

**Better medicines for children:
Elucidating patient acceptability to guide
flexible solid oral dosage form design**

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Thesis submitted for the degree of Doctor of Philosophy

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September 2017

Declaration

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

September 2017

Acknowledgements

First and foremost, I would like to acknowledge the Centre for Doctoral Training in Targeted Therapeutics and Formulation Sciences for giving me the opportunity and financial support to conduct this research, with the funding provided by the Engineering and Physical Sciences Research Council (EPSRC grant: EP/I01375X/1). Thanks to all those who make this fantastic collaborative programme possible.

I would like to express my most profound gratitude to all those who accompanied, guided and supported me in this journey. In particular, to my PhD supervisors, Catherine Tuleu, Mine Orlu and Terry Ernest. I cannot possibly express in just a few lines my immense admiration. You make an exceptional team and your direction has been invaluable. Your devotion to making better medicines for patients is exemplary.

Special acknowledgements to the members of the SPaeDD-UK consortium who made possible the comparative acceptability study in adults and children, Hannah Batchelor, Punam Mistry, Joanne Bennett and Alastair Coupe (along with my PhD supervisors). Similarly, thanks to my colleagues who put their hard work into the (oro)dispersible tablets research, Ben Bowles, Karolina Dziemidowicz and Andrew Edwards. I would also like to thank the MSc and MPharm students who contributed to my work.

My sincere gratitude goes to all volunteers who participated in the sensory evaluation studies, for their selfless help to this research. Thanks to those who helped me hands on during the studies, Sejal Ranmal, Mariagiovanna Scarpa, Jessica Soto, Abeer Ahmed, Sara Hanning, Alex Keeley (and apologies to those who I may have failed to mention).

Thanks to those who made my life easier during the PhD, the Sensory Pharmaceuticals™ research group, inhabitants of Research Space 308, my flatmates of Mansão Ibérica, Los Boycarios, my London Family, my parents and my brother, and to Laura, who listened, supported, enlightened me and endured through my most crazy moments.

Abstract

A medicine will not elicit its desired therapeutic effect if the patient is not *able* or *willing* to take it. The specific needs of the target population must be taken into account in the design of medicines. Evaluation of the effect of formulation factors on patient's acceptability could guide the development of better medicines for children. Flexible solid oral dosage forms, including multiparticulates and (oro)dispersible formulations, offer advantages over conventional solid and liquid dosage forms to meet the needs of paediatric patients. These advantages include favourable stability profile, suitability for taste masking, flexibility of dose titration and convenient administration.

The overall aims of this research were to identify barriers for the development of acceptable medicines for children, to explore methodology for palatability and patient's acceptability testing and to generate evidence of acceptability of flexible solid oral dosage forms. Methodological tools for the assessment of palatability and acceptability were developed and the use of such tools was explored through a series of investigations in healthy volunteers using model placebo formulations. Pharmaceutical formulation work was performed to optimise formulation design and choice of excipients, integrating manufacturability and patient's acceptability criteria.

A direct comparison between palatability and acceptability outcomes in children and adults was performed, which highlighted the value of conducting studies in adults to provide initial guidance on formulation design. Some of the key formulation factors that affect acceptability of flexible solid oral dosage forms were identified, which can be used to guide the development of more palatable and acceptable medicines. This research also evidenced methodological barriers in the assessment of palatability and patient's acceptability which are thoroughly discussed in this thesis and will need to be overcome in the future. The knowledge generated by this research is applicable not only to the development of medicines for children, but also for other subsets of the population.

Impact statement

The lack of acceptable medicines for children is a burden to patients, caregivers and healthcare professionals. Medicines designed to meet the needs of the target patient population can facilitate administration and improve patient's adherence, having positive repercussions on the wellbeing of patients and the healthcare system.

Previous research suggests enormous cost-saving potential of dispensing solid dosage forms to children instead of liquids, indicating that the main limitation to this practice is the size of the solid formulations available (Lajoinie et al., 2014). Flexible solid oral dosage forms such as multiparticulates and (oro)dispersible formulations offer potential to overcome this barrier by providing ease of swallowing and facilitating administration. The present research continues to support the use of solid dosage forms in children by providing evidence of the suitability of multiparticulates in children (4-12 years).

The development of acceptable medicines for children must encompass a three-fold endeavour: (1) understanding patient needs, (2) optimising methodology and criteria for acceptability testing and (3) improving formulation design (Ternik et al., 2017). The research described in this thesis attempts to tackle these three forefronts. This research provides evidence to optimise methodology for palatability and acceptability testing and exemplifies the use of palatability and patient's acceptability studies to guide excipient selection and improve dosage form design.

As such, the evidence and knowledge generated in this research can be valuable to formulation scientist working on the development of future medicines for children and to regulatory agencies making decisions on marketing authorisations and PIP applications. Ideally, patient's acceptability should be measured as a secondary outcome in clinical trials and, hopefully, this research is a step forward in this process. The outcomes of this research will be informative to researchers and regulators with the aim to optimise methodology for the evaluation of palatability and patient's acceptability.

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Abbreviations

API	Active Pharmaceutical Ingredient
CDT	Centre for Doctoral Training
CG	Carrageenan gum
CI	Confidence Interval
CMC	Carboxy-Methyl Cellulose
CQA	Critical Quality Attributes
CTIMP	Clinical Trials of Investigational Medicinal Products
DT	Dispersible Tablet
EMA	European Medicines Agency
EPSRC	Engineering and Physical Sciences Research Council
ERN	Ethics Research Number
FDA	Food and Drugs Administration
FDC	Fixed-Dose Combination
GG	Guar Gum
GRAS	Generally Regarded As Safe
HPMC	Hydroxy-Propyl-Methyl Cellulose
IDDSI	International Dysphagia Diet Standardisation Association
JAR	Just About Right (scale)
L-HPC	Low-substituted Hydroxy-Propyl Cellulose
MCC	Microcrystalline cellulose
MAS	Medication Acceptance Scale
MCS	Manufacturing Classification System

NM.....	Not Measured
ODF.....	Oro-Dispersible Film
ODMT.....	Oro-Dispersible Mini-Tablet
ODT.....	Oro-Dispersible Tablet
PIP.....	Paediatric Investigational Plan
PSD.....	Particle Size Distribution
PVA.....	Poly-Vinyl Alcohol
PVAc.....	Poly-Vinyl Acetate
QTT.....	Quality Target Product Profile
REC.....	Research Ethics Committee
RPM.....	Revolutions Per Minute
SATMED-Q.....	Satisfaction with Medicines Questionnaire
SD.....	Standard Deviation
SEM.....	Scanning Electron Microscopy
SPaeDD-UK.....	Smart Paediatric Drug Development - UK
SSF.....	Sodium Stearyl Fumarate
TS.....	Tensile Strength
TSQN.....	Treatment Satisfaction Questionnaire for Medication
USP.....	United States Pharmacopoeia
VAS.....	Visual Analogue Scale
WHO.....	World Health Organisation
XG.....	Xanthan Gum
YPSG.....	Young Person's Steering Group

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“A problem well-stated is a problem half-solved”

Charles Kettering

Chapter 1

Introduction

This chapter introduces the background of the thesis. The current formulation strategies for the development of oral paediatric medicines are described and their benefits and limitations critically discussed. Then, considerations in the design and implementation of palatability and acceptability studies of medicinal products are explored. Finally, previous studies of acceptability of flexible solid dosage forms are systematically reviewed, with emphasis on methodological aspects as well as evidence of acceptability of different dosage form designs. After a detailed overview of the research field, scientific knowledge gaps are identified and the overall aims of the experimental work described within this thesis are outlined.

1.1 Formulating medicines for children

Paediatric patients require different oral medications than other subsets of the population due to their continuing development hence dosing and administration requirements (EMA, 2013). Conventional formulations are not designed for this patient group, thus manipulation and compounding of medicines, as well as unlicensed or *off-label* use, have become common practice (Conroy et al., 2000; Richey et al., 2013). Age-appropriate dosage forms developed to meet the needs of the paediatric population are therefore desired. Since the Paediatric Regulation (Regulation EC 1902/2006) came into force in Europe (and parallel regulations in other parts of the world), the development of medicines specifically designed for children is not only a moral but also a regulatory obligation. Companies willing to bring a new drug product into market need to consider the needs of paediatric patients under a Paediatric Investigational Plan (PIP) and to develop a specific formulation for children.

The development of pharmaceutical products is a challenging task due to the broad range of pharmaceutical and clinical aspects that must be considered to ensure the quality, safety and efficacy of the final product. The development of paediatric medicines is even more complex due to the additional needs and demands of this target population with respect to adults (van Riet-Nales et al., 2016). The numerous criteria that must be considered to meet with the needs of patients, caregivers, manufacturers and healthcare providers has been classified into three main categories: (i) factors related to efficacy and ease of use, (ii) those related to patient safety, and (iii) factors influencing the access of patients to medicines, as detailed in Table 1.1 (Sam et al., 2012).

Table 1.1. List of requirements for age-appropriate oral drug delivery systems, according to Sam et. al, 2012 (Sam et al., 2012).

Benefit/risk	Criterion for drug product	Product requirements
Efficacy/Acceptability	Dosage	Dose flexibility Acceptability of size/volume
	Preparation /administration	Easy and convenient handling Easily administered (correct use)
	Compliance	Minimal impact on lifestyle Acceptable appearance and taste Minimal administration frequency
Patient safety	Bioavailability	Adequate bioavailability
	Excipients	Minimal number of excipients Tolerability
	Stability	Stable during shelf life Stable in-use
	Medication error	Minimal risk of dosing error
Patient access	Manufacturability	Robust manufacturing process Commercial viability
	Affordability	Acceptable cost to patients/payers Easily transported and stored Low environmental impact

The pharmacokinetic and pharmacodynamic profile of a drug varies broadly depending on the developmental stage of a child, necessitating dose flexibility to suit the dosing requirements across all age groups (Batchelor and Marriott, 2013). Excipients commonly regarded as safe may represent a safety risk for children adding other considerations into the formulation development (Salunke et al., 2013). Palatability and ease of swallowing are also considered critical attributes for the acceptability of medicines intended for children, who possess distinct preferences and swallowing abilities than other subsets of the population. In many cases, the dependence on caregivers also influences the administration and acceptability of medicines (Ivanovska et al., 2014).

The manufacturing process of pharmaceutical products must be robust and able to deliver medicines of adequate quality at affordable price. Packaging and administration devices must be seen as an integral part of the product as these affect the overall quality, acceptability and cost (Kozarewicz, 2014; Wening and Breitzkreutz, 2011). The affordability of medicines is crucial for the development of pharmaceutical products for global market, including developing countries (Sosnik et al., 2012). The utilisation of cost-effective and readily-available technologies is desired to maximise the affordability and accessibility of medicines, which ultimately benefits patients. Therefore, balance between innovative technologies and patient access to medicines must be sought.

Considering the number of parameters that needs to be fulfilled, flexible technology platforms which enable the delivery of multiple drugs, dose strengths and release profiles should be prioritised to broaden acceptability to a larger population group (EMA, 2013; WHO, 2012). There are cases where paediatric age-appropriate formulations are not only favourable for children but also for other special patient groups, including elderly and adults with swallowing difficulties (Hanning et al., 2016; Liu et al., 2014). Targeting a larger patient population may improve the commercial viability of paediatric products but caution must be taken to ensure that this practice does not undermine the requirements of each patient group.

1.1.1 Limitations of conventional solid and liquid dosage forms

Liquid formulations have been, traditionally, the formulation of choice for paediatric patients, based on their suitability for dose titration (e.g. using an oral syringe) and ease of administration to young children compared to tablets or capsules. However, liquid dosage forms have several drawbacks with regards to patient's safety and acceptability. For instance, taste-masking of liquids is technologically challenging and poor taste of liquid medicines is perhaps the major barrier to patient's acceptability (Venables et al., 2015). Similarly, controlled release from liquid formulations is problematic, resulting in the need to administer multiple doses throughout the day. In addition, the stability of liquid medicines (physical, chemical and microbiological) is poor as compared to solid formulations. To overcome these challenges, additional excipients are often required, such as sweeteners to improve the taste and/or preservatives to improve stability. Unfortunately, these excipients often have poor and/or unknown safety profile, which can put patients at risk. Finally, liquid formulations are often more expensive to produce, store and transport, which poses an important barrier to improve access to age-appropriate essential medicines for young children, especially in low- and middle-income countries (Robertson et al., 2009).

Due to the inherent limitations of liquid dosage forms with respect to solid dosage forms, the efforts of formulation scientists have been directed towards the development of solid formulations over liquids. However, conventional solid dosage forms may not be suitable for paediatrics and other patients with swallowing difficulties, which results in the need for manipulation and compounding (Richey et al., 2013; Stegemann et al., 2012). Another limitation of conventional tablets is their poor flexibility of dose; inevitably pill splitting has become common practice to obtain various dose strengths, despite the safety and efficacy risk of this practice (Margiocco et al., 2009; van Riet-Nales et al., 2014). Smaller tablets and capsules emerge as an alternative to conventional solid dosage forms with improved dose flexibility and ease of swallowing. Several studies have

shown that pre-school children and neonates are able to swallow single mini-tablets (Klingmann et al., 2015; Spomer et al., 2012; Thomson et al., 2009). Nevertheless, the maximum dose that can be delivered by single-unit mini-tablets will always be limited by their small size and, in consequence, several of these small-sized tablets will be required to achieve the targeted dose. The administration of multiple mini-tablets is further discussed in the section dedicated to multiparticulate formulations.

1.1.2 The era of flexible solid dosage forms

In recent years there has been an increased focus on the development of age-appropriate formulations for children, supported by modifications in the regulatory framework (Turner et al., 2014). This has resulted in a noticeable increase in formulation designs that has been investigated and commercialised, including multiparticulate formulations, (oro)dispersible tablets, oral thin films and chewable formulations. Such solid dosage forms, which do not require to be swallowed whole, can be grouped under the definition of flexible solid dosage forms (WHO, 2012). These formulations may provide advantages over conventional solid and liquid medicines, facilitate administration to paediatric patients and improve patient's acceptability.

1.1.2.1 *Multiparticulate formulations*

Multiparticulate drug delivery systems are composed of multiple solid dosage units, such as pellets or mini-tablets. Multiparticulates, in the form of pellets or beads, are highly spherical granules of small diameter (typically below 1.5 mm) and narrow size distribution, usually prepared by fluidised bed technologies such as active layering or direct pelletisation (Priese et al., 2014). Mini-tablets can also be considered under the definition of multiparticulate formulations when administered in multiplicity; mini-tablets have a diameter of 1-3 mm and can be prepared using conventional tableting equipment fixed with specialised accessories (Tissen et al., 2011). Characteristic advantages and limitations of multiparticulate drug delivery systems are summarised in Table 1.2.

Table 1.2. Potential advantages and disadvantages of multiparticulates as a technology platform for the preparation of age-appropriate medicines for children.

Product characteristic	Advantages	Disadvantages
Efficacy/Acceptability		
Dosage	Excellent flexibility of dose Small size/swallowing is aided	Grittiness/mouthfeel may be an issue
Preparation	Flexibility of administration	Need for preparation or reconstitution
Compliance	Ease of functionalisation Suitable for taste masking	
Safety profile		
Bioavailability	Targeted release profiles can be achieved Avoidance of dose dumping	Co-administration with food/drinks may alter bioavailability
Excipients	Use of Generally Regarded As Safe (GRAS) excipients	
Stability		Food-drug compatibility needs to be studied
Medication error		Limited control over dose intake when mixed with food
Patient access		
Manufacturability		May need specialise equipment or accessories
Affordability	Manufacturing technology readily available	Packaging/dosing technology may need to be developed

Multiparticulate products are usually suitable for controlled release and taste masking by means of film-coating technologies, which can benefit patient's acceptability. Moreover, multiparticulates can be expected to be easier to swallow than monolithic dosage forms (i.e. tablets and capsules) based on their reduced size. However, there is a lack of evidence on the size and amount of multiparticulates that is acceptable to patients of different ages, although recent FDA guidance suggests a maximum size of 2.5 mm (FDA, 2012a). The quantity and size of multiparticulates given in a single dose can influence, not only the ability to swallow the formulation, but also the mouthfeel and overall palatability. Previous studies suggest that oral grittiness perception might be a barrier to palatability and acceptability of multiparticulates (Kimura et al., 2015; Lopez et al., 2016).

The multi-unit composition of multiparticulates offer attractive opportunities for the preparation of fixed-dose combinations and products with targeted release profiles which can reduce the burden of repeated administration (Desai et al., 2013). This can be achieved by simply combining multiparticulates with different APIs and/or different release characteristics into the same dosage form. An advantage of multiparticulates over single-unit formulations is that controlled release can be provided while avoiding the risk of dose-dumping (Abdul et al., 2010). Multiparticulates also offer potential for dose titration although this would require the utilisation of dosing devices to allow dose adjustment; research has been conducted in this direction with devices ranging from dosing spoons to electronic dispensers (Wening and Breitzkreutz, 2010)

Multiparticulates can be administered directly in the mouth or dispersed in a vehicle prior to administration as preferred; water, milk, juice or apple sauce are potential vehicles commonly proposed (WHO, 2009). The administration in admixture with food ('sprinkling') is often indicated to improve the organoleptic properties and thus the acceptability of these formulations. However, the need for product preparation may actually have a negative impact on the overall acceptability of the product as shown in recent studies (Den Uyl et al., 2010; MacDonald et al., 2006). Co-administration of drug products with food or drinks also poses safety concerns, such as poor control over dose intake and impact on drug's bioavailability (Batchelor et al., 2014).

1.1.2.2 (Oro)dispersible tablets

Dispersible and orodispersible tablets (DTs and ODTs) are designed to disintegrate within a matter of seconds, avoiding the need for swallowing the tablet as a whole (Liang and Chen, 2001). DTs are intended to be dispersed in a vehicle (typically water) before administration, whereas ODTs are designed to be dispersed directly in the mouth. In practice, ODTs may be dispersed directly in the mouth or pre-dispersed in a suitable vehicle, as preferred, offering great flexibility of administration. In some cases, when the disintegration/dissolution is sufficiently fast, the use of water can also be avoided. Owing

to these benefits, patients' acceptability and compliance can be improved with respect to conventional formulations. The main benefits and limitations of (oro)dispersible tablets as a formulation of choice for the paediatric population are summarised in Table 1.3 and are further discussed below.

Table 1.3. Potential advantages and disadvantages of (oro)dispersible tablets as a technology platform for the preparation of age-appropriate medicines for children.

Product characteristic	Advantages	Disadvantages
Efficacy/Acceptability		
Dosage		Various dosage strengths required
Preparation	Flexibility of administration Swallowing is aided Water is not required (ODTs)	Lack of mechanical strength
Compliance	Preferred over conventional formulations	Controlled-release is challenging Taste masking is challenging
Safety profile		
Bioavailability	May be improved by buccal absorption	
Excipients		Excipients of unknown safety profile may be required
Stability		Packaging and storage conditions can be critical
Medication error		Retention time in mouth may alter bioavailability
Patient access		
Manufacturability		Difficult to balance mechanical strength and fast disintegration
Affordability	Manufacturing technology readily available	Some technologies subjected to intellectual property rights

Although DTs and ODTs facilitate administration and swallowing, this formulation design does not bring an advantage in terms of dose flexibility with respect to conventional tablets, meaning that various dosing strengths would be required to fulfil the needs of all populations. DTs and ODTs are often porous and fragile (to aid quick disintegration),

thus tablet splitting is usually contraindicated which may further reduce dose flexibility (Buck and Health, 2013). To overcome these limitations, dose flexibility could be achieved via a multi-step process where the tablet is pre-dispersed in water and, subsequently, the required dose is measured and administered using an oral syringe, as indicated in a recently marketed ODT (FDA, 2012b). Alternatively, the preparation of 'orally disintegrating mini-tablets' (ODMT) is an interesting opportunity to combine the benefits of multiparticulates and ODTs (Stoltenberg and Breitzkreutz, 2011).

Since the drug is subject to the patients' taste buds in the mouth, taste masking is a requirement of orally disintegrating formulations with unpleasant tasting APIs. Improved palatability is traditionally achieved by addition of sweeteners and flavours to the formulation. However, the efficacy of this approach is often limited and, in addition, the use of these excipients poses safety concern (especially for paediatric patients) (Walsh et al., 2014). Coating of the drug particles represent an effective way of taste masking, however technologically more challenging (Stange et al., 2014; Walsh et al., 2014). Nevertheless, patented ODT technologies have been able to overcome this challenge through the preparation and subsequent compression of microencapsulated drugs for improved organoleptic properties and/or polymer coated particles for customised release (Venkatesh et al., 2012).

1.1.2.3 Orodispersible films

Orodispersible films (ODFs) based on polymeric matrices can be designed to disintegrate quickly in the mouth releasing the active ingredient. Swallowing is aided by the quick disintegration/dissolution of ODFs in the oral, eliminating the need of water for their administration. An added benefit of films in comparison to tablets is their increased flexibility of dose, since different strengths can be achieved by simply cutting films of the required size (Hoffmann and Breitenbach, 2011). A summary of advantages and disadvantages of ODFs is provided in Table 1.4.

Table 1.4. Potential advantages and disadvantages of orodispersible films as a technology platform for the preparation of age-appropriate medicines for children.

Product characteristic	Advantages	Disadvantages
Efficacy/Acceptability		
Dosage	Excellent dose flexibility	
Preparation	Water is not required Swallowing is aided	
Compliance	May be preferred over conventional formulations	Controlled-release is challenging Taste masking is challenging
Safety profile		
Bioavailability	May be improved by buccal absorption	
Excipients		Excipients of unknown safety profile may be required
Stability		Specialised packaging often required
Medication error		Retention time in mouth may alter bioavailability
Patient access		
Manufacturability	Continuous manufacturing can be achieved	Uniformity of dose may be challenging Only low doses can be incorporated
Affordability		Technologies subjected to intellectual property rights Manufacturing process is sometime solvent-based

An important limitation of ODFs is that taste masking and controlled release result technologically challenging. The utilisation of coating techniques for these purposes is limited by the own nature of the manufacturing process which usually involves solubilisation of the API (Hoffmann and Breitenbach, 2011). In some cases, sustained release has been achieved through the preparation of multi-layered films by combining layers with different release-controlling polymers. However, the fast-disintegrating advantage is not purposeful anymore as they are often designed to adhere onto the buccal mucosa and release the active ingredient in a timely manner (Mura et al., 2015).

ODFs are composed of a polymeric matrix with a drug embedded, typically manufactured by means of solvent casting method (Hoffmann and Breitenbach, 2011). Regardless of the manufacturing method, the amount of drug that can be loaded in ODFs is very limited (typically less than 60-70 mg (Nagaraju et al., 2013)) owing the ODFs reduced size (2 - 9 cm²) and thickness (25 µm to 2 mm), thus only potent drugs with specific physicochemical properties can be successfully delivered. Moreover, the need for specialise manufacturing and packaging equipment may reduce the viability of ODF technologies. In fact, several ODF products have been recalled from the market due to manufacturing issues and poor revenue (Buck and Health, 2013).

1.1.2.4 Chewable formulations

Chewable formulations (i.e. chewable tablets, soft-chews and chewing gum) are designed to be mechanically processed in the mouth to aid disintegration and/or dissolution of the API. These products offer administration advantages in that swallowing is aided (or avoided in the case of chewing gum) and water is not required. However, as in the case of ODTs, chewable products do not offer an advantage in terms of dose flexibility with respect to conventional tablets. The main advantages and limitations of chewable formulations are summarised in Table 1.5.

Disintegration and swallowing of chewable dosage forms is aided by the patient by means of chewing and/or sucking. Taste and mouthfeel become critical attributes and thus a considerate decision should be made on the selection of excipients (Mishra et al., 2009). Sugar-based fillers and sweeteners such as mannitol, sucrose and sorbitol are often used to improve palatability. A specific disadvantage of chewable products is their poor suitability for taste masking and controlled release by coating techniques, since the formulation is subjected to a great mechanical stress upon administration. In addition, the drug release process and thus the therapeutic effect is dependent on the patient's chewing ability, which may result in intra- and inter-individual variability.

Table 1.5. Potential advantages and disadvantages of chewable formulations as a technology platform for the preparation of age-appropriate medicines for children.

Product characteristic	Advantages	Disadvantages
Efficacy/Acceptability		
Dosage		Various dosage strengths required
Preparation	Water is not required Swallowing is aided	
Compliance	May be preferred over conventional formulations	Controlled-release is challenging Taste masking is challenging
Safety profile		
Bioavailability	May be improved by quick disintegration and dissolution May be improved by buccal absorption	Bioavailability may be altered depending on chewing ability
Excipients		Excipients of unknown safety profile may be required
Stability		Soft-chews may be problematic due to water content
Medication error		Retention time in mouth may alter bioavailability Possible overdose if misused as confectionary
Patient access		
Manufacturability		May need specialised equipment or accessories
Affordability	Manufacturing technology readily available	

Although available data suggest that chewable tablets are safe and well-tolerated in children from 2 years of age (Michele et al., 2002), the need for chewing of the dosage form may represent a limitation for the applicability of chewable formulations in neonates and elderly patients. In terms of medicated chewing gum, there is a lack of evidence about its safety in young children and current guidelines only recommend its use for children of 6 years or older (EMA, 2006). Besides, concerns have been raised about the possible misused of these products which may be appreciated by children as confectionery (EMA, 2006).

1.2 Formulation design and patient's acceptability

Selection of the most appropriate formulation design and excipients needs to be guided by a compendium of patient's safety, manufacturability and end-user requirements. Attempts have been made to define the most appropriate formulation for each particular patient subgroup (EMA, 2006; Sam et al., 2012). However, given the paucity of evidence, these attempts have often been based on the opinions and experience of healthcare professionals rather than scientifically sound evidence of patient's acceptability.

Patient's acceptability has been defined by the EMA as "*the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended*", and it is influenced by the characteristics of the end-users (age, ability, disease type and state) and the characteristics of the medicinal product (EMA, 2013). The characteristics of the medicinal product that can play a role on patient's acceptability include palatability (e.g. taste, smell and texture), swallowability (e.g. size and shape), appearance (e.g. colour, shape and embossing), complexity of modification prior to administration (if required), required dose (e.g. dosing volume for liquids or quantity for solids), required dosing frequency and duration of treatment, selected administration device (if any) and primary and secondary container closure system (Kozarewicz, 2014).

Palatability is a key element of the medicinal product and often regarded as one of the main elements influencing acceptability of oral medicines (although not the only parameter that requires consideration). Palatability, as it relates to oral medicines, can be defined as "*the overall appreciation of a medicine by organoleptic properties such as appearance, smell, taste, aftertaste and mouth-feel*" (EMA, 2013). In particulate, taste, texture and dose volume have been identified as the main barriers to palatability and acceptability and most common reasons for manipulation of paediatric oral medicines (Venables et al., 2015).

Patient's acceptability is the first step required to ensure patient's adherence to a therapeutic regime. Previous research suggest that subject-reported attitudes towards taking a medication or to continue with a therapeutic regime are good predictors of patient adherence (Godin et al., 2005; Kreivi et al., 2014). Obviously, patients '*not able*' and/or '*not willing*' to take their medicines are not going to obtain any therapeutic benefit. As such, evaluation of palatability and patient's acceptability should form an integral part of the pharmaceutical development studies and the Paediatric Investigational Plan (PIP), as recommended by the EMA (EMA, 2013). Selection of the most appropriate formulation design and excipients must be guided by evidence gathered in such studies.

Patient's acceptability must be considered at an early stage of the drug product development pathway rather than just tested on the final product. In this regard, *in vitro* tools and animal models offer opportunities to assess and predict organoleptic properties of APIs and/or formulations, even when toxicological data is not yet available (Mohamed-Ahmed et al., 2016). Nevertheless, studies in human subjects remain the gold standard for palatability and acceptability testing. Some of the key considerations when conducting such *in vivo* studies are outlined below.

1.2.1 Palatability and acceptability testing: methodological considerations

Clinical Trials of Investigational Medicinal Products (CTIMPs) must adhere to the European Clinical Trials Directive (2001/20/EC), the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Good Clinical Practice Directive (2005/28/EC). However, palatability and acceptability are not pharmacological effects, therefore the purpose of palatability and acceptability studies falls outside this definition and such tests are not classified as CTIMPs. Nonetheless, when a palatability study is nested within another clinical study it may be classified as a CTIMP (Batchelor et al., 2015). Although assessment of the palatability and patient acceptability would not be classified as CTIMP

in most cases, such studies would be subject to local research governance policies, e.g. Research Ethics Committees (Batchelor et al., 2015).

Despite the requirement to evaluate palatability and patient's acceptability of paediatric medicines as part of the PIP, there is limited guidance on how to perform such studies (Kozarewicz, 2014). Paradoxically, there is a guideline on the demonstration of palatability and acceptability of veterinary medicinal products, including study design, number of animal subjects required and selection of outcome measures (EMA, 2012), but similar guidance for studies in humans is not available. Interestingly, the food industry took the lead in investigating palatability and acceptability in human subjects and a range of Sensory Standards are available for the evaluation of food products (Mason and Nottingham, 2002). Specific guidance on the design of acceptability studies of food products in children can also be found in the literature (Guinard, 2000). Some of these standards for food evaluation might be applicable to testing of pharmaceuticals, although caution is advised when transferring knowledge between both fields given the potential differences in objectives and endpoints.

Due to the lack of standardise methodology, a variety of study designs and assessment tools have been used in the evaluation of palatability and acceptability of drug products. Such tools include visual analogue scales (VAS), hedonic scales, Likert-type scales, rank order assessment and verbal descriptive responses, used solely or in combination (Davies and Tuleu, 2008; Mistry and Batchelor, 2017; Squires et al., 2013). Other outcome measures employed in previous research include observations of facial expressions during administration, ability to swallow the dosage form, prevalence of complaints or refusal to take the medicine, time taken to administer the medicine and willingness to use or take the medicine again (Mistry and Batchelor, 2017). Proxy-reported outcomes and assistance provided by parents or caregivers were common in studies with younger children (Squires et al., 2013).

As recommended by the EMA, palatability and acceptability studies should be carried out in the target population age group, since sensory perception, swallowing function and cognitive abilities will vary with age and developmental stage (EMA, 2013). Differences in patient acceptability, attitudes and preferences for different dosage form designs as a function of age is a matter that is not well understood; although differences can be expected even within children of different ages, as supported by a recent study (Ranmal et al., 2016). Despite the acknowledged differences between patient groups, paediatric drug development still relies vastly on adults' data, given the ethical and practical barriers of conducting studies in children. Nevertheless, pilot studies in adults can provide valuable information, not only to improve the formulation but also to optimise the study design and outcome measures of palatability and acceptability.

Palatability and acceptability testing can be carried out in patients or in healthy volunteers. Studies with patients are often nested to a clinical trial (where acceptability measures are recorded as a secondary outcome), e.g. (Guffon et al., 2012; Musiime et al., 2014); whereas studies with healthy participants are purposely designed with the primary objective to measure palatability and acceptability, e.g. (Ameen et al., 2006). Traditionally, acceptability and adherence were measured simultaneously in clinical trials by merely counting the number of doses not taken by the patient, although this practice provides very limited information about the causes for refusal. More recently, a few clinical trials have used more specific measures of acceptability, such as hedonic scales, VAS scales and other tools discussed before, e.g. (Cohen et al., 2009; Musiime et al., 2014; Nasrin et al., 2005). Similarly, acceptability studies in healthy participants tend to use specific evaluation tools, since this is the primary objective of such studies.

In terms of the characteristics of the formulation, acceptability studies can be carried out using drug-loaded formulations or placebo. Exploratory studies using placebo aim to obtain fundamental understanding of acceptability and preference for different dosage form designs. For example, to determine acceptability of mini-tablets in young children,

e.g. (Klingmann et al., 2013; Spomer et al., 2012). On the contrary, studies with drug-loaded samples aim to obtain specific information about a formulation of interest. For example, to establish the efficiency of different taste-masking strategies to conceal the taste of a certain API, e.g. (Liew et al., 2014; Mishra et al., 2009; Preis et al., 2015).

Palatability is regarded as the most important determinant of acceptability (especially for liquid and dispersible formulations) and, as such, some studies have focussed on the evaluation of palatability as a surrogate of patient acceptability. In these studies, the swirl and spit methodology is often employed, whereby participants place the formulation in their mouth for a short time and then spit it out without swallowing it. This approach is useful to minimise the risk of adverse reactions, although it is limited in its resemblance of the real use of a drug product. Individuals participating in taste panels can be untrained or, alternatively, trained panellists (i.e. experts trained to distinguish specific palatability attributes and their intensity). The benefit of trained panellists is that they can provide better discrimination between samples (Mason and Nottingham, 2002). However, research suggests that untrained panellists can provide the same level of discrimination as trained panellists when the number of subjects in the former is sufficiently large (Husson and Pages, 2003; Mason and Nottingham, 2002).

The number of test samples that can be evaluated in a single study will vary depending on the study design, methodology and population. Studies nested to a clinical trial often focus on one or two formulations only, whereas palatability and acceptability studies in healthy volunteers usually investigate several formulations at a time. In such cases, it will be appropriate to test a larger number of samples using a swirl and spit methodology than if samples are required to be swallowed. In general terms, the number of samples should always be kept to a minimum to minimise discomfort and fatigue and maintain participants' motivation (Mason and Nottingham, 2002); this is particularly important for studies involving children participants.

1.3 Evidence of acceptability of flexible solid dosage forms

During the past decade, evidence on the evaluation of palatability and acceptability of different dosage form designs have been extensively reviewed (Davies and Tuleu, 2008; Drumond et al., 2017; Liu et al., 2014; Mistry and Batchelor, 2017; Ranmal, 2014; Squires et al., 2013; Thompson et al., 2013; van Riet-Nales et al., 2010). All previous reviews coincide that there is very limited evidence on patient's acceptability of different dosage form designs in peer-reviewed journals. Evidence of acceptability of flexible solid dosage forms (i.e. multiparticulates, orodispersible tablets, orodispersible films and chewable tablets) is particularly important given the potential of these formulations for children, although especially limited given the novelty of these technology platforms.

Although recent reviews in the field exist, it was deemed appropriate to perform a literature review to fill in the gaps of previous reviews. For example, Drumond et al. and, previously, Van Riet-Nales et al. focussed on comparative studies which included two or more different dosage form designs (Drumond et al., 2017; van Riet-Nales et al., 2010); however, studies of palatability and acceptability of a single dosage form might also provide illustrative information about patient acceptability. In addition, the systematic review by Liu and co-workers and Squires and colleagues were directed toward special populations (such as paediatrics and geriatrics), excluding studies in adults (Liu et al., 2015; Squires et al., 2013); although valuable information can be found in adult trials, for example regarding outcome measures and evaluation tools employed.

A semi-systematic literature review of the evidence of acceptability of flexible solid dosage forms was carried out, which included a systematic literature review of Embase, Medline and PubMed databases (January 2011 to April 2017), plus a review of the primary references included in previous systematic literature reviews, including studies since 1990 (Drumond et al., 2017; Liu et al., 2014; Ranmal, 2014; Squires et al., 2013; van Riet-Nales et al., 2010).

A systematic review of the literature on acceptability of flexible solid dosage forms was conducted using the key words shown in Table 1.6. The search was combined with Boolean operators (“AND”), using any of the search terms shown in Table 1.6 (“OR”). The search obtained 496 hits which were thoroughly screened.

Table 1.6. Search terms for systematic literature review of Embase, Medline and PubMed.

Keywords	Synonyms
Population	Subject, volunteer, children, infant, paediatric, adolescent, adult, elderly, geriatric
Formulation	Granule, sprinkle, pellet, bead, fast-dis*, rapidly-dis*, *dispersible, mini-tablet
Assessment	Accept*, swallow*, palatability, satisfaction, preference

In addition, primary references included in previous literature reviews of the research field were also screened (Drumond et al., 2017; Liu et al., 2014; Ranmal, 2014; Squires et al., 2013; van Riet-Nales et al., 2010). These reviews comprised a total of 89 records (excluding duplicate studies).

Screened studies were selected for full review based on the following inclusion criteria:

- (1) assessment of one or more oral flexible solid dosage form, such as multiparticulates (i.e. pellets/coated-granules/mini-tablets administered in multiplicity), (oro)dispersible tablets (including orodispersible, dispersible and effervescent tablets), orodispersible films, and chewable formulations;
- (2) reported one or more outcome(s) of palatability, swallowability, patient’s acceptability, satisfaction or preference;
- (3) compared outcomes between formulations (e.g. flexible solid dosage form versus conventional formulation) or investigated a single formulation (no comparator); and
- (4) were carried out on a population larger than 10 subjects.

Articles were excluded based on the following exclusion criteria:

- (1) studies not related to oral flexible solid dosage forms (e.g. studies of conventional tablets or capsules, studies of formulations not related to the oral route etc.); and
- (2) methodological information was insufficient to interpret acceptability results.

The identification and selection process of articles for this semi-systematic literature review is depicted in Figure 1.1.

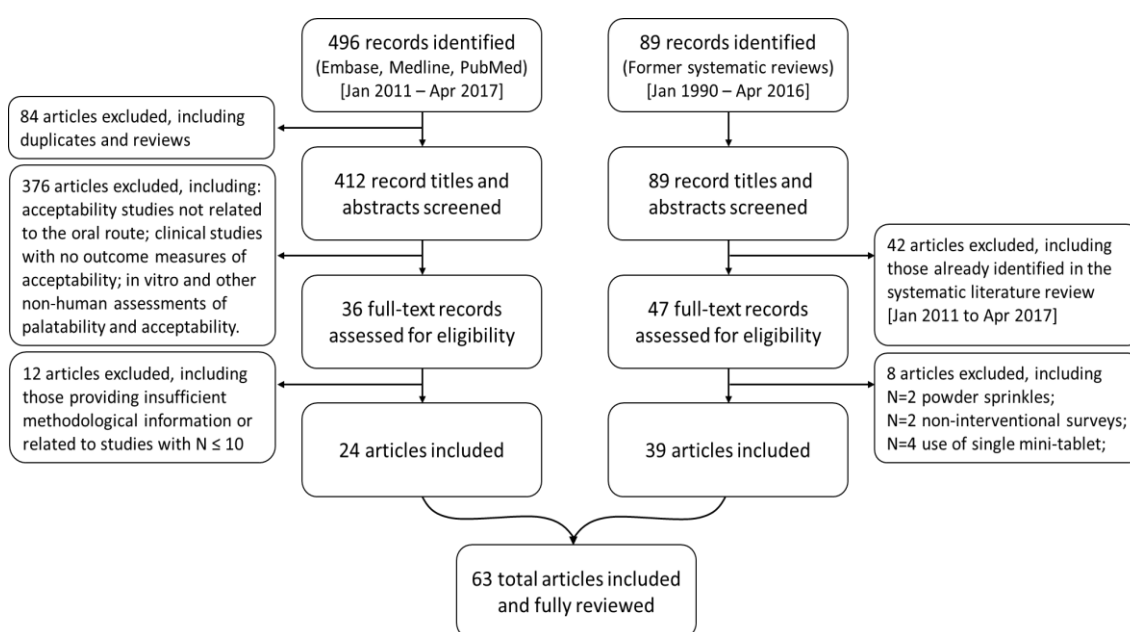


Figure 1.1. Flow-chart illustrating selection process for inclusion in the semi-systematic review.

1.3.1 Results of a semi-systematic literature review

1.3.1.1 *Multiparticulates formulations*

This review combined studies of mini-tablets as well as pellets or coated granules within the scope of multiparticulate formulations. Evidence about products labelled for ‘sprinkle’ (i.e. indicated to be co-administered with food or drinks) was only considered relevant when an indication was given that the dosage form was coated or taste-masked (i.e. powders or granules for oral solution/suspension were not considered multiparticulates).

Similarly, minitables were only considered relevant to this section when administered in multiplicity (i.e. studies relating to the administration of a single minitab were not included). Evidence of acceptability of multiparticulate dosage forms in children and adults' populations is summarised in Table 1.7.

Several studies have investigated palatability and acceptability of multiparticulates in children. Saez-Llorens and co-workers performed two studies in children (1-12 years) receiving famciclovir sprinkles dispersed in 5 mL of Ora-Sweet, a single-dose study (51 subjects) and a multi-dose study (100 subjects); children and their caregivers rated the formulation as 'well' or 'very well' accepted in 56.6% of occasions (Saez-Llorens et al., 2009). Zannikos et al. investigated rabeprazole coated beads dispersed in 10 ml of strawberry flavour vehicle in children (1-11 years) and found the formulation to be broadly acceptable, with 85.1% of caregivers reporting 'good' to 'excellent' palatability and ease of swallowing (Zannikos et al., 2011). Similarly, van de Vijver and colleagues evaluated ease of swallowing of pancreatin coated mini-tablets in 16 children (0.5-3 years) and found swallowing to be 'fair' to 'good', although limited conclusions regarding overall acceptability were reached by the authors (Van de Vijver et al., 2011).

A recent exploratory study with placebo mini-tablets in children volunteers indicated that 2-year-old and 3-year-old children could swallow up to 10 mini-tablets dispersed in a starch-based jelly in 75% and 93% of occasions respectively (Kluk et al., 2015). The sequential study designed involved certain training of children, since participants were presented with the jelly formulation first (containing no solids), followed by one 2-mm mini-tablet, ten 2-mm mini-tablets, one 3-mm mini-tablet and, finally, ten 3-mm mini-tablets, during five consecutive days (mini-tablets dispersed in jelly in all cases). These findings served as a confirmation of the suitability of solid formulations in pre-school age children, after a few studies showing acceptance of a single mini-tablet (Spomer et al., 2012; Thomson et al., 2009), and even favourable acceptance over syrups (Klingmann et al., 2013; van Riet-Nales et al., 2013, 2015).

Table 1.7. Evidence of acceptability of multiparticulate formulations (i.e. coated pellets/granules and mini-tablets administered in multiplicity).

Population	Dosage form	Assessment tool(s)	Summary of outcome(s)	References
Children				
Children, N=16 (0.5-3 years)	Coated mini-tablets (pancreatin, 2 mm)	Caregiver reported ease of swallowing [4-point Likert-type scale]; no comparator	Ease of swallowing varied from 'poor' to 'excellent', being 'fair' to 'good' on average	(Van de Vijver et al., 2011)
Children, N=27 (1-11 years)	Coated beads (rabeprazole, 470 µm)	Caregiver reported palatability [4-point Likert-type scale]; no comparator	Most parents found palatability to be good (40.7%) or excellent (44.4%)	(Zannikos et al., 2011)
Children, N=151 (1-12 years)	Sprinkles (famciclovir)	Subject reported (> 5 years) and caregiver reported (< 5 years) taste and acceptability [5-point hedonic scale]; no comparator	Taste of sprinkles dispersed in OraSweet was rated mostly neutral (53.2%) and were 'well' or 'very well' accepted by 56.6%	(Saez-Llorens et al., 2009)
Children, N=60 (2-4 years)	Mini-tablets (placebo, 2-3 mm)	Researcher observation of formulation intake [5-point criteria]; single versus 10 mini-tablets at a time and 2-mm versus 3-mm mini-tablets [sequential design]	Most children (75% of 2 years and 93% of 3 years) swallowed 10 mini-tablets dispersed in starch-based jelly; chewing reflect increased with amount and size of the mini-tablets	(Kluk et al., 2015)
Children, N=77 (3-13 years)	Minitab (pellet) sprinkles (lopinavir/ritonavir)	Caregiver reported acceptability (issues with administration); compared to syrup (<4 years, N=45) and to conventional tablets (>4 years, N=32) [crossover design]	Administration issues were more common with syrups than minitabs but more common with minitabs than tablets; taste was similar for syrup and minitabs, both worse than tablets	(Kekitiinwa et al., 2016; Musiime et al., 2014)
Children, N=15 Adults, N=5 (4-64 years)	Taste-masked granules (phenylbutyrate)	Subject reported bitterness and acceptability [100-mm VAS]; compared to other medication if taken previously (N=14 children) [sequential design]	Reduced bitterness score (11.6 versus 55.2%) and higher acceptability (85.1 versus 17.7%) of taste-masked granules; 10 out of 14 subjects preferred granules compared to other forms	(Kibleur et al., 2014)
Children, N=108 (6.7±3.6 years)	Sprinkle microspheres (valproate)	Subject reported palatability (children > 4 years, N=53) [5-point hedonic scale] and caregiver reported ease of use; compared to liquid taken previously [sequential design]	Palatability of sprinkles (3.83) was significantly higher than solution (2.09) and administration issues were significantly lower with sprinkles (15.7%) than liquid (68.5%)	(Verrotti et al., 2012)
Children, N=40 (0.5-3 years)	Microgranules (pancreatin)	Caregiver reported preference; smaller granules in multi-dose container with measuring spoon compared to larger granules in capsule [crossover design]	Preference for multiparticulates in multi-dose container over capsule (51% versus 23%), due to practicability; effect of granule size on preference was not reported	(Munck et al., 2009)
Children, N=150 (5-7 months)	Taste-masked sprinkles (iron supplement)	Caregiver reported adherence and satisfaction; compared to oral drops [parallel design]	Higher willingness to use sprinkles again (80%) than drops (69%)	(Geltman et al., 2009)

Table 1.7. (Continued).

Children, N=98 (0.5-1 year)	Sprinkles (iron supplement)	Caregiver reported ease of use and acceptability; compared to crushed tablets and spreadable lipid formulation [parallel design]	Sprinkle was reported as 'easy giving' (96.9%) and 'child accepted' (89.6%); acceptability was comparable between formulations	(Adu-Afarwuah et al., 2008)
Children, N=302 (2-14 years)	Coated microgranules (valproate, <400 µm)	Subject reported acceptability [2 to 4-point hedonic scale] and caregiver reported ease of use; compared to liquid if taken previously (N=199) [sequential design]	Microgranules were well accepted (≈80% positive hedonic response), but 20% of carers reported administration issues; microgranules were preferred over liquid	(Motte et al., 2005)
Children, N>490 (0.5-2 years)	Coated sprinkles (iron supplement)	Caregiver reported adherence and ease of use; compared to oral drops [parallel design]	Preference for sprinkles – Only 6-16% of children objected to take sprinkles versus 74-93% who objected to take drops	(Zlotkin et al., 2003, 2001)
Children, N=12 (5-16 years)	Coated sprinkles (valproate)	Subject and caregiver reported preference; compared to syrup [crossover design]	Sprinkle formulation was preferred based on palatability and ease of administration	(Cloyd et al., 1992)
Adults				
Adults, N=18 (22.5±1.0 years)	Mini-tablets (placebo, 3 mm)	Subject reported ease of taking dosage form [VAS scale]; compared to ODMT, ODT and conventional tablet [direct comparison]	Ease of taking 2 mini-tablets was considered better than a conventional tablet, but ease of taking 5 or 10 mini-tablets at a time was considered similar to a conventional tablet	(Hayakawa et al., 2016)
Adults, N=30 (20-25 years)	Pellets (placebo, 90-263 µm)	Subject reported oral grittiness [VAS scale] and preferred formulation; comparison between various pellet sizes and amounts and media viscosity [direct comparison]	Grittiness perception increased as the size and amount of multiparticulates increased and as the viscosity decreased; very viscous media was less preferred despite reducing grittiness	(Lopez et al., 2016)
Adults, N=15 (23.0±2.6 years)	Spherical granules (placebo, 250-850 µm)	Subject reported feeling of roughness and total palatability [VAS score]; comparison between various particle sizes [direct comparison]	Rough mouth-feel increased with increasing size of multiparticulates. A 244 µm threshold was proposed to minimise rough mouth-feel	(Kimura et al., 2015)
Adults, N=21 (23-55 years)	Mini-tablets and pellets (placebo, 2-3 mm) (placebo, 250-850 µm)	Subject reported oral perceptibility [4-point VAS scale] and researcher reported ease of dispersion; comparison between media of varying viscosity [direct comparison]	Multiparticulates were more perceptible as size increased. Gels with medium viscosity performed best at dispersing and reducing oral perceptibility of multiparticulates	(Kluk and Sznitowska, 2014)
Adults, N=13 (19-50 years)	Coated microgranules (phenylbutyrate)	Subject reported bitterness, saltiness, sweetness and acceptability [100-mm VAS]; compared to uncoated granules [direct comparison]	Uncoated granules were significantly more bitter and salty and were less acceptable than coated granules (42.1 versus 78.8%, respectively)	(Guffon et al., 2012)

Other studies have focussed on preference of multiparticulates over other dosage form designs, rather than acceptability *per se*. Studies comparing multiparticulates to liquid dosage forms in children have commonly showed preference for the solid over the liquid form. For example, a range of studies showed acceptance of iron supplement sprinkles and preference for these compared to oral drops in children with anaemia (Adu-Afarwuah et al., 2008; Geltman et al., 2009; Zlotkin et al., 2003, 2001). Likewise, three studies involving children suffering from epilepsy consistently showed preference for sprinkle formulations over syrup (Cloyd et al., 1992; Motte et al., 2005; Verrotti et al., 2012). Taste-masking of the poorly palatable drug was often reported as the key attribute which determined patients' and caregivers' preferences for sprinkles.

In a recent study, children showed preference for sprinkles over syrup after 12-week antiretroviral therapy; 72% of children below 12 months and 64% of children between 1 and 4 years preferred the multiparticulate dosage form (Kekitiinwa et al., 2016; Musiime et al., 2014). For those preferring syrups, key issues with pellets were problems masking the pellets with food and food refusal, and concerns about not giving the whole dose. However, multiparticulates overcome the storing and transporting issues of syrups, which was an advantage for caregivers. Similar outcomes were shown for children on antiretroviral therapy who swapped from syrup to scored-tablets at a median age: 2.9 years, their caregivers showing preference for the solid form based on convenience, e.g. less transportation issues and easier dosing (Nahirya-Ntege et al., 2012).

The study by Kibleur and co-workers, which evaluated palatability and acceptability of phenylbutyrate coated-granules, highlighted the importance of taste-masking as a key advantage of multiparticulates (Kibleur et al., 2014). When subjects had prior experience with a different formulation of the same drug (14 out of 25 subjects), they were asked to report their preference, results showing that 10 out of 14 subjects preferred the multiparticulate form. Four additional subjects, which were not under phenylbutyrate treatment due to the impossibility to take the marketed formulation, also reported better

acceptance of the coated granules. Vomiting and taste disturbances (dysgeusia), which are described as 'frequent' in the SmPC of marketed phenylbutyrate products, were not reported with the new formulation (Kibleur et al., 2014). This study was supported by a previous trial in children and adults which indicated reduced saltiness and bitterness and improved acceptance with the taste-masked formulation (Guffon et al., 2012).

Munck et al. (2009) evaluated caregivers' preferences for two different presentations of pancreatin sprinkles, a multi-dose bottle with a measuring spoon versus single-dose capsules which needs to be opened to measure the dose and administer the contents. Caregiver's reported preference for the multi-dose container presentation (51%, with 26% showing no preference for either formulation), giving reasons of 'practicability' and 'fewer symptoms' (which could potentially be ascribed to better control over dose titration using the measuring spoon provided with the multi-dose container). The authors reported that the multi-dose presentation contained microgranules of smaller size than the capsules, although no reference to the effect of particle size on acceptability was provided in their manuscript (Munck et al., 2009).

In most of the studies in children, multiparticulates are co-administered with foodstuff. Usually, caregivers were given the opportunity to decide between a range of liquid or semi-solid foodstuff, which included milk, jam, yogurt and porridge, e.g. (Adu-Afarwuah et al., 2008; Kekitiinwa et al., 2016; Verrotti et al., 2012). In two studies, multiparticulates were given in a small volume (5-10 ml) of a sweetened or flavoured pharmaceutical vehicle (Saez-Llorens et al., 2009; Zannikos et al., 2011). Only two studies reported direct administration of multiparticulates: Klibeur et al. (2014) reported direct intake of taste-masked granules (N=25), whereas Adu-Afarwuah et al. (2008) reported that just 3-4% of parents (out of 98) followed this practice when given freedom to administer iron sprinkles as desired. Association between the administration vehicle and patients' acceptability was not explored in any of these studies.

Multiparticulates are often designed as a paediatric formulation and, as such, most studies have evaluated acceptability of multiparticulates in children. However, a few studies of multiparticulates in adult populations were also identified. Exploratory trials with placebo multiparticulates in healthy adults include that of Hayakawa et al. (2016), who investigated the ease of taking mini-tablets compared to conventional tablets, ODTs and oro-dispersible mini-tablets (ODMT) in 18 healthy adults. Results indicated that a single mini-tablet, ODMT or ODT was significantly easier to take than a conventional tablet. However, administration of 5 and 10 mini-tablets at a time obtained similar ratings for 'ease of taking' than the conventional tablet (*n.b.* the total weight of 10 mini-tablets was equivalent to that of a conventional tablet). The administration of several ODMTs at a time was not investigated in this study.

Kimura et al. investigated palatability of placebo multiparticulates in healthy adult volunteers, with focus on rough mouthfeel. Four different multiparticulate sizes were investigated within the range of 250-850 μm (at a fixed amount of 75 mg) using a swirl and spit methodology. The authors concluded that rough mouth-feel increased with increasing size of the multiparticulates and proposed a maximum threshold of 244 μm to minimise rough mouthfeel. However, the experience of roughness with particles of larger size was reported to be 'tolerable' (Kimura et al., 2015).

Two other placebo exploratory studies in adult populations were identified, which investigated the effect of different administration media on perception of multiparticulates in the mouth using a swirl and spit methodology. Kluk and Sznitowska investigated the applicability of oral hydrogels (prepared to different viscosity levels) as media for the administration of pellets and mini-tablets (Kluk and Sznitowska, 2014). Participants reported reduced feeling of solids in the mouth with vehicles of higher viscosity. Similarly, a previous study by our research team investigated oral grittiness of placebo pellets dispersed in HPMC hydrogels at different viscosity levels, concluding that increasing viscosity of the media helped reducing oral grittiness perception (Lopez et al., 2016).

1.3.1.2 (Oro)dispersible tablets

This section includes tablets designed to be dispersed in a suitable vehicle before administration (e.g. dispersible and effervescence tablets) as well as tablets intended to be dispersed directly in the mouth (e.g. orodispersible and sublingual tablets). Only eight studies in children were identified, whereas twice as many studies were found and reviewed in adults. Based on the needs of the target population, most studies in children have focussed on the evaluation of dispersible tablets, as opposed to studies in adults which mainly focussed on orodispersible tablets (Table 1.8).

Several studies investigated dispersible tablets in children, consistently supporting acceptability of this dosage form design, even in neonates (Nasrin et al., 2005; Ogutu et al., 2014; Winch et al., 2006). A few studies also showed preference of dispersible tablets over other paediatric formulations, such as syrups (Ameen et al., 2006; Nasrin et al., 2005; Ogutu et al., 2014). In a study of two Fixed Dose Combination (FDC) antimalarial dispersible tablets, 67 and 82% of caregivers found the two formulations 'simple' or 'very simple' to use, respectively, and a similar proportion preferred them over syrups (Ogutu et al., 2014). Difference in acceptability between the two dispersible tablets could be attributed to difference in taste between both formulations, which were 'liked' or 'very much liked' by 56 and 72% of participants, respectively.

Acceptability of ODTs have only been evaluated in children older than 5 years. Three studies were identified showing excellent acceptance of ODTs with 100% successful intake (Cohen et al., 2005), preference over syrup (based on patients attitudes, as syrup was not included as comparator) (Tolia et al., 2005) and preference over conventional tablets (Lottmann et al., 2007). Interestingly, Lottman and co-workers showed preference for dispersible over conventional tablets in children below 12 years, but the opposite behaviour in children over 12 years, in a cohort of 210 children on nocturnal enuresis treatment (Lottmann et al., 2007). This was supported by a study investigating end-user perceptions and preferences for different dosage forms (Ranmal et al., 2016).

