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# Assessment of the textural and mouthfeel attributes of ODTs and their importance to patient acceptability

by

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# Abstract

The mouthfeel attributes of medicines are important to patient adherence and, therefore, treatment adherence and effectiveness. Presently, there is no standardised criteria for determining mouthfeel acceptability because research in this area is still limited. The work presented in this thesis aims to better understand the physical characteristics and textural attributes of orodispersible tablets (ODTs) and to relate these findings to oral perception during ODTs consumption.

A wide range of formulated ODTs, commercially manufactured ODTs and different commercial fillers were assessed regarding their physical characteristics and measured using several instruments. Measurements from the use of the different tools, for example, the texture analyser (TA), have allowed the identification of disintegration, swelling, residue, hardness, and adhesiveness. Textural and physical features are influenced by the balance of ingredients and the choice of the method that is used to manufacture an ODT. These characteristics were also distinguishable between commercially available ODTs and fillers, which may imply variation in mouthfeel and, as a result, acceptability of commercial ODTs.

The gold standard approach to assess mouthfeel attributes and patient acceptability is an *in vivo* sensory examination involving human participants. A sensory study was undertaken using placebo ODTs. Decreased perception of roughness, hardness, stickiness, residue, and dryness are important to improved acceptability. In summary, the TA can be used to identify a range of parameters that impact on the textural and physical features of ODTs. Their identification is worthwhile to know how best to formulate and manufacture ODTs that have an enhanced mouthfeel and patient acceptability.

# Thesis outline

## Introduction

The introduction chapter provides the context to scientific topics that are pertinent to orodispersible tablets (ODTs) and their acceptability. In addition, the main factors that negatively impact the acceptability of an oral medication and patient adherence are discussed. Then, the concept of using ODTs to enhance the acceptability of medications is introduced. Also, the role of laboratory instruments that can be used to assess the texture and mouthfeel of a solid oral dosage form to enhance patient acceptance of novel pharmaceutical formulations is discussed. Lastly, the main principles of human acceptability testing, especially for pharmaceutical products, are addressed.

## Thesis Problem

The mouthfeel of a medicine influences its acceptability, patient adherence, and effectiveness. However, there are currently no standardised criteria for determining mouthfeel attributes, as research into mouthfeel and its relationship to acceptability is still limited. This thesis investigates the physical and textural properties of ODTs and how they would affect oral perception and, therefore, the acceptability of ODTs.

## Methods

Numerous ODT formulations with varying compositions and manufacturing characteristics were developed to identify the factors that affect the main physical and textural properties of ODTs. A variety of laboratory tools were used to identify textural differences between commercially available ODTs, obtained from NHS and community pharmacies, and different commercial fillers. The findings highlight how differences would result in the different

mouthfeel attributes experienced by patients, and, therefore, their acceptance and adherence to their medicines. Lastly, an *in vivo* sensory study involving human participants was conducted to evaluate several mouthfeel attributes of ODTs and to identify the associations between them and the overall acceptability.

## Results

Several physical and textural characteristics of ODTs, such as disintegration, swelling, residue, hardness, and adhesiveness, have been identified by using a variety of in *vitro* instruments, in particular the texture analyser (TA). Textural and physical characteristics of ODTs are largely determined by their ingredients, in terms of quantity and variety, as well as their preparation methods. These tools were also able to identify several physical and textural characteristics between commercially available ODTs. In addition, the results have revealed that the commercially available ODTs differed in terms of their physical properties and texture, which may indicate variation in mouthfeel perception and, consequently, acceptability. There were several main textural differences between commercially available tablets, including not only disintegration but also residue, hardness, and wettability. A common usage of such excipients in ODTs, such as mannitol and MCC, does not necessarily imply that the tablets will have the same textural characteristics, and thus oral perceptibility. The source and grade of the excipients, as well as the method used to prepare the ODTs, are all potential factors that may influence the characteristics of these tablets. The sensory study found that several mouthfeel characteristics, such as sweet taste, disintegration time, residue volume, and roughness, hardness, stickiness, and dryness, are important to the palatability and acceptability of ODTs. In addition, a reduction in the perception of roughness, hardness, stickiness, residue, and dryness is crucial for the improvement of ODTs' acceptability.

## Conclusion

To manufacture ODTs with the suitable textural and physical properties, it is necessary to control and balance the ratios of the excipients used, such as binders and fillers. Similarly, the method of preparing ODTs and the parameters of the manufacturing process, such as the compression force, can influence the textural properties. By identifying and employing the optimal compression force and granule size, it is possible to manufacture ODTs with optimal textural features such as hardness and roughness. Several *in vitro* tools, and particularly the TA, can be utilised to great effect in the early stages of ODT formulation development, resulting in formulations with improved textural characteristics, and consequently, improved mouthfeel and acceptability. The complex nature of acceptance necessitates that the evaluation of acceptability should be extended beyond simple yes/no assessments. It is critical to distinguish between taste and mouthfeel attributes during *in vivo* sensory assessments, and to develop a standardised method.

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# List of Abbreviations

| | |
|---|---|
| ODT | Orodispersible tablets |
| API: | Active pharmaceutical ingredient |
| TA: | Texture analyser |
| TPA: | Texture profile analysis |
| CP: | Crospovidone |
| LHPC: | Low-substituted hydroxypropyl cellulose |
| CCS: | Croscarmellose sodium |
| Mg St: | Magnesium stearate |

# Introduction and Literature Review

## 1.1 Aims of project

This thesis integrates knowledge from the fields of pharmaceutical science, food development science, and sensory studies to better understand how orodispersible tablets are perceived and accepted by patients. The orodispersible tablets have been investigated in terms of their overall characteristics, textural nature, and mouthfeel attributes with regards to overall patient acceptability. The goal of this thesis was to provide a better understanding of the textural attributes of tablets that might impact on the perception of orodispersible tablets during processing in the mouth.

### 1.1.1 Objectives:

- To make use of instrumental (*in vitro*) tools to describe several aspects of tablets, particularly their textural nature.
- From the quality evaluation of commercially available orodispersible tablets, to identify the variations in composition that impact on mouthfeel and acceptability.
- From evaluating the mouthfeel characteristics of orodispersible tablets when given to volunteers, to determining the relationship between mouthfeel characteristics and acceptance.
- To relate the findings from instrument measurements with the mouthfeel experience of volunteers and the tablets' acceptability.

### 1.1.2 Aims of this chapter

This chapter provides a review of the scientific topics that relate to orodispersible tablets and their acceptability. The key issues that influence the acceptability of an oral medication and patient adherence are presented. Orodispersible tablets are discussed with regard to improving the acceptability of a medication. Next, lab instruments that can assess the mouthfeel of a solid oral dose form are addressed, as well as the role such equipment has played in increasing the acceptance of novel pharmaceutical formulations. Lastly, the fundamentals of measuring human acceptability, particularly for pharmaceutical products, are discussed.

## 1.2 Acceptability

Oral medications are the most widely available dosage forms because they are more widely accepted and easier to administer. Around 90% of medicines are administered orally, with 10% administered via various other routes (1). The effectiveness of a treatment depends on patient adherence, which is influenced by the acceptability of a pharmaceutical product (2, 3). Acceptability of medicines 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" (4).

Acceptability is determined by user characteristics such as age, individual health status, behaviour, disabilities, background and culture, and prior expectations, as well as oral medicinal product characteristics such as *(i)* palatability (e.g., taste, mouthfeel, texture); *(ii)* swallowability; and *(iii)* appearance (5). Inadequate acceptance can impair the efficacy of treatment since it raises the probability that prescribed medicine will be refused or discontinued. (6, 7, 8). Lack of adherence, or failing to take medications as prescribed, is responsible for nearly 125,000 deaths and more than $290 billion in treatment costs each year(9).

Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have emphasised the need of assessing medication acceptability among patients who will receive the treatment (4, 10, 11, 12). However, there is a lack of standard methods for assessing acceptance and of a coordinated strategy between industry and regulators. Assessing the acceptance is a complex task as there are multitude of factors that can affect acceptance (Table 1.1). Much of the research that has investigated patient acceptance has focused on the taste of drugs and the patients' overall ability to take them. However, it is critical to use broader assessments of acceptability that include not only taste but other relevant factors that include mouthfeel, aftertaste, and smell (13, 14).

**Table 1.1 Factors influencing acceptability of medicines in children and the elderly.** *Data collected from EMA documents (4, 12).*

| Factors related to end-user characteristics | Factors related to medicinal product characteristics |
|---|---|
| Health conditions (e.g., difficulty in swallowing, disability) | Palatability (taste, mouthfeel, aftertaste, and smell) |
| Age characteristics | Swallowability or chewability (e.g., size, shape) |
| Patients' expectations | Dosage form of a medical product and route of administration |
| Risk of choking or aspiration | Complexity of dosing modification |
| Where the product will most likely be used (e.g., hospital or community) | Dose (e.g., number of tablets per single dose, frequency, duration) |
| The need for caregiver assistance | Appearance (colour, shape, embossing) |
| | Container, administration device, measuring device, and packaging |
| | Any related pain or discomfort to administration |
| | Handling (e.g., ability to mix with food or drinks, picking up small tablets) |
| | Clear and readability of user information |
| | Storage conditions |

### 1.2.1 Difficulty of swallowing

Solid oral dose forms have a bad reputation for being difficult to swallow, which can lead to problems with acceptance. Although swallowing difficulties are common in patients with dysphagia (15, 16), they are also common among other people of all ages, including children, adults, and the elderly (17, 18, 19, 20). According to a study, approximately 60% of individuals with swallowing issues tried to self-reformulate their medicines to make swallowing easier (1).

Furthermore, tablet swallowing issues might cause patients to stop taking medication. Missed doses have been reported in 23% of adults due to swallowing issues (18), and more than 50% of children were not able to swallow a standard size tablet (19). Aside from age-related physiological changes, age-related diseases and medication side effects are the major reasons why dysphagia is more common in the elderly (21). The clinical prevalence of dysphagia among independently living elderly was found to be 27%, while the prevalence rate can be higher than 60% in specific settings such as institutionalised settings (22). In the paediatric population, the age of the child and the size of the oral medicines are the most important factors that impact on the ability to swallow a tablet (23, 24). The majority of prescribed paediatric oral solid medicines are larger than 10 mm, indicating a gap between the size of the formulations and the child's ability to swallow them (24).

### 1.2.2 Palatability

Acceptability of oral dosage forms in either paediatric (6) or adult populations (14) depends primarily on their palatability. Palatability is defined as "the overall appreciation of a (often oral) medicine by organoleptic properties such as smell, taste, aftertaste and texture (i.e. mouthfeel), and possibly also vision and sound"(25). Palatability refers to all interactions between the medicinal product and all senses from the time it is removed from its packaging

until it is consumed. The terms "flavour" or "taste" are commonly used interchangeably to describe "palatability". However, it is crucial to recognise their meanings and use exact terms when evaluating pharmaceutical formulations because they have different meanings in the field of sensory science.

#### *1.2.2.1 Taste*

Taste refers to the sensations (sweet, sour, salty, bitter, and umami) induced by stimulation of the taste buds on the tongue and oral cavity mucosa (26). The majority of active pharmaceutical ingredients are unpalatable due to their taste, which has been highlighted as a barrier for 64% of children refusing administration of an oral formulation (6). Also, it has been reported that 19% of elderly people consumed food or drink before or after taking a medicine to mask the taste or to make swallowing easier (27). Adults and children have varied taste perceptions, which can lead to differences in preference and, as a result, acceptability of an oral medical formulation (26).

It's critical to mask unpleasant medicine, especially if the active pharmaceutical Ingredient (API) is released within the oral cavity via solid oral dose forms such as orodispersible tablets (ODTs). Masking the taste of the API can make use of several approaches including using flavours (28), sweeteners, polymeric coatings (29), ion exchange resins (30), cyclodextrins (31), microencapsulation (32), chemical modifications , and viscosity modifications.

#### *1.2.2.2 Mouthfeel*

Several studies have shown that taste is the most important factor influencing palatability and a medicine’s acceptability (25, 26, 33, 34, 35, 36, 37). However, there has been little research on the mouthfeel of medicines, and specifically texture which has been identified as a barrier to the oral acceptability of medicines (38, 39). The mouth contains a large number of neurons

and sensory receptors making it one of the most highly innervated areas of the human body (40). Accordingly, mouthfeel is determined by whether the oral sensations are pleasant or unpleasant, which is critical following the administration of an oral formulation. The relevance of oral sensations (mouthfeel) to medical acceptability will be discussed in this subsection.

The physical/textural characteristics of the oral medicines, as well as the state and motions of the mouth, influence how it is perceived by the mouth. Also, mouthfeel is a very dynamic process resulting from changes in the physical characteristics of consumable materials as they are manipulating in the oral cavity (41). In sensory science, mouthfeel is defined as a physical sensation formed in the mouth by a consumable product that is distinct from taste (42). In food science, texture and mouthfeel are two terms that are partially interchangeable; since texture is 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 kinaesthetic” (43). However, mouthfeel is a broader term that “includes all of the tactile (feel) properties perceived from the time at which solid, semi-solid or liquid foods or beverages are placed in the mouth until they are swallowed” (41). The term "mouthfeel" involves all components of oral perception, including touch, pain, and temperature sensations, whereas the term "texture" refers to a product's physical and structural characteristics that may be perceived by touch. Mouthfeel encompasses all product textural features (e.g. smoothness, grittiness and hardness) as well as other precipitable attributes such as hot/cold, after-feel, astringency, and residue.

In contrast to taste, overall oral perception (mouthfeel) is more complex because it is not limited to a single perception. For example, more than 50 mouthfeel attributes related to medical nutrition products have been reported and they are classified into eight categories (Figure 1.1) (44). A variety of oral receptors transmit sensations caused by interactions with oral medications to the brain via the trigeminal nerve, where they are integrated into a conscious

sensation. Afferent signals to the brain are sent by somatosensory receptors located in the mouth including mechanoreceptors (touch), and nociceptors (heat, cold, warmth and pain) (40).

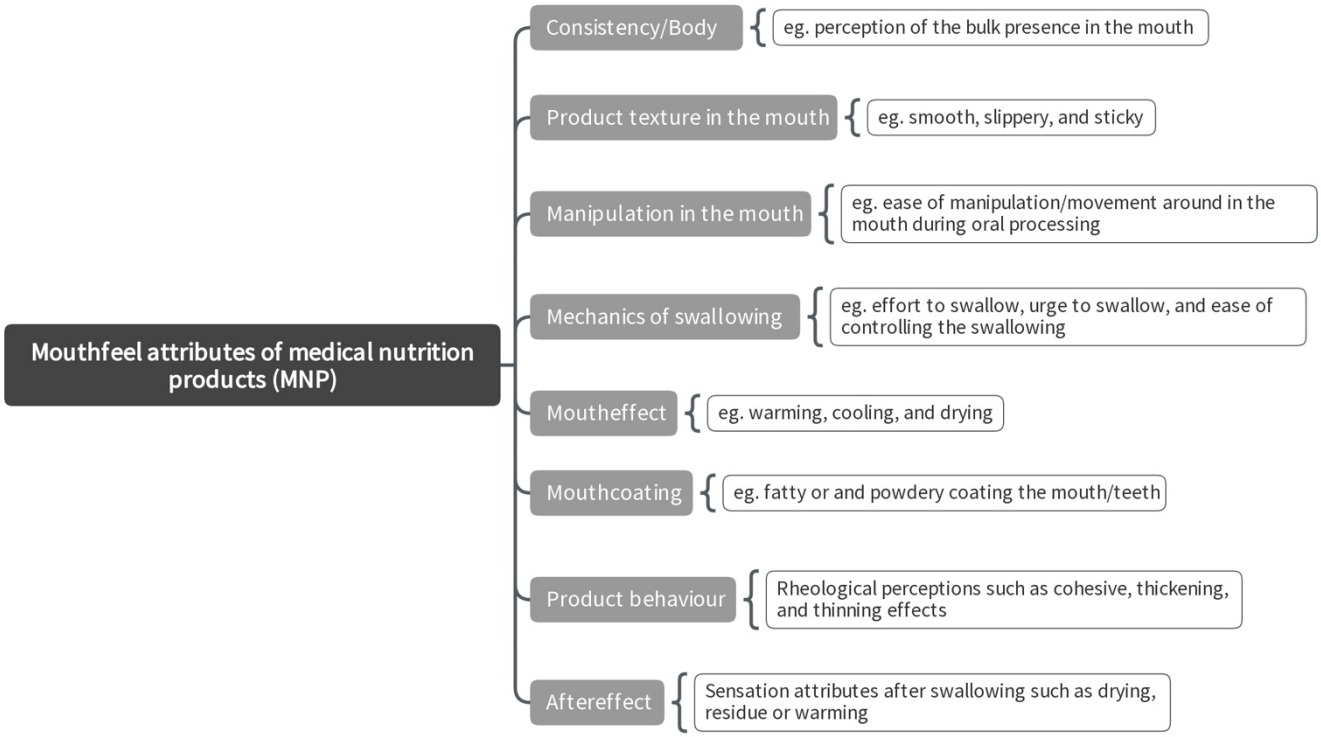



**Figure 1.1 Examples of the reported mouthfeels attributes that are related to medical nutrition products.** *Data obtained from a systematic characterisation study of mouthfeel attributes of medical nutrition products (44).*

Mouthfeel can influence acceptability and preference of a dosage form; for example, tablets are preferred over powder (14), and sprinkles (13). The unpleasant mouthfeel of the medication has been identified as a reason for medication refusal in children (6) and as a barrier to proper administration in adult (45). To avoid mouthfeel issues, it is important to understand the formulation properties that cause an unpleasant mouthfeel.

Each type of oral medicinal formulation may have different key mouthfeel properties that are critical for their acceptability. For example, the oral perception of roughness limited the acceptability of orally dispersible tablets (ODTs) (46). Similarly, stickiness mouthfeel was identified as a significant determinant of acceptability of orally dispersible films (47). Furthermore, grittiness sensations reduce the acceptability of multi-particulate formulations (48) and chewable tablets (49). Different oral dosage forms may have a different time of residence in the mouth, which can have a significant impact on mouthfeel and acceptability if the residence time is prolonged. Conventional tablets have a much shorter residence time in the mouth than other formulations that must disintegrate or are chewed in the mouth, such as ODTs, films, and chewable tablets. Although research on the mouthfeel of medicines is still limited, understanding the sensitivity of oral surfaces to differences in the textural of the oral formulations is required to advance this field. To produce medicines that are acceptable, product characteristics that reduce or promote acceptability must be identified. Following that, acceptable-by-design medicines must be validated in a targeted population.

## 1.3 Orodispersible tablets to improve acceptability

Tablets are most widely used as a solid dosage form. There are a number of advantages that include low manufacturing costs, high stability, high dose loading and uniformity, and the ability to manage drug release (50). The disadvantages are some patients experience a difficulty in swallowing and often dosage forms for children are not available. Tablets can be prepared in many different sizes, shapes, and forms. The most common types of tablets are conventional tablets, orodispersible tablets, effervescent tablets, chewable tablets, buccal and sublingual tablets, and vaginal pills. Orodispersible tablets disintegrate in the mouth in a matter of seconds without the need to drink water to swallow them. Orodispersible tablets are defined as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" (51). In the literature, this type of tablet is referred to by many terms as orodispersible, orally disintegrating, or orally dispersible tablets. These terms are being used interchangeably, but all of the terms are abbreviated to ODT. In this research, they will be referred to as orodispersible tablets (ODT), according to European Pharmacopeia 10.0 (52). ODTs circumvent the swallowing difficulty of conventional tablets, but their dispersion in the mouth may lead to unpalatability. ODTs may also be readily dispersed in a liquid to provide a fractional dose for a child. Furthermore, the administration of ODTs does not necessitate any prior preparations in contrast to other oral formulations. For example, effervescent tablets must be dissolved in a large amount of a suitable liquid before administration, causing issues for elderly patients and children (53).

### 1.3.1 Preparation of orodispersible tablets

ODTs can be made in a variety of ways, including techniques that are similar to the ones that are used to make conventional tablets, such as direct compression and granulation, as well as methods that are distinctive, such as freeze-drying and moulding (54, 55, 56). Direct

compression is the most often used and the recommended approach, due to its simplicity, existing experience in the field, and low production costs (57). This approach produces ODTs with a relatively long disintegration time, especially when a large load of compression force is used to make ODTs (58). However, the availability of superior excipients, such as superdisintegrants and sugar-based excipients, enables and augments using the direct compression method to manufacture ODTs (59). In addition, the wet granulation method is known to improve flowability, homogeneity, and compressibility, which could be beneficial in the case of low dose loading and for poor flowability excipients. Also, the wet granulation method can help to improve ODT stability while allowing for rapid disintegration (60).

A number of co-processed excipient systems (ready-to-fill excipients) have been introduced to make ODT production more efficient and simpler. Ready-to-fill excipients are produced by combining two or more known excipients, listed in a pharmacopoeia, in an industrial process such as granulation to create a substance with improved properties (61, 62). The mixture of the ready-to-fill excipients systems is beneficial for maintaining a homogeneous distribution of the composition and preventing segregation (63). In addition, the co-excipient mixture can be industrially modified to help produce the desired tablet characteristics, such as quick disintegration. For example, the use of the spray-drying technique to process ready-to-fill excipients results in very porous granules that are appropriate for rapid tablet disintegration (64). Examples of ready-to-fill excipients are commercially available and they vary in their composition, as shown in Table 1.2, and, therefore, their binding and disintegration behaviours (65, 66).

**Table 1.2 Examples of several commercially ready to fill excipients.** *Data of names, composition, and particle size are shown in this table which was modified with permission from Springer Nature (65, 66).*

| Names of ready to fill excipients | Composition | Particle size (μm) |
|---|---|---|
| CombiLac | 70% lactose, 20% microcrystalline cellulose, 10% native corn starch | 160 (35–65% below) |
| Compressol SM | 80-90% D-mannitol, 10-15% sorbitol, < 2% silicon dioxide | 126 |
| Di-Pac | 97% sucrose, 3% maltodextrin | 149 (75% above) |
| Emdex (USP-NF) | 92% dextrose, 4% maltose, 4% maltodextrin | 190-220 |
| F-Melt type C | 55–70% D-mannitol, 10–25% microcrystalline cellulose, 2–9% xylitol, 5–13% crospovidone, 2–9% dibasic calcium phosphate anhydrous | 120.8 |
| F-Melt type M | 55–70% D-mannitol, 10–25% microcrystalline cellulose, 2–9% xylitol, 5–13% crospovidone, 2–9% magnesium aluminometasilicate | 122.3 |
| Granfiller D 211 | D-mannitol, microcrystalline cellulose, carmellose, crospovidone | 63 |
| Hisorad | D-mannitol, microcrystalline cellulose, croscarmellose sodium | 60 |
| Ludiflash | 90% D-mannitol, 5% crospovidone, 5% polyvinyl acetate dispersion | 170–210 |
| Ludipress | 93% lactose, 3.5% medium-molecular weight povidone, 3.5% crospovidone | 200 (40–60% below) |
| MicroceLac | 75% lactose, 25% microcrystalline cellulose | 160 (35–65% below) |
| Pearlitol Flash | 80–85% mannitol, 15–20% maize starch | 200 |
| Pharmaburst 500 | 85% mannitol, < 10% silicon dioxide, < 10% sorbitol, 5% crospovidone | 130 |
| ProSolv ODT | 60–70% mannitol, 15–30% MCC, < 10% fructose and silicon dioxide, 5% crospovidone | 52 |
| SmartEx QD 100 | D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose | 86 |
| SmartEx QD 50 | D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose | 57 |
| StarCap 1500 | 90% corn starch, 10% pregelatinized starch | 90 |

### 1.3.2 Orodispersible tablets and patient adherence

In order to ensure correct drug administration and improve patient adherence, there is the need to consider a variety of acceptability factors during drug development. ODTs promote patient adherence, particularly in patients who have swallowing difficulties (67). Conventional tablets need to be swallowed whole, whereas ODTs dissolve in the mouth and leave behind a residue that also needs to be swallowed. However, a clinical investigation has shown that the swallowing of ODT's residue differs from the swallowing of conventional tablets, and that dysphagia patients preferred ODTs (16). According to this study (36 adult dysphagia patients), ODTs required fewer swallow attempts and less time during swallowing; they also required less effort and had a shorter time of breath holding during swallowing than for conventional tablets (16). ODTs can assist swallowing problems and enhance patient acceptance and, as a result, their adherence to their medicines. Effervescent tablets also assist swallowing problems but need to be first dissolved in water rather than taken directly. Therefore, in some circumstances there is a convenience benefit to ODTs.

Patients with chronic illnesses such as depression, diabetes, and hypertension, particularly those with multiple disorders, have poor drug adherence (68, 69, 70, 71). Patient adherence to their medicines can be improved by using ODTs instead of conventional tablets. For example, switching to an ODT formulation improved glucose control in diabetic patients who had previously struggled to adhere to their voglibose medication (72). Also, a lansoprazole ODT was found to have higher adherence and acceptance than a conventional tablet in the treatment of gastroesophageal reflux disease (73, 74). In addition, ODTs have been proven to be more acceptable for patients with schizophrenia and depression due to their high efficacy, adherence, ease of administration, and a positive attitude toward therapy (75, 76). However, ODTs formulations were reported as the most common formulation with a link to several mouthfeel

attributes (77). The need for a quick disintegration time, taste masking, and a pleasant mouthfeel makes formulating acceptable ODTs problematic (46).

### 1.3.3 Mouthfeel as a barrier to developing acceptable orodispersible tablets

In comparison with conventional tablets, ODTs disintegrate in the mouth before being swallowed, with the mouthfeel impacted not only by the texture of the surface of the tablets, but also by the disintegration, as well as the texture and amount of fragmented material (46, 77). Due to those interactions between the ODTs and the oral cavity, it is important to thoroughly monitor mouthfeel and the acceptability of ODTs. Furthermore, ODTs stay in the mouth for longer time than conventional tablets, leading to an increase in the sensory awareness. As a result, acceptability studies for this type of dosage form are becoming increasingly popular. Several mouthfeel attributes have been linked to ODTs in published acceptability studies (Table 1.3) (77).

**Table 1.3 The number of reported studies of the mouthfeel attributes of orodispersible tablets.** *The right- hand column shows the number of studies in which an excipient was used. The table has been modified with permission from Elsevier (77)*

| Mouthfeel attribute | Number of ODT studies | Number of studies that used excipients for dispersible tablets |
|---|---|---|
| Disintegration time | 28 | |
| Grittiness/roughness | 19 | |
| General palatability/mouthfeel/acceptance | 11 | 1 |
| Ease of administration/ Swallowing | 2 | |
| Numbness | 4 | |
| Dry mouth | 1 | 1 |
| Astringency | 2 | |
| Cooling | 1 | |
| Bubble-, pulp-, powder-like | 1 | |
| Residual material | 3 | |
| Urge to drink | 2 | |
| Adhesiveness/cohesiveness | 1 | |

Tablet disintegration refers to the fragmentation of a compacted tablet into many particles (78). Disintegration is not a direct textural characteristic; rather, it is an aspect of the sample-mouth interactions that can influence other texture and mouthfeel attributes. The disintegration of the ODTs is commonly assessed in the literature, as seen in Table 1.3. Existing regulations to quantify the disintegration time of ODTs are likely the impetus for studying disintegration. According to *the European pharmacopeia,* ODTs are required to disintegrate in less than 3 minutes (79). *The US pharmacopeia* stipulates the maximum disintegration time for ODTs is 30 seconds (80). The rationale to this disparity is not entirely clear; however, it might be attributable to the lack of a single, unified definition of ODTs regarding various stipulations. Even so, due to the need for a fast disintegration, superdisintegrants have been used to manufacture ODTs. Superdisintegrants facilitate ODTs disintegration by a variety of mechanisms including swelling, wicking, and strain recovery (59). Thus, it is crucial to comprehend the effect of not only the endpoint of disintegration but also the overall disintegration behaviour on the texture and mouthfeel. Only a few studies have looked at the mouthfeel attributes of ODTs other than disintegration such as grittiness/roughness and residue (Table 1.3).

Numerous studies have brought to attention an association between *in vitro* and *in vivo* endpoint of disintegration; this will be discussed briefly in the next section. However, limited research has been conducted to identify a connection between other textural changes that can influence mouthfeel. For example, a study was conducted utilising a textural analyser (TA) and an advanced statistical tool (PLS) to predict the amount of residue and palatability in relation to disintegration behaviour (81). The model for this study was built based on ODTs' characteristics (e.g., filler or super disintegrant ratio and type, and granule size), the measurements of the TA, and the human assessments. This study revealed that the filler type

and ratio have a significant impact on the perceptions and palatability of ODTs. In addition, the use of TA provided a promising prediction of the disintegration time, residue, and palatability of ODTs.

## 1.4 Mouthfeel and acceptability assessment

Medicine acceptability monitoring is a relatively new but growing regulatory concept. New regulatory guidance for paediatric medicines has been issued, requiring acceptability testing for new products designed for children (12). Despite increased interest and demand for acceptability/palatability evaluation, little guidance on appropriate and solid testing strategies exists. Mouthfeel of the ODTs encompasses all of the textural changes that are caused by dosage form attrition, the sensation of fine particles, and the characteristics of formulation itself or the released materials leading to viscosity or adhesiveness. The presence of saliva, as well as the intensity of disintegration and dissolution of the ODTs in the mouth, influencing the sensory perception of the ODTs. For these multifactorial sensations, assessment of the mouthfeel of the ODTs is a complicated task.

Oral medicines' mouthfeel attributes can be studied using sensory (*in vivo*) or instrumental (*in vitro*) studies. Even so, conducting *in vivo* acceptability studies remains the gold standard approach, and involves a number of disadvantages, such as a long-time commitment, a lengthy ethical approval process, a significant financial expense, and a high degree of variability across participants. It is therefore important to consider the use of laboratory-based tools.

## 1.4.1 Instrumental testing

Sensory evaluation is a relatively new concept to the development of pharmaceutical products. Therefore, a standard instrumental method for evaluating the texture and mouthfeel of ODTs is not available, and, therefore, a variety of methodologies have been employed for this purpose (77). The most common approaches to assessing the quality of ODTs include measuring mechanical qualities (e.g., breaking force and friability), disintegration time, dissolution, taste masking, and stability (82). Thus, it is important to develop *in vitro* testing methods that can evaluate the textural characteristics of solid oral formulations in a simple and effective manner. The use of *in vitro* methodologies during drug development would reduce drug development costs and enhance their acceptance. Many *in vitro* tools for analysing mouthfeel have been reported in the literature, but the most of the reported methods are inconsistent and unstandardized (77). A number of methodologies need to be utilised to examine a product's sensory properties due to the intricacy of the sensory characteristics related to oral medicines. Since most *in vitro* methods are developed to evaluate a single parameter, it is challenging to fully explain sensory perception using a single method (83).

### *1.4.1.1 Disintegration*

Among the pharmacopoeia tests, only the disintegration test is related to mouthfeel attributes. However, the disintegration tester was initially intended for conventional instant release tablets, and the settings of the test are distinctive from the conditions found in the mouth. The volume of the disintegration media in the pharmacopoeia tester (800 ml) is vastly different from the volume of saliva (0.70 ml) in the oral cavity (84). Consequently, various tools have been used to determine the disintegration time. This variation in approaches to assessing oral disintegration is well-known; a recent paper analysed multiple reported methods to identify one that correlated best with *in vivo* data for a group of six tablets (82). Table 1.4 shows a variety of *in vitro* methods to measure disintegration time and how this correlates with the

findings from giving tablets to volunteers. In the studies, there are a variety of test conditions, including volume (~30 µl to 1000 ml), disintegration media (e.g. water, artificial saliva, or buffer), and temperature (37 °C, 25 °C or room temperature) (77). Despite the variability in the reported techniques, the use of many of the items of equipment has provided excellent correlations to human data (Table 1.4). However, the correlation between findings varied based on the formulations tested and the test parameters, and, therefore, it is difficult to arrive at the best testing method (77). Also, these tests provide an evaluation of the disintegration time without providing an understanding of the water intake or disintegration dynamics (85).

**Table 1.4 The number of reported studies involving the use of the different *in vitro* tools to assess disintegration of orally disintegrating formulations and its range of correlations to human data.** *The non-italic values for rs were the correlation values derived from data assuming a linear relationship, whereas the italic values for r were the stated correlation values by the study. The table was modified with permission from Elsevier (77).*

| ***In vitro* method used** | **$r_s$ min** | **$r_s$ max** | **Number of ODT studies** |
|---|---|---|---|
| USP disintegration apparatus | 0.0035 | 0.9952<br>*r=0.9806* | 22 |
| Petri dish | 0.3895 | 0.9935<br>*r=0.83* | 15 |
| TA | 0.6149 | 0.9996 | 6 |
| OD-mate | *r=0.936* | 0.9451<br>*r=0.97* | 3 |
| Disintegration test on wire cloth | - | 0.8169 | 1 |
| Tricorptester | - | Two samples only | 2 |
| Drop method | - | not available | 1 |
| Modified Tensiometer | - | Single sample | 1 |
| Water bath shaker | - | 0.9617 | 1 |
| Goniometer | - | Single sample | 1 |
| Modified USP II Dissolution apparatus | - | Single sample | 2 |
| Clamp method | - | *r=0.975 (p<0.05)* | 1 |
| Cell method | - | *r=0.999 (p<0.01)* | 1 |
| Frame method | - | *r=0.991 (p<0.01)* | 1 |
| Modified sieve method | - | 0.993 | 1 |

#### *1.4.1.2 Grittiness/roughness*

It is common practice to use the terms "roughness" and "grittiness" interchangeably when evaluating the mouthfeel of oral medications. However, grittiness relates to the sensation of a particulate and is often a bulk characteristic (86), while roughness refers to the extent of surface irregularity (87). Both roughness and grittiness can be precipitated by powder, multi-particulate formulations, or formulations that disintegrate or that are chewed in the mouth.

