found to correlate with contact angle (CAt_{max}, R^2=0.830), which could lead to the incorrect statement

that the wetting properties of tablet sample reflect the perception of bitterness. The true reason for this correlation lies in the fact that the wetting properties provided information about the durability of the coating in wet conditions (Chapter 3.4.3). This, in turn, can indicate whether the coating forms a sufficient barrier for efficient taste-masking. The lower CAt_{max}, the weaker the coating, which results in quick release of quinine molecules, and hence perception of bitterness. CAt_{max} was also associated with the volume of water consumed. The link between these variables can be explained as follows: in the mouth the tablet is wetted by saliva, which creates a lubricating layer on the surface of the tablet to allow easy passage during the swallowing process. For the lubrication layer to be effective, it needs to stay on the tablet surface, i.e. a tablet which absorbs the saliva would impede lubrication. By measuring CAt_{max}, the interaction between water and tablet (coated tablet) can be established. As shown in Chapter 3.4.3, low values of CAt_{max} indicated water absorption by a tablet. It could be argued that by absorbing the water, the tablet reduced the volume of lubricant available, therefore more water was needed to swallow the tablet. These two examples show that correlation does not indicate causation.

This thesis describes the relationship between tribology and oral sensory perception of conventional tablets for the first time. Correlations were demonstrated between friction of tablets (COF_{10} and COF_{30}) and multiple sensory attributes (Table 6.4). For perceived ease of swallowing, rank (of ease of swallowing), slipperiness and stickiness the relationship was linear ($R^2 > 0.8$, (Figure 6.1)). The link between these attributes and friction is logical, thus the interpretation of correlation can be literal. Notably, the highest correlation with stickiness was found for the COF at 10 seconds, while for slipperiness it was found at 30 seconds. This can be explained by combination of two factors: increasing sliding speed during the test (v_s (t_{10}) = 1.6 mm/s, v_s (t_{30}) = 4.6 mm/s) and the fact that slipperiness assessment in the mouth

requires faster oral movements than stickiness assessment. An alternative explanation is that during testing a tablet undergoes structural changes, the same as it would in the mouth during sensory assessment. These structural changes resulted in variation of friction during the test. Similarly, sensory perception is also sensitive to product changes, which is reflected by different attributes being most intense at different times during a product's residence in the mouth (de Wijk et al., 2011).

Considering the link between thin film tribology (COF_B and COF_M) and sensory attributes, the correlations are significant, yet not linear. It is important to acknowledge that lack of a linear correlation, should not lead to a dismissal of the results from instrumental methods. Yet, more caution is necessary to interpret these correlations. In this thesis, it was hypothesised that a coating dissolves/disperses in the mouth of the participant, thus the lubricity of the dispersed coating affects the mouthfeel. As discussed in Chapter 2.2.3.2, the lubricity of the dispersed coatings was related to their viscosity, oil content and presence of insoluble particles. Many previous studies explain the tribology–sensory correlation with foods in similar ways (de Wijk and Prinz, 2005, Dresselhuis et al., 2008a, Laguna et al., 2017, Laiho et al., 2017, Krop et al., 2019). Based on the findings in this thesis, thin film tribology cannot be used as a predictor of sensory attributes but can help the understanding of mouthfeel perception.

Linking tribology measurements to sensory attributes is a fast-developing trend in food science, in particular for liquid and semi-liquid products (Sarkar and Krop, 2019, Shewan et al., 2019). Reports on solid foods are limited to bread, where firmness, chewiness, and dryness have been positively correlated with tribological measurements (Kiumarsi et al., 2019). The low precedence of solid foods in tribological testing, can be attributed to the fact

that only certain types of tribometers allow such testing (Chapter 1.4.3.1.2). In addition, tribological measurements for liquids allow the study of microstructure and behaviour of individual components (e.g. particles or droplets), while for solids, tribology only allows the study of surface properties. However, in case of OSDFs, which are swallowed as a whole, it is the surface which triggers the mouthfeel perception; thus, application of tribology is relevant.

6.4.2 Benefits of multifactorial modelling

Correlations established with Pearson's R are limited to one pair of variables. As sensory perception of oral medicine is multifactorial in nature, a predictive model based on multiple variables, would be more accurate (Szczesniak, 1987, Sarkar and Krop, 2019). Performing PCA allowed exploration of the data as a whole to observe trends. The results were interpreted using graphical representation of samples and sensory attributes projections in the biplot. Analysis of sample clustering and attributes' projections helped to describe the sensory characteristics of tablets, identify similar tablets, as well as distinguish between tablets of higher and lower palatability.

As discussed by Szczesniak (1987), instrumental methods cannot directly predict consumer (patient) acceptance of a product, as the acceptance is a hedonic response based not only on sensory but also psychological input. Nevertheless, taking into account the multifactorial nature of acceptability, a predictive model could be built (e.g. ODT (Casian et al., 2018), rice (Okabe, 1979), peanuts (Lee and Resurreccion, 2006), kimchi (Cho et al., 2015), sausage (Lopez et al., 2012)). Firstly, the relationship between sensory attributes and acceptability need to be demonstrated. Secondly, the intensity of mouthfeel attributes would need to be linked with consumer liking (this concept is also discussed in Chapter 7.4, where appropriate

sensory evaluation methodology is proposed). Then, the instrumental method with predictive capacity would need to be developed. Once data from all these steps is pulled together, a model could be built using sophisticated statistical methods, e.g. PLS regression. Notably, the first study of this kind involving oral medicines has been performed on ODTs (Casian et al., 2018), and was able to predict palatability and volume of residue in the mouth.

6.4.3 Challenges of *in vivo/in vitro* predictions

In food sciences, significant developments have been made in the fields of texture/mouthfeel predictions. These advances have resulted from a long learning curve with many mistakes along the way, thus, top food scientists advise caution in interpretation and generalisation of correlations found (Stokes et al., 2013, Szczesniak, 1987, Adhikari et al., 2001, Sarkar and Krop, 2019). Their main reservations relate to:

- multimodality of sensory attributes,
- insufficient understanding of the principles of perception of a given attribute,
- insufficient understanding of the mechanistic principles underlying the correlations,
- nature of instrumental tests, failing to mimic the oral environment,
- difficulties in comparing experiments, due to (i) the variability of human panels and (ii) non-standardised *in vitro* methodologies.

Therefore, the development of generalised correlations is key to increase knowledge on mouthfeel perception, and ultimately to lead to harmonisation of *in vivo* and *in vitro* methodologies for oral pharmaceuticals.

Despite the challenges, attempts to bridge sensory and instrumental methods for oral pharmaceuticals has been undertaken by several researchers (Lopez et al., 2016, Casian et al., 2018) and also in this thesis. Due to the interest in this area, taking the lessons from food sciences means that advances inevitable and likely to be imminent.

6.4.4 Practical implications

Up to this stage, the study presented in this chapter has established linear correlations which can predict the sensory attributes of conventional tablets from instrumental data. Attributes which were predicted accurately were smoothness, slipperiness, and ease of swallowing. These attributes were also found to determine the acceptability of tablets in children and adults (Chapter 4.4.5 and 5.3.6). As discussed previously (Chapter 1.2), the need to develop acceptable formulations, especially for paediatrics, has been emphasised by regulators. The capability to predict acceptability determinants *in vitro*, therefore, has considerable beneficial practical implications. It would bring multiple benefits to the pharmaceutical industry. For example, in the research and development process, *in vivo* acceptability studies are costly and time consuming. *In vitro* methods could benefit the formulation development process as a screening tool to enable selection of optimised samples for human testing. As such, the ability to shift part of the acceptability evaluation to preclinical *in vitro* studies is an awaited advancement. *In vitro* predictive tools have the potential to advance the development of acceptable medicines. In the manufacturing process, standardisation of the methods developed could lead to their incorporation into routine *in vitro* quality testing of final manufactured batches. In this manner, it also has the potential to improve brand profile. Increased acceptability and a preference for particular brand is beneficial for products where there is consumer choice such as medicines that can be bought without prescription. Overall, acceptable medicines benefit patients due to improved adherence and thus better treatment outcomes.

6.4.5 Limitations

There are some limitations to this study. Due to lack of standards, the *in vivo* methodology was developed in-house. Several sensory attributes were not included in the analysis as they did not overlap between the 1st and 2nd study. To surpass these limitations, future studies would benefit from a standardised *in vivo* methodology, where the questionnaires, procedures, and assessed attributes would be exactly the same.

Moreover, the study only incorporated a limited number of tablet types: two sizes, two shapes, and eight coatings, hence is not representative of the vast array of tablet formulation possibilities. Extending the spectrum of OSDF analysed by including, for example, 2 mm minitablets, caplets, soft and hard capsules would increase the power of correlations.

6.5 Conclusions

Considering the multifactorial nature of sensory perception, multivariate statistical analysis is required to generate more accurate, predictive results. In this study, multivariate PCA analysis was used to explore the *in vivo* data from the two sensory studies. Sample clustering proved useful in describing the sensory characteristics of tablets. It also allowed tablets with higher and lower palatability to be identified. However, higher level statistical analysis, encompassing the entirety of the *in vivo* and *in vitro* data would allow a predictive model to be built which would encompass all measurable attributes. Further work would involve using partial lease squares regression for predictive modelling.

Even in the absence of data from a vast array of OSDF, this study has revealed links between mouthfeel attributes and instrumental analysis of conventional tablets using pairwise statistical analysis. For the first time, the linear relationship between tribology and the oral sensory perception, i.e. ease of swallowing, slipperiness, and stickiness, of conventional

tablets is described. Moreover, strong correlations between perceived smoothness and instrumentally measured tablet roughness have been established. While these results need to be interpreted with caution due to the infancy of the research area, interpretation of the links established increases the understanding of the processes underlying sensory perception and importantly, it appears that the linear equations obtained for these correlations can be used as a predictive tool.

7 Lexicon

7.1 Introduction

Sensory science measures how people perceive and respond to sensory stimuli. This knowledge permits a systematic understanding of the relationship between formulation properties of a product and consumer preferences.

The study of oral medicine acceptance and palatability is challenging without an understanding of the factors that govern the sensory experiences triggered when taking a medicine. Unlike in food sciences, the knowledge of patients' sensory experience during medicine administration is limited. Food scientists have developed and validated an extensive lexicon of terms to describe the sensory experiences triggered by different product attributes, with precise and unambiguous meanings. These clearly defined terms comprise sensory attributes that can be further evaluated and scaled using a range of products that act as intensity references. For example, gelatine dessert, potato chip and thin bread wafer can be used to anchor low, medium and high levels of roughness respectively (Lawless and Heymann, 2010d). The terminology for pharmaceutical sensory studies needs to be created separately to food sensory analysis due to the different oral residence-time of the product and different acceptability definitions. It is not essential for a medicine to provide a pleasant impression, rather a neutral taste and texture, or "non-disturbing" experience is desirable (EMA, 2013). The lack of diversity in the sensory attributes of pharmaceutical products, leads to difficulties in obtaining a reference intensity scale.

A lexicon of sensory attributes is necessary to have well defined sensory tasks and clear communication of meanings (Dubois, 2006). The initial step required to advance the field of pharmaceutical sensory analysis is to generate an adequate lexicon. In food science, lexicon

development starts with the generation of a list of words/phrases relevant to the product by a trained panel or a large group of consumers who test and describe the product (Lawless and Civille, 2013). The next step is to analyse the appropriateness and semantics of each attribute. According to several authors, attributes which are generated in the highest numbers are the ones most relevant for consumers (Henley, 1969, Szczesniak and Kahn, 1971, Antmann et al., 2011). Relevant attributes must then be associated with explicit definitions. The final step is to discuss the intensity scale of each attribute and identify product references for maximum and minimum intensity. In this way, a lexicon for a food product can be built up, with the provision that a lexicon is never complete, and should be revised and updated e.g. when a new product appears for which current lexicon is not sufficient (Lawless and Civille, 2013). For pharmaceuticals, a product specific lexicon can be created in an analogous way. A validated lexicon for conventional tablets would be useful during development to describe the sensory properties of a new product in a standardised way. Providing that the attributes are scalable and the cut-off for a pleasant/unpleasant intensity is known, a sensory evaluation would precisely determine whether a product would be palatable or not.

Sensory wheels are widely used in food science to help assessors define taste, flavour and other characteristics of a product (Lawless and Civille, 2013). A sensory wheel is a comprehensive collection of all the sensations that can possibly be triggered by a product. By categorising and subcategorising the sensations, an assessor can easily orientate within the attributes; the most general descriptors lie inward, and more specific outward (Figure 7.1). As discussed by Imamura (2016) sensory wheels allow understanding of the sensory attributes of the product and facilitate systematic assessment. In turn, using sensory wheel benefits product developers, quality control, and ultimately the patient.

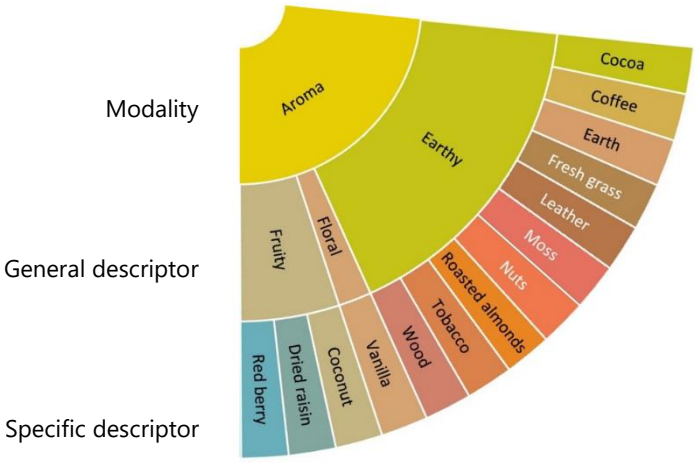

Figure 7.1 A segment of chocolate sensory wheel representing categorisation of sensory attributes, retrieved from De Pelsmaeker et al. (2019) with permission of Elsevier.