Table 1.8. Evidence of acceptability of (oro)dispersible tablet formulations (i.e. dispersible, effervescence, orodispersible and sublingual tablets).

Population	Dosage form	Assessment tool	Summary of outcomes	References
Children				
Children, N=123 (0-5 years)	Dispersible tablet (zinc supplement)	Caregiver reported administration issues and adherence; no comparator	Almost 90 % of children accepted the 10-day course of treatment and only 6.5% of caregivers reported administration issues	(Winch et al., 2006)
Children, N=303 (0.25-5 years)	Dispersible tablet (zinc supplement)	Caregiver reported acceptability and adherence; no comparator	DTs were reported equal or more acceptable than other medicines by 93.1% and 83.5% were willing to use it again	(Nasrin et al., 2005)
Children, N=210 (2-8 years)	Dispersible tablet (roxithromycin)	Caregiver reported acceptability based on intake/refusal and ease of use; no comparator	DT was found to be convenient by 76% of caregivers; only 8 children refused medication (due to taste or vomiting)	(Moniot-Ville et al., 1998)
Children, N=250 (0.5-5 years)	Dispersible tablet (antimalarial FDCs)	Caregiver reported acceptability and ease of use; two fixed-dose combination (FDC) products compared [parallel design]	Caregivers considered DTs simple to use (82%, 67%), reported good palatability (72%, 56%) and preferred DTs over syrup (76.8%, 62.3%) for both FDC products	(Ogutut et al., 2014)
Children, N=102 (4-8 years)	Effervescent tablet (ranitidine)	Subject reported taste preference and caregiver reported willingness to use; compared to syrup [crossover design]	Most children (71%) preferred taste of the (citrus) effervescent tablet over the (peppermint) syrup; most caregivers (71%) would prefer the tablet	(Ameen et al., 2006)
Children, N=210 (5-15 years)	Sublingual lyophilisate (desmopressin)	Subject/caregiver reported ease of use [VAS scale] and subject reported preference; compared to conventional tablet [crossover design]	Children below 12 years preferred ODT whereas children over 12 years preferred conventional tablet; ease of use was comparable with both formulations	(Lottmann et al., 2007)
Children, N=104 (6-11 years)	Orodispersible tablet (lansoprazole)	Subject reported degree of liking [5-point hedonic scale] and preference; compared to syrup [parallel design]	The proportion of children who liked the syrup was lower than the proportion who liked the ODT; (strawberry) ODT was preferred over (peppermint) syrup by 92%	(Tolia et al., 2005)
Children, N=62 (5-11 years)	Orodispersible tablet (ondansetron)	Subject reported taste sensation and willingness to take medication again; compared to placebo ODT [parallel design]	ODT was taken by 100% of participants; only 4 of 31 would not want to use it in the future; the taste of drug-loaded ODT was scored lower than that of the placebo	(Cohen et al., 2005)

Table 1.8. (Continued).

Adults				
Adults, N=150 (18-80 years)	Orodispersible tablet (placebo)	Subject reported attitudes/preferences; towards dosage forms; no comparator	Patients on oral antidepressants expressed preference for ODTs (84%) over other dosage forms and stated they would be more likely to take this type of tablet every day (75.4%)	(Wade et al., 2012)
Adults, N=228 (> 18 years)	Orodispersible tablet (amlodipine)	Subject reported palatability (including ease of ingestion) [interview]; no comparator	Most patients reported ODT as easy to ingest (99.6%) due to 'quick dissolution', 'not being rough in the mouth' and having a 'good taste'	(Fukui-Soubou et al., 2011)
Adults, N=687 (52.4±14.6 years)	Orodispersible tablet (mirtazapine)	Subject reported acceptability of ODT design; no comparator	Most patients (80%) accepted the ODT formulation based on easy opening, choice of tablet, taste, texture and ease of use	(Danileviciute et al., 2009)
Adults, N=64 (18-55 years)	Orodispersible tablet (olanzapine)	Subject reported impressions [7-point Likert-type scale] and caregiver reported attitudes toward medication and compliance [5-point Likert-type scale]; no comparator	Impressions about the medication showed positive acceptance, with scores improving over a 6-week assessment period	(Kinon et al., 2003)
Adults, N=76 (39.7±13.1 years)	Orodispersible tablet (budesonide or placebo)	Subject reported acceptance of taste, handling and administration time and formulation preference [interview]; compared to viscous suspension [parallel design]	Patients preferred the effervescent tablet for oral dispersion over the viscous suspension (80% versus 17%); no data was reported about taste or ease of use	(Miehke et al., 2017)
Adults, N=524 (35.6±11.3 years)	Sublingual tablet (buprenorphine/naloxone)	Subject reported preference in terms of taste, mouthfeel, ease of administration and overall preference; compared to oral thin film [crossover design]	Patients favoured the sublingual tablet for taste (77.5%), mouthfeel (72.6%), ease of taking (71.5%), and overall preference (70.2%)	(Gunderson and Sumner, 2016)
Adults, N=30 (18-63 years)	Oral lyophilisate (cetirizine)	Subject reported palatability (taste, sweetness, bitterness, mouthfeel, aftertaste, disintegration and overall acceptability) [hedonic and JAR scales]; low versus high levels of flavouring agents [direct comparison]	Effective taste-masking, with at least 80% acceptance, was achieved with β -cyclodextrin and cherry/sucralose flavour; no difference in preference between low and high flavour levels (53.3% versus 46.7%, respectively)	(Preis et al., 2015)
Adults, N=16 (22-55 years)	Orodispersible tablet (donepezil)	Subject reported taste, after taste, mouth feel, ease of handling and acceptance [5-point Likert-type scale]; comparison between various types of fillers [direct comparison]	The bitter taste of the drug was masked using ammonium glycyrrhizinate; most palatable ODT was prepared using co-processed lactose/starch (85/15) as filler	(Liew et al., 2014)

Table 1.8. (Continued).

Adults, N=89 (41.0±12.1)	Orodispersible tablet (lamotrigine)	Subject/caregiver reported ease of use [7-point Likert-type scale]; compared to conventional tablets taken previously [sequential design]	Preference for ODT; ODT considered to be extremely easy to use in 49% occasions compared to 3% for the conventional tablet	(Sajatovic et al., 2013)
Adults, N=175 (35.3±11.1 years)	Orodispersible tablet (olanzapine)	Patient reported preference; compared to conventional tablet [crossover design]	ODT (61%) over conventional tablet (27%), but preference shift towards the dosage form taken lastly in the crossover design	(Bitter et al., 2010)
Adults, N=35 (18-65 years)	Orodispersible tablet (zolmitriptan)	Subject reported degree of liking [5-point Likert-type scale]; compared to conventional tablet and nasal spray [mixed design]	Patients preferred the ODT (42.9%) and nasal spray (40.0%), due to convenience and rapid onset, over the conventional tablet (17.1%)	(Dowson et al., 2007)
Adults, N=36 (64.5±11.8 years)	Orodispersible tablet (placebo, 340 mg)	Subject reported ease of swallowing [5-point Likert-type scale]; compared to conventional tablet [crossover design]	Dysphagic patients (>75%) found ODTs easier to swallow than conventional tablets; greater proportion reported concern swallowing tablets compared to ODT (42% versus 25%)	(Carnaby-Mann and Cray, 2005)
Adults, N=61 (71.8±8.3 years)	Orodispersible tablet (levodopa/carbidopa)	Subject reported preference; compared to conventional tablets taken previously [sequential design]	Preference for ODT over conventional tablet (45% versus 20%, with 35% showing no preference), due to ease and speed of use and reduced concern about swallowing	(Nausieda et al., 2005)
Adults, N=365 (52±12 years)	Orodispersible tablet (ondansetron)	Subject reported taste acceptability; compared to conventional tablet [parallel design]	The taste of ODT was acceptable to most patients (89%) who received it	(Davidson et al., 1999)
Adults, N=27 (30±9.2 years)	Sublingual tablet (buprenorphine/naloxone)	Subject reported, acceptability, taste, mouthfeel and ease of administration [100-mm VAS scales], after-taste [4-point Likert-type scale] and preference; compared to oral thin film [crossover]	The new formulation received higher VAS ratings for taste, mouthfeel and overall acceptability and a lower proportion of subjects reported unpleasant aftertaste; 88.9% preferred the new formulation	(Fischer et al., 2015)
Adults, N=53 (36±11.2 years)	Sublingual tablet (buprenorphine/naloxone)	Subject reported taste and overall formulation experience (disregarding effects/side effects) [10-point Likert-type scale] and preference; compared to marketed sublingual tablet [crossover]	The new formulation (containing sucralose and menthol to mask the bitter taste) received significantly higher ratings for taste and acceptability and was preferred over commercial tablet (77.4%)	(Fischer et al., 2015)

In line with the findings in children, a range of studies in adults have shown preference for ODTs compared to other dosage forms, including oral suspension (Miehlke et al., 2017), orodispersible films (Fischer et al., 2015; Gunderson and Sumner, 2016) and conventional tablets (Bitter et al., 2010; Carnaby-Mann and Crary, 2005; Nausieda et al., 2005; Sajatovic et al., 2013). Reasons for acceptance and preference of ODTs included ease and speed of use, rapid onset of action and ease of swallowing (Danileviciute et al., 2009; Dowson et al., 2007; Nausieda et al., 2005). Based on the ease of swallowing, ODTs might be particularly suitable for patients with swallowing difficulties. In this regard, 75% of 36 dysphagic patients preferred ODTs over conventional tablets because the former were easier to swallow (Carnaby-Mann and Crary, 2005), as supported by a previous study with dysphagic patients (Bayer et al., 1988).

Appropriate taste is a critical attribute of orodispersible tablets however technologically challenging to achieve. In the study by Cohen and colleagues in children 5-11 years, placebo ODTs demonstrated better taste than ondansetron ODTs, suggesting taste-masking was only partially achieved (Cohen et al., 2005); which is supported by a previous study of ondansetron ODTs in adults (Davidson et al., 1999). On the contrary, amlodipine ODTs palatability was reported to be appropriate by 99.6% of 228 adult patients in open-ended interviews with doctors (Fukui-Soubou et al., 2011). Differences in outcome measures and, particularly, differences between taste of the two APIs would explain these contradictory findings. Indubitably, some APIs will be more challenging to taste-mask due to their inherent strong taste; however, selection of the most appropriate dosage form and formulation design can enhance the chances of success. Two previous studies in children showed preference for citrus flavoured ranitidine effervescent tablets and strawberry flavoured lansoprazole ODTs compared to peppermint flavour syrups of the same drug (Ameen et al., 2006; Tolia et al., 2005).

Unfortunately, studies investigating acceptability and patient preferences as a secondary outcome of a clinical trial do not usually describe the formulations composition, which

hinders association between formulation factors and patient reported outcomes. Conversely, those studies which focus on the development of new formulations tend to describe the formulation in sufficient detail to establish a relationship between formulation design and palatability or acceptability outcomes. For example, Liew and co-workers concluded that appropriate masking of the bitter tasting drug donepezil hydrochloride was achieved using ammonium glycyrrhizinate as novel taste-masking flavouring agent, although the formulation also contained starch, mannitol and menthol, among other excipients which could contribute to the overall palatability of the formulations (Liew et al., 2014).

A recent study by Preis and co-workers focussed on the development of cetirizine hydrochloride oral lyophilisates (Preis et al., 2015). A combination of β -cyclodextrins, sucralose and black cherry flavour was employed as taste-masking system, which was selected based on preliminary evaluations using an *in vitro* electronic taste assessment tool (e-tongue). Then, two formulations were prepared, with high versus low flavour and sweetener content, and evaluated based on a swirl and spit methodology in a panel of 30 adult volunteers. The higher level of flavouring agents was deemed too sweet by 50% of the adult volunteers, as opposed to 30% who thought the sweetness level was right and 20% who thought it was not enough. Despite these palatability findings, the authors reported adequate acceptance of both formulations in 80% or more of the volunteers and no significant differences between high and low level of flavour (Preis et al., 2015).

1.3.1.3 Orodispersible films

Only two studies of orodispersible films were identified in this literature review, one in adults and one in children; results are summarised in Table 1.9. Additionally, two studies reported a comparison between ODTs and ODFs in adult subjects, both of which indicated preference of the tablet design, as described in the previous section (Fischer et al., 2015; Gunderson and Sumner, 2016).

Rodd and co-workers investigated the acceptability of vitamin D film strips compared to oral drops in neonates, under 5 weeks of age (Rodd et al., 2011). Researchers used a modified Medication Acceptance Scale (MAS) initially developed by Kraus and colleagues to evaluate child's reactions to medication based on facial expressions, reactions upon ingestion and amount of dose swallowed (Kraus et al., 2001). Additionally, caregivers reported acceptance on a questionnaire based on 10-point Likert-type scales, which included an 'overall rating' of the formulation and 'willingness to continue using' the dosage form, among other questions. Both researchers' observations and caregiver-reported outcomes indicated better acceptance of the film formulation over oral drops. Patient's compliance was also recorded, based on total medication consumption at the end of the trial; results were in line with previous findings showing also higher compliance scores for oral films than drops.

A study of acceptability of oral films in the adult population was also identified. An antiemetic (dexamethasone) orodispersible film was developed and its oral acceptability compared against that of a conventional tablet in adult patients on chemotherapy (Nishigaki et al., 2012). Patients reported similar taste for both formulations, suggesting appropriate taste-masking in the oral films, which contained cocoa flavour; besides, the film formulation received significantly better ratings for 'amount' (i.e. dose volume) and 'ease in taking'. However, films contained 4 mg of dexamethasone compared to 0.5 mg in tablets, which meant that some patients had to ingest up to 16 tablets at a time to get the right dose. Thus, it is difficult to elucidate whether the improvement in patient's acceptability was caused by the dosage form design or by the significantly higher number of dosage units that the patient had to take due to the difference in drug loading.

1.3.1.4 Chewable formulations

Evidence of acceptability of chewable formulations is summarised in Table 1.10. Studies on medicated chewing gum were not identified in either children or adults, thus only

studies with chewable tablets have been described in this section. Although chewable tablet medications in the market are approved and prescribed for children from 2 years, as shown by a previous review (Michele et al., 2002), no studies of acceptability of chewable tablets were identified in the peer-reviewed literature in children below 6 years.

A multicentre study was carried out in children 6-11 years old assessing patients' and caregivers' preferences for montelukast chewable tablets compared to cromolyn metered dose inhaler (Volovitz et al., 2000). Both children and their caregivers showed preference for the chewable form versus the inhaler (82% vs. 17% and 87% vs. 13%, respectively). Volovitz and colleagues reported results of this multinational study (including 17 countries), whereas Bukstein and co-workers reported results of a single-centre study conducted in United States; it was not possible to determine whether both reports belong to the same study, but both used the same methodology and showed comparable results. That is the only peer-reviewed evidence to support chewable tablets in children that was available in the public literature.

Other studies evaluated acceptability of chewable tablets in adult populations. Three studies investigated the acceptability of calcium supplements compared to powders for oral solution. Reginster et al. and Den Uyl et al. followed a similar study designs, both excluding pregnant women in their studies (Den Uyl et al., 2010; Reginster et al., 2005); whereas Baxter et al. precisely focussed on pregnant women as subject of their study (Baxter et al., 2014). Irrespective of the studied population, all studies found better acceptance of chewable tablets than oral powders. However, Baxter and co-workers also introduced conventional tablets as a comparator, showing strong preference of pregnant women for conventional over chewable tablets. Finally, a study comparing lanthanum chewable tablets with an oral powder showed preference for powders in patients with chronic kidney disease, which were deemed easier to take, mainly due to avoidance of chewing up the medicine (Mukai et al., 2014).

Table 1.9. Evidence of acceptability of orodispersible film formulations

Population	Dosage form	Assessment tool	Summary of outcomes	References
Adults				
Adults, N=19 (41-70 years)	Orodispersible film (dexamethasone)	Subject reported taste, amount and ease in taking [3-point Likert-type scale]; compared to tablet [crossover design]	Taste was scored similar for film and tablet (appropriate taste-masking); amount and ease in taking significantly better for film	(Nishigaki et al., 2012)
Children				
Children, N=41 (< 6 weeks)	Film strip (vitamin D supplement)	Researcher observation of ingestion [8-point criteria] and caregiver reported acceptance [10-point Likert-type scale]; compared to oral drops [crossover design]	Films strips received better ratings of acceptance by researchers and parents, 85% of whom preferred the film strip; this was aligned with higher compliance scores	(Rodd et al., 2011)

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Table 1.10. Evidence of acceptability of chewable formulations

Population	Dosage form	Assessment tool	Summary of outcomes	References
Adults				
Adults, N=79 (33-85 years)	Chewable tablet (lanthanum)	Subject reported compliance and ease of taking medication; compared to oral powder taken subsequently [parallel design]	Granules were easier to take for 46.8% of patients compared to chewables (25.3%), mainly due to avoidance of chewing	(Mukai et al., 2014)
Adults, N=130 (18-39 years)	Chewable tablet (calcium supplements)	Subject reported preference (only preferred dosage form was tested); compared to conventional tablet, unflavoured and orange flavoured oral powders [discrete-choice design]	Pregnant women selected conventional tablets most commonly (62%), followed by chewable tablets (19%), flavoured powder (12%) and unflavoured powder (5%)	(Baxter et al., 2014)
Adults, N>170 (30-87 years)	Chewable tablet (calcium supplements)	Subject reported acceptability (administration, taste, time spent and convenience) [11-point Likert-type scale] and preference; compared to powder for oral solution [crossover design]	Ratings consistently higher for chewable tablet than powder; just over two thirds (67-73%) reported preference for the chewable form compared to soluble powder, in both studies	(Den Uyl et al., 2010; Reginster et al., 2005)
Children				
Children, N>300 (6-11 years)	Chewable tablet (montelukast)	Subject/caregiver reported adherence and preference; compared to metered-dose inhaler (cromolyn) [crossover design]	Preference for chewable tablets over inhaler in children (82% versus 17%) and their parents (87% versus 13%)	(Bukstein et al., 2003; Volovitz et al., 2000)

1.4 Identifying knowledge gaps and research needs

There is a need to develop better medicines for children. Current medicines in the market are not always suitable for children, thus manipulation and compounding has become common practice. The development of age-appropriate pharmaceutical products is a challenging task due to the combined demands of industry, healthcare providers, caregivers and patients. Flexible solid dosage forms arise as suitable alternatives to conventional formulations with higher potential to meet such demands.

Novel dosage form designs bring new opportunities in the field, but some technologies are still limited in their ability to meet the needs of all patients. For example, ODFs are becoming increasingly popular although there are technical barriers that need to be overcome to broaden the spectrum of APIs and doses that can be delivered; until these barriers are overcome, ODFs cannot be considered a *flexible technology platform* capable of meeting the needs of broad populations. Similarly, chewable tablets could be appropriate in some cases but, given the need to chew up the formulation, they have lower potential to be transferable to some of the patients in most need, such as geriatrics and neonates. Further consideration will not be given to ODFs and chewables, which were deemed out of the scope of this thesis.

Some of the reviewed technology platforms for the preparation of age-appropriate medicines for children are already proving relative success. ODTs have been commonly used by industry in recent years to enable product line extension as well as addressing paediatric patient needs. Meanwhile, pellets and mini-tablets offer potential advantages for paediatric patients although there is still, even if encouraging, limited evidence to support their suitability for young children. The focus of the research described in this thesis was directed towards enhancing evidence of palatability and acceptability of these dosage form designs which hold high potential to become the formulations of choice for children and other patients in need.

There is still limited evidence and thus lack of understanding of the effect of drug product design on patient acceptability (van Riet-Nales et al., 2010). Although a range of studies investigating acceptability of flexible solid dosage forms in children were identified, details about the formulation were often not provided. In studies with (oro)dispersible tablets, the formulation composition is critical since the tablet needs to disperse rapidly and provide appropriate palatability, but information about excipients is very rarely disclosed (often due to intellectual property). Similarly, studies with multiparticulates not always provided essential details about the formulation, such as particle size, shape or amount of multiparticulates and vehicle used (if any). Research is required in this field to allow correlation between formulation factors and patient acceptability.

It is acknowledged that patient acceptability is influenced not only by formulation attributes but also characteristics of the patient (e.g. disease type and stage). In this regard, acceptability studies performed in the targeted patient population could provide a more accurate insight into the *true* acceptability of the formulation. On the other hand, in studies nested to clinical trials, it can be difficult to deconvolute the effect of the dosage form design from the effect of the efficacy/safety balance of the drug product (e.g. appearance of adverse events). In contrast, studies in healthy subjects using placebo formulations can provide fundamental understanding of acceptability of different dosage form designs, which will be the focus of the work described in this thesis.

Exploratory studies using placebo mini-tablets have dramatically changed our views on appropriateness and acceptability of solid dosage forms in children, indicating that solid dosage forms can be accepted by children from just 6 months of age (Klingmann et al., 2013; Spomer et al., 2012; Thomson et al., 2009). These findings provide the foundation to conduct further studies of flexible solid dosage forms in children. Interestingly, such studies have focussed on the investigation of mini-tablet with a diameter of 2 to 3 mm, although there is still very scarce evidence of acceptability of multiparticulates of smaller size. Tableting technologies can be used to prepare small tablets of a minimum diameter

around 2 mm, however, multiparticulate formulations based on pharmaceutical pellets or beads can be manufactured to smaller sizes, typically below 1 mm. Investigation of acceptability of such multiparticulate formulations is considered paramount.

In their Expert Meeting Report on Dosage Forms of Medicines for Children, the World Health Organisation (WHO) identified a list of critical research needs in the development of age-appropriate paediatric medicines, including (i) investigation of the particle sizes than can be comfortably and safely ingested at different ages, (ii) requirements for 'granularity' (i.e. size of the components of the medicine) and 'texture' or 'mouth feel' (i.e. the feeling of a suspension in the mouth) and (iii) development of standards for palatability and acceptability testing of pharmaceuticals (WHO, 2008). The experimental work described in this thesis attempts to bring some insight into these unexplored scientific questions.

1.5 Thesis Aims and Outline

The overall aims of this thesis are:

1. To review knowledge and identify barriers for the development of age-appropriate medicines for children (Chapter 1).

Although liquid dosage forms have been the formulation of choice for paediatrics, there has been a recent shift towards solid dosage forms. Research and development of flexible solid dosage forms, which can be administered in more than one manner, should be prioritised. These include multiparticulate formulations and (oro)dispersible tablets, which offer combined benefits of solids and liquid formulations, such as favourable stability profile, flexible dose titration and ease of administration.

2. To optimise methodology for palatability and acceptability testing of pharmaceutical products in children and adults (Chapter 2 and Chapter 3).

The European Paediatric Regulation established an obligation to develop acceptable medicines for children. The design and development of paediatric medicines should be driven by the needs and preferences of the patient. However, ten years after this regulation came into force, there is still a lack of standardised methodology for palatability and acceptability testing. Development of *best practices* for palatability and acceptability testing could guide the development of better medicines.

3. To generate evidence to fill some of the knowledge gaps around acceptability of flexible solid dosage forms (Chapter 3, Chapter 4 and Chapter 5).

Despite potential benefits of flexible solid dosage forms, evidence of acceptability is still scarce. Evaluating and understanding the effect of different formulation factors on palatability and patient's acceptability is paramount to enable patient-centric design of these formulations. This includes the effect of particle size, dose volume and liquid vehicle on acceptability of multiparticulates and the effect of excipients composition on palatability and acceptability of (oro)dispersible tablets.

Specific aims and objectives are outlined further in each chapter.

Chapter 2

Optimisation of research methodology for assessment of palatability and acceptability of multiparticulates

This chapter describes a screening study to develop methodology for the assessment of palatability and acceptability of multiparticulate formulations. Twenty-four untrained adult panellists evaluated placebo formulations with different amounts and sizes of the multiparticulates; formulations dispersed in water were compared to multiparticulates administered directly in the mouth as a dry dose. During an initial session samples were evaluated using a swirl and spit methodology to allow familiarisation of the participants with the samples and the evaluation tools and, in a follow-up session, participants swallowed the samples reproducing the normal administration of a medicine. Based on the results of this trial, the methodology was optimised for future research.

2.1 Introduction

Multiparticulate formulations offer a range of potential advantages over conventional tablets and capsules for the paediatric population, such as ease of swallowing, increased flexibility of administration, and suitability for taste-masking and controlled-release (Lopez et al., 2015). Taste issues can be overcome via film-coating of multiparticulates to prevent release of the (poor tasting) drug(s) in the mouth. In turns, oral grittiness (i.e. rough mouth feel) becomes a major determinant of palatability of multiparticulates (Kimura et al., 2015; Lopez et al., 2016). Oral grittiness could have a detrimental effect on palatability and thus patient's acceptability and compliance to a therapeutic regime. Evaluation of the effect of different formulation factors on grittiness and overall palatability of multiparticulates could guide the development of more palatable formulations that are better accepted by patients.

Multiparticulates could be administered directly in the mouth followed by water or, conversely, pre-dispersed in a suitable vehicle (such as water) to be taken as a suspension (EMA, 2006). The influence of the administration technique on palatability and product acceptance has not been investigated yet. Besides, the amount of multiparticulates that can be accepted in a single dose is unknown and the combined effect of size and amount of multiparticulates on palatability remains unclear. A previous study by Kimura et al. (2015) evaluated the effect of particle size on rough mouthfeel and overall palatability using a fixed amount of multiparticulates equal to 75 mg (Kimura et al., 2015). In the present study, greater amounts of multiparticulates were used, which would allow delivery of less potent drugs, such as antibiotics and anti-inflammatory drugs, which require doses greater than 100 mg (WHO, 2009). The effect of the administration approach and the amount and size of multiparticulates was evaluated simultaneously in the present study.

Previous studies of palatability and acceptability of multiparticulates have been based on a swirl and spit methodology whereby palatability attributes are evaluated by placing a sample in the mouth and swirling it around for a predefined period of time before spitting it out (Kimura et al., 2015; Kluk and Sznitowska, 2014; Lopez et al., 2016). This methodology is generally accepted for the assessment of organoleptic properties of pharmaceutical products (most commonly taste assessment), e.g. (Kim et al., 2013; Mahrous et al., 2016; Maniruzzaman et al., 2012). However, swallowing of the samples would allow evaluation of ingestion and post-ingestion phenomena (e.g. ease of swallowing and presence of residual sample in the mouth after swallowing), which are also deemed important to the overall product acceptability. In the study described in this chapter, multiparticulates were evaluated via swirl and spit methodology and, in a subsequent session, after swallowing of the samples to reproduce the normal administration of a medicine. This allowed familiarisation of the participants with the formulations and evaluation tools during the initial swirl and spit session.

Evaluation of palatability and patient acceptability of placebo formulations in healthy volunteers can provide fundamental knowledge and understanding of dosage form design acceptability (Ranmal et al., 2016). Such studies require special consideration of a range of test methods and conditions which help to minimise biases which can arise by psychological and physiological factors (Table 2.1).

Table 2.1. Methodological considerations in the design of sensory evaluation studies, such as palatability and acceptability testing; adapted from (ASTM, 2003; Mason and Nottingham, 2002).

Parameter	Considerations
Population	
Skill development	Test and evaluation tools should be designed based on the skills of participants (age, developmental stage, health condition, etc.)
Prior training	No need for training, but participants should be briefed in terms of method, questionnaire, length of trial and number of samples
Number of subjects	Varies based on objective, test design and scope. In general, pilot study = 20+ participants; consumer panel = 100+ participants
Testing area	
Location	Easily accessible but in quiet position. Close proximity to preparation area, but separated. A separated waiting room can be useful.
Space	Sufficient space for movement of tasters and serving samples. Participants must be given sufficient level of intimacy while testing.
Interferences	Area must be free from noise and odours. Lighting, temperature and relative humidity should be constant, comfortable and controllable.
Study design	
Procedure	Affective test (consumer preference or acceptance), analytical test (discrimination/description of attributes) or combination of both
Presentation	Samples should be blinded and presented in randomised order Information about treatments should not be provided to participants
Timing	Length of the trial kept to a minimum to reduce fatigue, but sufficient time between samples to minimise discomfort and carry over effects
Evaluation tool	Hedonic scales, Likert-type scales, Visual Analogue Scales (VAS) or Just-About-Right scales (JAR) are commonly used
Legal aspects	
Safety	It is responsibility of the investigators to make sure that no harm occurs as a result of faulty products or test facilities
Ethics	Studies should be reviewed by a Research Ethics Committee (REC) Participants must provide written consent to participate

A questionnaire for data collection was purposely designed for this study, using a range of hedonic scales and open-ended questions. This questionnaire was designed on the basis of previous research which gathered opinions and preferences of children and adolescents (Mistry et al., 2016). Design of an age-appropriate data collection form was considered important as this would allow transferability to studies in children in the future. A group of untrained panellists was recruited for the study to measure acceptability in a model population, without specific knowledge or training on palatability evaluation. Research suggest that untrained panellists can provide the same discrimination as trained panellists when the number of subjects in the former is sufficiently large (Husson and Pages, 2003). Previous studies have demonstrated that 15-18 participants are enough to detect significant differences between samples using categorical scales (Hayakawa et al., 2016; Kimura et al., 2015). A designated room at UCL School of Pharmacy was prepared for the study, based on the considerations listed in Table 2.1.

2.2 Aims and objectives

The aims of this study were to develop methodology for palatability and acceptability testing; to investigate the size and amount of multiparticulates that can be accepted by a model population of healthy adults; and to investigate the effect of the administration approach (dry dose versus pre-dispersion in water) on palatability and acceptability.

2.3 Materials and methods

2.3.1 Materials

Microcrystalline cellulose (MCC) pellets (Cellets®) were provided by Pharmatrans Sanaq AG (Basel, Switzerland); a range of particle sizes were procured and characterised (Table 2.2). From those, Cellets 200 and Cellets 500 were used in the sensory evaluation study described in this chapter. Buxton spring water was procured from Nestle Waters Ltd. (Rickmansworth, Hertfordshire, UK); transparent 30ml polypropylene universal

tubes from Wheaton Ltd. (Rochdale, Lancashire, UK); and white plastic cup (180cc) were purchased from Office Depot Inc. (Raton, Florida, USA).

Table 2.2. Particle size descriptors of Cellets as provided by the manufacturer.

Sample ID	Particle size (μm) [†]	Sphericity	Swelling (ml/g)
Cellets 200	200-355	≥ 0.9	≤ 2
Cellets 350	350-500	≥ 0.9	≤ 2
Cellets 500	500-710	≥ 0.9	≤ 2
Cellets 700	700-1000	≥ 0.9	≤ 2

[†] Particle size provided by supplier, $\geq 85\%$ of particles within given range

2.3.2 Material characterisation

The morphological features of Cellets were imaged using Scanning Electron Microscopy (SEM). Samples were adhered onto aluminium stubs (TAAB Laboratories, Reading, U.K.), sputter coated with gold under vacuum and then imaged at different magnification levels using a Quanta 200F instrument (FEI, Hillsborough, OR, USA). The aspect ratio of the particles was calculated as $d_{\text{min}}/d_{\text{max}}$ (where d_{max} is the major diameter and d_{min} is the minor diameter) and the circularity factor was calculated as $4\pi A/P^2$ (where A is the area and P is the perimeter), by taking measurements of more than 50 particles using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

The particle size distribution of the granules was assessed by laser diffraction using a Mastersizer 3000 fitted to an Aero S and a Hydro MV feeding systems for dry and wet dispersion, respectively (Malvern Scientific, Worcestershire, UK). The air pressure and feeding rate were optimised to allow dry dispersion of the particles. Wet dispersion method was carried out using deionised water as dispersant; samples were pre-dispersed in deionised water for nearly 60 min before analysis to allow water sorption equilibrium. Six replicates of each sample were tested; average values of six replicates were calculated for D_{10} , D_{50} (median diameter) and D_{90} parameters.

2.3.3 Sensory evaluation experiments

2.3.3.1 Study design

Twenty-four healthy adult volunteers were enrolled in a single-centre, randomised, factorial, two-session, single-blind sensory evaluation. The study was approved by UCL Research Ethics Committee (ERN_4612-007) and was conducted in dedicated facilities at UCL School of Pharmacy.

The study was conducted in two sessions taken place in two separate days (Figure 2.1). During the first session samples were evaluated using a 'swirl and spit' methodology whereby subjects placed the sample in their mouth for approximately 5-10 seconds before spitting it out. For the second session subjects were asked to swallow the sample. The same range of samples were evaluated in both sessions of the study, allowing comparison between both testing methodologies.

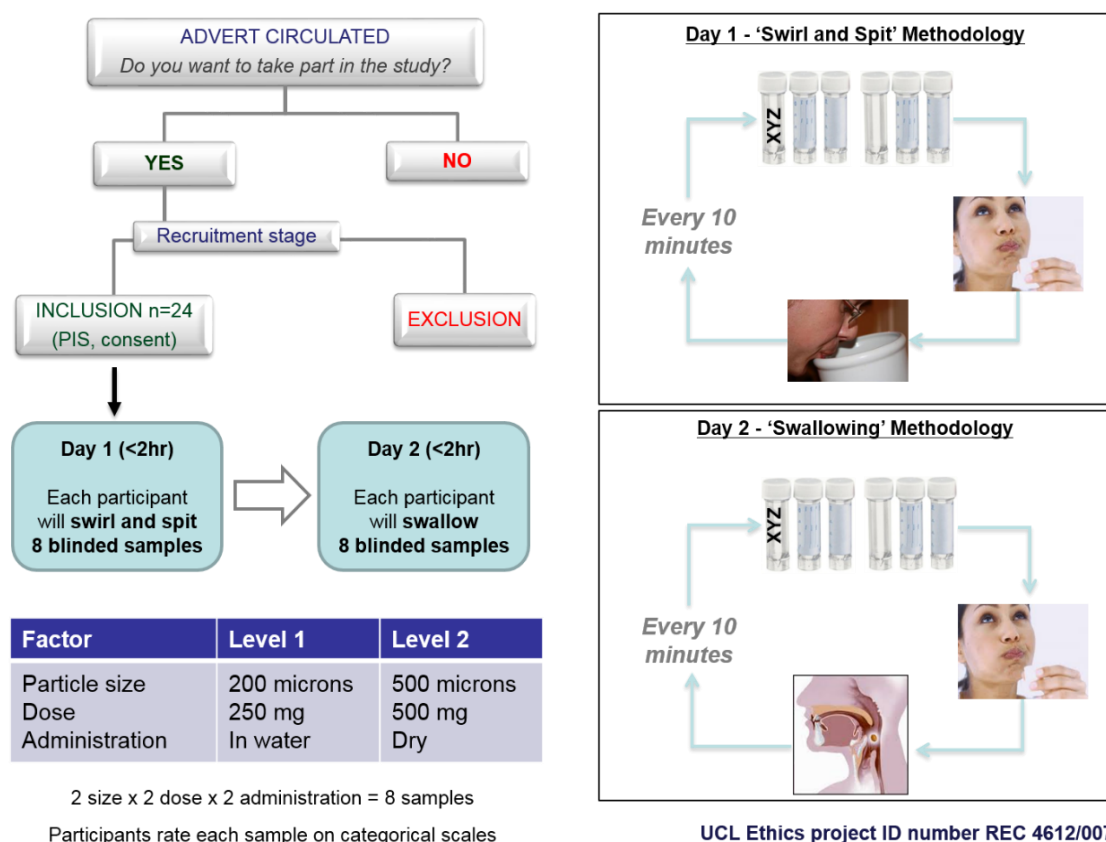


Figure 2.1. Diagram depicting the randomised, factorial, two-session, single-blind study design.

During each session, volunteers were handed samples of Cellets in transparent plastic tubes, blinded with a random 3-digit code. The administration sequence was individually randomised for each participant. Samples contained a predefined amount of Cellets (either 250 or 500 mg) of distinct particle size distribution (either 200-350 μ m or 500-710 μ m), as shown in Table 2.3. Half of the samples were pre-dispersed in 10ml of water (wet administration) whereas the other half were given as a dry amount of Cellets to be administered directly in the mouth followed by water (dry administration). In the case of pre-dispersed samples, subjects were advised to turn the sample upside down before administration to aid homogenous dispersion of Cellets. A 5-10-minute interval was respected between samples to minimise subject discomfort and carryover effect.

Table 2.3. List of formulations assessed in sensory evaluation experiments.

ID	Administration	Particle size (μm)	Amount (mg)
F1	Dry	200-355	250
F2	Dry	200-355	500
F3	Dry	500-710	250
F4	Dry	500-710	500
F5	Wet	200-355	250
F6	Wet	200-355	500
F7	Wet	500-710	250
F8	Wet	500-710	500

A plastic cup with 150 ml of water was provided alongside each sample and volunteers were asked to take as much water as needed to wash the sample out of their mouth (session 1) or to achieve complete sample intake (session 2). The volume of water consumed per sample was back-calculated by measuring the volume of water left in the cup after each sample. Additionally, subjects had free access to water during the inter-sample intervals to clean their palate.

2.3.3.2 Evaluation tool and outcome measures

A digitalized questionnaire (Qualtrics.com) was used for data collection. Immediately after sample expectoration or swallowing (session 1 and 2, respectively) volunteers were asked to rate several sample attributes using 5-point hedonic scales, including ease of swallowing (session 2 only), grittiness, sample volume and taste (Figure 2.2). Volunteers could also provide voluntary written feedback using their own words. Finally, the future willingness of the volunteers to take multiparticulates was measured using a bipolar (yes/no) question: “If this was a medicine, would you be willing to take it every day?”.

How did you find swallowing this sample?



If this was a medicine what did you think of the grittiness of the sample?



If this was a medicine what did you think of the overall volume of the sample?



If this was a medicine what did you think of the overall taste of the sample?



Figure 2.2. Hedonic scales for evaluation of swallowing, grittiness, sample volume and taste.

2.3.3.3 *Measurement of dosing accuracy*

During the first session of the study (swirl and spit methodology) it was observed that a significant proportion of volunteers did not take the full amount of multiparticulates, leaving a substantial residue in the dosing vial. During the second session of the study (swallowing methodology), sample vials were recovered immediately after administration by the volunteers and the remaining amount of Cellets in the sample was quantified to evaluate dosing accuracy. In the case of samples administered as a dry dose the residual amount of Cellets was directly weighed out. For samples administered pre-dispersed in water residual samples were oven-dried at 60 °C until constant weight was reached. The quantity of residual Cellets was expressed as a percentage of the initial amount dose.

2.3.3.4 *Data analysis*

The number of participants required to detect significant differences between samples was estimated based on power calculations assuming parametric unimodal distribution, significance (α) of 0.05 and 80% power; a sample size of 14 would show the difference between two samples where the difference was 1 face and the standard deviation was also 1 face on the 5-point hedonic scale. This is supported by previous studies which demonstrated that a group of 15-18 participants is sufficiently large to detect significant differences between samples based on a swirl and spit methodology and using categorical scales for sample evaluation (Hayakawa et al., 2016; Kimura et al., 2015).

For data analysis, the different categories of the hedonic scales were assigned numeric scores (1-5) from lowest to highest stimuli perception, respectively. The volume of water consumed and the amount of multiparticulates left in the dosing vials were treated as non-normally distributed variables based on the Kolmogorov–Smirnov test. Statistical analysis was performed using non-parametric Kruskal-Wallis analysis of variance followed by Dunn’s test as *post hoc* for pairwise comparison, both with 95% confidence. Minitab 17 (Minitab Inc., State College, Pennsylvania, USA) was used for data analysis.

2.4 Results and discussion

2.4.1 Material characterisation

Microcrystalline cellulose pellets used as model multiparticulates were characterised as white, non-friable, rounded particles. SEM images of model multiparticulates revealed their spherical morphology and smooth surface properties, as shown in Figure 2.3. Average particle circularity was determined to be ≥ 0.85 and the aspect ratio ≥ 0.90 for all particle size fractions, demonstrating highly spherical morphology.

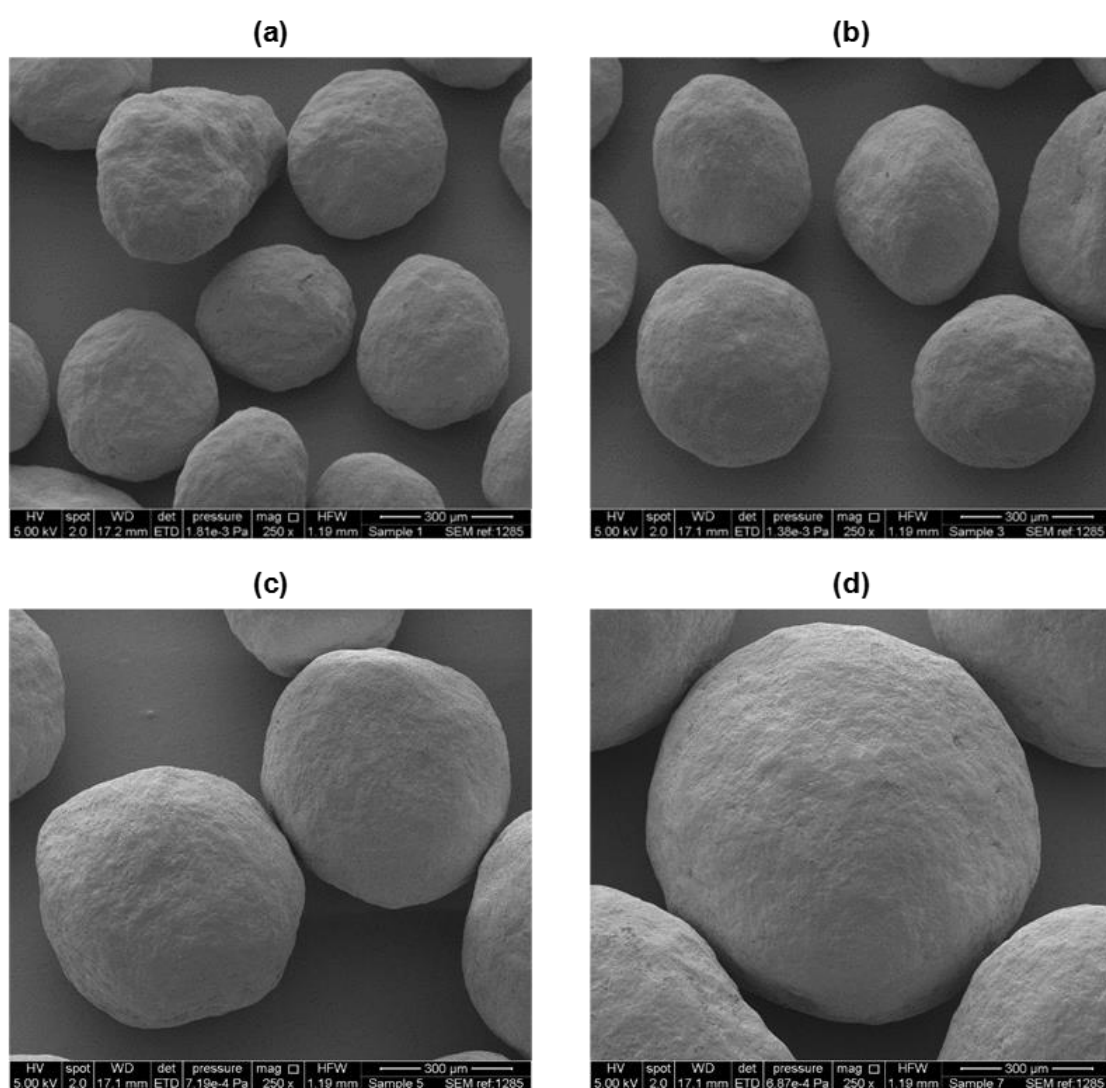


Figure 2.3. SEM micrographs of Cellets with 250x magnification: (a) Cellets 200, (b) Cellets 350, (c) Cellets 500 and (d) Cellets 700. Cellets 200 and Cellets 500 were investigated in the present exploratory study, whereas other size fractions were used in future investigations.

All samples exhibited a narrow, symmetric, unimodal particle size distribution, as shown in Figure 2.4. When assessed by dry dispersion method, the median particle size of Cellets 200, 350, 500 and 700 was 274, 401, 616 and 888 μm , respectively. When Cellets were dispersed in water their median particle size shifted to 305, 494, 635 and 942 μm , respectively. This subtle increase in particle size (11-23% increase with respect to their original size) can be attributed to water sorption and moderate swelling of the cellulosic particles, although all samples retained their narrow, unimodal size distribution.

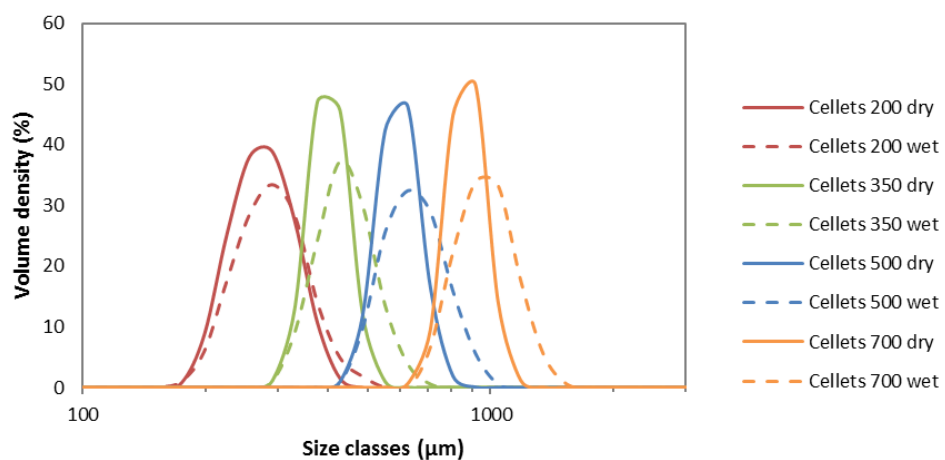


Figure 2.4. Particle size distribution of Cellets assessed by laser diffraction using dry dispersion (solid lines) and wet dispersion (dotted lines) methods.

2.4.2 Sensory evaluation study

2.4.2.1 Demographics

A total of 24 volunteers (10 male and 14 female) participated in the sensory evaluation study. The average age was 26 years, with a standard deviation of 3 years (min. 21 years, max. 33 years) and median at 25 years.

2.4.2.2 Comparison between testing methodologies

Results of hedonic rating for grittiness, sample volume and taste obtained in Session 1 (swirl and spit) and Session 2 (swallowing methodology) are shown in Figure 2.5.

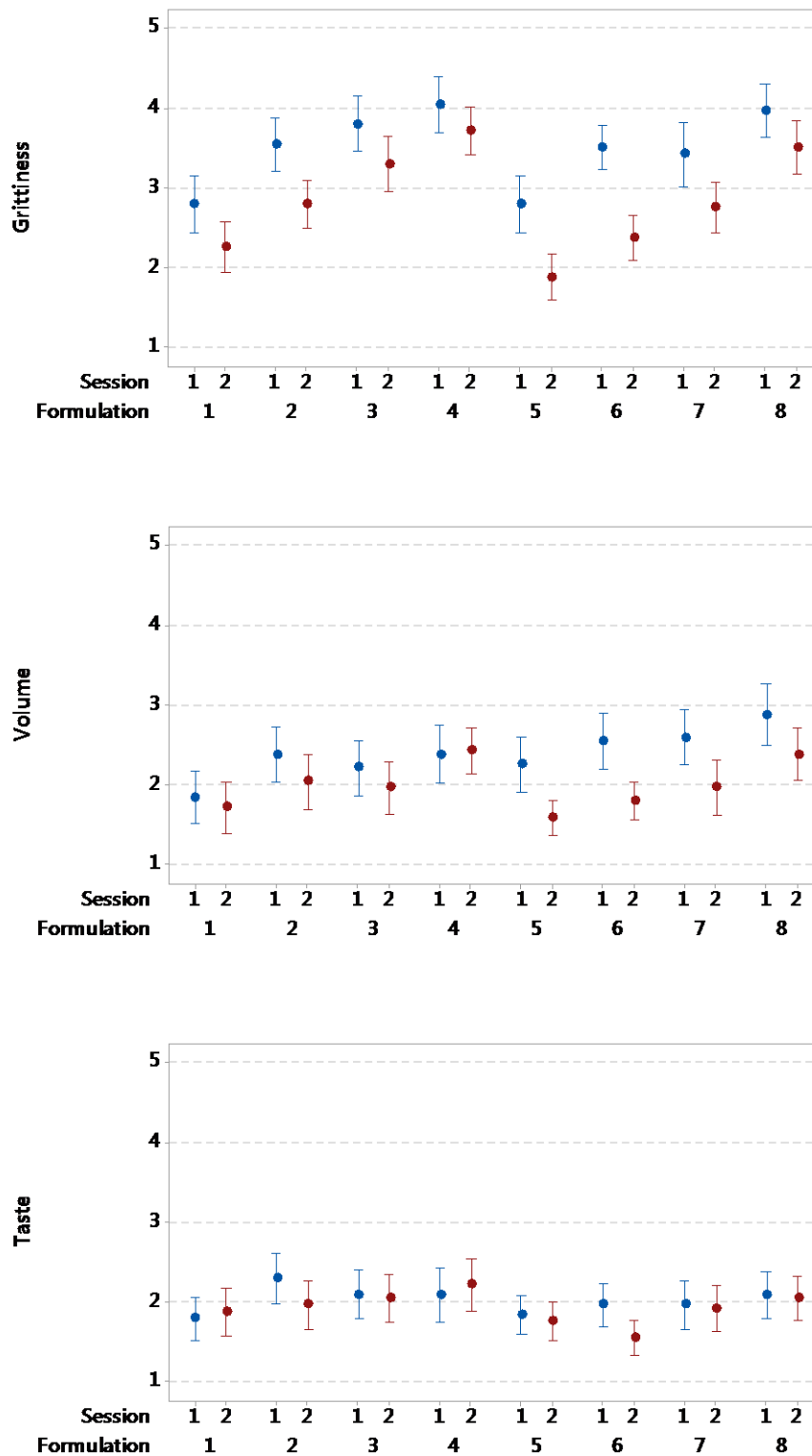


Figure 2.5. Interval plots for grittiness, sample volume and taste as a function of formulation (1-8) and testing methodology (session 1 = swirl and spit; session 2 = swallowing). Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean.

Ratings of grittiness perception were consistently higher when assessed by swirl and spit methodology (Session 1) than when participants swallowed the samples (Session 2); the difference between both sessions of the study was statistically significant ($p < 0.001$). Similarly, the sample volume was considered larger when assessed by swirl and spit methodology than when the samples were swallowed by the volunteers ($p < 0.001$); with greater differences being found for samples administered wet (i.e. pre-dispersed in water, Formulations 5-8) compared to those administered as a dry form (i.e. directly in the mouth, Formulations 1-4). On the contrary, no significant differences were found between testing methodologies in the assessment of taste ($p = 0.191$).

Discrepancies between both testing methodologies could be ascribed to differences in retention time in the mouth and oral processing of samples, which would result in dissimilar appreciation of the sensory stimuli being evaluated. During the first session, participants were instructed to swirl the sample around the mouth for a period of approximately 5-10 seconds before spitting it out whereas in the second sessions participants were instructed to swallow the sample normally (i.e. no instruction regarding retention time in the mouth was given). The duration of the oral preparatory phase in a normal swallowing of samples which do not require mastication can be expected to be shorter than 5 seconds based on previous research; moreover, subjects would attempt to position the sample between the tongue and the hard palate for subsequent transport to the throat rather than swirling the sample around the mouth (Soares et al., 2015).

The longer retention time and swirling of the samples in the mouth would explain the overestimation of the tested stimuli by the former methodology compared to the latter. This was supported by anecdotal feedback, e.g. *“Given the administration, the grittiness is bearable; however, if tried to move the pellets around in the mouth the feeling would be different”* (Participant 07, Formulation 1); or *“as [the sample was] swallowed quickly [it was] not as easy to assess as in the previous [swirl and] spit test”* (P15, F5). However, differences in taste perception were not apparent between both sessions. This could be

explained by the fact that samples were neutral tasting receiving most ratings towards the positive end of the scale (i.e. oral processing of samples becomes trivial as the samples have a plain taste anyway).

Despite the differences in results with regards to the absolute ratings of grittiness and sample volume, the trends obtained in both sessions (i.e. the relative ratings between formulations) were almost identical, as shown in Figure 2.5. This suggests that both methodologies could be equally valid when the aim is to compare between samples and to identify sample preferences. Moreover, all participants performed the swirl and spit session before the swallowing session and thus differences in results could be due to carry over effects; habituation of the participants to the gritty feeling of the samples would explain the more positive results obtained during the second session of the study.

Nevertheless, given the differences found between testing methodologies (or, at least, between sessions of the study), further evaluation of results was carried out using the data obtained during the second session, when participants had to swallow the sample. This methodology can be considered more representative of the actual administration of a medicine. In addition, information about the swallowing phase can only be obtained using this methodology and not with the swirl and spit approach.

2.4.2.3 Effect of the administration approach

Pre-dispersion of multiparticulates in water (i.e. wet administration) had a beneficial impact on grittiness and ease of swallowing, as demonstrated by the reduction of mean hedonic ratings (Figure 2.6). This was supported by anecdotal voluntary feedback, e.g. *“it was very gritty initially but felt less so after taking water”* (P08, F4) or *“since it was given as a powder they [Cellets] stuck on tongue and teeth more than other [wet] samples”* (P15, F2). Differences between dry and wet samples were more significant for ease of swallowing ($p = 0.011$) than grittiness ($p = 0.031$). The administration approach had no significant impact on the rating of sample volume ($p = 0.634$) or taste ($p = 0.264$).

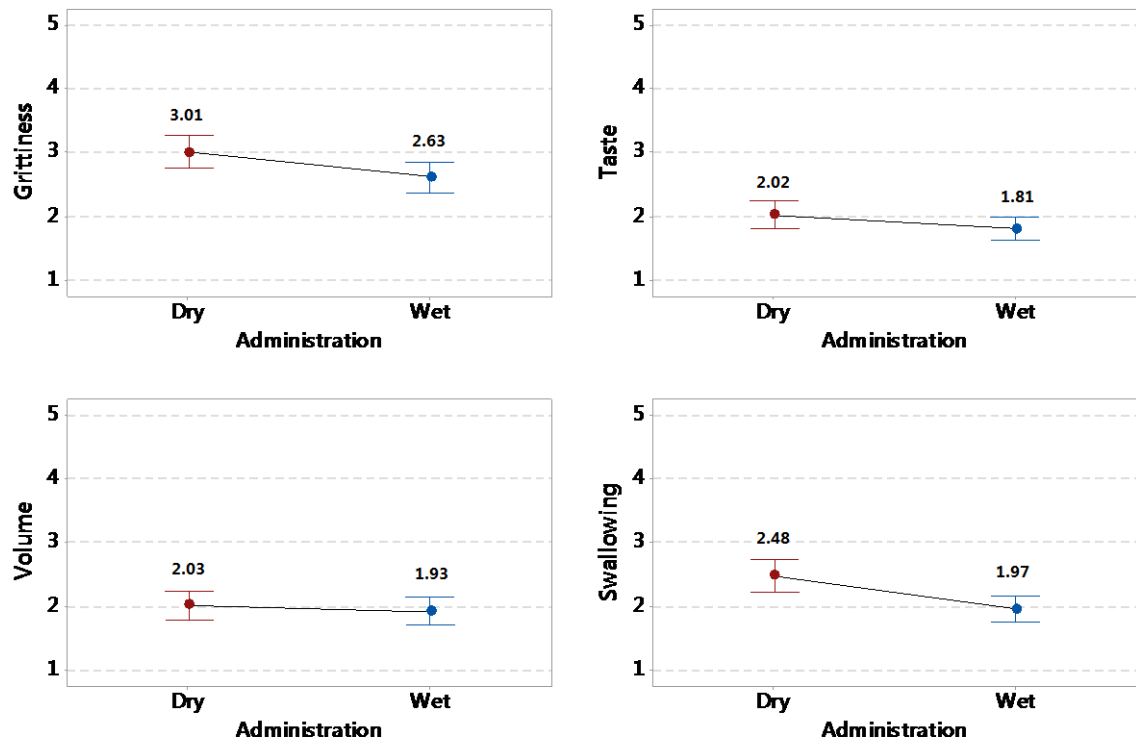


Figure 2.6. Interval plots for grittiness, taste, sample volume and ease of swallowing as a function of the administration approach (Dry: multiparticulates administered directly in the mouth followed by water; Wet: multiparticulates pre-dispersed in water before administration). Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean.