Disintegration involves breaking the bulk of the ODTs into fragments that are easily swallowed when combined with saliva to form a cohesive material. The size of disintegrated fragments and the rate of disintegration can influence the sense of grittiness and roughness. For instance, the size of fragments/granules has been reported to impact on the sense of the grittiness/roughness of ODTs (46). For food consumption, chewing food until a smooth bolus is formed is a key step in the swallowing process. Most people chew their food until the residual fragments are smaller than 2 mm in size before swallowing (88). For tablets that are intended to be dispersed in water before administration, a smooth dispersion is achieved when the particles are small enough to pass through a sieve with a nominal mesh aperture of 710 μm (89). It has been observed that ODTs with core granules larger than 264 μm cause a rough feeling in the mouth (46). However, this size is significantly larger than the tongue sensitivity, which can perceive particles as small as 6–10 μm (90).

Since excipients constitute a significant component of solid oral dosage forms, the type and ratio of excipients might influence grittiness. Therefore, the roughness and grittiness of ODTs can be anticipated from the physical characterization of the excipients, API, and the pre-tableting formulations (e.g. granules). A number of techniques (e.g. particle size, particle hardness, sphericity, and morphology) have been reported to evaluate roughness and grittiness, but none of them have a direct connection to human mouthfeel (77).

#### *1.4.1.3 Adhesiveness/cohesiveness*

The degree to which a material adheres to the tongue, teeth, or palate determines its adhesiveness (also known as "stickiness"). Adhesive material can be difficult to be removed from the mouth. In food development science, measuring the adherence of foods to surfaces is critical for anticipating texture perception and minimising preparation difficulties (91). Adhesiveness is commonly assessed as the force necessary to remove the sample from a surface of a test component that represents oral teeth, tongue, or palate (77). Cohesiveness refers to the extent to which the tested material sticks to itself. Cohesiveness measurement is useful in food sensory evaluation since it indicates the needed level of chewiness and, consequently, the ease of swallowing (92). Due to the disintegration-induced change in the form of ODTs in the mouth, evaluating adhesiveness and cohesiveness can be a challenging task. In general, adhesiveness and cohesiveness of food products are evaluated using tensile test equipment or a TA; a similar tool has been used for evaluating various solid oral dosage forms, such as film formulations (47). Depending on the type of dosage form, adhesiveness may have a positive (e.g., mucoadhesive tablet) or negative impact (e.g., ODT) (77).

#### *1.4.1.4 Further sensations*

Oral medicines can induce discomfort even after administration, as the sensation of taste and texture of the medication may remain in the mouth. Several textural sensations following administration of ODTs have been reported in the literature, including the presence of residue and dryness and urge to drink (Table 1.3). The relationship between those feelings and a particular *in vitro* characteristic (granule size) has been reported (46). Additional sensations such as numbness or astringency after administration are often specifically related to the API rather than the entire formulation (93). For instance, it has been reported that granules with thicker coatings to the API cause less numbness (94).

#### *1.4.1.5 Recent developments (textural analyser)*

*In vitro* approaches that better simulate the anatomy and physiology of the mouth can produce stronger correlations to sensory data. There have been recent improvements to the *in vitro* tools that are used to assess the texture of oral formulations with a view to mimicking the environment of the oral cavity. For example, several textural properties of oral formulations, such as the adhesiveness of orally disintegrating films (47), hardness, elasticity, gumminess of pastille (95), and chewing gum (96), have been assessed using the TA. The TA assesses the mechanical characteristics of a material by applying a controlled force in order to produce a response curve of its deformation (97). In addition to measuring mechanical and textural properties, TA can also be used to determine the disintegration profile of ODTs. The use of the TA to evaluate the disintegration profile of ODTs allows for the adjustment of the force on tablets during disintegration, thus simulating the tongue's disintegration forces (81). For further simulation of the disintegration of ODTs in the mouth, the TA has been adapted to imitate the oral cavity regarding temperature, humidity, and the flow of saliva (98, 99).

### 1.4.2 *In vivo* testing

Human sensory analysis is recognised as the gold standard method for assessing the acceptability of medicines, but there is still a lack of conduct of such studies within the pharmaceutical development industry. Instead, study methods that are used in the food industry have been adapted to medicines. However, such approaches have not been validated (100). Several literature reviews have addressed the issues of using multiple non-standardized methods to assess the acceptability of non-comparable oral medicines (3, 33, 101, 102). A particular issue is medicine acceptability studies have failed to take into consideration the many different attributes of acceptability (27). Assessments of palatability of oral medical formulations have been discussed in several reviews (33, 77, 101, 103, 104, 105), and the palatability of oral dosage forms is commonly described as an overall hedonic response to the examined product, which frequently refers just to the taste.

In food sciences research, the palatability of a product involves routine *in vivo* evaluation. Therefore, the extensive history of *in vivo* sensory evaluation of food products is a valuable source of methods that can be adapted to use for oral medicines (26). Although food science *in vivo* methodologies may not be applied directly to medicine, the various approaches are still applicable to the field of pharmaceutical product development. In food science, a trained panel of healthy adults (n=10–12) conducts sensory testing on a product, and consumers also perform hedonic testing (n=50–100) (106). This approach may face a number of obstacles that limit its applicability in the pharmaceutical industry. For example, only a few companies specialise in offering expert panellist services for oral medications, such as Senopsys in the United States and SLR Pharma in Ireland. Also, seeking consumers of oral medicines is a challenging task, particularly for a new or an orphan medicine.

For medicines, acceptability studies may be undertaken using medicines and patients (7), or may just make use of a placebo formulation given to healthy volunteers (107). They may be conducted as a medicine is developed, as a post-market survey, or at both stages. The studies must be undertaken in an appropriate setting which may vary depending on the study design. Suitable settings would include residences, care facilities, pharmacies, hospitals, clinics, health centres, public areas, and sensory laboratories. It is recommended that palatability testing should be carried out throughout all phases of the pharmaceutical development process, including the early phases (108). This enables the detection and resolution of acceptability issues prior to the conduct of end-user acceptance studies. Patients are often the final users of pharmaceutical products, and acceptance testing must take-into-account the fact that patient acceptability may differ from that of healthy people. Acceptability studies for medical products, such as paediatric formulations, must be conducted on populations that are similar to the target demographics for which the products are intended. Age must be taken-into-account in acceptability studies due to the wide variety of differences in preferences and sensory attitudes, as well as anatomical, physiological, and cognitive development among people of varying ages. The preferences for taste and texture, as well as sensory sensitivity, differ by age group (109, 110, 111). As a result, testing the acceptability of a formulation must be determined for an age group rather than for the wide-ranging age group.

### *1.4.2.1 Methods and tools*

The population to choose is the most crucial aspect to determining acceptability. Various ways to determine acceptance can be utilised depending on the population selected. Adult patients are frequently assessed using preference questionnaires, whereas children's assessment methods vary according to age (112). In both cases, drug acceptability studies should be designed to be uncomplicated for participants, and to take into consideration the age and health status of the group. The participant must be able to comprehend the terms and tools that are used throughout the acceptability evaluation (3). For example, it's critical to employ age-appropriate methods for participants whereby their language comprehension is limited, for example, children. Adopting game-based methods reduces the burden of language and increases a child's interest and attractiveness in the study (113). Also, the tools could be presented in an eye-catching manner, such as by employing simple facial scales (Figure 1.2) to assist participants to express their opinion during the assessments (108).

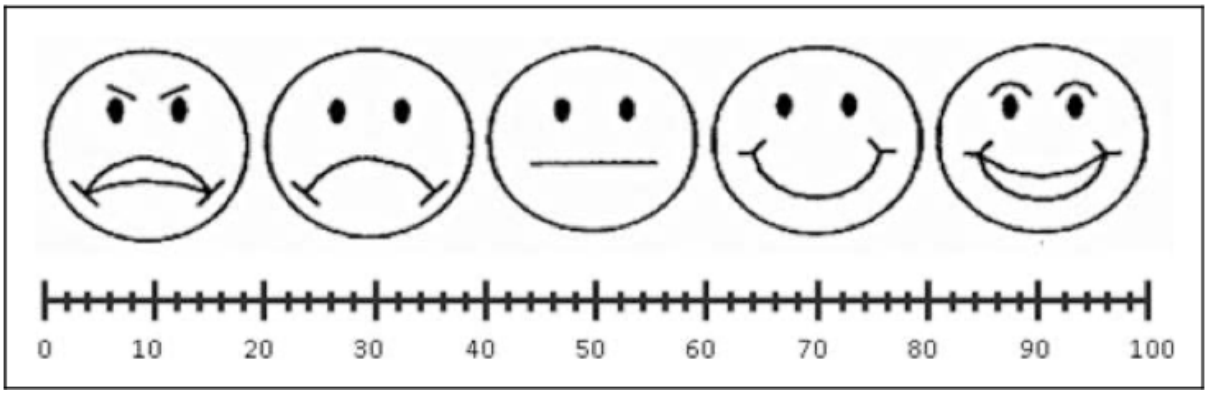



**Figure 1.2 Example of facial emojis was utilised on a five-point scale with a corresponding 100-point visual analogue scale (VAS),** *The scale revised with permission from Springer Nature (108)***.**

The tools listed below are the most commonly used, either separately or in combination, *in vivo* studies to assess acceptance (3, 26, 77):

- Participant-responsible testing tools:

I. Questionnaires

II. Ranking/preference technique

III. Scaling methodology (facial hedonic scale, visual analogue scale - VAS, Likert Scale)

IV. Descriptive methods that depend on verbal responses

- Researcher-responsible testing tools:

I. Interview

II. Observation

III. A technique for detecting unpleasant facial expressions using Facial Action Coding System - FACS

The validity of a method is related to how well it corresponds with scores of other measures (114). In order to standardise and establish a valid approach for analysing the acceptability of medicines, it is necessary to compare numerous tools. According to a previous study, both VAS and 5-point face hedonic scales exhibited a high correlation of responses in a large sample (ages 2–17 years old and using a variety of oral medicines) and have been determined to be reliable scaling tools that can be used alternately (115). Researchers' observations would help demonstrate the patient's ability to take the drug as directed. Although facial expressions and behaviours were not a true indicator of unacceptability, they were more useful in detecting the child's ability to take the drug as prescribed (115).

### *1.4.2.2 Acceptability criteria*

Medicines have a unique set of acceptability criteria compared to other products. When it comes to food, for example, the idea is to produce a product with an attractive appearance and a pleasant sense perception. For an oral drug, however, the goal is for it to be taken easily rather than as a source of pleasure in order to be effective. This emphasises the significance of distinguishing taste or mouthfeel acceptance/preference from palatability. For oral medicines, the taste and mouthfeel of a medicine need to be sufficiently palatable, but not necessarily pleasant; it could, for example, be neutral to ensure acceptability. First and foremost, the endpoint acceptability margin must be pre identified. A product is generally considered adequately acceptable if it is accepted by 80% of the sample population (102). This principle is applicable to measure the endpoint of acceptance scores obtained using binary questions or any scaling methods. The interpretation of acceptability scores obtained using binary (yes/no) questions and hedonic scales are somewhat simple compared to VAS methods which require acceptability cut-off values to statistically determine the endpoints. The majority of existing studies lack scientific and statistical basis for defining scale endpoints. However, acceptability has been defined as a neutral to positive responses on the hedonic scale (e.g., the three smiley faces on right of Figure 1.2), which was significantly correlated with the positive responses from binary questions (yes/no from the user) (102). On the other hand, VAS scores need more careful statistical considerations to ensure the ranking of the neutral or positive scores on a scale (46, 115).

For acceptability assessment in clinical studies, the failure of assessment tools to account for the many varied aspects of acceptability has been criticised (27). A useful approach is to look at a specific acceptance factor and compare it to the total acceptability, such as distinguishing the taste (115) or rough mouthfeel (46) and then compare these aspects to the overall acceptability. This provides more scientific data for future studies to define the most relevant

characteristics and determine their impact on acceptability. Also, it's also critical to examine a number of acceptability features in order to identify the most relevant factors that influence a medical formulation's acceptance. For example, a useful way to examine acceptance of ODTs is by distinguishing positive aspects (smooth, sweetness, disintegration time, watery) from those that may have a negative influence (rough, bitterness, excessive residue/powdery feeling, sticky) (93). Acceptability may considerably increase by addressing all of the problematic aspects that reduce a product's acceptance and this knowledge can then be used in the development of new products.

## 1.5 Importance of the knowledge gap

Regulators have recognized the need to investigate the acceptance of medications by end-consumers (4, 10, 12). Although the field of acceptability studies is expanding, there is a lack of standardised methods. More comprehensive assessments of acceptability are required rather than just using a simple yes or no questionnaire. Identifying essential acceptance qualities and establishing a link with formulation parameters might aid in the production of more appropriate pharmaceutical formulations. Thereafter, *in vitro* techniques might be included into the process of developing pharmaceutical products with the desired properties. The pharmaceutical development field can benefit substantially from early measures to enhance acceptance because medications with proven acceptance qualities have the potential to reduce the chance of therapy-related unpleasantness and should enhance life quality, including for different age groups.

# Materials and General Instrumental Methods

## 2.1 Material

Microcrystalline cellulose (Primecel ™), and low-substituted hydroxypropyl cellulose (LHPC-21 and LHPC-22) were kindly provided by Chemlink Specialities Harke Group, d-mannitol and maize starch were purchased from Thermo Fisher Scientific™, magnesium stearate, and croscarmellose sodium (CCS) was purchased from Sigma-Aldrich®. Crospovidone (CP) was purchased from Alfa Aesar.

Placebo ODTs: Granfiller-d ™ (GNF-D211 and GNF-D215), SmartEx®, and Hisorad ™ were kindly provided by Chemlink Specialities Harke Group. Commercial ODTs: donepezil hydrochloride 10 mg orodispersible tablets (McDermott Laboratories Ltd), mirtazapine 45 mg orodispersible tablets (Aurobindo Pharma Ltd), ondansetron 8 mg orodispersible tablets (Bluefish Pharmaceuticals AB), and risperidone 20 mg orodispersible tablets (KRKA, d.d., Novo mesto) were kindly provided by Queen Elisabeth hospital (Birmingham). Calpol® Fastmelt (McNeil Products Ltd) and Imodium Instants® (McNeil Products Ltd) were purchased from a local community pharmacy.

## 2.2 ODTs preparation

### 2.2.1 Powder mixtures:

Each ingredient was sieved through an 80-mesh sieve before mixing. Each formulation (Table 2.1) was physically mixed until homogeneity in a rotator mixer (Stuart, UK). All of the excipients except the lubricant were mixed in the small drum-shaped container that was fitted into the mixer at 45 degrees. All of the ingredients were thoroughly mixed using a modest speed of 25 rpm. The mixing period lasted 10 minutes, after which the lubricant was added and mixed for a further 2 minutes before the mixture was ready for tabletting.

**Table 2.1 The formulations' content of different ratio of excipients.** *MCC, microcrystalline cellulose; LHPC, low-substituted hydroxypropyl cellulose; CCS, croscarmellose sodium; MG St, magnesium stearate.*

| Ingredients/ Formulation | CP1 | CP 2 | CP 3 | CP 4 | CP 5 | CP 6 | CP 7 | LH1 | LH2 | CC1 |
|---|---|---|---|---|---|---|---|---|---|---|
| **MCC %** | 25 | 20 | 15 | 5 | 25 | 25 | 25 | 25 | 25 | 25 |
| **Mannitol %** | 69.5 | 69.5 | 69.5 | 69.5 | 64.5 | 59.5 | 49.5 | 64.5 | 64.5 | 64.5 |
| **Starch %** | 0 | 5 | 10 | 20 | 5 | 10 | 20 | 5 | 5 | 5 |
| **Crospovidone %** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | - | - | - |
| **LHPC-21 %** | - | - | - | - | - | - | - | 5 | - | - |
| **LHPC-22 %** | - | - | - | - | - | - | - | - | 5 | - |
| **CCS %** | - | - | - | - | - | - | - | | | 5 |
| **Mg St %** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

### 2.2.2 Granule mixtures:

The wet granulation method was used to prepare granules of different core sizes. All intragranular ingredients (MCC, mannitol, starch**,** crospovidone) were sieved and mixed in the same manner as previously specified. Granules were produced by wetting the intragranular mixture with a distilled water and then passing the resulting wet, cohesive material through a sieve (sieve mesh of 355, 500, 710, or 1180 µm). Wet granules were dried in a hot air oven (60 °C) for 45 minutes before being sieved through a slightly larger mesh screen of each used sieve to remove any aggregates. Granules were mixed with magnesium stearate and then compressed into ODTs.

### 2.2.3 Tableting:

The one punch tablet manual hydraulic press machine (Specac, UK) equipped with a 10 mm die set was used to manufacture ODTs. The compression force utilised to prepare 250 mg of ODT was manually adjusted to 0.8 ton, unless otherwise stated. The ODTs were transferred and stored in a tightly sealed container for 24 hours before being evaluated.

## 2.3 Tablet characterisation

### 2.3.1 Measurements of orodispersible tablets' thickness, diameter, and weight

The diameter and thickness of the produced ODTs were measured using a digital metre calliper. The weight of the prepared ODTs was measured using a balance. These measurements will be required in forthcoming evaluations, in addition to ensuring the uniformity of the prepared

ODTs. All measurements were obtained in triplicate and data are the mean ± standard deviation.

### 2.3.2 Breaking force

The breaking force of the ODTs was measured using a breaking force tester (Copley TBF 1000, Nottingham, UK). Then, the following equation was used to determine the tensile strength :

$$\sigma = \frac{2\,B}{\pi\,D\,T}$$

(Equation 2.1)

In this equation, B represents the breaking force of the tablet (N), D its diameter (mm), and T its thickness (mm). All measurements were obtained in triplicate and shown as the mean ± standard deviation.

### 2.3.3 Friability

In order to determine the percentage of friability of the manufactured tablets, the USP friability test was utilised (116). Six ODTs were softly brushed off before being weighed and placed in a friability tester (Copley FRV 200i, Nottingham, UK). The test lasted 4 minutes and consisted of 100 rotations at 25 rounds per minute. After the excessive dust were removed, the ODTs were re-weighed to determine their final weight. The following equation was used to determine the percentage of friability:

$$\%\ \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

(Equation 2.2)

### 2.3.4 Disintegration and textural assessments

The disintegration profile of ODTs was evaluated utilising a TA.XT plus texture analyser (Stable Micro Systems Ltd., UK) with a 5 kg load cell. The texture analyser (TA) was equipped with a 10 mm probe (P/0.5 • P/1R) and thermal cabinets to regulate the test temperature. The testing procedure was derived from two previous studies (98, 99). A tablet was put in a custom-built test rig and positioned below the probe. The rig has a mesh that allows a disintegrating medium to just cover the mesh's surface (Figure 2.1). The sample dimensions and test parameters were entered into the Exponent Connect software (Stable Micro Systems Ltd., UK) before running the test. The test began after a volume (4.5 ml at 37 ± 2 °C) of distilled water was dispensed into the rig using a syringe. The probe was vertically moved toward the sample at a rate of 1 mm/s until a trigger force of 1 g was met. As soon as the probe contacted the ODT at the trigger force, the TA was programmed to apply a fixed 2.5 g weight for a predetermined time period. The obtained distance versus time graph (Figure 2.2) was then used to determine disintegration and textural characteristics (onset of disintegration, rate of disintegration, disintegration time, swelling, residue). The test was repeated three times and the results are provided as the mean ± standard deviation (SD).

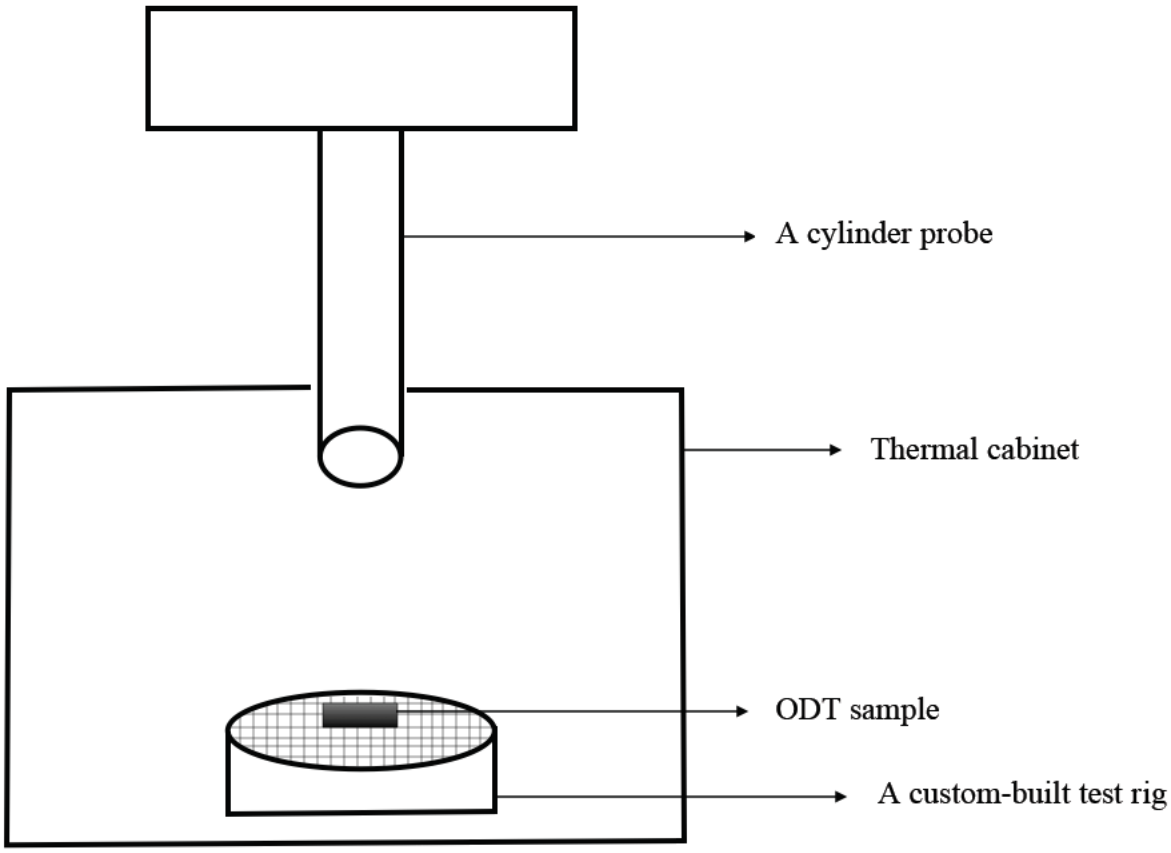



**Figure 2.1 A diagram illustrating the design of TA for testing the disintegration of orodispersible tablets.**

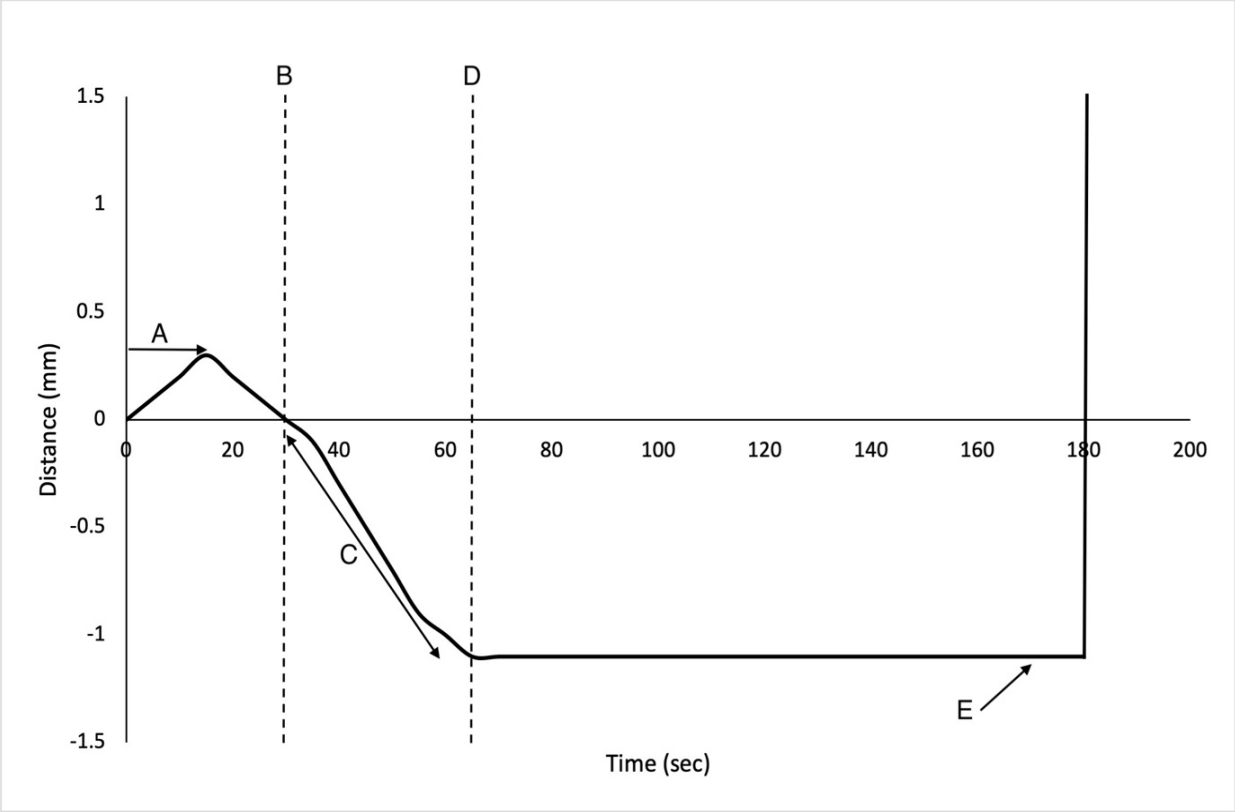



**Figure 2.2 A graph of the disintegration profile obtained by the texture analyser.** *The graph was used to determine (A) swelling; (B) the onset of disintegration; (C) rate of disintegration; (D) end point of disintegration / disintegration time; (E) residue.*

Texture profile analysis (TPA) was performed to measure further textural features (hardness, adhesive and cohesive) using two compression cycles. The testing procedure was adapted from a previous study (117). The TA was equipped with a (10 mm) diameter cylinder probe. A sample of ODTs was placed on a filter paper (55 mm) that had been moistened with 1 ml of distilled water (37 ± 2 °C) and left for 30 seconds and until the surface of the tablets was entirely wet. To avoid deforming the wet tablets, the probe was lowered until it reached the surface of the tablets, at which point a trigger force (0.1 g) was achieved. Then the tablets were compressed at 1 mm/sec for % 30 strain which equivalent to ≅ 1 mm distance, after which the probe was returned at the same speed to the starting position prior conducting a second compression cycle. Additional test parameters were pre-test and post-test speeds of 2 mm/sec. Characteristics of texture were extracted from a plot of force vs time (Figure 2.3). The test was repeated in triplicate and the results were provided as the mean ± standard deviation (SD).

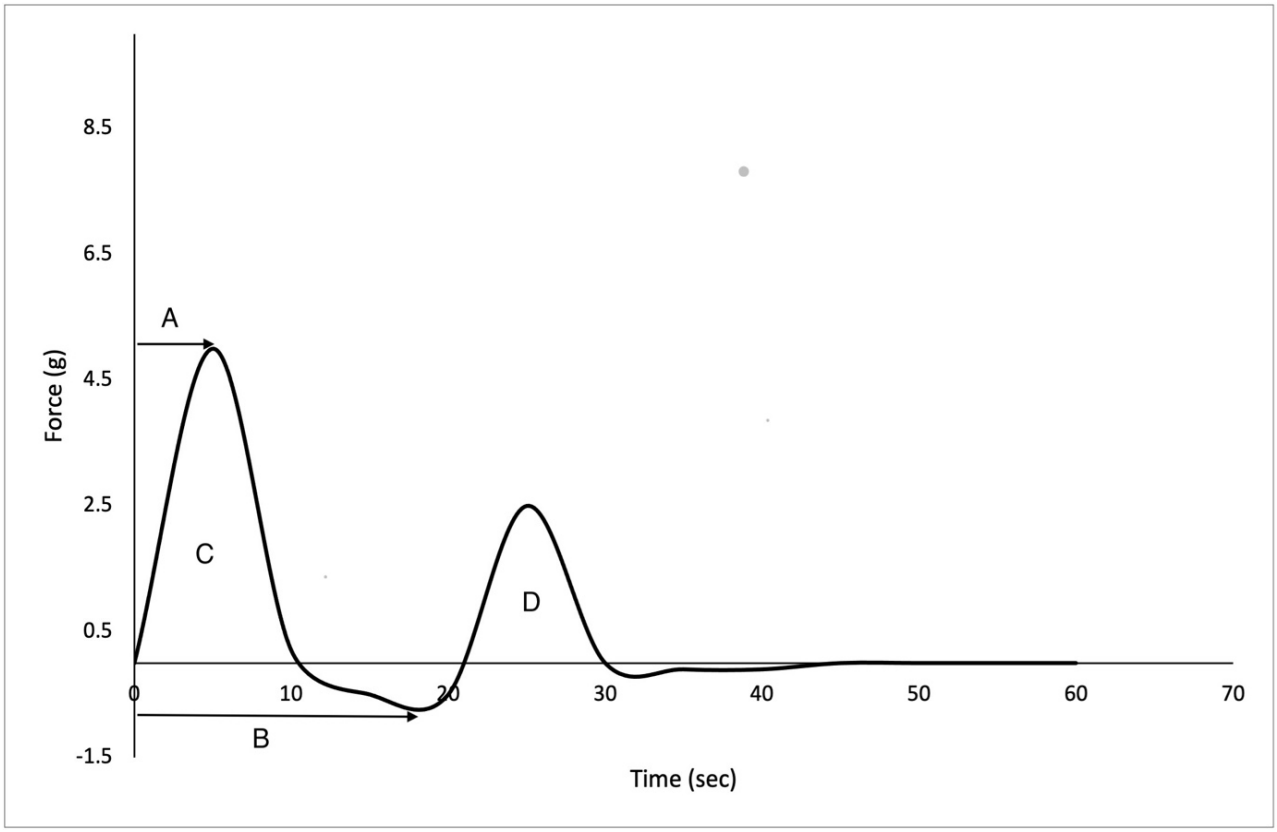



**Figure 2.3 A graph of the texture profile analysis (TPA) obtained by the texture analyser.** *The graph was used to determine (A)the hardness; (B) the adhesive force; (C-D) the cohesiveness by calculating the area under the curve (AUC of D/AUC of C).*

### Wettability

Wettability was determined by measuring wetting time and water absorption ratio (118). Tissue paper was folded in half and placed in 6 mL of water in a small Petri dish. The tablet was placed on tissue paper for examination. This resulted in water being absorbed into the tablet from the bottom of the tablet. The wetting time was determined by measuring how long it took for water to reach the centre of the top surface of the tablet. The water absorption ratio (%) was calculated by weighting the tablet using the given equations:

$$\text{water absorption ratio (\%)} = \frac{W1-W0}{W0} \times 100$$

(Equation 2.3)

where $W_0$ is the initial dry weight (mg) of the tablet and $W_1$ is the final saturated weight after being hydrated (mg).

## 2.4 Statistical analysis

The findings of the instrumental tools are displayed as the mean and standard deviation. Since the hypothesis of (approximate) normality of the observations could not be verified, the Kruskal-Wallis test was utilised. The differences between the samples were compared using the Kruskal-Wallis test followed by Dunn's multiple comparisons test, as a post hoc test, with Tukey corrections. Investigation of correlations between various metrics was performed using Spearmon's correlation coefficient ($r_s$). A p-value of $\leq 0.05$ was regarded as statistically significant. Prism 9.3.1 was used for those statistical testing (GraphPad Software, San Diego, CA, USA).

# *In Vitro* Assessment of Orodispersible Tablets and Textural Attributes

## 3.1 Introduction

Mouthfeel is a highly dynamic process caused by a continual change in the physical properties of consumable materials as they are manipulated in the oral cavity (41). All aspects of the oral interactions with a dosage form can be identified as mouthfeels, including disintegration, hardness, adhesiveness/cohesiveness, and after-feeling. To evaluate the mouthfeel of ODTs, it is necessary to understand the specific properties that can influence the texture and oral perception. In food sciences, for example, springiness is a desired attribute associated with freshness and fluffy texture, and a food engineer needs to be aware of the elements of food that might increase this attribute. For drug formulations and ODTs in particular, the factors that contribute to desirable attributes, such as disintegration, and undesirable attributes such as hardness need to be recognised and evaluated as they will affect the sensory feel of the final product. The variation in many physical textural properties of the oral medicines increases the need to employ a variety of methods to investigate a product's sensory properties (43). This emphasises the need for effective tools to comprehend the dynamics of the disintegration process, as well as the changes in tablet structure that occur during that period, which may impact on ODT's texture and sensory attributes. In this chapter, the factors that impact the texture of ODTs will be evaluated using both direct assessments, such as disintegration, hardness and adhesive properties, as well as indirect tests, such as tensile strength and friability.