A deeper understanding of the oral perception of medicines is important at multiple levels. Firstly, to identify attributes influencing palatability and acceptability. Secondly, to explore the sensitivity of the patient to different sensory attributes perceived during medicine intake in order to determine the range of intensity of these attributes within the limits of acceptability. And lastly, to develop a lexicon of attributes to standardise the vocabulary used. Ultimately, lexicons for all oral dosage forms could be used as a product development tools to predict acceptability and palatability during clinical testing.

7.1.1 Aims of this chapter

In this chapter, the sensory attributes of conventional coated tablets, as a model oral medicine were explored to:

1. Generate a sensory wheel containing comprehensive collection of all the attributes that can possibly be triggered by a tablet;
2. Develop a lexicon of attributes which are most relevant for tablets.

To achieve that two sets of tablet samples were used. Methodology was adapted from the one used in food sciences.

7.2 Materials and methods

7.2.1 Formulations

In the work presented in this chapter two batches of tablets were used: oval T_A and round T_B, both prepared by a contracted manufacturer to allow human consumption. A brief description of the tablets is given in Table 7.1. For full quantitative details on the composition refer to Chapter 2, methods section (Table 2.2).

Table 7.1 List of formulations used in the study.

	Formulation	Sample description	Coating ingredients	Tablet core shape	Final coating level (w/w)*
First set of samples	T_A	Uncoated	-	oval	0%
	T_ACoat-1	Standard commercial	Opadry® 03F mix (HPMC-based)	oval	3%
	T_ACoat-2	Slippery commercial	Opadry® EZ Swallow white (HPMC-based + guar gum and MCT)	oval	3%
	T_ACoat-3	Slippery commercial	Opadry® EZ Swallow white Opadry® EZ Swallow clear (HPMC-based + guar gum and MCT)	oval	3% + 1%
Second set of samples	T_BCoat-4	Standard reference	HPMC 5, glycerol	round	4%
	T_BCoat-5	Lipid-based	Lubritab®, Capmul® MCM, HPMC 5, talcum, titanium dioxide	round	4%
	T_BCoat-6	Slippery	HPMC 5, xanthan gum, glycerol, talcum, titanium dioxide	round	4%
	T_BCoat-7	pH dependent	Eudragit EPO readymix, titanium dioxide	round	4%
	T_BCoat-8	Insoluble – soluble polymer	HPMC 5, Surelease®, glycerol, talcum, titanium dioxide	round	4%

*as declared by manufacturer
HPMC – hydroxypropyl methylcellulose
MCT – medium chain triglycerides

7.2.2 Procedure

Building-up a lexicon for a tablet requires a multi-step process. Figure 7.2 presents the pathway taken in this study. Firstly free-text, descriptive analysis was employed with

a first set of tablet samples, without giving any suggestive clues to the assessors. Then, the collected attributes were validated with second set of tablet samples.

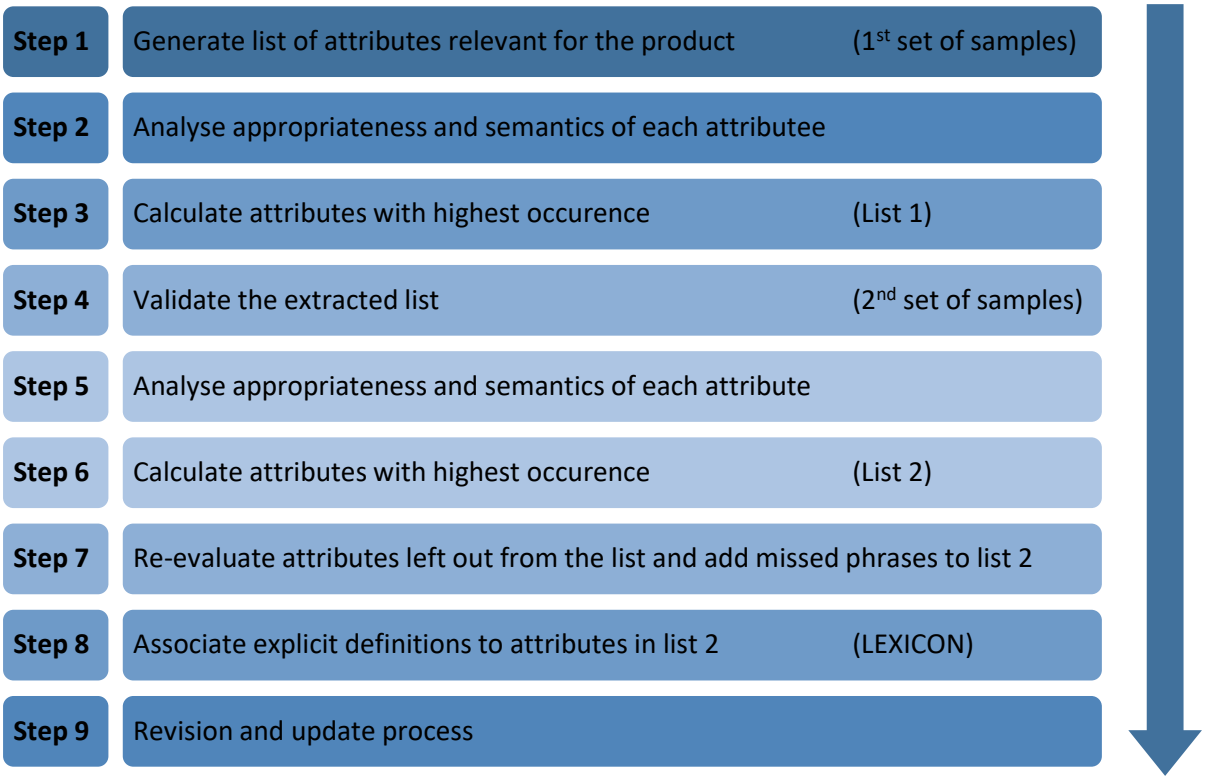

Figure 7.2 Process of building a lexicon for tablets; Step 9 is a prospective process, undertaken when current lexicon requires amendments.

7.2.2.1 Data collection

Data collection of words and phrases describing the tablets was done during the two clinical studies discussed in previous chapters. During the first study (Chapter 4), the sensory assessment of the 1st set of samples (T_A) was performed and the list of attributes relevant for the product was generated (Figure 7.2, Step 1). The "sensory panel" consisted of 83 healthy untrained adult participants. The methodology is described in Chapter 4.3.5. In brief, all participants were presented one uncoated tablet and three coated tablets, containing no flavour, in a randomised order. A palate cleanser was provided before each sample. The participants were instructed to hold the tablet in their mouth, one at a time, for

10 seconds and feel its surface with their tongue. After assessment, the tablet was spat out or swallowed, according to each participant's preference. Immediately after, the participants were asked to "describe in 3 words how the product feels in the mouth" (free text) (Appendix C). Based on the words and phrases collected, an alphabetical list of attributes was created (List 1). List 1 was created after data cleaning (see below) and did not include hedonic terms.

During the second study (Chapter 5), sensory assessment of a 2nd set of tablet samples (T_B) was performed and List 1 of the attributes was validated (Figure 7.2, Step 4). Validation involved using the attributes from List 1 to describe the 2nd set tablets (T_B) so as to determine which attributes allowed the participant to describe the sensory properties. The sensory panel comprised 52 healthy untrained adult participants. The methodology is described in Chapter 5.2.5. In brief, all participants received five coated tablets, containing a bitter flavour (quinine), in a randomised order. A palate cleanser was provided before each sample. The participants were instructed to hold the tablet in their mouth, one at a time, for 5 seconds and feel its surface with their tongue. After assessment, the tablet was spat out or swallowed, according to each participant's preference. Immediately after, the participants were asked to "describe in 3 words how the product feels in the mouth" (free text) (Appendix G). They were presented with attributes from List 1 as a prompt. The attributes which were chosen from List 1 were regarded as "validated" as they were relevant for the description of tablets. Participants were also allowed to add words or phrases not already on List 1.

Between the first and second clinical studies, there were a few differences in the sensory assessment procedure. Tablets of T_B batch contained bitter agent – quinine, which taste was masked with a coating layer. Thus, in the second study, the uncoated tablet was not included to prevent carry over effect of quinine's strong taste from the uncoated tablet to the coated

ones. Furthermore, the assessment time was 5 seconds, in contrast to 10 seconds in the first study, to provide better discrimination between taste-masking effects of the coatings as this was the primary purpose of the study.

7.2.2.2 Data analysis

7.2.2.2.1 Data cleaning

Quantitative descriptive analysis was performed on participant "free text" comments in study 1. Comments were transcribed, unified grammatically, and shortened without any change of meaning. The qualifiers (e.g. little, slightly) and illegible responses were disregarded. The appropriateness and semantics of each attribute were then analysed (Figure 7.2, Steps 2 and 5). Terms with redundant, vague meanings or non-existent words were excluded. For example, *non-descript* or *unambiguous* were deemed vague descriptions. Also, terms like *uninvasive* or *an object in the mouth* were eliminated as they were not appropriate to sensory perception.

7.2.2.2.2 Hedonic terms

Hedonic terms (e.g. pleasant, bad) were excluded from the lexicon development step. Based on their semantics, a positive, negative, or neutral connotation was assigned to observe trends of use.

7.2.2.2.3 Lexicon development

The frequency of collected attributes was calculated (Figure 7.2, Steps 3 and 6).
The attributes with more than 7 mentions were considered for inclusion in the lexicon. Sensory attributes were subjected to term reduction. It is assumed that the number of attributes for efficient sensory evaluation is about 20 (Vannier et al., 1999), which was the aim for term reduction. The attributes which had opposite meanings were reduced to a single

term, e.g. *dissolving/ not dissolving* were reduced to *dissolving*. Terms which described intensities of a single attribute were also reduced to one term, e.g. *gluey, tacky* were reduced to *sticky;* also, synonyms were deleted, e.g. moves *easily/slides easily/movable* were reduced to *moves easily*. Ambiguous attributes e.g. *clear*, which can express different meanings, such as *clean, plain*, or *transparent*, were excluded from the lexicon to reduce the risk of misinterpretation. The descriptors mentioned most frequently were revisited and definitions for these terms were established (Figure 7.2, Steps 7 and 8). Definitions were created based on the sensory analysis standard (International Organization for Standardization, 2008) and the sensory evaluation handbooks (Meilgaard et al., 2006, Lawless and Heymann, 2010c), Cambridge English Dictionary (2019) or other lexicons.

7.2.2.2.4 Generating a sensory wheel

A sensory wheel was generated by collective analysis of data from both tablet batches. The collected attributes, after data cleaning and terms reduction, were grouped into categories based on the sense involved the perception of each sensory attribute. For example, *smooth* was allocated to the tactile category, *sweet* to taste, and *shiny* to the visual category. An additional category, motion, was created to gather descriptors referring to movement of the tablet sample or changes of sample occurring during assessment. Hedonic terms were excluded. The sensory wheel was generated using XLSTAT version 2019.4.1 (Addinsoft).

7.2.2.2.5 Sample types comparison

Separate from generation of the lexicon and sensory wheel, the attributes collected from both studies were analysed to compare the sensory perception of the different sample types. The tablet samples used for both studies were categorised into three different types;

uncoated T_A tasteless, coated T_A tasteless and coated quinine flavoured T_B tablets (Table 7.1). The attributes related to each tablet sample type across the two studies was compared to determine the impact of coating and flavouring on taste and mouthfeel. For each tablet sample type, the relative frequency of attributes was calculated. The attributes which were mentioned in at least 5% of comments are reported (Koch et al., 2012).

7.3 Results

7.3.1 Generating descriptors

The participants generated 883 comments in the first study (n=83 adults) and 730 comments in the second study (n=52 adults) (Table 7.2). The responses varied from single word (e.g. *smooth*) or even exclamations (*Ugh*) to full sentences (e.g. *didn't think it would ever dissolve if I couldn't swallow it*). A full list of participant comments is available in Appendix D and Appendix H . Table 7.3 presents the hedonic terms used by participants, assigned to a positive, neutral or negative meaning. These hedonic terms were not included in the lexicon.

Table 7.2 Frequency of collected participants' comments and terms.

Number of cases	First study	Second study
All comments	883	730
Valid comments	808	719
Varying non-repetitive terms	130	123
Hedonic terms	30	17
Sensory terms	100	106
Shared sensory terms	69	
Unique sensory terms	31	37

Table 7.3 Hedonic descriptions used by participants.

Positive	Neutral	Negative	
acceptable	*not too bad*	*bad taste*	*not nice*
comfortable	*not as bad as the*	*bad aftertaste*	*odd*
fine	*others*	*bad texture*	*strange*
good	*not bad*	*disgusting*	*terrible*
nice	*not uncomfortable*	*distasteful*	*ugh*
palatable	*not unpleasant*	*horrible*	*uncomfortable*
pleasant	*ok*	*I don't like it*	*unpleasant*
preferred		*I didn't enjoy this tablet*	*untasty*
started to like it		*nasty*	*weird taste*
tasty		*not good*	*yuk*

7.3.2 Lexicon development

The lexicon was built to capture and define attributes that are fundamental for the sensory description of tablets. After data cleaning, one hundred sensory non-repetitive terms were collected using the first tablet sample set. These were analysed for frequency of occurrence. As a result, List 1 consisting of 74 terms was created (Table 7.4). These terms were validated using the second tablet sample set, where participants chose the best terms from List 1 to describe tablet samples. Note that attributes including *bitter*, *sticky*, *smooth, rough*, *slippery*, and *aftertaste*, although relevant for the tablet lexicon, were not included in the list, because participants were rating them separately on the VAS as part of the study. Table 7.4 shows all the words from List 1 and their frequency of use during validation (within 2nd study). Participants used 61/74 of suggested words and generated further 37 terms.