2.4.2.4 Effect of amount and size of the multiparticulates

Oral grittiness was the main barrier to palatability and acceptability, receiving more negative ratings than the rest of the attributes tested (Figure 2.7). This was expected based on previous studies which already reported grittiness as an important palatability barrier, even though smaller particles (Lopez et al., 2016) or inferior amounts of multiparticulates (Kimura et al., 2015) were investigated. Participants reported feeling of multiparticulates in their “mouth”, “lips”, “tongue”, “teeth”, “gums” and “throat” within their voluntary open-ended feedback, regardless of the evaluation technique (swirl and spit or swallowing). Participants reported feeling of grittiness even after swallowing the sample, e.g. “I could fill the ‘bits’ in my mouth even after drinking water” (P08, F6)

Grittiness perception from multiparticulate formulations increased with increasing amount and size of Cellets, as shown in Figure 2.7. Samples containing the largest amount and size of Cellets (i.e. 500 mg of Cellets 500) received grittiness mean scores greater than 3, both when administered as a dry form (3.71) or pre-dispersed in water (3.50). In contrast, samples containing fewer Cellets of the smallest size (i.e. 250 mg of Cellets 200) scored about 1.5 points lower on average (2.25 when administered dry and 1.88 when administered wet). Differences in grittiness perception between formulations were statistically significant ($p = 0.003$ for amount and $p < 0.001$ for size effect).

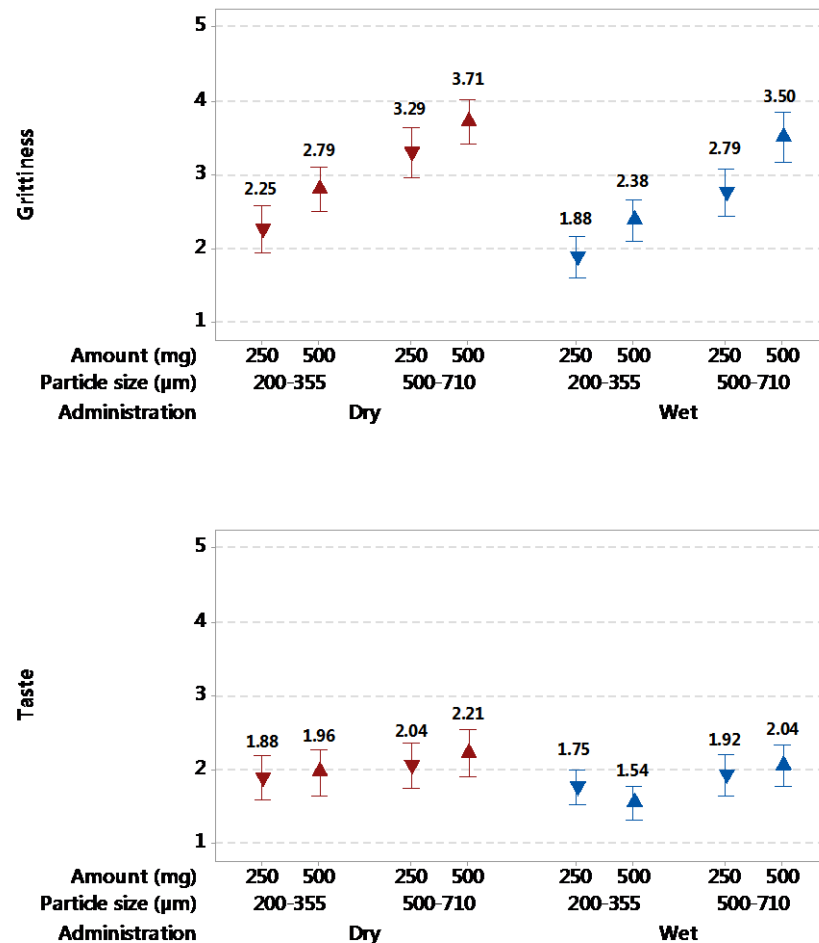


Figure 2.7. Interval plots for grittiness and taste as a function of the administration approach, the size of the multiparticulates and the amount administered. Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean.

Placebo cellulose pellets used as model multiparticulates were considered “*tasteless*” and “*plain*”, as described by the volunteers. In agreement, the mean scores for taste were below 3 for all samples investigated. This is a positive outcome since the samples are intended to represent a taste-masked formulation, which would have no strong taste (if the polymer coating works as intended, avoiding drug release in the mouth). There were minimal differences between samples (Figure 2.7), which were not statistically significant based on the amount ($p = 0.854$) or the size ($p = 0.074$) of multiparticulates.

The sample volume seemed acceptable for an adult population, receiving mean scores below 3 for all formulations investigated (Figure 2.8). This was supported by voluntary feedback, where participants described the volume as “*suitable*”, “*not excessive*” or “*acceptable*”. Although these results suggest that the amount of Cellets was acceptable, the volume of water used for pre-dispersion of wet samples (10 ml) seemed to be too large for some volunteers, who reported their concern, e.g. “*the volume is much, the liquid in the sample make the drug [Cellets] hard to be all swallowed*” (V17, F8). The volume of water used for pre-dispersion of wet samples was described as “*a mouthful*” by the adult volunteers, which suggests that this volume would be too large for a paediatric population. Moreover, a significant effect in volume perception was recorded when the amount of Cellets was doubled from 250 to 500 mg and when the size of the particles was increased from 200-355 to 500-710 μm ($p = 0.016$, in both cases); sample volume being considered larger as the size and/or amount of particles increased.

Overall, ease of swallowing obtained neutral to positive ratings (Figure 2.8), although swallowing issues were reported in some cases. Swallowing difficulties were associated to the multi-unit composition of the formulations and thus the difficulty to swallow the full amount of Cellets in a single gulp, e.g. “*needed several mouthfuls of water to wash the sample completely away*” (P01, F6), or “*particles kept getting stuck in back of my teeth - not easy to swallow*” (P13, F2). Swallowing was considered more troublesome with larger Cellets ($p < 0.001$). Surprisingly, the amount of Cellets had no significant effect on the

reported ease of swallowing ($p = 0.131$), although the trend suggests that 500 mg were slightly more difficult to take than 250 mg (Figure 2.8). Only one participant reported the need to chew on the Cellets to aid swallowing of the formulation (P03, F8).

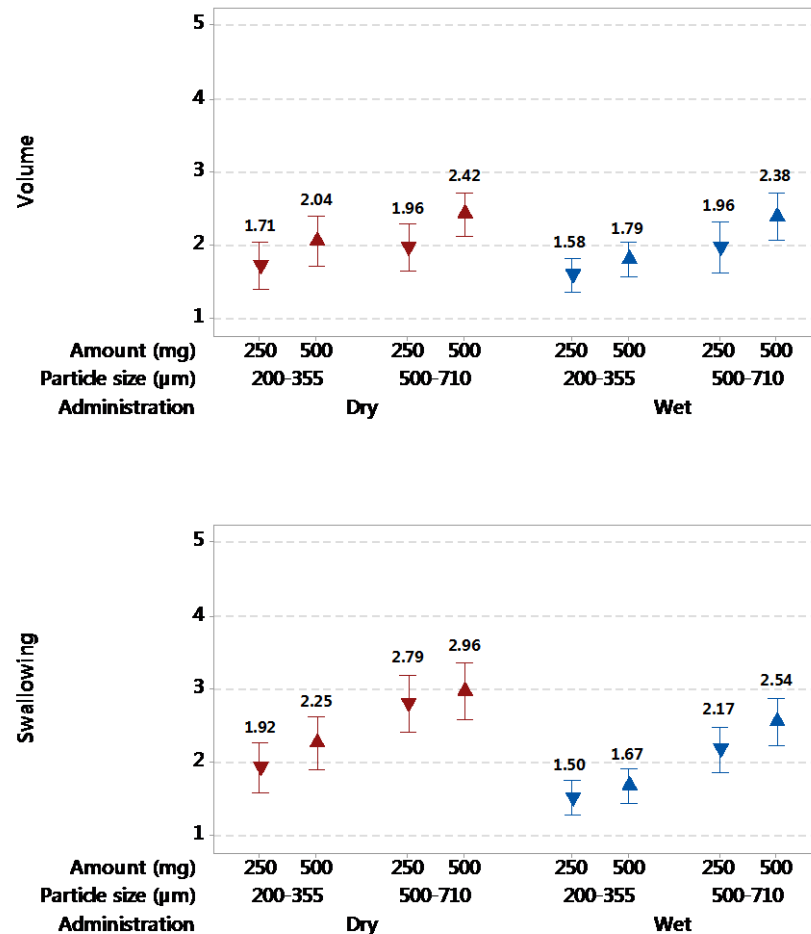


Figure 2.8. Interval plots for sample volume and ease of swallowing as a function of the administration approach, the size of the multiparticulates and the amount administered. Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean.

As shown herein, the mean hedonic scores of sample attributes can be used to compare between formulations and assess the effect of formulation factors on preferences. In addition, it might be beneficial to assess percentage scores (e.g. the proportion of participants who rated sample attributes in the neutral-positive range of the scale), as this would be informative of the acceptability of the sample.

2.4.2.5 Acceptability based on hedonic ratings

Although grittiness was the main barrier to palatability, as described above, more than half of the participants rated grittiness in the neutral-positive range for five out of eight samples (Figure 2.9). Furthermore, those formulations containing smaller multiparticulates (Cellets 200) received over 70% of neutral to positive ratings for grittiness perception. In contrast, taste was not an issue for the participants of the study since more than 85% of them provided neutral to positive evaluation for this attribute.

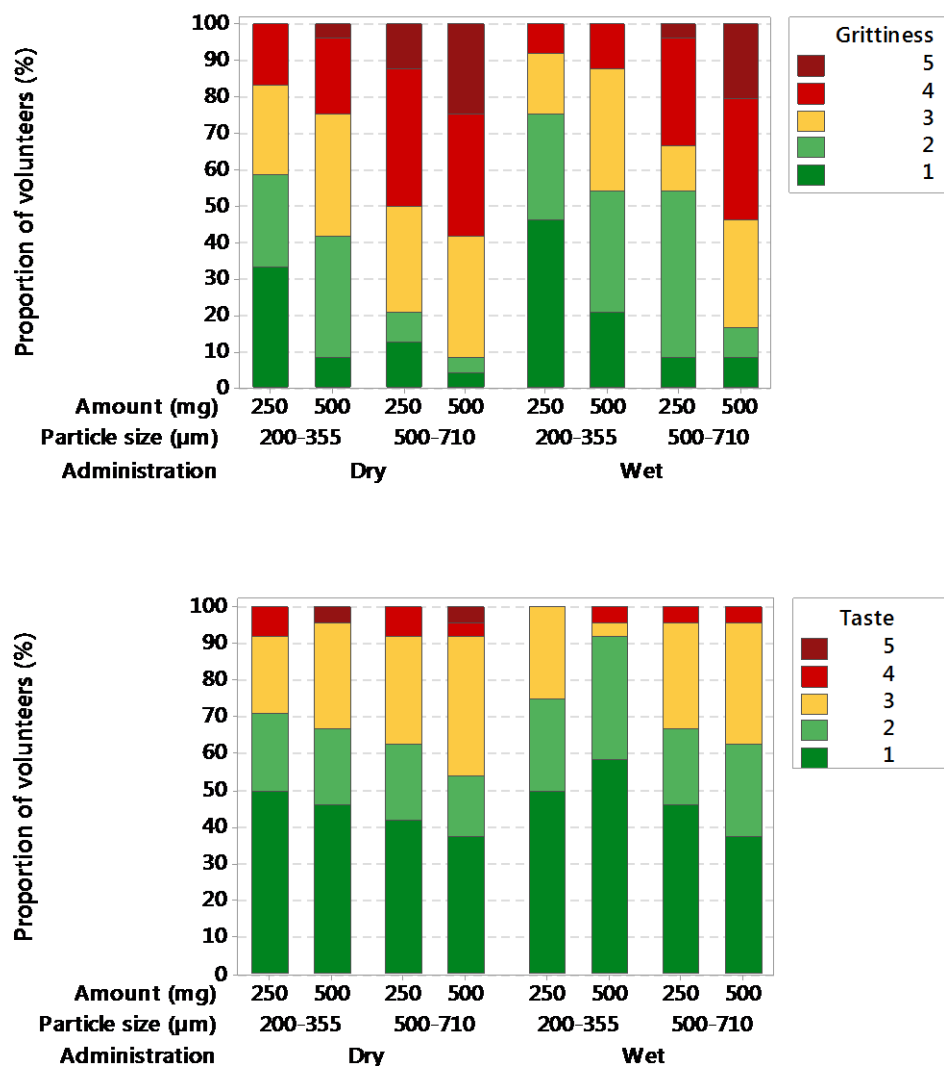


Figure 2.9. Ratings of grittiness and taste (1 – best possible rating and 5 – worst possible rating) as a function of the administration approach, the size of the multiparticulates and the amount administered. Results expressed as percentage of the total respondents (N = 24).

Over 80% of the participants rated sample volume in the neutral-positive range of the scale for all formulations, confirming appropriateness of sample volume for the studied population (Figure 2.10). In terms of ease of swallowing, over 50% of the participants rated all formulations in the neutral-positive range, and this proportion increased to over 80% for samples pre-dispersed in water. Overall, samples containing 200-355 μm particles pre-dispersed in water obtained over 80% of neutral-positive responses for all attributes evaluated (regardless of the amount of particles, either 250 or 500 mg).

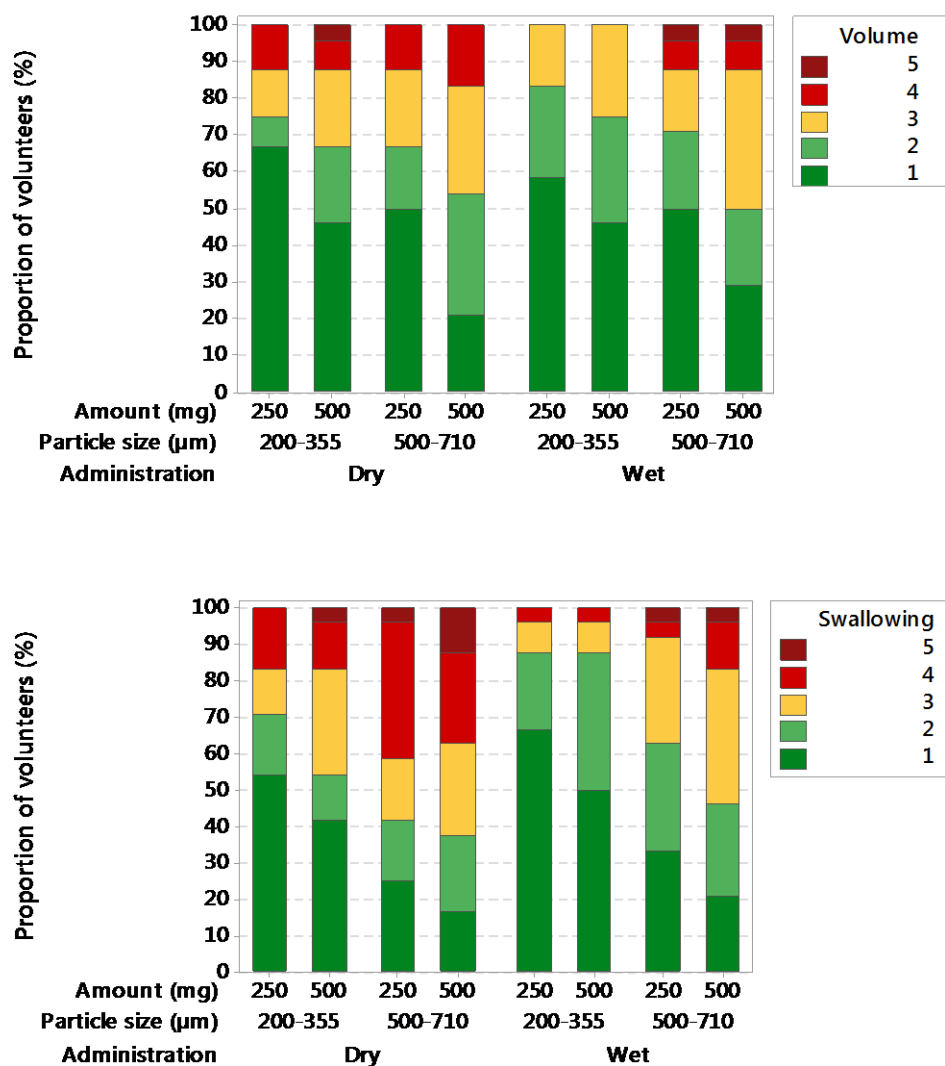


Figure 2.10. Ratings of sample volume and swallowing (1 – best possible rating and 5 – worst possible rating) as a function of the administration approach, the size of the multiparticulates and the amount administered. Results expressed as percentage of the total respondents (N = 24).

2.4.2.6 Willingness to take multiparticulates as a medicine

The proportion of participants willing to take the sample every day if it was a medicine was calculated as a predictive measure of future acceptability (Figure 2.11). Participants were more willing to take multiparticulates every day when these were pre-dispersed in water before administration ($p = 0.003$), and the willingness to take the sample every day also increased with decreasing particle size ($p < 0.001$) and amount of multiparticulates ($p = 0.049$), in agreement with their hedonic evaluation of the samples. In other words, participants reported to be more willing to take every day those samples which they rated positively, as it can be expected. For samples of 200-355 μm pre-dispersed in water over 80% of the volunteers would be willing to take the formulation every day.

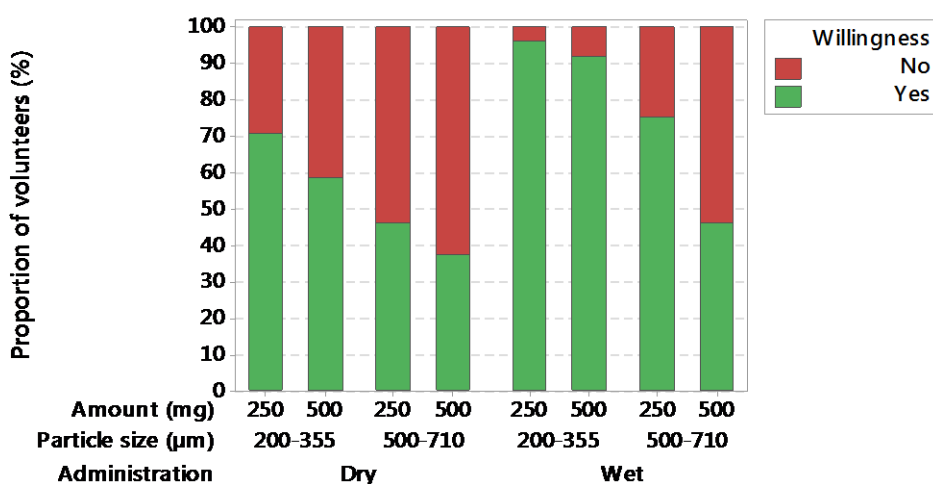


Figure 2.11. Proportion of volunteers 'willing to take the sample everyday if it was a medicine', expressed as a percentage of the total population ($N = 24$).

Samples which participants would be willing to take every day received mean scores of 2.30 for grittiness, 1.61 for taste, 1.59 for sample volume and 1.66 for ease of swallowing; whereas samples which participants would not be willing to take every day received mean scores of 3.79 for grittiness, 2.49 for taste, 2.70 for sample volume and 3.27 for ease of swallowing (Figure 2.12). This provides an indication of the association between both outcome measures (hedonic ratings and willingness to take multiparticulates).

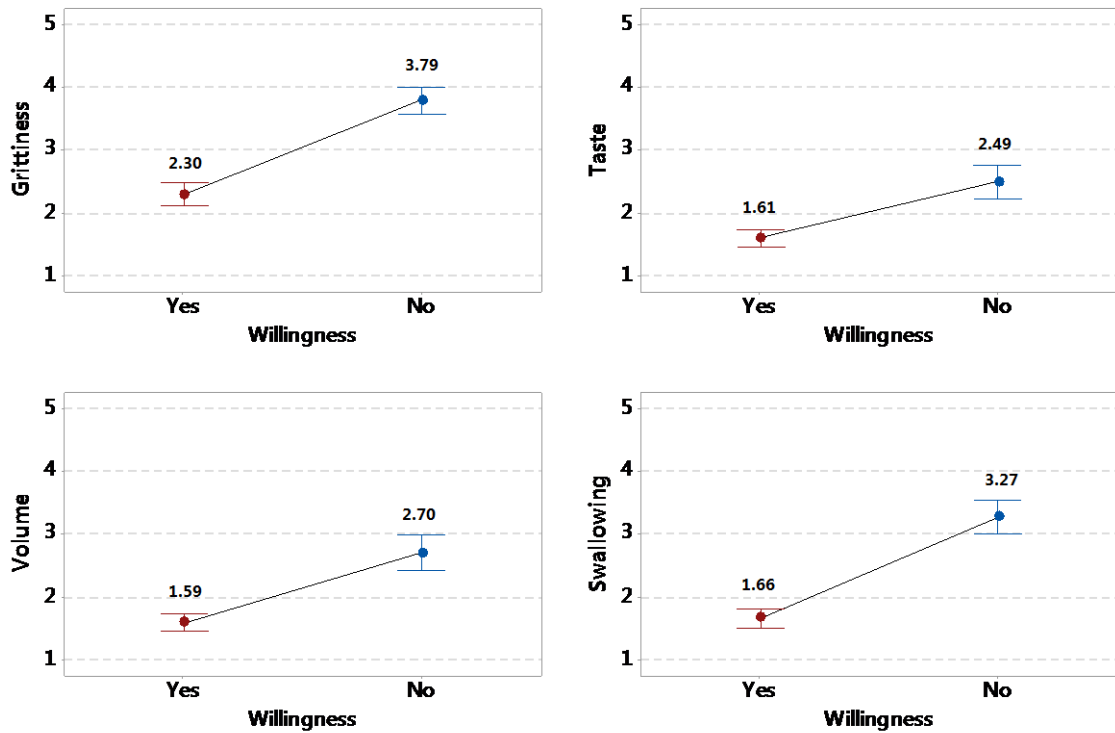


Figure 2.12. Interval plots for grittiness, taste, sample volume and ease of swallowing for samples that participants would be willing or not willing to take every day. Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean.

2.4.2.7 Volume of water consumed

Participants had free access to spring water after sample intake to facilitate swallowing of multiparticulates. The volume of water consumed during sample administration was recorded and results are shown in Figure 2.13.

The average volume of water consumed per sample was 46 ml, although there was a large inter-individual variability (min. 0 ml, max. 150 ml and median 37 ml). The volume of water consumed was larger for samples administered dry (56 ml on average) than for samples pre-dispersed in water (37 ml on average). This difference was statistically significant based on Kruskal-Wallis test ($p < 0.001$). The volume of water needed to complete sample intake increased as the particle size ($p = 0.007$) and the amount of multiparticulates ($p = 0.016$) increased.

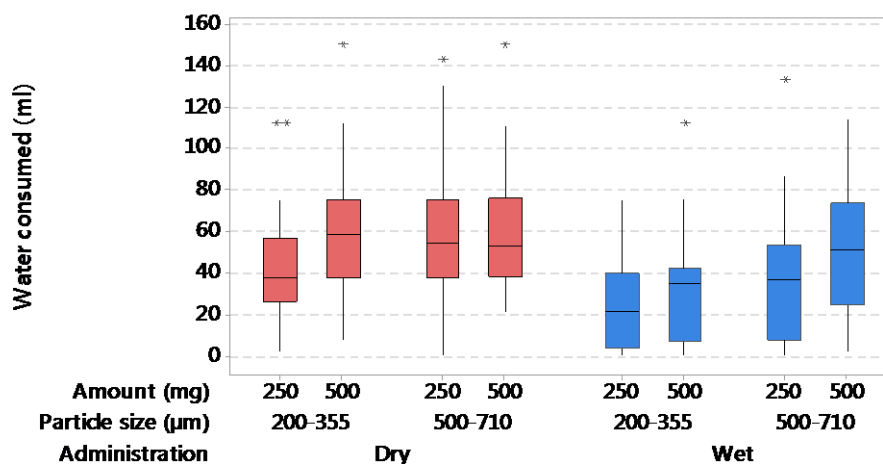


Figure 2.13. Volume of water consumed as a function of the administration approach, the size of the multiparticulates and the amount administered. Centre lines show the median, box limits indicate the 25th and 75th percentiles and outliers are denoted by asterisks. Water used to pre-disperse wet samples (10 ml) was not considered part of the water consumed.

2.4.2.8 Dosing accuracy

Dosing vials were recovered after sample administration and the residual amount of Cellets left in the vial (if any) was quantified (Figure 2.14). Differences were found between dry and wet samples ($p < 0.001$). Volunteers achieved good dosing accuracy with dry samples, leaving a very small proportion of Cellets behind (2.17% w/w on average, with respect to the initial amount). On the contrary, wet samples seemed to be more difficult to administer, as suggested by the larger amount of Cellets found in the recovered vials (10.45% w/w on average). Administration issues with wet samples were identified and reported by some of the volunteers, e.g. “*even with a good mix there are always Cellets that remain in the flask*” (P04, F5, leftover = 23.2% w/w); or “*the issue was trying to get the Cellets out of the flask, almost impossible!*” (P14, F7, leftover = 22.3% w/w). This can be explained by the fact that multiparticulates settled down very quickly and it was virtually impossible to administer the sample as a homogeneous suspension. The size and amount of multiparticulates did not have a significant effect on the dosing accuracy ($p = 0.774$ for size and $p = 0.628$ for amount).

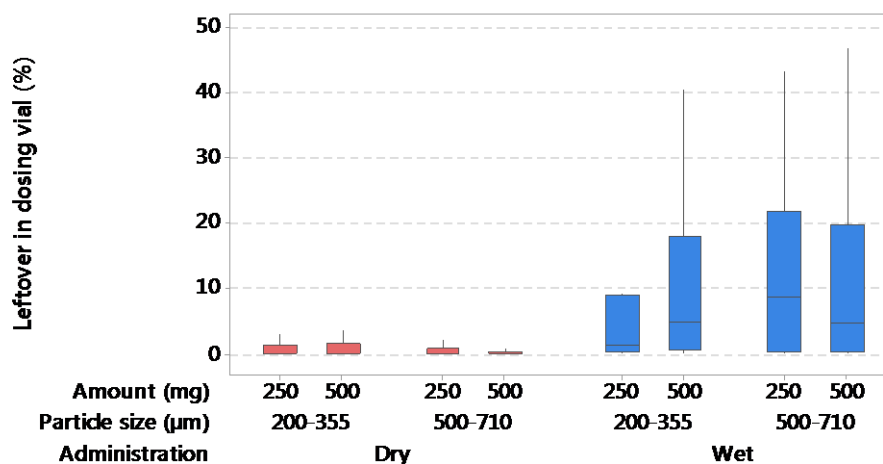


Figure 2.14. Quantity of Cellets remaining in dosing vial after sample administration (expressed as % w/w of the initial amount of multiparticulates) as a function of the administration approach, the size of the multiparticulates and the amount administered. Centre lines show the medians, box limits indicate the 25th and 75th percentiles and outliers are denoted by asterisks.

The poor dosing accuracy obtained with wet samples suggests that the administration approach and/or the dosing device were not appropriate to deliver the sample. This could be simply solved by the patient by rinsing the residual particles in the vial with more water, as reportedly done by some of the volunteers, e.g. “*some particles were left in the tube so I needed to rinse it*” (P09, F6, leftover = 1.5% w/w). Nevertheless, consideration must be given to the dosing device and administration approach in future studies and during product development of multiparticulate formulations.

2.5 Conclusions

Placebo multiparticulate formulations were investigated in a group of twenty-four healthy adult volunteers in a pilot study to develop methodology for palatability and acceptability testing. During an initial session, samples were tested using a swirl and spit methodology and on a follow-up session participants were asked to swallow the samples. Differences between swirl and spit and swallowing methodologies were observed and hypothesised that these differences were the results of a dissimilar retention time and oral processing

of the samples in each testing approach. However, all participants performed the swirl and spit session before the swallowing session and thus differences in results could also be explained by carry over effects. Based on the difference in results between sessions, it was decided to evaluate differences between formulations based on the results of the swallowing session.

Evaluation of the samples by swallowing them rather than by swirl and spit methodology restricted the number of test samples that could be evaluated on a single session but, in turn, provided important information about the ease of swallowing the formulations. Swallowing the samples is preferred for being more representative of the normal administration of a medicine. This method could also be used in future studies to investigate post-ingestion phenomena, such as the presence of residual sample in the mouth after swallowing.

Overall, methodology for the evaluation of palatability and patient acceptability was successfully developed in this study. Results demonstrated that the study design, evaluation tools and number of participants employed were appropriate to detect differences between samples and rank them in order of preference. Moreover, values on hedonic scales and responses about the 'willingness to take the sample as a medicine' provided an indication of the overall acceptability of the samples. Association between hedonic ratings and willingness to take the sample as a medicine suggested internal consistency (reliability) of the outcome measures.

Eight different formulations were tested, half of them were given as a dry dose and the other half were pre-dispersed in water. Participants evaluated a range of sample attributes using hedonic scales. Overall, grittiness perception was found to be the main barrier to palatability and acceptability. Grittiness increased with increasing particle size and amount of multiparticulates, in line with previous studies (Lopez et al., 2016). Swallowing also became more troublesome as the amount and size of multiparticulates

increased, following same trend as grittiness perception. Moreover, the administration approach had a great influence on the acceptability of the product; pre-dispersed samples were considered less troublesome to swallow and less gritty. The taste of Cellets was deemed “*neutral*”, proving that Cellets can be used as a good surrogate of taste-masked multiparticulate formulations. In terms of sample volume, formulations containing either 250 or 500 mg of Cellets were both considered acceptable by the participants of the study. Ratings for taste and sample volume were positive for all formulations and were not affected by the different formulation factors, namely the administration approach, particle size and amount of multiparticulates.

In addition to hedonic ratings of sample attributes, the willingness of participants to take multiparticulates in the future as a medicine was recorded using a bipolar scale. The willingness to take the sample in the future increased for samples pre-dispersed in water as well as for samples containing the smaller size and amount of multiparticulates. This outcome measure proved to be highly linked to the hedonic evaluations of the samples, which indicated correlation between the sample palatability and the willingness to take the sample (i.e. patient acceptability), as it could be expected. As such, this tool might be useful to obtain a comprehensive, net evaluation of the samples.

Issues were found when administering wet formulations due to rapid settling down of multiparticulates in water, which resulted in poor dosing accuracy. This could be overcome in the future by using a different administration device, such as a dosing spoon instead of a dosing vial. In addition, the volume of water used for pre-dispersion needs to be suitable for the intended population. An aliquot of 10 ml was considered mouth-filling and was reported to be too large by some adult volunteers. Thus, a smaller volume is suggested when targeting paediatrics. Nevertheless, additional water was needed to achieve full sample intake. This varied greatly between individuals, but on average the volume of water consumed was 20-60 ml (depending on the formulation).

Chapter 3

Palatability and acceptability of multiparticulates: a comparison between children and adults

This chapter describes a study of palatability and patient acceptability of multiparticulate formulations which encompasses a direct comparison between children and adults. Seventy-one children (4-12 years) and sixty-one adults participated in this study to evaluate the effect of multiparticulate size and the presence of polymeric coating on palatability and acceptability. A mixed-model approach was used for data collection, which included researcher observations (e.g. facial expressions) and subject-reported outcomes (e.g. ratings on hedonic scales). Comparison of outcome measures provided information of the suitability of different data collection tools to evaluate palatability and acceptability in both populations. The benefits and limitations of conducting studies in adult participants as a proxy in the development of paediatric medicines were explored.

3.1 Introduction

Multiparticulates are considered a flexible solid dosage form often proposed as an alternative to conventional solid and liquid formulations for children (EMA, 2006; WHO, 2012). However, evidence to support the utilisation of multiparticulate formulations in children is still limited, even if encouraging. Several randomised trials have recently investigated the acceptability of a single mini-tablet (2-3mm in diameter) in children and neonates (0-6 years) (Klingmann et al., 2015, 2013; Spomer et al., 2012; Thomson et al., 2009; van Riet-Nales et al., 2013), although there is very limited evidence of the administration of multiple mini-tablets at a time (Klingmann et al., 2016; Kluk et al., 2015). Moreover, previous studies with smaller multiparticulates (up to 1 mm in diameter, which could be easier to swallow than larger mini-tablets) have only involved adult participants (Kimura et al., 2015; Lopez et al., 2016). More studies are thus required.

Evaluation of palatability and patient acceptability should form an integral part of the pharmaceutical development studies and the Paediatric Investigational Plan (PIP), as recommended by the EMA in their Guideline on Pharmaceutical Development of Medicines for Paediatric Use (EMA, 2013). Patient's acceptability has been defined as the "*ability and willingness*" of the patient and their caregiver (defined as users) to use the medicine as intended (EMA, 2013). Therefore, acceptability is a multidimensional concept, although the large majority of studies reported in the literature have focussed on a single attribute, such as "*palatability*", "*ease of administration*", or "*ability to swallow the formulation*". For example, previous studies with mini-tablets have investigated the success in swallowing the formulation as a surrogate of patient acceptability (Klingmann et al., 2015, 2013; Kluk et al., 2015; Thomson et al., 2009). In the present study, the ability to swallow the formulation was complemented with other outcome measures of acceptability based on researcher observations and subject reported outcomes.

Ideally, palatability and acceptability testing of paediatric medicines should be carried out in the intended population group, i.e. children (EMA, 2013). However, the pharmaceutical development of paediatric medicines still relies on data from adult populations; although correlation between acceptability in children and adults remains unknown. Therefore, studies investigating the link between children and adults' perceptions of medicines are desirable. Benefits of conducting studies in adults include relative simplicity of safety, ethical, logistic and methodological considerations. Testing with children requires special consideration to their language development, motor skills, and social and psychological development. A guideline of children's skills and behaviours as they relate to sensory evaluation was proposed by the ASTM International in their Standard Guide for Sensory Evaluation of Products by Children (ASTM, 2003), as shown in Table 3.1.

Special attention must be given to the wording of the questions, since children have limited vocabulary and tend to repeat adults' statements and to respond affirmatively to positively-phrased questions (Guinard, 2000). In this study, 'taste', 'texture' and 'sample

volume' were evaluated, as these factors have been identified as significant barriers to the acceptability of oral medicines based on work conducted in a large population of children and adolescents (Venables et al., 2015). The questionnaire used was designed based on previous research which gathered opinions and preferences of children and adolescents (Mistry et al., 2016). Mistry et al. involved the Young Person's Steering Group (YPSG) from the NIHR Clinical Research Network: West Midlands in the design of tools for patient-reported outcomes to ensure age-appropriateness of the scales and wording, so that it can be used without caregiver's involvement (Mistry et al., 2016).

Table 3.1. Summary of skills and behaviours of children, adapted from (ASTM, 2003).

Skill/behaviour	Toddler (1- 3 years)	Pre-school (3-5 years)	Readers (5-8 years)	Pre-teen (8-12)
Language	Cannot read/write Rely on facial expressions	Early language development Can respond to questions	Developing vocabulary skills Early reading/writing	Increasing verbal ability Self-expression improves
Motor skills	Gross motor skills, fine motor skills still limited	Gross and fine motor skills increasing	Hand to eye and other fine motor skills refining	Fine motor skills developed
Attention span	Gaged by eye contact and body movement	Gaged by eye contact or involvement with task	Limited by understanding of task and interest level	Increasing attention span Holding interest still critical
Reasoning	Limited, but concept on "no" becoming a factor	Limited, but beginning to be able to verbalise likes and dislikes	Developing with increased learning of cause/effect concepts	Full ability for understanding and reasoning
Decision making	Do not make complex decisions, but "yes/no" can be decisive	Limited, but able to choose one thing over another	Ability to decide is increasing, but influence of adult approval is evident	Capable of complex decision making
Use of scales	Do not understand scales	Understanding of simple scales begins	Understanding increasing. Simple is best	Understand scales with instruction.
Adult involvement	Trained observer and caregiver	Trained interviewer with or without caregiver	Trained interviewer Able to self-administer	Trained interviewer Able to self-administer

In addition to subject-reported outcomes (i.e. questionnaires and scales to be filled by the participants), researcher observations can also be used. Behavioural observations used in sensory evaluation studies include hand and eye movement, facial expressions, time of consumption and other means of interaction with the product (ASTM, 2003). Guidance on investigation of medicinal products to support labelling claims encourages the use of researcher observations in studies involving children (FDA, 2009; Matza et al., 2013). Thus, in this study, facial expressions and behaviours were recorded.

Due to limited language, motor skills and attention span of children, the length of the testing sessions and the number of products that can be evaluated should be kept to a minimum (ASTM, 2003). Screening studies in the adult population can be a successful technique to reduce the number of samples and refine the study design (ASTM, 2003). The present study was guided by the preliminary trial described in Chapter 2; the main differences between both investigations are outlined in Table 3.2.

Table 3.2. Comparison of exploratory trial in adults and current trial in adults and children.

Parameter	Exploratory trial	Current trial	Remarks
Administration	Dry dose vs. wet dose (in water)	Pre-dispersed samples only	Significantly worse palatability expected from dry dose and wet dose expected in practice
Particle size	Two sizes investigated	Four sizes investigated	Study extended to a broader size range as this is a critical formulation attribute
Coating	Uncoated samples	Uncoated vs. coated samples	Coated samples expected in practice but logistically more difficult to obtain
Amount	250 vs. 500 mg	500 mg	Larger dose was well tolerated in pilot study and allows delivery of less potent drugs
Volume	10 ml of water	3 ml of water	Volume of water used for pre-dispersion of samples (10 ml) was considered too large
Dosing device	Dosing vial	Dosing spoon	Administration issues reported with dosing vial due to rapid sedimentation of particles
Total samples	8 per participant	3 per participant	Number of samples reduced to account for short attention span of children compared to adults

Evidence of acceptability of multiparticulates is still limited and more trials are required to investigate the impact of formulation factors on patient's acceptability. For example, the size of multiparticulates might have an impact on ease of swallowing and mouthfeel perception. Larger multiparticulates can be expected to be less palatable and thus less acceptable than those of smaller size (Lopez et al., 2016). But particle size is an important feature of solid dosage forms which can have an impact on other properties of the formulation too. For instance, the release rate from coated granules has been shown to be proportional to their surface area, thus exponentially thicker coatings were required to control drug release from smaller granules (Ragnarsson and Johansson, 1988).

Another important formulation factor which requires consideration is the application of polymeric coating. Multiparticulates are often designed for taste-masking, thus the final formulation would be film coated with a reverse-enteric coating (which is insoluble in saliva but releases the drug content at the lower pH of the stomach). A smooth polymeric film coating could improve surface properties by reducing surface roughness, which could have a positive impact on palatability. However, the application of a polymeric coating could also increase the size of the multiparticulates, which could have a negative impact on patient acceptability. There is very scarce evidence of the effect of coating on palatability and acceptability. Nevertheless, a previous study of acceptability of mini-tablets (2 mm in size) in infants and pre-school children found no significant differences in acceptability between coated and uncoated minitablets (Klingmann et al., 2013).

3.2 Aims and objectives

The aims of this study were to evaluate palatability and acceptability of multiparticulates in healthy adults and children volunteers and compare the results in both population; to explore different methodologies and enhance knowledge of palatability and acceptability testing; and to assess the effect of formulation factors (particle size and presence of polymeric coating) on palatability and acceptability of multiparticulates.

3.3 Materials and methods

3.3.1 Materials

Microcrystalline cellulose pellets (Cellets®, Pharmatrans Sanaq, Basel, Switzerland) were used as model multiparticulates. The sizes investigated included those at 200-355, 350-500, 500-750 and 700-1000 µm diameter and each particle size fraction was investigated in the form of uncoated and coated multiparticulates (Table 3.3). Coated multiparticulates were produced under Good Manufacturing Practices by Pfizer (Sandwich, United Kingdom) by coating Cellets® with Kollicoat® Smartseal 30D, a reverse enteric coating polymer intended for taste-masking applications.

Table 3.3. Summary of multiparticulate formulations investigated by children and adults.

Sample	Particle size (µm)	Polymer coating	Fixed amount (mg)
C200-u	200-355	Uncoated	500
C350-u	350-500	Uncoated	500
C500-u	500-710	Uncoated	500
C700-u	700-1000	Uncoated	500
C200-c	200-355	Coated	500
C350-c	350-500	Coated	500
C500-c	500-710	Coated	500
C700-c	700-1000	Coated	500

3.3.2 Material characterisation

The particle size distribution of multiparticulates was assessed by laser diffraction using a Mastersizer 3000 fitted to an Aero S accessory for dry dispersion (Malvern Scientific, Worcestershire, UK). The air pressure and feeding rate were optimised to allow dry dispersion of the particles. Six replicates of each sample were tested; average values of six replicates were calculated for D₁₀, D₅₀ (median diameter) and D₉₀ parameters. The morphological features of Cellets were imaged using Scanning Electron Microscopy

(SEM). Samples were adhered onto aluminium stubs (TAAB Laboratories, Reading, U.K.), sputter coated with gold under vacuum and then imaged at different magnification levels using a Quanta 200F instrument (FEI, Hillsborough, OR, USA).

3.3.3 Sensory evaluation study

3.3.3.1 Study design

A palatability and acceptability study of multiparticulate formulations was conducted in children (inclusion criteria: 4-12 years old) and adults (inclusion criteria: 18-40 years old). The study in children was approved by the University of Birmingham Research Ethics Committee (ERN_15-1028) and took place in a designated room at Think-Tank Science Museum (Birmingham, United Kingdom); the study in adults was approved by the University College London Research Ethics Committee (ERN_6062-001) and was conducted in a designated room with a dispensary at the UCL School of Pharmacy. Adult participants and parents/carers of children participants received a detailed information sheet and signed informed consent; the study was also explained to children, who assented to participate in the study. The study design is outlined in Figure 3.1.

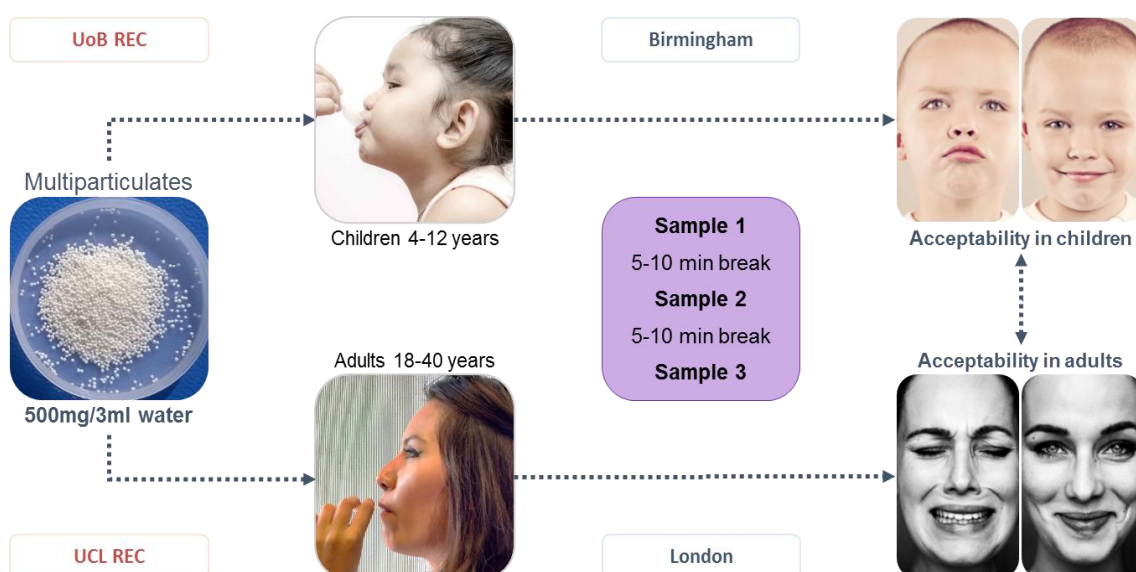


Figure 3.1. Schematic representation of the study design for the evaluation of palatability and acceptability of multiparticulate formulations in children and adults.

Each participant received three 500 mg samples of placebo multiparticulates on a medicine spoon with approximately 3 ml of spring water that was added immediately before sample administration (Figure 3.2). Samples were self-administered by the participants, except for a few cases where the sample was administered to the child by one of the researchers to avoid spillages. Participants had free access to spring water as required to complete sample intake. An interval of 5-10 minutes was maintained between samples to minimise subject discomfort and carry over effect.



Figure 3.2. Samples of 500 mg of multiparticulates dispersed in 3 ml of spring water on a medicine dosing spoon. Particle size of the multiparticulates varies, from left to right: 200-355, 350-500, 500-710 and 700-1000 µm. Each size was available as coated and uncoated versions.

The study took place over eight sessions (S1 - S8), with 6 to 14 participants per session to ensure a balanced ratio between participants and researchers (4-6 researchers). The first part of the study (S1 - S4) was dedicated to the evaluation of the effect of particle size and thus each participant received three samples of varying particle size (all samples were polymer coated for this part of the study). The second part of the study (S5 - S8) was dedicated to the evaluation of the effect of coating and thus each participant received two samples of identical particle size, one coated and one uncoated, plus an additional uncoated sample. The dosing schedule is summarised in Table 3.4.

Table 3.4. Dosing schedule for the sensory evaluation of multiparticulates. Numbers indicate the order in which samples were administered in each of the eight sessions (S1-S8).

Sample	S1	S2	S3	S4	S5	S6	S7	S8
C200-c	1	3		2	1			
C350-c	2		3	1		2		
C500-c		2	1	3			2	
C700-c	3	1	2					1
C200-u					2	3		
C350-u					3	1		
C500-u							1	3
C700-u							3	2

3.3.3.2 Evaluation tools and outcome measures

Researcher observations

Participants' facial expressions and negative behaviours towards the samples were recorded prior to, during and post sample intake using a 12-point tick chart (Table 3.5). Each participant was observed by two researchers who evaluated the occurrence of facial expressions and behaviours listed on Table 3.5. Spontaneous verbal judgement of the samples was also recorded in researcher observation sheets.

Table 3.5. Researcher observations 12-point tick chart for assessing negative facial expressions and behaviours of participants prior to, during and after sample intake.

Negative behaviours		Facial expressions
Before administration	After administration	During administration
<input type="checkbox"/> Refuses test sample	<input type="checkbox"/> Spits out test sample	<input type="checkbox"/> Pursed lips
<input type="checkbox"/> Voices resistance	<input type="checkbox"/> Voices disgust	<input type="checkbox"/> Nose wrinkle
<input type="checkbox"/> Cries/screams	<input type="checkbox"/> Cries	<input type="checkbox"/> Brow bulge (frown)
<input type="checkbox"/> Requires restraint	<input type="checkbox"/> Vomits	<input type="checkbox"/> Eyes squeezed shut

The proportion of participants who swallowed the complete dose of multiparticulates (as opposed to those who spat out the sample or refused it) was determined as a simple and objective measure of the overall patient acceptability, as used in previous studies with mini-tablets (Klingmann et al., 2015, 2013; Kluk et al., 2015; Thomson et al., 2009).

The sum of negative facial expressions and behaviours was calculated to investigate participants' affective response and sample preferences. The proportion of participants who showed no negative facial expressions during sample intake was determined as a measure of acceptability based on facial expressions. Negative reactions recorded during sample intake are expected to be a good indicator of sample dislike, based on previous research with school-aged children (Zeinstra et al., 2009).

Subject-reported outcomes

Subject-reported outcomes were collected using a paper-based structured questionnaire (Figure 3.3) that was filled in by the participants of the study immediately after sample intake. The questionnaire was designed based on previous research which gathered opinions and preferences of children and adolescents (Mistry et al., 2016).

Samples were evaluated using 5-point hedonic scales (from 1 – extremely liked to 5 – extremely disliked) for four different palatability attributes: grittiness, sample volume, overall mouthfeel and overall taste. The proportion of participants who rated all sample attributes in the neutral to positive range (hedonic rating = 1-3) was calculated as a measure of acceptability based on hedonic ratings. Participants could also provide voluntary open-ended feedback, which was used to facilitate interpretation of results.

After completion of hedonic ratings, participants answered the following bipolar question: “If this was a medicine, would you be willing to take it every day?”. The proportion of participants that responded positively to this question was calculated as a predictive measure of future acceptability.

ACCEPT: Multi-Particulates



Making children's medicines better: What do tiny particles feel like in your mouth?

To be completed by participants aged 5-12 years
(Your parents/guardians can help you if you wish)

How old are you? _____

What number sample did you try? **1** **2** **3**

1. Please rate the grittiness of the sample.

(Grittiness means that you can feel 'bits' in the sample)



Not Gritty
(No bits)

Very Gritty
(Lots of bits)

2. What did you think of the overall volume of the sample?

(Volume means the amount you had to take)



3. What did you think of the overall mouthfeel of the sample?

(Mouthfeel means how the sample felt in your mouth)



Figure 3.3. Paper-based structured questionnaire used for data collection of subject-reported outcomes of palatability and acceptability.

4. What did you think of the overall taste of the sample?



5. Can you still feel any of the 'bits' in your mouth?

Yes

No

6. If this was a medicine, would you be willing to take this every day?

Yes

No

Any other comments about this sample:

Figure 3.3 (Continued). Paper-based structured questionnaire used for data collection of subject-reported outcomes of palatability and acceptability.

The total volume of water consumed for each sample was calculated by providing free access to water in cups with a pre-measured volume (150 ml). Additionally, the proportion of participants that reported that they could still feel the bits in their mouth after sample administration was determined based on participants' responses to the bipolar question "*Can you still feel any of the 'bits' in your mouth?*".

3.3.3.3 *Statistical analysis*

The number of participants required to detect significant differences between samples was estimated based on power calculations assuming parametric unimodal distribution, significance (α) of 0.05 and 80% power; a sample size of 14 would show the difference between two samples where the difference was 1 face and the standard deviation was also 1 face on the 5-point hedonic scale. This is supported by previous studies which demonstrated that a group of 15-18 participants is sufficiently large to detect significant differences between samples using categorical scales (Hayakawa et al., 2016; Kimura et al., 2015). Therefore, to enable analysis of the effect of particle size and coating on results, a minimum of 14 participants would be required in each part of the study.

Statistical analysis of researcher observations and subject-reported outcomes was performed using non-parametric Kruskal-Wallis analysis of variance followed by Dunn's test as *post hoc* for pairwise comparison, with 95% confidence. Size effect was estimated by analysis of subjects in Sessions 1-4 only as this enables a better within subject comparison of sizes. Similarly, coating effect was estimated by analysis of subjects in Sessions 5-8, excluding the sample with dissimilar size (i.e. sample 3). Association between evaluation parameters was investigated using Chi-Squared Test for Association with 95% confidence. The volume of water consumed was treated as a non-normally distributed continuous variable based on Kolmogorov–Smirnov test and analysis was carried out by Kruskal-Wallis test with 95% confidence. Minitab 17 (Minitab Inc., State College, Pennsylvania, USA) was used for data analysis.

3.3.4 Contributors statement

This research was a collaborative work between UCL School of Pharmacy and the University of Birmingham with support of the **CDT in Targeted Therapeutics and Formulation Sciences**, which is funded by the EPSRC, and the **SPaeDD-UK (Smarter Paediatric Drug Development)** consortium, which is co-funded by Innovate UK and industrial partners: AstraZeneca, BMS, GlaxoSmithKline, Juniper and Pfizer.

My personal contribution to this research is outlined below:

- Contributed to decisions regarding formulation attributes, including the ranges of particle size investigated, the amount of multiparticulates per dose, the volume of water used for pre-dispersion and the selection of administration device.
- Collaborated in the study design, including maximum number of formulations to be assessed per participant and total number of participants required.
- Participated in the design of data collection tools, providing scientific input on type of scales that should be used and the range of attributes that should be evaluated.
- Prepared the application to the UCL Research Ethics Committee, implemented the study and monitored data collection for the study in adult participants.
- Participated in data collection for the study in children participants.
- Carried out the statistical analysis and interpretation on the overall data obtained in the studies conducted in both children and adult participants.

I would like to acknowledge other contributors, namely Ms Punam Mistry and Dr Hannah Batchelor, (University of Birmingham), Dr Joanne Bennett and Dr Alastair Coupe (Pfizer Global R&D), alongside my PhD supervisors Dr Terry Ernest (GlaxoSmithKline), Dr Mine Orlu and Dr Catherine Tuleu (UCL School of Pharmacy).

3.4 Results and discussion

3.4.1 Morphological characterisation of multiparticulates

All samples exhibited a narrow, symmetric, unimodal particle size distribution (Figure 3.4). The median particle size of uncoated multiparticulates was 279, 413, 594 and 871 μm , for Cellets 200, 350, 500 and 700, respectively. The coated versions of Cellets were slightly larger, with median particle size of 290, 448, 615 and 921 μm , respectively. This represents a 3.5-8.5% increase with respect to their original size due to the application of the polymeric film around the particles. Thus, uncoated and coated versions of multiparticulates can be considered to have equivalent size, as such minor difference should not be expected to influence mouth-feel perception.

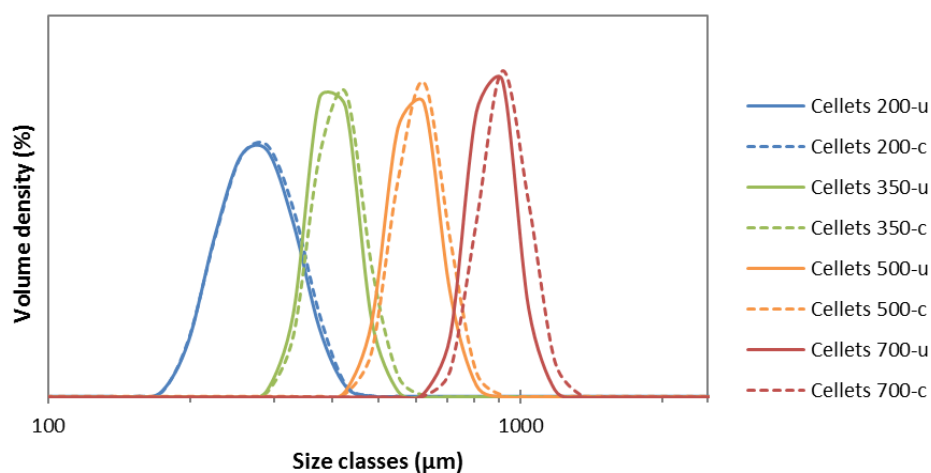


Figure 3.4. Particle size distribution of Cellets by laser diffraction (dry dispersion method).

SEM micrographs of multiparticulates are shown in Figure 3.5. The SEM images showed the highly spherical morphology of the model multiparticulates, which was maintained after coating of the particles. The surface of the multiparticulates was very smooth for both uncoated and coated versions, although coated particles showed presence of powder material on the surface, which could be ascribed to the addition of talc during manufacturing as adsorbent and anti-tacking agent.