The texture of the ODTs can be impacted by the variations in the composition and the manufacturing process. ODTs can be prepared with a variety of excipients in different proportions. For the chosen excipients, mannitol is commonly used as a diluent or a filler for

manufacturing ODTs because of its pleasant taste and mouthfeel. In addition to the sweetening effects, sugar alcohols groups, such as mannitol, produce a cooling sensation when they dissolve due to the heat absorption reaction (119). ODTs are commonly prepared using a mixture of mannitol and microcrystalline cellulose. Microcrystalline cellulose (MCC) is used as a binding agent besides its disintegrating properties. MCC can be used in a variety of concentrations, such as a disintegrant (5% – 15%) or a binder (20% – 90%) (120). Starch also has a multipurpose use, including as a diluent, disintegrant, binder, or as a thickening agent. Starch is commonly used as a disintegrant at a concentration of 3–25 %, and as a binder for tablets prepared using wet granulation method (120). Starch has a potential to improve mouthfeel due to its disintegrating properties as well as its role as a viscosity-modifying excipient (121). Thickening agents or viscosity enhancers can improve the mouthfeel of the ODTs by masking the grittiness feeling (122). Superdisintegrants are key excipients that aid the rapid disintegration of ODTs. The ideal superdisintegrant must be safe, compatible with other ingredients, effective at low concentration, and have a pleasant mouthfeel (59). Superdisintegrants facilitate ODT breakdown through different mechanisms such as swelling, wicking, or strain recovery (123). Crospovidone (CP), as a superdisintegrant, has been shown to improve the mouthfeel of ODTs by smoothing out the rough texture. (124). In this study, ODTs prepared with different superdisintegrants were compared to crospovidone to assess their effects on the texture and features of the tablets.

Beside the compositions of the tablets, the manufacturing process can substantially affect the tablets' features and texture. Compared to conventional tablets, the preparation of ODTs uses low compression forces to convert small particles of the ingredients into a solid dosage form. The compression force is a major factor that can impact several features of the tablets such as disintegration. The impact of compression force on tablet features can be caused by a change

in tablet texture and the intra bounds between the particles. An increase in compression force can cause a decrease in tablet porosity, which can lead to an increase in tensile strength and disintegration time (125). The method used to prepare tablets can also impact on the tablet's features such as the mechanical strength. For tablets that have the same porosity, the tensile strength of tablets prepared by the wet granulation method is ten times greater than that of tablets prepared by the direct compression method (125). This chapter will examine the ODTs prepared using four compression forces and using either direct compression or wet granulation method.

The aim of this work is to understand the factors that can change the texture of the ODTs by looking at (i) factors related to the composition of the tablets (such as the binder/diluent ratio), (ii) factors related to the manufacturing process (such as granulation or direct compression methods) using the TA and common pharmacopoeia methods. A secondary aim of this work is to assess the correlation between the *in vitro* tools used for assessing the textural and physical features of ODTs.

## 3.2 Results and discussion

### 3.2.1 Disintegration

#### *3.2.1.1 Impact of composition on the disintegration of orodispersible tablets*

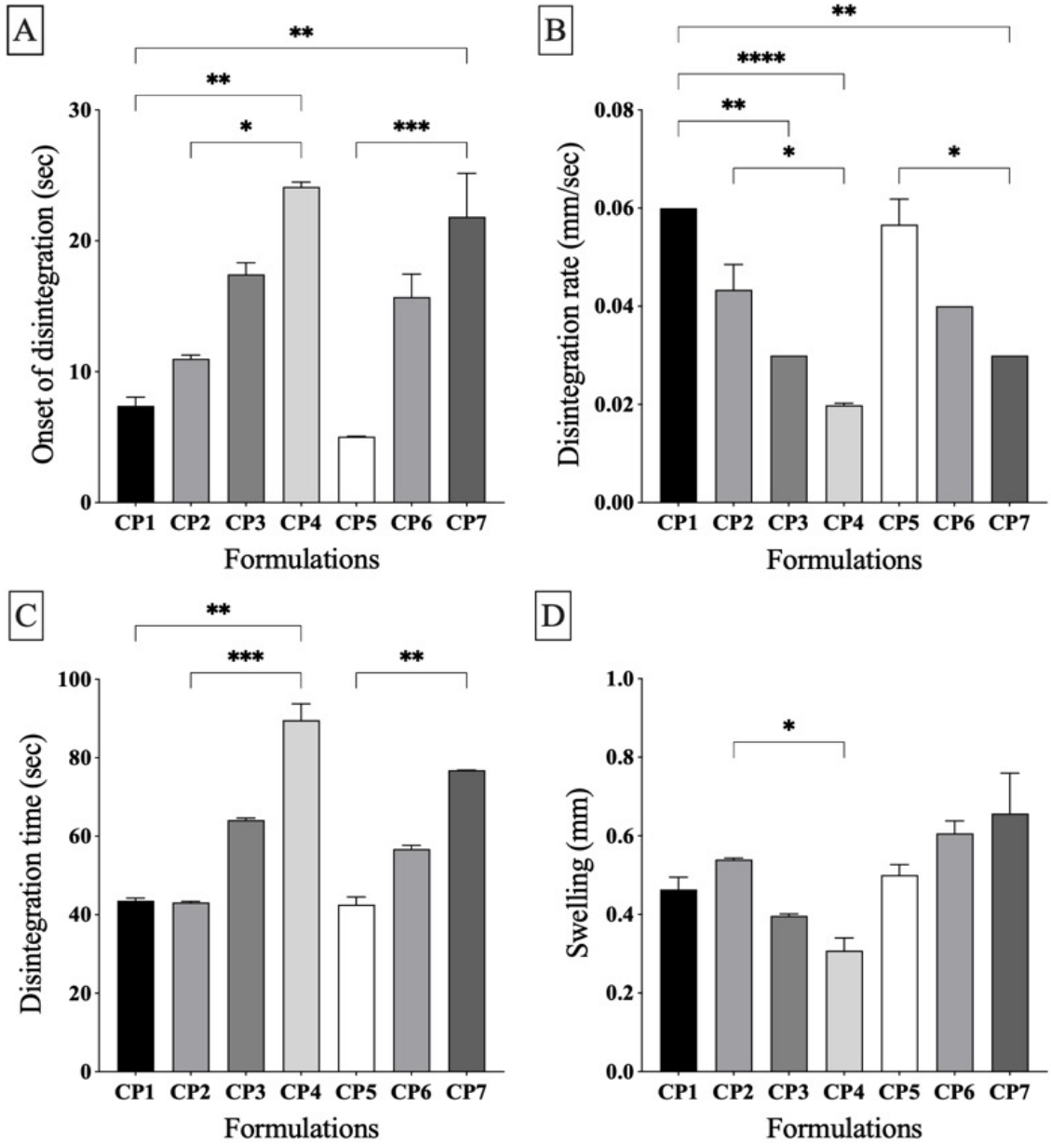
The impact of various ratios of different excipients on the disintegration of the ODTs was measured using the TA. In contrast to the pharmacopoeia disintegration tester, the TA can measure different aspects of the disintegration including the onset, the rate, the endpoint, and the swelling. Figures 3.1 and 3.2 summarise the impact of composition on ODT disintegration. In a first instance, the impact of adding starch (5-20%) and concomitantly decreasing either the MCC or mannitol content was studied (Figure 3.1). Tablets that contained 10% or more of starch had an onset of disintegration that was significantly delayed compared to CP1 tablets that contained no starch. For CP4 and CP7 tablets containing 20% starch, the onset of disintegration was 3.4 times slower than for CP1 ODTs, which contained no starch. For ODTs made with a higher starch content, the impact of starch was to slow down the rate of disintegration (Figure 3.1 B). The rate of the disintegration for CP4 tablets containing 20% starch was 0.02 ± 0.001 mm/sec compared to ca. 0.06 ± 0.005 mm/sec for ODTs made without starch or with 5% starch. CP4 (20% starch) had the longest disintegration time (89.6 ± 4.2 seconds), while CP1(0%), CP2 (5%) and CP5 (5%) all had short disintegration times of ca. 44 ± 2 seconds (Figure 3.1 C). A closer inspection of the results revealed that for ODTs containing 20% starch, the disintegration time was shorter for ODTs with a higher MCC content. Indeed, CP4 tablets (5% MCC) had a disintegration time of 89.6 ± 4.2 seconds compared to 76.8 ± 0.02 seconds for CP7 tablets (25% MCC).

The swelling of the ODTs during the disintegration process was measured as a distance unit of the increase in tablet size (mm). The swelling of the tablets varied somewhat depending on the

starch and the MCC content (Figure 3.1 D). Decreasing the amount of MCC to 15% or less significantly reduced the swelling distance even though the amount of the starch was variable, as compared to CP1 tablets. For CP4 tablets that contained 5% MCC, the swelling distance was 0.3 ± 0.03 mm compared to 0.47 ± 0.03 mm for CP1 tablets that contained 25% MCC. The swelling of the tablets was increased by increasing the content of starch in the tablets (10% or more) while the amount of MCC was constant (25%), as compared to CP1 tablets that had no starch and the same amount of MCC. The swelling increased from 0.47 ± 0.03 mm for CP1 tablets to 0.6 ± 0.03 mm and 0.66 ± 0.1 mm for CP6 and CP7 tablets (both containing 10% or higher of starch). Tablets that were compressed from ingredients that were mixed with just 5% starch had a similar swelling distance to CP1 tablets that included no starch.

Understanding the factors that can influence different disintegration properties can help improve understanding of textural changes and their potential effects on mouthfeel. The disintegration of ODTs is not only determined by the type of excipients, but also by their proportion. The disintegration was extremely prolonged for the tablets (i.e CP4 ) containing a very small amount of MCC and a high amount of starch. Aside from its disintegrant properties, MCC increases liquid transfer into a tablet matrix by facilitating diffusion and capillary action (126). The combination of MCC with mannitol can enhance tablet compressibility (127); however, excessive MCC (> 40%) may affect the taste and texture of the tablets (128). Starch was also a major determinant of the disintegration of ODTs. Starch and other traditional disintegrants are commonly utilised in conventional tablets, despite the fact that they are not as effective as superdisintegrants and that their larger content has negative effects on other characteristics like hardness and flow (129). The undesirable effect of a high starch content on the disintegration of ODTs can be attributed to its viscosity-increasing properties. To develop an optimal formulation, it is critical to balance the amount of the excipients as a high amount

of viscosity enhancer can lead to the formation of gel layers, and thus loosen the dispersibility feature of the tablets (122). The results from this study have shown that the ratio of MCC and starch impacts mainly on swelling. Both MCC and starch tend to swell upon contact with the disintegration media (120). The swelling of the tablets is an important textural change that can initiate the disintegration process. CP1 and CP5 tablets exhibited superior disintegration properties regarding the three major characteristics of disintegration studied, with CP5 exhibiting a faster rate of disintegration. To develop an optimal formulation, it is critical to balance the amount of the excipients as a high amount of viscosity enhancer can lead to the formation of gel layers, and thus loosen the dispersibility feature of the tablets (122).



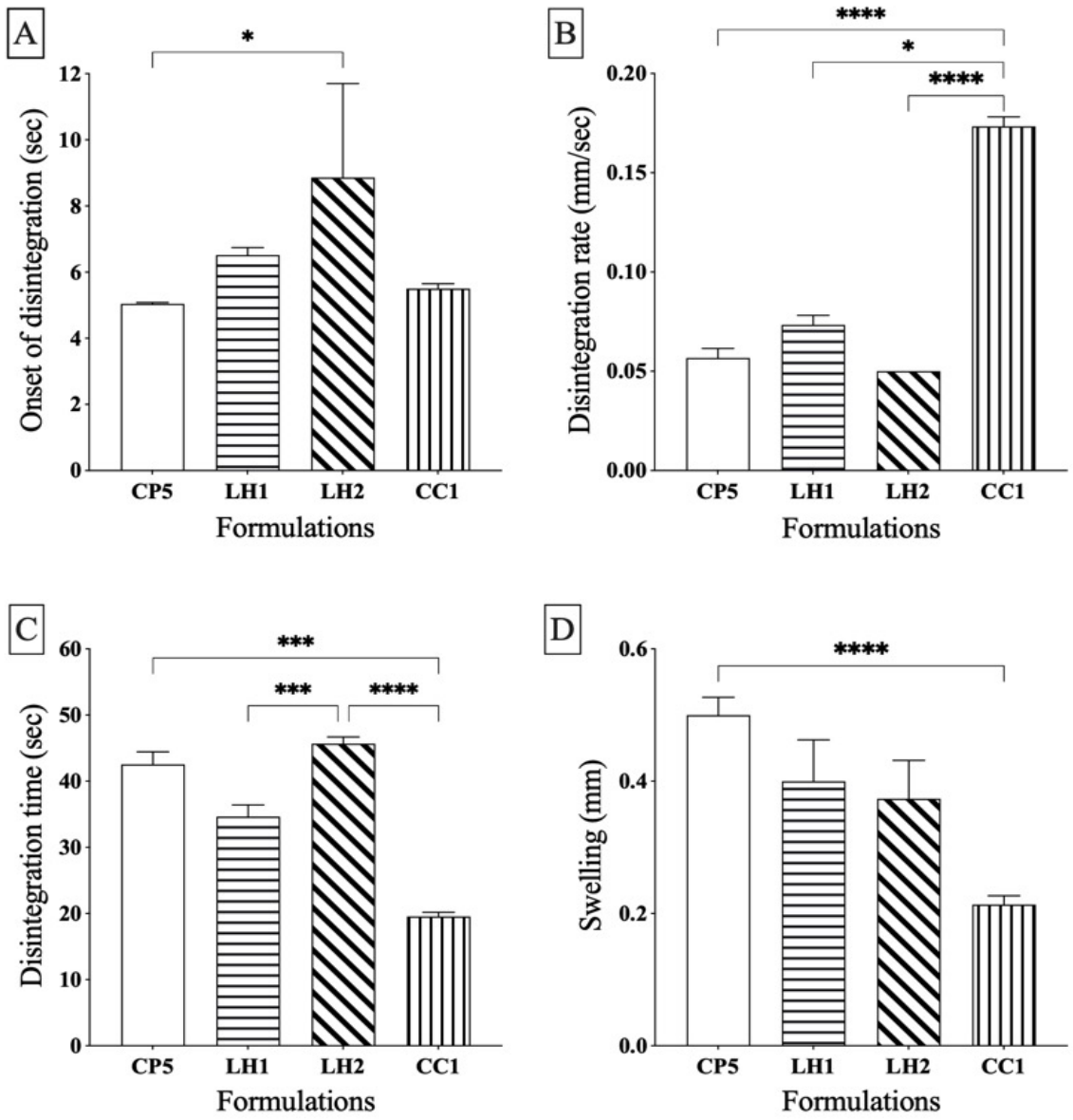

| | CP1 | CP 2 | CP 3 | CP 4 | CP 5 | CP 6 | CP 7 |
|---|---|---|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 20 | 15 | 5 | 25 | 25 | 25 |
| **Mannitol %** | 69.5 | 69.5 | 69.5 | 69.5 | 64.5 | 59.5 | 49.5 |
| **Starch %** | 0 | 5 | 10 | 20 | 5 | 10 | 20 |
| **Crospovidone %** | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.1 The impact of excipient composition on the disintegration of orodispersible tablets.** *The tablets CP1 to CP7 contain different ratios of excipients as shown in the table below the figure. Disintegration was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs. MCC, microcrystalline cellulose; MG St, magnesium stearate. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

Figure 3.2 shows the disintegration features of the tablets that contained different superdisintegrants. For the tablets LH1, LH2, and CC1, the superdisintegrant in the CP5 tablet (CP) was changed to LHPC-21, LHPC-22, and CCS, respectively. The use of the superdisintegrant LHPC-22 led to a delay in the start of disintegration of the ODTs. The onset of the disintegration increased moderately, from 5 ± 0.1 seconds for CP5 to 9 ± 2.5 seconds for the LH2 tablet (Figure 3.2 A). Also, the use of LHPC-22 led to a slightly slower rate of disintegration of 0.05 ± 0.001 mm/sec as compared to 0.07 ± 0.005 mm/sec for LH1 tablets containing LHPC-21 (Figure 3.2 B). According to a prior study on conventional tablets, LHPC-21 has superior disintegration characteristics over LHPC-22 (130). The use of CCS as a superdisintegrant significantly enhanced the disintegration of the ODTs. CC1 tablets had the fastest rate of disintegration (0.17± 0.005 mm/sec) as compared to the ODTs prepared using the other superdisintegrants (Figure 3.2 B). Also, the disintegration time significantly declined by using the superdisintegrant of CCS as compared to the use of CP or LHPC-22. For CC1 tablets that contained CCS the disintegration time was 20 ± 1 seconds as compared to 43 ± 2 seconds for the CP5 tablets that contained CP as a superdisintegrant (Figure 3.2 C). These results differ from assessment of the endpoint of disintegration of CP and CCS by some workers (122), but they are broadly consistent with an earlier finding of other workers (131). These differences can be explained by the observed differences in the function of the CP obtained from different sources (suppliers) that relate to differences in surface morphology and particle shapes, porosity, and water intake.(132). For all the ODTs prepared using different superdisintegrants, the disintegration time was within the required maximum limit which is less than three minutes (79).

The swelling of the tablets differed for the ODTs that contained different superdisintegrants (Figure 3.2 D). The use of CCS as a superdisintegrant considerably reduced the swelling of

CC1 tablets as compared to that of the superdisintegrants CP, LHPC-21 and LHPC-22. For CC1 tablets, the swelling distance was 0.21 ± 0.01 mm as compared to 0.5 ± 0.03 mm for CP5 tablets. Overall, the superdisintegrants CP, LHPC-21 and LHPC-22 led to similar swelling distances for the ODTs. The swelling is a recognised effective mechanism for a number of superdisintegrants, which enables rapid disintegration (133). However, disintegration is not only attributable to a single element since the solubility and compression properties of other excipients influence the rate and mechanism of tablet disintegration (134). Because CP has a smooth mouthfeel when compared to other superdisintegrants [10, 15], it was chosen for further ODT assessments, such as the effects of manufacturing process on tablets' texture and physical features.




| | CP 5 | LH1 | LH2 | CC1 |
|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 25 | 25 | 25 |
| **Mannitol %** | 64.5 | 64.5 | 64.5 | 64.5 |
| **Starch %** | 5 | 5 | 5 | 5 |
| **Superdisintegrants 5%** | CP | LHPC-21 | LHPC-22 | CCS |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.2. The impact of using different superdisintegrants on the disintegration properties of orodispersible tablets**. *The superdisintegrants in the CP5, LH1, LH2, and CC1 tablets have been replaced by CP, LHPC 21, LHPC 22, and CCS, respectively. Disintegration was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs. CP, crospovidone; LHPC, Low-substituted hydroxypropylcellulose; CCS, croscarmellose sodium. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001*

#### *3.2.1.2 The impact of manufacturing factors on the disintegration of orodispersible tablets*

Figures 3.3 and 3.4 summarise the disintegration properties of the CP5 ODTs that were prepared using different manufacturing methods. The disintegration was significantly delayed when the CP5 tablets were compressed by high forces (Figure 3.3). Compressing the tablets by a force of 1.2 ton significantly delayed the onset of disintegration to 11 ± 2 seconds, as compared to 5 ± 0.5 seconds when the compression forces of 0.4 and 0.6 tons were used (Figure 3.3 A). Also, the rate of the disintegration was significantly slower for the CP5 tablets that were pressed by forces higher than 0.4 ton (Figure 3.3 B). High compression forces led to considerable delay in the disintegration time of the CP5 tablets, as compared to tablets prepared using the lowest compression force (0.4 ton). For the tablets compressed by a force of 1.2 ton, the disintegration time was 50 ± 4 seconds as compared to 37 ± 1 seconds for the tablets prepared using a force of 0.4 ton (Figure 3.3 C). These results were expected, as it has been previously reported that applying a high compression force delays the disintegration of ODTs due to the influence of compression force on porosity (58). The comparable disintegration rate when employing compression forces greater than 0.6 Ton minimised the variations in the disintegration's endpoint; nevertheless, an effect on the disintegration's onset time was clearly observed.

The swelling of CP5 tablets prepared using different compression forces is shown in Figure 3.3 D. The ODTs prepared with a very small compression force exhibited a substantial reduction in swelling. Compression by a force of 0.4 ton significantly decreased the swelling distance to 0.15 ± 0.02 mm as compared to 0.5 ±0.04 mm when higher compression forces were used. This might be explained by that the very low compression force led to brittle tablets that did not need high swelling force to disintegrate. Compressing the tablets by forces of 0.6, 0.8, and 1.2

ton led to comparable swelling features. Swelling initiates disintegration by allowing particles to swell and expand in all directions, hence creating space between them (135).

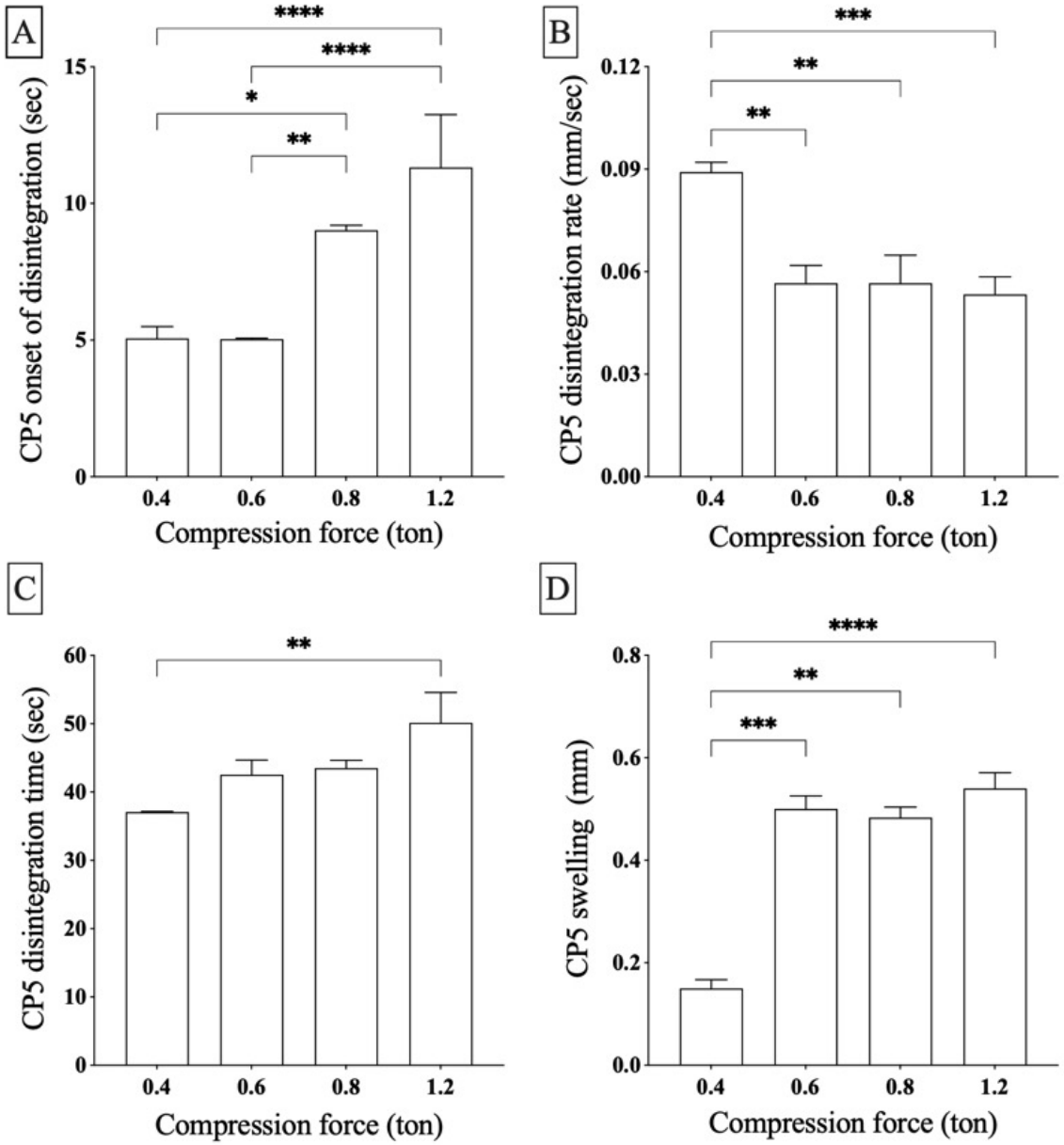



**Figure 3.3 The impact of different compression forces on the disintegration properties of orodispersible tablets.** *CP5 tablets prepared using different compression forces. Disintegration was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

Figure 3.4 also displays the disintegration properties of CP5 tablets that were prepared from either powder or granules that were obtained by the wet granulation method. The disintegration of the CP5 ODTs was significantly prolonged when very large granules, that were obtained from a 1180 μm mesh, were used. When the ODTs were prepared from the granules obtained from 1180 μm mesh, the onset of disintegration time was substantially increased to 36 ± 13 seconds as compared to ca. 7 ± 1 seconds for CP5 tablets made from powder and smaller granules (Figure 3.4 A). Furthermore, the use of granules obtained from the 1180 μm mesh reduced the rate of the disintegration of the tablets to 0.007 ± 0.005 mm/sec as compared to 0.06 ± 0.005 mm/sec for tablets that were directly pressed from powder (Figure 3.4 B). In addition, the disintegration time of the tablets was extensively increased to 163 ± 36 seconds by using the granules obtained from the 1180 μm mesh, as compared to 43 ± 2 seconds for the CP5 tablets made from powder (Figure 3.4 C). For ODTs prepared from smaller granules, the disintegration somewhat improved as compared to tablets that were prepared using direct compression method. The rate of the disintegration was increased to 0.22 ± 0.05 for tablets prepared from small granules (355 μm mesh) as compared to 0.06 ± 0.005 mm/sec for tablets that were made directly from powder (Figure 3.4 B). Also, the disintegration time was slightly reduced to 19 ± 3 seconds when using the wet granulation method (355 μm mesh), as compared to 43 ± 2 seconds for CP5 tablets prepared using the direct compression method (Figure 3.4 C). In conclusion, the disintegration of ODT prepared from granules derived from small meshes was superior to that of granules derived from extremely large meshes (i.e 1180 μm mesh). This can be attributed to the surface area contacting the disintegrating media decreases as particle size increases (78, 136, 137).

Figure 3.4 D shows the swelling of CP5 tablets prepared using either powder or granules of different sizes. The use of the wet granulation method to prepare ODTs, particularly from small granules, reduced tablet swelling. The preparation of CP5 tablets from granules that were obtained from 355 μm mesh significantly reduced the swelling distance to 0.32 ± 0.04 mm, as compared to 0.5 ± 0.03 mm for the tables that were directly compressed from powder. However, the increase of the granule size can increase the swelling of the tablets prepared using the wet granulation method. The swelling of the tablets that were prepared using the granules obtained from a large mesh (1180 μm) significantly increased to 0.62 ± 0.04 mm, as compared to the swelling of the tablets prepared from smaller meshes. The use of granules obtained from meshes of sizes 355 μm, 500 μm, and 710 μm led to comparable disintegration properties of the tablets. The effect of granule size on the disintegration of the prepared tablet has been tested previously, by using pharmacopoeia method, and the investigators reported no significant differences (138). This can strengthen the applicability of TA to provide a deeper understanding of the disintegration of ODTs. The effect of granule size on the disintegration of the prepared tablet has been tested previously, by using the pharmacopoeia method, and the investigators reported no significant differences (138). This strengthens the applicability of TA to provide a deeper understanding of the disintegration of ODTs.

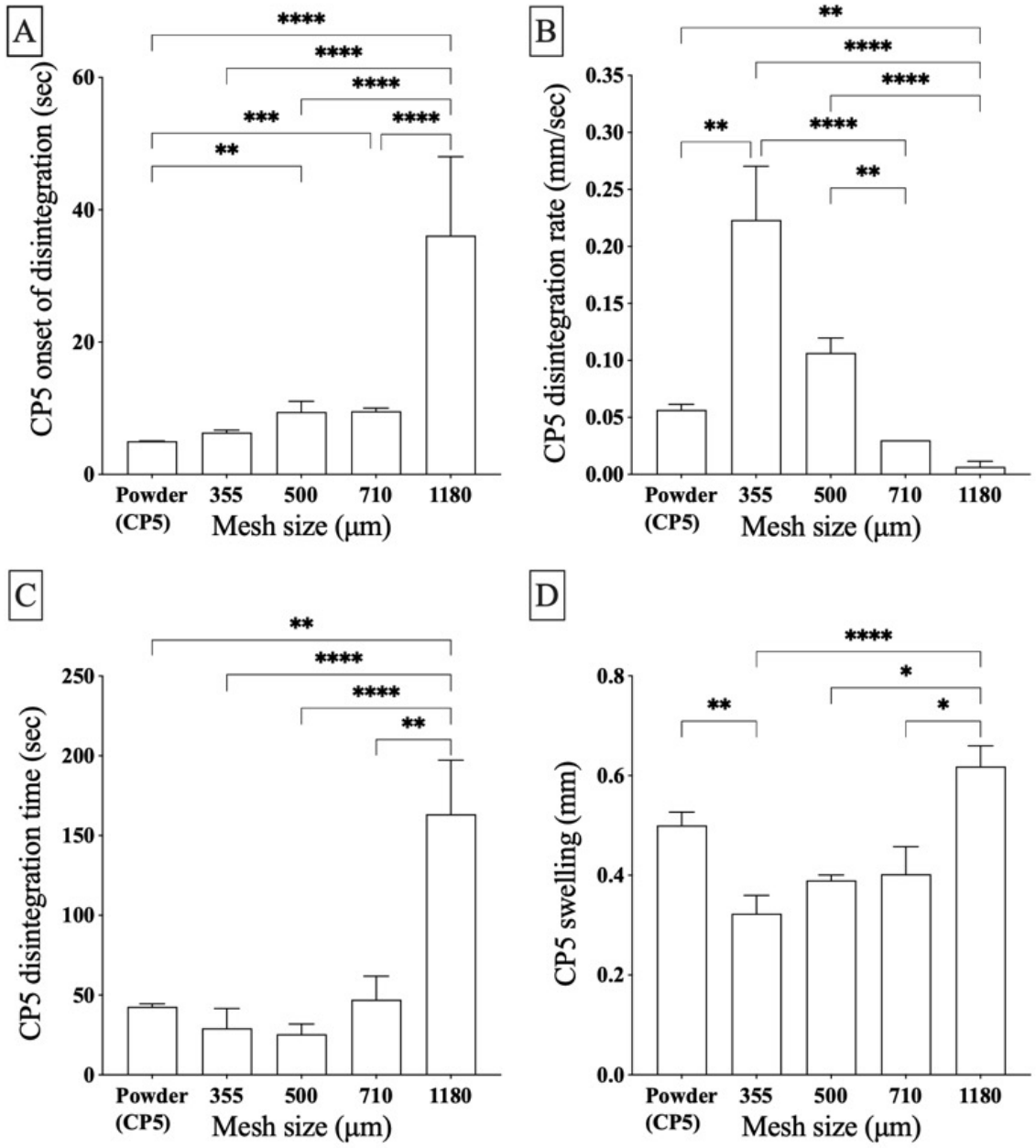



**Figure 3.4 The disintegration properties of orodispersible tablets prepared from granules using wet granulation method.** *CP5 tablets prepared using direct compression and wet granulation methods Disintegration was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

## 3.2.2 Hardness and roughness

### *3.2.2.1 Impact of composition on the orodispersible tablets' hardness and roughness*

There is no standard method for evaluating mouthfeel attributes that are associated with hardness and roughness. Therefore, several mechanical and textural methods were used to evaluate the factors that can influence the above tablet's features, and, in turn, mouthfeel. Softer tablets and tablets that leave a small smooth residual after disintegration are likely to be more palatable. In this study, pharmacopoeia methods were used to assess the mechanical properties such as tensile strength and friability. The measurement of the mechanical strength is important to ensure that tablets can endure the rigidity of handling, packaging, or transportation. In addition, mechanical strength can be a major factor that can affect the appearance and texture of the tablet, as well as the mouthfeel. TA measurement was used to assess different textural attributes, such as hardness and residue after disintegration, that can be related to a rough mouthfeel. The term "hardness" is often used in the pharmaceutical development field to define the necessary force to break a dosage form in a given plane. The USP, on the other hand, distinguishes between tensile strength and hardness which is the resistance of a dosage form's surface to penetration or indentation by a tiny probe (139). Also, the residue of ODTs after being disintegrated into small particles can impact on mouthfeel and palatability. Beside a roughness of mouthfeel, the excessive amount of residue can make swallowing more difficult and increase the urge to drink.