Table 7.4 List 1: Seventy-four terms collected with the first table sample set with frequency of use with the second sample set; shaded area - List 2: thirty-eight most frequently used attributes.

neutral	35	*dusty*	11	*floury*	6	*gloopy*	1
chalky	30	*light*	11	*soft*	6	*minty*	1
dry	26	*plastic*	11	*thick*	6	*pointy*	1
solid	25	*doesn't fall apart*	10	*pasty*	5	*spongy*	1
chemical	24	*doesn't melt*	10	*artificial*	4	*aniseedy*	0
movable	20	*glazed*	10	*gooey*	4	*big*	0
moves easily	19	*silky*	10	*melts*	4	*disintegrating*	0
rounded	19	*alkaline*	9	*not movable*	4	*falls apart*	0
bland	18	*clingy*	9	*shiny*	4	*fizzy*	0
plain	18	*grainy*	9	*solvent taste*	4	*fluffy*	0
small	18	*no flavour*	9	*creamy*	3	*furry*	0
matte	17	*dissolving*	8	*granular*	3	*gelatinous*	0
synthetic	16	*gluey*	8	*gritty*	3	*glutinous*	0
unnatural taste	16	*no edges*	8	*not tacky*	3	*large*	0
slick	15	*doesn't dissolve*	7	*starchy*	3	*mushy*	0
powdery	13	*mobile*	7	*adherent*	2	*pliable*	0
clean	12	*slimy*	7	*bumpy*	2	*soggy*	0
hard	12	*tacky*	7	*loose*	2		
no taste	12	*tasteless*	7	*crumbly*	1		

Selection of descriptors

The data set of the attributes most frequently mentioned (over 7 times) during the first and second study (List 2) (Table 7.4) was revisited and considered for the lexicon. After term reduction, twenty-two terms were selected and defined as presented in Table 7.5. Of these, ten were related to texture, three to taste, two to flavour, two to visual perception, three to change-of-state of the sample, and the remaining two were not classified. A reference product and scale were not assigned for each attribute, due to the sparsity of knowledge on the intensity range appropriate to OSDFs and ethical considerations regarding the use of actual medicines as reference products. The use of placebo tablets was considered but dismissed as they may not be a relevant reference point for all attributes.

Table 7.5 Tablet lexicon with sensory attributes definitions. Definitions were based on [1] ISO standard, textbooks [2] Meilgaard et al. (2006), [3] Lawless and Heymann (2010c), [4] Cambridge English Dictionary (2019) or other lexicons [5] (Civille et al., 2010), [6] (Kim et al., 2013), NA - not available.

Attribute	Definition	Ref
Texture		
Chalky	A term used to describe texture associated with chalk, dry sensation in the mouth	[2]
Dry	Free from moist or liquid, perception of moisture being absorbed by product	[1], [4]
Powdery	Amount of fine particles on the surface or as bulk product	[5]
Slippery	Degree to which sample slides across the tongue/palate	[2]
Adhesiveness	Degree to which the sample adheres to mouth surfaces: lips, tongue, palate, teeth (with increasing intensity level: tacky, clinging, gooey – gluey, sticky – adhesive)	[1]
Slimy	Covered in a sticky, smooth, liquid substance, as liquid covering snails	[4]
Smooth	Having regular/even surface, lack of lumps or abrasive particles	[2]
Rough	Degree of irregularity/unevenness of the product's surface; assessed by rubbing the surface	[5]
Granularity	Containing particles/granules detected by assessed by rubbing product between tongue and palate (with increasing intensity and particle size: smooth, gritty, grainy, beady, granular, coarse, lumpy)	[1]
Hard	Force required to compress/break the sample	[1]
Taste		
Sweet	Basic taste sensation characteristic to sucrose and other sugars	[1]
Bitter	Innately aversive basic taste sensation characteristic to caffeine	[1]
Tasteless	Having no taste, lack of chemical stimulation of taste buds	[4]
Flavour		
Chemical	Flavour associated with artificial products	NA
Aftertaste	Taste or odour sensation that occurs after the elimination of the product	[1]
Visual perception		
Size	Relative description of size (small – large)	[4]
Gloss	The tendency of a surface to reflect light (Shiny – Matte**)**	[1]
Change-of-state		
Dissolving	Degree to which the core of the sample dissolves in contact with saliva	NA
Disintegrating	Degree to which the core of the sample breaks up into small parts in contact with saliva	NA
Solid	Keeping a clear shape, object without any spaces or holes, integrity of shape	[2]
Other		
Ease of swallowing	The amount of effort required to swallow the sample	[6]
Neutral	Lack of dominant or noticeable characteristics	[1]

7.3.3 Sensory wheel

Organisation of terms into a sensory wheel provides an overview of sensory attributes for a tablet product and makes finding terms associated with the particular attributes of a product easier than if using a list. The relevant attributes collected in both studies,

excluding hedonic terms, were grouped into categories based on the type of stimuli, and presented in a form of sensory wheel (Figure 7.3). Five categories were used: touch, taste, vision, motion, and others.

Attributes perceived by touch were further organised into groups related to product surface, structure, and hardness of the sample. Due to their relative abundance, terms describing varying levels of stickiness were assigned a separate group. Participants reported a sensation of 4 out of 5 basic tastes; only umami was not represented. Even though tablets were unflavoured, some responses mentioned a *minty* or *aniseedy* flavour. Several terms describing the visual perception of the tablets were collected, these related to size or surface. None of the participants generated attributes describing smell or hearing perception. Some participants reported that the sample underwent a change of structure in the mouth (e.g. *disintegrate, dissolve, and melt*). These were grouped into a motion category.

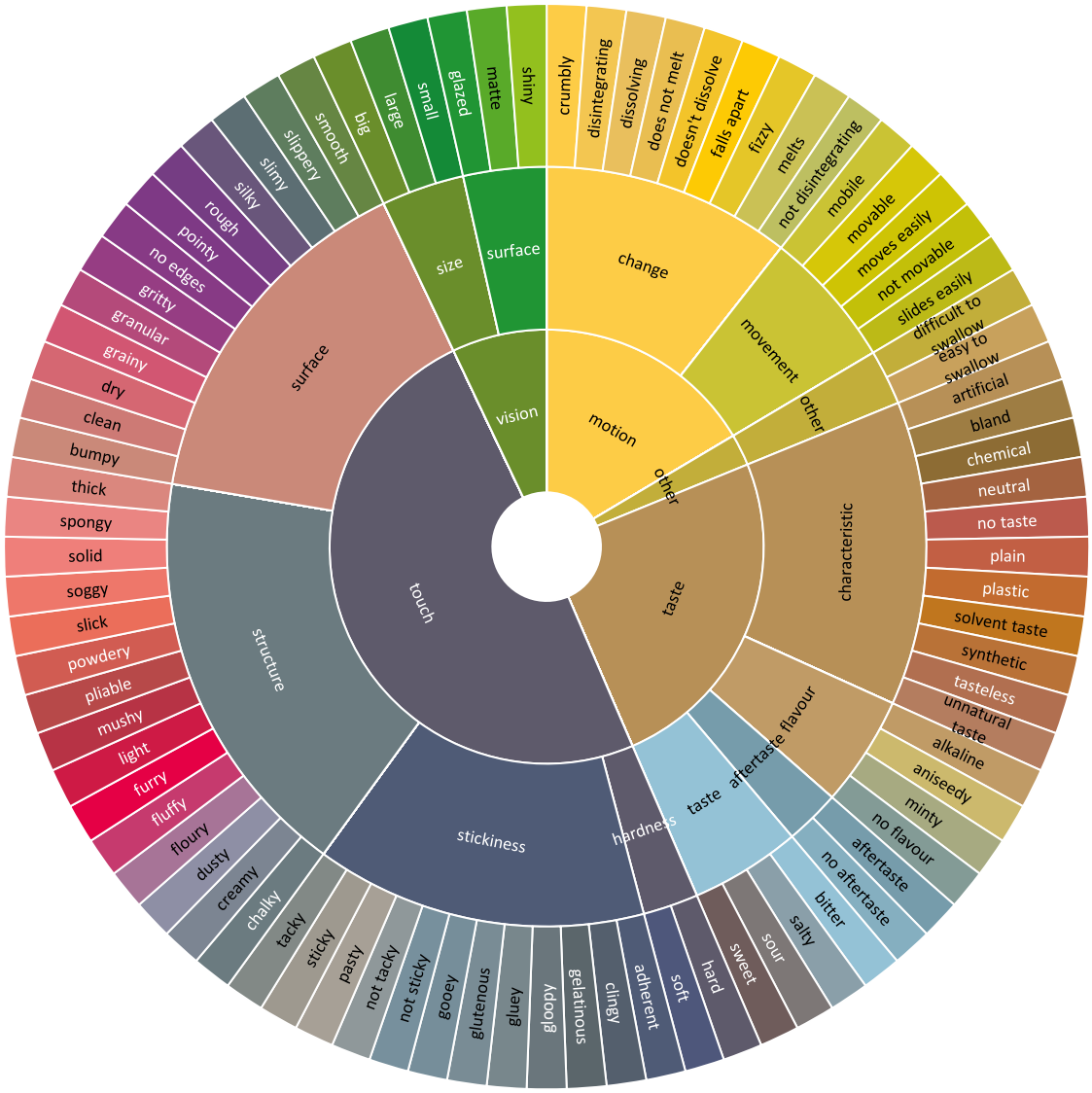

Figure 7.3 Sensory wheel for conventional tablets.

7.3.4 Comparison between samples types

Figure 7.4 shows the attributes used to describe the three sample types: uncoated T_A tasteless, coated T_A tasteless and coated quinine flavoured T_B tablets, only the terms reported in at least 5% of the participant comments for each tablet type are given. Comparison of terms used to characterise coated vs. uncoated tablets highlighted potential sensory issues with a product that may increase/reduce the acceptability Among coated tasteless tablets (T_ACoat-1–3) terms like *smooth*, *slippery* and *neutral/tasteless* dominated. In contrast, the uncoated tablet (T_A) was described as *rough*, *powdery* and *dissolving*. A higher

number of attributes relating to change of structure were reported for the uncoated tablet (28% mentions of *dissolves* and 6% mentions of *melts*), suggesting that it was a common occurence during the oral processing of this tablet.

The second set of tablets (T_B) were given to participants alongside a list of attributes to choose from (List 1). Participants were prompted by the list and so, were more likely to choose attributes on the list resulting in more attributes with frequencies of >5% (Figure 7.4). The most popular attributes associated with quinine flavoured tablets were *neutral, chalky* and *dry* (Figure 7.4C). As participants were asked not to use the following words *bitter*, *sticky*, *smooth, rough*, *slippery*, and *aftertaste*, these attributes are missing from the Figure 7.4C.

The descriptive analysis of the tablet samples revealed potential sensory issues which may pose an issue with acceptabilty. For example, the attributes used to describe uncoated tablets (T_A) included terms that were associated with low acceptability, like *rough* or *sticky*. (the association was described in Chapter 4.4.5). Further attributes, like *powdery*, or *chalky*, although not yet related to low acceptability, may pose an issue hence their impact on acceptability might be worth studying. In contrast, coated tasteless tablets (T_ACoat-1–3) were described with acceptable attributes: *smooth* and *slippery* (the association was described in Chapter 4.4.5). Some attributes were shared with both the coated and uncoated tablets (Figure 7.4 A, B), like *sticky* or *rough*, but with very different frequencies.

The attributes in Figure 7.4C shows the terms used to describe the coated quinine flavoured tablets (T_B). Several of the attributes for these tablets can be regarded as acceptable sensory properties: *neutral*, *movable*, while others may pose acceptablity issues: *chalky*, *chemical*.

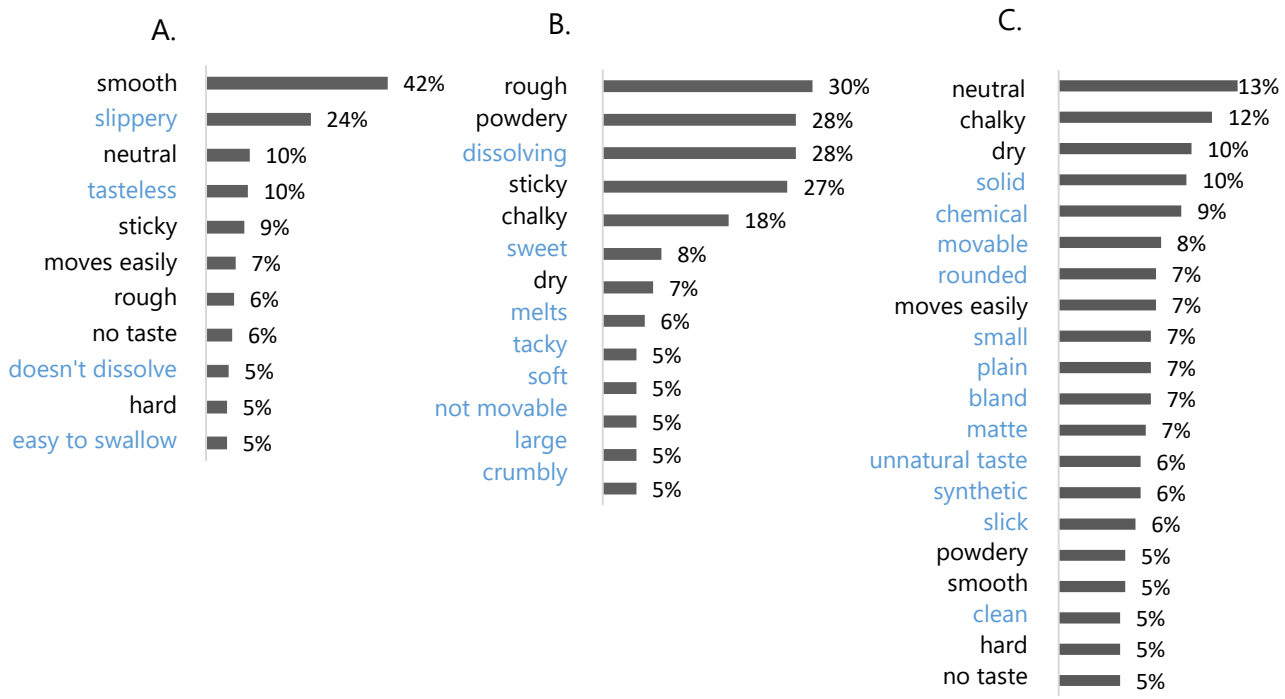

Figure 7.4 Frequency of terms describing A. Coated T_A tablets (n=249), B. Uncoated T_A tablets (n=83), and C. Coated T_B tablets (n=260); attributes in blue are unique for the sample type.