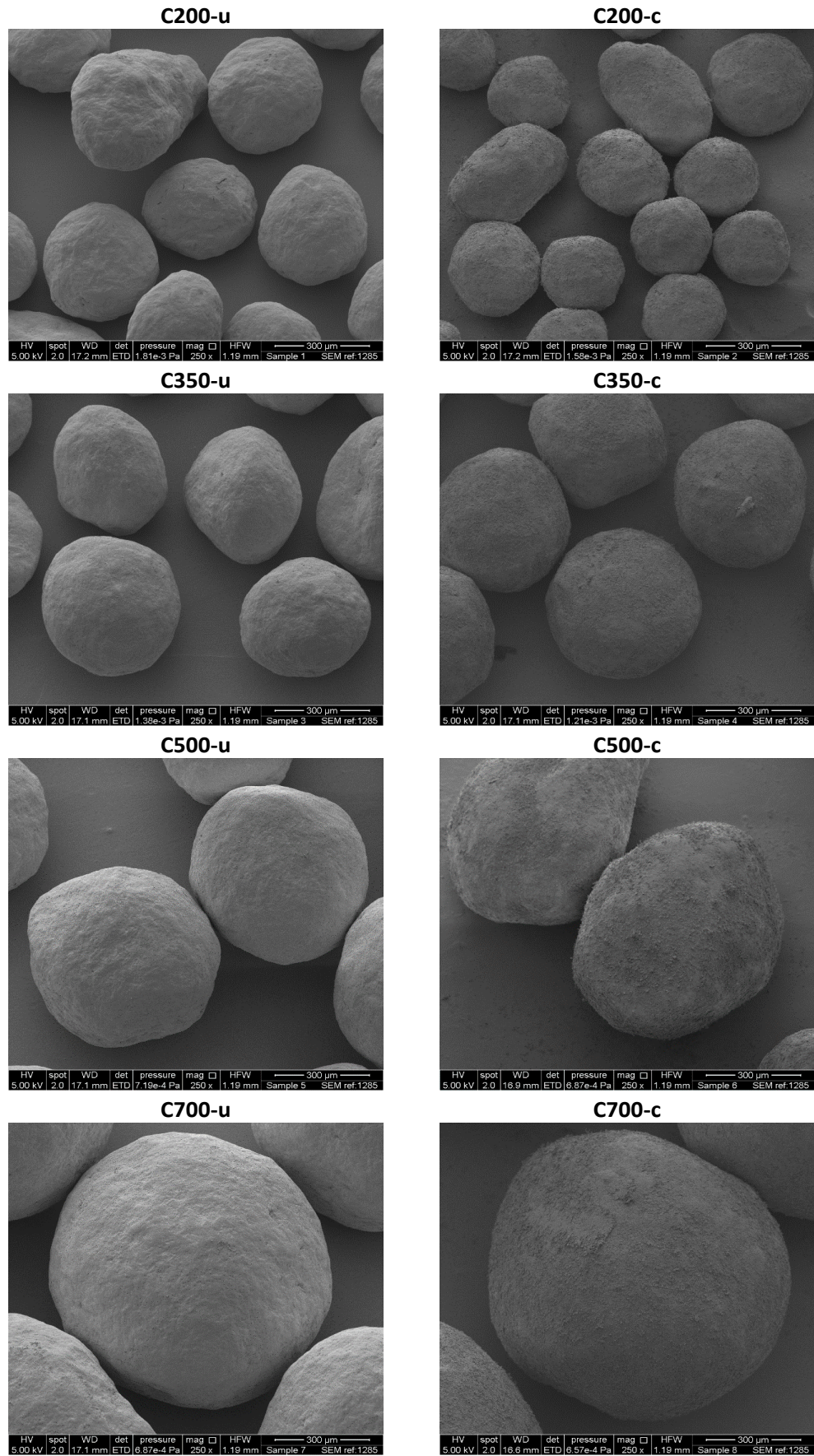


Figure 3.5. SEM micrographs of uncoated and coated Cellets with 250x magnification.

3.4.2 Demographics

A total of 132 participants were recruited, 71 children (4-12 years; median = 7 years) and 61 adults (18-37 years; median = 22 years). Demographics are summarised in Table 3.6.

Table 3.6. Demographic characteristics of the study participants.

Session	Children		Adults	
	N	Age (Ave \pm SD)	N	Age (Ave \pm SD)
1	9	6.6 \pm 1.7	6	25.3 \pm 5.2
2	13	8.2 \pm 2.2	12	23.0 \pm 5.3
3	8	6.6 \pm 2.2	8	20.6 \pm 3.0
4	7	7.0 \pm 2.1	7	20.7 \pm 2.1
Part 1 total	37	7.2 \pm 2.1	33	22.4 \pm 4.5
5	8	7.1 \pm 2.3	7	23.6 \pm 4.9
6	7	8.7 \pm 2.0	7	24.7 \pm 4.3
7	12	6.8 \pm 1.5	6	26.5 \pm 4.3
8	7	6.9 \pm 2.4	8	26.6 \pm 4.9
Part 2 total	34	7.3 \pm 2.1	28	25.4 \pm 4.6
Grand total	71	7.2 \pm 4.0	61	23.7 \pm 4.7

3.4.3 Acceptability of multiparticulates: comparison between children and adults

3.4.3.1 *Success in swallowing the formulation*

The proportion of participants who swallowed the complete dose of multiparticulates, as opposed to those who spat out the sample or refused it, was 92% in children and 100% in adults (Figure 3.6). The sample was refused by five different children, two of whom refused two samples; the age of the children that refused the samples ranged from 5-8 years with a median of 7 years. The sample was spat out by eight children, two of whom spat out two samples; the children that spat out the sample ranged from 4-10 years with a median of 8 years.

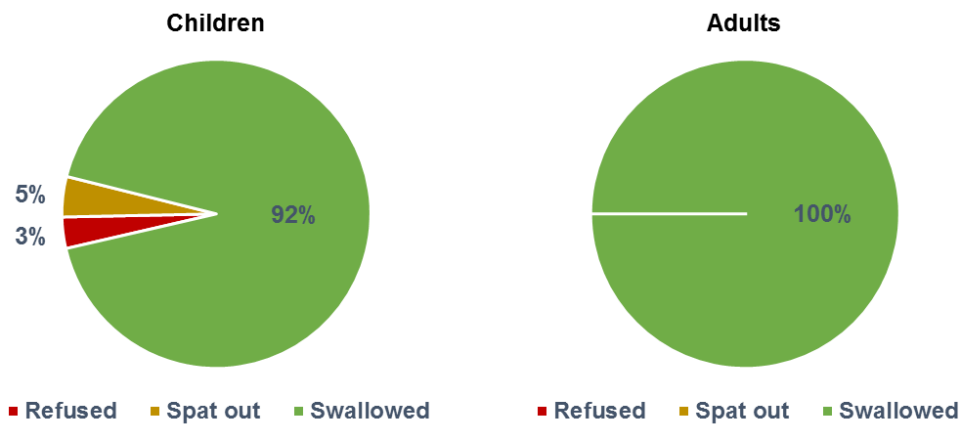


Figure 3.6. Proportion of participants who swallowed, spat out or refused multiparticulates.

There were 10 occasions (5%) where children voiced resistance to taking the sample, and 20 occasions (9%) where children voiced disgust after sample administration. Other negative outcomes such as crying, screaming or vomiting were never observed in children participants before, during or after sample intake. No such negative behaviours were observed in adult participants, as it could be expected.

3.4.3.2 Researcher observations of negative facial expressions

Display of negative facial expressions upon sample administration was more common in children, although it was detected in both population groups (Figure 3.7).

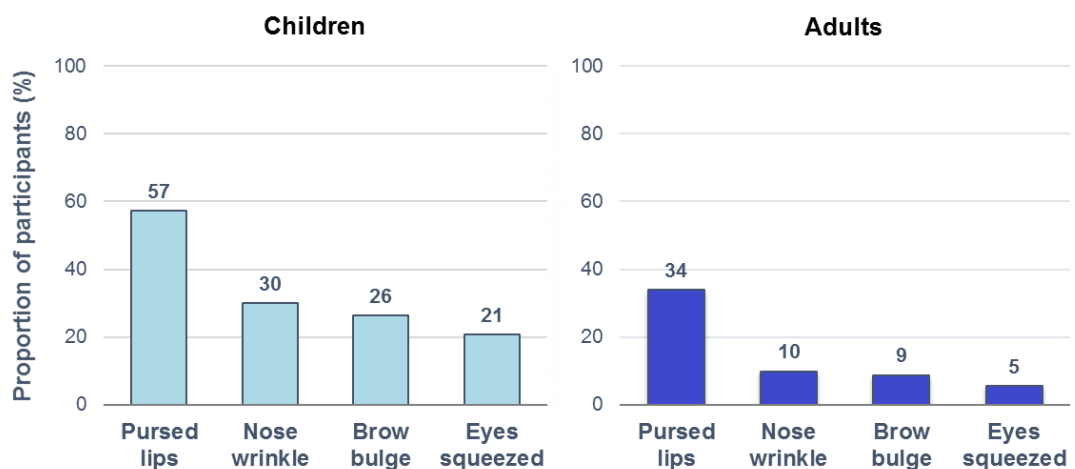


Figure 3.7. Proportion of participants displaying negative facial expressions upon sample intake.

Overall, researcher observations of negative facial expressions denoted a certain level of dislike or discomfort with the samples. The most commonly observed negative facial expression was ‘pursed lips’ (with 57% of children and 34% of adults displaying this behaviour), followed by ‘nose wrinkle’ (30% and 10%), ‘brow bulge’ (26% and 9%) and, lastly, ‘eyes squeezed’ (21% and 5%, respectively).

Children displayed one or more negative facial expression 149 times (70%), whereas this measure accounted for 76 (42%) in adults. In other words, children showed neutral or positive attitudes towards the samples in 57 (27%) occasions and adults in 107 (58%) occasions. Seven children (3%) refused the sample and thus facial expressions were not recorded. Differences between populations were significant ($p < 0.001$).

3.4.3.3 Subject-reported outcomes using hedonic scales

Participants rated four different sample attributes using 5-point hedonic scales: grittiness, mouthfeel, taste and sample volume. Overall, grittiness was the most negatively rated attribute, with a median of 4 in both adults and children (Figure 3.8). The most favourably rated item was sample volume (median of 2 and 3 in adults and children, respectively).

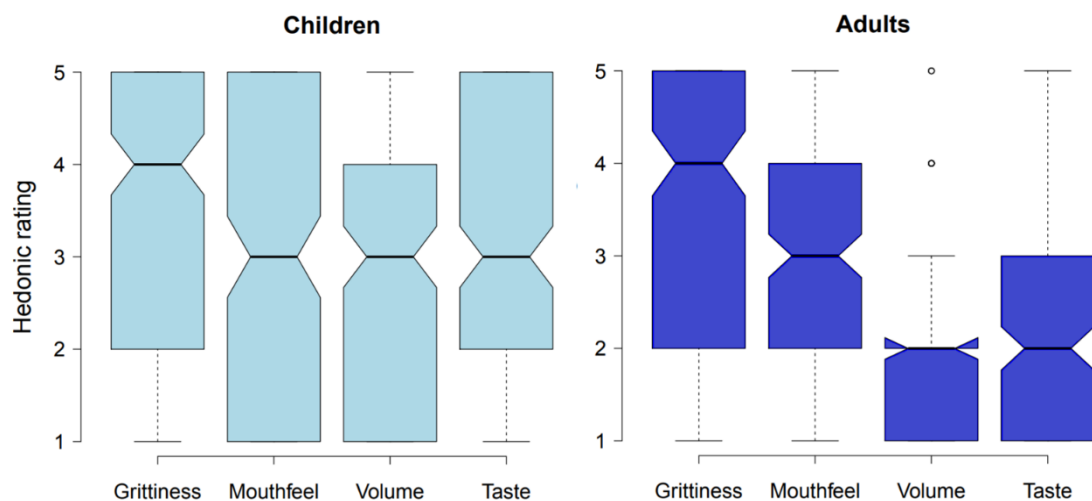


Figure 3.8. Rating of palatability attributes in hedonic scales (1 - best possible rating to 5 - worst possible rating). Centre lines show the median, box limits the 25th and 75th percentiles, notches represent the 95% confidence interval of the median and outliers are denoted by dots.

Overall, ratings of palatability descriptors were significantly worse in children than in adults, particularly for taste and sample volume. Adult participants rated at least one palatability attribute in the negative range of the scale in 105 cases (57%), whereas this value accounted for 145 (68%) in children. Therefore, multiparticulates received neutral-positive evaluations in 61 (29%) occasions by children and 78 (43%) by adults, in close agreement with the findings based on researcher observations. Seven children (3%) refused the sample and thus hedonic ratings were not recorded. Differences between both populations in ratings of palatability descriptors were significant ($p < 0.001$).

Participants' spontaneous descriptions of the samples support the findings of hedonic scales; samples were often described as "*tasteless*" or as having "*no flavour*" but the feeling in the mouth was found to be "*gritty*" and "*sandy*". Interestingly, the feedback provided by children often denoted the lack of flavour as a negative aspect of the formulation, e.g. "*it was horrible because it had no flavour*" or "*if it had a flavour it would be nice*". This could explain the negative ratings given to taste in contrasts with adults. Moreover, children often employed the term "*gritty*" as a negative attribute of taste instead of mouthfeel, e.g. "*I hated the gritty taste*" or "*the taste was bad because it was gritty*". This interconnection of responses to different sample attributes could have also contributed to the negative ratings of taste provided by children.

Interconnection of responses in hedonic scales was common not only in children but also in adults. A significant association was found between each possible pair of palatability descriptors in both population groups ($p < 0.001$). This suggests the existence of a 'halo effect' by which participants' responses to one attribute were influenced by their opinion and responses to other attributes. For example, when the mouthfeel of the sample was disliked, the taste of the sample would tend to be disliked too. This may indicate that the measures relate to the overall acceptance of the sample rather than to each parameter individually. Such phenomenon can be expected in sensory evaluation studies involving untrained panellists (Mason and Nottingham, 2002; Prescott et al., 2011).

In terms of the use of scales, differences between paediatric and adult populations were evident. In general, children used preferentially the extremes of the hedonic scales, as expected based on previous research (ASTM, 2003), whereas adults' responses were evenly distributed throughout the five points of the hedonic scales (Figure 3.9). As previously discussed, ratings of sample volume and taste were significantly worse in children than adults, which could suggest different sensitivity and/or differences in the interpretation of palatability descriptors between populations.

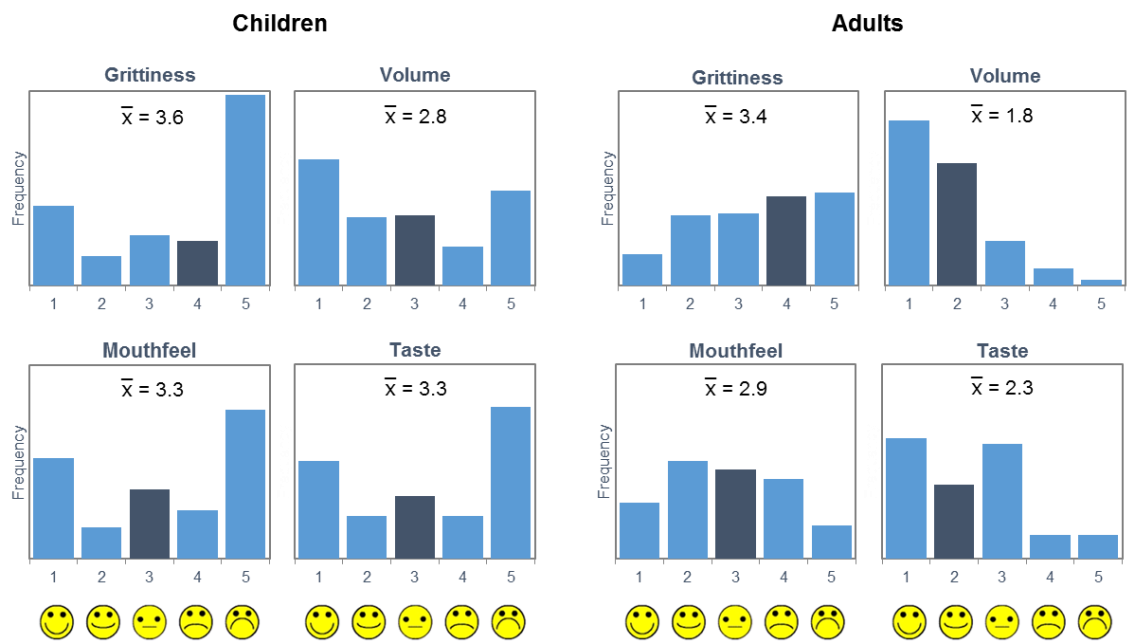


Figure 3.9. Histograms of ratings using hedonic scales. Dark blue bar represents median.

3.4.3.4 Willingness to take multiparticulates every day as a medicine

The proportion of participants willing to take the sample every day if it was a medicine was calculated as a predictive measure of future acceptability (Figure 3.10). Overall, children reported their willingness to take the sample every day in 63 occasions (30%), while their response was negative in 143 occasions (67%); seven children (3%) refused the sample and thus their response was not collected. Adults reported willingness to take the sample every day in 135 cases (74%), compared to 48 negative cases (26%); differences between both populations being significant ($p < 0.001$).

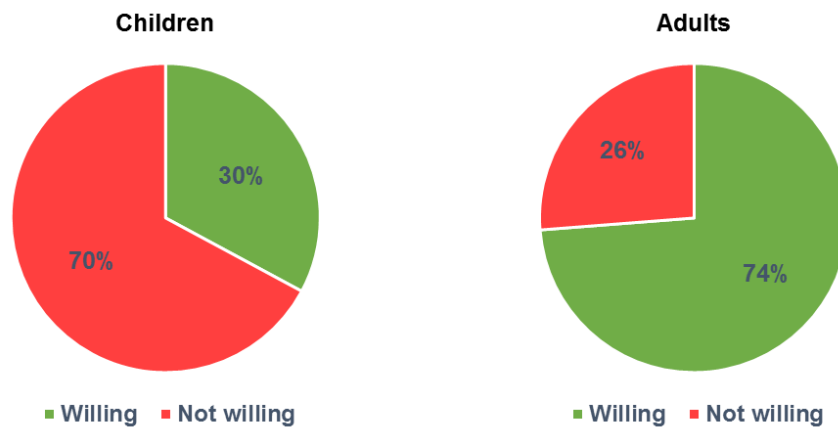


Figure 3.10. Proportion of volunteers ‘willing to take the sample every day if it was a medicine’. Seven children (3%) refused the sample and thus, although their willingness response was not collected, these were reported as not willing to take the sample every day if it was a medicine.

A significant association was found between ratings of palatability descriptors and the willingness of participants to take the sample every day. This means that those patients who rated palatability positively would tend to be more willing to take the sample every day, as it could be expected. This association between hedonic ratings and willingness to take the sample is depicted in Figure 3.11. This association was stronger for grittiness, mouthfeel and taste ($p < 0.001$ in all cases) than it was for sample volume ($p = 0.004$).

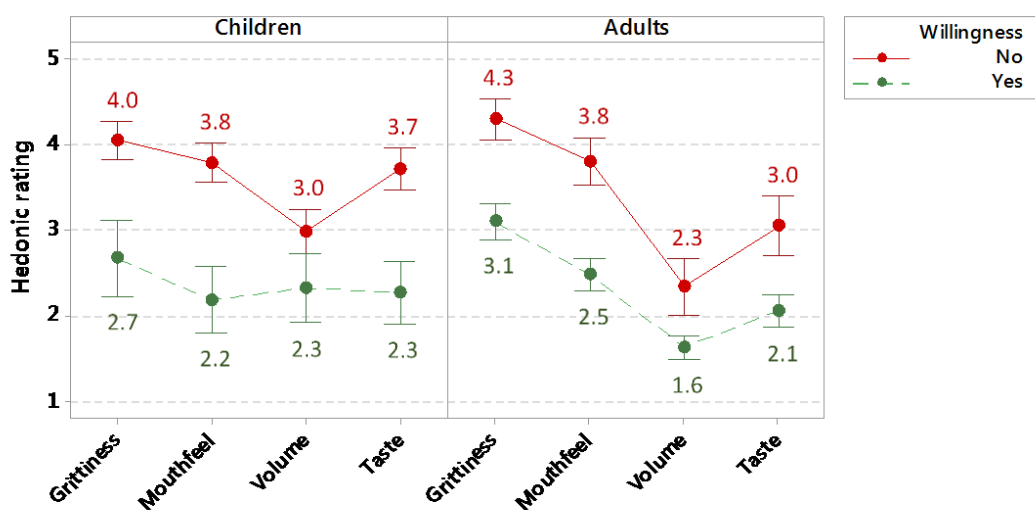


Figure 3.11. Hedonic rating as a function of the reported willingness to take the sample every day. Markers represent the mean hedonic rating and bars show the 95% CI for the mean.

3.4.3.5 Comparison between outcome measures

The reported willingness to take the sample every day by children (30%) was aligned with their positive outcome based on researcher observations (23%) and hedonic ratings (29%), whereas adults reported to be willing to take the sample (74%) more frequently than expected based on researcher observations (58%) and hedonic ratings (43%). Results are summarised in Table 3.7 and graphically depicted in Figure 3.12.

Table 3.7. Comparison of multiparticulates acceptability outcomes in children and adults.

Evaluation criteria	Outcome	Children	Adults
Success swallowing	Sample swallowed	196 (92%)	183 (100%)
	Sample refused/spat out	17 (8%)	0 (0%)
Facial expressions †	No negative expressions	57 (27%)	107 (58%)
	Negative expressions	149 (70%)	76 (42%)
Hedonic ratings †	All hedonic ratings \leq 3	61 (29%)	78 (43%)
	At least one rating $>$ 3	145 (68%)	105 (57%)
Willingness †	Willing to take daily	63 (30%)	135 (74%)
	Not willing to take daily	143 (67%)	48 (26%)

† Seven children (3%) refused the sample, thus their negative facial expressions and responses to hedonic ratings and willingness to take the sample every day were not recorded.

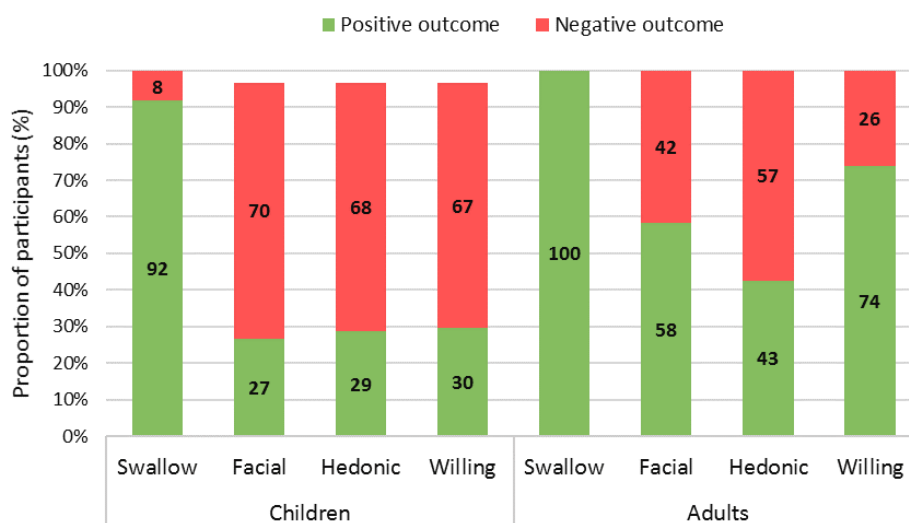


Figure 3.12. Comparison of multiparticulates acceptability outcomes in children and adults.

More detailed analysis of the link between outcome measures revealed that 21% of children and 58% of adults would be willing to take multiparticulates every day as a medicine despite their negative ratings of the samples using hedonic scales (Figure 3.13). This indicates that some participants (especially adults) would be willing to take the sample even if palatability was not acceptable, which suggests that their responses were influenced by psychological factors such as the perceived need to take a medicine.

From those participants who showed acceptance based on hedonic ratings, 95% of adults but only 53% of children reported their willingness to take multiparticulates every day as a medicine. Therefore, the reliability of adult responses was confirmed but the validity and reliability of children reported outcomes can be questionable. Children might have negative perceptions about the use of medicines (Ranmal, 2014), which could hinder their willingness to take medicines even if palatability is acceptable. Additionally, some children might have difficulties using the scales appropriately. Expert guidance on the design of evaluation tools for studies involving children highlights the difficulty of using subject-reported outcome measures and encourages the use of researcher observations instead (ASTM, 2003; FDA, 2009; Matza et al., 2013).

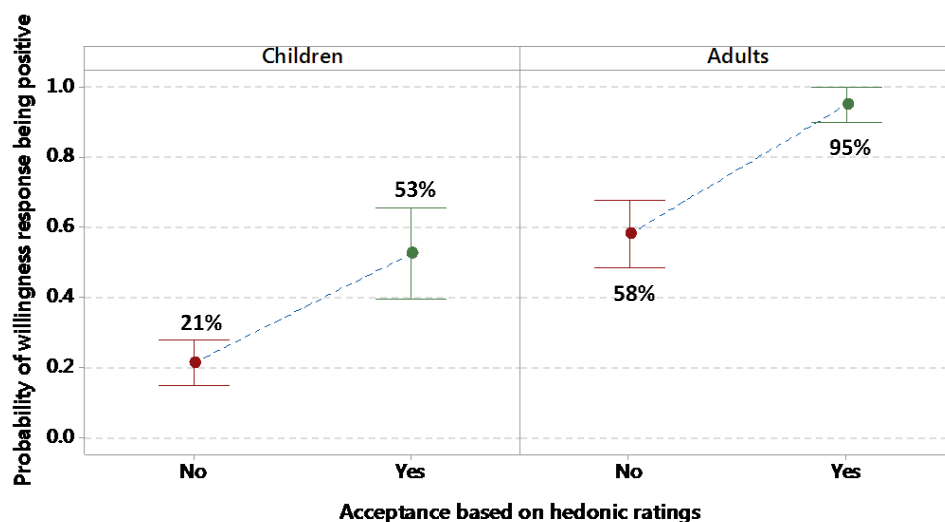


Figure 3.13. Probability of participants to report willingness to take multiparticulates every day as a function of their responses to hedonic scales (samples were considered accepted based on hedonic ratings when all sample attributes were rated in the neutral to positive end of the scale).

Evaluation of negative facial expressions showed that 27% of children and 59% of adults would be willing to take multiparticulates every day despite showing facial signs of non-acceptance (Figure 3.14). These values were comparable to those obtained for hedonic ratings and support the hypothesis that some participants (especially adults) might be willing to take medicines even if they dislike them.

However, from those participants who showed acceptance based on facial expressions, only 40% of children and 84% of adults reported their willingness to take the sample every day. This compared to 53% and 95%, respectively, based on hedonic ratings. Thus, researcher observations of facial expressions seemed less sensitive than hedonic ratings to predict the willingness of participants to take multiparticulates. Poor correlation between outcome measures suggests questionable reliability of responses. There are several potential explanations: Firstly, facial expressions could have been the results of ingestion of a novel material rather than signs of non-acceptance. Moreover, participants (especially young children) might not understand the question about their 'willingness to take the sample every day'. Finally, some participants (especially children) could reject medicines even if they think palatability is acceptable.

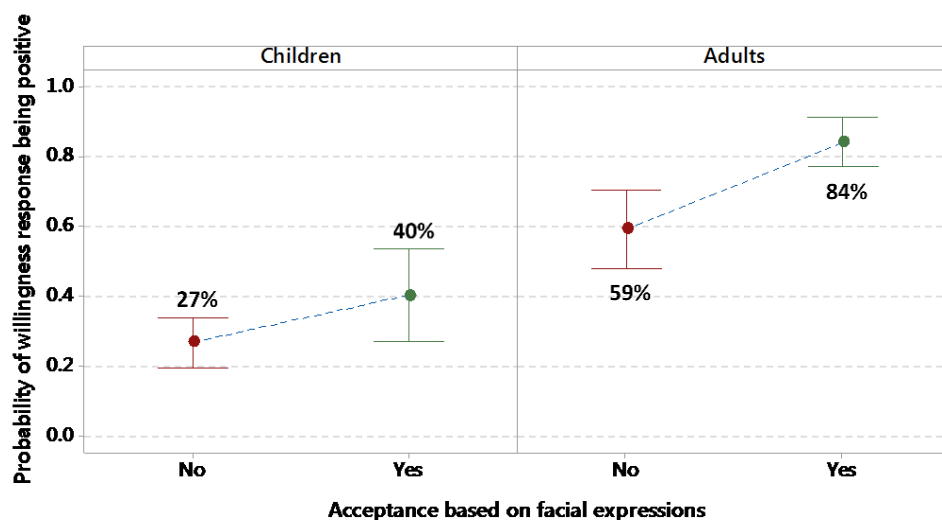


Figure 3.14. Probability of participants to report willingness to take multiparticulates every day as a function of their negative facial expression (samples were considered accepted based on facial expressions when no negative facial expressions were observed during sample intake).

3.4.4 Effect of formulation factors on palatability and acceptability

Eight different formulations were evaluated in this study, consisting on four sizes of multiparticulates, each available as coated and uncoated versions. However, each participant only evaluated three formulations. The first part of the study (Sessions 1-4) was dedicated to the analysis of the effect of particle size on palatability and acceptability and thus each participant had three samples of different particle size. The second part of the study (Sessions 5-8) was dedicated to the analysis of polymeric coating on palatability and acceptability and thus each participant evaluated coated and uncoated multiparticulates of the same particle size. Based on this study design, analysis of the effect of formulation factors was performed on Sessions 1-4 and Sessions 5-8 separately to enable within subject comparison of size and coating effects, respectively.

3.4.4.1 *Effect of formulation factors on researcher observations*

Looking at the proportion of participants who swallowed the formulations (as opposed to those who refused or spat out the sample), children accepted multiparticulates in 92% of attempts and adults accepted multiparticulates in all cases. Therefore, analysis of the effect of size and coating on acceptability was impractical. Based on this outcome measure, multiparticulates were well accepted regardless of the formulation properties.

Similarly, based on researcher observations of negative facial expressions, no significant differences between different multiparticulate sizes and between coated or uncoated samples were found in either children ($p = 0.923$ and $p = 0.800$ for size and coating effects, respectively) or adults ($p = 0.551$ and $p = 0.795$, respectively).

Differences between samples were expected based on previous research and were demonstrated by analysis of subject-reported outcomes such as ratings on hedonic scales, as outlined later in Section 3.4.4.2. Since no differences between samples were found based on researcher observations, this indicates that researcher observations were less discriminative than subject-reported outcomes.

3.4.4.2 *Effect of formulation factors on subject-reported outcomes*

Ratings of sample attributes on hedonic scales revealed acceptance of the sample by 29% of children and 43% of adults. Looking at the effect of different formulation factors, adults perceived larger particles as being 'grittier' ($p < 0.001$). On the contrary, there was no real evidence of size effect in children ($p = 0.214$), although the larger two sizes received higher grittiness scores on average than the lower two sizes. There was some evidence of a coating effect on hedonic ratings in adults, with coated samples scoring lower on average, although this was not statistically significant ($p = 0.079$). The presence of polymeric coating had no significant effect on hedonic ratings in children ($p = 0.451$).

Subject-reported willingness to take multiparticulates every day as a medicine suggested acceptance by 30% of children and 74% of adults. Considering formulation factors, particle size had a significant effect on the reported willingness to take the sample every day by adult participants, who showed preference for smaller particles ($p = 0.042$), in agreement with their responses to hedonic scales. In the case of children, particle size had no significant effect on the willingness to take the sample every day ($p = 0.479$), which is also in agreement with their responses to hedonic scales. The effect of coating on the reported willingness to take the sample every day as a medicine was trivial in both children and adults ($p = 0.571$ and $p = 0.778$, respectively).

A detailed analysis of the effect of formulation factors on subject-reported outcomes of palatability and acceptability is outlined below:

Effect of multiparticulate size

As it can be expected based on previous research, adult participants perceived larger multiparticulates as being less palatable, based on ratings of grittiness ($p < 0.001$) and mouthfeel ($p = 0.001$), as shown in Figure 3.15. The grittiness score for the 200-355 μm multiparticulates was 2.6 on average, compared to 4.2 for the 700-1000 μm multiparticulates. Similarly, the mouthfeel score for the smallest particles was 2.1 on

average, compared to 3.3 for the largest particles. Surprisingly, children showed no preference towards any particle size based on hedonic ratings of grittiness ($p = 0.504$) and mouthfeel ($p = 0.590$). Children rated grittiness between 3.2 and 4.0 on average and mouthfeel between 3.0 and 3.6 on average. The negative ratings of grittiness and mouthfeel provided for all samples together with the broad inter-individual variability in children could have hindered evaluation of the *true* effect of particle size on grittiness and mouthfeel. Moreover, the ability of children to interpret and independently rate the different hedonic descriptors was further dubious, as previously discussed.

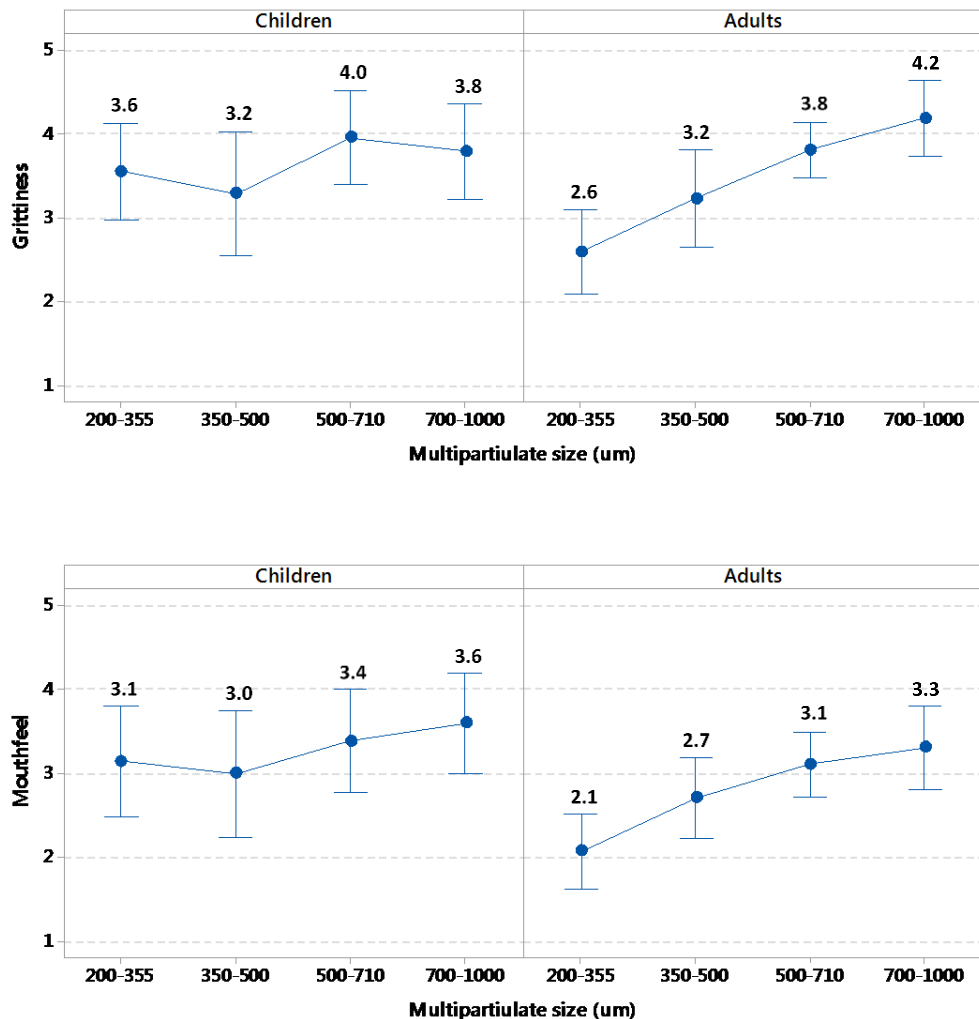


Figure 3.15. Interval plots for grittiness and mouthfeel as a function of multiparticulate size (results of Sessions 1-4), by population group. Markers represent the population average hedonic rating (1 - best possible and 5 - worst possible) and bars show the 95% CI for the mean.

Although children provided similar grittiness and mouthfeel scores regardless of the size of the multiparticulates, scores of 'sample volume' worsened with increasing particle size ($p = 0.065$), as shown in Figure 3.16. Children scored the largest particles 1.0 point higher on average than the smallest particles. In the case of adults, the two larger sizes also received higher scores than the smaller two sizes ($p = 0.042$), although the effect of size on ratings of sample volume was less ostensible than in children. It seemed that, since larger multiparticulates felt coarser in the mouth, participants rated the sample volume as being larger, despite the quantity of multiparticulates being the same.

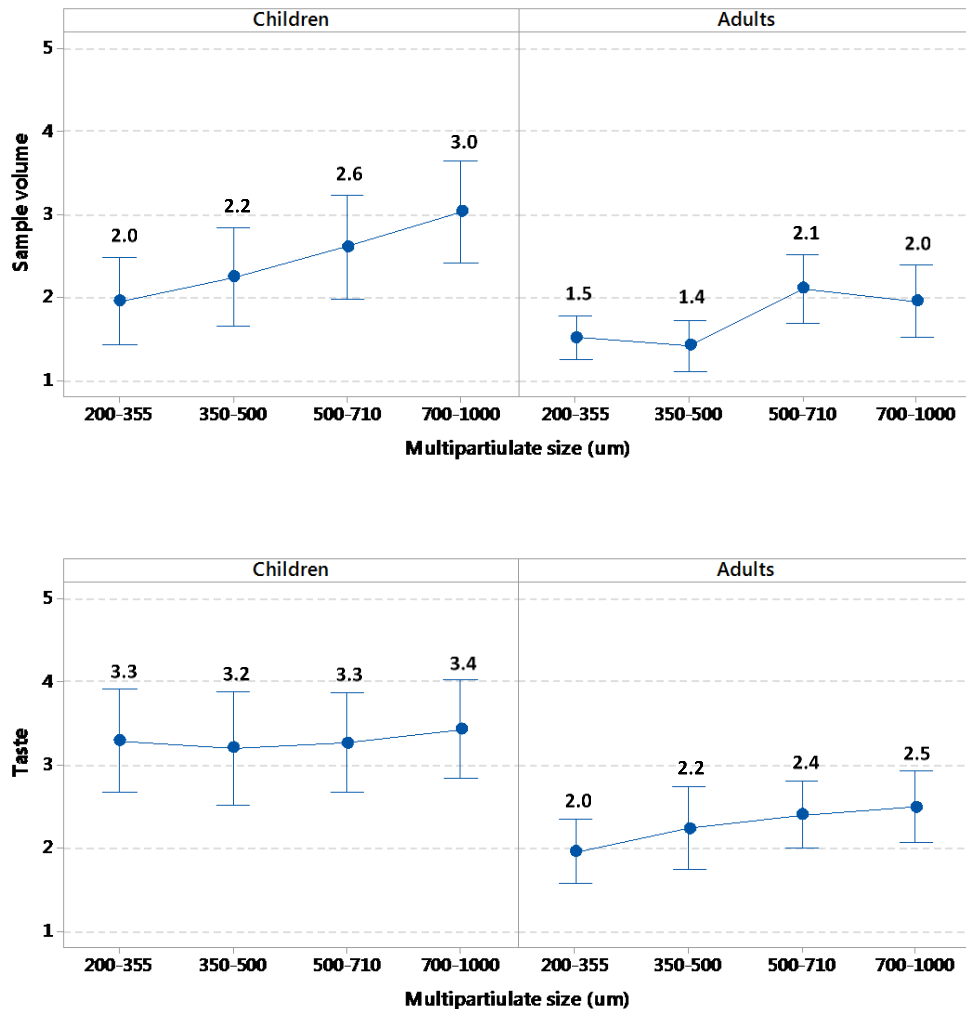


Figure 3.16. Interval plots for sample volume and taste as a function of multiparticulate size (results of Sessions 1-4), by population group. Markers represent the population average hedonic rating (1 - best possible and 5 - worst possible) and bars show the 95% CI for the mean.

As shown in Figure 3.16, the size of the multiparticulates had no effect on the taste of the sample, for either adults ($p = 0.238$) or children ($p = 0.951$). However, children rated the taste of the samples in the negative range of the scale on average (3.2 – 3.4), whereas adults provided positive ratings for taste on average (2.0 – 2.5). This could be mainly ascribed to the lack of flavour of the sample, which could have been considered a negative attribute for children in contrast with adults. The inability of (some) children to interpret the different palatability attributes and rate them independently could have also contributed to the negative ratings of taste. As discussed before, a significant association was found between different palatability descriptors in both children and adults, which indicates that participants' responses to one attribute were influenced by their opinion and responses to other attributes. This halo effect would also explain why adults rated the taste of the samples more negatively as the size of the multiparticulates increased.

Particle size had a significant effect on the reported 'willingness to take the sample every day if it was a medicine' by adult participants (Figure 3.19), who showed preference for smaller multiparticulates ($p = 0.042$) but not in children ($p = 0.479$), in agreement with their responses to hedonic scales.

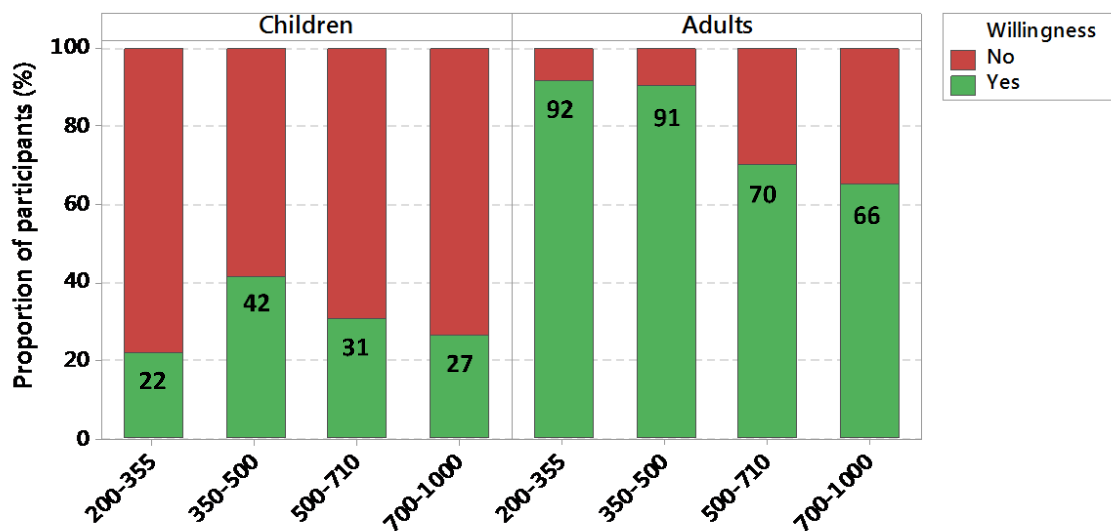


Figure 3.17. Willingness to take the multiparticulate sample every day if it was a medicine as a function of the size of the multiparticulates.

Effect of presence or absence of polymeric coating

There was some indication that the polymeric coating reduced grittiness and improved mouthfeel, since average ratings by adults improved by 0.5 and 0.3 points, respectively (Figure 3.18). However, differences in grittiness and mouthfeel between samples were not significant ($p = 0.225$ and $p = 0.523$, respectively). Similarly, negligible differences were found on the ratings of grittiness and mouthfeel in children ($p = 0.226$ and $p = 0.432$, respectively). Negligible differences between samples could be attributed to the smooth surface of both coated and uncoated multiparticulates, as demonstrated by SEM.

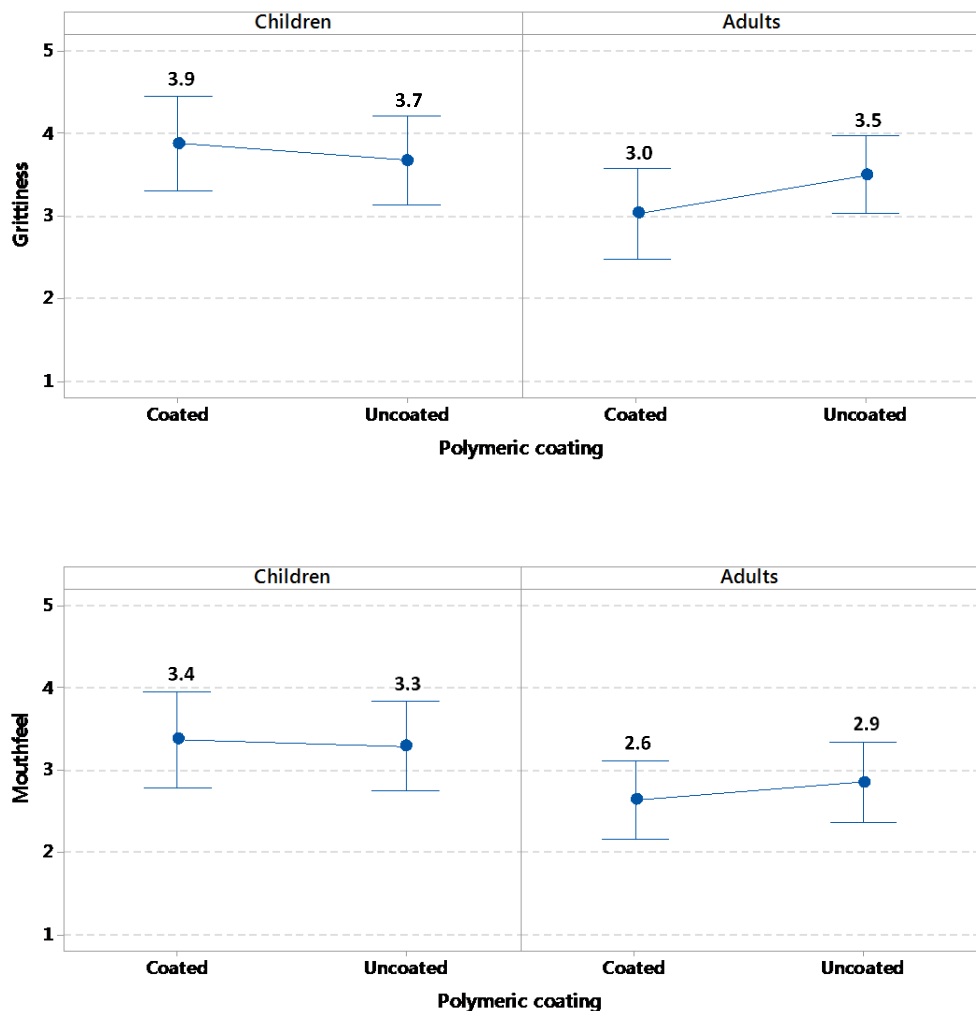


Figure 3.18. Interval plots for grittiness and mouthfeel as a function of polymeric coating (results of Sessions 5-8), by population group. Markers represent the population average hedonic rating (1 - best possible rating and 5 - worst possible rating) and bars show the 95% CI for the mean.

Ratings of sample volume and taste were in line with the previous findings in that the presence or absence of polymeric film coating did not have a significant impact on palatability (Figure 3.19). There was some effect of coating on the ratings of sample volume by children, who rated uncoated samples at 2.8 on average compared to 3.4 for coated versions, although this difference was not statistically significant ($p = 0.075$). The effect of polymeric coating on sample volume was negligible in adults ($p = 0.386$). Ratings of taste were not influenced by the presence or absence of coating in either children ($p = 0.753$) or adult participants ($p = 0.600$).

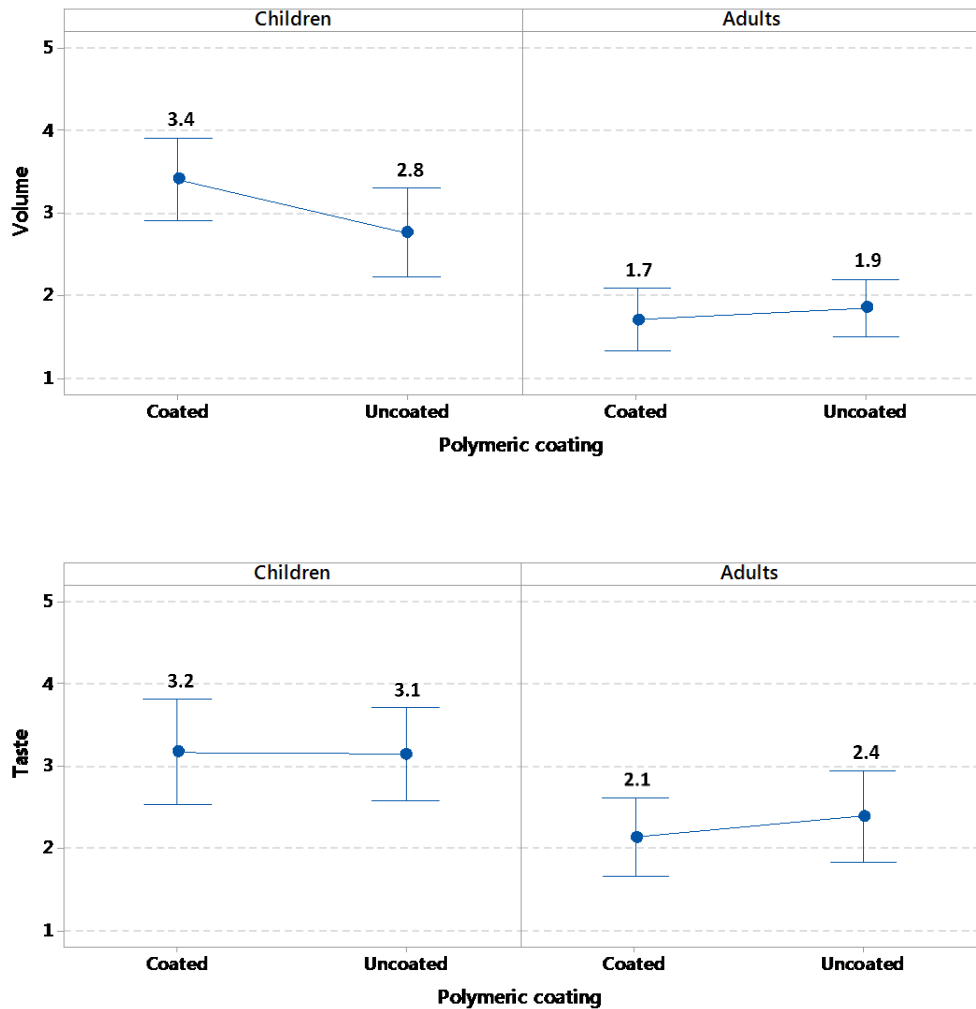


Figure 3.19. Interval plots for sample volume and taste as a function of polymeric coating (results of Sessions 5-8), by population group. Markers represent the population average hedonic rating (1 - best possible rating and 5 - worst possible rating) and bars show the 95% CI for the mean.

Since all samples contained the same amount of multiparticulates and the effect of polymeric coating on ratings of palatability was estimated between samples with the same particle size, differences in ratings of sample volume in children remained unexplained. Misinterpretation of palatability descriptors and the inherent intra-subject variability in responses could have contributed to the effect of polymeric coating on ratings of sample volume by children.

In line with the ratings of palatability attributes, the effect of coating on the reported willingness to take the sample every day as a medicine was trivial in both children and adults ($p = 0.788$ and $p = 0.571$, respectively), as shown in Figure 3.20. Children were willing to take coated and uncoated multiparticulates in 26 and 29% of occasions, whereas adults would be willing to take these in 71 and 64% of occasions, respectively.

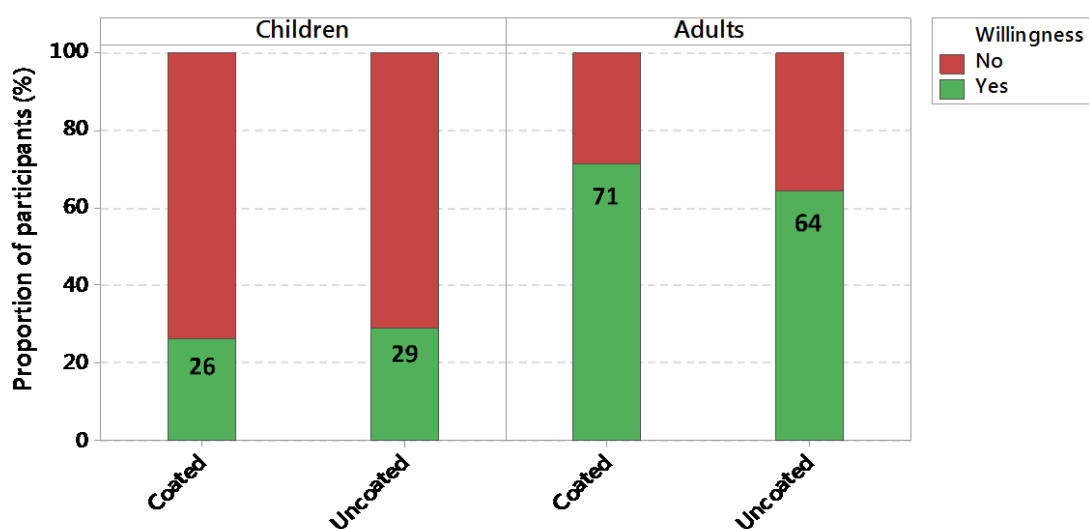


Figure 3.20. Willingness to take the multiparticulate sample every day if it was a medicine as a function of presence of polymeric film coating.

In summary, the presence or absence of polymeric coating did not have a significant impact on the ratings of palatability in either population group. Results were aligned with previous findings which suggested no significant differences in acceptability between coated and uncoated minitables (Klingmann et al., 2013).

3.4.4.3 Water consumed and residual multiparticulates in the mouth

In addition to the small volume of water used to pre-disperse multiparticulates on the dosing spoon (ca. 3 mL), participants had free access to spring water to complete sample intake. Children consumed 51 mL of water on average (median = 40 mL, min = 0 mL, max = 242 mL), whereas adults consumed 63 mL on average (median = 56 mL, min = 0 mL, max = 150 mL). The water consumed was comparable between formulations, regardless of the particle size and coating (Figure 3.21); consequently, differences between samples were not significant in either children ($p = 0.291$) or adults ($p = 0.161$).

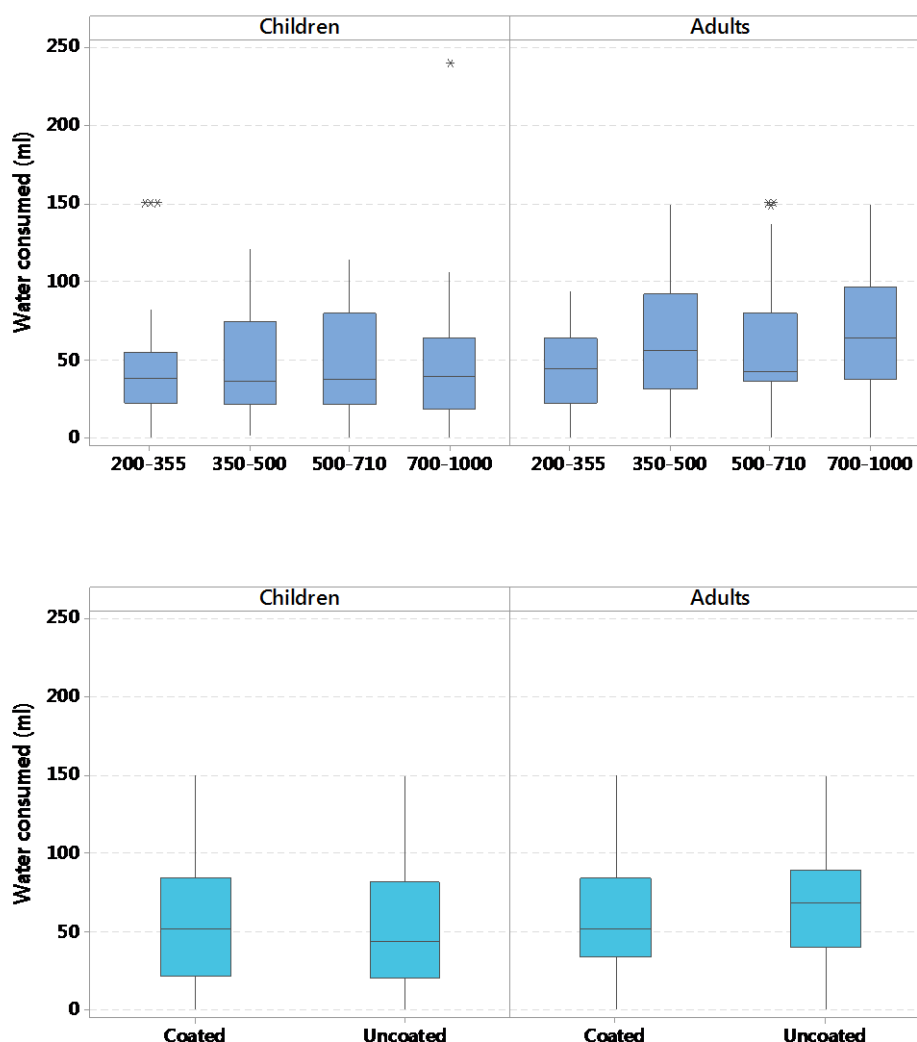


Figure 3.21. Volume of water (ml) consumed during the administration of multiparticulates, as a function of their size and coating. Centre lines show the median, box limits represent the 25th and 75th percentiles and outliers are denoted by asterisks.