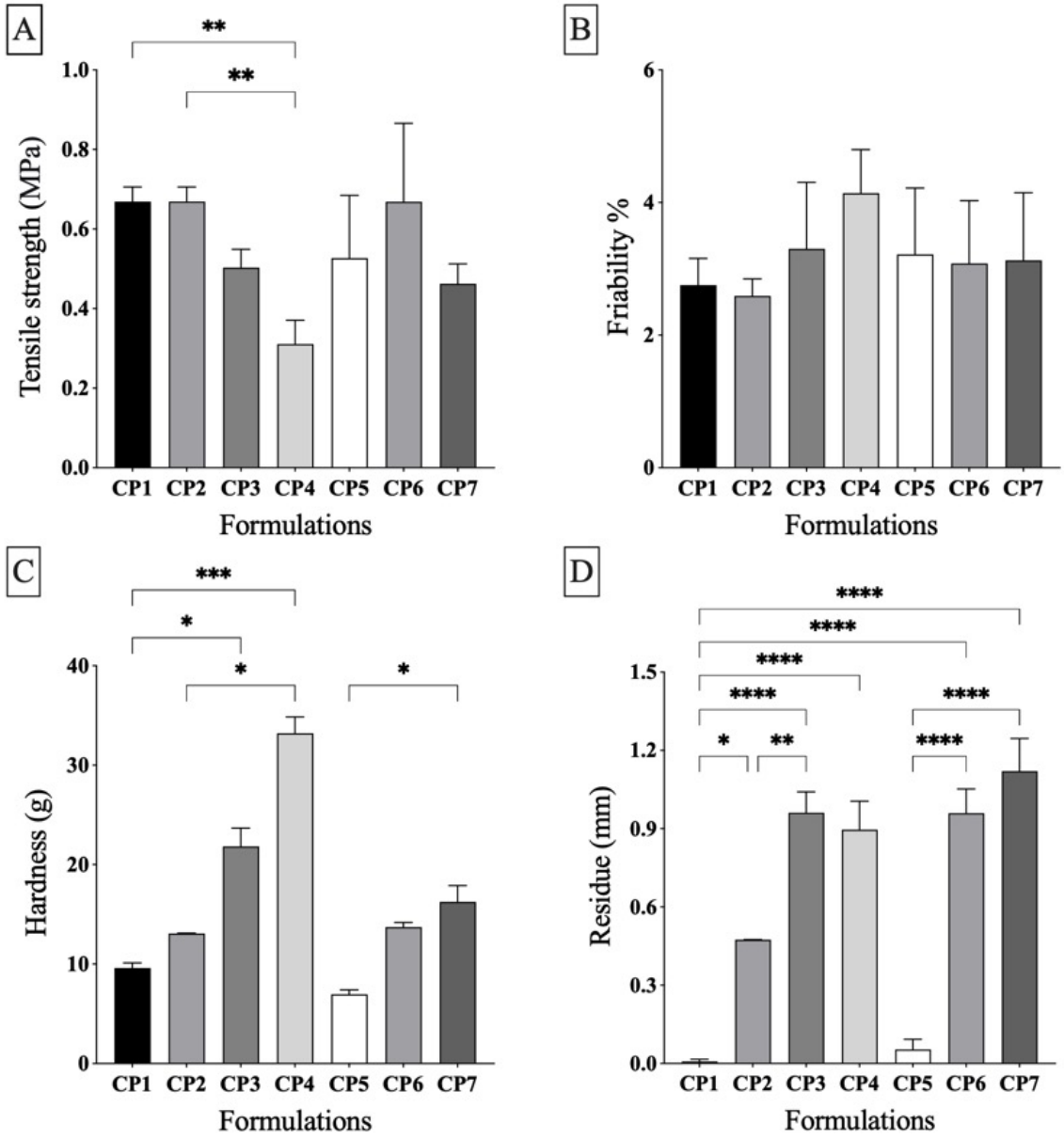
To study the composition factors that can impact on hardness and roughness, the ODTs were examined using mechanical and textural methods (Figures 3.5 and 3.6). The tensile strength and friability of the tablets were changed by decreasing the amount of MCC, as shown in Figure 3.5 A-B. The use of 15% or less of MCC decreased the tensile strength of the tablets. For CP4 tablets that contained 5% MCC, the tensile strength was 0.31 ± 0.06 MPa, as compared

to 0.67 ± 0.04 MPa for CP1 tablets that contained 25% of MCC. Tensile strength and friability were comparable for ODTs that contained similar and high amounts of MCC and that had different starch and mannitol ratios. Also, using different ratios of the starch and mannitol to prepare the ODTs slightly changed the friability of the tablets (Figure 3.5 B). From the measurements of tensile strength, the amount of the binder (MCC) was seen to be critical to whether tablets were resilient to fracture. MCC has excellent compaction qualities as well as an extremely strong binding property (140). The change in mechanical properties was primarily attributable to MCC and starch, which can function as binders, as opposed to mannitol, which is employed mainly as a diluent in tablet formulations (120). Furthermore, it was observed that tablets containing only mannitol had very little effect on mechanical strength, regardless of porosity (141).MCC has excellent compaction qualities as well as an extremely strong binding property (140).

The use of different ratios of the excipients had substantial effects on the hardness of the tablets, as shown in Figure 3.5 (C). Tablets that contained a high amount (10% or more) of starch were harder than the CP1 tablets that contained no starch. Also, compression of ODTs that contained a low amount of MCC led to tablets that were harder than the tablets that contained 25% MCC. CP4 tablets that were compressed from ingredients containing 20% starch and only 5% MCC had the highest hardness (33 ± 1.7 g), as compared to 16 ±1.6 g for CP7 tablets that contained the same amount of starch and 25% MCC and to 9.6 ± 0.5 g for the CP1 tablets that contained 25% MCC and no starch. Compressing the tablets, such as CP2 and CP5 tablets, from ingredients that were mixed with just a small amount of starch and a somewhat high ratio of MCC had a hardness that was similar to the CP1 tablets. CP5 tablets contained only % 5 starch and a high amount of MCC (25%) had the lowest hardness value of 7 ± 0.45 g. In contrast to the previous methods, the hardness of the tablets when measured by the TA revealed that MCC

is a critical excipient with regard to reducing the hardness of wet tablets. Also, the TAP data shows that a high amount of starch increased the tablets' hardness, particularly when the tablets contained a low amount of MCC. CP5 contained an appropriate balance of MCC and starch had the lowest hardness. A possible explanation is that the hardness of the wet tablets is more related to the excipients' wettability, which will be discussed later in this chapter, ($r_s$ = 0.736, Table 3.1). Although both MCC and starch can act as binders, MCC's higher wettability and disintegration properties allow water to pass easily through the tablets and soften them (142, 143).

Tablets prepared using different ratios of the excipients showed a substantial variation in the amount of the residue (Figure 3.5 D). For the tablets that contained a high amount (10% or more) of starch, the amount of the residue was substantially increased compared to tablets that contained low amounts of starch. The residue of CP7 tablets that contained 20% starch was 1.12 ± 0.13 mm as compared to 0.05 ± 0.04 mm for CP5 tablets that contained 5% starch. The lowest amount of the residue was 0.01± 0.01 mm and for the CP1 tablets, and for the CP5 tablets was 0.05 ± 0.4 mm. To sum, the residue was reduced when the tablets had a modest amount of starch, especially when the tablets contained a high amount of MCC. The smallest residue was found for CP5 tablets, where the MCC/starch ratio was appropriate. The residue cannot be linked to a single factor, such as the variance in particle size between the excipients. Despite the smaller particle size of starch compared to MCC, the residual amount was significantly influenced by several properties, including disintegration ($r_s$= 0.832, Table 3.1), adhesiveness ($r_s$= 0.656, Table 3.1), and wettability ($r_s$= 0.770, Table 3.1), indicating that the overall properties of the excipient mixture are important influencing factors of the residual amount.



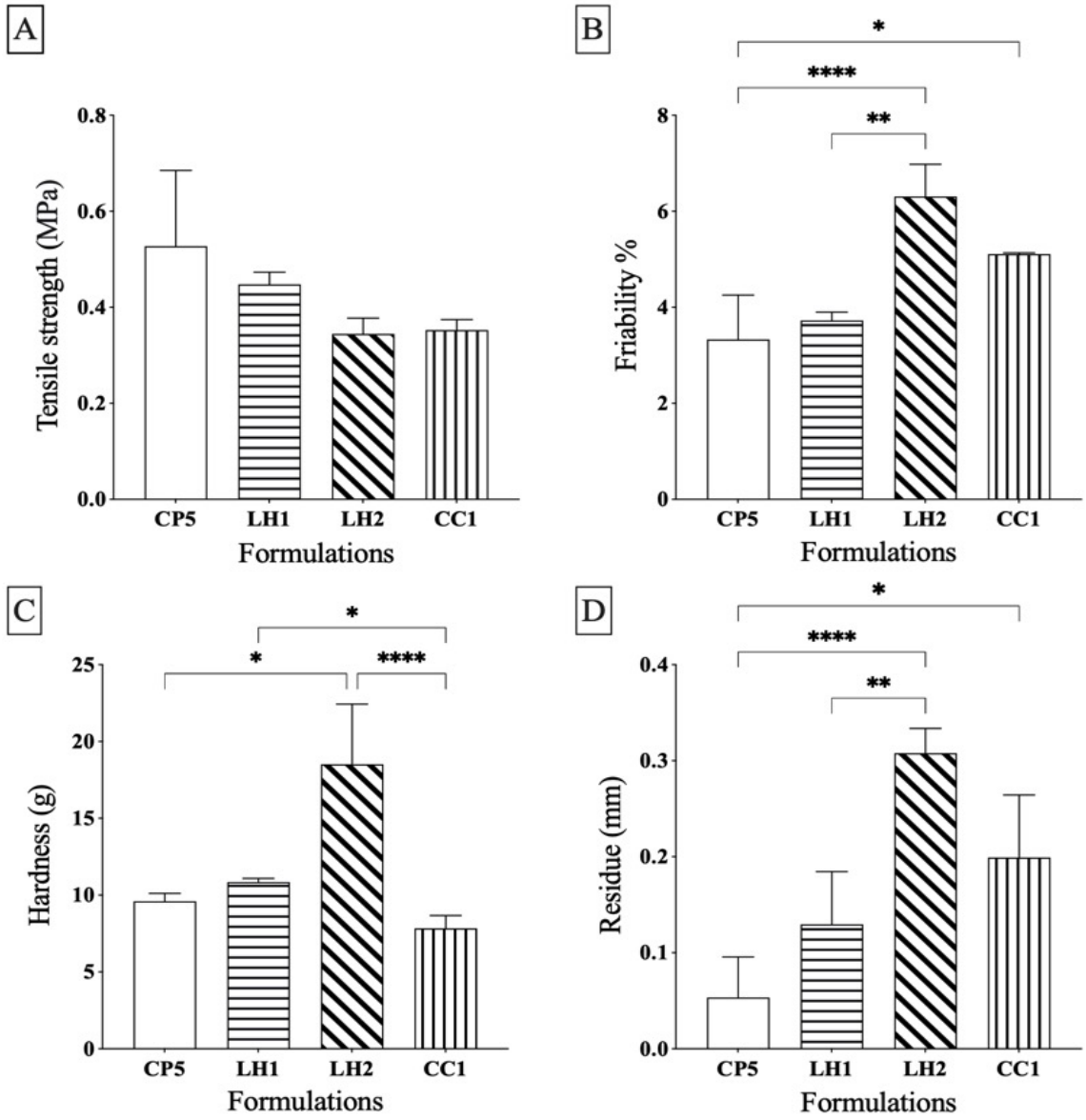

| | CP1 | CP 2 | CP 3 | CP 4 | CP 5 | CP 6 | CP 7 |
|---|---|---|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 20 | 15 | 5 | 25 | 25 | 25 |
| **Mannitol %** | 69.5 | 69.5 | 69.5 | 69.5 | 64.5 | 59.5 | 49.5 |
| **Starch %** | 0 | 5 | 10 | 20 | 5 | 10 | 20 |
| **Crospovidone %** | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.5 The hardness and roughness of orodispersible tablets containing different ratios of excipients were examined using mechanical and textural methods.** *The tablets CP1 to CP7 contain different excipients as shown in the table below the figure. Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. MCC, microcrystalline cellulose; MG St, magnesium stearate; CP, crospovidone; LHPC, Low-substituted. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

For the tablets CP5, LH1, LH2, and CC1, the tensile strength of tablets was slightly changed by the use of the superdisintegrants CP, LHPC-21, LHPC-22, and CCS. The tensile strength was 0.53 ± 0.16 MPa for the CP5 tablets as compared to 0.3 ± 0.03 MPa for the LH2 and CC tablets (Figure 3.6 A). The friability of the tablets that contained the superdisintegrants CP and LHPC-21 was lower than that for tablets that contained LHPC-22 and CCS (Figure 3.6 B). The friability of CP5 and LH1 tablets, which contained CP and LHPC-21 as a superdisintegrant, was low at 3.7 ± 1%. When compared to CP5 tablets, the tablets prepared with the superdisintegrants of LHPC-22 and CCS had a significant increase in friability to 6.3 ± 0.7% and 5.1 ± 0.03%, respectively. Even though the type of superdisintegrants had a small effect on the tensile strength, the friability was more responsive to compositional and tensile strength variations. The negative relationship between breaking force/tensile strength and friability has been reported (144). Using CP as a superdisintegrant improved the mechanical properties required for manufacture and handling problems; but these measures are insufficient for predicting mouthfeel. The negative relationship between breaking force/tensile strength and friability has been reported. The friability of ODTs decreased exponentially as their breaking force increased. (144).

Figure 3.6 (C) shows the hardness of the tablets that contained different superdisintegrants. The use of LHPC-22 as a superdisintegrant significantly increased the hardness to 18.5 ± 3.9 g compared to 9.6 ± 0.5 g for tablets that were prepared using CP as a superdisintegrant. The use of LHPC-21 and CCS as superdisintegrants led to a hardness that was similar to that of the CP-containing CP5 tablets. The highest hardness for the tablets made with LHPC-22 was associated with the lowest disintegration features. The time of ODTs to start disintegration was also shown to be correlated with the hardness ($r_s$= 0.565, Table 3.1). The values obtained for the residue of the tablets that were prepared using different superdisintegrants are shown in

Figure 3.6 (D). As compared to the use of CP as a superdisintegrant, the residue was significantly increased by using the superdisintegrants LHPC-21, LHPC-22 and CCS. The residue increased from 0.05 ± 0.04 mm for CP5 tablets containing CP to 0.31 ± 0.03 mm and 0.2 ± 0.07 mm for LH2 tablets containing LHPC-22 and CC1 tablets containing CCS, respectively. Moreover, the tablets that contained CP as a superdisintegrant showed better results in the assessments of the hardness and residue, as compared to the tablets that contained the superdisintegrants LHPC-101, LHPC-102, and CCS. These findings support previous observations whereby CP has a smooth mouthfeel as compared to the use of other superdisintegrants leading to a rough mouthfeel (127). In addition, data shown that TA might provide better understanding into evaluating hardness and roughness (residue) than mechanical testing.




| | CP 5 | LH1 | LH2 | CC1 |
|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 25 | 25 | 25 |
| **Mannitol %** | 64.5 | 64.5 | 64.5 | 64.5 |
| **Starch %** | 5 | 5 | 5 | 5 |
| **Superdisintegrants 5%** | CP | LHPC-21 | LHPC-22 | CCS |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.6 The hardness and roughness of orodispersible tablets contained different superdisintegrants were examined using mechanical and textural methods.** *The superdisintegrants in the CP5, LH1, LH2, and CC1 tablets have been replaced by CP, LHPC 21, LHPC 22, and CCS, respectively. Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. CP, crospovidone; LHPC, Low-substituted hydroxypropylcellulose; CCS, croscarmellose sodium. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

#### *3.2.2.2 The impact of manufacturing factors on the hardness and roughness of orodispersible tablets*

Figures 3.7 and 3.8 show the effect of different compression forces and granule size on CP5 tablets as measured using various mechanical and textural methods that are related to hardness and roughness attributes. The tensile strength of the CP5 tablets was significantly increased using high compression forces to press the tablets (Figure 3.7 A). For CP5 tablets, compressing the tablets by 1.2 ton significantly increased the tensile strength to 1.3 ± 0.1 MPa as compared to 0.1 ± 0.01 MPa for the tablets that were pressed using a force of 0.4 ton. As expected, the tensile strength was significantly and continuously increased using higher compression forces ($r_s$ = 0.776, Table 3.1) to compress the tablets. Also, the friability for CP5 tablets was impacted by the use of different compression forces, as shown in Figure 3.7 (B). The friability was progressively decreased using higher compression forces to prepare the tablets. The use of a very low compression force (0.4 ton) to prepare the ODTs led to fragile tablets. Compressing the tablets by a very low compression force (0.4 ton) significantly increased the friability to 28 ± 2.8% as compared to compression of the ODTs by higher forces. For the tablets prepared using the force of 0.6 ton, the friability was reduced from 3.2 ± 1.16% to 0.9 ± 0.8% for the tablets compressed by 1.2 ton. Thus, the friability was decreased by preparing the tablets using high compression forces ($r_s$ = -0.557, Table 3.1).

The use of different compression forces to prepare CP5 tablets had a slight effect on the hardness and the amount of the residue of the wet tablets, as shown in Figure 3.7 (C-D). The hardness of CP5 tablets prepared by 0.4 ton was high (12.5 ± 2 g) as compared to the use of other compression forces. The hardness and amount of the residue were relatively similar for the tablets that were pressed by 0.6, 0.8 and 1.2 tons. The residue was 0.06 ± 0.04 mm for the tablets prepared by 0.6 ton as compared to 0.16 ± 0.05 mm for the use of a compression force

of 0.4 ton. This also shows that the ability of tablets to resist breaking force and friability (mechanical stress) may not be replicated when the tablets become moist, as in the TA measurements.

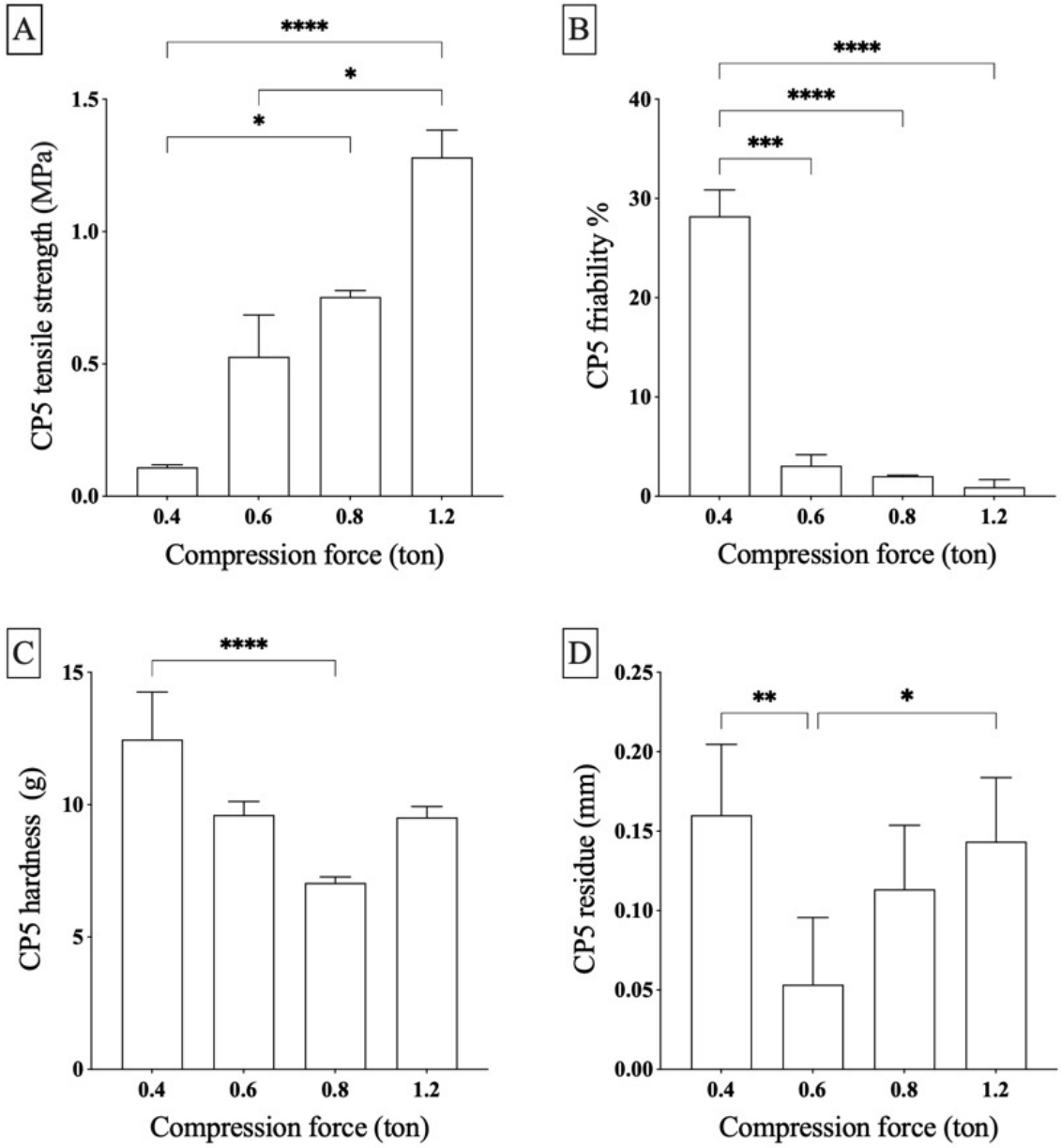



**Figure 3.7 The hardness and roughness of orodispersible tablets prepared by different compression forces were examined using mechanical and textural methods.** *CP5 tablets prepared using different compression forces. Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

The tensile strength and the friability of CP5 tablets was impacted slightly by preparing the ODTs from either a mixture of powder (previously studied) or granules that were obtained by various sizes meshes (Figure 3.8 A-B). The use of the granules that were obtained from the largest (1180 μm) mesh substantially increased the tensile strength as compared to the tablets that were prepared from powder or granules obtained from the smaller meshes. For the granules obtained from the 1180 μm mesh, the tensile strength was 0.8 ± 0.03 MPa as compared to 0.5 ± 0.15 MPa for the CP5 tablets made from powder. The tablets prepared from granules had a comparable increase in the tensile strength when the meshes of 355 μm 710 μm, and 500 μm were used. Also, from comparison of the tablets prepared from powder, the friability was substantially decreased by preparing the tablets using the wet granulation method. For the granules obtained from the 355 μm mesh, the friability was 1.4 ± 0.2% compared to 3.1 ± 1% for the tablets prepared from powder. Larger granules enhance the packing fraction of tablets, indicating a higher degree of plastic deformation and fragmentation during compaction, as well as an increase in the surface area of the fragmented particles, both of which contribute to an increase in particle-particle bonding (145). Larger granules enhance the packing fraction of tablets, providing a higher degree of plastic deformation and fragmentation during compaction, as well as an increase in the surface area of the fragmented particles, both of which contribute to an increase in particle-particle bonding (145).

The hardness and the residual amount of CP5 tablets prepared from powder or granules of various sizes is shown in Figure 3.8 C-D. The use of powder to prepare the tablets led to a significant reduction in the hardness to 9.6 ± 0.5 g compared to the tablets prepared from granules (c.a 29 ± 2.5 g). Also, the residue of the tablets was substantially increased when using the granules obtained by large meshes (710 μm and 1180 μm) as compared to CP5 tablets that

were made from powder or smaller meshes. For the CP5 tablets prepared from powder, the residue was 0.05 ± 0.04 mm as compared to 1.98 ± 0.2 mm for the tablets prepared from the granules using 1180 μm mesh. Also, the use of granules obtained from small (355 μm and 500 μm) meshes led to a slight increase in the amount of the residue as compared to the tablets that were directly compressed from powder. To sum, the residue of the tablets was substantially increased when using granules to prepare tablets as compared to CP5 tablets made from powder. For the tablets prepared from granules, the increase in the size of the mesh led to a steadily increased in the residue. The lowest residue was for the CP5 tablets prepared from powder, or tablets prepared from granules obtained using small meshes. This is consistent with previous work that has linked larger granules to a rougher sensation, and a greater desire to drink water (46).

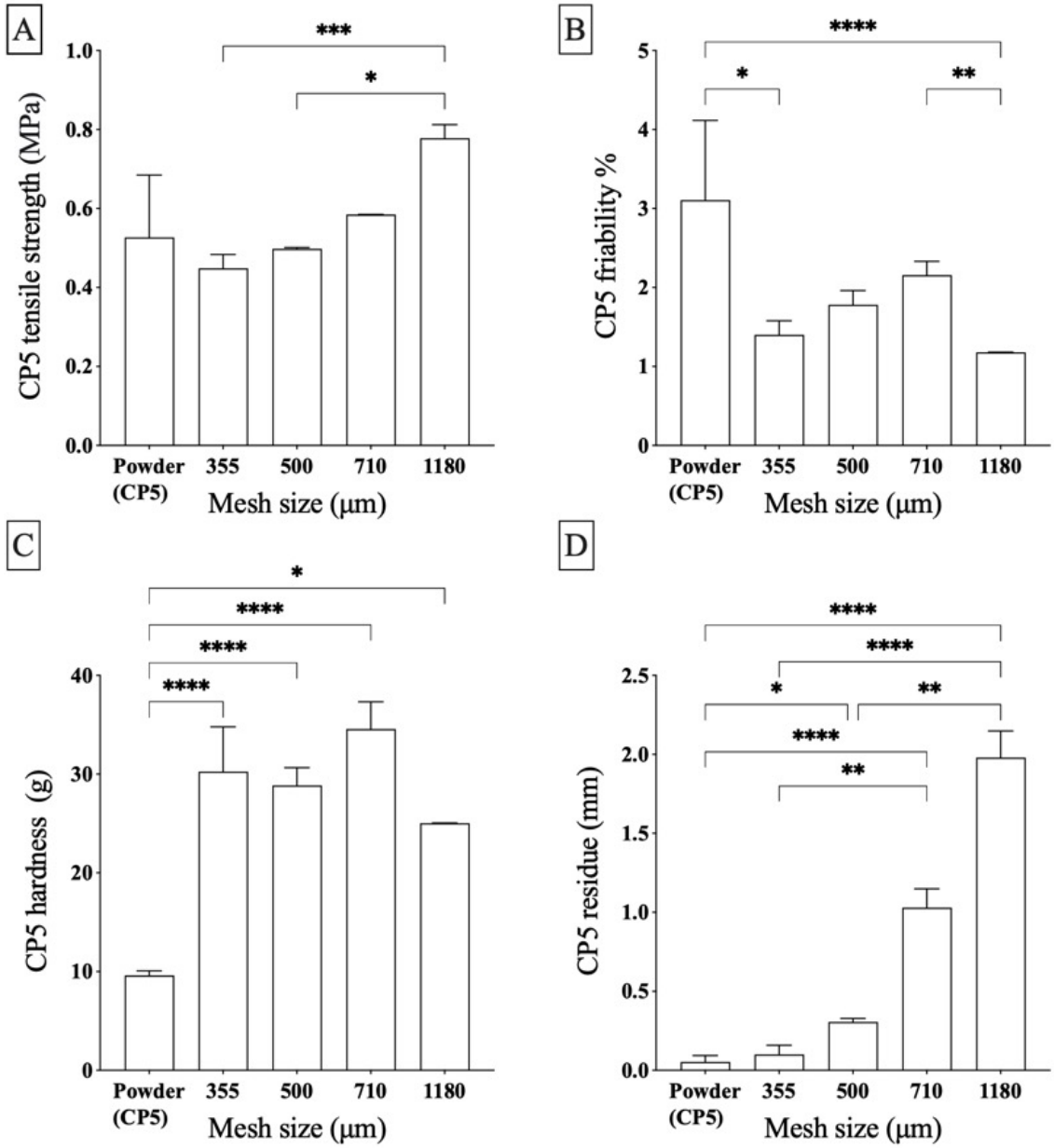


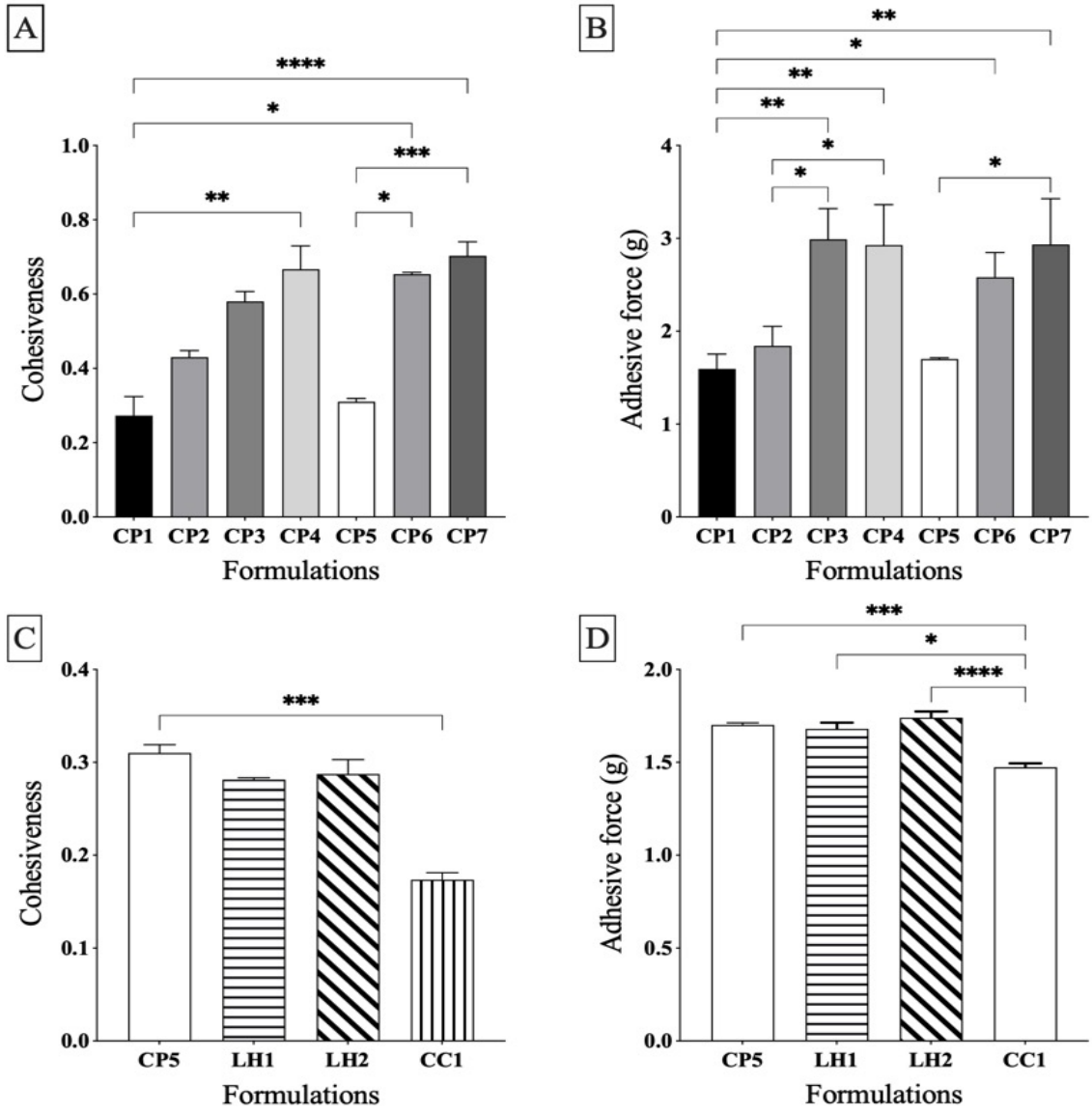

**Figure 3.8 The hardness and roughness of orodispersible tablets prepared from granules of different sizes were examined using mechanical and textural methods.** *CP5 tablets prepared using direct compression and wet granulation methods. Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0. 05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

## 3.2.3 Adhesive properties

### *3.2.3.1 The impact of tablet's composition on the adhesive properties of orodispersible tablets*

The adhesive properties of the ODTs after adsorbing the disintegration media is shown in Figures 3.9-3.10. The cohesiveness of the tablets was changed substantially by the use of different ratios of the excipients, as shown in Figure 3.9 (A). Using 10% or more of starch to prepare the tablets led to a significant increase in cohesiveness. For the CP4 and CP7 tablets that contained 20% starch, the cohesiveness was 0.7 ± 0.06 as compared to 0.27 ± 0.05 for CP1 tablets that contained no starch. The stickiness of the ODTs after adsorbing the disintegration media was measured by the adhesive force. The adhesive force of the tablets was changed using different ratios of the excipients, as shown in Figure 3.9 (B). The use of 10% or more of starch to prepare the tablets significantly increased the adhesive force. For CP4 and CP7 tablets that contained 20% starch, the adhesive force was 2.9 ± 0.4 g as compared to 1.6 ± 0.2 g for CP1 tablets that were prepared without starch. Compressing tablets from ingredients with just 5% starch led to a cohesiveness and adhesiveness that was similar to that observed for CP1 tablets, such as CP2 and CP5 tablets. The higher the adhesive properties of ODTs, the longer the sample is in contact with the oral cavity, potentially leading to delayed disintegration and increased stimulation of the sensory system. The TPA findings revealed that changes in tablet cohesiveness and stickiness are primarily caused by changes in tablet composition. The use of a significant amount of starch (10% or more) within the tablets increased both the cohesiveness and the stickiness. Among all the formulations that contained starch, the lowest cohesion and stickiness were seen for CP5 tablets that included only a modest amount of starch. This could be due to starch's cohesiveness in addition to its function as a viscosity enhancer (120).