7.4 Discussion

7.4.1 Nature of sensory assessment of tablets

The patient's sensory experience when taking an oral medicine is important in the assessment of its acceptability. Yet, there is limited understanding of the sensory stimuli which are most critical for acceptance of medicines. This study explored the sensory attributes of a tablet, as a model OSDF, and gathered the vocabulary used by patients (consumers) to describe the samples.

The descriptive analysis of tablet samples revealed that various senses were involved in the perception of OSDFs. The participants mainly used expressions related to touch, taste and vision with a notable absence of any attributes related to hearing or smell. The reasons for absence of vocabulary relating to these two senses lies in the sample characteristics. Firstly, the auditory perception of medicine (or food) is specific to products which create

sounds during mastication (i.e. chewing gum or crisps). Yet, the tablet samples in this study were not chewed (they were swallowed whole). Secondly, the tablets were odourless, hence there was no olfactory stimulation. Nevertheless, many medicines contain volatile substances, thus the perception of smell is expected for some flavoured or API containing products.

In foods, the dominant sensations of texture change over time (Stokes et al., 2013). OSDFs are not expected to stay in the mouth for as long as a food sample. Despite the shorter occupancy in the mouth the OSDFs change can be still identified. During oral processing, the tablet is moistened with saliva and its surface is sheared by tongue-palate-teeth movements, which changes the tablet structure (and tablet coating structure), and thus the temporal sensations perceived by the patient. The texture is more likely to be of importance for an ODT rather than conventional tablet. In a study by Kimura et al. (2015) the perceived roughness of ODTs differed at various points of administration: during ingestion, after spitting out, and one minute after administration. The sensory evaluation presented in this chapter also found that several attributes mentioned sample change, e.g. *falling apart, dissolving* suggesting that sensory analysis for conventional tablets should be performed in a time-dependent manner. To capture of perceptual taste/texture changes of OSDFs over time, methodology could be adopted from the Temporal Dominance of Sensations (TDS) technique which is well established in food sciences (Varela and Fiszman, 2012). The fact that the tablets samples in this study were described as *dissolving/disintegrating* could impact perception of other texture characteristics.

Descriptive analysis of a tablet is an objective description of the sample, thus itself it cannot confirm product acceptability. It is the hedonic assessment which may provide a better

predictor of acceptability. However, using descriptive analysis one can find a spectrum of attributes that dominate the sensory perception and need further evaluation for acceptability. Once the dominant attributes for a particular product are determined by descriptive analysis (and organized in a lexicon), they can be then included in a standardized palatability assessment. Such assessment would involve scaling the intensity of an attribute and assigning to it a hedonic score. In future, having a database of multiple sensory evaluations coupled with hedonic assessments (made by large consumer population), one could predict the hedonic response just based on a sensory evaluation (made by small trained panel). This way sensory evaluation can be an accurate predictor of acceptability.

A lexicon brings great value to such form of acceptability assessment, as it contains attributes which dominate the sensory perception of the product and unambiguous definitions. Therefore, lexicon constitutes a list of the attributes which can be then assessed individually for acceptability (e.g. "On a scale 0-10, how rough is the product? How acceptable is the roughness of the product?").

Lexicon development using lay participants gave rise to many hedonic terms not relevant to sensory evaluation. Unlike a panellist trained to use only objective attributes, a lay person tends to use simpler language and hedonic terms in their evaluation (Chollet and Valentin, 2001). For a consumer hedonic terms express their feelings better than an objective description of mouthfeel. Notably, the list of words with a negative connotation was longer than that of the positive ones (Table 7.3). Two explanations are possible; the product was not acceptable enough, and/or the tablets were not designed to create sensory pleasure, so high number of positive hedonic terms should not be expected. Although hedonic terms are not

included in lexicons, they may be presented to lay participants as type of words "not to use" in sensory evaluation.

7.4.2 Challenges in lexicon development

The vocabulary collected during these studies was used to map the overall participant perception of tablets. The analysis showed that the texture vocabulary used to describe OSDFs is rich and differ largely between sample types. The vocabulary used for sensory evaluation of OSDF is not standardized (Scarpa, 2019). Demonstrating this, a feeling of fine particles on the surface was described using different attributes: i.e. *chalky, floury, powdery, and dusty*. On the other hand, the same word, i.e. *clear*, can express different meanings, such as *clean, plain*, or *transparent*, resulting in different evaluation of this word. In addition, various terms can build intensity scale of specific property, i.e. adhesiveness, ordered as: *tacky, clingy, gluey,* and *sticky*. Without presenting a definition of each attribute to the participant, one cannot be sure the exact perception described.

The complexity of descriptive analysis lies in the language specificity of the individual. In particular, the choice of word depends on the richness of one's vocabulary, and the mother tongue of each participant. Moreover, texture can be characterized differently across the world due to varying food and language culture (Varela et al., 2008). The type of words collected might also be compromised where panels of participants are not trained. We hypothesise, that participants used words such as *dissolving, melts, crumbly,* to indicate that a tablet disintegrated in the mouth. This suggests that lay participants do not know pharmaceutical jargon (e.g. *disintegrate*), and clear definition of terms is necessary for unambiguous communication. A formal lexicon with defined terminology may reduce ambiguities in the interpretation of the descriptive analysis of OSDFs.

The analysis of tablet attributes presented in this chapter constitutes the first step in building a formal lexicon for OSDFs. According to accepted standards, the full lexicon includes a list of terms and definitions that describe the product, as well as a set of references that clarify the terminology (Lawless and Civille, 2013). However, certain difficulties arise while developing the lexicon for pharmaceutical sensory analysis. First, there are gaps in knowledge of the textural attributes which are relevant to OSDFs and are critical for patients' acceptability. Secondly, obtaining reference products for medicines may be complex due to need to obtain references to good manufacturing practice, GMP, (or at least human consumption) standards. However, this issue would be mitigated once a complete set of standardised references is developed, which could then be mass produced and used as industry standards. Some references could be acquired from food sciences, i.e. taste reference for antibiotics with metallic taste ($FeSO_4$), or quinine sulfate as bitter stimuli (Lawless et al., 2004).

7.4.3 Practical implications of tablet lexicon and sensory wheel

This study provides several potential future applications. Firstly, it expands the knowledge of sensory attributes relevant for tablets by identifying attributes not previously known to be associated with tablets. By defining taste, flavour, or other characteristics of a medicine we can improve our knowledge on patients' preferences. Secondly, analysis of the collected terms has established a first step to build a standardised vocabulary and provide accurate definitions that will benefit future palatability and acceptability studies.

Based on terms collected in these studies, this chapter presents the creation of the first sensory wheel for OSDFs. It visually represents a comprehensive collection of participants' sensations triggered by tablets. The wheel created includes a wider range of vocabulary than

the lexicon and as yet, the attributes are not defined. Based on experiences from the food sciences, developing a sensory wheel requires use of a wide range of samples in order to capture all potential sensory attributes (Koch et al., 2012). As limited number of samples was used in this study, it is expected that as the research in this area grows and evolves, certain attributes would be removed from the wheel, while others would be added.

The lexicon and sensory wheel created in this work may facilitate the distinction between tablet samples. The lexicon can be used as a tool for descriptive analysis of tablets, where each attribute is scalable and the acceptability of it can be defined. Whereas the sensory wheel can be used to find fine differences between samples, which are related to more detailed attributes. Both tools allow standardisation of sensory assessment and acceptability evaluation, and thereby have the potential to inform product development.

7.4.4 Limitations

Study limitations include the use of participants not trained for sensory analysis, which could decrease the spectrum of appropriate vocabulary used. Moreover, some participants were not native English speakers, which limited their word choice. A limited number of samples in the tablet product category was used. The work has been done in an adult population and hence is not necessarily transferable to a paediatric population or people, who have different sensory perceptions. Finally, the reference products for selected attributes were not assigned. This was due to difficulty to find products with similar attributes and a similar manner of consumption amongst food products and also an ethical consideration with using medicinal products as references.

7.5 Conclusions

This study used descriptive analysis methods to gather a range of vocabulary describing the taste, mouthfeel and overall impression of a tablet. The data collected provides a valuable insight into the sensory experience while taking a tablet, as a model oral solid medicine. A comparison of terms used to characterise coated vs. uncoated tablets has the potential to highlight potential sensory issues with a product that may affect the acceptability. This knowledge could be used to develop a tablet with preferable sensory attributes. The vocabulary gathered could be used to improve the understanding of acceptability and palatability of medicines.

Furthermore, the list of frequently used descriptors established a basic lexicon for sensory analysis of tablets. The lexicon can be used in sensory and hedonic evaluation of product attributes, where the intensity of attributes is scaled, and then assess hedonically. Although lexicon for tablets is not fully translatable, these data could steer future sensory analysis of other OSDF, e.g. orally dispersible tablets, films, capsules, chewable tablets.

This preliminary study has generated multiple options for future research and development. Training a testing panel and using this trained panel to evaluate the same set of tablets would inform the completeness of the proposed lexicon. Comparison of the vocabulary generated by the trained and untrained panel would provide information on which group gives the more specific description of the product. It would also provide information on the vocabulary for a product specific to the actual consumers of the product. Further work could look to build lexicons for different formulations, e.g. ODTs, or liquids, and look for relationships between these lexicons with regard to acceptability. In addition, as the issue of

the product references for each attribute was not addressed within this study, this also generates another avenue for further research.

8 Conclusions and future work

This research combines knowledge from food science, sensory analysis, and pharmaceutics with the aim to advance understanding of patients' sensory perception and acceptability of conventional coated tablets. To do so, a range of conventional coated tablets were evaluated *in vivo* and *in vitro* and the results of both approaches were correlated. This chapter describes the overall outcomes of this work and proposes ideas for future research to build on work presented within this thesis.

8.1 *In vitro* experiments

In this thesis the hypothesis was made that instrumental methods can provide information on tablet mouthfeel. Current literature provides a solid background to use *in vitro* methods as a tool relating mouthfeel to physical properties of food samples, e.g. tribology explaining lubrication mechanisms. Thus, food-based methodologies were adapted for testing of pharmaceutical tablets. Instrumental methods were developed with consideration of oral processing of tablets under biorelevant oral conditions: a wet environment, appropriate shear, low load force and range of speeds.

Two *in vitro* methods were developed – surface tribology and thin film tribology (as detailed in Chapter 2) – that were able to distinguish between different coating formulations, which proved them feasible to evaluate friction of tablet coatings in context of oral processing. For the first time, a linear relationship between tribology and the oral sensory perception, i.e. ease of swallowing, slipperiness, and stickiness, of conventional tablets was presented. Moreover, strong correlation between perceived smoothness within the mouth and instrumentally measured tablet roughness (Chapter 3) was established. While these results need to be interpreted with caution due to the infancy of the research area, interpretation of

the links established increases the understanding of the processes underlying oral sensory perception of medicines. Importantly, it appears that the linear equations obtained for these correlations can be used as a predictive tool (Chapter 6).

8.2 *In vivo* experiments

Within this work, the *in vivo* data on the acceptability of tablets with various coatings was collected in two separate sensory studies (Chapter 4 and 5). The participants were evaluating several attributes to provide a complete picture of their sensory experience during administration and ingestion of a tablet. Pulling these results together, the attributes which had a positive impact on overall palatability, and so acceptability, were low bitterness, low stickiness, high smoothness, high slipperiness, and a pleasant aftertaste. The findings highlighted the presence of the coating as important for improving tablet palatability.

The sensory studies involved three distinct populations: children (between 4-12 years old), adults, and older adults (over 65 years old). The differences in sensory perception and tablet acceptability between different age groups has been exposed. The difference in hedonic perception of the samples between adults and children implied that they are not interchangeable in acceptability testing. Moreover, older adults were not sensitive enough to perform sensory evaluation due to dulled senses and resulting lack of discriminatory power, but their ability to swallow the dose remains crucial for acceptability testing. Alongside age difference, gender was found to be a factor in terms of the sensitivity of the participant to discriminate between the different mouthfeel of coated tablets, with females being more sensitive. In this light, the need for evaluation of acceptability in the target population cannot be over-emphasized.

8.3 General conclusion

A theme that recurred in this thesis was the multifactorial nature of acceptability. It is without doubt, that complete assessment of acceptability is not possible using a simple yes/no question. The complexity of the sensory experience during administration/ingestion of a tablet was further reinforced by the vast number of attributes that participants used to describe the tablets. These attributes have been extracted and organized into a lexicon for effective communication among researchers and participants for future studies (Chapter 7). Being able to break down acceptability assessment into to more specific and well-defined attributes can be beneficial for product development. Evaluating the components individually enables identification of those factors that are most strongly linked to overall acceptance to provide an understanding of how to optimise the formulation. This is where correlating *in vivo* and *in vitro* data has considerable practical implications. The capability to predict individual sensory attributes *in vitro*, could benefit the formulation development process as a screening tool to enable selection of optimised samples for human testing. The ability to shift part of the acceptability evaluation to preclinical in vitro studies would offer significant advantages, especially in the light of recent regulations, which require the acceptability of paediatric drug formulations to be demonstrated prior to registration. The methodologies presented in this thesis have the potential to provide a formulator with a decision-based toolkit to guide the development process, with the provision that further work is required to are refine and optimise the methods using a larger sample set, i.e. including a wider range of tablet variants.

Translated into benefits for the patient, the present work broadens the knowledge on the acceptability of conventional coated tablets, providing manufacturers with information

that can promote the development of palatable products, consequently improving patients' adherence and benefiting patients' quality of life.

8.4 Future work

During the work on this thesis many questions were answered, but even more have been raised. The findings of this thesis open multiple avenues for future research and development. Future work involves two work streams: research in the field of instrumental and sensory assessment. Several research questions are listed in Figure 8.1. Answering them would build the knowledge to understand the processes underlying perception of mouthfeel of oral medicines and factors affecting its acceptability, and this way pave the road to the development of standardised methodologies. Further research leads to bridging *in vitro* and *in vivo* methods by means of multifactorial modelling, which can accelerate the understanding of factors affecting acceptability of oral medicines and provide tools to predict acceptability. Ultimately the developed tools could be implemented during *in vitro* acceptability screening to ensure acceptability of every product developed.