After rinsing their mouth with water, participants were asked if they could still feel the multiparticulates in their mouth. Overall, adults reported that they could still feel residual particles in their mouth in 97 occasions (53%), whereas children reported they could feel remaining particles in 116 occasions (56%). In general, the reported feeling of residual multiparticulates increased with increasing particle size (Figure 3.22), although this effect was not statistically significant in either children or adults ($p = 0.057$ and $p = 0.106$, respectively). Coating had no significant impact on the reported feeling of residual multiparticulates in either children or adults ($p = 0.620$ and $p = 0.427$, respectively).

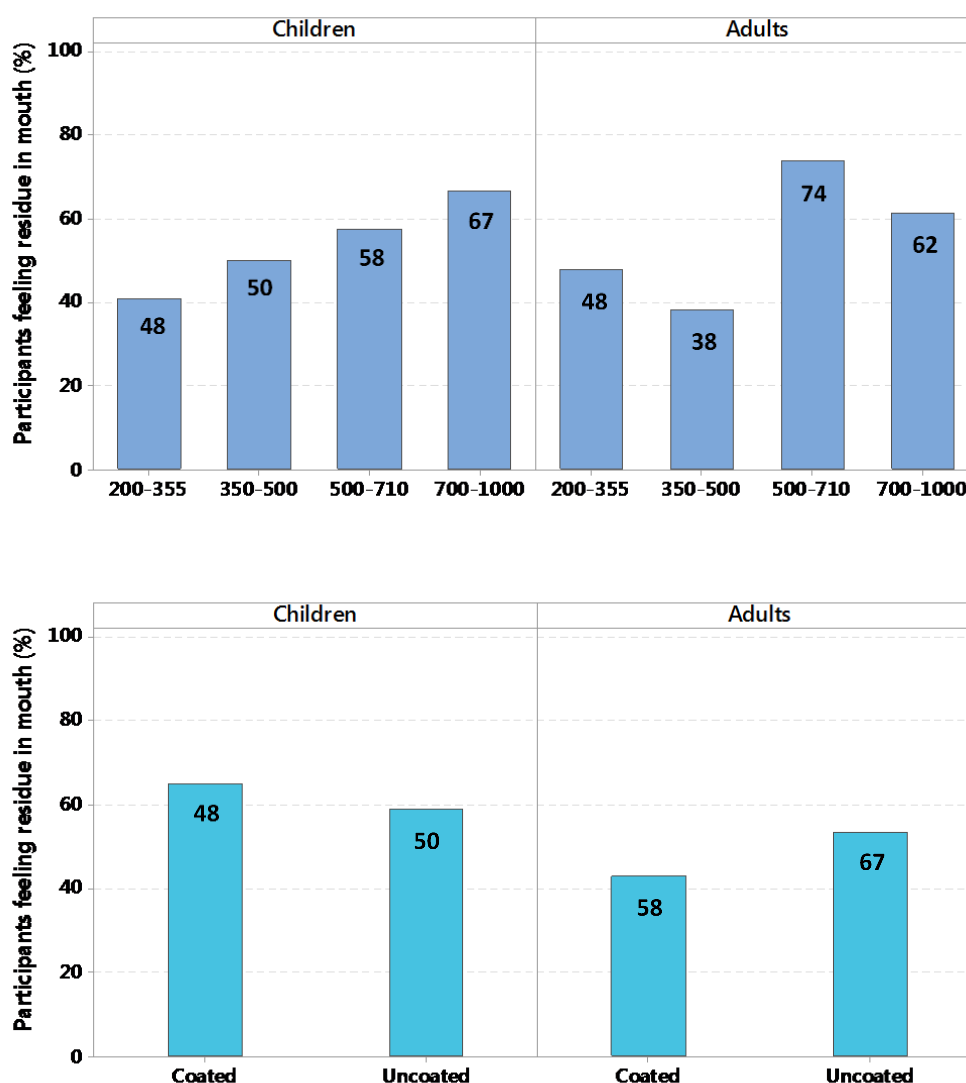


Figure 3.22. Proportion of participants that reported they could still feel residual multiparticulates in their mouth after administration of multiparticulates, as a function of their size and coating.

3.5 Conclusions

Results of this trial indicate acceptability of multiparticulates based on voluntary sample intake. Healthy adults swallowed the multiparticulate samples in all occasions, whereas healthy children accepted the sample in 92% of the occasions. Although the sample was refused or spat out by some children (3% and 5%, respectively), no undesirable effects such as coughing or vomiting with the sample were observed or reported.

However, researcher observations and subject-reported outcomes denoted some level of discomfort and sample dislike by the participants of the study. Review of the number of occasions where participants showed no negative facial expressions, acceptability of multiparticulates could be determined as 27% in children and 58% in adults. These results were in line with the subject-reported outcomes for palatability, where only 29% of children and 43% of adults scored every palatability descriptor in the neutral to positive range of the hedonic scales. Moreover, the willingness to take the sample every day if it was a medicine was determined to be 30% in children and 74% in adults, based on subject-reported outcomes. These values were in contrast with the more optimistic results of acceptability obtained by simply measuring the proportion of volunteers who took the sample. Overall, adult participants showed broader acceptance than children, as consistently shown by each of the different outcome measures.

Discomfort and dislike of the samples could be ascribed to the 'gritty' feeling in the mouth produced by multiparticulates, as demonstrated by the overwhelming proportion of negative ratings given to 'grittiness' and supported by spontaneous verbal judgment of the samples. These findings are aligned with previous research in adults (Kimura et al., 2015; Lopez et al., 2016), as well as in the preliminary trial described in Chapter 2. In addition, over half of the participants reported a feeling of residual multiparticulates in the mouth after sample intake. Long-lasting sensation of rough mouthfeel was previously reported in a study in adults using a swirl and spit methodology (Kimura et al., 2015).

Development of a suitable vehicle for the administration of multiparticulates could have a beneficial impact on the final formulation via masking the presence of particles. Typical vehicles recommended for sprinkle products include apple sauce and yogurt that provide both flavour and viscosity to improve the overall palatability (including taste and texture) of multiparticulates. The results of this trial led to the development of oral vehicles for the administration of multiparticulates which is the focus of the work described in Chapter 4. Investigation into swallowing aids for the administration oral solid formulations have been the focus of previous research, with some products already in the market in the form of sprays, pastes or jellies (Bunupuradah et al., 2006; Diamond and Lavalley, 2010; Kluk and Sznitowska, 2014).

As demonstrated in this trial, the methodology used to assess acceptability determines the percentage of participants that report the sample to be acceptable. Results indicate that a simple measure of the subject's ability to take a sample might not be sufficient to evaluate patient's acceptability, understood not only as the ability but also the willingness to take the product. Despite of the vast number of participants that accepted to take the sample, researcher observations and subject-reported outcomes showed a significant proportion of participant's discomfort and dislike. Researcher observations of facial expressions and behaviours, participants' hedonic ratings and spontaneous verbal judgement of the samples provided a valuable insight into patient's acceptability and sample preferences.

A significant association was found between hedonic ratings and willingness to take the sample every day, which confirms the link between palatability and acceptability, as supported by previous research (Baguley et al., 2012). Adults, however, were more willing to take the sample every day than expected based on hedonic rating, which suggests that psychological factors such as the perceived need to take a medicine might have influenced their response. In terms of sample preferences, children showed no significant preference for any sample, although there was some evidence to suggest

preference for the two smaller sizes. Meanwhile, adults showed strong preference for smaller multiparticulates based on hedonic ratings and willingness to take the sample every day. The presence of film coating on the multiparticulates did not seem to influence palatability and acceptability of the samples in either children or adults.

Overall, the results of this trial suggest that multiparticulates could be used as a suitable formulation platform for the administration of medicines to adults and children as young as 4 years old, although palatability might be a barrier to patient's acceptability due to the gritty mouthfeel of this type of formulation. This study should be extended to younger children based on the positive results of this trial in terms of safe administration.

Chapter 4

Development of oral vehicles to improve palatability and acceptability of multiparticulates

This chapter describes a set of experiments to investigate the applicability of liquid vehicles based on hydrocolloids as media for the administration of multiparticulates. A range of vehicles commonly used in practice for the administration of oral medicines were identified and characterised to be used as benchmark. Then, liquid vehicles with varying rheological properties were developed using hydrophilic polymers. Palatability and acceptability of placebo multiparticulates dispersed in such vehicles were evaluated in a panel of healthy adult volunteers to determine the target rheological properties of liquid vehicles for the administration of multiparticulates.

4.1 Introduction

Multiparticulate formulations emerge as a flexible solid oral dosage form with potential to overcome limitations of conventional solid and liquid medicines for the delivery of drugs to a broad range of patients, including paediatrics, geriatrics and patients with swallowing difficulties. However, previous studies involving children and adults participants suggest that the gritty feeling in the mouth produced by these hard spheroids might be a barrier to palatability and patient acceptability (Kimura et al., 2015; Lopez et al., 2016). A potential solution to overcome palatability and patient's acceptability issues could be co-administration with a suitable vehicle which could help to conceal the presence of multiparticulates in the sample.

Medicines are known to be mixed with liquid and semi-solid foodstuff to allow administration to children in clinical practice (Akram and Mullen, 2015, 2012). This includes tablets and capsules which are manipulated to be dispersed into foodstuff, but also multiparticulates which are purposely designed to be 'sprinkled' onto food or drinks,

e.g. (Adu-Afarwuah et al., 2008; Musiime et al., 2014; Verrotti et al., 2012). Solid medicines are also known to be mixed with thickened fluids to allow dosing to patients with swallowing dysfunctions (Fusco et al., 2016; Manrique et al., 2016); food thickeners promote safer swallowing by increasing the viscosity of food and beverages (Steele et al., 2015). However, this is not without the risks that mixing medication with foodstuff could alter bioavailability and introduce poor control over dose intake (EMA, 2013).

The development of a standard pharmaceutical vehicle for the administration of multiparticulates could overcome some of the limitations of co-administration with food. The EMA mandates evaluation of the potential impact on patient acceptability, dosing accuracy, compatibility and drug bioavailability of the proposed vehicle(s) for co-administration with medicines (EMA, 2013). That task becomes very impractical when medicines can be mixed with a range of foods with different composition and physical properties (e.g. rheology, pH, ionic strength). However, if the liquid vehicle is rationally designed and provided as part of the final product these investigations are more controlled and therefore facilitated. Ideally, such liquid vehicle should be formulated as a solid product for reconstitution given the inherent limitations of liquids. Some of the attributes which require consideration during the development of liquid vehicles for the administration of medicines are summarised on Table 4.1.

Table 4.1. Quality Target Product Profile (QTPP) for a pharmaceutical liquid vehicle

Critical Quality Attributes (CQAs)	Target requirements
Patient safety	Excipients Generally Regarded As Safe (GRAS)
Manufacturability	Scalable for production at commercial scale
Reconstitution	Rapid reconstitution in water with minimal mixing
Suspendability	Forms stable suspensions during in-use conditions
Dosing accuracy	Appropriate instructions and dosing device provided
Palatability	Acceptable appearance, mouth-feel and taste
Bioavailability	Do not interfere with drug product bioavailability

The rheological properties of a pharmaceutical liquid vehicle require especial attention as these will have an impact on several critical quality attributes, such as suspendability, palatability (particularly appearance and mouth-feel) and drug bioavailability. In this regard, an essential excipient in the development of liquid vehicles for the administration of medicines will be viscosity modifiers or thickening agents. Hydrocolloids that have been frequently used as thickening agents include starch and modified starch, xanthan gum, galactomannans like guar gum and locust bean gum, acacia gum and cellulose derivatives like methylcellulose, hydroxypropyl cellulose and carboxymethyl cellulose. The thickening effect produced by these substances will depend on the type of hydrocolloid used, its concentration, the liquid in which it is dispersed and the temperature (Saha and Bhattacharya, 2010).

The link between rheology and texture or mouth-feel perception has been extensively studied (especially in food products), although there are still many unknowns given the complexity and multifactorial nature of texture perception and palatability (Stokes et al., 2013). The link between rheology and swallowing is also not fully understood given the complexity of such physiological process, although thicker liquids have been found to facilitate swallowing and reduce the risk of penetration-aspiration in patients with swallowing dysfunction (Steele et al., 2015). There is insufficient evidence to support delineation of viscosity boundaries related to such clinical outcomes, and there is no consensus for a shear rate that should be used as a reference for viscosity (Steele et al., 2015). Viscosity measurements made at shear rates around 50 s^{-1} have been found to correlate with initial thickness perception and are commonly used as a reference value to compare between samples (Chen and Engelen, 2012; Stokes et al., 2013).

Development of media for the administration of multiparticulates and evaluation of its effect on palatability has been the focus of two recent studies (Kluk and Sznitowska, 2014; Lopez et al., 2016), both of which concluded that the use of polymeric hydrogels as administration vehicles could help conceal the presence of particles, reducing oral

grittiness perception. However, both studies focussed on a swirl and spit methodology, which overlooks other important sample attributes such as ease of swallowing. Moreover, neither of those studies investigated the palatability of the liquid vehicles alone, which limited their understanding on the effect of the palatability of the vehicle on the overall palatability and acceptability of the final formulations.

4.2 Aims and objectives

The aim of this work was to define the target rheological properties for an oral vehicle for the administration of multiparticulates with improved palatability and acceptability. Secondary objectives included to develop oral vehicles with contrasting rheological characteristics; and to evaluate the effect of oral vehicles on palatability and acceptability of multiparticulates in a study with healthy adult volunteers.

4.3 Materials and methods

4.3.1 Materials

Model multiparticulates: Microcrystalline cellulose pellets (Cellets) were provided by Pharmatrans Sanaq (Basel, Switzerland). Oral suspending vehicles and oral paediatric medicines: Ora-Plus® (“Suspending vehicle A”) was supplied by Perrigo (Dublin, Ireland); SyrSpend® SF PH4 (“Suspending vehicle B”) and Simple syrup were supplied by Fagron (Waregem, Belgium). Nurofen® children Ibuprofen Oral Suspension 100mg/5ml (“Ibuprofen suspension A”, Reckitt Benckiser), Fenpaed® Ibuprofen sugar-free Oral Suspension 100mg/5ml (“Ibuprofen suspension B”, Pinewood Laboratories), Calpol® Infant Paracetamol Oral Suspension 120mg/5ml (“Paracetamol suspension A”, McNeil Products) and Boots® Paracetamol Oral Suspension 120mg/5ml (“Paracetamol suspension B”, The Boots Company) were purchased from a local Pharmacy. Food thickeners and food products: The xanthan-gum-based food thickener Resource® ThickenUp® (“XG thickener”) was provided by Nestle Health Science (Gatwick, Sussex,

UK) and the starch-based food thickener Multi-thick® (“Starch thickener”) was provided by Abbott Nutrition (Lake Bluff, Illinois, USA); both food-thickeners were prepared to two different consistency levels (Stage 1 and Stage 2) following manufacturers’ instructions. Vanilla-flavoured full-fat yogurt (Onken®), vanilla-flavoured fat-free yogurt (Onken®), vanilla-flavoured soya-based yogurt (“Dairy-free yogurt”, Alpro®) and vanilla-flavoured fromage-frais (“Children yogurt”, Petit Filous®) were purchased from a local supermarket (Waitrose, London, UK). Excipients for development of polymeric hydrogels: Xanthan gum (“XG”, Xantural 180) was supplied by CP Kelco (Leatherhead, Surrey, UK); sodium carboxymethyl-cellulose (“CMC”, Blanose 7HF-PH) was provided by Ashland (Covington, Kentucky, USA); guar gum (“GG”) and vanillin were procured from Sigma-Aldrich (Irvine, Ayrshire, UK).

4.3.2 Preparation and characterisation of liquid vehicles

4.3.2.1 *Preparation of liquid vehicles*

Polymeric hydrogels in the range of 0.15 – 1.50% (w/v) were prepared by slow addition of hydrophilic polymer (XG or CMC) into 100 ml of water under continuous stirring at room temperature. Samples were left stirring overnight to ensure complete polymer hydration and stored in the fridge for a maximum of one week. Samples were allowed to equilibrate to room temperature for at least 60 minutes before testing.

4.3.2.2 *Rheological characterisation*

A Bohlin CVO rotational rheometer system (Malvern Instruments Ltd, Malvern, UK) was used to investigate the flow properties of the samples using a cone and plate geometry (40 mm diameter, 4 ° angle; gap size adjusted to 250 µm). A shear sweep measurement mode was employed, whereby the shear rate of the sample was advanced across the range of 0.1 to 200 s⁻¹, with ascendant logarithmic progression. The temperature of the samples was maintained at 25 ± 0.2 °C throughout testing.

The resulting data (shear rate vs. shear stress) was fitted to the power law model (equation 1) to describe the flow properties of the samples:

$$\sigma = K\gamma^n \quad (1)$$

where σ is the shear stress (Pa), γ is the shear rate (1/s), K is the consistency index (Pas), and n is the flow behaviour index (dimensionless).

The consistency index (K) corresponds to the viscosity at a shear rate of 1 s^{-1} and is a measure of the *thickness* of the sample; whereas the flow behaviour index (n) provides an indication of the deformation behaviour, where a value of 1 indicates Newtonian behaviour, 0-1 indicates shear-thinning behaviour and values greater than 1 indicate shear-thickening. The values of K and n were used to describe the rheological properties and compare between samples. In addition, the apparent viscosity at 50s^{-1} (η at 50s^{-1}), a reference shear rate for oral processing and swallowing, and the apparent viscosity at 0.1s^{-1} (η at 0.1s^{-1}), a reference shear rate of the sample at rest, were measured by the rheometer along the ascendant shear ramp. This procedure was repeated three times for each sample.

4.3.2.3 Polymer hydration experiments

A test was developed to measure the hydration behaviour of hydrocolloids. A Bohlin CVO rotational rheometer system (Malvern Instruments Ltd, Malvern, UK) was adapted by fitting a glass petri dish (50 mm diameter, 15 mm height) as sample holder (Figure 4.1). A 40-mm diameter, 4° angle plate was fitted to the instrument and the gap set at $250 \mu\text{m}$ (from the base of the petri dish). The petri dish was filled with 10 ml of deionised water and a test sample of 100 mg of polymer was added while the viscosity was measured at a fixed shear rate of 10 s^{-1} , at 30 second intervals for 30 minutes ($\eta_{t=x}$). Separately, a sample of 100 mg of hydrophilic polymer was dispersed in water under continuous stirring at room temperature and left stirring overnight to ensure full hydration;

the viscosity of such sample was then determined at a shear rate of 10 s^{-1} to be used as a reference of viscosity after full hydration ($\eta_{t=\infty}$). Results of the hydration test were expressed as viscosity of the test sample compared to the viscosity of the fully hydrated sample ($\eta_{t=x}/\eta_{t=\infty}$, normalised viscosity). Experiments were conducted in triplicate.

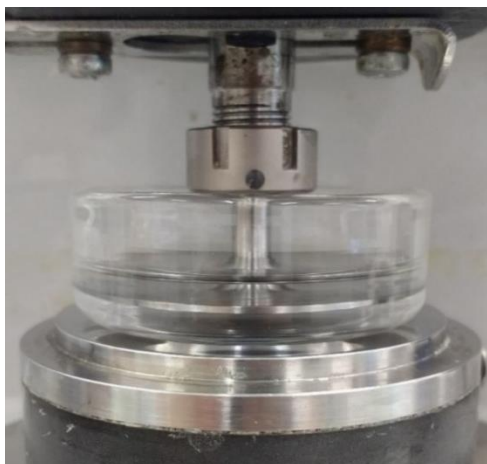


Figure 4.1. Adapted set up of rotational rheometer using a petri dish as sample holder.

4.3.2.4 Sedimentation time

The ability of the oral vehicles to maintain multiparticulates in suspension was calculated based on sedimentation experiments. A sample containing 500 mg of Cellets and 50 ml of a liquid vehicle was filled into a 50-ml graduated plastic tube (30 x 115 mm; conical bottom; TPP Techno Plastic Products, Trasadingen, Switzerland). The tube was turned upside down until homogeneous dispersion of the particles. Then, the sample was left standing and sedimentation of Cellets in the media was recorded during a 30-minute period using a video camera (Samsung ST66, Samsung, Daegu, South Korea). The time taken for Cellets to clarify the top 15 ml of the dispersant (approximately one third of the media volume) was determined. This experiment was adapted from that described by Kluk and co-workers (Kluk and Sznitowska, 2014). Experiments were repeated using multiparticulates of two extreme particle sizes, Cellets 200 (200-355 μm) and Cellets 700 (700 – 1000 μm), to account for the effect of particle size on sedimentation. The experiment was conducted in triplicate.

4.3.3 Sensory evaluation study

4.3.3.1 Sample preparation

Liquid vehicles were prepared as described in Section 4.3.2.1, with addition of 0.1% vanillin (when required) just before addition of the polymer (Table 2.3). The small amount of vanillin was added to mask any potential taste and smell of the polymers, which could have a negative impact in results. Spring water and vanilla-flavoured water were used as controls, to account for the effect of the flavouring agent.

Table 4.2. List of liquid vehicles assessed in sensory evaluation experiments.

ID	Vehicle	Polymer conc. (% w/v)	Consistency level	Flavour
Water	Water	N/A	Thin	None
Water + v.	Water	N/A	Thin	0.1% vanillin
XG L1	XG in water	0.25	Level 1	0.1% vanillin
XG L2	XG in water	0.50	Level 2	0.1% vanillin
XG L3	XG in water	1.00	Level 3	0.1% vanillin
CMC L1	CMC in water	0.50	Level 1	0.1% vanillin
CMC L2	CMC in water	1.00	Level 2	0.1% vanillin
CMC L3	CMC in water	1.50	Level 3	0.1% vanillin

Liquid vehicles were prepared within five days of the sensory evaluation study and kept in the fridge between manufacturing and testing (samples were allowed to equilibrate to room temperature for at least 90 minutes before sensory evaluation). Immediately before administration, Cellets (250 mg) were pre-dispersed in the liquid vehicles (approximately 3 ml, for a total volume of 5 ml) inside 25-ml plastic dosing cups using wooden stirrers to ensure homogenous dispersion of the samples. Subsequently, samples were transferred from the dosing cup onto 5-ml plastic medicine spoons that were handed to participants of the study for tasting.

4.3.3.2 Study design

Thirty healthy adult volunteers were enrolled in a single-centre, randomised, single-blind, 3-treatment, crossover sensory evaluation. The study was approved by UCL Research Ethics Committee (ERN_4612-011). The study was conducted in three sessions taken place in three separate days. On each day, participants tested samples of liquid vehicles without Cellets ('no particles'), with Cellets 200 ('smaller particles') and with Cellets 700 ('larger particles'). Participants were divided into six group to ensure that all possible sequence orders between treatments were considered, as shown in Figure 4.2.

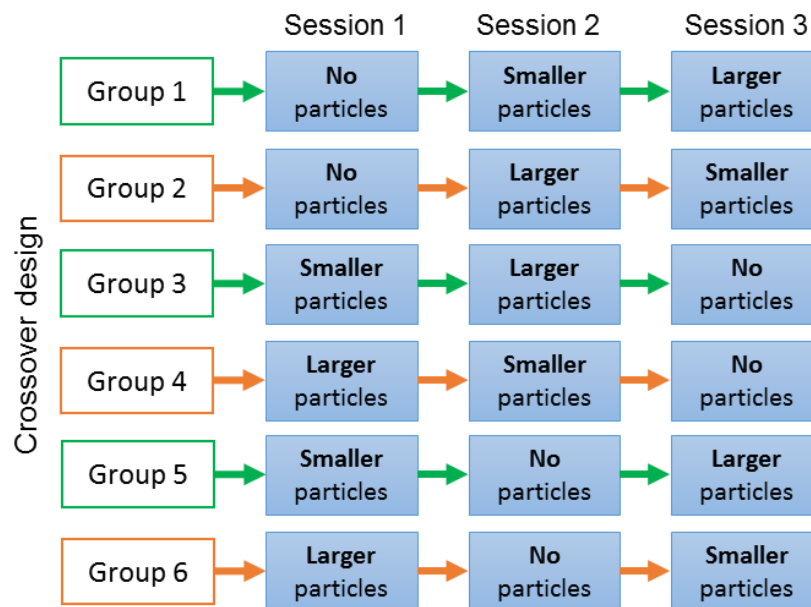


Figure 4.2. Overview of the 3-way crossover study design where all possible sequence orders between treatments were considered (T1: no particles; T2: small particles; T3: large particles).

During each session, participants were handed eight samples of liquid vehicles on a dosing spoon (Figure 4.3), with or without Cellets (as per the study design depicted in Figure 4.2), in a randomised order. They were instructed to place the sample in their mouth and swallow it, then drink water as required. Participants had free access to spring water to complete sample intake and clean their palate. To minimise subject discomfort and carryover effect 5-10-minute intervals were respected between samples.

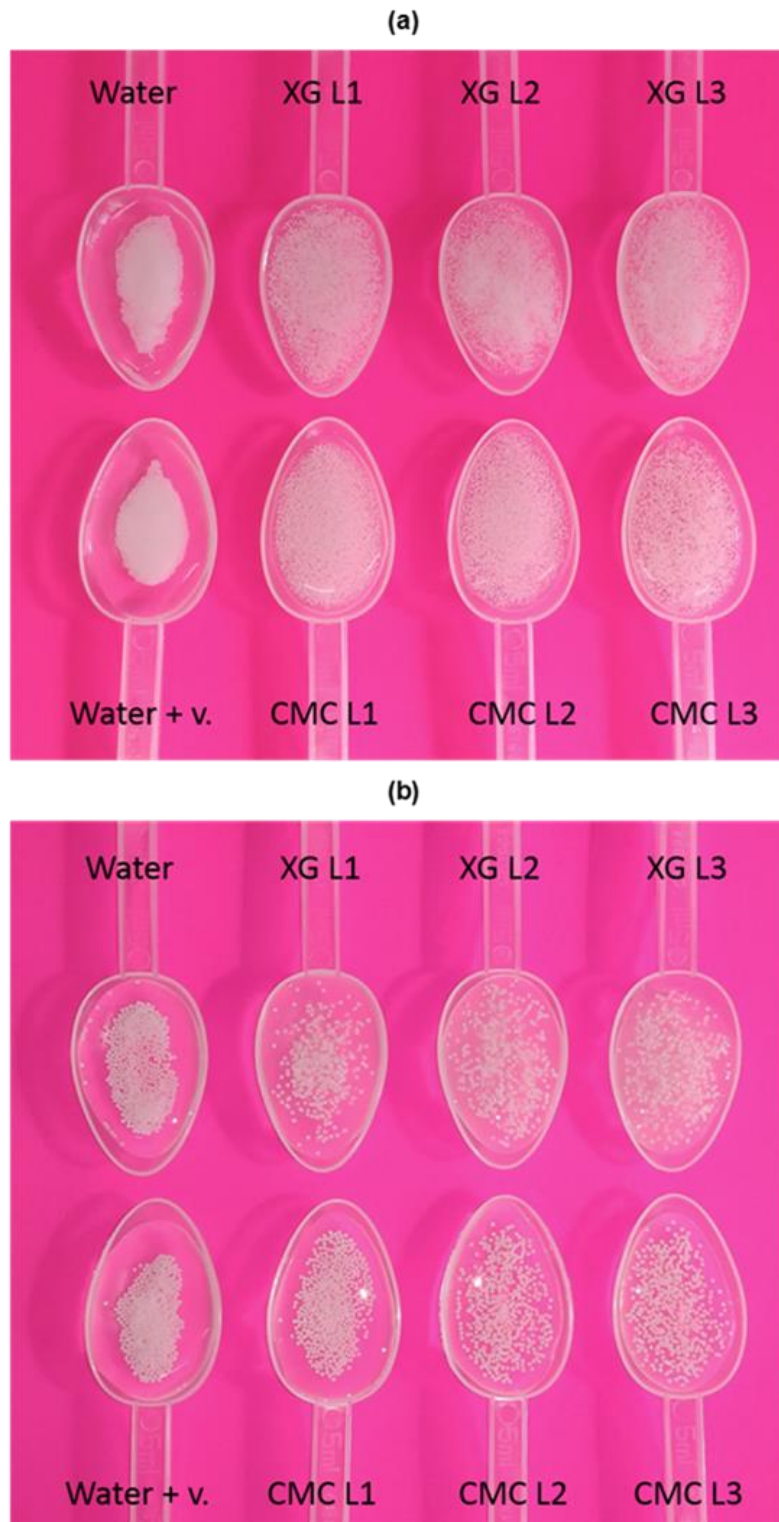


Figure 4.3. Photographs of samples composed of 250 mg of Cellets 200 (a) and Cellets 700 (b) dispersed in different liquid vehicles on 5-ml plastic medicine spoons. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is depicted as L1 (Level1), L2 (Level 2) and L3 (Level 3). The set of samples of liquid vehicles without multiparticulates was not photographed and is not shown in the image.

4.3.3.3 Evaluation tool and outcome measures

A digitalized questionnaire (Qualtrics.com) was used for data collection. Immediately after swallowing the sample, volunteers were asked to rate several sample attributes using 5-point hedonic scales; the attributes evaluated included appearance, ease of swallowing, mouth-feel and taste. In addition, the feeling of particles in the mouth during sample intake (i.e. grittiness perception) and the feeling of particles in the mouth after samples intake and after rinsing their mouth with water (i.e. residue in mouth) was assessed using 5-point magnitude scales. Finally, the future willingness of the volunteers to take multiparticulates was measured using a bipolar (yes/no) question: “*If this was a medicine, would you be willing to take it every day?*”. Participants could also provide voluntary feedback of each sample attribute using their own words.

4.3.3.4 Data analysis

The different categories of the 5-point scales were assigned numeric scores (1-5) from lowest to highest stimuli perception, respectively. Statistical analysis was performed using the non-parametric Kruskal-Wallis one-way analysis of variance with 95% confidence, followed by Dunn’s test as *post hoc* for pairwise comparison. Minitab 17 (Minitab Inc., State College, Pennsylvania, USA) was used for data analysis.

4.4 Results and discussion

4.4.1 Rheological properties of model liquid formulations

The rheological characteristics of a range of model liquid formulations were evaluated to be used as benchmarks in the development of liquid suspending media for the administration of multiparticulates. The products evaluated included (1) oral suspending vehicles commonly used for the manufacture of extemporaneous preparations for paediatric patients, (2) paediatric medicines in the form of oral suspensions, (3) commercially available thickening agents commonly used to modify the consistency of

food stuff for patients with swallowing dysfunction and (4) various types of yogurts as an example of food product known to be used by parents and caregivers to aid administration of medicines to children.

The rheological characteristics of the different products evaluated are summarised in Table 4.3. Differences in consistency and rheological behaviour were found between samples, which are detailed below for each set of products.

Table 4.3. Rheological characteristics of model liquid formulations, including oral suspending vehicles, medicines in the form of oral suspensions, food thickeners and various types of yogurt.

Product ID	Viscosity η at $0.1s^{-1}$ (Pas)	Viscosity η at $50s^{-1}$ (Pas)	Power law		
			K (Pas)	n (-)	R ²
Suspending vehicle A	0.79	0.05	0.46	0.46	0.996
Suspending vehicle B	6.04	0.14	1.52	0.38	0.976
Simple syrup	0.13	0.13	0.11	1.00	0.999
Ibuprofen suspension A	31.15	0.31	5.87	0.26	0.992
Ibuprofen suspension B	12.01	0.18	3.10	0.27	0.995
Paracetamol suspension A	5.09	0.24	1.84	0.49	0.994
Paracetamol suspension B	3.36	0.16	1.44	0.45	0.983
XG thickener Stage 1	8.92	0.15	3.32	0.21	0.998
XG thickener Stage 2	25.49	0.29	9.16	0.12	0.971
Starch thickener Stage 1	1.14	0.13	1.03	0.48	0.997
Starch thickener Stage 2	114.8	0.95	16.73	0.26	0.991
Full-fat yogurt	91.00	0.72	9.69	0.33	0.986
Fat-free yogurt	45.86	0.50	4.51	0.42	0.974
Children yogurt	24.20	0.66	5.16	0.47	0.997
Dairy-free yogurt	135.07	0.69	14.35	0.23	0.996

η at $50s^{-1}$: Viscosity at shear rate = $50 s^{-1}$, reference shear rate of swallowing.

K: Consistency index, calculated by fitting a power law model to rheology data.

n: Flow behaviour index, calculated by fitting a power law model to rheology data.

R²: coefficient of determination of the power law fitting to rheology data.

The large majority of samples exhibited some degree of shear-thinning behaviour (as shown by the value of the flow index behaviour, “n”, lower than 1), with exception of simple syrup, which is known to be a Newtonian fluid. Interestingly, the rheological properties of oral suspending vehicles commonly used in paediatric extemporaneous preparations varied noticeably between different brands ($K = 0.5-1.5$ Pas and $n = 0.38-0.46$). Their different behaviour can be explained by differences in composition; Oral suspending vehicle A is based on a combination of MCC, CMC, XG and CG (plus buffers and preservatives), whereas Oral suspending vehicle B is based on modified food starch (plus buffers and preservatives).

Similarly, the consistency and flow index behaviour of liquid medicines (oral suspensions) varied between medicines containing different drugs ($K = 1.4-5.9$ Pas and $n = 0.26-0.49$). Although only small differences were found between different brands of bio-equivalent medicines containing the same drug ($K = 3.1-5.9$ and $n = 0.26-0.27$ for ibuprofen; $K = 1.4-1.8$, $n = 0.45-0.49$ for paracetamol). Both ibuprofen oral suspensions contain XG as rheology modifier, paracetamol suspension A contains a combination of XG and dispersible cellulose (MCC/CMC), and paracetamol suspension B contains dispersible cellulose (MCC/CMC) and hydroxyethyl cellulose, as listed in their Summary of Products Characteristics (SmPCs).

Thickening agents used to assist with the management of dysphagia can be prepared to different consistency levels to target the patient needs; as the swallowing dysfunction worsen the consistency level is usually increased to promote safer swallowing (Wright et al., 2006). However, large differences in rheological behaviour were found between brands of food thickeners when prepared to the same consistency level ($K = 1.0-2.3$ and $n = 0.21-0.48$ for Stage 1; $K = 9.2-16.7$ and $n = 0.12-0.26$ for Stage 2). These findings are supported by previous research which demonstrated differences in consistency and organoleptic properties of commercial thickeners (Pelletier, 1997).

Finally, the rheological properties of various types of yogurts were investigated. Broad differences in rheology were found between yogurts ($K = 4.5-14.4$ and $n = 0.23-0.47$). Fat-free yogurt exhibited the thinnest consistency among the yogurts tested whereas dairy-free yogurt based on hulled soya beans showed the thickest consistency. Again, these results highlight the importance of the ingredients used in the resulting rheological properties of the product.

Although the organoleptic properties and performance of the product will be determined by its rheological characteristics, vehicles commonly used in practice for the administration of medicines do not share common rheological properties. On the contrary, a range of fluids with varying consistency and shear thinning behaviour have been identified. Thus, it would be necessary to study a range of different consistencies and flow behaviours to establish the target rheology characteristics of suspending media for the administration of multiparticulates.

4.4.2 Development of suspending media for multiparticulates

4.4.2.1 *Rheological properties of polymeric hydrogels*

XG and CMC were selected as model excipients to develop polymeric hydrogels for the administration of multiparticulates. XG and CMC are Generally Regarded As Safe (GRAS) excipients commonly used in paediatric medicines and, additionally, they exhibit rapid hydration in water and are commonly used in medicines formulated as solid products for reconstitution into oral solutions or suspensions.

The rheological properties of XG and CMC hydrogels were explored as a function of the concentration of polymer and results are summarised in Table 4.4. The consistency index of XG and CMC-based polymeric hydrogels increased as the concentration of polymer dispersed in water increased, as it can be expected. The increase in viscosity was more pronounced for XG than it was for CMC, revealing the higher 'thickening power' of XG (Figure 4.4). In addition, XG hydrogels exhibited a strong shear thinning

behaviour whereas CMC hydrogels showed a much lower degree of shear thinning; the flow behaviour index (n-value) of XG-based hydrogels was lower than that of CMC-based hydrogels throughout the range of concentrations tested (Figure 4.5).

Table 4.4. Rheological characteristics of XG and CMC hydrogels prepared at a range of concentrations (0.15-1.50% w/v).

Polymer	Concentration (% w/v)	Viscosity η at 0.1s ⁻¹ (Pas)	Viscosity η at 50s ⁻¹ (Pas)	Power law		
				K (Pas)	n (-)	R ²
XG	0.15	0.53	0.02	0.06	0.51	0.995
XG	0.25	1.81	0.07	0.56	0.39	0.984
XG	0.50	16.15	0.18	2.98	0.19	0.964
XG	0.75	41.70	0.27	5.69	0.15	0.980
XG	1.00	66.07	0.41	9.39	0.13	0.955
XG	1.50	79.29	0.57	18.13	0.13	0.975
CMC	0.15	0.04	0.03	0.04	0.90	0.998
CMC	0.25	0.11	0.04	0.08	0.79	0.993
CMC	0.50	0.33	0.13	0.28	0.69	0.994
CMC	0.75	1.46	0.30	1.03	0.63	0.988
CMC	1.00	2.85	0.50	2.54	0.51	0.987
CMC	1.50	14.54	1.15	9.50	0.45	0.992

The contrasting rheological characteristics of XG and CMC made them ideal candidates to investigate the effect of shear thinning behaviour on their performance as a vehicle for the administration of multiparticulates. Based on previous research, shear thinning fluids can be expected to be easier to swallow than Newtonian vehicles, as the former would flow better when pushed by the tongue towards the throat (Steele et al., 2015). However, it could be hypothesised that shear thinning fluids would be less effective in ‘masking’ the presence of particles as these fluids would ‘get thinner’ (i.e. reduction in consistency) under oral processing (e.g. when pushed by the tongue towards the palate).

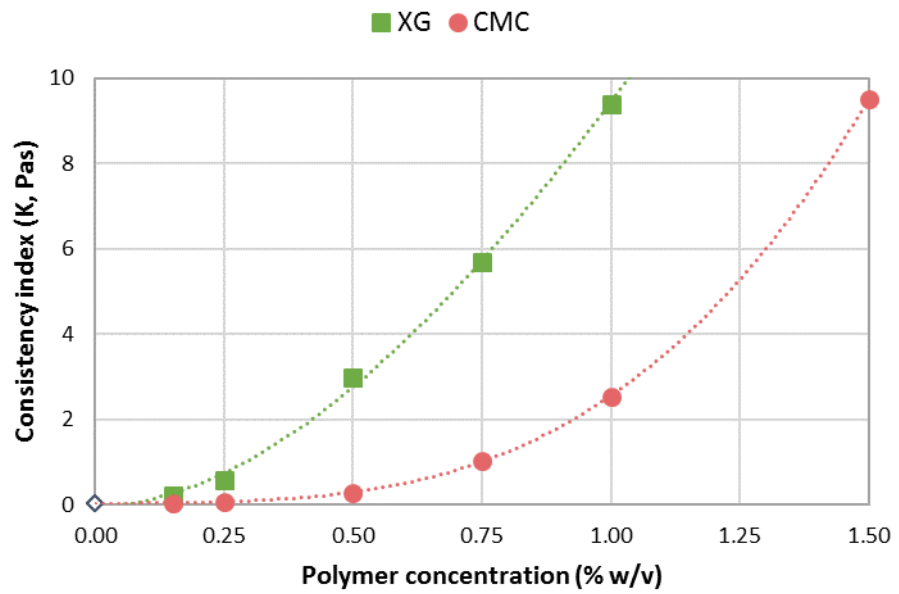


Figure 4.4. Consistency index of XG (filled squares) and CMC (filled circles) hydrogels as a function of the polymer concentration.

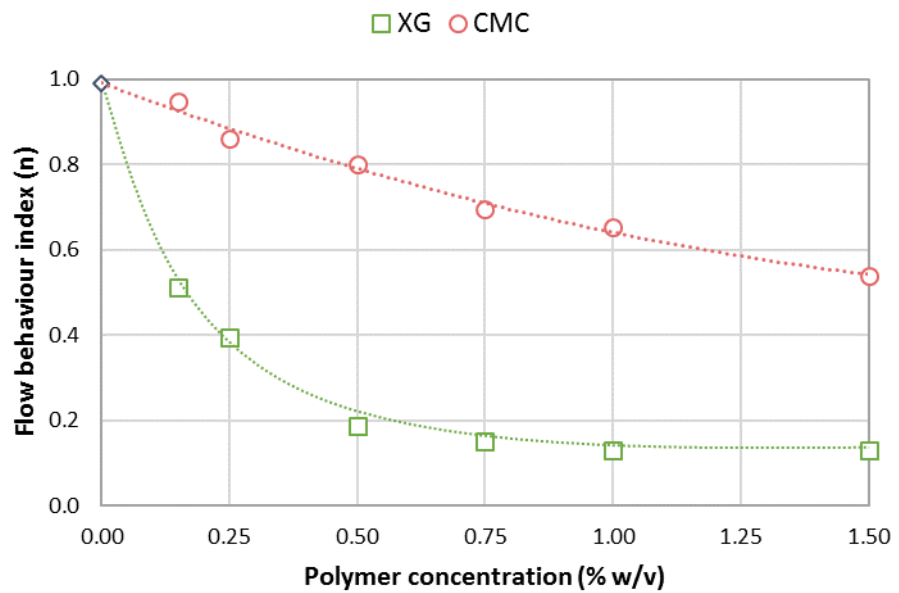


Figure 4.5. Flow behaviour index of XG (open squares) and CMC (open circles) hydrogels as a function of the polymer concentration.

4.4.2.2 Hydration behaviour of hydrocolloids

Rapid hydration in water is a desirable property for thickening agents intended for use as part of a solid product for reconstitution so that, once the formulation is added to water, reconstitution into a stable suspension occurs in a short period of time. The hydration and thickening behaviour of hydrocolloids was evaluated using a rotational rheometer with an adapted set up. The results of such experiments are illustrated in Figure 4.6.

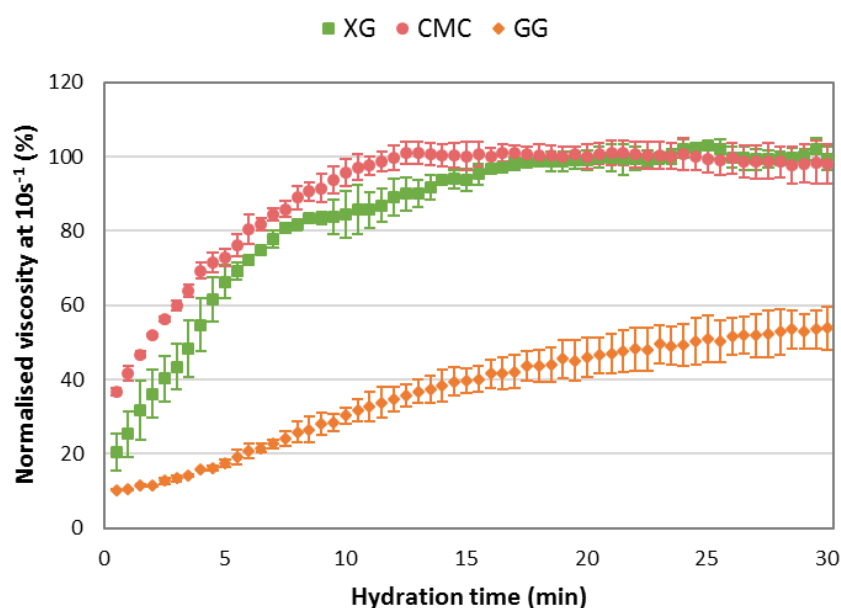


Figure 4.6. Viscosity of hydrocolloids at shear rate of 10s^{-1} during hydration experiments in water. Results expressed as normalised viscosity with respect to the viscosity of fully hydrated samples.

As shown in Figure 4.6, full hydration and thickening of XG and CMC hydrogels occurred within 10 minutes under the conditions of the experiment (where polymers were dispersed in water by the rotational movement of the rheometer plate). Full hydration and thickening can be expected to be quicker with more efficient mixing under in-use conditions (e.g. mixing with a spoon in a glass or dosing cup). The hydration rate of XG and CMC was much faster than that of guar gum (GG), which was used as a comparator based on previous experiments that suggested slow hydration of GG compared to other hydrocolloids (Sanchez et al., 1995).

4.4.2.3 Ability to maintain multiparticulates in suspension

Sedimentation time of multiparticulates in polymeric hydrogels was determined by measuring the time lapse between homogeneous dispersion of multiparticulates and clearance of the top layer of the liquid vehicle (15 out of 50 ml). Results of sedimentation time as a function of the media viscosity are depicted in Figure 4.7.

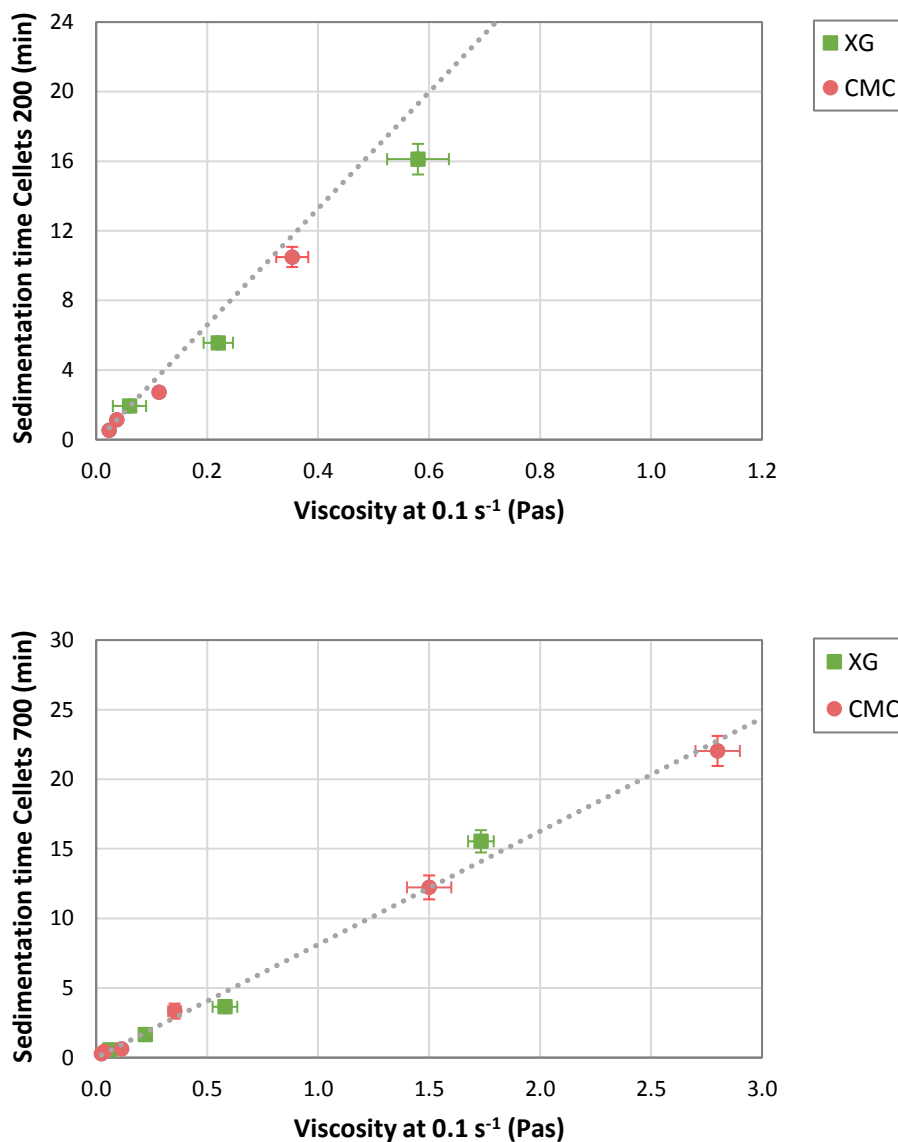


Figure 4.7. Sedimentation time of multiparticulates of two different sizes, Cellets 200 (top) and Cellets 700 (bottom), as a function of the apparent viscosity at 0.1 s⁻¹ (very low shear rate, representative of the sample at rest) of XG and CMC hydrogels prepared with increasing polymer concentration. A trendline was fit to the data by linear regression (dotted line). *n.b.* the scale range is different in each graph to improve visualisation.

Sedimentation time increased with increasing viscosity of the media and decreased with increasing size of the multiparticulates, as shown in Figure 4.7. This behaviour can be expected, in accordance to Stoke's law:

$$v = \frac{d^2(\rho_p - \rho_f)g}{18\eta} \quad (2)$$

where v is the velocity (m/s) of a spherical particle in suspension with a diameter equal to d (m), ρ_p and ρ_f are the mass densities (kg/m³) of the particle and the fluid, respectively, and g is the gravitational acceleration (≈ 9.8 m/s²). Since v is equal to distance over time (i.e. time required for the particle to travel a certain distance), sedimentation time must be inversely proportional to diameter of the particle and directly proportional to the viscosity of the media.

An ideal suspending vehicle should be able to maintain multiparticulates in suspension from dispersion of the particles in the media until administration by the patient. The viscosity required to maintain multiparticulates in suspension for five minutes (as an arbitrary measure of the estimated time spent by patients to take oral medicines) was determined from the plots in Figure 4.7. Results showed that hydrogels with an apparent viscosity at 0.1s^{-1} equal or higher to 0.2 and 0.6 Pas would be sufficient to maintain a homogeneous suspension of multiparticulates larger than 200 and 700 μm , respectively, for at least five minutes.

This means that XG hydrogels prepared at 0.25% w/v would be sufficient to maintain both Cellets 200 and Cellets 700 in suspension, whereas a higher concentration of CMC (1.00% w/v) would be required to maintain the larger Cellets in suspension for at least 5 minutes, as depicted in Figure 4.8. The lower concentration of XG required to maintain multiparticulates in suspension could be expected based on its stronger thickening power and its shear thinning character, which means that viscosity of XG hydrogels at low shear rates (i.e. shear rates relevant during sedimentation) is higher than CMC hydrogels.

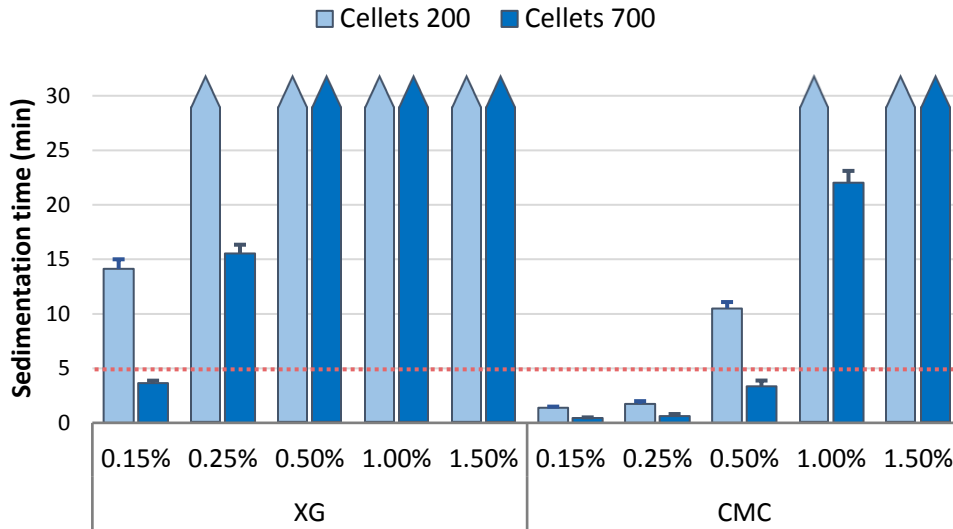


Figure 4.8. Sedimentation time (minutes) of Cellets 200 and Cellets 700 in XG and CMC hydrogels prepared with increasing polymer concentration (% w/v). Sedimentation was observed for a maximum period of 30 minutes; bars extending over that limit represent sedimentation times longer than 30 minutes.

4.4.2.4 Selection of liquid vehicles for sensory evaluation

As discussed in Section 4.4.1, there is no evidence to suggest an appropriate consistency level for liquid vehicles used for the administration of oral solid dosage forms, based on the range of vehicles used in common practice. Therefore, XG and CMC hydrogels were prepared and evaluated at different consistency levels (Figure 4.9), with the aim to investigate the effect of viscosity on palatability and patient acceptability. XG hydrogels were investigated at 0.25, 0.50 and 1.00% w/v whereas CMC hydrogels were prepared and studied at 0.50, 1.00 and 1.50% w/v.

These concentrations were targeted to meet the International Dysphagia Diet Standardisation Initiative (IDDSI) descriptors for Level 1, Level 2 and Level 3 consistency levels, respectively (Cichero et al., 2017). According to this framework, Level 1 fluids are “thicker than water but flow through a teat/nipple and straw”, Level 2 fluids “require effort to drink through a straw and flow quickly off a spoon” and Level 3 fluids are “difficult to suck through a straw and pour slowly off a spoon”.

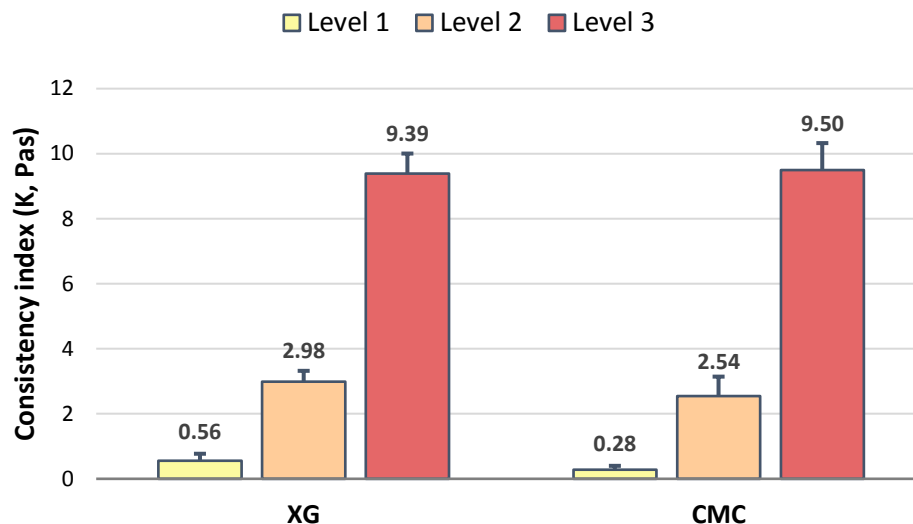


Figure 4.9. Consistency index of XG and CMC hydrogels prepared to three different consistency levels: Level 1 – Syrup (yellow), Level 2 – Custard (orange), Level 3 – Pudding (red) as described by the IDDSI (Cichero et al., 2017).