Figure 3.9 (C-D) shows the adhesive properties of the tablets that were prepared using several superdisintegrants. The superdisintegrant in the CP5 tablet (CP) was changed to LHPC-21, LHPC-22, or CCS. The cohesiveness and stickiness of the tablets were slightly affected by the type of superdisintegrant used. However, the fast disintegration of CC1 tablets, which contained CCS, was associated with a reduction in cohesion and stickiness as compared to the tablets that contained other superdisintegrants. The data from this study have revealed a significant correlation between disintegration and adhesive properties (Table 3.1), and fast disintegration of the tablets can reduce the time of contact between the tablets and the contacted surface, resulting in a decrease in adhesive properties.




| | CP1 | CP 2 | CP 3 | CP 4 | CP 5 | CP 6 | CP 7 | LH1 | LH2 | CC1 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 20 | 15 | 5 | 25 | 25 | 25 | 25 | 25 | 25 |
| **Mannitol %** | 69.5 | 69.5 | 69.5 | 69.5 | 64.5 | 59.5 | 49.5 | 64.5 | 64.5 | 64.5 |
| **Starch %** | 0 | 5 | 10 | 20 | 5 | 10 | 20 | 5 | 5 | 5 |
| **Superdisintegrants 5%** | CP | CP | CP | CP | CP | CP | CP | LHPC-21 | LHPC-22 | CCS |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.9 The impact of different ratios of excipients and superdisintegrants on the adhesive properties of orodispersible tablets.** *The ODTs contain different excipients as shown in the table below the figure. Adhesive properties were assessed by measuring (A,C) the cohesiveness (B,D) the adhesive force. MCC, microcrystalline cellulose; MG St, magnesium stearate; CP, crospovidone; LHPC, Low-substituted hydroxypropylcellulose; CCS, croscarmellose sodium. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

### *3.2.3.2 The impact of manufacturing factors on the adhesive properties of orodispersible tablets*

The adhesive properties of CP5 tablets prepared using different compression forces and granules are shown in Figure 3.10. CP5 tablets compressed by higher forces showed a slightly higher cohesiveness and a lower adhesive force as compared to the use of low compression forces. The use of a compression force of 1.2 ton increased the cohesiveness to 0.38 ± 0.01 as compared to 0.3 ± 0.01 for the tablets that were prepared using 0.6 ton (Figure 3.10 A). Also, the use of 0.8 ton and 1.2 ton to compress the tablets substantially reduced the adhesive force as compared to using smaller compression forces. Using a compression force of 1.2 ton reduced the adhesiveness to 1.5 ± 0.05 g as compared to 1.75 ± 0.06 g for the tablets that were pressed using 0.4 ton (Figure 3.10 B). To sum, although the modification in compression force was not expected to have a substantial impact on cohesiveness and stickiness, the TAP indicated modest differences. The use of a high compression force to manufacture the tablets can increase the cohesiveness ($r_s$ = 0.686, Table 3.1), while slightly minimising the stickiness.

The use of granules of different sizes to prepare the CP5 tablets led to a significant increase in the cohesiveness and adhesive force as compared to the tablets prepared directly from powder. The cohesiveness of the tablets directly compressed from the powder was 0.3 ± 0.01 as compared to 0.38 ± 0.01 for the tablets prepared from granules that were obtained by using a 355 μm mesh (Figure 3.10 C). The adhesiveness of CP5 tablets prepared from granules of different sizes was significantly increased compared to tablets that were prepared from powder. As shown in Figure 3.10 (D), the advice force of the tablets directly compressed from the powder was 1.7 ± 0.01 g as compared to 2.2 ± 0.07 g for the tablets that were prepared from granules obtained by the use of the 355 μm mesh. The change in the size of the meshes led to small differences in the cohesiveness and adhesiveness of the tablets prepared from granules. However, the wet granulation method appears to be capable of producing tablets with

stronger cohesiveness and stickiness properties. This can be linked to the strong bonds between the granules as strong solid bridges that keep the granule together form during the drying process of granule production (146).

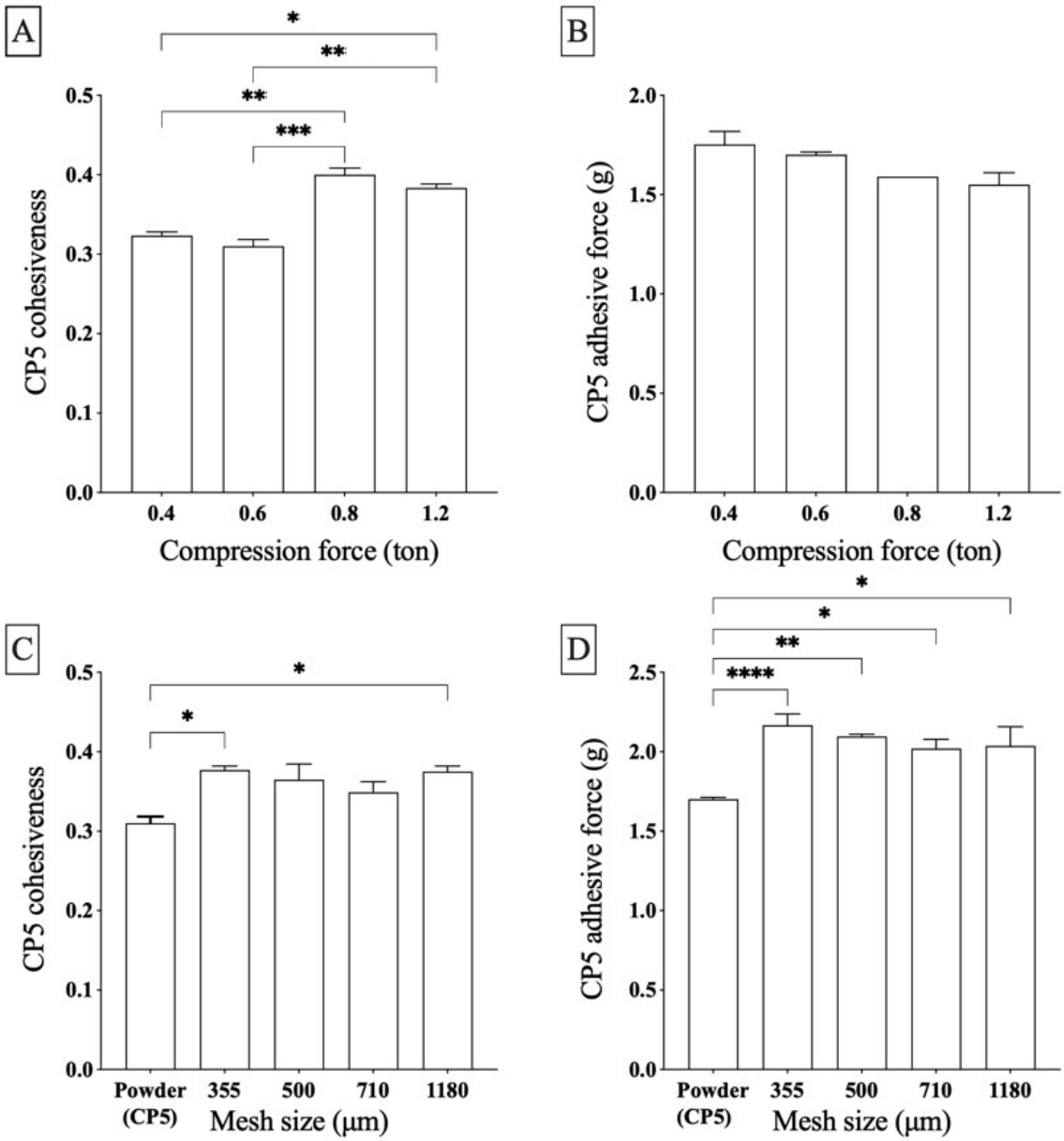



**Figure 3.10 The impact of different manufacturing processes on the adhesive properties of orodispersible tablets.** *CP5 tablets prepared using different compression forces and wet granulation method. Adhesive properties were assessed by measuring (A,C) the cohesiveness (B,D) the adhesive force. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

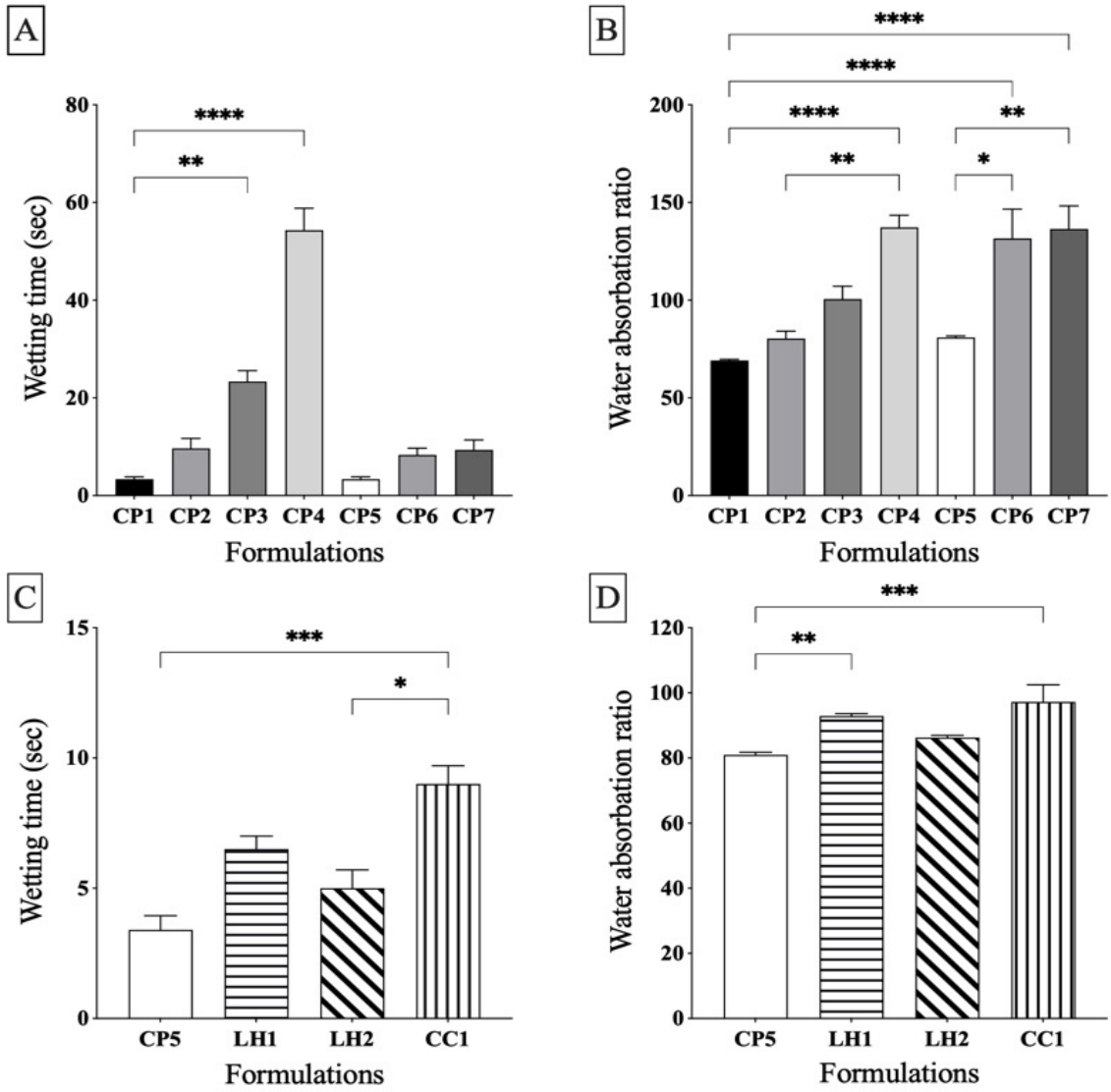
## 3.2.4 Wettability of orodispersible tablets

### *3.2.4.1 The impact of tablet's composition on the wettability of orodispersible tablets*

The wettability of the ODTs after fully adsorbing the disintegration media is shown in Figures 3.11-3.12. The wettability was used to evaluate the ability of the tablets to adsorb the disintegration media. The wettability can affect the disintegration properties, but it can also be used to assess mouthfeel for ODTs, such as the dry sensation after tablet administration. The wettability was evaluated from the water absorption ratio and wetting time. Using different ratios of MCC and starch to prepare the tablets led to a significant increase in the wetting time, as shown in Figure 3.11 (A). The use of a low amount of MCC, while increasing the starch content, to prepare the tablets significantly increased the wetting time. For CP1 tablets that contained 25% MCC, the wetting time was 3 ± 1 seconds as compared to 54 ± 8 seconds for the CP4 tablets that were prepared from ingredients containing 5% MCC. The effect of using different ratios of the excipients on the water absorption ratio is shown in Figure 3.11 (B). Preparing the tablets from a mixture of excipients that contained 10% or more starch led to a substantial increase in the water absorption ratio. For the CP4 and CP7 tablets that contained 20% starch, the water absorption ratio was 137 ± 9% compared to 69 ± 1% for the CP1 tablets that contained no starch. The smallest water absorption ratio was for the tablets that contained no starch or just a small amount (5%) of starch. From comparison to the CP1 tablets, the water absorption ratio slightly increased from 69 ± 1% to 81 ± 1% for CP5 tablets that contained 5% starch. The rate and amount of disintegration medium that the tablets can absorb varies depending on the excipients' characteristics. The wetting time of the tablets that contained a large amount of MCC and mannitol had a faster wettability, whereas the starch had a minor influence. This could be due to the high internal porosity and the large surface area of MCC, which allows fluids to penetrate tablets more easily, resulting in "wicking" (64, 147). Also, mannitol's hydrophilicity allows water to penetrate through MCC powders (148). Regarding

measurement of the water absorption ratio, a significant increase was found for the tablets that were made from a mixture of excipients comprising 10% or more starch. However, the tablets that had no starch or only a modest amount of starch (5%) had the lowest water absorption ratio. This can be due to starch's ability to absorb moisture as a hygroscopic substance (120).

Figure 3.11 (C) shows the effects of the different superdisintegrants on the wetting time. From comparison to the CP5 tablets, the wetting time was significantly increased by using the superdisintegrants of LHPC-21, LHPC-22 and CCS. The wetting time of the CP5 tablets prepared using CP as a superdisintegrant was 3 ± 0.5 seconds as compared to 9 ± 1 seconds for the use of the superdisintegrant of CCS. This can be due to CP's multifunctional disintegrating mechanism, which allows the tablet to be effectively moistened despite its modest water absorption (149). The use of different superdisintegrants instead of the CP to prepare the ODTs led to an increase in the water absorption ratio, as shown in Figure 3.11 (D). For the CP5 tablets, the water absorption ratio significantly increased from 81 ± 1% to 97 ± 5% for the tablets that were prepared from the superdisintegrant of CCS. The tablets prepared from the superdisintegrant LHPC-21 had a water absorption ratio of 93 ± 1%. This is in consistent with previous work which has shown that CP has a low absorption ratio (149).




| | CP1 | CP 2 | CP 3 | CP 4 | CP 5 | CP 6 | CP 7 | LH1 | LH2 | CC1 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Microcrystalline cellulose (MCC) %** | 25 | 20 | 15 | 5 | 25 | 25 | 25 | 25 | 25 | 25 |
| **Mannitol %** | 69.5 | 69.5 | 69.5 | 69.5 | 64.5 | 59.5 | 49.5 | 64.5 | 64.5 | 64.5 |
| **Starch %** | 0 | 5 | 10 | 20 | 5 | 10 | 20 | 5 | 5 | 5 |
| **Superdisintegrants 5%** | CP | CP | CP | CP | CP | CP | CP | LHPC-21 | LHPC-22 | CCS |
| **Magnesium stearate (Mg St) %** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

**Figure 3.11 The wettability of orodispersible tablets prepared from different ratio of excipients and superdisintegrants.** *The ODTs contain different excipients as shown in the table below the figure. Wettability was assessed by measuring (A,C) the wetting time (B,D) the water absorption ratio. MCC, microcrystalline cellulose; MG St, magnesium stearate; CP, crospovidone; LHPC, Low-substituted hydroxypropylcellulose; CCS, croscarmellose sodium. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

### *3.2.4.2 The impact of manufacturing factors on the wettability of orodispersible tablets*

For the CP5 tablets compressed by different compression forces, the wetting time slightly increased by the use of high compression forces, as shown in Figure 3.12 (A). The use of compression forces of 0.8 and 1.2 tons slightly increased the wetting time to 8 ± 3 second compared to 5 ± 2 second for the tablets prepared by 0.4 ton. The compression of CP5 tablets using different compression forces had a minimal effect on the water absorption ratio, as shown in Figure 3.12 (B). For a high compression force of 1.2 ton, the water absorption ratio was 88 ± 6% compared to 80 ± 1% for the tablets that were prepared by 0.6 ton.

The wetting time was measured for CP5 tablets that were prepared from powder or granules obtained using different sizes of meshes, as seen in Figure 3.12 (C). The tablets prepared from the mixture of powder had the shortest wetting time of 3 ± 0.5 seconds as compared to 12 ± 2.7 seconds for the tablets that were prepared from granules obtained using the 355 μm mesh. The wetting time of the tablets was changed slightly by the use of different meshes to prepare the tablets using the wet granulation method. The water absorption ratio of the CP5 tablets that were manufactured from powder or granules obtained by various sizes of meshes is shown in Figure 3.12 (D). From comparison to CP5 tablets made from powder or small meshes, the water absorption ratio was substantially increased for the tablets prepared from granules using the meshes of 710 μm and 1180 μm. For tablets prepared from granules obtained using the 710 μm mesh, the water absorption ratio was 101 ± 4% as compared to 81 ± 1% for the tablets that were compressed directly from powder. The tablets prepared from granules obtained by larger meshes had a significant increase in the water absorption ratio as compared to the use of smaller meshes. When compared to the tablets made from powder, the water absorption ratio of the CP5 tablets made from granules was progressively increased by using granules obtained from larger meshes ($r_s$ = 0.715, Table 3.1). This could be due to the higher porosity of tablets made

from larger granules. It has reported that an increase in the size of granules results in a drop in particle density and a rise in porosity of the tablets (145).

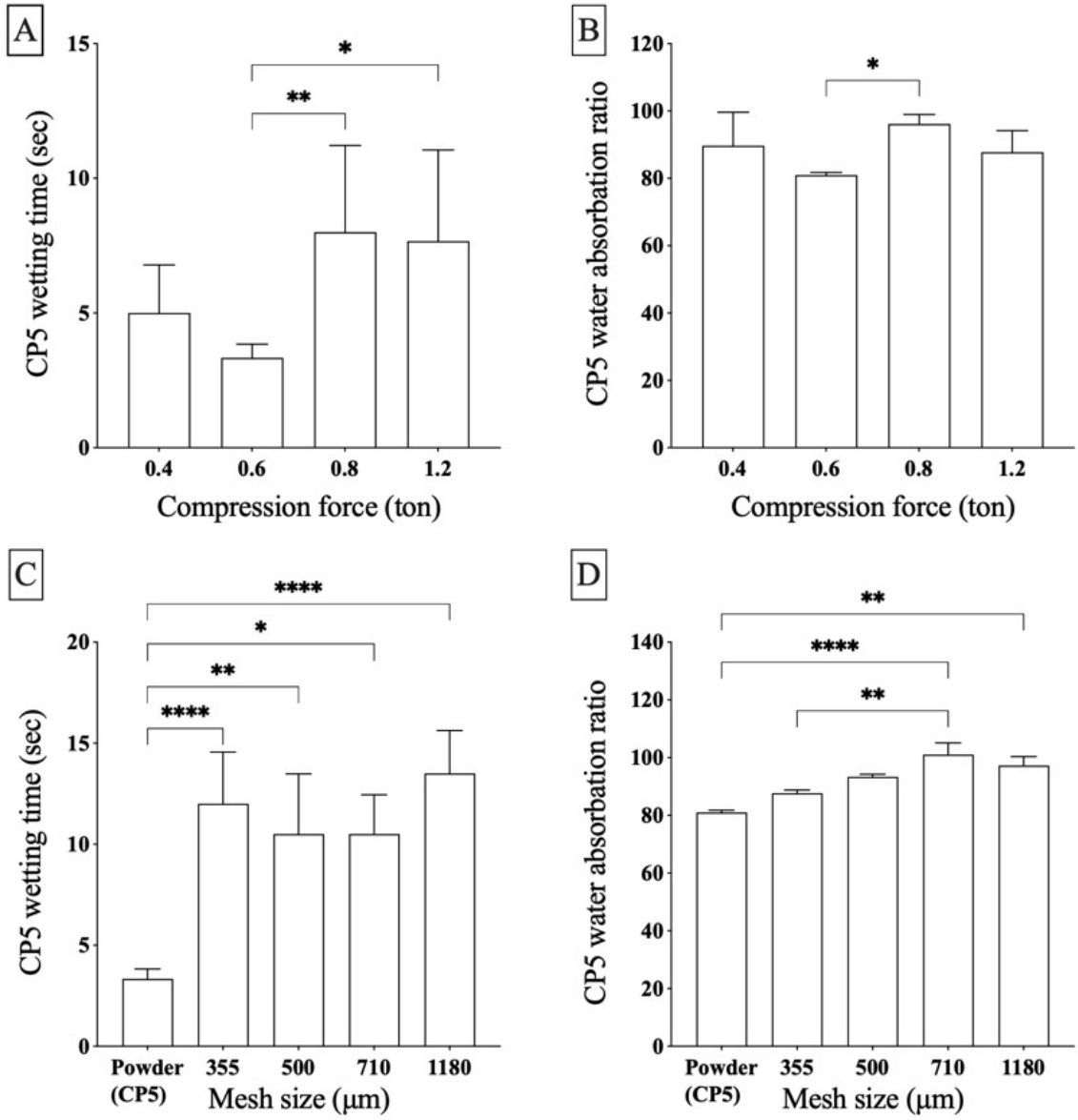



**Figure 3.12 wettability of orodispersible tablets prepared using different compression forces and wet granulation method.** *CP5 tablets prepared using different compression forces and wet granulation method. Wettability was assessed by measuring (A,C) the wetting time (B,D) the water absorption ratio. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

### 3.2.5 Correlation of the *in vitro* tolls

Spearman's correlation analysis was utilised to identify correlations between all of the indices used to evaluate the textural and physical properties of ODTs in this chapter, as shown in Table 3.1. Spearman's correlation coefficient (rs) is a measure of the linear relationship between two variables and is expressed as a number between -1 (negative relationships) and +1 (positive relationship). All analyses were conducted at a significance level of $p < 0.05$. According to the findings, several *in vitro* measurements were found to be significantly ($p < 0.05$) related to each other. Most of the disintegration properties of the ODTs, such as disintegration onset, rate, and end point, were well correlated. The time of disintegration was significantly associated ($r_s = 0.748$, Table 3.1) with the onset of disintegration. The swelling of the ODTs had a significant but smaller correlation with the other disintegration features. Furthermore, the disintegration properties, such as the onset of disintegration ($r_s = 0.832$, Table 3.1), were strongly correlated with the amount of residue that remained after ODTs disintegration. Moreover, the disintegration characteristics were well correlated with the adhesive properties and wettability of the ODTs, particularly the onset of disintegration.

The measurements of the mechanical features of the ODTs and the parameters associated with the rough mouthfeel showed some correlation. Tensile strength was inversely related to friability ($r_s = -0.757$, Table 3.1), whereas hardness was related to residue ($r_s = 0.659$, Table 3.1). Furthermore, some mechanical measurements and textural parameters associated with roughness/grittiness mouthfeel demonstrated some correlation with other tools for other textural attributes. Tensile strength was found to be related to swelling ($r_s = 0.694$, Table 3.1). Hardness and residue were both correlated to adhesiveness ($r_s = 0.513$, Table 3.1) and wettability ($r_s = 0.753$, Table 3.1).

The instrumental tolls of evaluating adhesive and wettability properties were also well correlated. Cohesiveness was found to have a significant relationship with adhesive force ($r_s$=0.689, Table 3.1). Furthermore, the adhesive properties were linked to the wettability properties of the ODTs. Finally, manufacturing factors (compression forces or mesh size used to make granules) correlated well with several in *vitro* assessments including wettability and mechanical assessments, as well as textural parameters associated with roughness and adhesiveness properties. A correlation (as presented between the TA measurements for ODTs) has not been established in the literature to date. However, a study compared the correlations between hardness, tensile strength, porosity, and compression force and disintegration time as determined by the TA instrument and the USP disintegration tester. The correlation factor ($r^2$) values for hardness, tensile strength, porosity, and compression force measured with the TA instrument were 0.92, 0.93, 0.77, and 0.99, whereas the $r^2$ values measured with the USP instrument were only 0.78, 0.77, 0.56, and 0.92 (98).

**Table 3.1 Spearman's correlation for all the used *in vitro* tolls, including textural measurements, and manufacturing factors**. *Only the significant value ($p < 0.05$) of correlation analysis is included ($n = 20$). (ns): No significant correlation was found.*

| | Onset of disintegration | Disintegration Rate | Swelling | Friability | Hardness | Residue | Cohesiveness | Adhesive force | Wetting time | Water absorption ratio | Compression force | Mesh size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Onset of disintegration** | ns | $r_s$ = -0.695 | ns | $r_s$ = -0.778 | $r_s$ = 0.565 | $r_s$ = 0.832 | $r_s$ = 0.732 | $r_s$ = 0.558 | $r_s$ = 0.770 | $r_s$ =0.849 | ns | ns |
| **Disintegration Rate** | $r_s$ = -0.695 | ns | rs = -0.496 | ns | ns | $r_s$ = -0.668 | $r_s$ = -0.555 | $r_s$ =-0.512 | ns | $r_s$ = -0.454 | ns | ns |
| **End point of disintegration time** | $r_s$ = 0.748 | $r_s$ = -0.961 | rs = 0.482 | ns | ns | $r_s$ = 0.671 | $r_s$ = 0.632 | $r_s$ = 0.456 | ns | $r_s$ = 0.553 | ns | ns |
| **Tensile strength** | $r_s$ = 0.798 | ns | rs = 0.694 | $r_s$ = -0.757 | ns | ns | ns | ns | ns | ns | $r_s$ = 0.776 | ns |
| **Friability** | $r_s$ = -0.778 | ns | ns | ns | ns | ns | ns | ns | ns | ns | $r_s$ = -0.557 | $r_s$ = -0.582 |
| **Hardness** | $r_s$ = 0.565 | ns | ns | ns | ns | $r_s$ = 0.659 | $r_s$ = 0.431 | $r_s$ = 0.822 | $r_s$ = 0.736 | ns | ns | $r_s$ = 0.788 |
| **Residue** | $r_s$ = 0.832 | $r_s$ = -0.668 | ns | ns | $r_s$ = 0.659 | ns | $r_s$ = 0.594 | $r_s$ = 0.656 | $r_s$ = 0.769 | $r_s$ = 0.770 | ns | $r_s$ = 0.752 |
| **Cohesiveness** | $r_s$ = 0.732 | $r_s$ = -0.555 | ns | ns | $r_s$ = 0.431 | $r_s$ = 0.594 | ns | $r_s$ = 0.689 | $r_s$ = 0.644 | $r_s$ = 0.583 | $r_s$ = 0.686 | ns |
| **Adhesive force** | $r_s$ = 0.558 | $r_s$ = -0.512 | ns | ns | $r_s$ = 0.822 | $r_s$ = 0.656 | $r_s$ = 0.689 | ns | $r_s$ = 0.656 | $r_s$ = 0.535 | ns | $r_s$ = 0.733 |
| **Wetting time** | $r_s$ = 0.770 | ns | ns | ns | $r_s$ = 0.736 | $r_s$ = 0.769 | $r_s$ = 0.644 | $r_s$ = 0.656 | ns | $r_s$ = 0.728 | ns | $r_s$ = 0.856 |
| **Water absorption ratio** | $r_s$ = 0.849 | $r_s$ = -0.454 | ns | ns | $r_s$ = 0.498 | $r_s$ = 0.770 | $r_s$ = 0.583 | $r_s$ = 0.535 | $r_s$ = 0.728 | ns | ns | $r_s$ = 0.715 |

## 3.3 Conclusions

The work described in this chapter has used a variety of instrumental techniques to assess the texture and characteristics of the tablets both directly and indirectly. The measurements of the used methods were able to distinguish differences between the tablets in terms of disintegration, hardness, roughness, sticking, and wettability. The findings have revealed that both the excipients and the manufacturing process can influence the texture and, thus, the mouthfeel of tablets. The TA can be a useful tool to assess a wide range of textural features of the ODTs, which, in turn, will improve the production of more palatable formulations. The excellent tablets were produced by properly balancing the ratios of the excipients, such as binders and fillers. Also, the superdisintegrant is an essential excipient that can affect disintegration as well as numerous textural characteristics, including residue, roughness, and wettability. Finally, the manufacturing process influences tablet characteristics. To make the best tablets, it's crucial to use the right compression force and granule size, especially in terms of hardness and roughness.

All the above methods will be used to investigate the textural and features that relate to the mouthfeel of several commercially available ODTs. The differences between several commercially available ODTs are presented in the next chapter.

# *In Vitro* Assessment of Commercially Available Orodispersible Tablets and Ready to Fill Excipients

## 4.1 Introduction

The rapid growth in the use of ODTs relates to various advantages. They can be administered without the need for water, making them more suitable for patients with swelling difficulties. In particular, ODTs are preferable for geriatric and paediatric patients, as well as any other group of patients who have a difficulty in taking conventional tablets. Solid dosage forms of APIs have a superior stability, and a primary benefit of using ODTs is the means to reduce the cost of treatment because medicine efficacy is maintained as compared to the use of liquid formulations.

The majority of drugs are unpalatable, with ODTs dosage forms facing various challenges that reduce their palatability. Texture and taste are limitations that may affect the palatability of ODTs, and thus their proper use of ODTs. ODTs are prepared with a low compression force, which results in insufficient mechanical strength, in order to assure a quick disintegration. Furthermore, the variety of methods and excipients used to prepare ODTs can result in variations in their features, which can directly or indirectly affect the texture of the ODTs, and thus the mouthfeel and acceptability.

A recent study has shown that the availability of ODTs in the market has increased (150). The medical applications of commercially available ODTs vary depending on the patient groups for whom they were developed. Commercially available ODTs are for both children and adults, with some used to relieve pain and others to treat more serious illnesses. Excipient's suppliers, on the other hand, design and manufacture ready-to-fill excipients (fillers) to facilitate the manufacturing of ODTs. Those fillers contain a mixture of excipients that are ready to be mixed

with an API and compressed into solid ODTs. Fillers have been designed to produce tablets that disintegrate fast, and they differ regarding aspects that can influence the features of the ODTs (58, 66).

The aim of the studies described in this chapter was to conduct a qualitative study to compare the textural differences between several commercially available ODTs and ODTs prepared from commercially available ready to fill excipients. A variety of *in vitro* methods have been used to gain a better understanding of the textural differences between the tablets. Commercially available tablets were examined to reveal how much variation there is in the features and texture of those tablets. The aim was to highlight how various potential differences affect mouthfeel, and, in turn, acceptability and medicine adherence. From the use of various measurements using different *in vitro* instruments to examine tablet characteristics, the endeavour was to determine how the different measurements provide a good indication of mouthfeel and patient acceptability.

## 4.2 Results and discussion

Several commercially available ODTs were chosen based on their availability within the NHS and local community pharmacies in the United Kingdom. The ODTs samples were obtained from various sources, as stated earlier in chapter two. The composition (active ingredients and excipients) of the commercially available ODTs that were selected for study is shown in Table 4.1. The commercial ODTs varied widely regarding their composition. Mannitol is the most common filler as found in all of the tablets, and crospovidone (CP) was used as a superdisintegrant in the majority of ODTs. Some ODTs (e.g. donepezil ODTs) included more than one superdisintegrant, whereas Imodium Instants®, which is manufactured using the freeze-drying method, did not have a disintegrant nor a lubricant. Magnesium stearate (Mg St) was used as a lubricant in all of the other evaluated commercially ODTs.

Most of the commercially available ODTs contained aspartame as a sweetener, except for donepezil, which contained acesulfame potassium. Some commercially available ODTs that can be used for children, such as Calpol® and risperidone, include a taste-masking agent, such as basic butylated methacrylate copolymer. Different flavouring agents were used for the rest of the commercial tablets, such as peppermint or strawberry flavours.

Calpol® and Imodium ODTs were the only ODTs that did not contain microcrystalline cellulose (MCC). In donepezil and risperidone ODTs, hydroxypropyl cellulose, which can be utilised as a binder, coating agent, and viscosity enhancer, is listed as an inactive ingredient. Calpol®, donepezil, mirtazapine, and ondansetron ODTs all included colloidal anhydrous silica, which works as an adsorbent, anti-caking agent, and glidant. Imodium Instants® contained gelatin because it was the only tablet that appeared to be manufactured using the freeze-drying method.