Fulfilling these aspirations requires collaborative work. Firstly, to leverage the knowledge and experience from the food industry; and secondly to involve academia, industry, and regulators, to ensure applicability of the research.

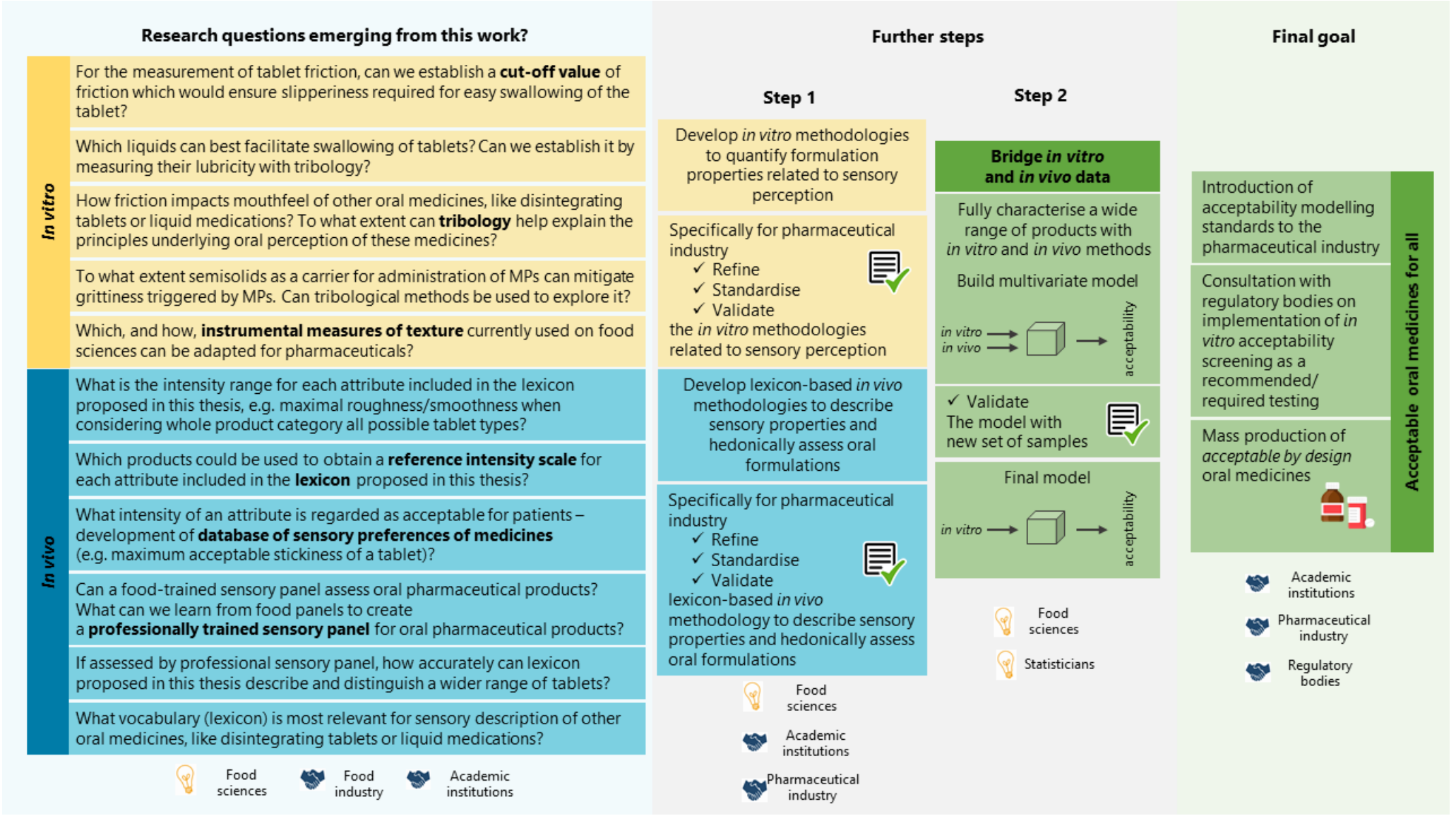

Figure 8.1 Future work; hands icon indicates need for collaboration, bulb icon indicates need to obtain resources and knowledge from other fields.

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Appendices

Appendix A

Participant information sheet – ease of swallowing and sensory evaluation of large tablets in adults

Tablet swallowability study information sheet

Researchers at the University of Birmingham, School of Pharmacy are investigating the swallowability of tablets as well as the mouthfeel of the tablets. This work is being funded by Colorcon who manufacture coating materials for tablets (www.colorcon.com).

You have received this information sheet as you have expressed an interest in participating in this study. We would like you to read this information sheet and note down any question you have so that you can ask us before you decide to participate in this study.

Why we are doing this research?

The swallowability of medicines is really important in ensuring that patients take their medication as directed. We know that many patients struggle to take tablets and capsules, so we are trying to develop innovative solutions for these patients.

This research will assess whether:

(i) A new film coating on tablets helps improve swallowability compared to existing products;
(ii) A new film coating provides better palatability than existing products.

The results from this study will be used to further develop tablet formulations and coatings to assist people with difficulty to swallow tablets and capsules. The coatings used in this study are Colorcon proprietary products and the results may be held confidentially by that company for the purpose of further developing tablet coatings rather than being published more widely.

As a participant what do I have to do?

All participants will be required to attend one 1.5 hour session at the School of Pharmacy, University of Birmingham. You will receive a £30 gift voucher as compensation and appreciation for participating in this study.

This study compares the swallowability of 4 tablets (one at a time); each participant will be required to swallow 4 placebo tablet samples (containing no drug) as well as assess the mouthfeel of 4 placebo tablet samples. This process will take approximately 1.5 hours to complete. Participants will be asked to mark on a scale how they rate the swallowability and mouthfeel of each product immediately after administration. The participant will be taking part in the study in groups of four.

All products are vegetarian, further details are provided on each product at the end of this document. There will be a cracker available to eat between samples (gluten free versions available).

Am I eligible to participate?

The study has the following **inclusion** criteria:

1. Between the age of 18 and 75 years
2. Participant is able to provide written consent
3. Participant reports no issues in ability to swallow a tablet

The study has the following **exclusion** criteria:

1. People under 18 years of age or over 75 years of age
2. Smokers
3. People who self-report illnesses, or other conditions that may compromise their taste or smell.
4. Individuals unable to speak or understand English
5. Dental care (visit to a dentist for anything other than a routine check-up) within the last 2 weeks
6. Allergy or intolerance of lactose

If you can answer yes to any of the statements above you are **not eligible** to participate in this study.

Are there any risks or benefits?

The study carries a very small risk of choking. The risk is very low and a trained first aider will be present at all times.

There are no direct health benefits to participants. However, the findings from this study will directly inform the development of coatings that may aid in the ease of swallowing tablets and has wider benefits to the community and healthcare professions. This will inevitably improve medicines adherence and provide cost savings in healthcare.

What will happen to my data?

All of the answers given will be kept private in a locked cupboard. Any data that is collected, transcribed and stored in electronic format will be completely anonymised prior to dissemination.

Only the research team, representatives of the sponsor and relevant regulatory authorities will have access to your data. All data will be stored for 10 years following the study which is in line with the University of Birmingham policy.

I am interested in taking part! What do I do now?

You need to contact Hannah Batchelor on either 0121 414 3717 or h.k.batchelor@bham.ac.uk to arrange a convenient time for you to participate in this study.

Even after you have agreed to participate you are able to withdraw from the study at any time and we will respect your decision. We will ask you why you have decided to withdraw but you do not have to disclose a reason if you do not want to. If you withdraw from the study during the assessment process you can request that any data previously collected be withdrawn.

If you agree to participate we will ask you to sign a copy of this document that we will keep with our records.

Any questions?

Additional important information about the study

The funder of the study is Colorcon Ltd. Colorcon's core business is the design and technical support of advanced coating systems, modified release technologies and functional excipients for pharmaceutical dosage forms.
Product details:

Product	Excipients	Coating excipients
Placebo tablet (1)	Lactose, starch, microcrystalline cellulose, mg stearate	None
Placebo tablet (2)	Same as above (1) plus Opadry coating – white	Opadry white (HPMC, Titanium dioxide and macrogol)
Placebo tablet (3)	Same as above (1) plus Opadry slippery coating – white	Opadry slippery white
Placebo tablet (4)	Same as above (1) plus Opadry slippery coating – white & clear	Opadry slippery white and clear

Appendix B

Informed consent – ease of swallowing and sensory evaluation of large tablets in adults

Tablet swallowability study consent form

I, the undersigned, confirm that (please initial box as appropriate):

1.	I have read and understood the information about the project, as provided in the Participant Information Sheet	
2.	I have been given the opportunity to ask questions about the project and my participation.	
3.	I voluntarily agree to participate in the study.	
4.	I understand I can withdraw at any time.	
5.	The procedures regarding confidentiality have been clearly explained (e.g. use of names, pseudonyms, anonymization of data, etc.) to me.	
6.	I acknowledge that the data will be stored at the University of Birmingham for period of 10 years, with the access restricted only to the research team, the representatives of the Sponsor and applicable regulatory bodies.	
7.	The use of the data in research, publications, sharing and archiving has been explained to me.	
8.	I agree to sign and date this informed consent form.	

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Researcher	Signature	Date

Appendix C

Questionnaires – ease of swallowing and sensory evaluation of large tablets in adults

Background Questionnaire

Participant number: _____ Date:_____

Age range (years):

- ☐ <24
- ☐ 25-34
- ☐ 35-44
- ☐ 45-54
- ☐ 55-64
- ☐ >65

Gender:

- ☐ Male
- ☐ Female
- ☐ Prefer not to say

Please answer the following questions:

1. Have you previously experienced problems with swallowing tablets?
- ☐ Yes (proceed to question 1a)
- ☐ No (proceed to question 2)

1a. What caused problems with swallowing tablets?
- ☐ Size of tablet
- ☐ Taste of tablet
- ☐ Texture of tablet
- ☐ Aftertaste
- ☐ Dry mouth
- ☐ Other

2. Do you take any medicines (tablets/capsules)?
- ☐ No
- ☐ Yes, between 1-3 daily
- ☐ Yes, 4 or more daily

Assessment of swallowability and mouthfeel of coated tablets
RG # RG_17-152

Product assessment sheet – swallowing study

Part 1 Swallowing study

Participant number: _____ Date:_____

Please rinse your mouth with water before starting.

You may rinse again any time during study if you need it.

Please swallow the tablet sample in the way you always do. Take the samples in the order presented, from left to right.

Before each sample cleanse the palate with lightly salted crackers provided.

(If you have any questions, please ask the staff now)

Sample number: _____

Please complete the following scale. Mark the scale with X or line to indicate your response to each question:

The product is easy to swallow — The product is difficult to swallow

Please answer these questions:

1.	Did you manage to swallow the tablet?	Yes/No
2.	How many attempts did you make to swallow the tablet?	.....
3.	Did you chew the tablet?	Yes/No
4.	Did you feel that the tablet became stuck whilst in your mouth or during the swallow?	Yes/No
5.	Did you choke on the tablet (tablet was inhaled or cough occurred during swallowing)?	Yes/No

Assessment of swallowability and mouthfeel of coated tablets
RG # RG_17-152

UNIVERSITY OF BIRMINGHAM

After you have tasted all four products

1. Circle the number of your favourite sample (You must make a choice)

   121 565 489 605

2. Rank the four products from the easiest to swallow to the hardest to swallow?
   (1 = easiest to 4 = hardest)

Sample	Rank (1 to 4) (ties are NOT allowed)
121	
565	
489	
605	

3. Which of the four products did you think was acceptable in swallowability?
   (note that you can select as many or as few products as you like)

   121 565 489 605

Do you have any other comments on the swallowability of the products?

Thank you. Please now proceed to the second part of study.

Assessment of swallowability and mouthfeel of coated tablets
RG # RG_17-152

Product assessment sheet – mouthfeel study

Part 2 Mouthfeel study

Participant number: _____ Date:_____

Please, rinse your mouth with water before starting.
You may rinse again any time during study if you need it.

Before each sample cleanse the palate with lightly salted crackers provided.

*Please, place the tablet in the tongue. Hold it in your mouth for min **10** sec;*
you may keep it longer in the mouth if you need.

Feel the tablet surface with a tongue; rub the tablet against the palate, the palate is the hard part of the roof of your mouth.
Don't chew the tablet.

Afterwards, spit or swallow the tablet, according to your preference.

Read the questions before starting a test.

(If you have any questions, please ask the staff now)

Sample number: _____

Please complete the following scales. Mark the scale with X or line to indicate your response to each question:

1. Roughness

Immediately upon administration to the mouth, how does the tablet surface feel on the tongue?

Rough Smooth

2. Adhesiveness

Does the tablet stick to the palate?

Doesn't stick at all Tablet is very sticky

Assessment of swallowability and mouthfeel of coated tablets
RG # RG_17-152

3. Slipperiness

   Does the tablet resist movement?

   Stays in place — Slips easily

4. Palatability

   How does the tablet taste?

   Unpleasant — Pleasant

Describe in 3 words how the product feels in the mouth:

1.

2.

3.

Thank you for your participation!

Please return the questionnaires to the staff.

Appendix D

Participant comments – ease of swallowing and sensory evaluation of large tablets in adults

Palatability assessment of samples: transcription of participants' comments. Each line represents description of a single participant.