Polymeric hydrogels thickened to consistency Level 1 exhibited similar viscosity to that of oral suspending vehicles commonly used in paediatric extemporaneous preparations; as shown in the previous section, this consistency would be borderline for maintaining multiparticulates in suspension during in-use conditions, especially for multiparticulates of large size (over 700 μm). On the contrary, vehicles thickened to consistency Level 3 were characterised by viscosity comparable to that of a yogurt; these vehicles would maintain multiparticulates in suspension for prolonged periods of time (i.e. several days or weeks). Finally, vehicles thickened to Level 2 showed intermediate viscosity, which was comparable to that of model paediatric oral suspensions presented in Section 4.4.1.

4.4.3 Sensory evaluation studies

The suitability of XG and CMC vehicles as suspending media for the administration of multiparticulates was investigated in healthy adult volunteers, with emphasis on palatability, ease of swallowing and overall patient acceptability. Water was used as comparator (positive control, as gritty feeling in the mouth can be expected).

4.4.3.1 Demographics

A total of 30 volunteers (13 male and 17 female) participated in the sensory evaluation study. The average age was 23 years, with a standard deviation of 4 years (min. 19 years, max. 33 years) and median at 22 years.

4.4.3.2 Liquid vehicles without multiparticulates

Participants of the sensory evaluation study tested liquid vehicles without Cellets in one of the three sessions of the study. The analysis of liquid vehicles without Cellets was performed in order to gain fundamental understanding of the properties of the liquid vehicles, such as appearance, mouthfeel, taste and ease of swallowing.

All samples evaluated received average appearance ratings in the neutral to positive range of the scale (range: 1.70 – 2.37; Water – XG L2), except for XG L3 (average appearance rating = 3.17). According to participants responses to hedonic scales, the appearance of XG hydrogels was worse than the appearance of water and CMC hydrogels ($p < 0.001$), as shown in Figure 4.10. This was ascribed to the opaque appearance of XG hydrogels (in contrast with the transparent nature of water and CMC hydrogels), as supported by anecdotal feedback provided by the participants: e.g. “*I personally prefer when the sample is limpid, this one was a bit opaque and it gives you an idea of dirt*” (Participant 11, XG L3).

Appearance ratings of hydrogel samples worsened as the concentration of polymer in the liquid vehicle was increased (i.e. as the consistency level increased). This indicates that the appearance of very thick samples (which retain their shape when placed on a spoon) was considered less appealing than thinner fluids. This effect was very evident for XG samples, which were also affected by the increased in opacity as the concentration of XG increased. However, differences between CMC hydrogels thickened to different consistency levels were minimal.

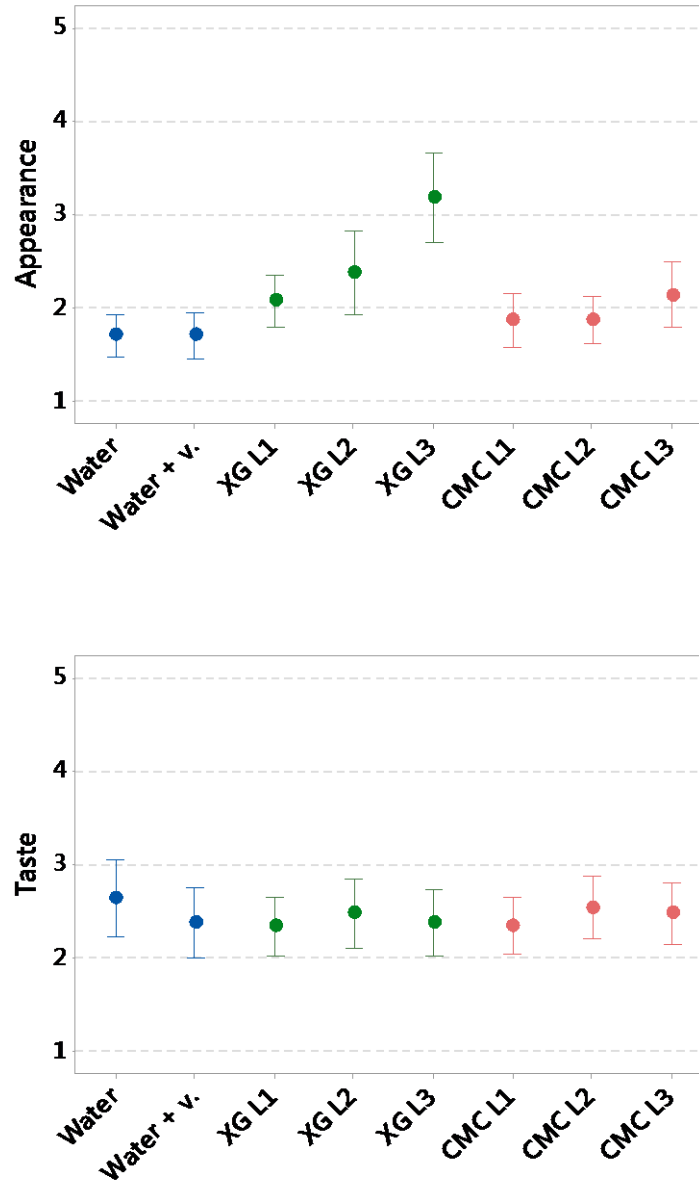


Figure 4.10. Interval plot for appearance (top) and mouthfeel (bottom) of different liquid vehicles. Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

The taste of all liquid vehicles evaluated received average ratings between 2 and 3 (range: 2.33 – 2.63; XG L1 – Water), which indicates acceptable neutral taste (Figure 4.10). Interestingly, samples containing vanillin received slightly better taste ratings than

pure water, although differences were negligible (not statistically significant). The very small differences between samples confirmed that the level of vanillin used was appropriate to mask the taste of the polymer without having a significant impact on results (as it was intended). However, the fact that average ratings for taste were closer to the centre of the scale than to the positive end of the scale may indicate participants' expectations of a more intense, sweetened or flavoured taste for samples intended as (part of) a medicinal product. This was reinforced by voluntary feedback; e.g. "*if this had added sugar/sweetener it would be a more enjoyable medicine to take*" (P05, CMC L3).

Mouthfeel ratings of XG and CMC hydrogels worsened as the consistency of the sample increased, revealing preference for thinner vehicles (Figure 4.11). However, all samples received average ratings in the neutral to positive range of the scale (range: 1.67 – 2.90; Water + v. – CMC L3), suggesting all vehicles prepared had an acceptable mouthfeel to be used as suspending media for the administration of multiparticulates. CMC hydrogels received slightly worse mouthfeel ratings than XG samples, which was attributed to a "*greasy*" or "*oily*" feeling in the mouth, as reported by the volunteers. The slimy texture of CMC hydrogels have been reported in previous research and attributed to its low degree of shear thinning (high n-value) (Cho et al., 2015; Szczesniak and Farkas, 1962). Nevertheless, mouthfeel differences between XG and CMC vehicles were not statistically significant, despite their contrasting rheological profiles.

All samples evaluated were considered 'easy to swallow' by healthy volunteers, receiving average ratings in the neutral to positive range of the scale (range: 1.07 – 2.57; Water + v. – CMC L3). This is not surprising as these samples were liquid vehicles (without multiparticulates) and subjects were healthy volunteers with normal swallowing function. However, samples were considered relatively more difficult to swallow as the consistency level increased ($p < 0.001$), as depicted in Figure 4.11. This can be attributed to the higher effort required to convey thicker fluids through the oral cavity, giving their higher viscosity (or, in other words, higher resistance to flow). In their open-ended

feedback, participants described the need to swallow repetitively to achieve full ingestion of thicker samples; e.g. “*the sample is very viscous and is difficult to swallow, it remains in my mouth after swallowing a few times*” (P22, CMC L3). This is in line with previous research as thicker liquids have been shown to increase the risk of post-swallow residue in the mouth and pharynx (Steele et al., 2015).

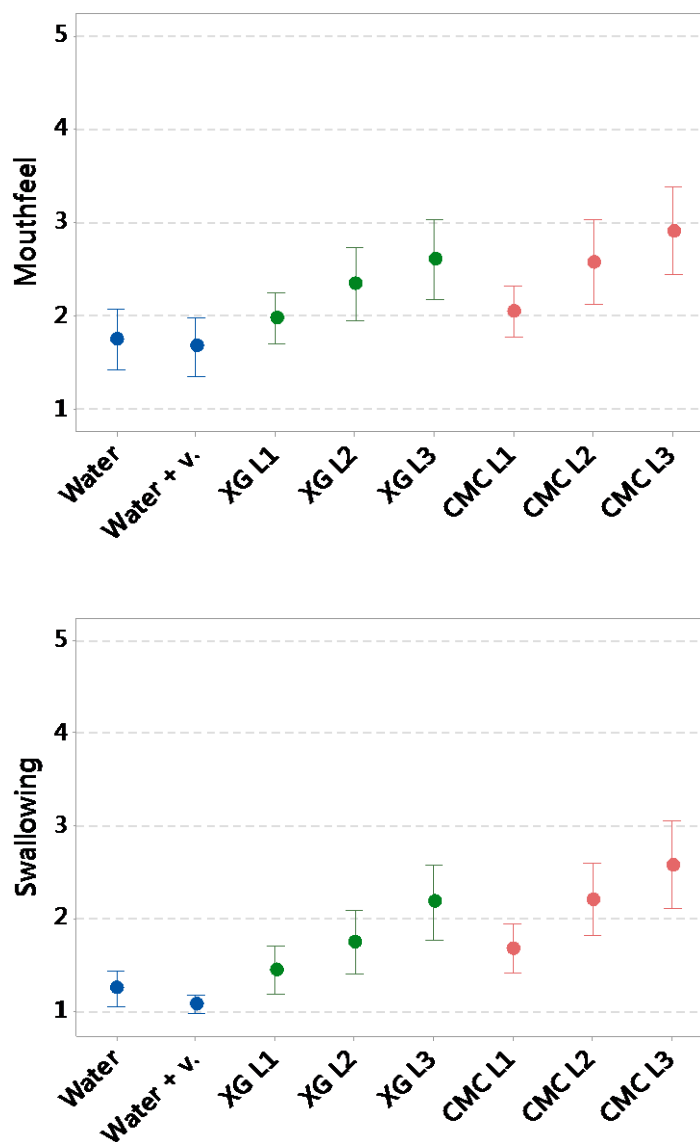


Figure 4.11. Interval plot for taste (top) and ease of swallowing (bottom) of different liquid vehicles. Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

It is well established that fluids with higher viscosity exhibit prolonged oral transit times as compared to thinner fluids such as water (Soares et al., 2015). This effect has been rationally exploited in the management of dysphagia, where texture modification has become one of the most common forms of intervention, since longer oral transit times favour control of the bolus minimising the risk of aspiration (Cichero and Lam, 2014; Soares et al., 2015; Steele et al., 2015). However, this seemed to have a detrimental impact for healthy volunteers with normal swallowing function, who preferred to swallow thinner fluids. Although thinner fluids were not expected to be easier or safer to swallow, they can be expected to be quicker to swallow, which seemed to have a positive effect on their hedonic responses.

The trends in ratings of ease of swallowing indicate that XG hydrogels were slightly easier to swallow than CMC hydrogels, which was supported by anecdotal feedback; e.g. *“this sample (CMC L2) is more difficult than the previous one (XG L2) in swallowing it as a whole, as it remains in my mouth after the first swallow”* (P10, CMC L2). Differences between both sets of hydrogels were statistically significant ($p < 0.018$). This can be explained by the stronger shear thinning behaviour of XG hydrogels, as shown in Section 4.4.2.1. Shear thinning fluids can be expected to be easier to swallow due to lower resistance to flow under shear (Steele et al., 2015).

Participants responses to certain samples attributes are expected to be influenced by their opinions and responses to other attributes, a phenomenon previously called ‘halo effect’ (Mason and Nottingham, 2002; Prescott et al., 2011). In this regard, responses to ease of swallowing and mouthfeel of XG hydrogels might have been negatively biased by the unpleasant appearance of the sample (especially those of thickest consistency). This was supported by open-ended responses, e.g. *“found it quite difficult to ingest it, would be better if it was more aesthetically pleasing”* (P15, XG L3). If this hypothesis was correct, perceived differences between XG and CMC hydrogels could have been maximised using vehicles which were not visually different.

4.4.3.3 *Multiparticulates dispersed in liquid vehicles*

The appearance of multiparticulate samples dispersed in different vehicles received average ratings around the neutral range of the scale (range: 2.70 – 3.40; CMC L1 – Water), as shown in Figure 4.12. The size of the multiparticulates had no influence on the ratings of appearance ($p = 0.074$), whereas the vehicle used had a significant impact on the appearance of the final formulation ($p < 0.001$). The appearance of samples dispersed in polymeric hydrogels (2.96 for XG and 2.77 for CMC hydrogels, on average) was considered better than that of Cellets dispersed in water (3.33 with and 3.40 without vanillin). This was explained by the more homogenous appearance of samples dispersed in thickened vehicles as compared to multiparticulates dispersed in water.

Cellets precipitated very quickly in water, due to its very low viscosity, leading to heterogenous samples with Cellets settled down on the bottom of the spoon and water on top. On the contrary, Cellets remained homogeneously dispersed in thicker hydrogels, which was considered a positive feature by the volunteers. Moreover, samples prepared in XG vehicles thickened to the highest consistency were rated more negatively than samples dispersed in other hydrogels, which can be expected based on the negative ratings of appearance received by this vehicle when evaluated without Cellets.

The taste of the samples worsened when multiparticulates were added into the formulation and when the multiparticulate size increased (Figure 4.12); from 2.44 on average without presence of multiparticulates to 2.63 and 2.89 on average with smaller and larger multiparticulates, respectively. As shown before for samples of liquid vehicles without multiparticulates, the taste of formulations with vanilla flavour was deemed better than the taste of samples prepared with pure water, by 0.43 points on average ($p < 0.001$). On the contrary, no significant differences were found between XG and CMC samples in terms of taste which, again, confirmed the successful masking of any potential inherent taste of the polymer by addition of a small quantity of vanillin.

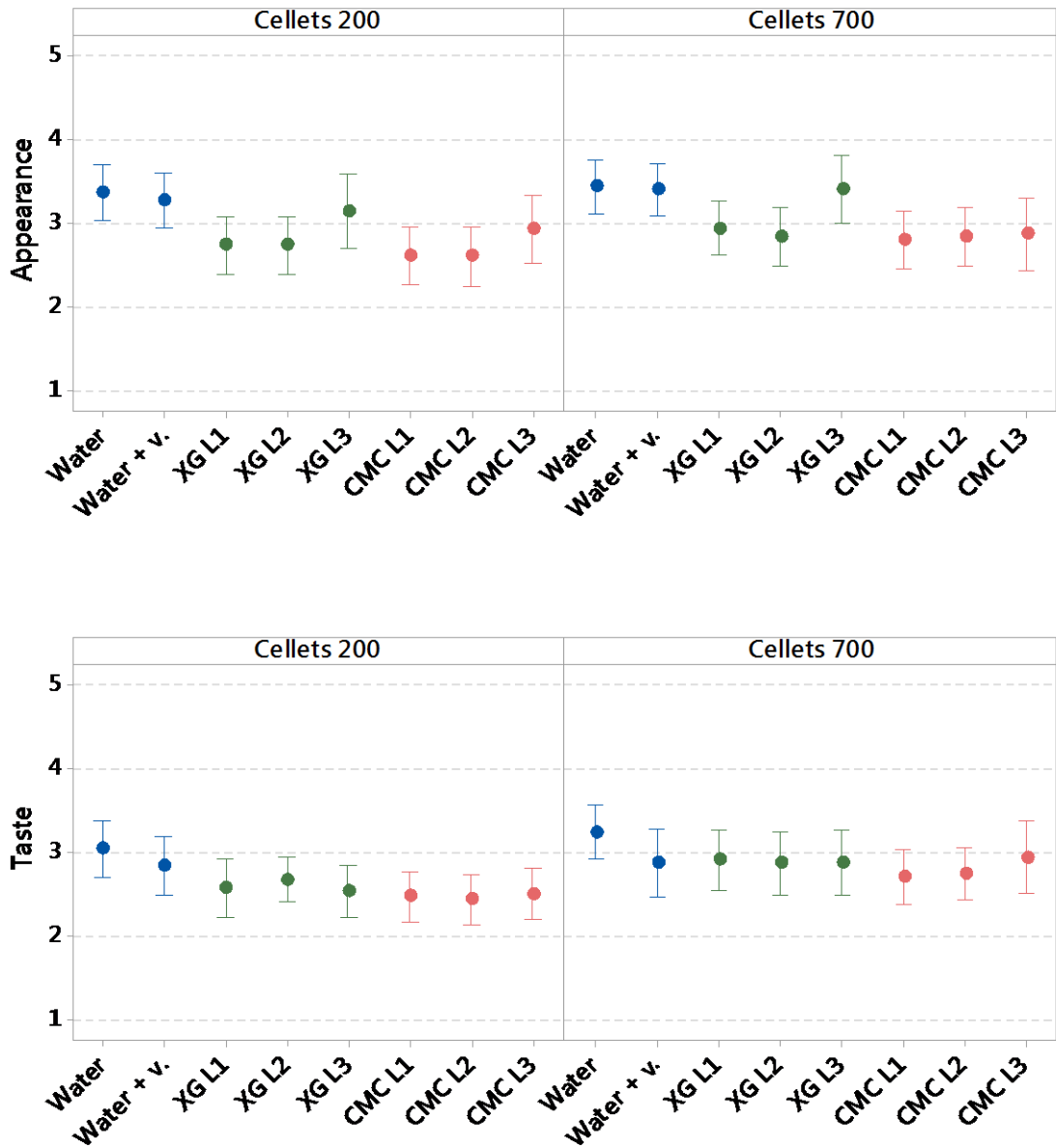


Figure 4.12. Interval plot for appearance (top) and mouthfeel (bottom) as a function of the vehicle used as suspending media and the size of the dispersed multiparticulates: 200-355 μm (Cellets 200) or 700-1000 μm (Cellets 700). Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

The mouthfeel of multiparticulates dispersed in liquid vehicles also received average ratings around the neutral range of the scale (Figure 4.13). Both the size of the multiparticulates and the vehicle used to disperse them had a significant impact on mouthfeel of the final formulation ($p = 0.001$ and $p < 0.001$, for size and vehicle, respectively). The mouthfeel of samples containing smaller multiparticulates was on average 0.30 points better than that of samples containing larger multiparticulates. In terms of the vehicle used, participants showed preference for samples dispersed in thickened vehicles over samples dispersed in water.

In addition, participants preferred hydrogels with low and middle-range consistencies (Level 1 and Level 2) over the extremely thick ones (Level 3). According to the participants of the study, those samples achieved a good balance by “concealing the presence of particles in the mouth” but not being too thick (which has a detrimental impact on mouthfeel, as established in Section 4.4.3.2). Samples thickened to Level 1 and Level 2 consistencies were rated on average 0.62 and 0.54 points better than water, respectively, whereas samples with Level 3 consistency were rated only 0.34 points better than water, on average.

As depicted in Figure 4.13, swallowing of multiparticulates was considered more difficult with increasing particle size, from 2.36 on average for smaller multiparticulates to 2.91 on average for larger multiparticulates ($p < 0.001$). Multiparticulates dispersed in polymeric hydrogels were easier to swallow than multiparticulates dispersed in water (by approximately 0.50 points), irrespectively of the size of the particles. Both XG and CMC hydrogels were similarly efficient in facilitating swallowing of the multiparticulates (2.52 and 2.49 on average, respectively). Therefore, no significant differences were found between XG and CMC hydrogels in terms of ease of swallowing when administered with multiparticulates, despite their different rheological properties and the differences found when administered without multiparticulates (Section 4.4.3.2).

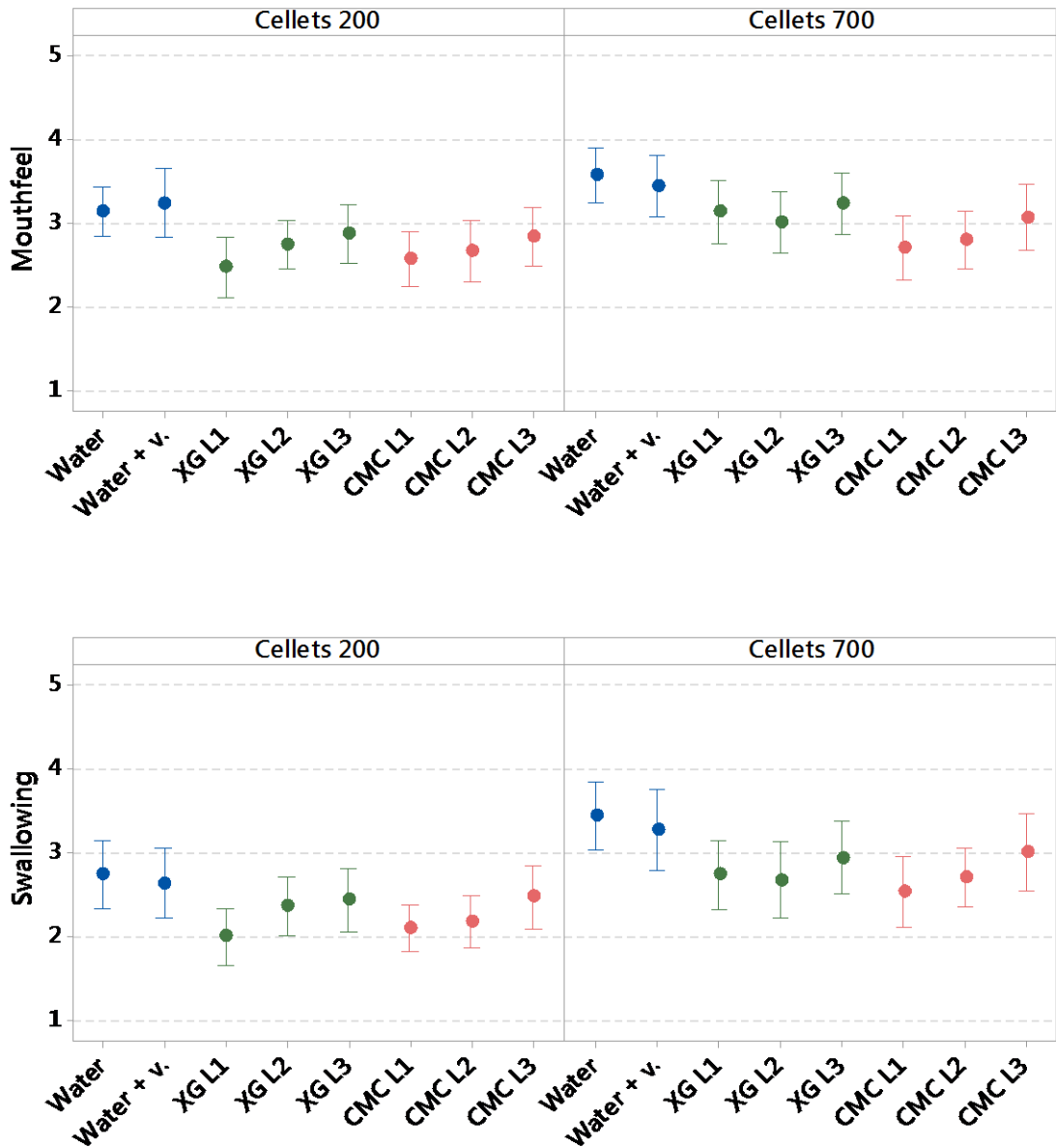


Figure 4.13. Interval plot for taste (top) and ease of swallowing (bottom) as a function of the vehicle used as suspending media and the size of the dispersed multiparticulates: 200-355 μm (Cellets 200) or 700-1000 μm (Cellets 700). Markers represent the population mean for the hedonic ratings (where 1 is the best possible rating and 5 is the worst possible rating) and bars show the 95% CI for the mean. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

In agreement with the results for mouthfeel perception, participants showed preference for swallowing samples with thin and middle-range consistencies (Levels 1 and 2) as opposed to thicker samples. These samples performed best at “*carrying the particles together*” as a bolus and “*providing cushioning*”, facilitating swallowing, while not being too thick to “*linger around*” in the oral cavity for long. The contrast between samples of different consistency was reported in open-ended responses; e.g.: “*the liquid in this sample was too runny and was unable to carry the particles along with it, so the liquid part was consumed first, leaving behind the solid part of the sample*” (P02, Cellets 200 in Water); or “*I feel that this sample has the correct viscosity that is able to hold the particles together and is able to be easily swallowed*” (P10, Cellets 200 in XG L1).

Participants ratings of ‘grittiness perception’ confirmed the results obtained for mouthfeel and ease of swallowing: polymeric hydrogels masked the presence of multiparticulates. As shown in Figure 4.14, grittiness perception was lower for polymeric hydrogel formulations than for samples dispersed in water by approximately 1.0 point, on average, both for smaller and larger multiparticulates. This was supported by voluntary feedback; e.g. “*without a thick solution to act as a lubricant and carry the particles along with it, the ‘grainy’ feeling was enhanced, making it very unpleasant to take*” (P02, Cellets 200 in water); compared to samples in thickened vehicles, e.g. “*it is viscous, but that masks the overall ‘particles feel’, which is good*” (P12, Cellets 200 in CMC L2).

The use of polymeric hydrogels to disperse multiparticulates also reduced the ‘residue in mouth’, i.e. the feeling of particles in the mouth after swallowing ($p < 0.001$), for multiparticulates of both sizes evaluated (Figure 4.14). As described above, the thickened fluids were able to carry the particles as a bolus from the mouth to the throat, reducing the amount of multiparticulates left in the oral cavity after swallowing. The residual feeling of particles was reduced by approximately 0.5 points on average when using polymeric hydrogels as vehicles, as compared to water.

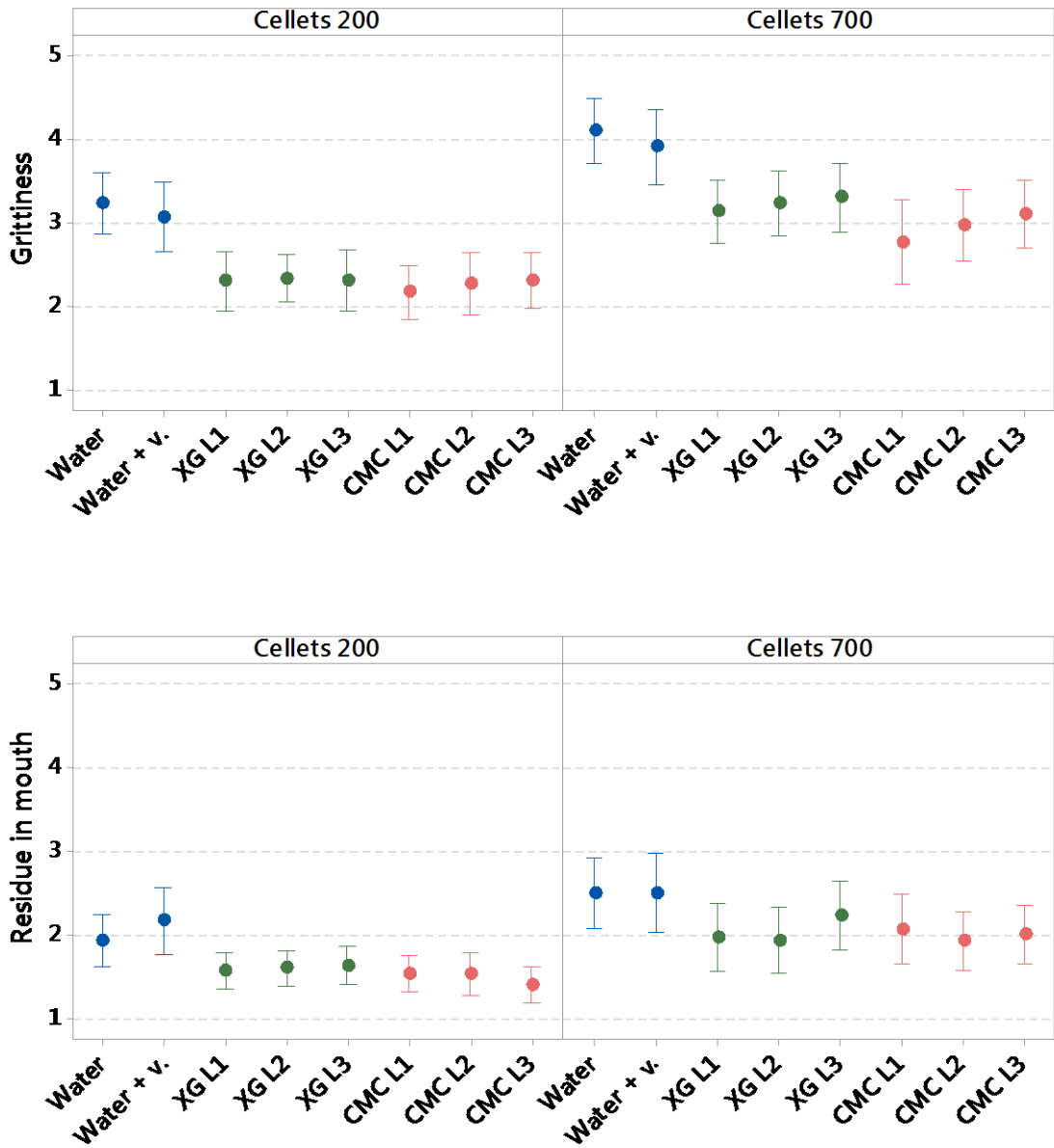


Figure 4.14. Interval plot for grittiness (top) and residue of multiparticulates in mouth after swallowing (bottom) as a function of the vehicle used as suspending media and the size of the multiparticulates: 200-355 μm (Cellets 200) or 700-1000 μm (Cellets 700). Markers represent the population mean for the 5-point magnitude scale (where 1 is the lowest possible and 5 is the highest possible intensity of the stimulus) and bars show the 95% CI for the mean. Water + v. represents water to which 0.1% w/v vanillin was added; the consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

As demonstrated in previous studies, grittiness perception increased with increasing size of the multiparticulates ($p < 0.001$); samples of smaller multiparticulates obtained an average grittiness score of 2.50 compared to the 3.31 scored on average by samples containing larger multiparticulates. The feeling of residual particles in the mouth also increased with increasing size of the multiparticulates, 1.67 on average for Cellets 200 compared to 2.14 on average for Cellets 700 (Figure 4.14).

Surprisingly, no significant differences were found between XG and CMC hydrogels in their ability to mask the presence of particles, either during sample intake or after swallowing of the samples; although the trend suggests that CMC vehicles performed better when using multiparticulates of larger size. Moreover, no differences were found between vehicles thickened to different consistency levels. These findings suggest that the rheological properties of the vehicles were less important than initially predicted. It is important to consider that the rheological properties of the vehicles could have been dramatically affected by addition of multiparticulates; the inclusion of the solid particles is expected to produce an increase in consistency and in shear thinning behaviour (Mueller et al., 2010). Investigation of the rheological properties of samples with multiparticulates was not possible in the present study, since the rheometer used was not suitable to measure samples with particles of such large diameter.

Contradictorily, anecdotal feedback indicated that thicker hydrogels performed better than thinner vehicles in terms of masking the presence of particles, e.g. *“less thick than other samples, thus I can feel the particles when I swallowed it; need to drink water to remove the particles”* (P16, Cellets 200 in XG L1). But perhaps the unpleasant mouthfeel of thicker samples negatively affected participants' assessments of grittiness perception. This highlights the multifactorial nature of palatability and mouth-feel perception, which is influenced not only by rheological properties such as viscosity and shear thinning behaviour, but also by other physicochemical properties such as density, stickiness, ductility and lubrication capacity (Stokes et al., 2013).

The results of these trial are summarised in Figure 4.15, where the radar charts show the mean result for each palatability attribute as a function of the size of the multiparticulates and the administration vehicle (water with vanillin, which was used as a control, was excluded from the graphs to aid clarity). The graphs show the overall improvement of the samples when using oral vehicles of consistency thicker than water. Slight preference for thinner vehicles is also apparent from the graphs.

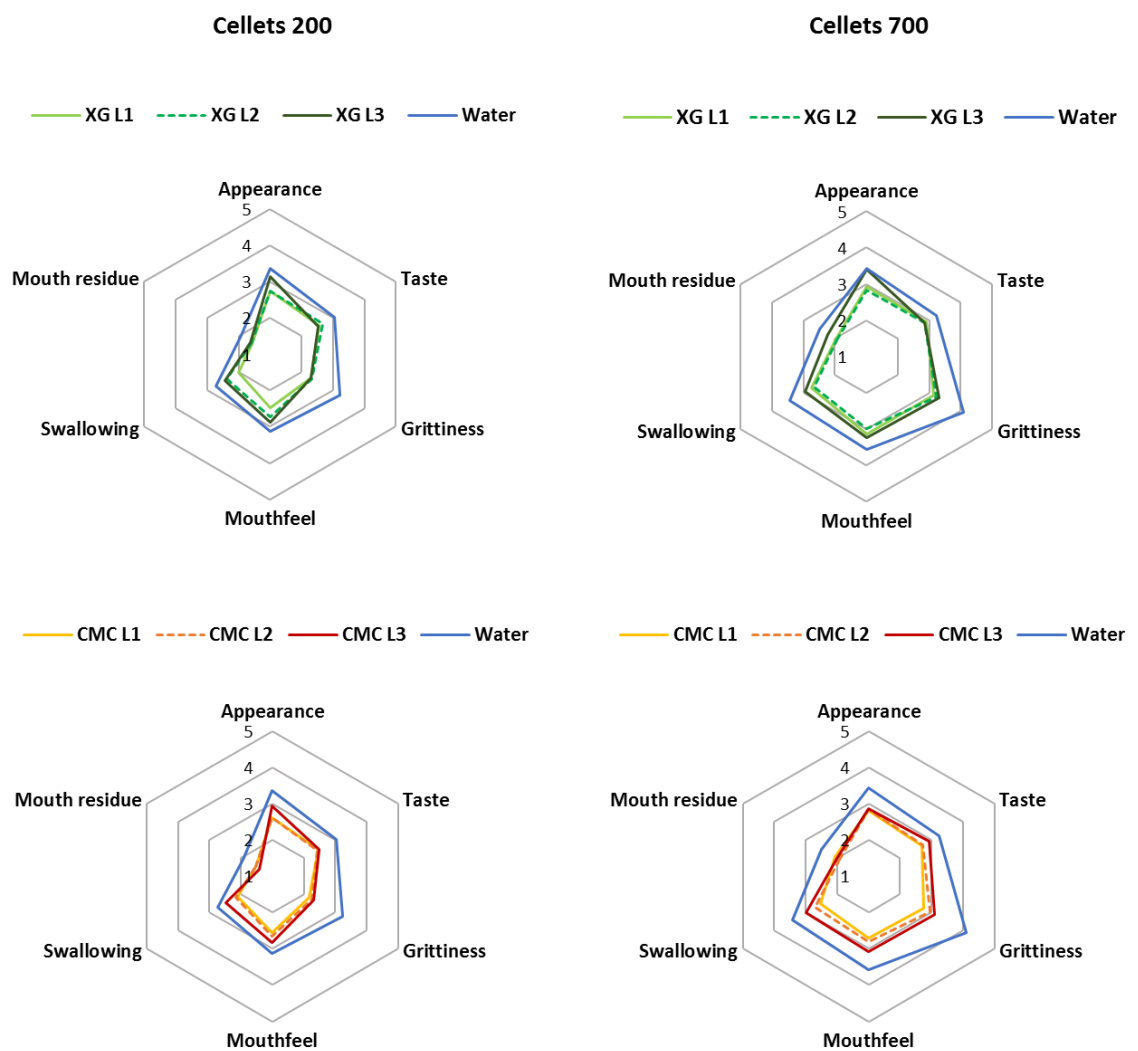


Figure 4.15. Radar chart for appearance, taste, grittiness, mouthfeel, ease of swallowing and residue of multiparticulates in mouth as a function of the vehicle used as suspending media and the size of the multiparticulates: 200-355 μm (Cellets 200) or 700-1000 μm (Cellets 700). Each palatability item is described by its population mean for the 5-point scale (where 1 is the lowest possible and 5 is the highest possible intensity of the stimulus). The consistency level of XG and CMC hydrogels is described as L1 (Level1), L2 (Level 2) and L3 (Level 3).

4.4.3.4 Willingness to take multiparticulates

As in previous studies with multiparticulates (Chapter 2 and Chapter 3), the willingness of the volunteers to take the formulation every day if it was a medicine was captured as a predictive measure of acceptability. Results are shown in Figure 4.16, as a function of the multiparticulate size and the vehicle used as suspending media.

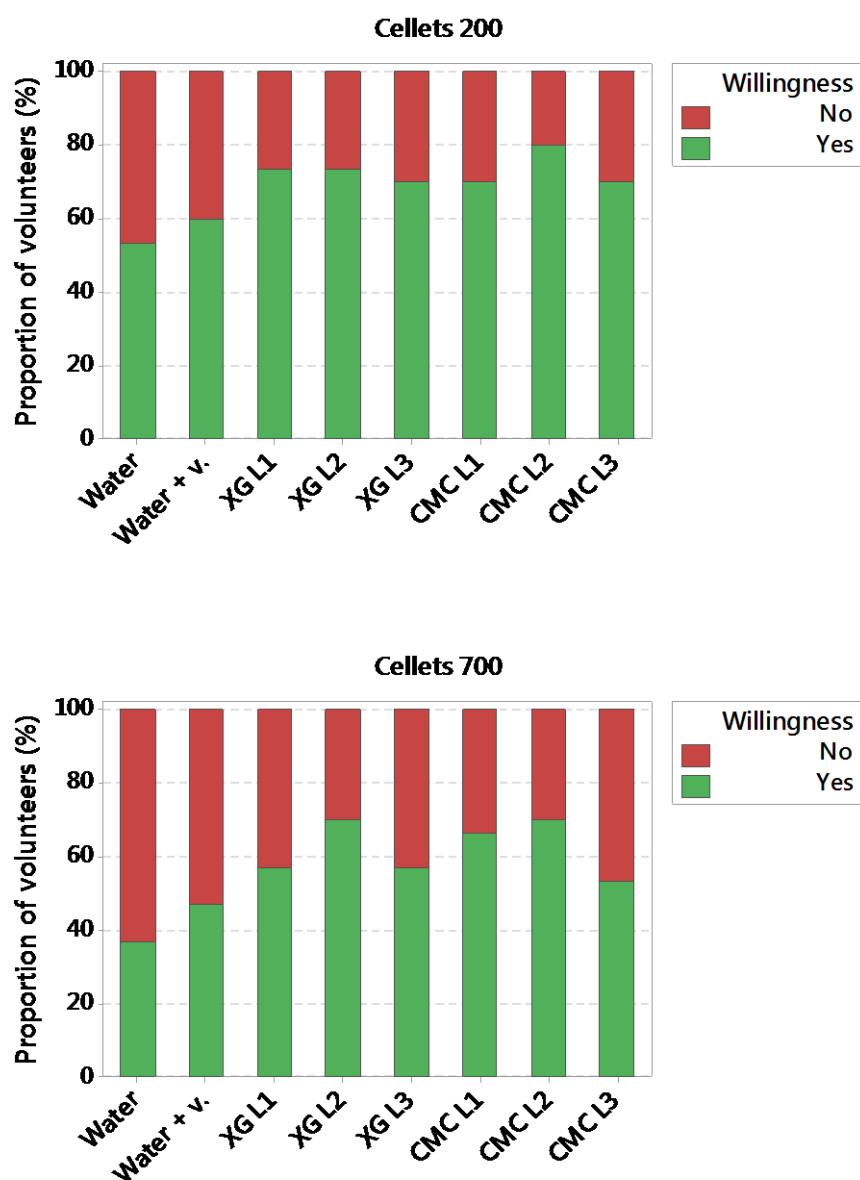


Figure 4.16. Proportion of volunteers ‘willing to take the sample everyday if it was a medicine’, expressed as a percentage of the total population (N = 30), for samples containing Cellets 200 (top) or Cellets 700 (bottom) dispersed in different liquid vehicles.

In agreement with our previous studies, the willingness to take the formulation decreased with increasing multiparticulate size ($p = 0.008$). On average, 69% of the participants were willing to take formulations containing smaller particles, in contrast with the 57% who reported to be willing to take formulations containing larger multiparticulates. These values varied along the range of vehicles with different consistencies ($p < 0.001$). Water samples were the least preferred, as participants were willing to take these samples as a medicine only in 53.3% and 36.7% of the occasions, for formulations containing smaller and larger Cellets, respectively. On the positive end of the ranking, CMC L2 obtained 80.0% and 70.0% and XG L2 received 73.3% and 70.0% of positive responses, when administered with smaller and larger multiparticulates, respectively.

The willingness of participants to take the formulation as a medicine was determined by their previous evaluation of the samples. All attributes studied (appearance, taste, mouthfeel, ease of swallowing, grittiness perception and residue in mouth) played an important role in participants' decision to be willing to take the formulation (Chi-squared test for association, $p < 0.001$ for all pair comparisons of sample attribute versus willingness). These findings reinforce the idea that patient acceptability is influenced by a broad range of formulation attributes, which all need to be identified and balanced to maximise patient acceptance of a medicinal product.

4.5 Conclusions

A set of liquid vehicles were developed using XG and CMC as model hydrocolloids, which produced hydrogels with contrasting rheological character (high and low degree of shear thinning, respectively). Such hydrogels were prepared at three different consistency levels (Level 1 – 'syrup', Level 2 – 'custard' and Level 3 – 'pudding') to investigate the effect of viscosity and shear thinning behaviour on the performance of the liquid vehicles as suspending media for the administration of multiparticulates. An *in vivo* sensory evaluation study was carried out in thirty healthy adult volunteers using

microcrystalline cellulose pellets as model multiparticulates, dispersed in oral hydrogels at a concentration of 250 mg in 5 ml. Multiparticulate formulations dispersed polymeric hydrogels and water (as a control) were administered on a medicine spoon and evaluated using a range of 5-point hedonic and magnitude scales.

The use of hydrogels as administration vehicles improved a range of sample attributes (compared to water formulations), including appearance, taste, mouthfeel, ease of swallowing and grittiness perception during and after sample intake. This improvement was apparent for samples containing multiparticulates of both sizes investigated (those over 200 and those over 700 μm). Surprisingly, differences between XG and CMC hydrogels were minimal despite their opposing rheological behaviour; i.e. both sets of hydrogels were equally effective at concealing the gritty feeling of multiparticulates and assisting swallowing. Although the strongly shear thinning XG hydrogels were easier to swallow and provided better mouthfeel than the CMC vehicles when assessed on their own (i.e. without multiparticulates), these differences vanished when multiparticulates were added into the formulation. If anything, CMC hydrogels seemed somewhat better at masking the grittiness of the coarser and thus more challenging multiparticulates.

Overall, polymeric hydrogels thickened to medium consistency (Level 2) demonstrated the best performance by virtue of their ability to conceal the grittiness of multiparticulates in the mouth and to aid swallowing of the formulation as a bolus, while maintaining a balanced consistency (not too thick) to ensure appropriate mouthfeel. These findings were in line with previous research in the field in that vehicles of very thick consistency tend to be disliked despite their ability to mask the presence of multiparticulates in the formulation (Kluk and Sznitowska, 2014; Lopez et al., 2016). The proportion of volunteers willing to take multiparticulates of the larger size was doubled by dispersing them in vehicles of middle consistency (from 36.7% in water to 70.0% in XG and CMC vehicles). For smaller multiparticulates, the willingness to take the product also increased, from 53.3% in water to 73.3 and 80.0% in XG and CMC vehicles, respectively.

Results of this study support previous research in that polymeric hydrogels could be used to improve palatability and acceptability of multiparticulate formulation. This study further indicates that swallowing of multiparticulates is facilitated using liquids of consistency thicker than water. With this in mind, multiparticulate formulations could be developed as a solid product for reconstitution into a liquid product with viscosity thicker than water. XG and CMC will both allow for the preparation as such products as these hydrophilic polymers exhibit rapid hydration and thickening in aqueous media. However, potential interaction with the API, in terms of drug release and *in vivo* bioavailability would also need to be considered during drug development studies. Moreover, there is also further need to investigate the acceptability of these vehicles in paediatrics and patients with swallowing difficulties, those who could benefit the most from these formulations.

Chapter 5

Evaluating manufacturability and patient acceptability to guide the choice of excipients in (oro)dispersible tablet formulations

This chapter describes an investigation of a range of co-processed excipients which may prove suitable for the preparation of (oro)dispersible tablets by direct compression. Excipients were pre-selected based on manufacturability criteria (compressibility, tablet friability, disintegration time and fineness of dispersion); then, a sensory evaluation experiment was carried out in a panel of healthy adult volunteers with the nine best performing excipients to investigate their organoleptic properties. Excipients were ranked in order of preference based on palatability evaluation and their overall acceptability was measured using 5-point facial hedonic scales. The most promising candidates for the preparation of (oro)dispersible tablets, ensuring robust manufacturing while maintaining appropriate palatability and patient acceptability, were identified.

5.1 Introduction

(Oro)dispersible tablets offer advantages over conventional solid and liquid dosage forms, which can be crucial for special populations such as paediatrics, geriatrics and patients with swallowing difficulties. (Oro)dispersible tablets are designed to disintegrate within a matter of seconds, avoiding the need for swallowing the tablet as a whole. As a solid product that is transformed into a liquid at the point-of-use, they offer improved stability over liquid formulations. Their administration can be adapted to the needs of the patient population (e.g. by pre-dispersing the tablet in a suitable vehicle before administration to facilitate administration to younger children).

Despite the acknowledged benefits of (oro)dispersible tablets, evidence of acceptability (especially in the paediatric population) is scarce, as established in the semi-systematic literature review presented in the introduction to this thesis. Details about the formulation

design and composition are often not provided in the literature, which hinders the rational development of acceptable formulations. Understanding the formulation parameters that affect patient acceptability and identifying excipients with favourable organoleptic profile could guide the rational development of more acceptable formulations.

(Oro)dispersible tablets can be manufactured by well-established techniques such as direct compression, which can expedite access to patients, although attaining the right balance between sufficient mechanical strength and quick disintegration can be challenging (Shukla, 2009). (Oro)dispersible tablets are required to disintegrate rapidly, have acceptable palatability and provide robust, cost-effective manufacturability on a commercial scale. As such, they often contain a range of excipients such as fillers, lubricants, disintegrants, sweeteners, dispersion aids and flavouring agents and the development process typically involves multiple investigations using a range of excipient grades and suppliers to attain the required functionality.

(Oro)dispersible tablet formulations need to comply with a series of requirements to ensure the quality of the final product. A list of requirements for (oro)dispersible tablet formulations is proposed in Table 5.1. These criteria were defined based on the properties of (oro)dispersible tablets that are required to produce a robust product that also delivers patient acceptability. Rationale for the specifications is provided below.

Table 5.1. Manufacturing specifications for (oro)dispersible tablets by direct compression.

Formulation property †	Ideal specification	Minimum requirement
Flowability (Carr's Index)	≤ 15%	≤ 25%
Maximum Tensile Strength	≥ 3.0 MPa	≥ 1.5 MPa
Ejection Shear	≤ 3.0 MPa	≤ 5.0 MPa
Friability	< 1% in 15 minutes	< 1% in 4 minutes
Disintegration Time	< 60 seconds	< 180 seconds
Dispersibility	Passes 250-µm screen	Passes 710-µm screen

† Palatability is also a key attribute for (oro)dispersible tablets, but specifications are not yet proposed

The excipients used within (oro)dispersible tablet formulations need to exhibit good flow properties to ensure minimal segregation of materials, hence appropriate content and weight uniformity. This is particularly important for tablets manufactured by direct compression (since granulation, which often improves flowability, is avoided). A Carr's index greater than 25 % is considered to indicate poor flowability, therefore a Carr's index equal or below than 25% was set as the minimum requirement. However, the addition of typically poor flowing APIs into the formulation is likely to increase the Carr's Index. Thus, Carr's Index of less than 15 %, which indicates good flowability, was used as the ideal specification (Lachman et al., 1986; Zhou and Qiu, 2010).

Tensile strength (TS) provides information about the crushing strength of the tablet. Tablets with TSs above 2.0 MPa are typically thought to be strong enough to withstand typical packaging and coating operations (Pitt et al., 2015; Zhou and Qiu, 2010). However, it has been shown that tablets with a TS as low as 1 MPa may be suitable when the product is not subjected to considerable mechanical stress and may also provide faster disintegration (Pabari, 2010; Pitt et al., 2015). Considering that drug substances are typically poorly compressible (and thus expected to have a negative impact on the tensile strength of the tablets), it was decided to set ideal and minimum specification values at ≥ 3.0 MPa and ≥ 1.5 MPa, respectively.

Ejection shear is the stress required to eject the tablet from the die after compaction. A low ejection shear is preferable because it suggests that there is a reduced likelihood of defects to the tablets and reduced likelihood of damage to the tablet punches, hence ensuring robust manufacturing and reducing manufacturing costs. A maximum ejection shear of 5.0 MPa is thought to be acceptable to minimise tablet defects and punch damage although a value of less than 3.0 MPa is preferable (Pitt et al., 2015). As such, these values were set as the ideal and minimum specification values for (oro)dispersible tablet formulations, respectively.

Friability testing is typically used to test the physical robustness of tablets (Saleem et al., 2014). Although tensile strength gives an indication of the mechanical properties of the tablets, friability testing is the pharmacopoeial standard to measure the tablets' resistance to mechanical stress. Friability is the tendency of a solid to break into smaller pieces and, as such, minimal friability is desirable. The current standard suggest that tablets need to be less than 1% friable during testing for 4 minutes in a friability tester (Saleem et al., 2014), which was set as the minimum requirement for (oro)dispersible tablets. Tablets that withstand a longer time of 10 minutes under stress conditions maintaining less than 1% friable were considered ideal in terms of mechanical strength.

Pharmacopoeial standards dictate that (oro)dispersible tablets need to disintegrate in less than 3 minutes (WHO, 2010). There is no consensus on the temperature used for disintegration testing of (oro)dispersible tablets, with specifications typically varying between 25 and 37 °C (World Health Organization, 2010). In this study, the minimum requirement for disintegration time was set at 3 minutes at 37 °C. However, since a number of currently marketed (oro)dispersible tablets have disintegration times between 30 seconds and 1 minute (Parkash et al., 2011), it was decided that an ideal specification for disintegration time would be less than 60 seconds at 37 °C. Faster disintegration times are desired to enhance patient convenience and acceptability,

Fineness of dispersion tests are performed to provide information on the expected mouthfeel of a dispersion (Brniak et al., 2015). The compendial test establishes that the dispersion is acceptable if it passes freely through a 710µm screen, which was set in this study as the minimum requirement. However, based on previous studies with ODTs, rough mouth-feel is expected to be pronounced for particles larger than 200 µm (Kimura et al., 2015). Therefore, the additional use of a screen with 250 µm nominal aperture may indicate improved mouthfeel compared to formulations that produce dispersions of larger particles. Thus, this was set as the ideal specification for fineness of dispersion.

On top of the requirements discussed above, palatability must be a critical consideration in the development of (oro)dispersible tablets. Properties such as appearance, taste and mouthfeel of the resulting dispersion can play an important role in patient acceptability. To date, there are no standards for palatability and acceptability of (oro)dispersible tablets. However, consideration must be given to the choice of excipients to ensure appropriate palatability, especially for medicines intended for paediatric patients (EMA, 2013). Patient acceptability should be evaluated at an early stage of the drug product development process rather than as a result of it.

The formulation development of (oro)dispersible tablets can be very tedious. One way to ease the product development could be to use co-processed excipients (Gohel and Jogani, 2005; Sreekanth et al., 2013). Co-processed excipients are the combination of two or more excipients, often prepared by spray drying, wet granulation and co-crystallisation (Jivraj et al., 2000; Rojas et al., 2012). Co-processed excipients may be advantageous by providing improved functionality in comparison to physical mixtures of individual excipients and reducing the number of separate materials required within the formulation (Russell, 2004), hence reducing development time and cost and improving patient access. Co-processed excipients could also provide improved organoleptic properties, based on a rational selection of excipients combined with advanced manufacturing techniques.

5.2 Aims and objectives

The aim of this research was to identify the most promising co-processed excipient(s) to be used within (oro)dispersible tablet formulations prepared by direct compression, based on manufacturability and patient acceptability criteria. Secondary objectives were to characterise a range of co-processed excipients against the manufacturability requirements set in Table 5.1; and to conduct a sensory evaluation study in adult volunteers to evaluate palatability and patient acceptability of co-processed excipients.

5.3 Materials and methods

5.3.1 Materials

The range of excipients investigated in this study and their individual constituents are presented in Table 5.2.

Table 5.2. Individual constituents of the co-processed excipients

Excipient name	Individual constituents	Particle size (μm) [†]
Avicel PH-102	100% microcrystalline cellulose (reference)	100
Avicel HFE-102	90% microcrystalline cellulose, 10% mannitol	100
Compressol SM	Mannitol, sorbitol, <2% silicon dioxide	126
CombiLac	70% lactose, 20% microcrystalline cellulose, 10% maize starch	160 (35-65% below)
Emdex	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 Grade M	55-70% D-mannitol, 10-25% microcrystalline cellulose, 2-9% xylitol, 5-13% crospovidone, 2-9% magnesium aluminometasilicate	122.3
Ludiflash	90% D-mannitol, 5% crospovidone, 5% polyvinyl acetate dispersion	170-210
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 50	D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose	57
SmartEx QD 100	D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose	86

[†] Particle size provided by supplier (median particle size unless otherwise specified).

Candidate co-processed excipients for (oro)dispersible tablets were selected based on a recent literature review (Rojas et al., 2012), with advice from excipient manufacturers. All excipients investigated were kindly supplied by their manufacturers, including: Avicel® HFE-102 (FMC biopolymers, Philadelphia, Pennsylvania, USA), Compressol® SM and Pharmaburst® 500 (SPI Pharma, Septemes Les Vallons, France), CombiLac® and MicroceLac® (Meggle Pharma, Wasserburg, Germany), Ludiflash® (BASF, Lampertheim, Germany), Emdex® and ProSolv® ODT (JRS Pharma, Cedar Rapids, Iowa, USA), F-Melt® Type C and F-Melt® Type M (Fuji Health Science, Toyama, Japan), Pearlitol® Flash (Roquette, Corby, Northamptonshire, UK), SmartEx® QD50 and SmartEx® QD100 (ShinEtsu, Tokyo, Japan); Avicel® PH-102 (FMC Biopolymers) was tested as a comparator against the co-processed excipients since it is a highly compressible non-co-processed excipient. Sodium starch fumarate (SSF) was used as lubricant (Pruv®, JRS Pharma, Cedar Rapids, Iowa, USA).

5.3.2 Powder and tablet characterisation

5.3.2.1 Powder flow testing

Analysis of the flow properties of the co-processed excipients was performed by tapped and bulk density analysis by USP method <616> using a Varian Tap Density Tester. Carr's index values were calculated to identify the flow properties of the excipients.

5.3.2.2 Tablet compressibility and ejection shear

All formulations were lubricated with 1% w/w sodium starch fumarate (SSF) by blending directly compressible excipients and lubricant for 2 minutes at 22 RPM using a low shear Turbula® blender.