**Table 4.1 The commercial orodispersible tablets that were included in this study.** *The compositions of commercially ODTs were obtained directly and indirectly from the supplier's safety sheets and the electronic medicines compendium (151). The weight, the thickness, and the diameter were examined by the researcher, and the findings are presented as a mean ± std dev (n = 3). The compositions of commercially ODTs were obtained directly and indirectly from the supplier's safety sheets and the electronic medicines compendium (151). The weight, the thickness, and the diameter were examined by the researcher, and the findings are presented as a mean ± std dev.*

| ODT | List of excipients | Weight (mg) | Thickness (mm) | Diameter (mm) |
|---|---|---|---|---|
| **Calpol® Fastmelt (Paracetamol)** | Mannitol, crospovidone, aspartame, basic butylated methacrylate copolymer, polyacrylate dispersion, colloidal anhydrous silica, strawberry flavour, magnesium stearate | 795 ± 9.7 | 4.9 ± 0.05 | 15 ± 0.5 |
| **Donepezil hydrochloride 10 mg orodispersible tablets** | Mannitol, microcrystalline cellulose, crospovidone (type A), sodium starch glycolate (type A), colloidal anhydrous silica, hydroxypropyl cellulose, acesulfame potassium, glycine, yellow iron oxide E172, magnesium stearate | 200 ± 0.8 | 3.3 ± 0.04 | 8 ± 0.2 |
| **Imodium Instants® (Loperamide hydrochloride)** | Mannitol, gelatin, aspartame, sodium hydrogen carbonate, mint flavour. | 13 ± 0.1 | 2.4 ± 0.05 | 2.3 ± 0.31 |
| **Mirtazapine 45 mg orodispersible tablets** | Mannitol, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, aspartame, strawberry guarana flavour: [maltodextrin, propylene glycol, artificial flavours, acetic acid], peppermint flavour: [artificial flavours, corn starch], magnesium stearate. | 175 ± 2.3 | 4.8 ± 0.12 | 10 ± 0.1 |
| **Ondansetron 8 mg orodispersible tablets** | Pharmaburst tm c1: [mannitol, sorbitol, colloidal anhydrous silica], crospovidone, microcrystalline cellulose, strawberry flavour, sodium stearyl fumarate, aspartame, magnesium stearate. | 175 ± 1 | 2.2 ± 0.05 | 10 ± 0.1 |
| **Risperidone 2 mg orodispersible tablets** | Mannitol, microcrystalline cellulose, crospovidone, povidone k-25, hydroxypropyl cellulose, basic butylated methacrylate copolymer, aspartame, red iron oxide, spearmint flavour, peppermint flavour, calcium silicate, magnesium stearate. | 200 ± 0.9 | 3.6 ± 0.03 | 8 ± 0.11 |

## 4.2.1 Assessment of commercially orodispersible tablets

### *4.2.1.1 Disintegration properties of the commercially orodispersible tablets*

Figure 4.1 shows the disintegration properties of the various commercially available ODTs. Among all of the commercially available tablets, Imodium® ODTs showed an exceptionally fast disintegration. Imodium® and Calpol® ODTs started to disintegrate in less than 2 seconds, which was significantly faster than ondansetron ODTs, which took 23 seconds (Figure 4.1 A). The majority of commercially available ODTs began to disintegrate between 7.5 and 17.5 seconds after contact with the disintegrating media. Also, Imodium instants® disintegrated at a significantly faster rate (0.4 ± 0.01 mm/second) than the other ODTs, as seen in Figure 4.1 (B). Although the majority of the ODTs had a comparable disintegration rate (c.a 0.11 ± 0.03 mm/second), donepezil and ondansetron ODTs disintegrated at the slowest rate (c.a 0.05 ± 0.01 mm/second). Furthermore, the endpoint of disintegration for Imodium instants® was significantly faster (6.5 ± 0.05 seconds) than ODTs of Calpol®, donepezil, and ondansetron (Figure 4.1 C). Despite the fact that most of the ODTs completely disintegrated in less than 40 seconds, donepezil ODTs had a significantly longer disintegration time (70.5 ± 10.8 seconds) when compared to c.a 30 ± 4 for mirtazapine and risperidone ODTs.

The assessment of disintegration has revealed that the Imodium ODTs showed exceptional results regarding all aspects of the disintegration process. The appearance of the Imodium instants differs from that of other tablets, and it is reported that they were manufactured using freeze-drying technology (152). The freeze-drying method has the advantage of producing tablets with a very short disintegration time (153). The disintegration rate is crucial to knowing the intensity of disintegration, as seen for Calpol® ODTs. These tablets started to disintegrate quickly, but their end disintegration time was equivalent to that observed for the other ODTs. This may be because Calpol® ODTs are larger than Imodium Instants®. Donepezil ODTs were

the tablets that required the longest time to disintegrate among all the tested commercially ODTs. This might be due to one or a combination of factors; the manufacturing parameters such as the use of a high compression force, resulting in a high tensile strength. Additionally, the composition's characteristics, including the APIs, may have prolonged the disintegration time. The long disintegration time for donepezil ODTs was associated with a slow disintegration rate and high tensile strength, as shown in Figures 4.1-4.2. A high tensile strength can extend the disintegration time of ODTs because of an increase in tablet density and a decrease in tablet porosity (154). Also, the hygroscopic nature of colloidal anhydrous silica has been shown to increase the breaking force and, thus, the disintegration of donepezil ODTs (155). It has been reported that the addition of donepezil microspheres to the formulation of ODTs can cause the disintegration to be prolonged (156). All the above are only possible explanations for the prolonged disintegration properties of donepezil ODTs because of a lack of information from the manufacturer. Despite the differences in the onset and rate of disintegration between the commercially available ODTs, the majority of them disintegrated completely in less than 40 seconds, meeting the British pharmacopeia standards for appropriate ODTs. Existing guidelines require orodispersible formulations to disintegrate in less than 3 minutes, from *the European pharmacopeia* (79) or less than 30 seconds, from *the US pharmacopeia* (80).

Analysis of the swelling of the tablets during the disintegration process has revealed a variation in tablet swelling, as shown in Figure 4.1 (D). The swelling was significantly higher for mirtazapine and ondansetron ODTs than that seen for the other tablets. ODTs of mirtazapine and ondansetron swelled up to $0.75 \pm 0.03$ mm, and $0.46 \pm 0.04$ mm, respectively. On the other hand, Calpol®, Imodium, and donepezil ODTs did not swell much during their disintegration; the swelling was up to 0.11 mm. The factors that can augment the swelling of the ODTs have been discussed in depth in the previous chapter. Even though the mirtazapine and ondansetron

ODTs had a high swelling, this swelling did not lead to an improved disintegration, as compared to tablets that swelled less. In summary, the findings from this study have shown that commercially available ODTs differ regarding their disintegration and swelling features. These are factors that potentially influence the texture, mouthfeel, and acceptability of commercially available ODTs.

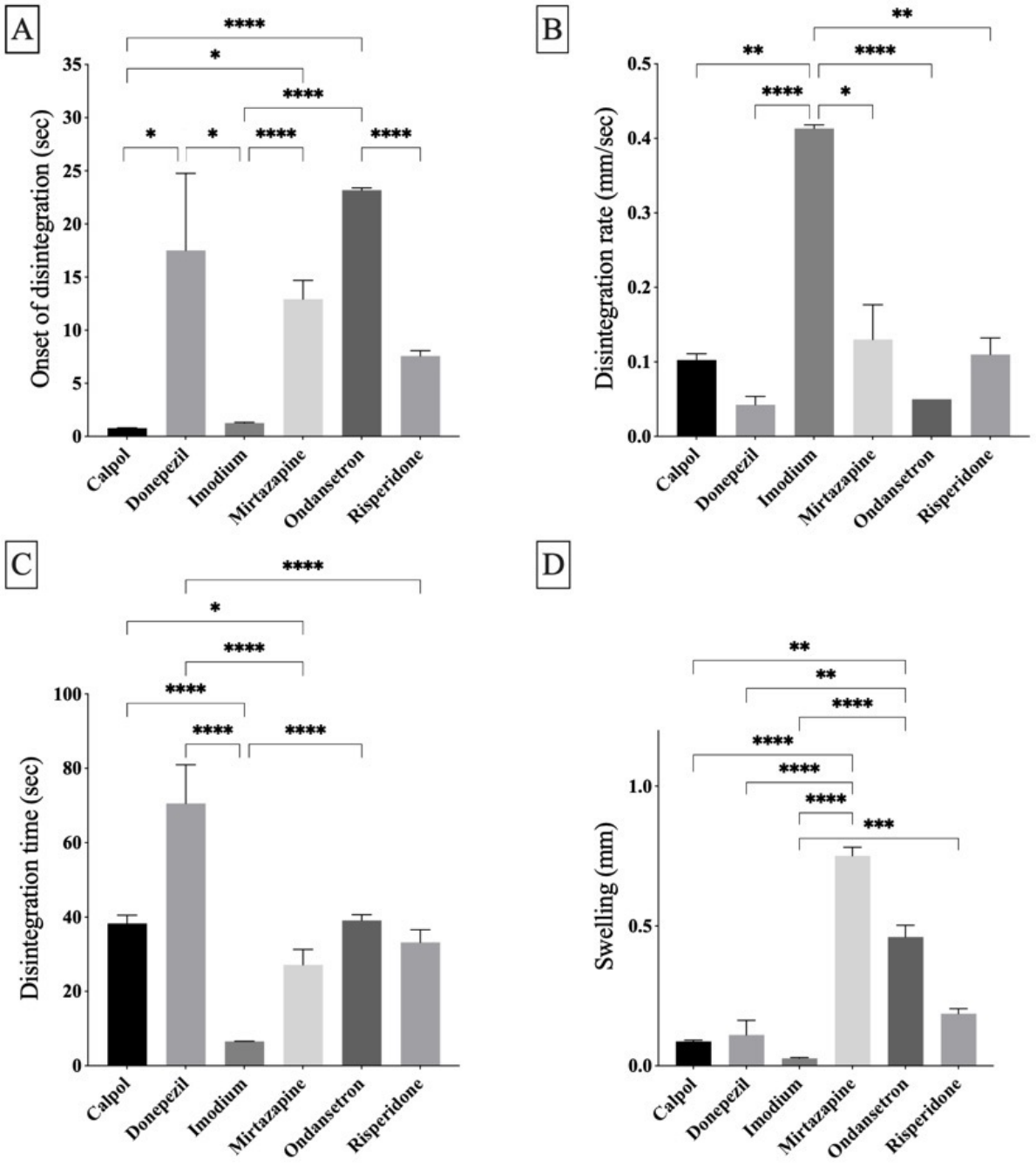



**Figure 4.1 The disintegrating properties of the commercial orodispersible tablets.**
*Disintegration of the commercial orodispersible tablets was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

#### *4.2.1.2 Hardness and roughness of commercially orodispersible tablets*

Due to a lack of established procedures for assessing mouthfeel qualities, such as hardness and roughness, different tools were employed to examine several parameters of the tablets regarding both the dry and wet forms. The hardness and the roughness of the tablets were investigated using tensile strength, friability, hardness, and residue. Due to the differences in the size of the tablets, the tensile strength was measured to evaluate the breaking force. Figure 4.2 shows the hardness and roughness assessments of various commercially available ODTs. Donepezil and risperidone ODTs had a significantly higher tensile strength (c.a 0.88 ± 0.01 MPa) than the Calpol® and mirtazapine tablets (Figure 4.2 A). The tensile strengths of Calpol®, mirtazapine, and ondansetron ODTs were comparable (c.a 0.4 ± 0.04 MPa), and mirtazapine ODTs had the lowest tensile strength (0.3 ± 0.02 MPa). The friability of the majority of the commercially available ODTs was minimal (less than % 2), as shown in Figure 4.2 (B). However, Calpol® ODTs were substantially more friable (% 8.1 ± 2.1) than the rest of the commercial tablets. Calpol® ODTs had the highest level of friability.

Imodium ODTs were resistant to being broken as they were flexible and easily compressed so the breaking and the friability tests were not suitable for this kind of tablet. Donepezil and risperidone ODTs were the most difficult to break due to their high tensile strength. High compression force is known to yield tablets with a high tensile strength (125), which may be the case here. However, the manufacturer has not disclosed how the ODTs were manufactured. Even though the tensile strength of the Calpol®, mirtazapine, and ondansetron ODTs was comparable, the Calpol® ODTs were significantly more friable than any other commercially available tablet. The large size of Calpol® tablets (Table 4.1) in comparison to the rest of the tablets may explain their high friability. The friability of the tablets is known to be affected by

their size and shape due to their impact on the intensity of stress at the points of contact during the friability test (157).

The TA can provide a more in-depth understanding of the differences that can affect roughness in terms of hardness and residual amount between commercially available tablets. Figure 4.2 (C) shows the hardness of wet commercially available ODTs which was analysed using the TA. The hardness of most of the commercially available tablets was less than 5 g. Calpol® and mirtazapine ODTs were found to be substantially harder than donepezil, Imodium®, ondansetron and risperidone tablets. Calpol® ODTs and mirtazapine ODTs were found to be the hardest tablets, with hardness ratings of 21.7 ± 2 g and 10.4 ± 1.3g, respectively. The Calpol® and mirtazapine ODTs had a larger thickness than the rest of the commercially available tablets. In food science, it has been observed that the hardness and tensile strength of a product increases proportionally with its thickness (158).

Also, the textural analysis shows variation in the amount of residue after the disintegration of the commercial tablets, as shown in Figure 4.2 (D). Even though the residue in most commercially available tablets was small, some tablets had a significant amount of residues such as mirtazapine and ondansetron. Compared to Calpol® and Imodium®, mirtazapine, and ondansetron ODTs had significantly higher residues. The highest residues were 2.6 ± 0.8 mm and 1.17 ± 0.1 mm for the ODTs of mirtazapine and ondansetron, respectively. Even so, the residue for most of the commercially available tablets was less than 1 mm. This clarifies that the use of similar excipients in different commercially available tablets does not imply that they will have similar characterisation, as they may differ due to particle size, manufacturing method, or due to the API itself. As demonstrated in chapter 5, several factors related to the manufacturing methods (e.g. granules particle size) can influence tablet properties including

residual amount. ODTs that are pleasant to patients have a soft mouthfeel and leave only a little smooth residue following disintegration (159).

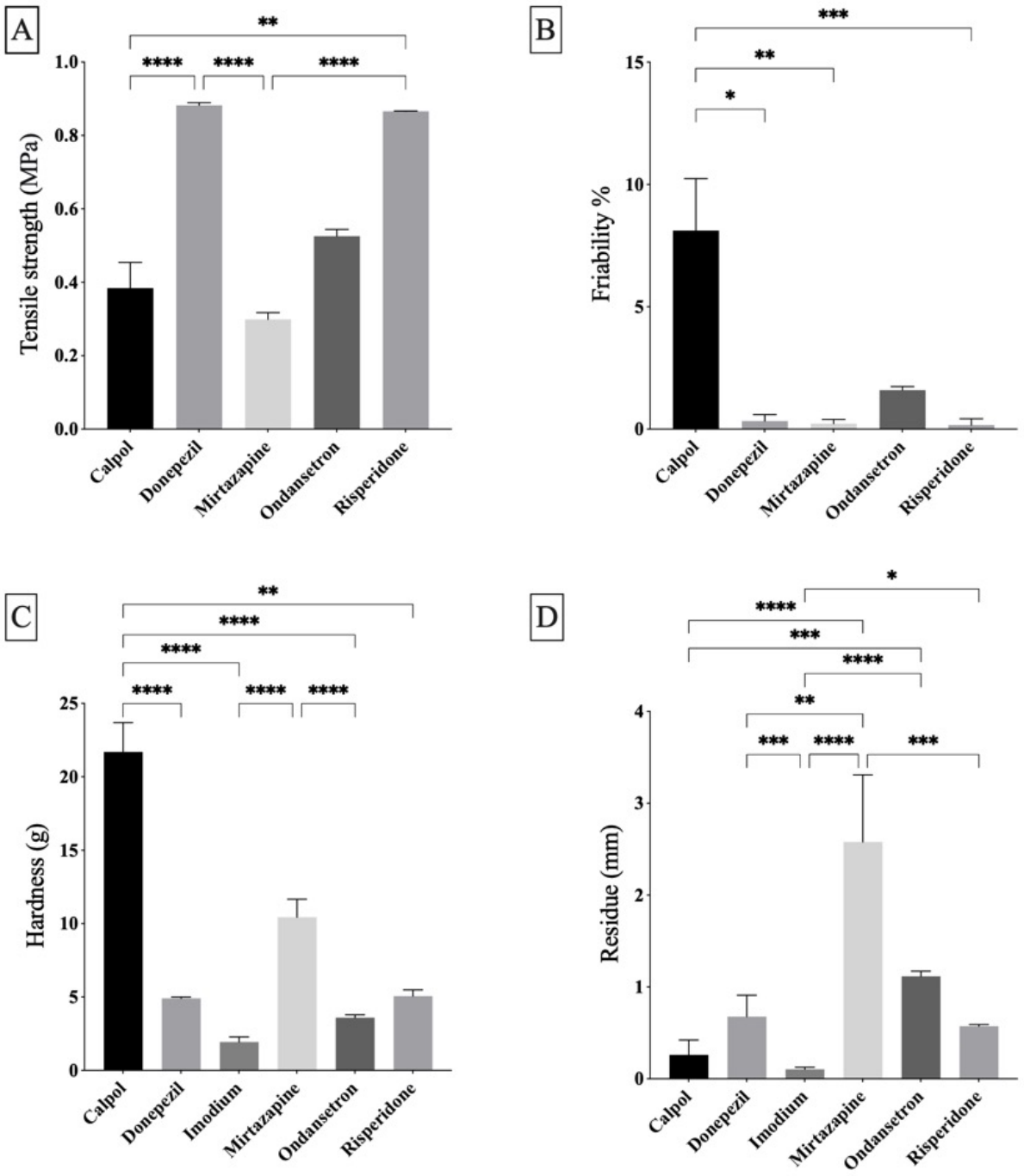



**Figure 4.2 The hardness and roughness of the commercial orodispersible tablets were examined using mechanical and textural methods.** *Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.)*

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#### *4.2.1.3 Adhesive properties of commercially orodispersible tablets*

The adhesive/cohesive characteristics of commercially available tablets were determined using the TA regarding cohesiveness and adhesive force (Figure 4.3). The majority of commercially available ODTs had a similar cohesiveness (less than 0.3). However, the cohesiveness of Imodium® (0.5 ± 0.04) and mirtazapine (0.34 ± 0.02) tablets was significantly higher than the tablets of Calpol®, donepezil, and risperidone. Imodium and Calpol® ODTs had high cohesiveness and adhesiveness as compared to all of the other commercial ODTs. The adhesiveness of Imodium tablets may be attributed to the adhesive properties of the gelatin that is commonly used in preparing ODTs when using the lyophilisation method. Gelatine has a wide range of applications in the pharmaceutical and medical fields due to its adhesive properties and gelling properties (120, 160). Also, Calpol® tablets showed a significant high adhesive force. This could be due to the large surface area of the Calpol® tablets compared to the rest of the tablets. Expanding the surface area can increase the contact between the tablets and the probe of the TA, and, thus, the measurement of adhesiveness. The larger surface area of contact of large and flat tablets results in a higher bio adhesive force than that for small and concave tablets (161).

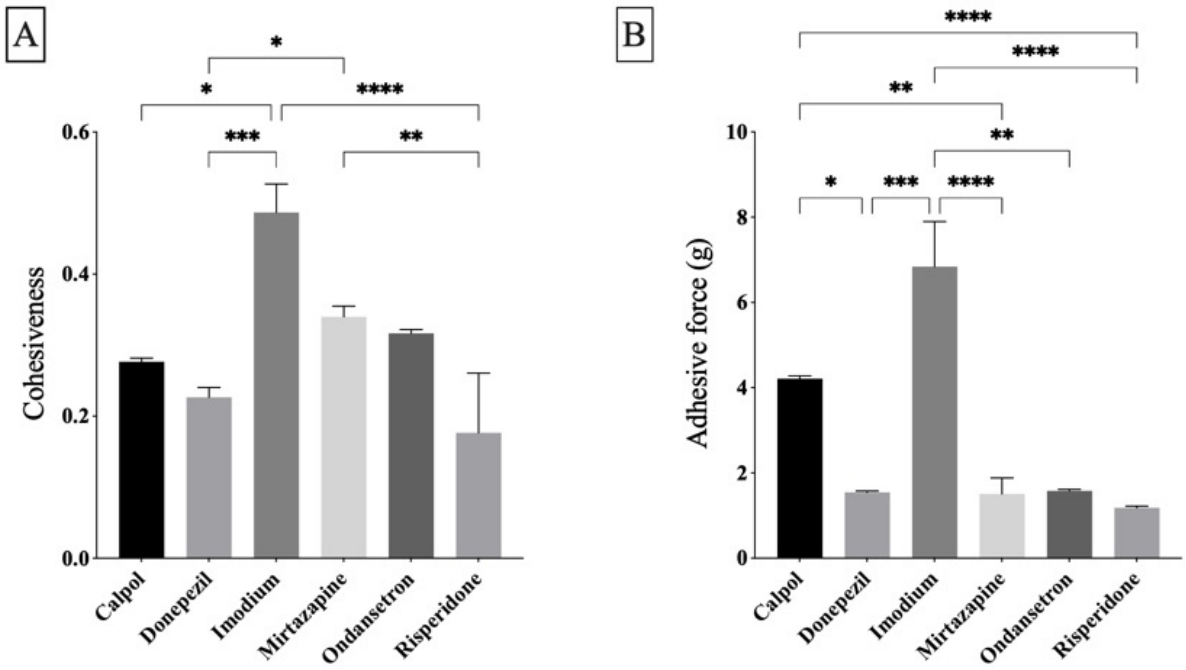


**Figure 4.3 The adhesive properties of commercial orodispersible tablets.** *Adhesive properties were assessed by measuring (A) the cohesiveness (B) the adhesive force. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

#### *4.2.1.4 Wettability of commercially orodispersible tablets*

The wettability of the commercially available ODTs was studied in terms of the wetting time and the water absorption ratio. The findings are shown in Figure 4.4. The wetting times for the majority of commercial ODTS were between 26 and 31 seconds. The main difference was for Imodium ODTs®, the smallest size tablets, that were prepared using the lyophilisation method. They had the fastest wetting time and the lowest water absorption ratio. Imodium ODTs had the fastest wetting time (3 ± 0.5 seconds), while the longest wetting time was 51 ± 7.5 seconds for mirtazapine ODTs, as shown in Figure 4.4 (A).

The water absorption ratio mostly followed a similar pattern (Figure 4.4 B). Donepezil ODTs has a higher ratio than Calpol® ODTs, despite having similar wetting times. Mirtazapine ODTs, on the other hand, had the longest wetting time, as well as the highest water absorption ratio. Ondansetron had a substantially higher water absorption rate than Calpol® and Imodium ODTs. The primary determining factor for the tablets' wettability is the morphology of the excipients used, as reported previously [18]. Differences in the tablets' wettability might affect mouthfeel by easing disintegration, altering texture, or causing a dry sensation. The wettability of commercially available tablets varied due to differences in their composition and the methods used to manufacture.

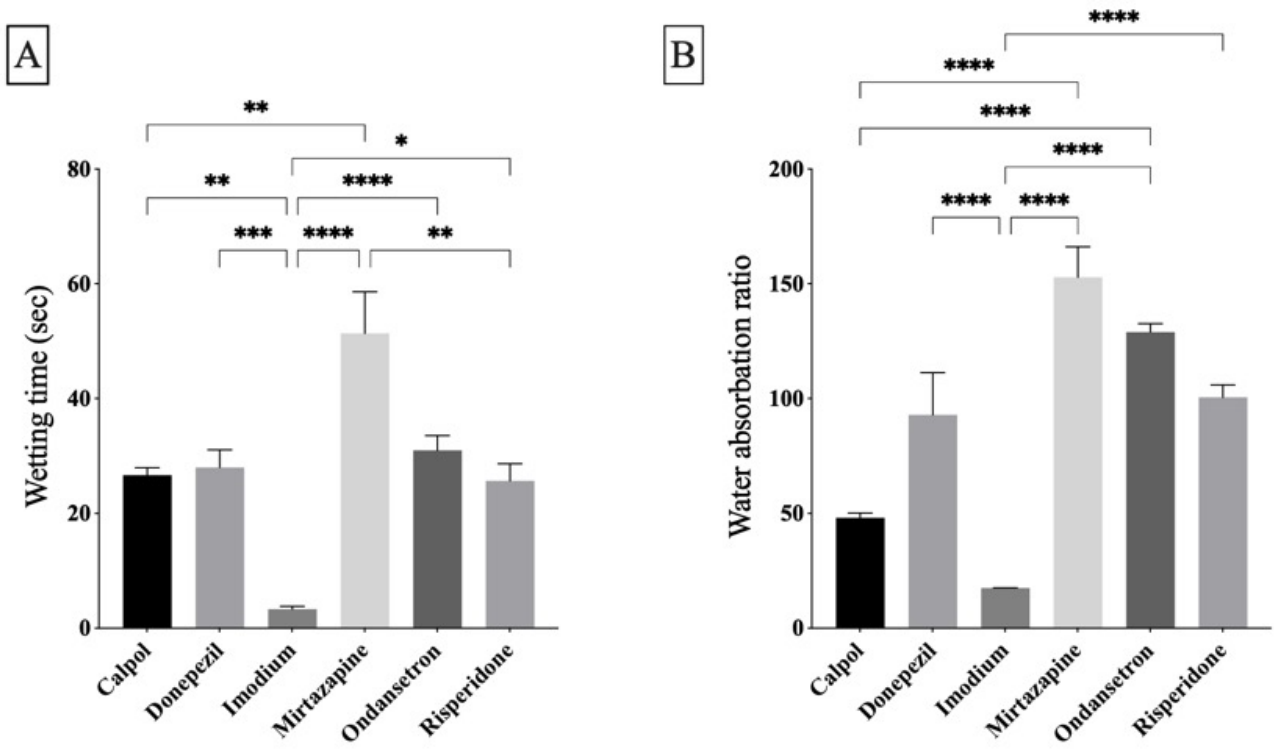


**Figure 4.4 Wettability of commercial orodispersible tablets.** *Wettability was assessed by measuring (A) the wetting time (B) the water absorption ratio. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

### 4.2.2 Assessment of placebo orodispersible tablets

Several commercially available co-processed excipient systems (ready-to-fill excipients) have been developed to enhance the efficacy and ease of ODT production. Numerous placebo ODTs consisting of several ready-to-fill excipients were employed in this study to determine their nature regarding mouthfeel palatability. (Table 4.2). Generally, the compositions of the commercially ready-to-fill excipients differed slightly. Mannitol which is a commonly used filler/diluent was present in all of the co-processed excipient systems. Only Smartex ODTs contained polyvinyl alcohol as a binder, whereas microcrystalline cellulose (MCC) was a common binder in the other commercially available ready-to-fill excipients. Most of the commercially available ODTs contained sucralose as a sweetener, except for Smartex which did not contain a sweetener.

As superdisintegrants, GNF ODTs prepared from Granfiller-D contained both crospovidone and sodium croscarmellose. Crospovidone (CP) was used in the Hisorad ODTs, whereas Low-substituted hydroxypropyl cellulose (LHPC) was used in the Smartex tablets. As to the lubricants used, calcium stearate was used in the Granfiller-D filler. Hisoard filler, on the other hand, contained stearyl fumarate sodium as a lubricant, whereas Smartex ODTs contained magnesium stearate (Mg St). Lubricants are typically employed in small amounts in the manufacturing of ODTs, and, therefore, the findings from this study will focus on the effects of the major excipients on the characteristics and the texture of ODTs.

**Table 4.2 The compositions of the placebo orodispersible tablets prepared from commercial ready to fill excipients.** *The composition and the particle size of placebo tablets prepared from commercial ready to fill excipients were obtained from the supplier's safety and information sheets. The weight and the thickness were examined by the researcher and presented as a mean ± std dev.*

| ODTs | List of excipients | Weight (mg) | Thickness (mm) | Median particle size (μm) |
|---|---|---|---|---|
| **GNF 211** | Granfiller-D: D-mannitol, microcrystalline cellulose, carmellose, crospovidone, sucralose, and calcium stearate | *201 ± 1.2* | 3 ± 0.1 | 100 |
| **GNF 215** | | *199 ± 1.1* | | 140 |
| **Hisorad** | D-mannitol, microcrystalline cellulose, croscarmellose sodium, sucralose, and stearyl fumarate sodium | *200 ± 1* | 3.3 *± 0.1* | 1*06* |
| **Smartex** | D-mannitol, polyvinyl alcohol, low- substituted hydroxypropyl cellulose, magnesium stearate | *201 ± 1* | 3.6 *± 0.1* | 100 |

#### *4.2.2.1 Disintegration properties of placebo orodispersible tablets*

Figure 4.5 shows the disintegration properties of placebo ODTs that contained different commercially ready to fill excipients. The disintegration properties of ODTs prepared with Hisoard and Smartex fillers were superior to those of GNF ODTs containing Granfiller-D; the onset of disintegration, the rate and times to disintegration were faster. GNF-211 and GNF-215 ODTs had a significant longest onset of disintegration (c.a 26.5 ± 0.5 seconds), compared to tablets prepared from Hisoard (13.5 ± 0.5 seconds) and Smartex filler (17 ± 0.5 seconds), as shown in Figure 4.5 (A). Also, the rate of disintegration was significantly faster for placebo tablets prepaid from Hisoard and Smartex compared to tablets prepared from Granfiller-D filler, as shown in Figure 4.5 (B). Hisoard tablets and Smartex tablets disintegrated at a fast rate (c.a 0.1 ± 0.01 mm/sec). The disintegration rate was slower (0.013 ± 0.005 mm/sec) and (0.05 ± 0.004 mm/sec) for GNF-211 and GNF-215 ODTs, respectively. Furthermore, the results have shown that the tablets prepared from Granfiller-D had a disintegration time that was significantly longer than that for Hisoard and Smartex (Figure 4.5 C). GNF-211 tablets had the longest disintegration time (88 ± 1 seconds), while GNF-215, Hisoard, and Smartex tablets had comparable disintegration times of less than 50 seconds. The Smartex ODTs completely disintegrated at the shortest time (23 ± 0.5 seconds).

The disintegration properties of the placebo tablets varied depending on the type of commercially available filler used to produce the tablets. The results showed that the tablets prepared from Hisoard and Smartex outperformed the tablets prepared from Granfiller-D in their disintegration properties. To illustrate, GNF-211 and GNF-215 ODTs that were prepared from Granfiller-D had the slowest rate of disintegration and the longest onset of disintegration. Even so, the time required for the tablets to completely disintegrate was less than 50 seconds for most of the placebo ODTs except GNF-211. Therefore, all the placebo ODTs met the

standards as prescribed by *the European pharmacopeia* (79). An expectation is that ODTs that had shorter disintegration time might achieve a higher acceptance by the end-users. It has been reported that the disintegration time is a main factor to the acceptance of ODTs (93).

Figure 4.5 (D) illustrates the slight variation in swelling of several placebo tablets during disintegration. Smartex ODTs had the smallest swelling (0.5 ± mm) among the commercial placebo ODTs. The ODTs prepared from Granfiller-D and Hisoard fillers had a significantly higher swelling than Smartex ODTs. The swelling of Hisoard tablets was (1.4 ± 0.01 mm) compared to that for GNF-211 tablets (1.1 ± 0.02mm). Regarding tablet swelling during disintegration, using the Smartex filler significantly reduced the swelling of the tablets more than the other placebo commercial fillers. In comparison to Granfiller-D and Hisoard fillers, the Smartex filler does not contain microcrystalline cellulose. Microcrystalline cellulose, which swells when it contacts the disintegration media, is a well-known excipient that is commonly used in the preparation of ODTs (120). The swelling of ODTs is associated with an increase in the size of the tablets, which causes disintegration to begin at the point of contact with the tongue (154). In summary, ODTs that disintegrate quickly might be perceived better in the mouth than those that swell more and disintegrate somewhat slowly. Extreme swelling is undesirable in ODTs because it can result in an unpleasant mouthfeel (82).