T_A
rough texture, slightly minty taste
sticky, rough
immediately started dissolving and sticky to the tongue
dissolves, pleasent, rough
nasty, chalky, rough
tasty, starting to dissolve
powdery, chalky texture
soggy, chalky, slimy
rough, sticky, tastes a little
unpleasant, chalky, dry
disgusting taste, coating melted so quickly (fastly), stays in place
fizzy, like baking powder, soft
stronger flavour, crumbly, powdery
rough, sticky, sweet
powdery, rough, dissolving
chalky, clingy
powderish, melting in the mouth
powdery, aftertaste
melted in the mouth, was not as expected, felt like there was no coating on the tablet
dry, a bit powdery at the end of the time/slimy, a bit fizzy at the end of the time
powdery, sticky
sticky, rough, weight loss
soft, chalky, difficult to move around
tasteless
evaporated on tongue, rough, powdery
rough, sticky
powdery, dry
the test not good, stay in place, become pices/powder
rough, dry, unpleasant
chalky, powdery, dissolves
dry, tacky, dissolving
dissolvable, not nice but not bad
chalky, melts

leaves a taste in the mouth, very rough on the palate, not pleasant
tacky, powdery, rough
rough, not easy to chew or swallow, sticky
dissolves quickly in mouth, sweet, strange, large
dissolves quickly, feels rough initially, difficult to swallow, 2 attempts with water
milky, fluffy, granular
powdery, tasted neutral, adherent
sticky, unpleasant texture
coating dissolves, sticky, stimulated saliva
initially dry, sweetish after a while, slightly powdery
felt as it would totally dissolve in the mouth, very unpleasant, quite large
powdery, dissolving slowly, comfortable
rough, alkaline, powdery
felt as though it was dissolving slowly, acceptable, gentle
fizzy, breakes apart, odd
terrible
mushy, sticky, ugh
chalky, dissolves quickly, unpleasant taste, very hard to move in mouth, horrible
very chalky, dissolves quickly, no aftertaste
rougher surface, sticks to the tongue, taste less pleasant
very chalky, alkaline taste, very strange unpleasant texture, melted in mouth but powdery also, very sticky
tablet felt softer as it was going to dissolve, tablet dissolved much more quickly than previous two, tablet was softer feel in mouth
tacky, disintegrated, yuk
dusty, crumbly, bitter
sticky, sweetish, dissolving
powdery, dissolves in mouth, sticky to swallow
nasty, glutenous, powdery
chalky, powdery
floury, sticky, resistant
chalky, rough, unpleasant
rough, falls apart easily, slightly sweet
rough, sticky, starts to dissolve
big, very sticky/powdery, bad/strong taste, but not bitter
dissolves, chalky, sticky
sticky, furry, uncomfortable
chalky, powdery, sticky
tacky, insolvent, quite a pleasant taste
large, dissolving, rough
loose, rough, uncomfortable
bad texture, slightly minty, soggy
dusty, slightly sticky, not too large
rough, pleasant taste
furry, gelatinous, large

comfortable, rough (ish), crumbly
I didn't like this one, horrible, rough, felt like it was dissolving
floury, sweet, unpleasant
spongy, soft, Pliable
crumbles, powdery, unpleasant
unpleasent, sweet, tastes like flour
T_ACoat-1
smooth
started to feel rough after 15s and could taste
solvent like taste which developed after few seconds, then powdery gritty texture after 20s
sticky
mealy, smooth, big
neutral
smooth, slightly sticky, nice
smooth, moves easily, slight taste
smooth, pleasant, easy
stick in the mouth, doesn't move easily, taste is not good
tasteless, sticky, hard, didn't begin to fall apart
chemical, lingering, hard
smooth, easy, neutral
shiny, plain, slippery
unpleasant taste, texture and aftertaste
feels more sticky than others
the coating seemed somewhat plastic feeling in the mouth, started to feel like melting in second 9
smooth
weird taste
slippery, no weight loss, smooth
smooth, than slight granulation, should swallow easily
swallowable, tastes bad
glue textured, stodgy
acceptable, smooth
smooth, comfortable
bad test, hard, no easy, slips
smooth, pleasant, slippery
smooth, slippery, chemically
powdery, pleasant, dry
sticky, dissolves a bit, broke in half and dissloves
gooey, aftertaste, smelly
very similar to 630, smooth texture, easy to move around
sticky, tacky
slippery, no taste, easy suck
neutral taste, slips but starts to dissolve slowly in the mouth, still possible to swallow
sweet, becomes more difficult to swallow as coating dissolves, didn't seem to swallow completely, 2 attempts with water
slipps, pleasant, solid

distasteful - tasted plasticky, smooth at first but it very quickly becomes unpleasant, almost starchy, starchy
an object in the mouth, smooth, slippery
no taste, didn't dissolve
smooth, quite large, not unpleasant to taste
ok, silky, bland
sticky, untasty, silky
tasteless until slight hint of mint when spat out, didn't feel it would ever dissolve, would be easy to swallow
grainy, bitter, sticky
slimy, bitter, smooth
starts smooth but becomes sticky, chalky after 7-8s, taste not bad until 8+ seconds when it becomes more pronounced
leaves an aftertaste, not pleasant, slimy texture
initially smooth then rougher, moves around easily, not as palatable as 531
very unpelasant taste, artificial, very smooth until first layer dissolves, was also very sticky, left a chalky residue on the tongue which was also unpleasant
best to take out of 4, slightly rough, strange taste
smooth, sticky, unpleasant
smooth, cardboardy, pleasant
neutral, easy, solid
pleasant, large, stickier
smooth, clean
slippy then chalky, unpleasant
tacky, resistant, neutral taste
smooth, neutral taste, easy
a little slippery/slimy, sticky, smooth
smooth, tasteless, neutral
light powder, tastes odd but not bad, rounded
soft, sticky yet not sticky, chalky
comfortable, mild taste, smooth
smooth, slippy, tasteless
non descript, just a tablet!, moves around palate, not unpleasant, no taste at all
unpleasant, synthetic
smooth, easy, bland
easy, no taste, smooth
slightly grainy, not too large, managable
feels a bit rougher the longer it stays on tongue
sweeter than others, comfortable, more unnoticable
smooth, neutral, pleasant
smooth, silky, no aftertaste
smooth, towards end of 10 seconds felt it might dissolve, a little sticky
glue like, unpleasantly sticky, obtrusive
solid, smooth, resistant
milky, bitter, sticky

T_ACoat-2
slight chemical taste
smooth, slippery, palatable
poor, sticky
bland, big
slightly sour
smooth, slippy, pleasant
smooth, moves easily if I tried, no flavour
average
doesn't taste, slip easily, smooth
almost sweet taste, smooth
aniseedy, solid (didn't crumble), pleasant
smooth, easy, clean
slippery, rough, uninvasive
sweeter
neutral, slippy
no taste, feels like some of coating left on roof of mouth
slippy, felt coating was stronger, did not melt in the mouth
a little dry, a little bumpy
slippery, no weight loss, smooth
comfortable, sticks, probably ok
smooth, unnatural taste, slippery
pleasant, slides easily, quite acceptable
comfortable, smooth
easy to slips, good test, hard
pleasant, creamy, smooth
smooth, neutral, slippery
smooth, acceptable, tasteless
large,unweidly, rough the longer in the mouth
aftertaste
smooth mostly, easy to move around, tasteless
moveable, nothing descriptive to say
smooth, easy to swallow, no taste
neutral, no taste, slippery, smooth, easy to swallow with water
smooth, doesn't dissolve, swallows easily
slimy, unplesant
smooth, passes easily in the mouth, textureless
fine, smooth
an object in the mouth, moves easily against the palate, does not stick
no taste, didn't dissolve in mouth
a bit gritty, neither pleasant or unpleasant, not too smooth
slightly sweet, smooth, slippery
sticky, slimy, slightly bitter
tasteless, hard, didn't think it would ever dissolve if I couldn't swallow it
slightly grany but not distracting, chemically taste, movebale

rough, chalky, sweet
fairly smooth with slight bumpy texture but pleasant enough, slips around fairly easily in mouth, taste not offensive, after 8s becomes very slightly chalky
thick, not unpleasant, swallowable
neutral taste, very slippery, felt it would be easy tgo swallow
very smooth and slipy, not sticky at all, not nice taste, artificial and bitter
tablet not too rough, table did not stick at all, slightly rough
slippery, tasteless, ok
dry feeling, easy to move around, no taste
preferred, easy, tasteless
menagable, slightly rough, neutral flavour
solid, smooth, clean
hard, bland
surface matt, mobile, tasteless
slightly rough, bit of taste, neutral
smooth, slightly chalky, slightly salty, not unpleasant
slightly rough, ok, slightly sweet
smooth, small, good, not unpleasant
rough, not dissolve
comfortable, tasteless, free-moving
smooth, slippy, tasteless
not tacky, slippy, not unpleasant, had no taste what so ever (or I have lost my sense of taste!)
smooth, plastic
smooth, comfortable, tasteless
antiseptic taste, unpleasant
solid, neutral, slightly large
neutral taste
very easily moves
comfortable, neutral, not unpleasant
rough on the tongue, slght aftertaste, moved around mouth easily
smooth, slippy, easy to move
slippery, uncomfortable, slimy
powdery outer coating, hard, slimy
rough, tasteless, more on a pleasant side

T_ACoat-3
normal
smooth, slippy, pleasant
pasty
silky smooth, slippery, pleasant feel
slippery, tasteless, imagine easy to swallow
smooth, pleasant, easy
coating does not melt easily, taste is acceptable, slips easily and quite smooth
smooth, almost grainy, with time, with time+mix with saliva, tasteless

paste like taste, smooth, easy
smooth, slippery, neutral
smooth, slippery, uninvasive
holds together
quite unusually sweet taste for a tablet
felt a slimy in mouth towards end
smoothish
smooth
smooth, slippery, no weight loss
slipps easily, not uncomfortable, taste improvement
slippery, smooth, taste bit unpleasant
tasteless, slippery
smooth, didn't cause me any problems
smooth
hard, stay in place, pleasant
smooth, pleasant, slippy
smooth, slippery, neutral
accetable, fairly smooth, ok
large, solid, no too bad
easy, ok, large
very smooth, slides easily, no aftertaste
slippy, smooth, shiny
slippery, no taste, easy to swallow
neutral taste, no taste, easy to swallow, doesn't dissolve, slippery
smooth, doesn't dissolve, swallows easily
coating sticks to the tongue, unpleasant, slimy
smooth, tablet became less smooth after approximately 20s, easy to take, fine
smooth, nice, I wish all tablets are like this product
slippery, smooth, not sticky
no taste, didn't dissolve
no taste at all, very slippy, no at all sticky
smooth, fairly slippery, bland taste
smooth, hard, tasteless
hard, tasteless, not sure if would have dissolve if I couldn't swallow it
neutral, slippery, plain
smooth, slightly bumpy, slippery
comfortable
slightly rough, a bit gloopy, slightly gritty texture
glue like, slimy, not pleasant
tasteless, comfortable balance between smooth+stickiness
smooth, strange taste, chalky
smoother than previous, not much different than 299, like previous
smooth, ok, slight taste
smooth, not too big, easy to suck

neutral, slippery, hard
smooth, slippery, pleasant neutral taste
clean, solid, pleasant
bland, smooth
smooth, mobile, tasteless
slightly rough, easy swallowable, tasteless
super smooth, very slippery, slightly salty/not unpleasant
smooth, slippery, neutral
slightly bitter, bad taste, slippery, average size feeling in the mouth
hard, sweet
smooth, tasteless, free-moving
super smooth, slick, nice
slippy, slides around, slight taste but not unpleasant
smooth, plastic
sticky, smooth, comfortable
odd taste after a few seconds, quite rough for a tablet
solid, mobile, not intrusive
slippery, pleasant taste
powdery, large, indigestible
neutral, not unpleasant, ok
weird aftertaste, only very slight though, silky, smooth
tasteless, didn't start to dissolve until right at end of time, smooth
light, feels glazed, pointy
slimy outer surface, solid, dry aftertaste
a bit bitter, slips easily, didn't feel edges of this tablet

Appendix E

Participant information sheet – MASCoT study

Parent/guardian information sheet
Children study

MASCoT – **M**outhfeel, **A**cceptability and **S**wallowability of **Co**ated small **T**ablets in children and adults

Researchers from the School of Pharmacy, University of Birmingham are investigating the acceptability, swallowability and mouthfeel of small tablets. The mouthfeel includes any sensations that you feel in your mouth, for example softness of cake, or crispiness of crisps.

Why are we doing this research?

The ability to swallow and pleasant mouthfeel of medicines are crucial to ensure that a patient, especially a child, is taking their medication as instructed. We know that many parents struggle to convince their children to take medication, often due to poor taste. Thus, we are investigating the use of coated small tablets which are designed for children.

The aim of this study is to find out:

1) Which coating on the small tablets makes them most acceptable to children?
2) Which coating effectively masks a bitter taste?

Do I have to take part?

No, you and the child in your care does not have to take part in this research. Their participation is voluntary.

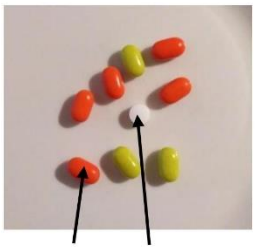
It is important that you understand why this research is undertaken and what it will involve before you decide whether the child in your care should participate. Please take your time to read the following and don't hesitate to ask if you have any questions.

As a parent/guardian what do I have to do?

We would like you to complete a questionnaire about the child in your care's experiences of taking oral medication and some demographic information (age, ethnicity, gender). The questionnaire will be anonymized. We will also ask you to assist the child during whole course of the study.

As a participating child what do I have to do?

We want the child in your care to tell us what they think about the small tablets. These are very small, smaller than a TicTac!



TicTac *Tablet*

Firstly, the child in your care will be asked to swallow 2 small tablets and report on how easy they were to swallow.

Then the child in your care will also be asked to put a tablet in their mouth and tell us how it feels – they will be asked to spit this tablet out after about 10 seconds. We will do this part twice.

Finally we will ask the child in your care to hold a tablet in their mouth until they can taste something bitter, and then spit out the tablet.

In between each tablet we will ask the child in your care to drink some water and have a cracker to make sure that they are ready to try the next tablet.

The child in your care can stop at any time if they decide they want to.

During the study we will ask the child in your care some questions about the tablet and ask them to fill in some scales like this one

Like very much

Dislike very much

Is the child in my care eligible to participate?