Tablets of 10.5 mm diameter (round, normal concave) and 500 mg \pm 5% weight were produced in triplicate at varying compression forces using a Phoenix compaction simulator. Each tablet was characterised for weight (Mettler Toledo Analytical Balance),

thickness (Mitutoyo Caliper) and hardness (Dr. Schleuniger Pharmatron Tablet Tester 8M). The compaction and ejection forces were captured by the compactor simulator for each individual tablet and used to determine tablet tensile strength, solid fraction, ejection shear and compaction pressure (Pitt et al., 1988). The maximum tablet tensile strength that was achieved was determined for the different formulations.

Compression profiles were used to determine the compaction pressure required to yield tablets with a target tensile strength of 1.5MPa; such tablets were then produced for disintegration, fineness of dispersion and friability testing.

5.3.2.3 Tablet friability

Tablet friability testing was performed by accurately weighing 10 tablets and placing them into a friability tester (VanKel Friabilator). Friability testing was performed for either 4 minutes (standard conditions) or 15 minutes (extended conditions) at 25 rpm. Following testing, the tablets were removed, dedusted and weighed to enable the calculation of the % friability. Those that lost more than 1% of their total weight were considered poorly friable and failed the test.

5.3.2.4 Tablet disintegration

Disintegration test was performed as per USP <701> except using four tablets instead of six at 37 ± 2 °C using a Pharmatron DisiTest 50 with discs. Disintegration times (DTs) were reported as the time taken for the last tablet to disintegrate.

5.3.2.5 Tablet fineness of dispersion

For each formulation, one tablet was immersed in 10 mL of water and allowed to disperse completely. The suspension was swirled to aid tablet dispersion and then poured through a sieve stack with 710 μ m and 250 μ m screens. The visual residue left on each screen was recorded. The test was passed if no residue was observed.

5.3.3 Physical characterisation of dispersions

5.3.3.1 *Optical microscopy*

The particle size and shape of excipients were investigated with the aim to link physical properties and palatability, especially mouth-feel. The morphological characteristics of excipients were investigated by optical microscopy. Excipients were pre-dispersed in water (1 g in 20 ml) and observed at different magnifications using an Evos FL optical microscope (Life Technologies, Carlsbad, CA, USA) with a digital camera incorporated.

5.3.3.2 *Particle size distribution*

The particle size distribution was assessed by laser diffraction using a Mastersizer 3000 (Malvern Scientific, Worcestershire, UK). All samples were analysed using both dry and wet dispersion methods. For the dry dispersion method, the air pressure and feeding rate were individually optimised for each excipient before measurement. For the wet method, approximately 1 g of sample was pre-dispersed in 20 ml of dispersant (deionised water). In both cases, at least three replicates of each sample were analysed.

In addition, the particle size of powder dispersions was compared to that of tablet dispersions. Tablets were dispersed in water and the particle size of the resultant dispersion was assessed by wet dispersion method. At least three replicates of each sample were analysed.

5.3.3.3 *Insoluble particle fraction*

The proportion of insoluble material in the co-processed excipients was measured by gravimetric analysis. Accurately weighed, 1 g of excipient was dispersed in 10 ml of water and the sample was swirled for approximately 1 minute to allow dissolution of the soluble components. Subsequently, the dispersion was filtered through a 0.45 µm filter by vacuum filtration. After filtration, the insoluble residue was collected from the Buchner funnel and was oven-dried at 60 °C until constant weight. The recovered insoluble

material was then weighed out to calculate the insoluble particle fraction, i.e. the proportion of insoluble material with respect to the total dry weight of the excipient. The experiment was conducted in triplicate for each sample.

5.3.4 Evaluation of palatability and patient acceptability

5.3.4.1 *Sensory evaluation study design and outcome measures*

Nine excipients were evaluated in a single-centre, single-blind, randomised, preference and acceptability testing. The study was approved by the University College London Research Ethics Committee (ERN_4612-015) and was conducted in designated facilities at UCL School of Pharmacy. Twenty-four healthy adult volunteers were recruited for the study (aged 19-38 years, mean age: 25.2 ± 4.8 years, 41.7% males). All participants received a detailed information sheet and provided written consent to participate.

The study was divided into two sessions (Figure 5.1). In Session 1, panellists tested each of the nine excipients investigated, in individually randomised order, in three blocks of three samples. Based on results of Session 1, the two least preferred excipients were excluded for Session 2 with the aim of improving discrimination between samples. In session 2, participants received seven samples in randomised order, two of which were repeated in the last block of samples. A weighted randomisation schedule was designed to ensure that all possible combinations of three excipients were evaluated. Repeated presentation of the same excipient never occurred within each group of three samples.

Test samples were prepared by dispersing 500 mg of powder excipient in 5 mL of purified water. The untrained panellists were provided three different blind samples at a time, up to a total of nine samples. They were instructed to invert the sample to ensure homogenous dispersion of the excipients and then taste the sample by swirling the contents in the mouth for approximately 10 seconds before spitting the sample into a receptacle provided. Participants had free access to spring water and unsalted crackers and were instructed to cleanse their palate before each sample.

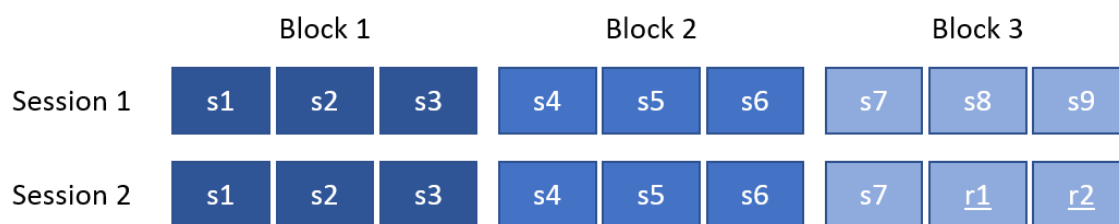


Figure 5.1. Sensory evaluation study design. In Session 1, each participant received nine samples (s1-s9) in randomised order, in three blocks of three samples. In Session 2, seven samples were tested, two of which were repeated (r1, r2) in the last block.

Subject-reported outcomes were recorded after evaluation of each group of three samples using an online structured questionnaire (Qualtrics.com). Participants were asked to rank the samples in order of their preference (forced-choice preference, no ties allowed). The volunteers were also asked to assign the key attribute that contributed to the ranking selection, from the following list: appearance, mouth-feel, taste, cooling sensation and smell. Overall acceptability was evaluated using 5-point hedonic scales anchored from (1) “very acceptable” to (5) “very unacceptable”. An open-ended feedback section was also implemented to obtain a qualitative response of palatability and acceptability, which was used to interpret the results.

5.3.4.2 Statistical analysis

For data analysis, samples were assigned numerical values based on subject-reported preference in each group of three random samples (-1, 0, +1, for ‘worst’, ‘middle’ and ‘best’ samples, respectively) and results of hedonic scales were assigned numerical values from 1 to 5 (from extremely acceptable to extremely unacceptable, respectively). Statistical analysis was performed using the non-parametric Kruskal-Wallis one-way analysis of variance with 95% confidence, with Dunn’s test for pairwise comparison. Results from Session 1 and Session 2 were compared and, given the negligible differences, analysis was carried on pooled data. Minitab 17 (Minitab Inc., State College, Pennsylvania, USA) was used for data analysis.

5.4 Results and discussion

5.4.1 Powder and tablet characterisation

5.4.1.1 Powder flow of co-processed excipients

Data generated from tapped/bulk density is presented in Figure 5.2. The results suggest that Compressol SM, Emdex, F-Melt Type M and ProSolv ODT have ideal flowability with Carr's index equal or less than 15 %. All other excipients evaluated showed acceptable flow behaviour with Carr's index values between 15 and 20 %. Out of all the excipients tested, Emdex showed the best flow with a Carr's index of 11 %; this can be explained by its non-hygroscopic, uniform porous spheres (Amin et al., 2012; Bolhuis et al., 1985).

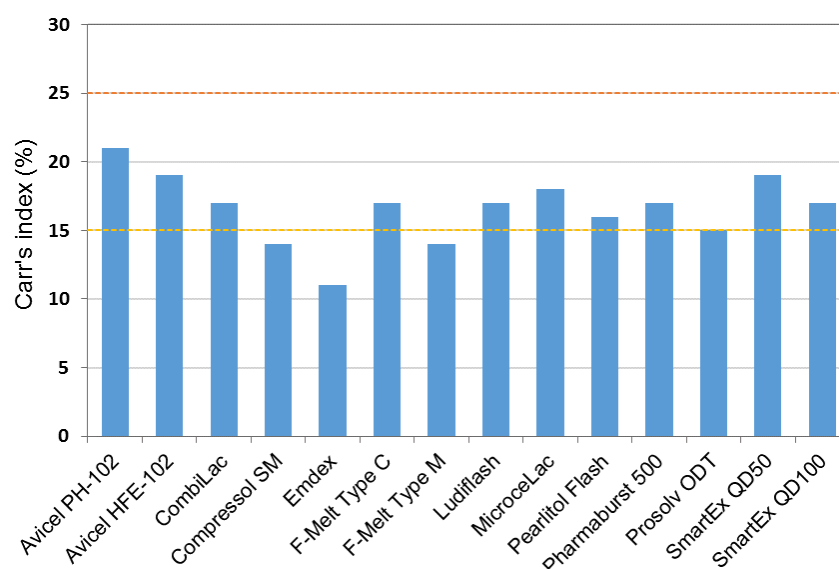


Figure 5.2. Carr's Index of co-processed excipients; results expressed as mean (N=3).

5.4.1.2 Tablet compressibility and ejection shear

Compression profiles for the co-processed excipients lubricated with 1% w/w SSF are presented in Figure 5.3, which shows the relationship between tensile strength of tablets as a function of the compaction pressure. A compression profile for Avicel PH102 was included to provide a benchmark for excellent compressibility (Thoorens et al., 2014).

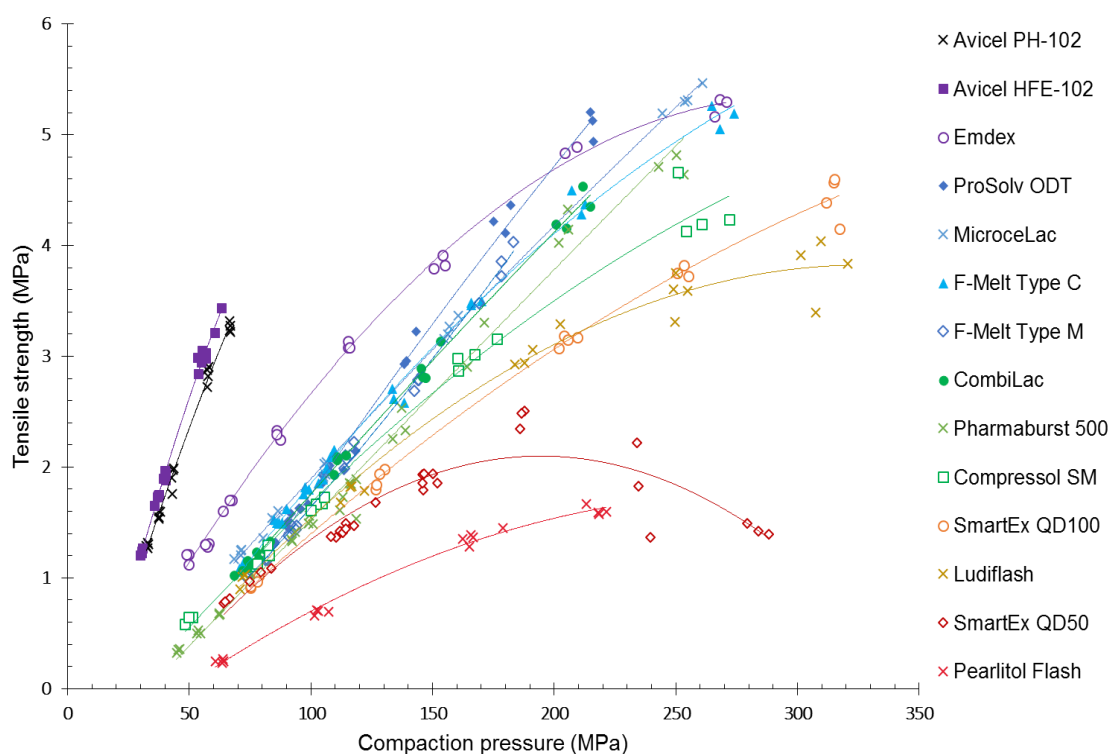


Figure 5.3. Tablet compression profiles (tensile strength as a function of the compaction pressure).

Formulations prepared using Avicel HFE-102, Emdex, ProSolv ODT, MicroceLac, F-Melt Type C and F-Melt Type M, CombiLac, Pharmaburst 500, Compressol SM, SmartEx QD100 and Ludiflash all showed excellent compressibility with maximum tablet TS above 3.0 MPa being achieved. SmartEx QD50 provided maximum TS greater than 2.0 MPa, although this was considered poor in comparison to other co-processed excipients; capping occurred when measuring hardness of SmartEx QD50 tablets manufactured at high compaction pressure, which explains the reduction in TS shown in Figure 5.3, thus tablets with TS greater than 3.0 MPa could not be prepared. Pearlitol Flash proved to be the least compressible of all co-processed excipients investigated, with a maximum TS of 1.61 MPa; capping was observed in tablets prepared at high compaction pressures, hindering the preparation of tablets with higher TS (Figure 5.4).

Avicel HFE-102 and Emdex showed particularly superior compressibility compared to the other excipients tested, producing very strong tablets at low compaction pressures.

Avicel HFE-102 is a mixture of 90% MCC and 10% mannitol produced by spray drying (Rojas et al., 2012); its compression profile highly resembled that of Avicel PH-102, which could be expected due to high concentration of MCC in both products (Thoorens et al., 2014). Emdex is a dextrose-based co-processed excipients which compresses by plastic deformation mechanism with low elastic energy, demonstrating excellent compression properties (Amin et al., 2012; Olmo and Ghaly, 1999).



Figure 5.4. Capping post-tableting (left) and after hardness testing (right), observed for tablets prepared using Pearlitol Flash and SmartEx QD50 at high compression forces (> 200 MPa).

Formulations containing ProSolv ODT, MicroceLac, F-Melt Type C and Type M and CombiLac contain a combination of plastic (MCC) and brittle (lactose or mannitol) deforming materials which explains their good compressibility (Gharaibeh and Aburub, 2013; Hentzschel et al., 2012). Similarly, Pharmaburst 500 and Compressol SM contain sorbitol which will provide good compressibility through plastic deformation and high mannitol content which will allow consolidation through brittle fragmentation (Amin et al., 2012; Rojas et al., 2013); the inclusion of silicon dioxide is thought to offset the hygroscopic nature of sorbitol in these co-processed excipients (Çelik, 2011). Ludiflash and SmartEx QD100 primarily contain mannitol which can be expected to provide brittle fragmentation under compaction leading to weak tablets (Al-Ibraheemi et al., 2013; Koner et al., 2015). However, Ludiflash and SmartEx QD100 still exhibited good compressibility, reaching tablet TSs above 3.0 MPa.

SmartEx QD50 has the same composition as SmartEx QD100 with the difference between grades being the particle size. SmartEx QD100, which contains a larger-sized fraction, showed superior compression properties than SmartEx QD50. Improved compressibility of larger particles has been previously attributed to increased fragmentation and better rearrangement upon compression (compared to smaller fractions), leading to stronger inter-particle bonding, although there may be other unknown differences between the grades not readily disclosed by the excipient supplier (Šantl et al., 2012). Meanwhile, poor compression and capping of Pearlitol Flash could be attributed to the viscoelastic nature of starch, which represents 15-20% of the co-processed excipient, providing good plasticity but high elastic recovery (Gharaibeh and Aburub, 2013; Li et al., 2013).

In terms of ejection, all co-processed excipients provided ejection shear results below 3.0 MPa when prepared to the target TS of 1.5 MPa.

5.4.1.3 Tablet Friability

All tablets prepared at TSs of 1.5 MPa were less than 1% friable after standard friability testing for 4 minutes, which suggests that all co-processed excipients investigated would allow for direct compression of tablets at a TS of 1.5 MPa whilst maintaining appropriate mechanical properties.

Formulations that displayed adequate compression properties (max. TS > 3.0 MPa), ideal disintegration times (below 60 seconds) and low tablet friability (<1% over 4 minutes) were investigated for extended friability over 10 minutes. The advantage of this test is that it provides a deeper insight into the tablets' ability to withstand manufacture, transportation and patient handling. All the studied formulations passed the extended friability test. Compressol SM, Emdex, Pearlitol Flash, ProSolv ODT and SmartEx QD 50 were not investigated for extended friability as these excipients failed to comply with requirements for compressibility, disintegration or standard friability.

5.4.1.4 Tablet disintegration

The primary attribute of (oro)dispersible tablets, as it related to patient acceptability, is their prompt disintegration in minimal liquid; therefore, the disintegration time of less than 60 seconds was set as the ideal requirement for (oro)dispersible tablets. Disintegration times for all formulations evaluated are graphically depicted in Figure 5.5.

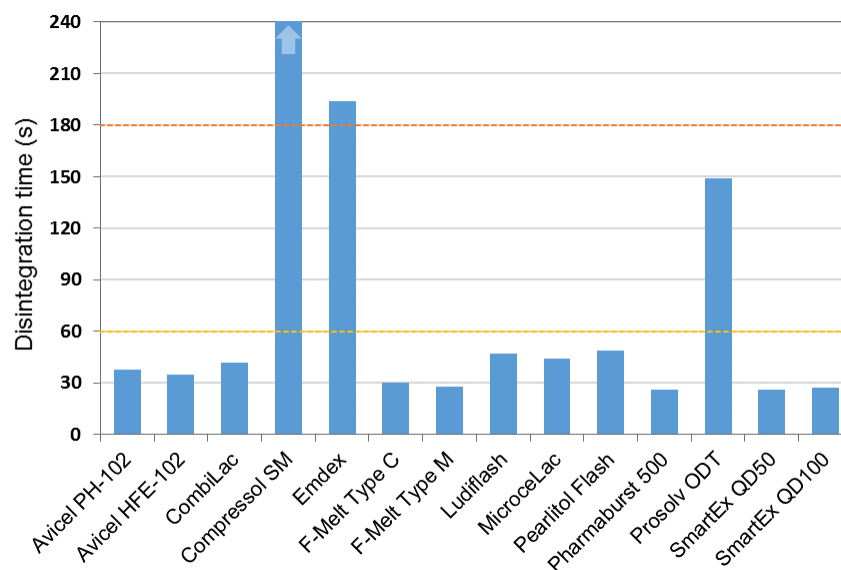


Figure 5.5. Disintegration time of co-processed excipients (oro)dispersible tablet formulations. Results expressed as the time taken for the last tablet to disintegrate (N=4).

Disintegration times varied from 26 seconds to over 7 minutes. Formulations yielding the shortest disintegration times contained Avicel HFE-102, CombiLac, F-Melt Type C and F-Melt Type M, Ludiflash, MicroceLac, Pharmaburst 500, Pearlitol Flash, SmartEx QD50 and QD100; all disintegrating in less than 60 seconds. In contrast, ProSolv ODT disintegrated in 2-3 minutes and formulations containing Compressol SM and Emdex exhibited disintegration times over 3 minutes (minimum requirement).

Both F-Melt products (Type C and Type M), Pharmaburst 500 and Ludiflash contain the disintegrant crospovidone which acts by wicking and swelling mechanisms, drawing water in by a capillary action associated with its porous morphology, resulting in rupturing

of interparticle bonds and disintegration (Pabari and Ramtoola, 2012). SmartEx QD50 and QD100 contain the disintegrant L-HPC which swells when it encounters water leading to rapid tablet disintegration (Kawashima et al., 1994). PVA in SmartEx products, as well as in Ludiflash, may contribute towards their short disintegration times (Patel and Vavia, 2010). The inclusion of silicon dioxide in Pharmaburst 500 and MCC in F-Melt Type C and Type M may also help to reduce the disintegration time for these formulations (Shihora and Panda, 2011). The fast disintegration of CombiLac and MicroceLac can be attributed to MCC, which acts by wicking on contact with aqueous fluids (Thoorens et al., 2014); while the quicker disintegration of the former can be ascribed to the additional maize starch (10% w/w) within its composition (Desai et al., 2016).

The formulations containing ProSolv ODT, Emdex and Compressol SM displayed long disintegration times. This could be expected for Emdex and Compressol SM since they contain no disintegrant in their composition; although it was unexpected from ProSolv ODT, which contains 5% crospovidone as disintegrant along with 15-30% MCC. Poor disintegration could be overcome by blending of co-processed excipients with additional disintegrants before compression. Potentially, additional disintegrant and API could be added simultaneously to the formulation to minimise processing steps. However, the aim of this work was to identify the most suitable co-processed excipients for (oro)dispersible tablets which can be used as an “all-in-one, just-add-API” platform excipients without additional disintegrant.

5.4.1.5 Tablet fineness of dispersion

Tablets were tested for the fineness of dispersion using 250 µm and 710 µm sieves. A positive outcome of the fineness of dispersion in 100 mL of purified water using 710 µm sieve is a pharmacopoeial requirement for (oro)dispersible tablets. In this study, however, a smaller volume of water (10 ml) and an additional smaller sieve were used to resemble in-use conditions in paediatrics and to increase discrimination.

Results for the tablet fineness of dispersion are summarised in Table 5.3. All formulations except those containing Avicel PH-102, Avicel HFE-102, Compressol SM and Pharmaburst 500 created smooth dispersions that passed through sieve screens with nominal mesh apertures of 250 and 710 μm . Avicel HFE-102 and Pharmaburst 500 tablets passed through the 710 μm screen but not the 250 μm screen. Avicel PH-102 and Compressol SM formed coarse dispersions which failed to pass through both the 250 and 710 μm screens. Results of the fineness of dispersion test could provide an indication of palatability, particularly mouth-feel, of the formulations. Coarse dispersions or poorly dispersed formulations would be expected to elicit a rough mouth-feel, as opposed to fine dispersions.

Table 5.3. Fineness of dispersion results for (oro)dispersible tablets dispersed in 10 ml of water.

Excipient	Dispersion fineness		Descriptor
	710 μm screen	250 μm screen	
Avicel PH-102	Fail	Fail	Inappropriate
Avicel HFE-102	Pass	Fail	Not ideal
CombiLac	Pass	Pass	Ideal
Compressol SM	Fail	Fail	Inappropriate
Emdex	Pass	Pass	Ideal
F-Melt Type C	Pass	Pass	Ideal
F-Melt Type M	Pass	Pass	Ideal
Ludiflash	Pass	Pass	Ideal
MicroceLac	Pass	Pass	Ideal
Pearlitol Flash	Pass	Pass	Ideal
ProSolv ODT	Pass	Pass	Ideal
Pharmaburst 500	Pass	Fail	Not ideal
SmartEx QD50	Pass	Pass	Ideal
SmartEx QD100	Pass	Pass	Ideal

5.4.2 Physical characterisation of dispersions

5.4.2.1 Optical microscopy

The perception of a powder in the mouth is dependent on physical properties such as size, shape and hardness of the material (Engelen et al., 2005). In other words, the morphology of the particles will influence the palatability of tested samples, particularly in terms of mouth-feel. The morphological characteristics of the co-processed excipients in water dispersion were thus investigated by optical microscopy. Optical micrographs of excipients in water are shown in Figure 5.6.

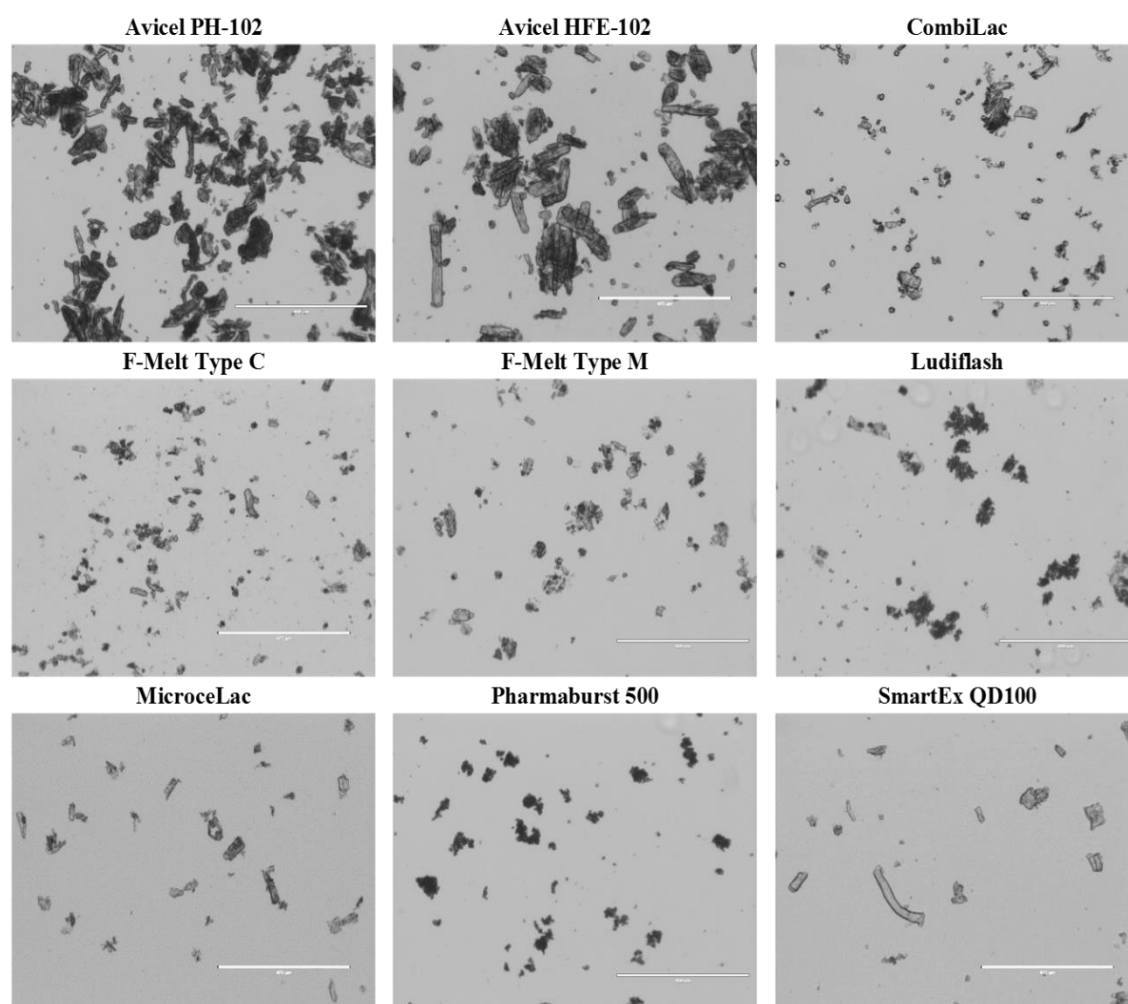


Figure 5.6: Optical microscopy images of the co-processed excipients (powder dispersed in water) at 10x magnification (scale bar: 400µm). Only those excipients with adequate compressibility (max. TS > 3.0 MPa), disintegration time (< 60 s) and friability (< 1% in 10 min.) were imaged.

Avicel PH-102 is based purely on water-insoluble microcrystalline cellulose (MCC). As shown in the micrographs, Avicel PH-102 was characterised by irregular MCC fibres which seemed to agglomerate in aqueous environment. Thus, Avicel PH-102 can be expected to elicit rough mouth-feel upon ingestion.

Similarly, the micrograph of Avicel HFE-102 clearly showed the irregular structures of MCC. The micrographs of F-Melt Type C and F-Melt Type M show almost identical irregular particles, possibly composed of a mixture of MCC plus the insoluble calcium and magnesium compounds present in their composition, respectively. It is likely that the particles present in CombiLac and MicroceLac are also MCC, since lactose is soluble in water; CombiLac micrographs also revealed small rounded particles attributable to starch. Ludiflash, Pharmaburst and SmartEx QD100, which are largely composed of the water-soluble mannitol, were characterised by small particles of insoluble materials, such as polyvinyl acetate in Ludiflash, silicon dioxide in Pharmaburst and low-substituted hydroxypropyl cellulose in SmartEx QD100; these excipients were predicted to have a relatively good mouth-feel.

5.4.2.2 Particle size distribution

The particle size distribution of the investigated excipients is presented in Table 5.4. All co-processed excipients had comparable particle size in dry form, with a median particle size between 81-125 μm . When dispersed in water, Avicel HFE-102 and Avicel PH-102 exhibited an increase in size with respect to the particle size measured by dry dispersion (D50 increased 6.3 and 17.1%, respectively); such increase was attributed to moderate swelling of the insoluble microcrystalline cellulose upon contact with water. In contrast, the large majority of excipients suffered a size reduction when dispersed in water, which can be explained by dissolution of the soluble components in the formulation; the reduction in median particle size ranged between -40.5 and -74.3%. These findings confirmed what shown in the optical micrographs, where Avicel products could be clearly identified by having coarser particles than other excipients.

Table 5.4. Particle size distribution of co-processed excipients measured by laser diffraction.

Excipient	PSD powder dry (μm)			PSD powder wet (μm)			Δ PSD (%)
	D10	D50	D90	D10	D50	D90	D50
Avicel PH-102	37	112	234	35	119	236	6.3
Avicel HFE-102	36	117	234	45	137	262	17.1
CombiLac	36	115	246	7	30	97	-74.3
F-Melt Type C	37	108	217	11	44	99	-59.4
F-Melt Type M	44	111	211	11	46	103	-58.7
Ludiflash	25	121	278	13	56	145	-53.7
MicroceLac	39	125	249	10	57	132	-54.1
Pharmaburst 500	23	98	199	18	54	106	-45.1
SmartEx QD100	36	94	200	21	56	114	-40.5

Δ PSD: Difference in mean particle size between dry and wet dispersion methods.

Since (oro)dispersible tablets are dispersed in saliva in the mouth or pre-dispersed in water before administration, the particle size of the water dispersion can provide relevant information of the particle size of excipients during in-use conditions. The particle size of co-processed excipients measured by wet dispersion method is depicted in Figure 5.7.

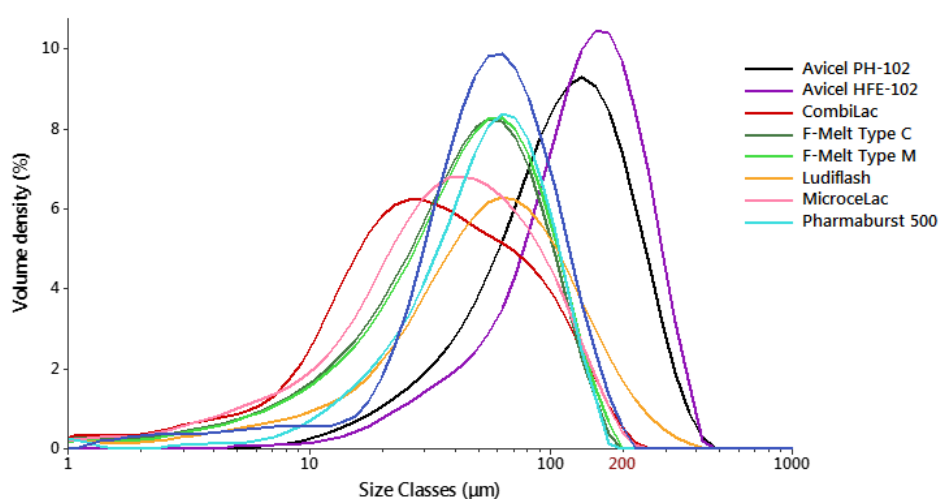


Figure 5.7: Particle size distribution of co-processed excipients evaluated by laser diffraction in wet dispersion using water as dispersant.

Particle size is known to be a critical parameter which influences palatability of excipients and based on previous studies with ODTs, rough mouth-feel is expected to be pronounced for particles larger than 200 μm (Kimura et al., 2015). As discussed before based on optical micrographs, Avicel HFE-102 and Avicel PH-102 exhibited relatively larger particle size than other excipients, with a median diameter larger than 100 μm and D_{90} larger than 200 μm . On the contrary, all other excipients showed a median particle size below 60 μm and D_{90} below 150 μm when dispersed in water.

The particle size of powder dispersions was compared to that of tablet dispersion (i.e. tablets prepared at 1.5MPa and subsequently dispersed in water) to assess the potential effect of compression on the particle size of excipients. As shown in Table 4, the particle size of excipients before and after compression was very similar, differences in median particle size being equal or smaller than 10.3%. The negligible differences found between the particle size distribution of powder and tablet dispersions justify the use of powders instead of tablets for the sensory evaluation analysis.

Table 5.5. Particle size distribution of powder and tablet dispersions in water by laser diffraction.

Excipient	PSD powder wet (μm)			PSD tablet wet (μm)			Δ PSD (%)
	D10	D50	D90	D10	D50	D90	D50
Avicel PH-102	39	119	236	42	126	250	5.9
Avicel HFE-102	45	137	262	50	150	285	9.5
CombiLac	9	32	101	7	30	97	-6.6
F-Melt C	11	44	99	10	44	106	0.0
F-Melt M	11	46	103	12	47	103	3.5
Ludiflash	13	56	145	14	61	148	8.2
MicroceLac	9	38	103	8	42	105	10.3
Pharmaburst 500	18	54	106	16	56	109	4.3
SmartEx QD100	19	54	110	12	51	111	-5.0

Δ PSD: Difference in mean particle size between powders and tablets dispersions in water.

5.4.2.3 Insoluble particle fraction

The amount of the insoluble material after dispersion of a tablet in water may impact palatability of the product upon administration. Although taste and mouth-feel are highly interconnected attributes and the same excipient could affect both taste and mouth-feel, it can be hypothesised that insoluble excipients will be the main determinants of mouth-feel, whereas soluble excipients will have a major impact on taste. The insoluble particle fraction (i.e. the proportion of insoluble material) in the co-processed excipients was calculated by gravimetric analysis and results are shown in Figure 5.8.

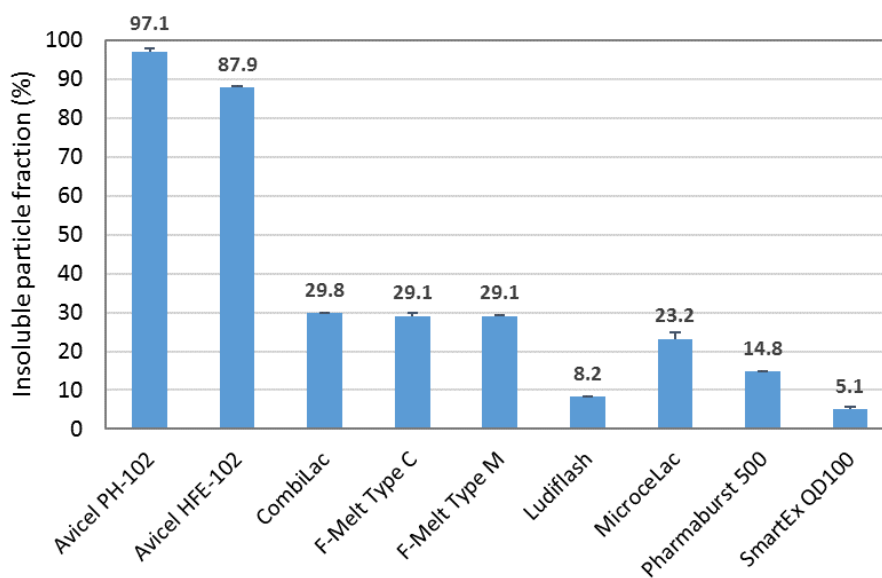


Figure 5.8. Insoluble particle fraction of excipients calculated by gravimetric analysis after excipient dispersion and dissolution of soluble components in 10 ml of water (N=3).

Large differences were found between co-processed excipients, with Avicel HFE-102 showing the greatest proportion of insoluble material (87.9%) and SmartEx QD100 the smallest insoluble particle fraction (5.1%). Most of the co-processed excipients however had less than 30% insoluble components, with the only exception of Avicel HFE-102. Avicel PH-102, a pure MCC excipient, served as a control since 100% insoluble particle fraction can be expected; 97.1 ± 0.7 % insoluble particle fraction was calculated for this excipient by gravimetric analysis, which demonstrates the accuracy of the test.

Moreover, the theoretical proportion of insoluble material in the co-processed excipients can be estimated based on their composition (Table 5.6). Excipients such as lactose and mannitol are highly water soluble and will readily dissolve in water, not contributing to the insoluble particle fraction. On the contrary, excipients such as MCC, polyvinyl acetate (PVAc) or silicon dioxide (SiO₂) are water insoluble and thus will not dissolve in aqueous media, possibly having a negative impact on mouth-feel and overall palatability. Other excipients such as crospovidone, starch or low-substituted hydroxypropyl cellulose (L-HPC), which are commonly used as disintegrants, swell when in contact with cold water and could also contribute to the amount of insoluble material in the dispersion. However, these polymeric excipients would form a soft, swollen dispersion, which could have a positive impact on palatability by creating a smooth, creamy mouth-feel (Buck et al., 2016). As shown in Table 5.6, there was a good agreement between the theoretical and the experimental insoluble particle fraction for all excipients evaluated.

Table 5.6. Theoretical and experimental insoluble particle fraction of excipients.

Excipient	Poorly soluble material(s)	Insoluble particle fraction (%)	
		Theoretical	Experimental [†]
Avicel PH-102	MCC (100%)	100	97.1 ± 0.7
Avicel HFE-102	MCC (90%)	90	87.9 ± 0.3
CombiLac	MCC (20%), starch (10%)	20-30	29.8 ± 0.1
F-Melt C	MCC (10-20%), CaHPO ₄ (2-9%), crospovidone (5-13%)	21-43	29.1 ± 0.9
F-Melt M	MCC (10-20%), Al ₂ Mg ₂ O ₂ (SiO ₃) ₃ (2-9%), crospovidone (5-13%)	21-43	29.1 ± 0.2
Ludiflash	PVAc (5%), crospovidone (5%)	5-10	8.2 ± 0.2
MicroceLac	MCC (75%)	25	23.2 ± 1.5
Pharmaburst 500	SiO ₂ (<10%), crospovidone (5%)	5-15	14.8 ± 0.2
SmartEx QD100	L-HPC (unknown %)	N/A*	5.1 ± 0.6

[†] Average result (N=3) ± standard deviation. * Composition of SmartEx QD100 is not available.

5.4.3 Palatability and acceptability of co-processed excipients

The best-performing excipients based on *in vitro* testing experiments were selected for a sensory evaluation study to assess palatability and acceptability (Table 5.7). Based on manufacturability criteria, nine excipients were selected, all of which showed adequate compressibility (max. TS > 3.0 MPa), disintegration time (< 1 minutes) and friability (< 1% in 10 minutes). Excipients of variable fineness of dispersion were purposely included in this study to investigate the effect of this variable on palatability.

Table 5.7. Summary of *in vitro* tablet characterisation experiments

Co-processed excipient	Max. TS (MPa)	Ejection shear [†] (MPa)	Friability (%) [†]		Dis. time [†] (secs)	Dispersion fineness [†]	
			4 min.	10 min.		710 µm	250 µm
<i>Top manufacturing performance – selected for sensory evaluation of palatability/acceptability</i>							
Avicel PH-102	>3.0	1.04	0.03	0.11	38	Fail	Fail
Avicel HFE-102	>3.0	0.90	0.02	0.11	35	Pass	Fail
CombiLac	>3.0	1.79	0.06	0.30	42	Pass	Pass
F-Melt Type C	>3.0	0.57	0.06	0.19	30	Pass	Pass
F-Melt Type M	>3.0	1.74	0.04	0.21	28	Pass	Pass
Ludiflash	>3.0	2.16	0.21	0.72	47	Pass	Pass
MicroceLac	>3.0	2.28	0.02	0.12	44	Pass	Pass
Pharmaburst 500	>3.0	0.74	0.08	0.55	26	Pass	Fail
SmartEx QD100	>3.0	2.08	0.18	0.82	27	Pass	Pass
<i>Low manufacturing performance – candidates for additional excipients in the final formulation</i>							
Compressol SM	>3.0	2.64	0.22	NM	426	Fail	Fail
Emdex	>3.0	0.57	0.32	NM	194	Pass	Pass
Pearlitol Flash	1.61	2.36	0.15	NM	49	Pass	Pass
ProSolv ODT	>3.0	0.84	0.09	NM	149	Pass	Pass
SmartEx QD50	2.45	1.42	0.61	NM	26	Pass	Pass

[†] Average result for tablets manufactured at target tensile strength 1.5 MPa; NM: Not measured, since only excipients with adequate compressibility (max. TS > 3.0 MPa), disintegration time (< 60 s) and standard friability (< 1% in 4 min.) were investigated for extended friability (during 15 min.).

Forced-choice preference ranking

Results of the forced-choice ranking comparison are presented in Figure 5.9, where the excipients are shown in order of preference, from most preferred to least preferred.

Overall, the top performer was SmartEx QD100, which was ranked as the most preferred excipient in 90% of the occasions and was the only excipient not selected as the least preferred sample by any of the participants. This was followed by F-Melt Type C, F-Melt Type M, MicroceLac, Ludiflash, CombiLac and Pharmaburst 500. Both Avicel HFE-102 and Avicel PH-102 were identified as the least preferred, being never ranked as the most preferred excipient by any participant and ranked as the least preferred option by more than 80% and 90% of participants, respectively.

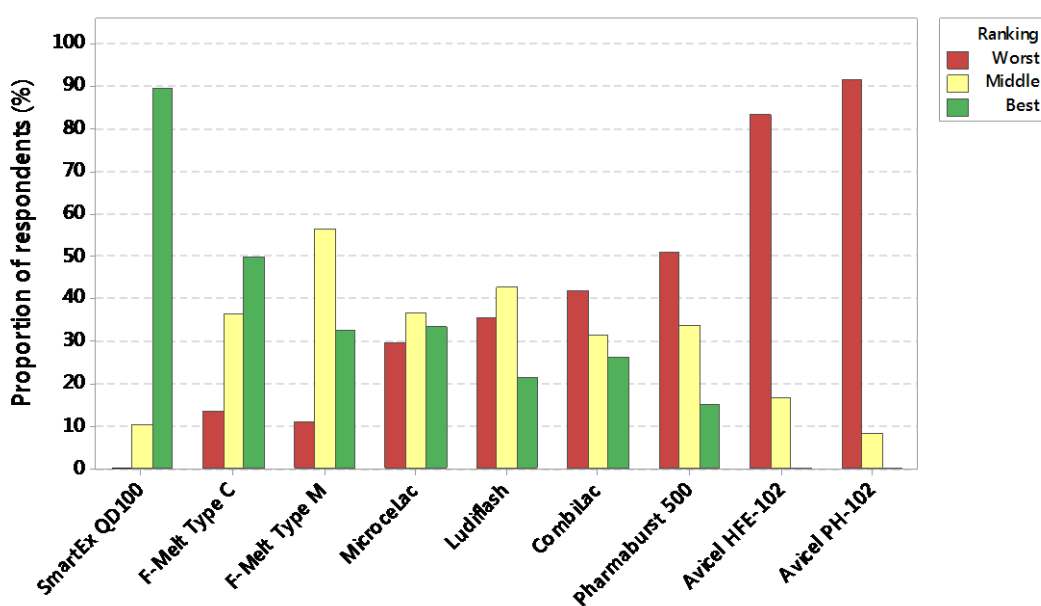


Figure 5.9: Forced-choice ranking order, shown as proportion of participants who selected each excipient as “best”, “middle” or “worst” within randomised combinations of three excipients.

Key palatability attribute

After participants ranked the samples in order of preference, they were asked to select the key palatability attribute (appearance, cooling sensation, mouth-feel, smell or taste) which explained their ranking. Results are shown in Figure 5.10.

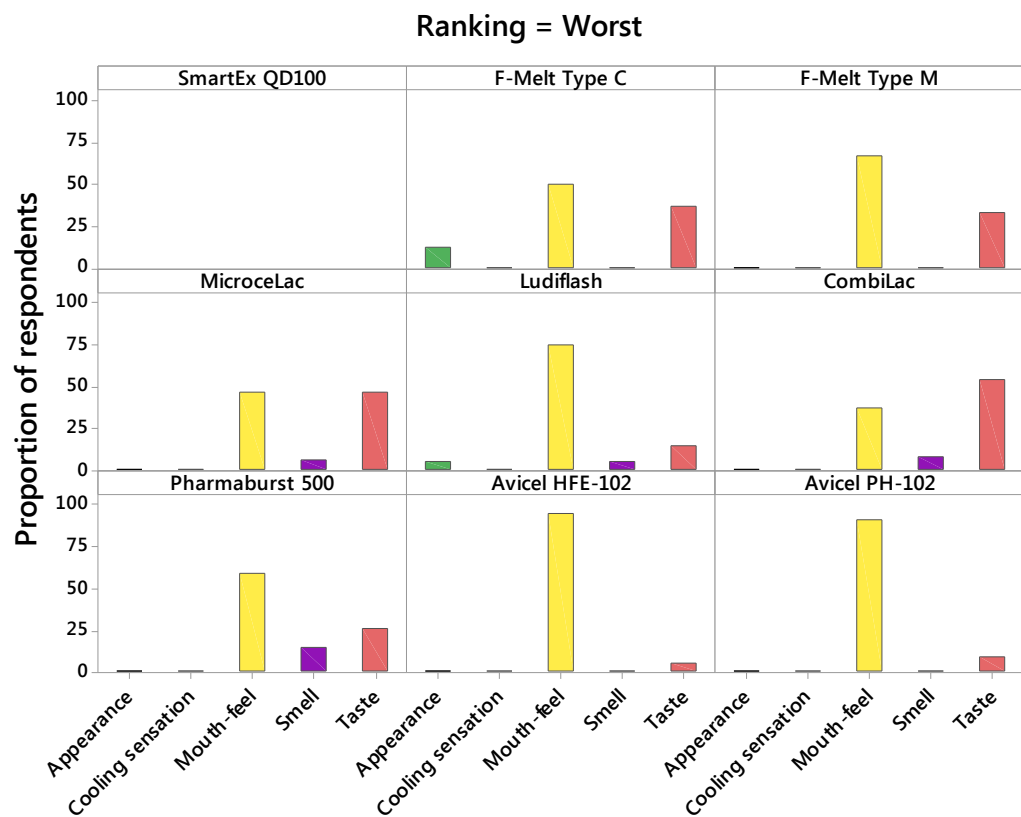
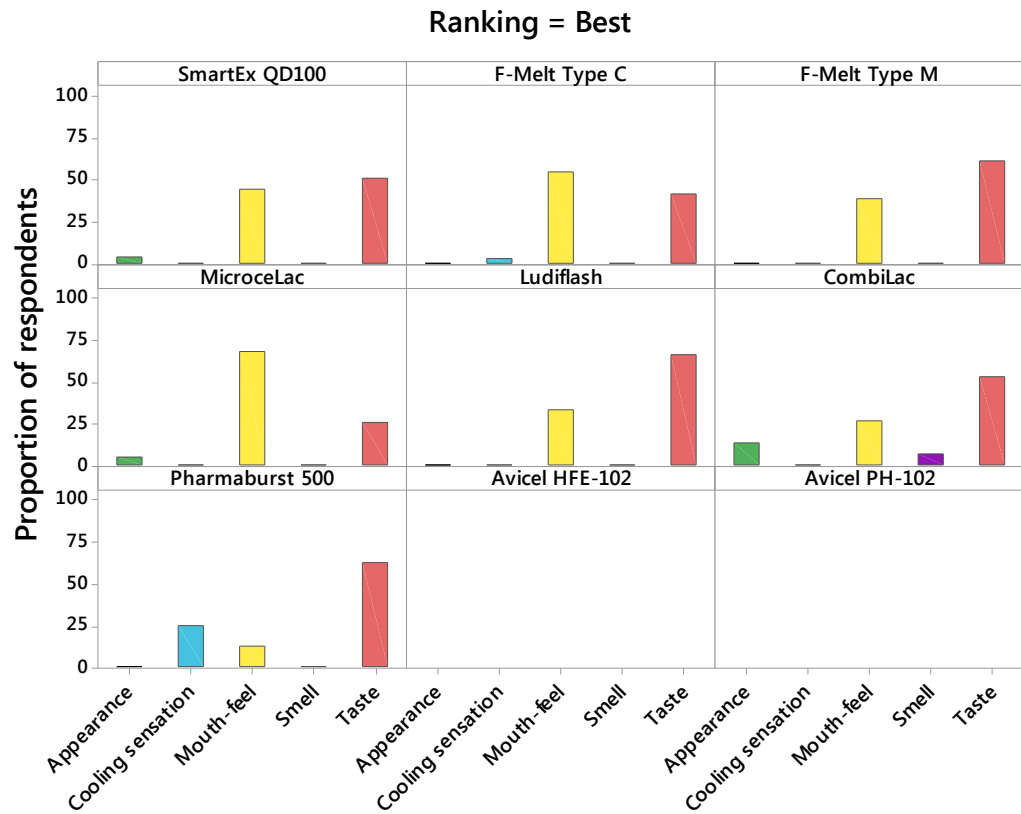


Figure 5.10. Key palatability attribute selected by participants to justify ranking of excipients dispersions as 'best' or 'worst' out of three random samples.

From those who ranked SmartEx QD100 as their preferred excipient, 49% suggested that the taste of the dispersion was the 'key attribute' and 44% referred to the mouth-feel of the sample as the main reason behind their choice (the remaining 7% reported that the clear appearance of the dispersion was the key attribute). As such, a balance between taste and mouth-feel seemed to drive perceptions of the appropriate palatability of SmartEx QD100. However, from those participants who ranked Avicel HFE-102 and Avicel PH-102 as their least preferred samples, an overwhelming majority referred to mouth-feel as the key attribute for their choice (95% and 91%, respectively). Rough mouth-feel from Avicel products was expected, as morphological characterisation of the samples revealed irregular MCC particles often larger than 200 μm . Overall, taste and mouth-feel were most commonly selected as key palatability attributes, whereas smell, cooling sensation and appearance seemed much less important factors.

Hedonic ratings of acceptability.

Participants rated the overall acceptability of the samples using a 5-point hedonic scale, where 1 corresponds to 'very acceptable' and 5 to 'very unacceptable' (Figure 5.11).

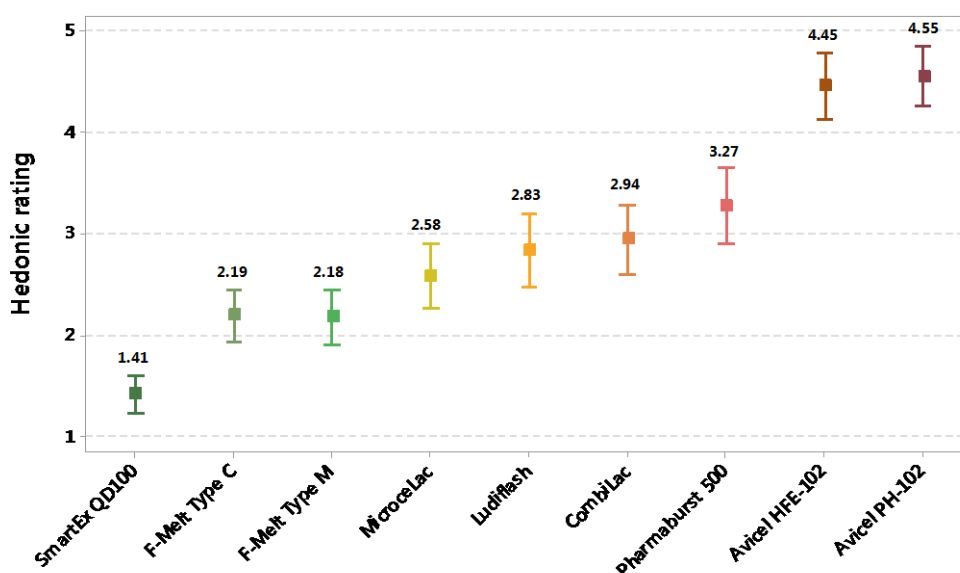


Figure 5.11: Interval plot of hedonic ratings (1 – very acceptable, 5 – very unacceptable). Markers represent the population mean and bars show the 95% CI for the mean.

Hedonic ratings confirmed the ranking of excipients. SmartEx QD100 seemed to be a very acceptable excipient, with a median rating of 1 (i.e. positive end of the scale). This was followed by F-Melt Type C, F-Melt Type M and MicroceLac, all with a median rating of 2, which suggests that these excipients were also acceptable. Ludiflash, CombiLac and Pharmaburst, with a median rating of 3, were considered neutral in terms of acceptance. Finally, Avicel HFE-102 and PH-102 were deemed very unacceptable, with median rating of 5 (i.e. negative end of the scale).

Interestingly, a potential correlation between fineness of dispersion and acceptability was identified. Pharmaburst 500, Avicel HFE-102 and Avicel PH-102 were the only excipients in this study to fail the 250 μm fineness of dispersion test and were also selected as the least preferred and least acceptable excipients. The association between fineness of dispersion through 250 μm sieve and hedonic ratings of acceptability was statistically significant ($p < 0.001$, Chi-square test for association). The negative effect of insoluble particle fraction and particle size on acceptability was also demonstrated ($p < 0.001$). Both particle size and insoluble particle fraction can be expected to affect fineness of dispersion which, in turn, will affect palatability (especially mouth-feel).

The particle size distribution analysis confirmed the relatively large particle size of Avicel products, which explains their poor fineness of dispersion and thus poor palatability. Meanwhile, Pharmaburst 500 is mainly based on the water-soluble excipient mannitol and its dispersion in water exhibited a small particle size ($D_{50} = 54 \mu\text{m}$, comparable to excipients such as SmartEx QD100 which passed the fineness of dispersion test. Thus, the reasons behind the poor dispersion of Pharmaburst 500 remain unexplained.

Hedonic ratings for each individual excipient are presented in Figure 5.12, where results are expressed as the proportion of participants who selected each level of the 5-point facial hedonic scale. A rational interpretation of results based on the individual composition of each excipient is attempted below.

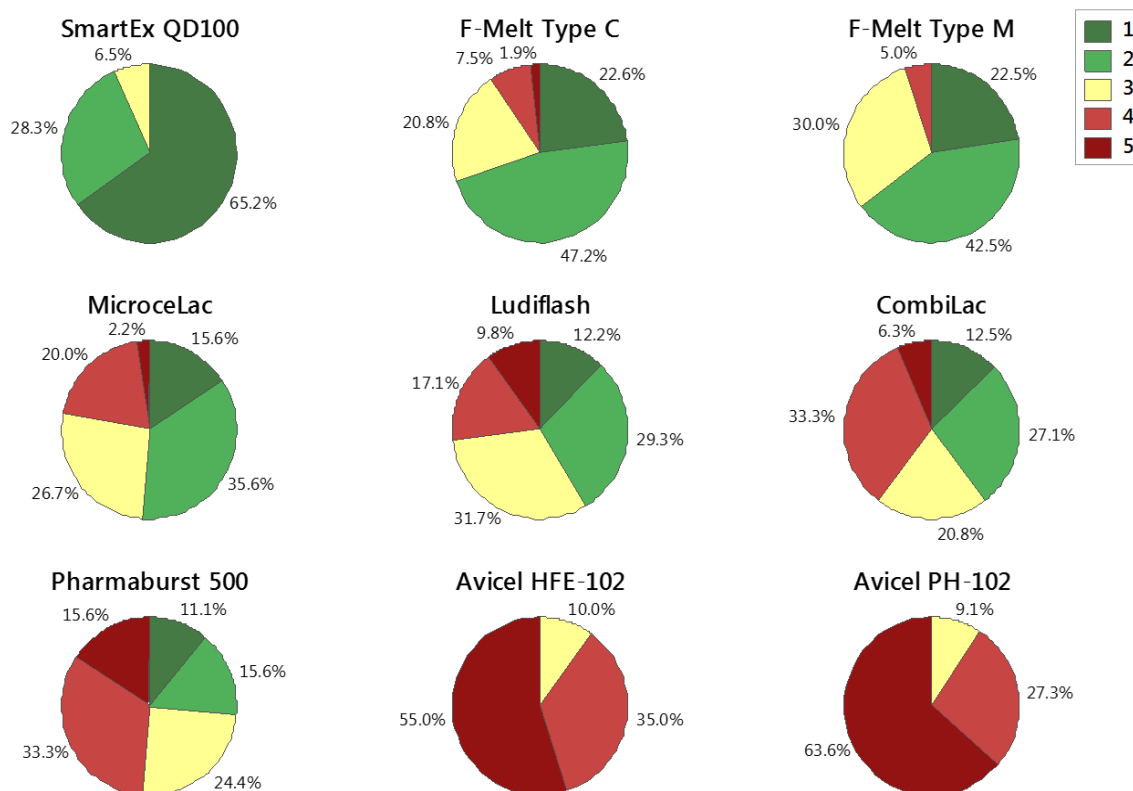


Figure 5.12: Hedonic rating for each excipient, showing the proportion of participants which selected each level of the 5-point hedonic scale (1 – very acceptable, 5 – very unacceptable).