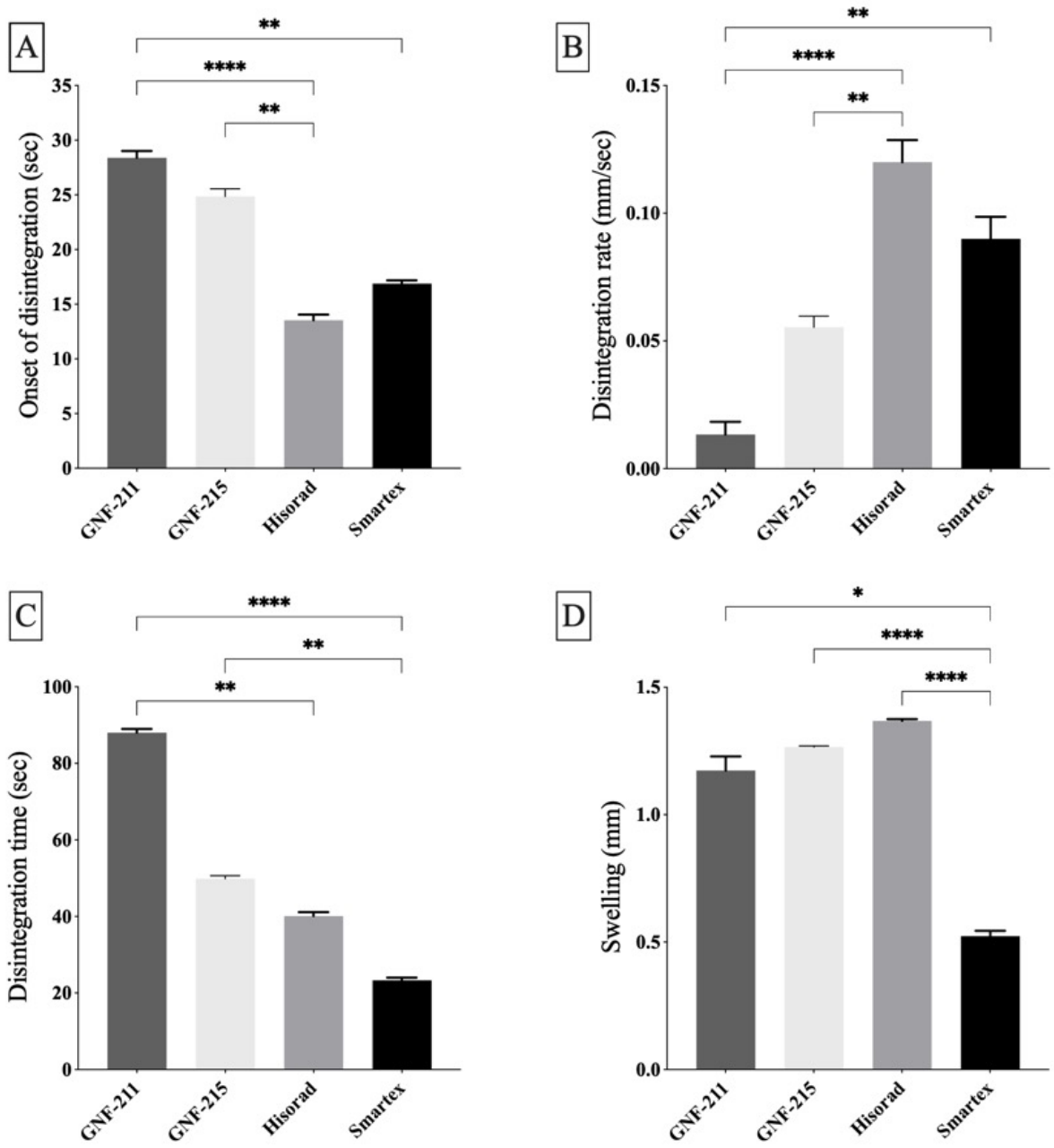


**Figure 4.5. The disintegrating properties of orodispersible tablets contained commercial different ready to fill excipients.** *Disintegration of orodispersible tablets was assessed by measuring (A) the onset of disintegration; (B) the disintegration rate; (C) the end point of the disintegration and (D) the swelling experienced by the ODTs. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001*

#### *4.2.2.2 Hardness and roughness properties of placebo orodispersible tablets*

The hardness and roughness of placebo ODTs were examined using mechanical and textural methods. The findings are shown in Figure 4.6. The tensile strengths of the tablets prepared from the commercially ready to fill excipients are shown in Figure 4.6 (A). The change in the ready to fill excipients led to minimal changes to the tensile strength of the placebo tablets prepared from excipients of GNF-211, GNF-215, and Hisoard. However, the tensile strength for Smartex tablets, which do not use MCC as a binder, was significantly lower (1.57 ± 0.1 MPa) than that of tablets manufactured using Granfiller-D (GNF) filler (c.a 2.1 ± 0.1 MPa). The friability of the placebo ODTs prepared from commercial fillers was comparable (Figure 4.6 B). All the placebo tablets had a friability of less than 1 percent.

Textual analysis of the wet placebo tablets has revealed how the type of the filler affects the hardness, and the amount of residue after the tablets have been disintegrated. Figure 4.6 (C) shows the hardness of wet placebo tablets examined using the TA. The hardness of the placebo tablets differed significantly depending on the ready-to-fill excipients. The hardness of Smartex tablets was significantly higher (21.3 ± 1.3 g) than the hardness of (> 8.5 g) of GNF-211, GNF- 215 and Hisoard tablets. The amount of the residue after the tablet had disintegrated is shown in Figure 4.6 (D). The change in ready-to-fill excipients had a significant impact on the residue amount. The ODTs prepared from Granfiller-D had a significantly higher residue compared to Hisoard and Smartex tablets. The largest amount of residue was for GNF-211 (2.6 ± 0.1 mm) and GNF-215 (1.5 ± 0.05 mm) tablets. The lowest amount of residue was (0.1 ± 0.02 mm) and (0.26 ± 0.01 mm) for Hisoard and Smartex tablets, respectively.

The textural properties that are associated with roughness were also observed to differ between the placebo tablets. The Smartex filler was found to produce the hardest tablets among all of

the placebo tablets. On the other hand, using Hisoard and Smartex filler led to a significant reduction in the amount of residue after the tablet disintegrated, as compared to the use of GNF filler. The absence of MCC in the Smartex tablet composition can result in a harder tablet surface, which was associated with a small swelling as described above. This view is consistent with the finding presenter in chapter 4 whereby MCC can reduce the hardness of tablet's surface but may increase the amount of residue. In comparison to GNF tablets, Hisoard tablets contained two types of superdisintegrants, which can reduce the amount of residue after disintegration. The large particle size in GNF-211 ODTs might explain the higher amount of residue, as compared to GNF-215. This might explain why ODTs that contain granules with larger particle size had a rougher mouthfeel (46). The amount of residue has been found to correlate well with the rough mouthfeel of ODTs (85).

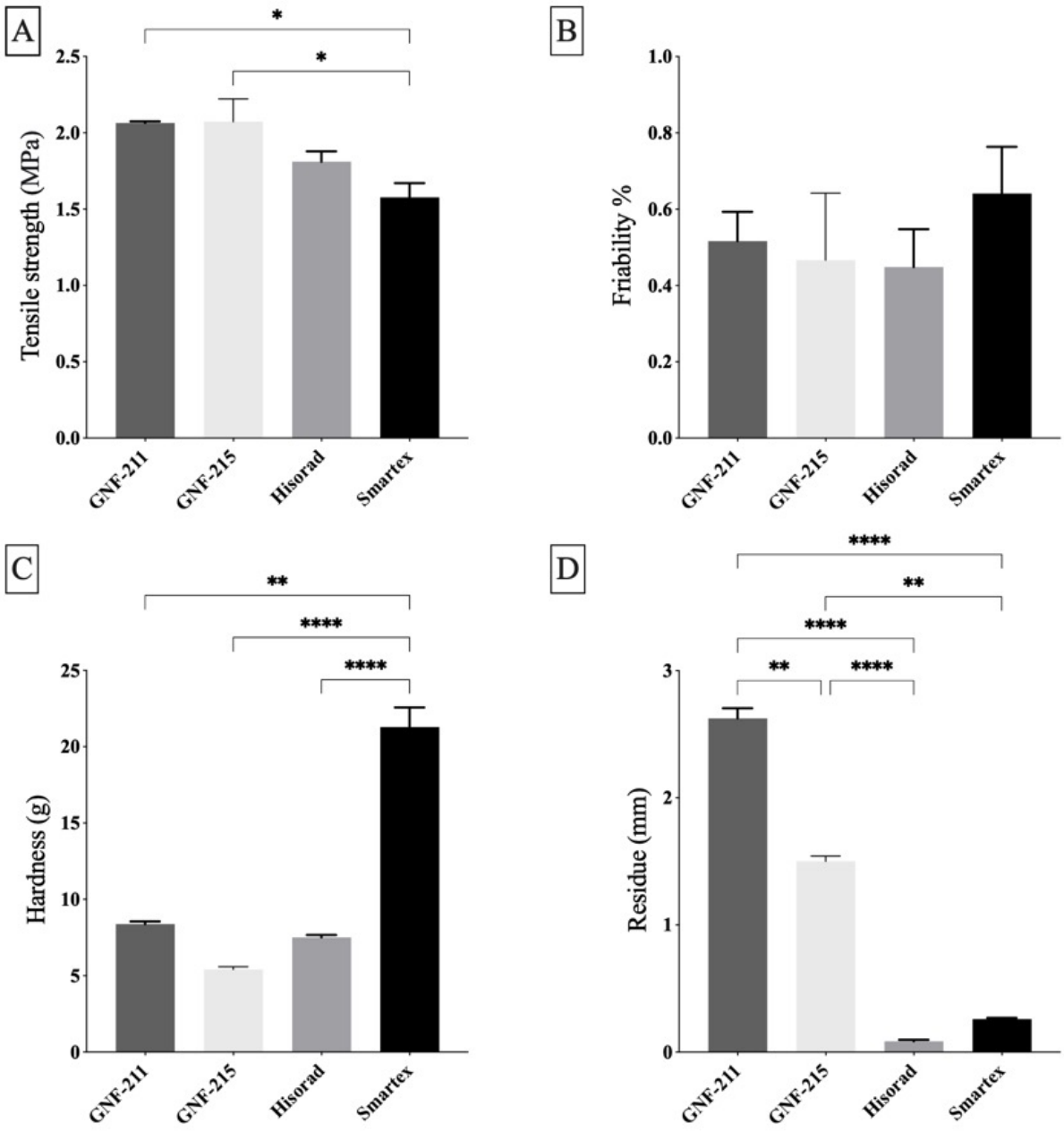


**Figure 4.6. The hardness and roughness of orodispersible tablets containing different commercial ready to fill excipients were examined using mechanical and textural methods.** *Hardness and roughness were assessed by measuring (A) the tensile strength (B) the friability (C) the hardness (D) the amount of residue after the tablets disintegrated. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.)*

#### *4.2.2.3 The adhesive properties of placebo orodispersible tablets*

Figure 4.7 shows the adhesive properties, assessed using the TA, of wet placebo tablets that contained different commercial fillers. As shown in Figure 4.7 (A), different placebo tablets had slight differences in cohesion. GNF-215 tablets, prepared from Granfiller-D, had a higher cohesiveness (0.21 ± 0.01), as compared to Hisoard and Smartex tablets (c.a 0.16 ± 0.002). Also, there were slight differences in the adhesive force measurements between the different placebo tablets (Figure 4.7 B). GNF-211 ODTs, containing Granfiller-D, had the highest adhesiveness (1.8 ± 0.05 g) compared to Smartex tablets (1.2 ± 0.03 g).

In general, the use of GNF filler to prepare placebo tablets resulted in a higher cohesiveness and adhesive force than that observed for tablets containing Hisoard and Smartex filler. Both the Hisoard and Smartex fillers resulted in tablets with relatively similar cohesiveness and adhesive force measurements. Even though the ODTs are prepared to disintegrate in the mouth, assessing the adhesive properties still needs to be considered as this might impact on the mouthfeel of the disintegrating tablets.

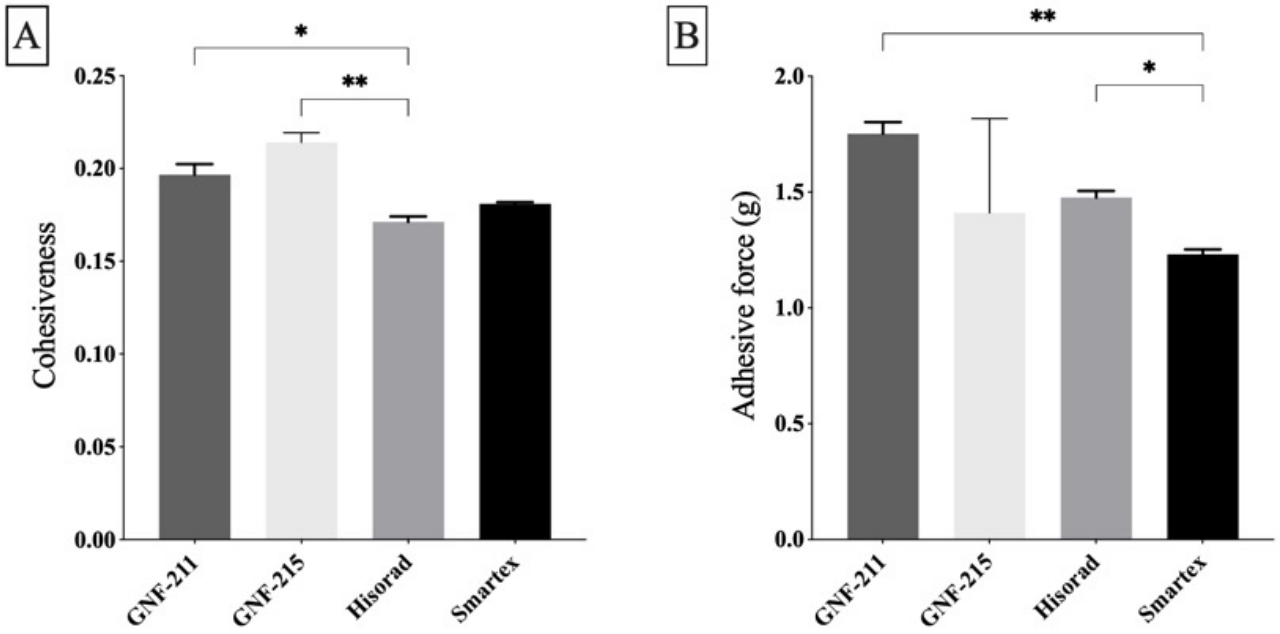


**Figure 4.7. The adhesive properties of orodispersible tablets contained different ready to fill excipients** *The differences between orodispersible tablets prepared from different commercially available ready to fill excipients. (A) The cohesiveness of ODTs prepared using several commercial fillers. (B) The adhesive force of ODTs contained different commercially ready to fill excipients. Data are presented as mean ± SD (n = 3).*

#### *4.2.2.4 The wettability of placebo orodispersible tablets*

A change to the excipients of the placebo tablets had some impact on the wetting time (Figure 4.8 A). The longest wetting time of all the placebo tablets was 26.6 ± 0.5 seconds for GNF-215. The wetting time of Hisoard and Smartex tablets (c.a 20 ± 1 seconds) were comparable to that for GNF-211 tablets (17.6 ± 1.3 seconds). The water absorption ratio was also impacted by changing the contents of the placebo tablets, as shown in Figure 4.8 (B). The water absorption ratio of the Smartex tablet was significantly lower (% 49 ± 4) than that of tablets made using the Hisoard (% 120.5 ± 2) and Granfiller-D (c.a % 90.3 ± 1) excipients. The lack of MCC in the content of Smartex tablets may explain the low absorption ratio, because MCC is well known for its large surface area and porosity. MCC is a popular binder excipient for ODTs because of its high water-absorption capacity within the inter-particle porosity (162).

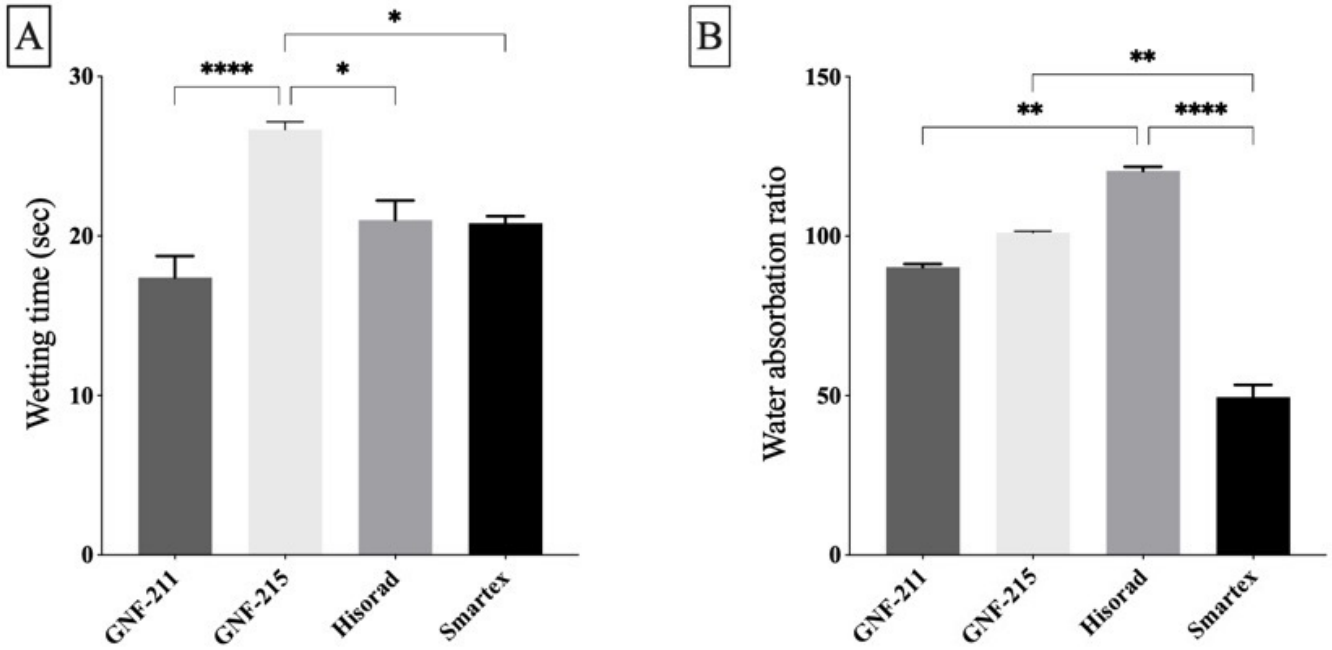


**Figure 4.8. wettability of orodispersible tablets contained different commercial ready to fill excipients.** *Wettability was assessed by measuring (A) the wetting time (B) the water absorption ratio. Values represent the mean ± SD of n = 3. Results were analysed using a Kruskal-Wallis statistic with Dunn's multiple comparisons test (GraphPad Prism 9.3.1). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, **** P ≤ 0.0001.*

## 4.3 Conclusions

This chapter has examined the use of a variety of instrumental techniques to evaluate the texture and characteristics of commercially available ODTs and placebo ODTs made of different types of commercially available fillers. The results have revealed that the commercially available ODTs and ready to fill excipients are different regarding the characteristics and texture. A similar use of excipients in tablets, such as mannitol and MCC, does not necessarily imply that the tablets will have the same features and textural attributes. The source and grades of the excipients, as well as the method of preparing the tablets, are all potential factors that can alter the tablets' characteristics. The main variables that differed between the tablets was not only disintegration, but also a variety of textural characteristics such as residue, hardness, and wettability. It is critical to monitor and balance the various tablet features in order to have excellent tablets that rapidly disintegrate and that also have excellent textural properties. Aside from the findings presented in this chapter, there is still the need to develop a better understanding about how the characteristics of ODTs and fillers can have an important influence on mouthfeel that is acceptable to patients, and, therefore, influence patient adherence.

The mouthfeel and acceptance of several placebo ODTs will be explored in the next chapter which presents a sensory study of ODTs that was undertaken in human volunteers.

# Mouthfeel and Acceptability Assessment of Placebo Orodispersible Tablets – *In Vivo* study

## 5.1 Introduction

Acceptability confirmation is a crucial step in the pharmaceutical development process. Patients' acceptance of their medicine must be carefully considered when developing pharmaceutical dose forms (35). Acceptability testing is indicated at several stages throughout the drug development process, particularly with the early stages. These kind of early evaluations can identify and resolve acceptability problems before proceeding to acceptance trials with patients as the end-users (108). Despite the current rise in awareness of assessing acceptability and palatability, there is a shortage of knowledge to carry out efficient trustworthy assessment. The mouthfeel that results from consuming any oral/enteral formulation has a significant influence on acceptability. Mouthfeel is a key feature of acceptability that must be evaluated, particularly for solid dose forms that will be dispersed in the mouth (105). Several acceptability aspects, including ease of swallowing (16) and patient adherence (72), have been shown to be enhanced by the use of ODTs. However, the development of acceptable ODTs is significantly hampered by a lack of knowledge regarding the ODT properties that are most likely to influence mouthfeel attributes and patients' preferences. By establishing a relationship between these attributes and ODTs' general acceptability, we may learn more about what factors are contributing to their acceptability. According to a previous study, roughness was suggested to have an impact on mouthfeel (46). However, there is a need for further research in the field of evaluating mouthfeel of ODTs to study further mouthfeel attributes.

The difficulty of conducting sensory study is exacerbated by the limited guidelines of proper methodologies to conduct such studies in the pharmaceutical industry. This study will attempt

to investigate the most expected mouthfeel attributes influencing ODT acceptability while trying to minimise the load on participants. This can aid in the development of useful approaches for studying sensory perceptions and advancing the field.

### 5.1.1 Aims of the sensory study

**Main aims**

1) Evaluate numerous key mouthfeel attributes that can influence the acceptability of small placebo ODTs.
2) Assess the overall acceptance of small placebo ODTs utilising sensory evaluation techniques.

**Secondary aims**

1) Determining if the mouthfeel properties influence the ease of administration of ODTs in term of the need to drink water.
2) Determine the previous mouthfeel issues experienced by participants, and whether it may impair their acceptance of ODTs.

## 5.2 Study design and procedure

Mainly, the study's approach is based on techniques used when assessing the sensory properties of foods. A crossover single-centre design was used to investigate how healthy people perceived the mouthfeel of placebo ODTs. Previous studies suggestions (102, 163), literature reviews on oral medicine sensory assessments (77, 164), and the feedback of an expert in the field (H Batchelor, personal communication, March 31, 2021) all had a part in the design of this study. The mouthfeel and palatability of the ODTs were evaluated in healthy adult participants using a 5-point facial hedonic scale which is one of three tools suggested by a previous acceptability study (115).

### 5.2.1 Ethical compliance

The protocol of this study was reviewed and approved by the Ethical Review Committee at the University of Birmingham (ERN_21-1018).

### 5.2.2 Participants

Participants in this study included healthy adults (18 years old or above). The required sample size of participants was determined using outcomes of similar previous acceptance studies. Based on effect size needed to find a difference between roughness mouthfeel of two groups of ODTs (46), sample size was calculated using g*power ($p<0.05$, power > 0.95%, and power level of 0.8) (165). This requires 23 evaluations for each group of sample. Since each adult participant would receive a total of three tablets for the entire study, a total of 30 people were required to allow for equal groups for randomisation. Participants were recruited through online advertisement and advertisement on pertinent noticeboards and in online newsletters sent to staff working in the College of Medical and Dental Sciences (University of Birmingham), as well as through networks connected to the research team.

Every interested participant received an electronic copy of a detailed participant information sheet (see Appendix A), and were given sufficient time to read and ask questions prior to taking part in the study. Adult participants were requested to read the participant information sheet and to determine their own eligibility before being scheduled for the study. Exclusion criteria included reported allergies or hypersensitivities to any of the ingredients, smoking, health conditions that might affect taste or smell, and lactose intolerance. Table 5.1 lists the inclusion and exclusion criteria for this study.

On the day of the study, the eligibility of participants was confirmed and documented using an assessment form by inquiring if they meet inclusion/exclusion criteria (see Appendix B). Prior to the start of the study, the aims and details of the research were explained to each participant verbally. Eligible participants were asked to read and sign the printed consent form and were provided with copies of the consent form and participant information sheet (Appendix C).

**Table 5.1 The inclusion criteria and exclusion criteria for participating in this study.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Healthy participants | Swallowing impairment for any reason |
| Adults (18 years old or above) | Lactose intolerance |
| Able to read and understand the participants information sheet | Any reported allergy/hypersensitivity to tablets ingredients |
| Participant is willing and able to give informed consent for participation in the study | Non-English speaking and has no-one with them to translate |
| | Does not consent to participate in the study |
| | Reported illnesses, or other conditions that may compromise their taste or smell |
| | Smoker |

## 5.3 ODT formulations

This study compared the mouthfeel of three placebo flat round (8 mm) ODTs that appeared identical (Figure 5.1). The placebo ODTs used in the study were made by direct compression of ready-to-fill excipients designed specifically for ODTs. Table 5.2 shows the composition of the different ODTs used. The samples were supplied free of charge by Chemlink Specialities Harke Group (Chemical supply and distributor, Manchester, UK). Safety data sheets and compliance declarations attesting to their appropriateness for human sensory testing were provided (Appendix E).

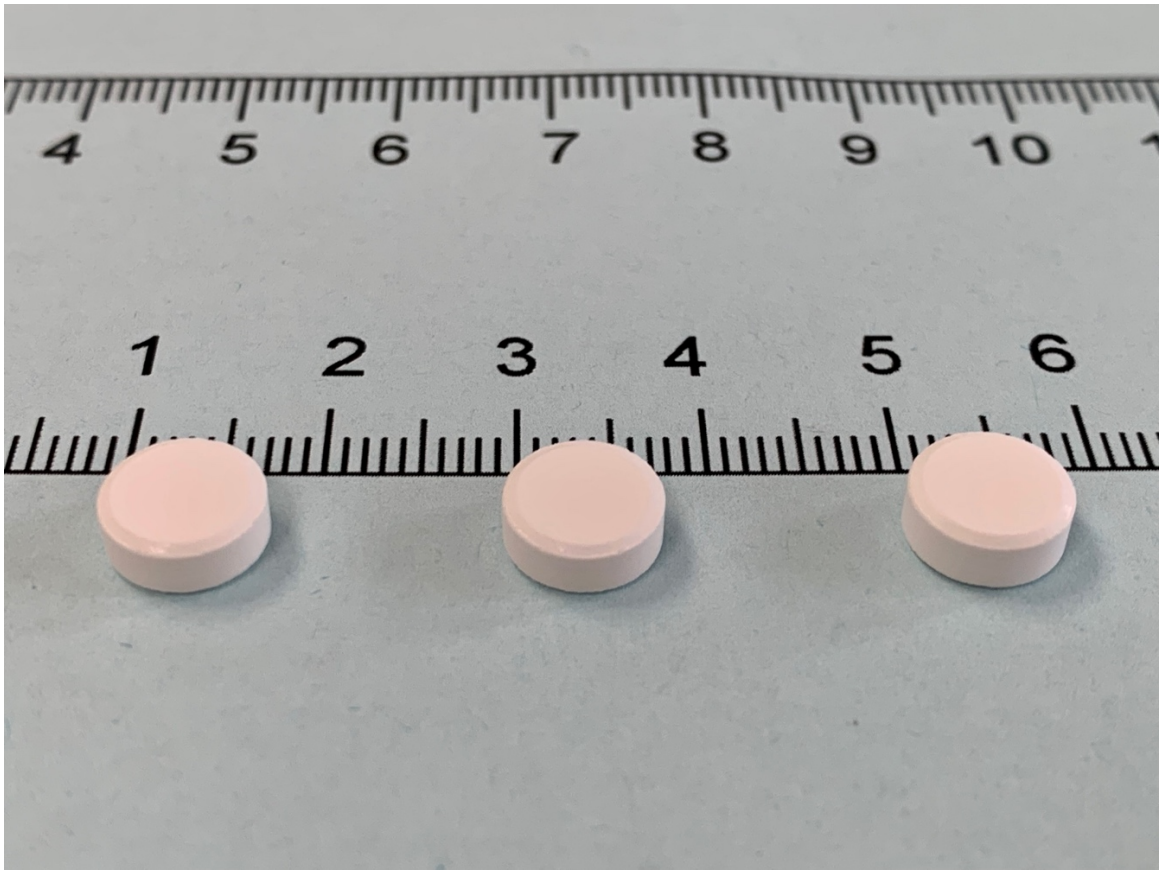


**Figure 5.1 The physical appearance of the placebo orodispersible tablets utilised in this study.**

**Table 5.2 The details of composition (excipients and median particle size) of placebo orodispersible tablets and their shape and weight.**

| Placebo ODTs | Composition | Median particle size | Tablet's weight, diameter and shape | Product Manufacturer |
|---|---|---|---|---|
| **Granfiller (GNF-211)** | D-mannitol, microcrystalline cellulose, carmellose, crospovidone, sucralose, and calcium stearate | 100μm | 200 mg, φ 8 mm, flat bevelled edge | Daicel Corporation |
| **Granfiller (GNF-215)** | D-mannitol, microcrystalline cellulose, carmellose, crospovidone, sucralose, and calcium stearate | 140μm | 200 mg, φ 8 mm, flat bevelled edge | Daicel Corporation |
| **Hisorad (HSR-D03)** | D-mannitol, microcrystalline cellulose, croscarmellose sodium, sucralose, and stearyl fumarate sodium | 106 μm | 200 mg, φ8 mm, flat-bevelled edge | Shin-Etsu Chemical Co., Ltd. |

## 5.4 Sensory study

The research was conducted at the University of Birmingham in an appropriate room. Data was collected from a single or a maximum of three simultaneous participants at various times during the day. Each session lasted a maximum of 45 minutes and provided an opportunity for participants to ask questions before confirming their enrolment and to provide feedback at the end. After providing informed consent, participants completed a questionnaire regarding their demographics (age, gender, and ethnicity) and any past mouthfeel issues (Appendix E). Before assessing each tablet, the participants were provided with plain crackers and a cup of spring water (at room temperature) as a palate cleanser. Using a palate cleanser allows all sensory

assessments to be made from a consistent baseline, and helps to remove saliva and sample residuals (166).

Each subject received three tablets in a random sequence. Randomization was applied to provide a variety of tablet evaluation sequences, using a predefined randomization list based on the number of participants, to reduce sequential influence (Appendix F). The randomization was performed by assigning the number of participants to groups of all possible sequences using the CHOOSE(ROUNDUP(RANK(RAND() function in MS Excel. This technique ensures that each serving sequence receives the same number of evaluations, hence minimising carry-over effects (106). Participants were instructed to take one tablet at a time and place it on their tongue to begin the mouthfeel test. The instructions permitted slight tongue movements but not excessive pressure on the tablets to speed up disintegration, such as chewing or sucking the tablets. Then, participants were asked to record the time between taking the tablet and perceiving that it had fully disintegrated. Participants were directed to stop the stopwatch when they could no longer feel the presence of big fragments on their tongue. Drinking water was accessible for rinsing the mouth and removing any residue. The participants were given cups with lids to spit out rinsing water and any residue that formed upon disintegration. The amount of water required to rinse the mouth and eliminate the residue was determined by comparing the mass of the cup of water, offered for this purpose, before and after each tablet was evaluated. Lastly, they were given time to assess several mouthfeel attributes and express their overall acceptance of the tablet on a 5-point scale; also, there was a section for additional written (free-text) feedback regarding any extra mouthfeel description at the end of the survey (Appendix E).

During the study, the researcher utilised a 7-point tick chart to note any negative verbal or facial reactions from participants (Appendix B). The descriptors for each negative reaction were

adapted from previous food and pharmaceutical sensory studies (107, 167). The overall number of negative expressions was determined to measure a participant's reactions and sample preferences. A larger overall number of negative reactions suggests that participants were less likely to prefer samples.

## 5.5 Data analysis

The data of a participant would be excluded only if the protocol was not followed. In this study, no responses were excluded on that basis. Participants had the right to withdraw at any time and up to 30 days after data collection, but there were no withdrawals from the study. Participants' responses on a 5-point facial scale were converted into scores ranging from 1 to 5 (e.g., sad face transformed to 1 and joyful face transformed to 5). A Friedman test was performed to detect differences in participant responses to each mouthfeel assessment. For pairwise comparisons, Wilcoxon's signed rank test was used. When pairwise comparisons were performed, the Bonferroni correction to the p value was applied (0.05 divided by number of tests) to allow for the consideration of the consequences of repeated testing. Also, Spearman's correlation coefficient ($r_s$) was also employed to identify correlations between the different metrics (e.g. mouthfeel responses, overall acceptance, negative facial reactions scores, and disintegration time). Spearman's correlation coefficient ($r_s$) is a measure of the monotonic association between two variables and is expressed as a value between - 1 (negative associations) and +1 (positive associations). All analysis was conducted at a significance level of $p < 0.05$. The SPSS statistical software, version 28.0, was utilised for the statistical analysis.

## 5.6 Results and discussion

### 5.6.1 Population demographics

The research recruited 30 adult volunteers ranging in age from 19 to 66 years. 60% (18/30) of the participants were male, and 50 % were between the ages of 25 and 34. Table 5.3 provides the demographic information from the questionnaires as well as whether participants have previously had mouthfeel issues with oral medications.

**Table 5.3 Data from a background section of a survey given to the participants.** *(n=30).*

| Demographic/ Number of participants | Frequency | Percent (%) |
|---|---|---|
| Age groups (years) | | |
| 18-24 | 2 | 6.67 |
| 25-34 | 15 | 50 |
| 35-44 | 8 | 26.67 |
| 45-54 | 1 | 3.33 |
| 55-64 | 2 | 6.67 |
| >65 | 1 | 3.33 |
| undisclosed * | 1 | 3.33 |
| **Gender** | | |
| Male | 18 | 60 |
| Female | 12 | 40 |
| **Ethnicity** | | |
| Arab | 8 | 26.67 |
| Asian | 11 | 36.67 |
| Black | 2 | 6.67 |
| White | 6 | 20 |
| undisclosed * | 3 | 10 |
| **Previous tablet mouthfeel issues** | | |
| No | 27 | 90 |
| Yes | 3 | 10 |

*The participant chose not to respond to the question.