Inclusion criteria:

1. Child aged between 4 and 12 years old, and accompanied by parent or legal guardian on the study day
2. Child weights more than 12 kg (1 stone and 12.5 pound)
3. Parent/legal guardian is able to read and understand this study information sheet
4. Child is able to understand English
5. Each child participant must give verbal assent for the study, alongside the parent/guardian consent

Exclusion criteria:

1. Child or parent/legal guardian unable/unwilling to consent
2. Child not allowed to consume quinine for any reason
3. Allergy or intolerance to lactose
4. Swallowing impairment for any reason
5. Reported illnesses or other conditions that may compromise their taste or smell

Are there any risks or benefits?

The study carries a small risk of choking. The risk is low, and a paediatric trained First Aider will be present at all times.

The small tablets contain quinine; the whole amount consumed by each child is equivalent to less than half a glass of tonic water (approximately 10 mg). This amount is not likely to have any effect on a child. It is advised to restrict other sources of quinine on the day of study (tonic water, bitter lemon).

All the samples are vegetarian and are prepared so that they are fit for human consumption.

What will happen to my data?

Data will be collected only after giving a consent to collect and process it, according to General Data Protection Regulation (GDPR). All the information collected will be kept strictly confidential in a secure locked cupboard at the University of Birmingham, in compliance with the Data Protection Act. The data will be anonymised before dissemination.

Only the research team and relevant regulatory authorities will have access to your data. After the study the data will be stored for period of 10 years, in line with the University of Birmingham's Code of Practice for Research.

Additional important information

You (or the child in your care) may decide to withdraw from the study at any time without consequences and we will respect your decision.

If you agree for the child in your care to participate we will ask you to give written informed consent before any data will be collected.

During the study there will be optional photo/filming for future public engagement work to promote age-appropriate medicines paediatric research. We will ask you if you agree for the child in your care to be photographed/filmed. The decision about photography/filming will not impact on your participation in the study.

I am interested in taking part! What do I do now?

For more information, and to arrange a convenient time for you to participate in this study, please contact the primary researcher:

Justyna Czarnocka: jkc689@student.bham.ac.uk

Hannah Batchelor: E-mail: h.k.batchelor@bham.ac.uk Phone: 0121 414 3717

Who to contact if I wish to discuss aspects of the study or to complain?

Please contact Birgit Whitman, the University's Head of Research Integrity and Governance, who is an independent point of contact for participants/parents/legal guardians:

E-mail: b.whitman@bham.ac.uk Phone: tel. 0121 415 8011

Participant information sheet
Adult study

MASCoT – **M**outhfeel, **A**cceptability and **S**wallowability of **Co**ated small **T**ablets in children and adults

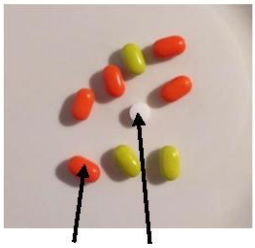
Researchers form the School of Pharmacy, University of Birmingham are investigating the acceptability, swallowability and mouthfeel of small tablets. The mouthfeel includes any sensations that you feel in your mouth, for example softness of cake, or crispiness of crisps.

Why we are doing this research?

The ability to swallow tablets and pleasant mouthfeel of medication are crucial to ensure that a patient, especially a paediatric patient, is taking their medication as instructed. We know that many parents struggle to convince their children to take medication. Thus, we are investigating whether coated small tablets are appropriate for children.

The aim of this study is to find out:

1) Which coating on the small tablets make them most palatable?
2) Which coating effectively masks a bitter taste?



TicTac *Tablet*

Do I have to take part?

No, you do not have to take part in this research. Your decision is fully voluntary. This is why it is important, that you understand why this research is undertaken and what it will involve before you give consent. Please take your time to read the following information and don't hesitate to ask if you have any questions.

As a participant what do I have to do?

We would like you to complete a questionnaire about your experiences of taking oral medication and demographic information about you. The questionnaire will be anonymized.

We will give you a total of 11 different tablets. Each small tablet - contains quinine as bitter agent. The tablets are coated with different types of coating.

Firstly, you will be asked to swallow 5 small tablets (one at a time) and report on how easy they were to swallow.

Then you will be asked to put a tablet in your mouth and tell us how it feels – you will be asked to spit this tablet out after about 10 seconds. We will do this part on 5 more tablets.

Finally we will ask you to hold a tablet in their mouth until you can taste something bitter and then spit out the tablet. This will only be done for one tablet.

In between each tablet we will ask you to drink some water and have a cracker to make sure that you are ready to try the next tablet.

You will use a 5-point facial scale to assess the samples, as shown below:

Like very much — Dislike very much

Figure 1 5-point facial hedonic scale

Am I eligible to participate?

The study has following **inclusion** criteria:

1. Above 18 years old and below 65 years old
2. Participant is able to read and understand study information sheet
3. Participant is able to read and understand English
4. Participant must give written consent for the study

The study has following **exclusion** criteria:

1. Not allowed to consume quinine for any reason including hypersensitivity
2. Allergy or intolerance to lactose
3. Swallowing impairment for any reason
4. Reported illnesses or other conditions that may compromise their taste or smell
5. Pregnancy
6. Smoking

Are there any risks or benefits?

The study carries a small risk of choking. The risk is low, and a trained First Aider will be present at all times.

The small tablets contain quinine; the whole amount consumed by participant is comparable to a glass of tonic water (approximately 25 mg). This amount is not likely to have any effect on a participant; however this need to be considered. It is advised to restrict other sources of quinine on the day of study (tonic water, bitter lemon).

All the samples are vegetarian and are prepared so that they are fit for human consumption.

How long it will take?

The study is scheduled for 90 minutes.

What will happen to my data?

Data will be collected only after giving a consent to collect and process it, according to General Data Protection Regulation (GDPR). All the information collected will be kept strictly confidential in a secure locked cupboard at the University of Birmingham, in compliance with the Data Protection Act. The data will be anonymised before dissemination.

Only the research team and relevant regulatory authorities will have access to your data. After the study the data will be stored for period of 10 years, in line with the University of Birmingham's Code of Practice for Research.

Additional important information

You may decide to withdrawal from the study at any time without consequences and we will respect your decision.

If you agree to participate we will ask you to give a written informed consent before any data will be collected.

During the study there will be optional photo/video taking for future public engagement work to promote age-appropriate medicine paediatric research. We will ask you if you agree to be recorded. The decision will not impact your participation in the study.

I am interested in taking part! What do I do now?

For more information, and to arrange a convenient time for you to participate in this study, please contact the primary researcher:

Justyna Czarnocka: jkc689@student.bham.ac.uk

Hannah Batchelor: E-mail: h.k.batchelor@bham.ac.uk Phone: 0121 414 3717

Who to contact if I wish to discuss aspects of the study or to complain?

Please contact Birgit Whitman, the University's Head of Research Integrity and Governance, who is an independent point of contact for participants:

E-mail: b.whitman@bham.ac.uk Phone: tel. 0121 415 8011

Appendix F

Informed consent – MASCoT study

Parent/Legal guardian consent form for the child in their care to participate in the MASCoT study

MASCoT – Mouthfeel, Acceptability and Swallowability of Coated small Tablets in children and adults

This information is collected as a part of a research project concerning the mouthfeel of the oral medications conducted by the School of Pharmacy at the University of Birmingham.

I, the undersigned, confirm that (please initial to confirm):

1.	I have read and understood the information about the project, as provided in the Participant Information Sheet (v1.0 29th January 2019).	
2.	I have been given the opportunity to ask questions about the project and participation of the child in my care.	
3.	I have received enough information about this study.	
4.	I understand I can decide for the child in my care to withdraw at any time; and that I will not have to give a reason; in which case I can decide to either keep or withdraw the permission to use the data already generated.	
5.	The procedures regarding confidentiality have been clearly explained to me (e.g. use pseudonyms, anonymization of data, etc.).	
6.	I acknowledge that the data will be stored at the University of Birmingham for period of 10 years, with the access restricted only to the research team.	
7.	The use of the data in research, publications, sharing and archiving has been explained to me.	
8.	I consent for my personal information to be collected and processed for the purpose of the study in accordance with General Data Protection Regulation (GDPR).	
9.	I confirm, that I have a legal responsibility for .... (*name and surname of a child*).	
10.	I agree for the child in my care .... (*name and surname of a child)* to participate in this study.	
11.	The child in my care gave oral assent to participate in the study.	

I confirm that I have read and understood all above mentioned statements.

Full name of a child _____

Full name of Parent/Legal guardian _____

Parent/legal guardian's signature _____ Date _____

Full name of Researcher _____

Researcher's signature _____ Date _____

MASCoT Consent form v1.0 Date: 29th January 2019

Adult participant consent for participation in the MASCoT study

MASCoT – Mouthfeel, Acceptability and Swallowability of Coated small Tablets in children and adults

This information is collected as a part of a research project concerning the mouthfeel of the oral medications conducted by the School of Pharmacy at the University of Birmingham.

I, the undersigned, confirm that (please initial to confirm):

1.	I have read and understood the information about the project, as provided in the Participant Information Sheet (v1.0 29th January 2019).	
2.	I have been given the opportunity to ask questions about the project and my participation.	
3.	I have received enough information about this study.	
4.	I understand I can withdraw at any time; in which case I can decide to either keep or withdraw the permission to use the data already generated.	
5.	The procedures regarding confidentiality have been clearly explained (e.g. use of pseudonyms, anonymization of data, etc.).	
6.	I acknowledge that the data will be stored at the University of Birmingham for period of 10 years, with the access restricted only to the research team.	
7.	The use of the data in research, publications, sharing and archiving has been explained to me.	
8.	I consent for my personal information to be collected and processed for the purpose of the study in accordance with General Data Protection Regulation (GDPR).	
9.	I agree to participate in this study.	

I confirm that I have read and understood all above mentioned statements.

Full name of participant _____

Participant's signature _____ Date _____

Full name of Researcher _____

Researcher's signature _____ Date _____

MASCoT Consent form v1.0 Date: 29th January 2019

Participant consent form for photo/video capturing of the child during the MASCoT study

MASCoT – Mouthfeel, Acceptability and Swallowability of Coated small Tablets in children and adults

This information is collected as a part of a research project concerning the mouthfeel of the oral medications conducted by the School of Pharmacy at the University of Birmingham.
The pictures/video will be used solely for the purpose of disseminating research and future public engagement work to promote age-appropriate medicine paediatric research. No personal information will be shared together with the photos/video.

I, the undersigned, confirm that (please initial to confirm):

1.	I have understood the aim and use of photos/filming.	
2.	I agree for the child in my care to be photographed/filmed.	
3.	I agree that the pictures/video taken shall remain the property of the author and the University of Birmingham may use these images publicly for the purpose of disseminating research and promoting research into paediatric medications.	
4.	I acknowledge that the photos/video will be stored at the University of Birmingham.	
5.	I consent for my personal information to be collected and processed for the purpose of the study in accordance with General Data Protection Regulation (GDPR).	
6.	I understand that this consent is perpetual, that I may not revoke it, and that it is binding.	

I confirm that I have read and understood all above mentioned statements.

Full name of a child _____

Full name of Parent/Legal guardian _____

Parent/legal guardian's signature _____ Date _____

Full name of Researcher _____

Researcher's signature _____ Date _____

MASCoT Consent form v1.0 Date: 29th January 2019

Appendix G

Questionnaires for children study – MASCoT study

mascot

Initial Questionnaire

Please fill the background questionnaire about the participant:

	Participant number	
Age of participant*		
Gender		
Ethnicity		
Have you/the child in your care previously experienced problems with swallowing tablets?*	Yes	No
If you answered YES to previous question, what caused problems with swallowing tablets?	☐ Size of tablet ☐ Taste of tablet ☐ Texture of tablet ☐ Aftertaste ☐ Dry mouth ☐ Other, please give details:	

*obligatory field

MASCoT Appendices v2.0 Date: 11th April 2019

mascot

Self-reported swallowability assessment

	Participant number	
FIRST SAMPLE	**Sample number:**	
Was the tablet easy or difficult to swallow?	 Very easy to swallow	Very difficult to swallow
SECOND SAMPLE	**Sample number:**	
Was the tablet easy or difficult to swallow?	 Very easy to swallow	Very difficult to swallow

Which tablet was the easiest to swallow?

1st 2nd

MASCoT Appendices v2.0 Date: 11th April 2019

Participant number	

Researcher observations of swallowability

12-tick chart:

	FIRST SAMPLE	SECOND SAMPLE
SAMPLE NUMBER:		
Amount of water used with the sample (mL)		
Negative facial expressions		
Lips pressed (AU 24)	☐	☐
Nose wrinkling (AU 9)	☐	☐
Eyes squeeze (AU 6+43)	☐	☐
Brows pulled together and lowered (AU 4)	☐	☐
Head shake (AU 84)	☐	☐
Voice disgust	☐	☐
Measure of success of taking a sample		
Completely swallowed	☐	☐
Partially swallowed	☐	☐
Chewed on	☐	☐
Sample spat out	☐	☐
Sample got stuck in throat	☐	☐
Refused to take sample	☐	☐

Any verbal comments made by the participant? Please cite.

Sign and date

SECOND SAMPLE		Sample number:				
1.	How bitter was the sample?	 Not bitter at all				 Extremely bitter
2.	How sticky was the sample?	 Not sticky at all				 Extremely sticky
3.	How smooth was the sample?	 Very smooth				 Very rough
4.	How slippery was the sample?	 Extremely slippery				 Not slippery at all
5a.	Do you feel any aftertaste?	Yes (move to 5b)		No (move to 6)		
5b.	How would you describe the aftertaste?	 Extremely pleasant				 Extremely unpleasant
6.	How much do you like the sample?	 Like very much				 Dislike very much

Which tablet did you prefer?