### 5.6.2 *In vivo* evaluation of mouthfeel and acceptability

Participants utilised a 5-points visual scale to evaluate mouthfeel and acceptability. Figure 5.2 compares the median results of the mouthfeel evaluation of three ODTs. The median scores and interquartile range (Q25, Q75) for each question based on mouthfeel evaluations of three ODTs are presented in Tables 5.4. Among the three ODTs, GNF-211 ODTs received slightly higher scores in the evaluations of residue, dryness, and any strong taste. Comparable ratings were assigned to the disintegration, roughness, hardness, and stickiness of all three ODTs. A substantially stronger taste was related to GNF-215 ODTs compared to ODTs of HSR-D03 ($p<0.0167$). After evaluating different mouthfeel attributes, the acceptability of each ODT sample was finally rated using a 5-point Likert scale. This was determined with the assumption that the participant would be more willing to take an ODT that would be extremely liked. GNF-211 ODTs had a slightly higher score in overall acceptability compared to GNF-215 and HSR-D03 ODTs (Figure 5.2 & Table 5.4).

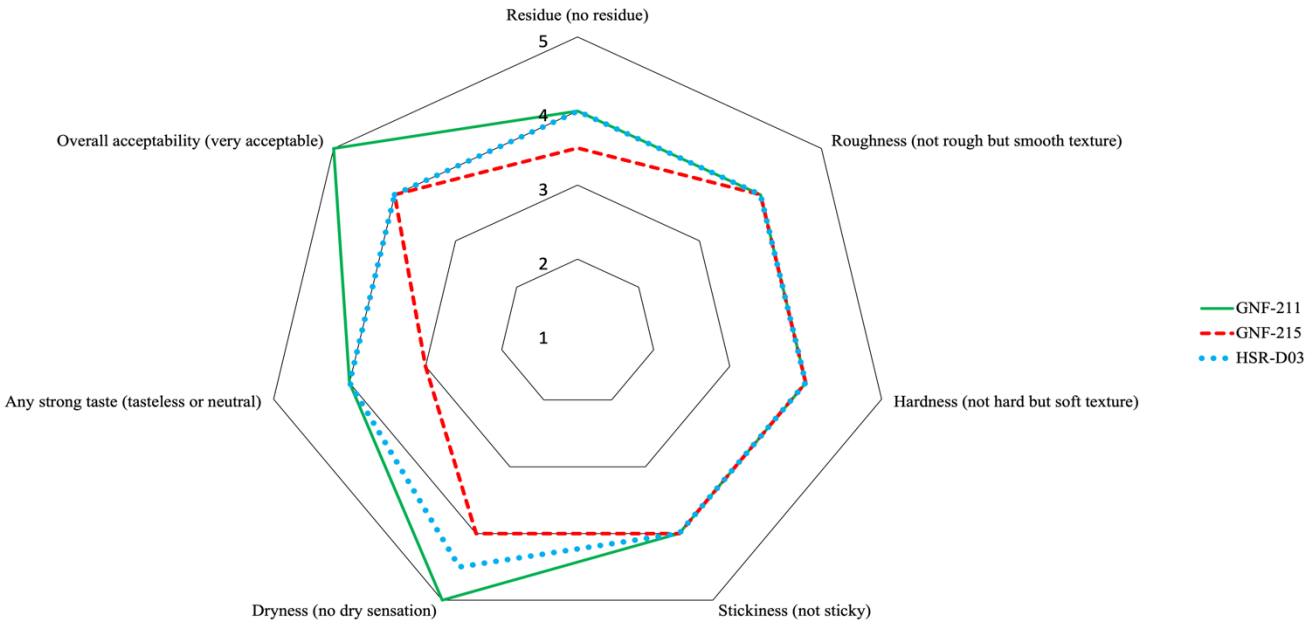


**Figure 5.25. Comparing the mouthfeel and acceptability of three ODTs using the median scores.** *. A score of 1 represents poor quality, while a score of 5 represents excellent quality (n=30).*

**Table 5.4 The median ratings and interquartile range (Q25, Q75) for each question based on mouthfeel evaluations of three orodispersible tablets.** *For all evaluations except disintegration, which was evaluated on a time scale (sec), a score of 1 indicates poor quality and a score of 5 indicates excellent quality. The median scores that shared a letter (b) are significantly different based on Wilcoxon test (p<0.0167 after Bonferroni correction) (n=30).*

| Mouthfeel attributes | GNF-211 | | | GNF-215 | | | HSR-D03 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Median | Q25 | Q75 | Median | Q25 | Q75 | Median | Q25 | Q75 |
| **Disintegration (sec)** | 27 | 21 | 46.5 | 30 | 24.5 | 39.25 | 29 | 21 | 47 |
| **Residue** | 4 | 2 | 4 | 3.5 | 2 | 4 | 4 | 2.75 | 5 |
| **Roughness** | 4 | 3 | 5 | 4 | 3 | 5 | 4 | 3 | 4 |
| **Hardness** | 4 | 3 | 5 | 4 | 3.75 | 5 | 4 | 3 | 5 |
| **Stickiness** | 4 | 3 | 5 | 4 | 3 | 5 | 4 | 3.75 | 5 |
| **Dryness** | 5 | 4 | 5 | 4 | 3 | 5 | 4.5 | 3.75 | 5 |
| **Any strong taste*** | 4 | 2 | 4.25 | $3^b$ | 2 | 4 | $4^b$ | 3 | 5 |
| **Acceptability** | 5 | 4 | 5 | 4 | 4 | 5 | 4 | 3.75 | 5 |

* The mouthfeel attribute was found significantly different based on Friedman test ($p<0.05$). The samples sharing a (b) were significantly different based on pairwise comparisons using Wilcoxon's signed rank test ($p<0.0167$).

### 5.6.3 Mouthfeel attributes influencing acceptability of orodispersible tablets

There were significant and moderate correlations between acceptance scores and various mouthfeel attributes, despite the minor sample differences (Table 5.5). In general, a participant's acceptability of the ODT samples was influenced by the anticipated attributes (residual amount, roughness, hardness, stickiness, dryness, and taste intensity). This highlights that several mouthfeel attributes are important in determining whether or not an ODT would be accepted by consumers. This suggested that ODT acceptability was impacted not only by its taste, but also by a combination of various mouthfeel attributes.

Tables 5.5 displays several significant correlations between the responses of adults (n = 90) to rank different mouthfeel attributes. Some of the significant correlations are as follows:

- The less amount of residue, the less rough the sample was felt ($r_s = 0.400$, $p<0.01$).
- The less hardness, the less rough the sample was felt ($r_s = 0.519$, $p<0.01$).
- The less rough ($r_s = -0.542$, $p<0.01$) / hard ($r_s = -0.333$, $p<0.01$) / sticky ($r_s = -0.403$, $p<0.01$) the sample was felt, the more acceptable it was ranked.
- The less residue ($r_s = -0.345$, $p<0.01$) and dryness feeling ($r_s = -0.493$, $p<0.01$), the more acceptable the sample was ranked.
- The less roughness ($r_s = 0.207$, $p<0.05$), dryness ($r_s = 0.349$, $p<0.05$), and strong taste ($r_s = 0.261$, $p<0.05$) was felt, the less amount of water (urge to drink) was needed.

In addition, the researcher counted the number of unpleasant facial expressions to determine whether participants were unhappy with the provided tablet. The total number of dislike expressions suggested which samples were less acceptable. Even though limited facial expressions were shown by adult participants, some facial expressions were observed such as

pursed lips and nose wrinkles (Table 5.6). The most prevalent facial expression was a pursed lip (seen in 5.6% of the tablet's assessments). GNF-215 ODTs were linked with slightly more negative facial expressions (7 expressions) than GNF-211 (5 expressions) and HSR-D3 (4 expressions).

**Table 5.5 Correlations between *in vivo* assessments of mouthfeel, taste, negative facial expression, amount of water (urge to drink) and acceptability**. *Data analyses are shown using Spearman's coefficient (n=90).*

| Mouthfeel attributes | Residue | Roughness | Hardness | Stickiness | Dryness | Any strong taste | Acceptability |
|---|---|---|---|---|---|---|---|
| **Residue** | -- | | | | | | |
| **Roughness** | 0.400** | -- | | | | | |
| **Hardness** | 0.179 | 0.519** | -- | | | | |
| **Stickiness** | 0.264* | 0.282** | 0.101 | -- | | | |
| **Dryness** | 0.035 | 0.227* | 0.061 | 0.332** | -- | | |
| **Any strong taste** | 0.032 | 0.149 | 0.096 | 0.230* | -0.053 | -- | |
| **Acceptability** | -0.345** | -0.542** | -0.333** | -0.403** | -0.493** | -0.246* | -- |
| **unpleasant facial expression** | 0.245 | 0.161 | 0.104 | 0.374* | 0.306 | 0.393* | -0.216* |
| **Amount of water (urge to drink)** | 0.115 | 0.207* | 0.173 | 0.012 | 0.349* | 0.261* | -0.254 |

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

**Table 5.6 The negative facial expressions observed on adult subjects during the mouthfeel evaluations of three placebo orodispersible tablets.** *Data are displayed as the frequency of each expression (n=90).*

| ODTs / Negative facial expression | Voice's disgust | Pursed lips | Nose wrinkle | Brow bulge/lower (frown) | Eyes squeezed shut | Total negative responses |
|---|---|---|---|---|---|---|
| **GNF-211** | 1 | 2 | 1 | 0 | 1 | 5 |
| **GNF-215** | 1 | 2 | 1 | 1 | 2 | 7 |
| **HSR-D03** | 0 | 1 | 1 | 2 | 0 | 4 |
| **Total** | 2 | 5 | 3 | 3 | 3 | 16 |

The findings of the examination of the mouthfeel and acceptance were comparable between men and women. Females, on the other hand, may have been more sensitive to the acceptability and mouthfeel attributes. This was highlighted by the fact that women evaluated acceptability and numerous mouthfeel parameters, such as residue, roughness, and taste, more negatively than males (Table 5.7). For example, 30.6% of female participants assessed the residue with a score of 2 or 1, which were considered negative responses, compared to 24.1% of male participants who gave the same scores. Similarly, 16.7% of women gave negative ratings (1, 2) for overall acceptability, whereas only 7.4% of males did so. Additionally, all previously reported mouthfeel/texture issues were ("sandy", "bulk residue", "chalky") identified by female participants. This is consistent with the observation that females can be more sensitive to the texture of coated tablets and their scores can be a reliable estimation of how children sense bitterness (163). However, male rated other mouthfeel attributes more negatively than female such as hardness, stickiness, and dryness. Food research revealed that gender can influence the detection of taste, smell, chewiness, and touch-feeling (shape), but not the perception of astringency and mouth irritation (168). This indicated the complex of mouthfeel assessments and the need to consider gender as an important variable.

**Table 5.7 The relationship between the gender of the participants and their scores to the mouthfeel assessments of placebo orodispersible tablets.** *Data were shown as frequency and percentages of positive and negative scores based on the gender (n=90).*

| Mouthfeel / Gender | | Female | | | Male | | |
|---|---|---|---|---|---|---|---|
| | | Count | % Within Gender | % Of Total | Count | % Within Gender | % Of Total |
| **Residue** | **Negative scores (1-2)** | 11 | 30.6% | 12.2% | 13 | 24.1% | 14.4% |
| | **Positive (3-5)** | 25 | 69.4% | 27.8% | 41 | 75.9% | 45.6% |
| **Roughness** | **Negative scores (1-2)** | 8 | 22.2% | 8.9% | 8 | 14.8% | 8.9% |
| | **Positive (3-5)** | 28 | 77.8% | 31.1% | 46 | 85.2% | 51.1% |
| **Hardness** | **Negative scores (1-2)** | 4 | 11.1% | 4.4% | 11 | 20.4% | 12.2% |
| | **Positive (3-5)** | 32 | 88.9% | 35.6% | 43 | 79.6% | 47.8% |
| **Stickiness** | **Negative scores (1-2)** | 3 | 8.3% | 3.3% | 8 | 14.8% | 8.9% |
| | **Positive (3-5)** | 33 | 91.7% | 36.7% | 46 | 85.2% | 51.1% |
| **Dryness** | **Negative scores (1-2)** | 2 | 5.6% | 2.2% | 10 | 18.5% | 11.1% |
| | **Positive (3-5)** | 34 | 94.4% | 37.8% | 44 | 81.5% | 48.9% |
| **Any strong taste** | **Negative scores (1-2)** | 10 | 27.8% | 11.1% | 12 | 22.2% | 13.3% |
| | **Positive (3-5)** | 26 | 72.2% | 28.9% | 42 | 77.8% | 46.7% |
| **Acceptability** | **Negative scores (1-2)** | 6 | 16.7% | 6.7% | 4 | 7.4% | 4.4% |
| | **Positive (3-5)** | 30 | 83.3% | 33.3% | 50 | 92.6% | 55.6% |

In food developments studies, texture and mouthfeel have earned considerably more consideration than in the drug development field (109, 169). Food texture is recognised to influence consumer product selection (170, 171). In pharmaceutical development studies, palatability is frequently evaluated as the overall acceptance quality without consideration of the dosage form's variables in determining user preference. There are limited studies that correlate a specific mouthfeel characteristic with a consumer's choice or acceptance of an oral medication. This type of research could be limited by the variety of oral formulations, varying times of residence in the mouth, and a tendency to focus on the matter of taste.

Understanding the relationship between taste, texture, mouthfeel, and acceptability is critical, particularly for ODTs that disintegrate in the mouth. Due to the complexity of the textural properties that may affect the mouthfeel and acceptability of ODTs, various assessment approaches may be necessary to identify these features. Several mouthfeel features, including sweet taste, disintegration time, volume of residue and roughness, have been highlighted in the literature as crucial for the palatability and acceptability of ODTs (46, 81). This chapter support those findings and highlights the potential effect of additional mouthfeel attributes, including hardness, stickiness, and dryness. To improve ODT's acceptance, additional research is required to determine all possible mouthfeel attributes and which textural features induce those feelings.

## 5.7 Study limitations

This study has certain limitations. Firstly, the provided tablet samples didn't actually represent commercially available ODTs. The placebo ODTs had a high degree of similarity in composition, and overall appearance. This was due to the difficulty of using actual ODTs (containing drugs) and the incorrect use of the term orodispersible tablets for certain commercial vitamin tablets, which are in fact chewable tablets. Second, rating the samples

mostly dependent on participant understanding because there was no standard reference to determine the maximum or minimum attribute intensities. This was driven by a lack of trained experts in the field of pharmaceutical formulations to conduct this type of studies. Consequently, different ODT samples and a larger number of participants are needed beside a more advanced model to validate the ability of used *in vitro* methods to predict mouthfeel of ODTs. In addition, advanced statistical analysis might be required rather than linear correlation which could not be performed in this study due to the previously mentioned limitations.

# Overall conclusions and future work

Patient perceptions and attitudes about ODTs were explored employing knowledge derived from the field of sensory analysis in food and pharmaceutical sciences. A wide range of conventional ODTs were investigated *in vivo* and *in vitro*, with encouraging results from existing and developed tools/methods. This chapter discusses the overall findings of this research and emphasises ideas for future investigations that might build on these findings.

## 6.1 Overall conclusions

### Importance of testing the acceptability using *in vitro* tools

The idea presented in this thesis is based-on-the-assumption that instrumental methods can generate data of the mouthfeel of ODTs. There are a variety of *in vitro* approaches for contributing mouthfeel to the physical properties of food samples, such as textural assessment for explaining chewiness and stickiness, as described in the current literature. Thus, methods used from the food industry were modified for evaluating orally pharmaceutical formulations. The development of *in vitro* techniques enables adaptation to oral cavity bioenvironmental conditions, such as the presence and volume of saliva and the applied force of tongue movement. The TA, among other tools, was able to examine numerous physical and textural aspects of the ODTs. In addition to its adaptability to mouth conditions, the TA enables direct evaluations of elements associated with mouthfeel attributes, such as disintegration, residue, and hardness. The usage of TA during the creation of ODTs may aid in developing an optimal formulation and producing ODTs with improved mouthfeel. Textural characteristics can be enhanced by managing and balancing the components as well as the process of making the ODTs.

Textural evaluations revealed that commercially available fillers and ODTs had distinct characteristics. The differences were associated with the frequent use of several excipients such as mannitol, known to have pleasant mouthfeel, in the commotions of the commercial products. Limited research has been conducted on the mouthfeel and acceptance of commercial ODTs. The variances in textural and physical characteristics may indicate diversity in mouthfeel and consequently acceptance of commercial ODTs. The use of *in vitro* tests in the production of ODTs can aid in determining the factors that influence the physical and textural characteristics of the tablets, as well as their acceptability among end users.

## Importance of considering mouthfeel attributes during acceptability assessments

In this work, a sensory investigation (*in vivo*) was conducted to investigate the mouthfeel attributes and acceptability of three different placebo ODTs. To obtain a comprehensive picture of the sensory experience during the ODTs consumption, the participants were asked to evaluate a variety of mouthfeel characteristics. Combining the findings together, several attributes had an influence on overall acceptance of the examined ODTs. A decrease in perceived roughness, hardness, stickiness, residue, and dryness was linked to a higher acceptance. The findings highlighted the need of distinguishing between taste and mouthfeel attributes, and complexity of this kind of study which emphasises the need for standardised methods. Despite the small differences between the examined placebo ODTs, the participants were able to rate one sample more positively than the others. Thus, it is important to assess the mouthfeel and acceptability of the target population while keeping in mind the gender as a possible influencing determinant.

This thesis has repeatedly emphasised the multifactorial nature of acceptance. The appropriate evaluation of acceptability goes beyond a simple yes/no inquiry. The difficulty of the sensory

studies is augmented by the diversity and complexity of the mouthfeel attributes. It may be helpful for pharmaceutical product development if the criteria used to determine acceptance were more specific to an oral dosage form. This research has attempted to highlight and improve the understanding of certain mouthfeel characteristics for ODTs. This might improve the formulation by identifying the variables that influence certain mouthfeel characteristics and, by extension, the level of acceptability. This research has attempted to identify the gap in information that may reduce a formulation's acceptance, present information on various ways to measure textural and mouthfeel, as well as present information of potential manufacturing factors that can be controlled to improve mouthfeel and acceptability of ODTs.

## 6.2 Future work

### Improvement of laboratory methods

Throughout the completion of this thesis, answers were sought to a number of questions, and new questions have been generated. Multiple opportunities and further improvements for further studies have been uncovered by the results of this thesis. Sensory assessments using both instrumental and clinical methods will be at the centre of future studies. More research could improve the TA to better imitate the oral cavity, such as the tongue surface and humidity. Furthermore, comparing various disintegrating media that better mimic the salvia may improve tool prediction, as well as employing the TA for other qualities that may be evaluated by this tool to reduce the number of tolls required.

### The need for reliable testing tools of acceptability

It may be simple to adapt more principles from the food sciences to enhance sensory evaluation of ODTs. It is crucial to identify the maximum value of each mouthfeel characteristic, as exceeding this value considers unpleasant and degrades the ODTs' acceptability. This may be

possible by utilising the findings of previous food research and developing expert-reviewed standard products to serve as a baseline against which new formulations must be tested. More research is required to bridge the gap between *in vitro* and *in vivo* approaches in order to confirm the potential of instrumental instruments to predict mouthfeel. In this respect there is the need to build an advanced model that takes-into-account multi-variables and that can be used for a broad range of ODTs.

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# Appendices

## Appendix A



UNIVERSITY OF BIRMINGHAM

**MAPOT – Mouthfeel and Acceptability of Placebo Orodispersible Tablets in adults**
**Participant Information Sheet – Sensory Evaluation Study**

Version 2.2, Dated: 22/11/ 2021
Research Team: Abdullah Asiri, Dr Geoff Brown, Dr Marie-Christine Jones

### 1. Invitation

You are invited to take part in a research study. Before you decide whether to take part, it is important for you to understand the purpose of this research and what it will involve. Please carefully **read** the following information, and you are welcome to **ask** if there is anything is not clear, or if you feel you need more details.

### 2. What is the purpose of the study?

The purpose of the study is to evaluate how you feel/sense the texture of orodispersible tablets, this kind of tablets tends to dissolve fast in the mouth without the need for water to swallow them, in the mouth (mouthfeel). Also, this study aims to examine if the change in the way we feel the tablets in our mouths can influence acceptability/palatability for adults. Evaluation the mouthfeel will include measuring several textural attributes of different orodispersible such as hardness. This sensory study would allow us to explore whether we can develop instrumental tests to predict the mouthfeel of orodispersible tablets.

### 3. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet, and you will be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you considered taking part in this study, you need to make sure your eligible and you met the following criteria:

- Adult (18 years old at least).
- Healthy.
- Non-smoker.
- You do not have any kind of swallowing impairments.
- You are not lactose intolerant.
- You don't have any reported allergy/hypersensitivity to the ingredients of the tablets.
- You don't have any reported illnesses, or other conditions that may compromise your taste or smell, such as COVID19.
- You can read and understand this study information sheet and consent form.

## 4. What will happen to me if I take part? What do I have to do?

After you sign the consent form, you will be invited to take part in the sensory study, which includes filling a paper-based structured questionnaire (accompanied by facial/visual analogue scales) immediately after sample intake. Also, you will be asked to provide a brief written description of the sample. A member of the research team will guide the study which will last up to 45 minutes.

In brief, you will be given 3 different orodispersible tablets in a random order and a paper-based structured questionnaire. In the beginning, you will be given some time to read the questions and understand what sensory attributes/features you will evaluate. For example, you will be asked to evaluate how hard or soft you felt the tablets were in the mouth. It is the researcher's responsibility to make sure you understand the questionnaire and you can ask for clarification at any time during the study. The questionnaire is built to be as simple as possible, and you will answer the questions by choosing a smiley face using a scale with 5-point smiley faces. Also, you will have the chance to freely describe how the tablets felt in your oral cavity.

Before taking each sample, you will be given some spring water in a cup and plain crackers (gluten-free version available) to remove saliva and any residuals from the samples and allow all sensory measurements to be made from a consistent baseline. After that, you will be asked to take one tablet at a time and place the tablet on your tongue without the need to bite, chew, or strongly move the tablet around your mouth. You will be asked to record the time (using the given timer) that the tablet takes to be fully disintegrated (the time from taking the tablets until you cannot feel any significant granules/parts are remaining on your tongue). Then, you should spit out the sample and start answering the questions. After each sample, you will be allowed to rinse your mouth with a given cup of spring water.

The information you give will remain confidential and will only be accessible to members of the research team. The study will be carried out in a dedicated room at the University of Birmingham and arranged conveniently for the people involved.

## 5. What are the possible advantages/disadvantages of taking part in this study?

By participating in this study, you will help us to understand the relation between how we feel the tablets in our mouths and the acceptability to take those tablets. Also, your participation will help us find out if we can assess the texture of the tablets from experiments conducted in the lab. This will allow us to evaluate whether the mouthfeel of ODTs can be predicted before giving them to patients and this will minimise the cost and efforts associated with medicine development. By participating in the study, you will be provided with a £10 voucher as compensation for your time.

Normally, tablets are made from active (the 'drug') and inactive ingredients that come together to form a medicine. In this study, we use only tablets which are placebo, this means they are made from inactive ingredients only, and the tablets does not contain any drug. Therefore, the risks of taking part in this study are limited. The size of the tablets is

small (smaller than M&Ms). Also, the tablets are designed to rapidly melt in the mouth, which minimises any choking risk. Even though there is no expected harm in swallowing the sample, you will be asked not to swallow the tablet, which might help you to concentrate on what you feel rather than getting distracted by swallowing the tablets.

This study will include only healthy adult volunteers who do not have reported allergies to any of the ingredients. The tablets have been made with well-known inactive ingredients that are commonly used in the medicinal and food industries which called excipients in the pharmaceutical field. The amount of the excipients within the tablets (d-mannitol, microcrystalline cellulose, croscarmellose, carmellose, polyvinyl alcohol , crospovidone, sucralose, calcium/ magnesium stearate) are small. These inactive ingredients/excipients do not have any therapeutic effects and are generally recognised as safe (GRAS) by the United States' Food and Drug Administration. These ingredients are important as they contribute to form the shape of tablets and can be useful for other reasons such as binding the ingredients together or breaking up the medicine at the right time. Even though the inactive ingredients are harmless, it is important to check the above ingredients especially if you have allergies to soy, dairy, gluten, or lactose.

## 6. What if there is a problem?

If you have a concern about any aspect of the study, you can contact the lead researcher Abdullah Asiri by phone at [redacted] or by email via [redacted] You can contact the researcher at any time (before or after the study) if you have any concern. Also, all research team members will do their best to answer your questions [redacted]. If you remain unhappy, you can withdraw from the study at any time. If you wish to withdraw, please let the lead researcher know by telephone or email. You can withdraw from the study at any point without giving an explanation. If you withdraw from the study after taking part, all your data will be deleted and the papers will be shredded unless it has been 30 days since you have participated in this study. In case the research team was not able solve your problem, you can contact the head of research governance and integrity at University of Birmingham via (Dr Birgit Whitman [redacted]).

## 7. Will my part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. If you consent to take part in this study, the information you have provided will remain strictly confidential at all times. Your personal details will not be passed to anyone outside the research team. In some cases, representatives of the University of Birmingham may require access to your information for audit purposes only. The information you have provided will be held securely on paper in a locked filing cabinet and electronically at the University of Birmingham on a password protected secure server. All data and participants information is protected according to university policies and General Data Protection Regulations 2018.

## 8. What will happen to the results of this study?

Only the findings of this study can be published on the website of the University of Birmingham and a medical journal publication or conference. Any personal data that can identify the participants will be destroyed and will not be published. Data of this study will be transformed into electronic versions and will only be held on university servers (All computers are password protected that are required for analysis purposes). The data will be stored as electronic files on University of Birmingham secure servers for ten years (in accord with The University of Birmingham' research data management policy') for research evidence to be accessible for verification purposes. Access to data will be limited to the research team and available to authorised researcher for verification. The electronic data will be destroyed in a secure manner ten years after the project presentation.

## 9. Who is organising this study?

The University of Birmingham will have overall responsibility for this study by acting as the research sponsor.

## 10. Who has reviewed the study?

An independent group of people has reviewed this study called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. The Research Ethics Committee has given this study a favourable opinion.

## 11. Contact for further information

You are encouraged to ask any question before or after completing the study. If you have any further questions about the study, you may contact the principal investigator via the contact details provided below.

Abdullah Asiri [redacted]
PhD Student
Room 363
School of Pharmacy
College of Medical and Dental Sciences
University of Birmingham
Birmingham
B15 2TT
Dr Geoffrey Brown [redacted]
Dr Marie-Christine Jones ( [redacted]

If you are happy to take part, then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the information sheet and consent form will be stored in the university and one will be retained in the research study files.

Thank you for taking the time to read this information sheet and for considering taking part.

## Appendix B

### Participant Assessment Sheet by Researcher

Participant number: .....

Sample group: .....

Confirmation of eligibility: .....

Water bottle/cup weight:
Before: .....  After: .....

| | Verbal and Physical responses | Mark if any is showed |
|---|---|---|
| First Sample | **Spits out** test sample before tablet completely disintegrated | |
| | **Voices** disgust | |
| | Verbal expressions | |
| | Pursed **lips** | |
| | **Nose** wrinkle | |
| | **Brow** bulge/lower (frown) | |
| | **Eyes** squeezed shut | |

| | Verbal and Physical responses | Mark if any is showed |
|---|---|---|
| Second Sample | **Spits out** test sample before tablet completely disintegrated | |
| | **Voices** disgust | |
| | Verbal expressions | |
| | Pursed **lips** | |
| | **Nose** wrinkle | |
| | **Brow** bulge/lower (frown) | |
| | **Eyes** squeezed shut | |

| | Verbal and Physical responses | Mark if any is showed |
|---|---|---|
| Third Sample | **Spits out** test sample before tablet completely disintegrated | |
| | **Voices** disgust | |
| | Verbal expressions | |
| | Pursed **lips** | |
| | **Nose** wrinkle | |
| | **Brow** bulge/lower (frown) | |
| | **Eyes** squeezed shut | |

Date: .....
Researcher's name: .....
Researcher's sign: .....

Version 2.2  1  22/11/2021

**Appendix C**

Consent Form

UNIVERSITY OF BIRMINGHAM

## MAPOT – Mouthfeel and Acceptability of Placebo Orodispersible Tablets in adults

**Consent Form**

Version 2.2, Dated: 22/11/2021

Research Team: Abdullah Asiri, Dr Marie-Christine Jones, Dr Geoff Brown,

Participant ID Number: _____

Please read the information below carefully and if happy to participate please initial the right-hand boxes. Then print your name and sign this form.

**Please mark ALL boxes**

1. I confirm that I have read and understand the participants information sheet dated: 22nd November 2021, version number 2.2 for the above project and have had the opportunity to ask questions, which were answered to my satisfaction. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time. ☐

3. I understand that even if I withdraw, the information provided will be used unless I specifically withdraw consent by notifying the lead researcher within 30 days after taking part in the study. ☐

4. I consent to the collection of personal information for the purpose of this project. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. I understand the information will be stored by the University of Birmingham for 10 years. ☐

5. I agree to take part in the project. ☐

Person giving consent
Print_____ Sign_____ Date_____
Person taking consent
Print_____ Sign_____ Date_____

The original consent form will be filed in the study file, with a copy provided to the participant together with the PIS.

**Appendix D**

DAICEL
The Best Solution for You

October 1st, 2019

To whom it may concern,

Re : Placebo tablets of Granfiller-D

Dear Sir/Madam,

We herewith confirm that the composition of placebo tablets of Granfiller-D is as follows.

Granfiller-D : 98.9%
Sucralose : 0.3%
Calcium Stearate: 0.8%

The placebo tablets are intended for sensory evaluation to feel rapid disintegration in oral cavity.

Sincerely yours,

[redacted]

Hideaki Yamamoto
Senior Manager
Pharma Solutions, New Business Development,
Daicel Corporation

April 30th, 2021

To whom it may concern,

Re : Placebo tablets of HiSORAD

Dear Sir/Madam,

We herewith confirm that the composition of placebo tablets of HiSORAD is as follows.

| | |
|---|---|
| HiSORAD | : 99.4% |
| Sucralose | : 0.1% |
| Stearyl fumarate sodium | : 0.5% |

The placebo tablets are intended for sensory evaluation to feel rapid disintegration in oral cavity.

Sincerely yours,

Yukiko Suganuma
Pharma Solutions, Business Development Center,
Daicel Corporation

## Appendix E

### Survey

**Participant number:** .....

**Sample groups:** ..... **Sample number:** .....

**Age:** .....

**Gender:** .....

**Ethnicity:** .....

**Previous tablet mouthfeel issues:** .....

| | | |
|---|---|---|
| 1) **How long** did the orodispersible tablet take to fully disintegrate? | ( ..... ) Secondes | |
| 2) Just before spitting out the sample, was the **amount of residue** high or low? | **No residue and complete dissolution**  | **Very high amount of residue** |
| 3) Was the **texture** of the sample **smooth** or **rough/gritty**? | **Very smooth texture**  | **Very rough/gritty texture** |
| 4) Was the **texture** of the sample hard or soft? | **Very soft texture**  | **Very hard texture** |
| **5)** Was the sample **sticky/adhesive**? | **No stickiness**  | Very sticky sensation |
| 6) Was there any **dry sensation** in the mouth after the administration? | **No dry sensation**  | **Very dry mouth sensation** |
| 7) Did the tablet administration associate with any strong **taste**? | **Tasteless/ neutral**  | **Very strong taste** |
| 8) How do you evaluate the general **acceptability/palatability** of the tablet? | **Very acceptable**  | **Very unacceptable** |
| 9) How do you describe the general mouthfeel of the tablet? Free text. | | |

## Appendix F

### Pre-Defined Randomization System

*Table 1: Pre-Defined Randomization System for all participants in this study.*

| Tablets | Code |
|---|---|
| Granfiller GNF 211 tablets | GNF 211 |
| Granfiller GNF 215 tablets | GNF 215 |
| HiSORAD HSR-D03 tablets | HSR-D03 |

| Groups | 1st Tablet | 2ed Tablet | 3ed Tablet |
|---|---|---|---|
| A | GNF 211 | GNF 215 | HSR-D03 |
| B | GNF 211 | HSR-D03 | GNF 215 |
| C | GNF 215 | HSR-D03 | GNF 211 |
| D | GNF 215 | GNF 211 | HSR-D03 |
| E | HSR-D03 | GNF 211 | GNF 215 |
| F | HSR-D03 | GNF 215 | GNF 211 |

| Participant number | Sample groups |
|---|---|
| 1 | A |
| 2 | A |
| 3 | D |
| 4 | B |
| 5 | A |
| 6 | E |
| 7 | C |
| 8 | E |
| 9 | F |
| 10 | A |
| 11 | D |
| 12 | B |
| 13 | F |
| 14 | E |
| 15 | E |
| 16 | F |
| 17 | C |
| 18 | B |
| 19 | C |
| 20 | B |
| 21 | D |
| 22 | A |
| 23 | C |
| 24 | D |
| 25 | C |
| 26 | F |
| 27 | D |
| 28 | F |
| 29 | B |
| 30 | E |