1st 2nd

MASCoT Appendices v2.0 Date: 11th April 2019

(same questionnaire form is given for 2 samples)

Participant number	

Researcher observations of mouthfeel

6-tick chart:

	FIRST SAMPLE	SECOND SAMPLE
SAMPLE NUMBER:		
Negative facial expressions		
Lips pressed (AU 24)	☐	☐
Nose wrinkling (AU 9)	☐	☐
Eyes squeeze (AU 6+43)	☐	☐
Brows pulled together and lowered (AU 4)	☐	☐
Head shake (AU 84)	☐	☐
Voice disgust	☐	☐

Any verbal comments made by a participant? Please cite.

Sign and date

mascot

Self-reported evaluation of bitterness onset

Participant number	

SAMPLE	Sample number:

Time of bitterness onset (sec): _____

How much do you <u>like</u> the taste?

Like very much — Dislike very much

MASCoT Appendices v2.0 Date: 11th April 2019

Questionnaires for adult study – MASCoT study

Initial Questionnaire

Please fill the background questionnaire about the participant:

	Participant number	
Age of participant*		
Gender		
Ethnicity		
Have you/the child in your care previously experienced problems with swallowing tablets?*	Yes	No
If you answered YES to previous question, what caused problems with swallowing tablets?	☐ Size of tablet ☐ Taste of tablet ☐ Texture of tablet ☐ Aftertaste ☐ Dry mouth ☐ Other, please give details:	

*obligatory field

MASCoT Appendices v2.0 Date: 11th April 2019

mascot

Self-reported swallowability assessment

	Participant number

FIRST SAMPLE	**Sample number:**
Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow
SECOND SAMPLE	**Sample number:**
Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow
THIRD SAMPLE	**Sample number:**
Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow
FOURTH SAMPLE	**Sample number:**
Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow
FIFTH SAMPLE	**Sample number:**
Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow

Which tablet was the easiest to swallow?

MASCoT Appendices v2.0 Date: 11th April 2019

Researcher observations of swallowability

Participant number	

12-tick chart:

	FIRST SAMPLE	SECOND SAMPLE	THIRD SAMPLE	FOURTH SAMPLE	FIFTH SAMPLE
SAMPLE NUMBER:					
Amount of water used with the sample (mL)					
Negative facial expressions					
Lips pressed (AU 24)	☐	☐	☐	☐	☐
Nose wrinkling (AU 9)	☐	☐	☐	☐	☐
Eyes squeeze (AU 6+43)	☐	☐	☐	☐	☐
Brows pulled together and lowered (AU 4)	☐	☐	☐	☐	☐
Head shake (AU 84)	☐	☐	☐	☐	☐
Voice disgust	☐	☐	☐	☐	☐
Measure of success of taking a sample					
Completely swallowed	☐	☐	☐	☐	☐
Partially swallowed	☐	☐	☐	☐	☐
Chewed on	☐	☐	☐	☐	☐
Sample spat out	☐	☐	☐	☐	☐
Sample got stuck in throat	☐	☐	☐	☐	☐
Refused to take sample	☐	☐	☐	☐	☐

Any verbal comments made by the participant? Please cite.

Sign and date

FIFTH SAMPLE		Sample number:				
1.	How bitter was the sample?	 Not bitter at all				Extremely bitter
2.	How sticky was the sample?	 Not sticky at all				Extremely sticky
3.	How smooth was the sample?	 Very smooth				Very rough
4.	How slippery was the sample?	 Extremely slippery				Not slippery at all
5a.	Do you feel any aftertaste?	Yes (move to 5b)			No (move to 6)	
5b.	How would you describe the aftertaste?	 Extremely pleasant				Extremely unpleasant
6.	How much do you like the sample?	 Like very much				Dislike very much

Please describe in 3 words the mouthfeel of the sample:

Which tablet did you prefer?

1st 2nd 3rd 4th 5th

MASCoT Appendices v2.0 Date: 11th April 2019

(same questionnaire form is given for 5 samples)

Researcher observations of mouthfeel

Participant number	

6-tick chart:

	FIRST SAMPLE	SECOND SAMPLE	THIRD SAMPLE	FOURTH SAMPLE	FIFTH SAMPLE
SAMPLE NUMBER:					
Negative facial expressions					
Lips pressed (AU 24)	☐	☐	☐	☐	☐
Nose wrinkling (AU 9)	☐	☐	☐	☐	☐
Eyes squeeze (AU 6+43)	☐	☐	☐	☐	☐
Brows pulled together and lowered (AU 4)	☐	☐	☐	☐	☐
Head shake (AU 84)	☐	☐	☐	☐	☐
Voice disgust	☐	☐	☐	☐	☐

Any verbal comments made by a participant? Please cite.

Sign and date

Self-reported evaluation of bitterness onset

Participant number	

SAMPLE	Sample number:

Time of bitterness onset (sec): _____

How much do you like the taste?

Like very much — Dislike very much

Appendix H

Participant comments – MASCoT study

Children comments collected during ease of swallowing and palatability parts: transcription of participants' comments.

T_BCoat-4

Ease of swallowing part	Palatability part
disgusting	*bad aftertaste*
easy	*i wouldn't take it everyday*
tasteless, bitter	*much easier to swallow*
that one was really hard to swallow	*that was nice and sweet*
very easy to swallow	*this was worse*
way too easy	*ugh*

T_BCoat-5

Ease of swallowing part	Palatability part
can't swallow it	*bitter*
easy	*didn't feel anything, very slippery, no taste, very young children can take it*
tasted bad	*got stuck between teeth*
tasteless bitter	*horrible*
	I didnt like it; like sand taste
	it disgusts me
	nice one
	tasted bad after 8 sec
	tasteless
	tastes weird
	very bitter

T_BCoat-6

Ease of swallowing part	Palatability part
easy	*did "thumbs down"*
very easy	*tasted nasty*
way too easy	*that was ok*

T_BCoat-7

Ease of swallowing part	Palatability part
awful	*disgust*
bland	*disgusting*
can't swallow it	*horrible*
easy peasy lemon squeezy	*rough*

if minty it would be easier	*tasted bad*
started to dissolve in my mouth straight away	*terrible*
tasted bad	*ugh*
too big, withdrew	*wouldn't try again*

T_BCoat-8

Ease of swallowing part	**Palatability part**
bland	*bad aftertaste*
can't swallow it	*bitter*
disgusting	*disgusting*
easy	*horrible*
eugcgh, tastes disgusting	*took some time + effort to swallow*
tasted bad	
tasted gross	
yucky	

Adult comments collected during palatability part: transcription of participants' comments.

Each line represents description of a single participant.

T_BCoat-4
moves easily, shiny, clean
movable, glazed, light
unambiguous, slimy, silky
neutral, okay, strong taste, slick, moves easily
not tacky, silky, melts, the coating totally dissolved by the end of 5s
bitter, quite sticky
dry, absorbant, sour
nice textural, in the beginning not bitter
rounded, hard, dense
slick, clean, rounded
round, unnatural taste, hard
chemical, grainy, solvent taste
dissolving, unnatural taste, granular
neutral, solid, small
edgy, smushy, flat
does not melt, chalky, chemical
chemical, alkaline, gooey
shiny, slick, no flavour
solvent taste, synthetic, starchy
bland, gluey, moves easily
slimy, glazed, no edges
chalky, powdery, dissolving

synthetic, no edges, matte,
movable, unnatural, light
chemically, doesn't fall apart, not tacky
dry, clingy, hard
synthetic, gooey, pasty
chalky, small, 'like paracetamol'
unnatural taste, chalky, dissolving
chemical, slimy, plastic
plain, smooth, hard
dissolving, bland, pasty
alkaline, movable, rounded
chalky, solid, dry
doesn't dissolve, small, rounded
moves easily, no edges, slick
rounded, movable, mobile
plastic, synthetic, rounded
chemical, matte, tacky
silky, pleasant, clean
gloopy, thick, does not melt
matte, rounded, does not melt
tasteless, neutral, light
adherent, alkaline, gluey
dusty, chalky, unnatural taste
aftertaste better
alkaline
smooth , chalky, silky
matte, smooth, strange taste, glazed

T_BCoat-5
moves easily, bland, gelly like, average small sized tablet
moves easily, neutral, glazed
obtrusive, nasty, smooth
nice, smooth, surprising bad aftertaste, small slick, doesn't fall apart
clean, plain, bland, dissolution of the tablet left greasy feeling on the tongue
neutral feelings!
pleasant, moveable
little bitter, neutral
bland, chalky, light
bland, neutral, solid
light, neutral, doesn't dissolve
silky, plain, doesn't fall apart
movable, no taste, solid
small, neutral, mobile

small, no taste, soft to touch
moveable, no edges, no flavour
neutral, rounded, plain
glazed, silky, no flavour
movable, neutral, solid
mover easily, slick, glazed
chalky, powdery, dry
plain, simple, small
movable, neutral, starchy
light, pleasant, movable
small, tasteless, clingy
no flavour, doesn't dissolve, soft
solid, clean, bland
neutral, solid, small
solid, matte, tasteless
powdery, plastic, chemical
bland, neutral, no taste
it seems neutral, with no flavour, with no taste
does not melt, moves easily, small
bland, movable, no taste
solid, doesn't fall apart, hard
rounded, neutral, movable
synthetic, plastic, solid
neutral, plain, light
gritty, unpleasant, clingy
clean, plain, solid
sweet, dusty, powdery
no taste, no flavour, clean
neutral, silky, matte
not a problem
bland, fake, plastic, didn't enjoy this tablet
no taste, does not melt, small
feels easy to swallow
no taste, pasty
smooth, clean, bland
slippery, extremely small aftertaste, slight stick, generally plain

T_BCoat-6
silky, movable, neutral
glazed, movable, solid
overt, tough, bad
dry, smooth, neutral, bit taste, gooey, slick
synthetic, creamy, tacky, after the dissolution of the coating (at the end of 10 secs) the stickiness of the core was left

started to like it at some point!

smooth

pleasant, nice, minimal bitter

easy

clean, soft, lubricated

no taste, slick, doesn't dissolve

neutral, small, rounded

dissolving, dusty, floury

unnatural taste, medicine-like

mobile, silky, chemical

bitter, dry, synthetic

moves easily, neutral, does not fall apart

moves easily, solid, rounded

slick, slimy, moves easily

movable, soft, clean

clingy, not movable, gluey

slimy, silky, smooth

soft, neutral, movable

slick, chemical, unnatural taste

light, moves easily, tasteless

plastic, slick, small

shiny, rounded, slick

chalky, matte

moves easily, slick, coated

starchy, pasty, moves easily

moves easily, doesn't fall apart, chemical

smooth, moves easily, quinine tasting

bland, chemical, synthetic

light, small, solid

artificial, rounded, moves easily

neutral, bland, tasteless

no taste, no edges, neutral

movable, mobile, shiny

plastic, synthetic, rounded

greasy, melts, slick

sticky, grainy, solid

gluey, melts, clingy

synthetic, unnatural taste, dry

no taste, no flavour, neutral

glazed, doesn't fall apart, plastic

not as bad as the others

clean, smooth, tasteless

strong bitter aftertaste

minimal taste

powdery, plain, sour

tasteless, slick, not much flavour, generally slippery, no strong bitter aftertaste

T_BCoat-7

plain, not movable, matte
dry, chalky, light
unpleasant, unassuming, chalky
unsmooth, bitter, slow, chalky, doesn't move easily, hard
synthetic, tacky, grainy
a bit sour maybe as well?
dry
dry, bad surface
stick, glued down
chalky, powdery
papery, dry, unnatural taste
neutral, solid, bland
chalky, bumpy, alkaline
dusty, chalky, bitter, artificial medicine-like taste
little tangy, hard
very firm, gluey, has sharp edges (pointy)
floury, loose, alkaline
chalky, doesn't dissolve, dusty
solid, light, doesn't dissolve
clingy, plain, neutral
does not melt, artificial, moves easily
dusty, hard, chalky
matte, dry, plastic
chalky, no edges, thick
easy, no flavour, mobile
chalky, matte, gluey
plain, dry, tacky
bland, neutral, plain
rough, neutral, dusty
pasty, floury, matte
powdery, no taste, not tacky
gooey, slimy, grainy round edges
a bit chalky, dry, plain
dry, matte, solid
granular, creamy, chalky
gritty, a little dry, small
matte, grainy, bumpy
solid, doesn't dissolve, chalky
matte, hard, solvent taste
spongy, unnatural taste, chemical

powdery, sticky, clingy

dry, neutral, plain

powdery, solvent taste, floury

slightly bitter, clingy, does not melt

chalky, floury, powdery

horrible

matte, dry, gritty

aftertaste not bad

taste like a cleaning product, alkaline, unnatural, chemical

plain, neutral, solid

immediate unnatural taste, slightly sticky, bit unpleasant

T_BCoat-8

not movable, plain, neutral

glazed, movable, solid

abusive, sticky, permcting

nice, smooth, good, rough, mobile, doesn't fall apart

little bit grainy, chalky, dry

bitter, but not terribly

semi-dry, slightly sticky

bad aftertaste, good surface

neutral, not much aftertaste

tacky, crumbly, absorbent

unnatural taste, chemical, bland

doesn't melt, clean, neutral

rounded, chemical, alkaline

powdery, unnatural taste, chemical

neutral, dry, tangy

chemical taste, smooth, slippery

gluey, slimy, melts

chalky, tacky, does not melt

alkaline, unnatural taste, doesn't melt

solid, no edges, movable

bad taste, grainy, unpleasant

dusty, strong flavour, dry

dry, unnatural taste, dissolving

synthetic, hard, glazed

unnatural, thick, movable

chemically, small, doesn't fall apart

minty, dry, small

adherent, thick, chemical

matte, chalky, dusty

grainy, chalky, powdery

dissolving, chemical, plastic
hard, mobile, chemical
dissolving, granular, thick
moves easily, no edges, soft
solid, synthetic, bland
hard, solid, slightly drying
rounded, loose, creamy
doesn't fall apart, chalky, solid
plastic, synthetic, rounded
synthetic, unnatural taste, tacky
clingy, rough, grainy
matte, chemical, gluey
chalky, powdery, dusty
slightly bitter, plain, clean
dusty, chemical, synthetic
dry, thick, artificial, tastes like paracetamol
bitter aftertaste
bland, unnatural
unnatural taste, floury, sharp
sticky, slightly bitter, slightly chemical