SmartEx QD100

SmartEx QD100 received remarkably positive responses, with no negative ratings (i.e. 100% ratings in neutral-positive range) and over 65% of participants scoring the highest possible ratings in the hedonic scale. The exact composition of SmartEx QD100 has not been published by the manufacturer, but it is known to contain mannitol (diluent, sweetener), polyvinyl alcohol (binder) and L-HPC (disintegrant). The overall success of SmartEx QD100 was reflected in the open-ended comments provided by the volunteers, describing SmartEx QD100 dispersions as ‘sweet’, ‘smooth’, ‘clear’ or ‘least powdery’. The small particle size (D_{50} in wet dispersion = 56 μm), insignificant proportion of insoluble material with respect to its dry weight (ca. 5%) and presence of mannitol could be responsible for a highly favourable mouth-feel and sweet taste.

F-Melt Type C and F-Melt Type M

The second and third highest scores were observed for F-Melt products, with over 90% of neutral-positive responses. Essentially, the composition of these excipients is identical with a difference of one component: F-Melt Type C contains dibasic calcium phosphate anhydrous (Fujicalin®) and F-Melt Type M contains magnesium aluminometasilicate (Neusilin®) (Krupa et al., 2012; Sona and Muthulingam, 2011). The acceptable palatability of F-Melt products in fast disintegrating tablets was previously attributed to the presence of mannitol within its composition (Moutasim et al., 2017). In this study, participants described F-Melt products as being 'moderately sweet' and having 'smooth' texture, which support previous claims.

Interestingly, these excipients contain 10-25% of microcrystalline cellulose, but the presence of this insoluble excipient with poor organoleptic profile did not affect the overall palatability. It can be hypothesised that the amount of MCC is not substantial as to elicit the negative palatability response. Moreover, other excipients in the F-Melt products composition could potentially mask the feeling of grittiness and/or the manufacturing process could have altered the mouth-feel of these excipients.

MicroceLac and CombiLac

MicroceLac and CombiLac were the only lactose-based co-processed excipients tested in this study. Lactose has been widely used as a filler in pharmaceutical preparations for many years, although its popularity has declined in favour of mannitol (Ohrem et al., 2014) due to commonly reported lactose intolerance (Eadala et al., 2009), and risk of API-excipient interactions caused by the Maillard-reaction (Bharate et al., 2010). The additional constituents of MicroceLac and CombiLac include MCC (for both) and maize starch (in CombiLac). Starch, as a viscosity-modifying excipient, is often used to promote physical stability of dispersions while enhancing their organoleptic profile by creating a smooth, creamy mouth-feel (Buck et al., 2016).

In this study, MicroceLac organoleptic profile was preferred to CombiLac (77.6% versus 60.4% neutral to positive responses). This could suggest that the presence of maize starch in CombiLac had a negative effect on its palatability, in contrast with the rationale to add starch to improve palatability. The anecdotal responses described the taste of CombiLac as 'plain' and 'slightly unpleasant'.

Ludiflash

Overall, Ludiflash obtained 73.2% of neutral-positive ratings, which suggests a positive organoleptic profile. Ludiflash is reported by its manufacturer to have creamy and smooth mouth-feel with neutral to mildly sweet, pleasant taste. Although the taste of Ludiflash was confirmed to be neutral in this study (with participants describing it as 'almost tasteless' and 'slightly sweet'), it was rated more negatively than other excipients such as SmartEx QD100 and F-Melt Type C and Type M (which perhaps had a sweeter taste).

Moreover, the presence of mannitol in high proportion (80% w/w) was expected to produce an acceptable mouth-feel for Ludiflash, although many volunteers described this excipient as 'grainy' and 'coarse'. When participants ranked Ludiflash as the worst sample, 75% justified their choice based on poor mouth-feel. The coarse feeling in the mouth perceived by some participants could be ascribed to polyvinyl acetate (PVAc), the only non-water-soluble excipient in its composition. Ludiflash had the third largest particle size ($D_{90} = 148 \mu\text{m}$) from the excipients investigated, after Avicel PH102 and HFE-102, which supports the results of the *in vivo* sensory evaluation.

Pharmaburst 500

It has been previously reported that, when compared against formulations containing pure MCC as filler (Avicel PH 101), the palatability of Pharmaburst 500 tablets are more acceptable due to the presence of a sweetener, mannitol, in its composition (Moqbel et al., 2016). This can be confirmed by the results obtained in this trial, where Pharmaburst 500 performed better than pure MCC (Avicel PH-102).

However, Pharmaburst 500 was still among the worst performing excipients in this palatability study, with just 51.1% of neutral-positive evaluation. Interestingly, the high polyol concentration (73.8-93.8% w/w, based on manufacturers specifications) did not result in a highly favourable organoleptic profile. The proportion of volunteers providing negative ratings on hedonic scales (48.9%) exceeded those providing positive ratings (26.7%). Participants reported mouth-feel (60%), followed by taste (26%) and smell (14%), as the key attributes for the negative evaluation of Pharmaburst 500. Perhaps the presence of insoluble silicon dioxide in the composition, even if in small quantity, could have negatively influenced the overall organoleptic profile of this excipient.

Avicel HFE-102 and Avicel PH-102

Avicel PH-102, a pure MCC excipient, was the least acceptable candidate tested in this study. Its grittiness was negatively perceived by the volunteers who described the mouth-feel as 'sandy' or 'chalky', and the lack of sweetener resulted in a 'neutral', 'bland' taste. Avicel PH-102 did not receive any positive response in the hedonic scale ratings, with an overwhelming 90.9% of negative evaluations. The rough mouth-feel of MCC is well acknowledged in the literature, e.g. (Ishikawa et al., 2001).

To improve palatability of MCC, spray-drying was used as co-processing technique to combine MCC with mannitol (70/30 ratio) in the development of Avicel HFE-102. Hypothetically, the presence of mannitol should improve the taste due to its sweetness. The cooling effect resulting from the negative heat of solution of mannitol (Kearsley and Deis, 2006) could be also beneficial to reduce the sandy mouth-feel of the cellulosic material (Rojas et al., 2012). However, this study showed that the difference between both products was not significant. Avicel HFE-102 showed only a minor improvement in organoleptic profile compared to Avicel PH-102. It is possible that the influence of mannitol was overwhelmed by the high concentration of MCC (90% w/w). Experiments demonstrated the large insoluble particle fraction of this co-processed excipient and the coarse size of the insoluble MCC particles (D_{50} in wet dispersion = 137 μm).

5.5 Conclusions

This study investigated a range of co-processed excipients that may prove suitable for the preparation of (oro)dispersible tablets by direct compression. Formulations containing Avicel HFE-102, CombiLac, F-Melt Type C, F-Melt Type M, Ludiflash, MicroceLac, Pharmaburst and SmartEx QD100 exhibited acceptable flow properties (Carr's index < 20), compressibility (max. tensile strength > 3.0 MPa) and ejection results (< 3.0 MPa at target tensile strengths) in addition to low friability (< 1.0% after 10 minutes) and short disintegration times (< 60 seconds), which suggest suitability for use in directly compressed (oro)dispersible tablet formulations. Such excipients were then further investigated to ascertain their organoleptic properties and patient acceptability.

Other possible excipients that may be used in directly compressed (oro)dispersible tablet formulations include ProSolv ODT, Emdex, Compressol SM, SmartEx QD50 and Pearlitol Flash. SmartEx QD50 and Pearlitol Flash provided tablets with rapid disintegration but failed to compress into tablets with maximum tensile strength greater than 2.5 MPa; thus, these excipients would only be suitable providing appropriate compressibility is achievable with the addition of an API into the formulation. On the contrary, formulations containing ProSolv ODT, Emdex and Compressol SM produced robust tablets but failed to disintegrate sufficiently fast and thus would benefit from additional disintegrants in the formulation. All these excipients which showed poorer performance based on *in vitro* testing and may require additional excipients in the formulation were not considered for palatability and acceptability testing under the criteria established for this investigation.

The sensory analysis of co-processed excipients revealed significant differences in their organoleptic profiles. SmartEx® QD100 was undoubtedly the most palatable out of the tested products, followed by F-Melt Type C, F-Melt Type M and MicroceLac (considered to have acceptable palatability), Ludiflash, CombiLac and Pharmaburst (with neutral

palatability). Avicel® HFE-102 was the least acceptable due to large and water-insoluble MCC particles that resulted in a gritty mouth-feel. Almost all co-processed excipients tested (with exception of Avicel HFE-102) provided improved palatability compared to the non-coprocessed excipient Avicel PH-102. Evaluation of particle size and shape, insoluble particle fraction of excipients and fineness of dispersion were proven to be useful to predict poor palatability in terms of granularity or mouth-feel.

In this regard, modification of the compendial fineness of dispersion test by using 10 ml of water as dispersant (instead of 100 ml) and 250 μm screen (instead of 710 μm) was proven valuable to increase discrimination between samples. The three co-processed excipients that failed the fineness of dispersion test through the 250 μm screen (namely Pharmaburst 500, Avicel HFE-102 and Avicel PH-102) were considered the least palatable, although two of those three passed through the 710 μm screen (which is the current pharmacopoeial standard). Excipients with particle size in wet dispersion larger than 200 μm were considered poorly acceptable which supports the use of this value as a threshold for maximum particle size of excipients used within (oro)dispersible formulations, as previously proposed (Kimura et al., 2015).

Chapter 6

General discussion, conclusions and future work

The research described within this thesis evidences the value of palatability and patient's acceptability testing to guide excipients selection and dosage form design. This chapter provides a general discussion of the work. Justification of the research is provided; experimental results and implications of the findings are overviewed; limitations and methodological considerations are discussed; and future work is outlined.

6.1 Importance of evaluating patient's acceptability

Children need better medicines. Medicines have been traditionally designed to meet the needs of *standard* patients. Paediatric patients (and other *non-standard* patient populations, such as geriatrics and patients with swallowing difficulties) have been neglected. The advent of the European Paediatric Regulation in 2007 (and parallel regulations in other parts of the world) plus new guidelines on Clinical Investigation of Medicinal Products in the Paediatric Population are changing the scenery, supporting the development of acceptable medicines (European Parliament and Council, 2006). Forthcoming regulations will set similar standards for older patients (EMA, 2018).

A medicine will not elicit its desired therapeutic effect if the patient is not *able* or not *willing* to take it. Our understanding of medicines' quality must evolve from the traditional balance of safety and efficacy to a more comprehensive balance of safety, efficacy and patient's acceptability. Patient's acceptability is determined by characteristics of the patient as well as characteristics of the medicinal product (EMA, 2018, 2013). The pharmaceutical characteristics of the medicinal product (e.g. route of administration, appearance, dosage form size and shape, dose volume and administration device) must be rationally designed to meet the needs of the target population.

It is well-established that pharmaceutical quality should not be merely tested on the final product but planned in advanced based on understanding of the product and processes (Quality by Design). Similarly, patient's acceptability should not be simply determined on the final product but investigated during the drug product development and the outcomes of such investigation used to guide drug product design. This would enable development of patient-centric medicines that are *acceptable by design* (Figure 6.1).

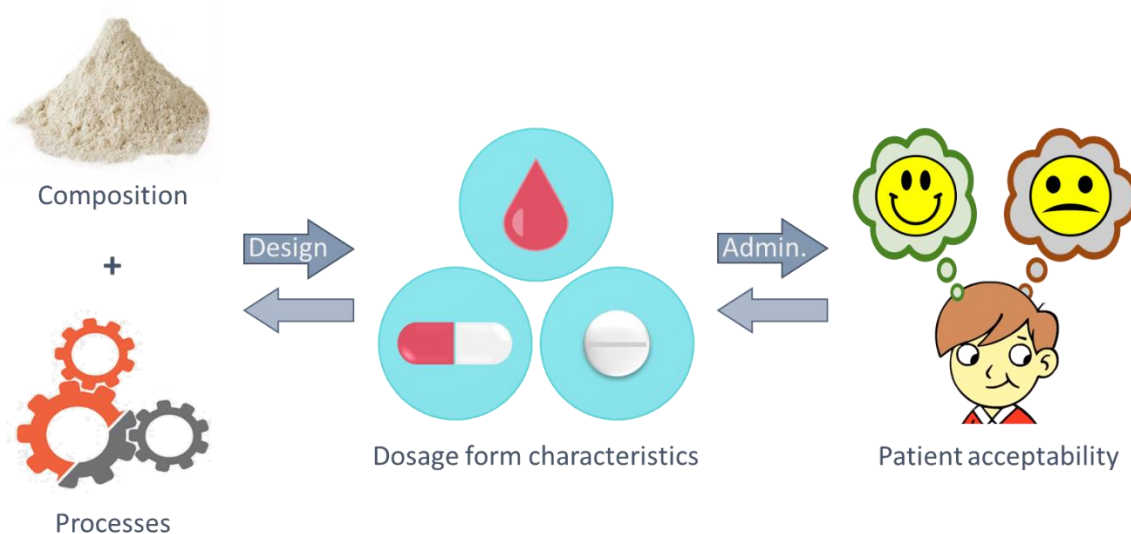


Figure 6.1. Diagram of the *Acceptability by Design* concept by which the selection of excipients, manufacturing process and dosage form are guided by understanding of patient's acceptability.

Companies are required to propose a formulation strategy in PIPs submitted early in the drug development process. The rationale for the choice of excipients and dosage form design needs to be discussed and justified. The research described within this thesis outlines an iterative process by which prototype formulations can be optimised based on sequential palatability and acceptability investigations which feedback into the selection of excipients and dosage form design until a final, acceptable product is reached.

The outcomes of this research intend to highlight points to consider during the drug development of acceptable medicines for children, support dosage form selection and complement PIP discussions and justifications.

6.2 Rationale for investigating flexible solid oral dosage forms

Liquid medicines are the traditional formulation of choice for paediatrics but the benefits of solid oral dosage forms over liquids are widely acknowledged. These include better stability profile (shelf life and in use), cost-effective, convenient and portable packaging and lower number of (potentially toxic) excipients. Recent exploratory studies using placebo mini-tablets have dramatically changed our views on appropriateness and acceptability of solid dosage forms in children and neonates (Klingmann et al., 2013; Kluk et al., 2015; Spomer et al., 2012; Thomson et al., 2009). These studies marked the beginning of a new stream of research, as the one described in this thesis.

The choice of formulation in paediatric drug development studies may be determined by the properties of the API, target age group and disease to be treated (Wang, 2015), as well as socio-cultural reasons (Walsh et al., 2017). Flexible solid dosage forms, such as multiparticulates and (oro)dispersible tablets, offer potential to be appropriate for a wide range of age groups and to accommodate a wide range of APIs. The adaptability of flexible solid dosage forms also means that they are suitable as *enabling formulations* in *bridging studies* to support paediatric drug development (Ricci, 2013). For instance, (oro)dispersible tablets can benefit from a well-established manufacturing platform while being a suitable formulation for both adults and children. Meanwhile, multiparticulate formulations could be filled into capsules to be swallowed whole by adolescents and adults and to be sprinkled into a suitable vehicle for young children. For such reasons, these flexible solid dosage forms were the focus of this research.

The aims of this research included: (1) to review knowledge and identify barriers for the development of age-appropriate medicines for children, (2) to optimise methodology for palatability and acceptability testing of pharmaceutical products in children and adults and (3) to generate evidence to fill some of the knowledge gaps around acceptability of flexible solid oral dosage forms.

6.3 Overview of original contributions and implications of the research

The main findings of the work described in this thesis are summarised below, in relation to the original aims and objectives:

- Review of the scientific literature identified lack of evidence on patient's acceptability of flexible solid dosage forms, despite acknowledged potential as formulations of choice for paediatrics. The literature review also demonstrated lack of standardised methodology for assessment of palatability and patient's acceptability.
- Methodology for the assessment of palatability and patient's acceptability of flexible solid oral dosage forms was developed, considering acceptability as ability and willingness to use a product as intended. When required, child-friendly questionnaires were designed to allow studies in children (minimum age of four years), without parents/caregivers' intervention.
- The swirl and spit methodology, typically used in the assessment of palatability, was compared to swallowing of the samples as methods to evaluate palatability and acceptability. The former methodology benefits from allowing assessment of a greater number of samples while the latter allows evaluation of ingestion and post-ingestion phenomena. Selection of the most appropriate method is required on a case by case basis depending on the objectives of the study.
- A key outcome of this research was the realisation of the duality of the concept of patient's acceptability. The ability to use a formulation as intended (e.g. ability to swallow a solid dosage form) does not always implies willingness to use it. The willingness to use a product is a broader aspect which depends not only on the skills of the patient to use a product but on other elements such as palatability and liking of the product. Evaluation of both aspects brings certain methodological challenges further explored in Section 6.4.

- Multiparticulates were found to be widely accepted by children in terms of ability to use as intended (i.e. swallow the complete dose). However, palatability issues related to oral grittiness perception were identified as a barrier to acceptability, as supported by previous research. Increasing particle size and amount of multiparticulates were found to be contributing factors to oral grittiness perception. Application of a polymeric coating did not seem to affect grittiness perception and overall acceptability. This information could guide the design of multiparticulate formulations.
- Barriers to the administration of multiparticulates were encountered as pellets quickly settled down in water, being unsuitable for administration using a dosing cup. The use of a dosing spoon ameliorated this issue. This finding highlighted the importance of selecting the right dosing device to achieve dosing accuracy.
- The presence of residual multiparticulates in the mouth after sample administration was a key issue identified in this research. This may have a critical impact on multiparticulates designed for taste-masking purposes since the prolonged residence time in the mouth might put at risk the integrity of the coating (by incentivising dissolution and/or chewing) leading to release of the (aversive) active ingredient. The residue in the mouth was rated in the positive range of the hedonic scales, suggesting small and acceptable deposit of multiparticulates. However, this perception can change dramatically if the aversive API is released in the mouth. This issue may thus require special attention when developing multiparticulate formulations.
- Model oral hydrogels were developed to investigate the effect of liquid vehicles for the administration of multiparticulates on palatability and patient's acceptability. Vehicles of viscosity higher than water were confirmed to improve palatability and acceptability of multiparticulates, as supported by previous research. A balanced viscosity should be sought to enable homogenous suspension of the particles while maintaining a thin, syrup-like consistency (which was favoured by participants).

- The most suitable co-processed excipients to use within directly compressible (oro)dispersible tablet formulations were identified, integrating manufacturability and patient's acceptability criteria. Particle size of the excipients (in water dispersion) and proportion of insoluble materials in their composition were found to be key parameters which affect palatability and patient's acceptability. This information can guide the development of (oro)dispersible tablet formulations. Evaluation of manufacturability and acceptability of formulations containing API will be required.
- An *in vitro* test was developed based on modification of the compendial fineness of dispersion test. A more restrictive setting was employed using 10 ml of liquid and a 250 µm nominal aperture sieve instead of 100 ml of liquid and a 710 µm sieve, as stated in the compendial test. This test was shown to be predictive of mouthfeel of the excipients and could expedite development of acceptable formulations by serving as a simple screening tool to pre-select candidates.
- Overall, the value of conducting palatability and patient's acceptability evaluations to guide drug product development was demonstrated.

6.4 Methodological limitations in the evaluation of patient's acceptability

The lack of standardised methodology for palatability and acceptability testing is a barrier for the development of paediatric medicines. Several limitations of the methodology employed in this thesis merit discussion. Some of these limitations, which will require special attention in future studies in the field, are discussed below:

Patient's acceptability definition and scientific interpretation

Patient's acceptability has been defined by the EMA as "*the ability and willingness of the patient and its caregiver to use a medicine as intended*". However, this definition is open to interpretation and there are no guidelines or standard criteria to measure acceptability in practice. Review of the scientific literature on patient's acceptability of oral dosage

forms revealed that the outcome measures of acceptability varied greatly between studies, as discussed in the Introduction to this thesis.

The heterogeneity in the outcome measures employed hinders interpretation of results and comparison between studies. The EMA acknowledges that “*different methods to measure patient’s acceptability may result in different outcomes*” (EMA, 2013). Ideally, pragmatic definition of patient’s acceptability should be developed, providing guidance on how this should be measured and interpreted. Given the lack of such guidance, outcome measures of acceptability were purposely defined in the present work.

Patient’s acceptability is a multi-dimensional variable, influenced by several factors such as appearance, palatability and swallowability. In an attempt to consider these contributing factors simultaneously, various outcome measures were employed in the present work, including the *ability* to swallow the dosage form, the *palatability* of the formulation and the *willingness* to take the product again. The different outcome measures provided complimentary results which require careful interpretation.

The EMA indicates that “*adequate patient’s acceptability is not to be understood as 100% acceptance of a medicine*”, but the limits applied in each study “*should be discussed and justified in terms of risk to benefit considerations*” (EMA, 2013).

Validity and reliability of the evaluation tools

Age-appropriate questionnaires were developed to obtain patient reported outcomes of palatability and acceptability. However, consistency and reliability in interpretation of the questionnaires by different participants was dubious (especially in children). Moreover, the ability of participants to independently rate each palatability criteria on the hedonic scale was questionable, since ratings to the different attributes were found to be associated with each other (in both children and adults). These phenomena can be expected, especially from untrained assessors, and a number of studies have addressed these issues in the past (Popper et al., 2004; Prescott et al., 2011).

Given the questionable reliability of patient reported outcomes in children (and in other patients with communication impairments), researcher observations are recommended in studies involving such populations (FDA, 2009; Matza et al., 2013). In the study in children described in Chapter 3, facial expressions were visually interpreted by the investigators of the study. Interpretation of observational responses is subjective and might be affected by factors unrelated to the formulation (ASTM, 2003). When facial expressions suggested some level of discomfort with the sample, it was difficult to determine which of those were signs of non-acceptance.

Results for the willingness of participants to take multiparticulates every day as a medicine also require cautious interpretation. Although this outcome measure could provide an indication of future acceptance, results are based on opinions of healthy participants after a single administration of the formulation. Nevertheless, previous research suggest that subject-reported attitudes towards taking a medication or to continue with a therapeutic regime are good predictors of patient adherence (Godin et al., 2005; Kreivi et al., 2014).

In this research, time and effort dedicated to developing robust evaluation tools had to be balanced with the need to obtain empirical data to answer the research questions.

Specific barriers for conducting acceptability studies in children

The work presented in this thesis continuous to highlight the methodological and logistic barriers of conducting studies involving children. One of the greatest challenges is the reduced number of samples that can be tested in a single session, due to limited attention span of children. This allows evaluation of a limited number of formulations and thus limited number of formulation factors. Screening studies (in adults) proved useful to reduce the number of samples and refine the study design before conducting studies in children, as supported by previous guidelines (ASTM, 2003; Guinard, 2000).

The use of scales may differ between children and adults (e.g. children's tendency to use preferentially the extremes of hedonic scales) and variability of results in children can be expected to be broader than in adults. Consequently, a larger number of children participants would be required to obtain the same level of significance.

In addition, subjective interpretation of questionnaires can introduce a certain degree of variability in the results. This effect can be expected to be greater in younger children and ameliorate with age due to cognitive and language skills development. The questionnaire used in the study described in Chapter 3 was designed based on previous research with children and adolescents (Mistry et al., 2016), and was considered appropriate to the age of the children who participated. However, consistency in the interpretation of questions and sample attributes was still doubtful. Further research is required to support the development of age-appropriate evaluation tools.

Generalisability and significance of results

The studies described in this thesis were conducted in healthy subjects, in controlled environments, under supervision of a research team. This allows no definitive conclusion of the acceptability of the formulations by patients in hospital settings or at home. Results of this research were not intended to guide prescribing choices in clinical practice but to illustrate the use of palatability and acceptability testing during drug development studies to guide dosage form design.

Arguably, the generalisability of outcomes such as acceptable size of multiparticulates or the preferred excipients in (oro)dispersible tablet formulations may be limited given the population size and the non-specific demographic. The evidence generated in this research is expected to help guide initial pharmaceutical development choices and product testing, rather than providing absolute guidance towards a final commercial product. Results of this research do not preclude the need to conduct product-specific acceptability studies during drug product development, on a case by case basis.

6.5 Future work: towards better medicines for children

Potential areas of future work have been suggested in relevant parts of this thesis; they are summarised here together with other areas which merit investigation.

- The most urgent research need is an agreeable and practical definition of patient's acceptability. This may appear a trivial matter of nomenclature, but its effects on interpretation of results and comparison between studies are paramount. Based on the current definition of acceptability provided by the EMA, a simple measure of the ability to swallow the formulation should not be considered synonym of acceptability, as performed in previous studies. Efforts need to be directed towards assessment of not only the ability but also the willingness to use the product as intended.
- A clear and practical definition of patient's acceptability would enable the development of much-needed standardised evaluation tools. Validated tools such as the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Satisfaction with Medicines Questionnaire (SATMED-Q) have been developed to measure patient's satisfaction (Bharmal et al., 2009; Ruiz et al., 2008). Although these tools already account for *convenience* and *satisfaction*, the information provided might be insufficient and/or inappropriate to determine patient's acceptability. However, these tools can serve as inspiration in the development of a Patient's Acceptability Questionnaire that can be systematically used in different studies.
- Additional work around patient's acceptability of flexible solid oral dosage forms is necessary to confirm and expand the results obtained in this research. Studies with multiparticulates should be extended to younger children based on the positive results obtained (in terms of ability to swallow the formulation) by school-aged children. The maximum size and amount of multiparticulates (and other solid dosage forms) that can be accepted by children of different ages continues to be an important incognita, which requires an evidence-based answer.

- Extra attention must be paid to evaluating the effect of formulation factors on residual multiparticulates in the mouth and the spontaneous reflex of chewing the particles. One of the key advantages of multiparticulates is their suitability for taste masking based on polymeric coatings. Prolonged retention in the mouth and chewing of the particles would compromise such advantage. It is crucial to identify the formulation factors which play a role in this response, e.g. size and amount of multiparticulates, hardness and surface properties of the particles, properties of the vehicle used for administration and dosing device if any.
- Future work should investigate (oro)dispersible tablets with addition of API in the formulation. Manufacturability and acceptability of (oro)dispersible formulations will be highly influenced by the physicochemical properties of the API and thus the formulation design (e.g. the need for taste-masking) must be considered on a case by case basis. Any of the top 6 or 7 co-processed excipients identified (out of 14 candidates initially assessed) may be worth revisiting depending on the target API.
- Researchers have already directed their efforts towards standardised approaches for selecting the most appropriate dosage form for paediatrics (Sam et al., 2012). Further work is required in this area. A Manufacturing Classification System (MCS) have been recently proposed to rank the feasibility of different pharmaceutical processing routes based on selected properties of the API and the needs of the formulation (Leane et al., 2014). In the same line of thinking, an Acceptability Classification System could be attempted to rank the appropriateness of different dosage form designs based on selected properties of the API and the needs of the target population.
- Further work which was deemed out of the scope of this research should investigate the generalisability and clinical significance of results obtained in palatability and acceptability studies conducted in healthy subjects. It is important to understand the predictive value of these studies on acceptability in the target patient population.

6.6 Conclusions

The development of paediatric medicines which fulfils safety, efficacy, acceptability and manufacturability requirements is a challenging task. The specific needs of the target population should be taken into account to establish the Quality Target Product Profile. Evaluation of palatability and patient's acceptability during drug development studies can contribute to define the Critical Quality Attributes as well as formulation and process parameters that may affect them. Only when these features are considered at an early stage of the drug development, medicines will be *acceptable by design*.

The EMA acknowledges that adequate patient acceptability can be demonstrated by different means, including data from clinical trials, human factor studies with healthy volunteers or actual patients, market experiences and scientific literature. Evaluation of acceptability of model (placebo) formulations in healthy (adult) volunteers can be valuable by (i) providing fundamental evidence of patient's acceptability to guide initial dosage form selection and (ii) generating knowledge to improve the design of future acceptability studies in the target population to optimise the final formulation.

The outcomes of this research highlight methodology gaps and areas for improvement in the evaluation of patient's acceptability. Unless successful and pragmatic criteria for the evaluation of acceptability are developed, there will always be a risk for medicines to lack fit for purpose. The available technology platforms for paediatric drug delivery do not meet the needs of all patients and innovation for better medicines will be misguided if suitable ways to measure acceptability are not developed. Collaborative endeavours from Industry, Academia and Regulators will be necessary to achieve this goal.

The methodology explored in this research can be applicable beyond the development of medicines for children. Not only children but also other subsets of the population can benefit from medicines designed to meet their needs and preferences.

Research publications

Journal articles

Lopez FL, Bowles A, Orlu Gul M, Clapham D, Ernest TB and Tuleu C. 2016. *Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers*. European Journal of Pharmaceutical Sciences; 92:156-62.

Sara M. Hanning, Lopez FL, Wong ICK, Ernest TB, Tuleu C and Orlu Gul M. 2016. *Patient centric formulations for paediatrics and geriatrics: Similarities and differences*. International Journal of Pharmaceutics; 512(2):355-59.

Lopez FL, Ernest TB, Tuleu C and Orlu Gul M. 2015. *Formulation approaches to paediatric oral drug delivery: Benefits and limitations of current platforms*. Expert Opinion on Drug Delivery; 12(11):1727-40.

Journal articles (in draft)

Lopez FL, Bowles BJ, Dziemidowicz K, Orlu M, Tuleu C, Ernest TB and Edwards A. Co-processed Excipients for Dispersible Tablets: Manufacturability.

Dziemidowicz K, Lopez FL, Bowles BJ, Edwards A, Ernest TB, Orlu M and Tuleu C. Co-processed Excipients for Dispersible Tablets: Patient Acceptability.

Lopez FL, Mistry P, Batchelor HK, Bennett J, Coupe A, Ernest TB, Orlu M, Tuleu M. Palatability and acceptability of multiparticulate formulations in children and adults.

Ranmal S, O'Brien F, Lopez FL, Ruiz f, Orlu M, Tuleu c, Walsh J, Liu F. Methodologies for assessing the acceptability of oral formulations among paediatric and geriatric patients: A systematic review.

Oral presentations

Lopez FL, Ernest TB, Orlu Gul M and Tuleu C. 2017. *Improving palatability and acceptability of oral multiparticulate formulations using hydrogels as administration vehicles*. 6th FIP Pharmaceutical Sciences World Congress, May 2017, Stockholm, Sweden.

Lopez FL, Mistry P, Batchelor HK, Bennett J, Ernest TB, Orlu M and Tuleu C. 2016. *Palatability and acceptability of multiparticulate formulations: Adults vs. children comparison*. 8th EuPFI Conference: 'Formulating Better Medicines for Children', September 2016, Lisbon, Portugal.

Awarded 'Best Oral Presentation', in Portugal, September 22, 2016

Poster presentations

Lopez FL, Bowles BJ, Dziemidowicz K, Orlu M, Tuleu C, Ernest TB and Edwards A. *Co-processed Excipients for Dispersible Tablets: Manufacturability*. AAPS Annual Meeting and Exposition, November 2017, San Diego, CA, USA.

Dziemidowicz K, Lopez FL, Bowles BJ, Edwards A, Ernest TB, Orlu M and Tuleu C. *Co-processed Excipients for Dispersible Tablets: Patient Acceptability*. AAPS Annual Meeting and Exposition, November 2017, San Diego, CA, USA.

Lopez FL, Ernest TB, Orlu Gul M and Tuleu C. *Evaluation of palatability of multiparticulate formulations by a panel of adult volunteers*. 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, April 2016, Glasgow, UK.

Lopez FL, Soto J, Ernest TB, Orlu Gul M and Tuleu C. *Could rodents perceive oral grittiness? A pilot study*. 7th EuPFI Conference: 'Formulating Better Medicines for Children', September 2015, Antwerp, Belgium.

Lopez FL, Bowles A, Clapham D, Ernest TB, Lewis J, Orlu Gul M and Tuleu C. *Perception of oral grittiness: Influence of formulation variables*. 6th EuPFI Conference: 'Formulating Better Medicines for Children', September 2014, Athens, Greece.

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Annexes

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A4	Sponsor/ Other Organisations Involved and Funding
	a) Sponsor: <input checked="" type="checkbox"/> UCL <input type="checkbox"/> Other Institution If your project is sponsored by an institution other than UCL please provide details:
	b) Other Organisations: If your study involves another organisation, please provide details. Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request. c) Funding: What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? If study is funded solely by UCL this should be stated, the section should not be left blank.

A5	Signature of Head of Department or Chair of the Departmental Ethics Committee (This must not be the same signature as the Principal Researcher)
	I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it. The project is registered with the UCL Data Protection Officer, a formal signed risk assessment form has been completed, and appropriate insurance arrangements are in place. Links to details of UCL's policies on data protection, risk assessment, and insurance arrangements can be found at: http://ethics.grad.ucl.ac.uk/procedures.php
	UCL is required by law to ensure that researchers undergo a Disclosure and Barring Service (DBS) Check if their research project puts them in a position of trust with children under 18 or vulnerable adults.
	HEAD OF DEPARTMENT TO DELETE BELOW AS APPLICABLE
	I am satisfied that checks: (4) have been satisfactorily completed (2) have been initiated (3) are not required
	If checks are not required please clarify why below.
	This research does not involve children under 18 or vulnerable adults.
	Chair's Action Recommended: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<i>A recommendation for Chair's action can be based only on the criteria of minimal risk as defined in the Terms of Reference of the UCL Research Ethics Committee.</i>

PRINT NAME: Brian Pearce

SIGNATURE



DATE: 15/8/15

SECTION B

DETAILS OF THE PROJECT

B1	<p>Please provide a brief summary of the project in <u>simple prose</u> outlining the intended value of the project, giving necessary scientific background (max 500 words).</p> <p>Palatability is a critical property of an oral formulation which influences patient acceptability and thus have an impact on patient compliance with a drug regime. Palatability, as the overall sensation of a product in the mouth, is composed of various factors including taste, mouthfeel, smell and even appearance. Taste of pharmaceutical products is more common (yet not systematic) to assess while not many studies look at other parameters; for example, grittiness and mouthfeel which are considered important factors that influence the acceptability of products such as oral powders, granules and multiparticulates (i.e. pellets, beads or spheroids).</p> <p>Currently, there is no standardised methodology for the assessment of oral grittiness of multiparticulate formulations. The aim of this study is to conduct an in-vivo sensory analysis using human panels to optimise methodology to assess grittiness and overall palatability of multiparticulate products.</p> <p>Samples will be composed of 250 or 500 mg of microcrystalline cellulose pellets commercially available (Cellets, Pharmatrans Sanaq) of two different particle sizes: Cellets 200 (212-355 microns) and Cellets 500 (500-710 microns). The drug-free pellets will be given to volunteers either as a "dry dose" or pre-dispersed in water in order to assess the influence of both administration techniques on grittiness perception and to identify the most appropriate administration methodology. Participants will be asked to give feedback of "grittiness", "taste" and "dose volume" (i.e. amount of multiparticulates) using hedonic scales. Feedback of the volunteers on the dose given will help to select the most appropriate dose for future studies.</p> <p>The study will be conducted in two sessions: During the first session, the widely used "swirl and spit" method will be used, in which participants swirl a small volume of the test sample in their mouth for some seconds before spitting it out. During the second session of the study, volunteers will be asked to swallow a small number of samples (from those they have already assessed by swirl and spit). The second part of the study aims to assess the importance of swallowing on the perception of oral grittiness, palatability and acceptability of oral formulations. Comparison of results from the first and second part of the study will inform of the validity of the "swirl and spit" method for the assessment of grittiness and acceptability of oral formulations.</p> <p>In this study there is no medicine in the particles, they are just made of microcrystalline cellulose which is a naturally occurring product that is often used in foods and as a bulking agent in tablets and vitamin supplements. It is completely safe to take the amount of microcrystalline cellulose within these samples and it will have no pharmacological effect on the participants.</p> <p>The study is anticipated to provide valuable information for effective assessment of palatability and acceptability of multiparticulates which can be used in future studies to guide the development of new formulations that are more acceptable to patients.</p>
B2	<p>Briefly characterise in <u>simple prose</u> the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken (max 500 words).</p> <p>Research methodology: Single blind, sensory (palatability) evaluation of commercially available products (Annex 1 – Flow diagram).</p> <p>Inclusion criteria: Healthy male or female adults, able to understand and speak English (Annex 2 – Recruitment advertisement). If smoker, they have to forbear smoking at least one hour before and during all the tests.</p> <p>Exclusion criteria: Antecedent deterioration of taste or smell. Recent dental care. Sensory disorders affecting the mouth or local anaesthetics into the mouth within 24 hours of the study. Swallowing dysfunction.</p> <p>Sample preparation: Placebo formulations (Cellets) will be given to subjects in a ready-to-administer form, either in dry form or pre-suspended in water.</p>

	<p>Samples will be prepared under strict quality measures in a dedicated area under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621; Sejal Ranmal 2074443) and according to standard operating procedures that have been approved by the PI, departmental safety officer and head of department Annex 3 – Standard Operating Procedures).</p> <p>Experimental protocol: First session – Swirl and Spit method – Samples numbered with a random code will be presented in a randomised order. Participants will "swirl" the sample within the mouth for 5 and then spit the sample into a receptacle provided. Immediately upon expectoration, they will rate the sample using a computerised questionnaire with categorical scales (Annex 4 - data collection form). Before and after each sample, participants will rinse their mouth with water. Participants will have access to plain unsalted crackers to clean their palate. An interval of 5 to 10 minutes will be respected between samples. All participants will taste a total of 8 samples. Second session – Swallowing method – Samples numbered with a random code will be presented in a randomised order. Participants will be asked to swallow the whole sample with the aid of water, but they will be alerted of the possibility to reject one or more samples if they don't feel confident to swallow the sample safely. Immediately, they will rate the sample using a computerised questionnaire (Qualtrics) with categorical scales (Annex 4 - data collection form). Before and after each sample, participants will rinse their mouth with water. Participants will have access to plain unsalted crackers to clean their palate. An interval of 5 to 10 minutes will be respected between samples. Participants will taste a maximum of 8 samples.</p> <p>Data processing and analysis: Multisample difference test: rating approach – evaluation by ANOVA with a statistical significance $p=0.05$ and post-hoc analysis [Tukey's honestly significant difference (HSD) test].</p> <p><i>Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).</i></p>
<p>B3</p>	<p>Where will the study take place (please provide name of institution/department)? If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998?</p> <p>UCL School of Pharmacy, in the pharmacy practice dispensary. Participants will be seated at individual computer stations and screened off from other volunteers.</p> <p>Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test).</p>
<p>B4</p>	<p>Have collaborating departments whose resources will be needed been informed and agreed to participate? <i>Attach any relevant correspondence.</i></p> <p>N/A</p>
<p>B5</p>	<p>How will the results be disseminated, including communication of results with research participants?</p> <p>Once recruited, participants will be assigned individual, anonymous codes only accessible by the researchers. The final results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations. A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. In such cases, an abstract of the overall outcomes will be shared with participants.</p> <p>Confidentiality will be maintained when results are disseminated. As the outcomes of the research do not lead to direct benefit to the participants involved, collecting and storing personal contact information has not been deemed justifiable simply for the purposes of disseminating the end results. Instead participants will be able to request and obtain the results themselves, if they wish to do so.</p>

B6	<p>Please outline any ethical issues that might arise from the proposed study and how they are addressed. Please note that all research projects have some ethical considerations so do not leave this section blank.</p> <p>Confidentiality: This study will not be intrusive since minimum personal data will be recorded (contact details, date of birth and gender). Participants will be assigned anonymous codes that are only accessible to the research team, and confidentiality will be maintained throughout the study and when results are disseminated. It will not be possible to identify individual participants from any publications.</p> <p>Participant burden: Test sessions will be restricted to a maximum of 2 hours to reduce burden on participants and minimise fatigue. There is a potential for the participants to suffer from temporary oral discomfort during tasting if the grittiness of the oral suspension is marked, although this is considered to be an unlikely event. If some participants show high discomfort the assessment will be immediately stopped. We have attempted to narrow down the number of samples to taste in order to reduce any inconvenience.</p> <p>Adverse events: The formulations are placebo (do not contain any active pharmaceutical ingredient). The potential for adverse effects, risks or hazards by swallowing of the formulation is therefore negligible. Moreover subjects have to rinse their mouth with water before and after each tasting.</p> <p>There is a potential for accidental choking while tasting and swallowing of the formulations tested, however this is considered to be a very unlikely event and based on previous experience of our research group. The dose given is based on paediatric indications (0.5g) and it is considered to be very safe and easy to swallow for adults with no swallowing dysfunction. Participants can refuse ingestion of any of the samples at any point during the study if they feel not capable or not comfortable swallowing the sample.</p> <p>If something should go wrong, first aid will be sought as necessary and the experiment will be stopped. We can seek for medical help on the premises (Dr Yucheng Sheng, MD; Dr Kirsten Harvey, MD). If someone complains, the supervisor or a third party (not directly involved in research team) Ms Joanna O'Brien (Institute Manager) can be contacted for further advice.</p> <p>The research team has previous experience in taste assessment studies using the swirl and spit method and sensory evaluations including swallowing of placebo formulations. The principal investigator has considerable experience of conducting and supervising such studies using volunteer panels including the following research:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Project ID</th> <th style="text-align: left;">Project Title</th> <th style="text-align: left;">Start Date</th> </tr> </thead> <tbody> <tr> <td>0851/001</td> <td>Bitterness-masking Evaluation of Pharmaceutical Excipients</td> <td>09/11/2008</td> </tr> <tr> <td>4612/001</td> <td>Amlodipine palatability assessment study</td> <td>18/03/2013</td> </tr> <tr> <td>4612/002</td> <td>Capsule acceptability study (CAPS): assessing the attributes influencing end-user attitudes</td> <td>28/02/2014</td> </tr> <tr> <td>4612/003</td> <td>Piperaquine Palatability Assessment Study</td> <td>01/03/2014</td> </tr> <tr> <td>4612/004</td> <td>Assessing the palatability of a novel asthma medicine</td> <td>02/02/2015</td> </tr> <tr> <td>4612/005</td> <td>Bitterness assessment of model Active Pharmaceutical Ingredients (APIs)</td> <td>02/02/2015</td> </tr> <tr> <td>4612/006</td> <td>Palatability assessment of three model Active Pharmaceutical Ingredients (APIs) in two platform dispersible tablet formulations</td> <td>18/03/2015</td> </tr> </tbody> </table>	Project ID	Project Title	Start Date	0851/001	Bitterness-masking Evaluation of Pharmaceutical Excipients	09/11/2008	4612/001	Amlodipine palatability assessment study	18/03/2013	4612/002	Capsule acceptability study (CAPS): assessing the attributes influencing end-user attitudes	28/02/2014	4612/003	Piperaquine Palatability Assessment Study	01/03/2014	4612/004	Assessing the palatability of a novel asthma medicine	02/02/2015	4612/005	Bitterness assessment of model Active Pharmaceutical Ingredients (APIs)	02/02/2015	4612/006	Palatability assessment of three model Active Pharmaceutical Ingredients (APIs) in two platform dispersible tablet formulations	18/03/2015
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SECTION C	DETAILS OF PARTICIPANTS
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C1	<p>Participants to be studied</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%;">C1a. Number of volunteers:</td> <td style="text-align: center;">24</td> </tr> <tr> <td>Upper age limit:</td> <td style="text-align: center;">40</td> </tr> <tr> <td>Lower age limit:</td> <td style="text-align: center;">18</td> </tr> </table> <p>C1b. Please justify the age range and sample size:</p>	C1a. Number of volunteers:	24	Upper age limit:	40	Lower age limit:	18
C1a. Number of volunteers:	24						
Upper age limit:	40						
Lower age limit:	18						

Sample size: N > 20 as this number are within the range of sample size of previous studies regarding taste assessment of medicines with non-trained panels and it is enough to apply statistics.

Age range: Taste sensitivity is known to vary with age, therefore "young adults" will be recruited in this study to resemble the paediatric population as closely as possible.

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

N/A

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

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

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

Yes No

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

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

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

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

C5 **Recruitment**

(i) Describe how potential participants will be identified:

Participants will be students and staff at UCL and potentially others outside UCL who receive the advertising email and meet the inclusion/exclusion criteria (healthy adults aged 18 to 40 years).

(ii) Describe how potential participants will be approached:

An email (annex 2) will be circulated using UCL announce to advertise the study. If needed a printed advertisement will also be placed around the School of Pharmacy. Potential volunteers interested in taking part will be invited to contact the research team directly using the contact details in these advertisements.

(iii) Describe how participants will be recruited:

Potential participants who show interest and contact the research team will be provided with a copy of the information sheet for their perusal. They will have at least 24 hours to consider whether or not to take part, and will be invited to ask questions or obtain further information if necessary. Those who decide to participate will then contact the research team to arrange suitable dates and times to undertake the study. Prior to the first session, a member of the research team will orally explain the study and take informed consent from the participant.

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

C6	<p>Will the participants participate on a fully voluntary basis? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Will UCL students be involved as participants in the research project? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.</i></p> <p>Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?</p> <p>Although stated in the information sheet and consent form, all participants will be reminded that their participation is completely optional and unrelated to the outcomes of their study and that it will not affect their relationship with the research team or with UCL (e.g. teaching matters).</p>
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C7	<p>CONSENT</p> <p>Please describe the process you will use when seeking and obtaining consent.</p> <p>The form attached will be used to obtain informed consent from participants. Those who initially show interest in the study (from the advertisements used) will contact the research team and be provided with the study information sheet. Following consideration, those willing to participate will contact the research team to be recruited onto the study. Prior to the first session, a member of the research team will orally explain the study to the participant, confirm their eligibility and answer any questions if necessary. The researcher will review the consent form with the participant to ensure all of the statements are well understood, and additional time to read the form will be provided if necessary. Two copies of the consent form will be signed, one for the participant and another to be retained by the research team.</p> <p><i>A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.</i></p> <p>In cases where it is not proposed to obtain the participants informed consent, please explain why below.</p>
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C8	<p>Will any form of deception be used that raises ethical issues? If so, please explain.</p> <p>No</p>
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C9	<p>Will you provide a full debriefing at the end of the data collection phase? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If 'No', please explain why below.</p>
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C10	<p>Information Sheets And Consent Forms</p> <p>A poorly written information sheet(s) and consent form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the information sheet and consent form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide information sheets and consent forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written information sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.</p>
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UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE



Optimisation of research methodology for grittiness assessment

Participant Information Sheet

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

This study has been approved by the UCL Research Ethics Committee
Project ID Number: REC 4612/007

Principal Investigator: Dr Catherine Tuleu
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5857
Email: c.tuleu@ucl.ac.uk

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

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

Details of the Study

What is the purpose and aim of this project?

Palatability is a critical property of an oral formulation which influences patient acceptability and thus have an impact on patient compliance. Palatability, as the overall sensation of a product in the mouth, is composed of various factors including taste, mouthfeel, smell and even appearance. Particularly, grittiness and mouthfeel are considered important factors that influence the acceptability of oral medicines such as oral powders, granules and multiparticulates (i.e. pellets, beads or spheroids).

The aim of this study is to conduct an in-vivo sensory analysis using human taste panels to find out the best way to assess the palatability of oral multiparticulates. The samples tested do not contain any medicine. They are composed of microcrystalline cellulose which is a naturally occurring product that is often used in foods and as a bulking agent in tablets and vitamin supplements.

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 40 years to take part.

If you have problems with the sense of taste or smell or if you have had any dental care or if you have any swallowing dysfunction, then unfortunately you will be unable to take part.

8

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL during 2 sessions over a 2-week period. You will be asked to commit less than 3 hours in total. If you decide to take part, you will be asked to attend both sessions.

During the first session we will ask you to place in your mouth various samples of microcrystalline cellulose particles; we will ask you to swirl the sample in the mouth for 5 seconds and then spit it out. We will ask you to rate the grittiness of the samples (i.e. rough mouth feel due to the presence of particles), the taste of the sample and the dose (i.e. the amount that you had to take). You will be asked to rinse your mouth out with water before and after each test.

During the second session we will ask you to swallow a small number of samples (8 or less) from those tested during the first session. We will ask you to rate the ease of swallowing of the sample, and we will ask you to rate again the grittiness of the sample, its taste and the amount taken. You will be asked to rinse your mouth out before and after each test. You will be allowed to reject ANY of the samples at any point of the study if you don't feel capable or confident enough to swallow it.

Are there any risks involved?

The samples you will be testing are placebo, this means there is no medicine in their composition.

If the samples you taste/swallow are very gritty, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples and vomit, however this is extremely rare. Nevertheless, a delay of 5 to 10 minutes will be respected between each tested solution to minimise fatigue and discomfort.

If you experience nausea or pain you must alert a member of the team and we will stop the study immediately. The researchers are trained in First Aid and medical doctors will be present to assess the situation. If necessary, we will also contact emergency services.

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

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

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

Who can I contact for more information?

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

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

Ms Joanna O'Brien
Institute Manager
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5814
Email: joanna.o'brien@ucl.ac.uk

Thank you for taking the time to read this information sheet



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

Title of Project: **Optimisation of research methodology for grittiness assessment**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): **4612/007**

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

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

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that I should not take part if I have had any dental care or medicinal treatment (except contraceptives) during the 15 days before the tests.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately without penalty.
- consent to the processing of my personal information for the purposes of this research study.
- understand that the information I have submitted will be published as a report and I can request a copy by contacting the researchers. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

Signed:

Date:

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

D1	<p>Have UCL's Risk Assessment Procedures been followed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If No, please explain.</p> <p>There is no significant risk - See annex 5 for UCL risk assessment form.</p>
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D2	<p>Does UCL's Insurer need to be notified about your project before Insurance cover can be provided? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.</i></p> <p>If Yes, please provide confirmation that the appropriate insurance cover has been agreed. Please attach your UCL insurance registration form and any related correspondence.</p>
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D3	<p>Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).</p> <p>This project hold little risk to the research which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.</p>
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D4	<p>Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please describe the nature of the risk or stress and how you will minimise and monitor it.</p> <p>The procedures may cause temporary physical discomfort (exposure to unpleasant mouth feel) during tasting if the test samples are very gritty. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, before and after each test sample, subjects will rinse their mouth with water. The participants will be provided with necessary instruction on properly testing the samples. The level of discomfort may evolve during the study. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the tasting will be immediately stopped.</p>
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D5	<p>Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?</p> <p>If Yes, please explain how you will deal with this.</p> <p>None</p>
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D6	<p>Please describe any expected benefits to the participant.</p> <p>Indirect benefit through contribution to patient care.</p> <p>Participants will contribute to the development of objective methodology for the assessment of oral grittiness which can be used in future studies. Participants will also contribute to increasing the knowledge of palatability and in particular grittiness of oral formulations. This will support the development of new formulations such as dispersible tablets and powders/granules for oral administration.</p>
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D7	<p>Specify whether the following procedures are involved:</p> <p>Any invasive procedure(s) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Physical contact <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Any procedure(s) that may cause mental distress <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Please state briefly any precautions being taken to protect the health and safety of the research participants.</p>
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D8	<p>Does the research involve the use of drugs? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please name the drug/product and its intended use in the research and then complete Appendix I</p> <p>Does the project involve the use of genetically modified materials? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, has approval from the Genetic Modification Safety Committee been obtained for work? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please quote the Genetic Modification Reference Number:</p>
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D9	<p>Will any non-ionising radiation be used on the research participant(s)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix II.</p>
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D10	<p>Are you using a medical device in the UK that is CE-marked and is being used within its product indication? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix III.</p>
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CHECKLIST

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

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

Please note that correspondence regarding the application will normally be sent to the Principal Researcher and copied to other named individuals.

2. REC application related to study presented in Chapter 3

UCL RESEARCH ETHICS COMMITTEE



8

**IMPORTANT: ALL FIELDS MUST BE COMPLETED. THE FORM SHOULD BE COMPLETED IN PLAIN ENGLISH UNDERSTANDABLE TO LAY COMMITTEE MEMBERS.
SEE NOTES IN STATUS BAR FOR ADVICE ON COMPLETING EACH FIELD. YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.**

APPLICATION FORM

SECTION A		APPLICATION DETAILS	
A1	Project Title: Sensory evaluation of oral multiparticulate formulations		
	Date of Submission: 08/01/2016	Proposed Start Date: 01/02/2016	
	UCL Ethics Project ID Number: 4612/010	Proposed End Date: 01/08/2016	
	If this is an application for classroom research as distinct from independent study courses, please provide the following additional details: Course Title: N/A Course Number: N/A		
A2	Principal Researcher <i>Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.</i>		
	Full Name: Dr Catherine Tuleu	Position Held: Reader in Pharmaceutics/Director of the Centre for Paediatric Pharmacy Research	
	Address: UCL School of Pharmacy 29-39 Brunswick square London WC1N 1AX	Email: c.tuleu@ucl.ac.uk	
		Telephone: 0207 753 5857	
		Fax: 02077535942	
Declaration To be Signed by the Principal Researcher			
<ul style="list-style-type: none"> ▪ I have met with and advised the student on the ethical aspects of this project design (<i>applicable only if the Principal Researcher is not also the Applicant</i>). ▪ I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: n/a ▪ I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the Data Protection Act 1998. My Data Protection Registration Number is: Z6364106/2015/12/31 ▪ I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements. ▪ I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee. ▪ I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate hazards to the participant. ▪ I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee. ▪ I will undertake to provide notification when the study is complete and if it fails to start or is abandoned. 			

SIGNATURE



DATE

16-12-15

A3	Applicant(s) Details <i>(If Applicant is not the Principal Researcher e.g. student details):</i>	
	Full Name: Felipe Lopez	
	Position Held: PhD Student	
	Address: UCL School of Pharmacy 29-39 Brunswick square London WN1C 1AX	Email: felipe.lopez.13@ucl.ac.uk
		Telephone: 02077535975
		Fax: 02077535942
	Full Name:	
Position Held:		
Address:		
	Email:	
	Telephone:	
	Fax:	

A4	Sponsor/ Other Organisations Involved and Funding
	a) Sponsor: <input checked="" type="checkbox"/> UCL <input type="checkbox"/> Other Institution If your project is sponsored by an Institution other than UCL please provide details:
	b) Other Organisations: If your study involves another organisation, please provide details. Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request. c) Funding: What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? If study is funded solely by UCL this should be stated, the section should not be left blank.

A5	Signature of Head of Department or Chair of the Departmental Ethics Committee <i>(This must not be the same signature as the Principal Researcher)</i>
	I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it. The project is registered with the UCL Data Protection Officer, a formal signed risk assessment form has been completed, and appropriate insurance arrangements are in place. Links to details of UCL's policies on data protection, risk assessment, and insurance arrangements can be found at: http://ethics.grad.ucl.ac.uk/procedures.php
	UCL is required by law to ensure that researchers undergo a Disclosure and Barring Service (DBS) Check if their research project puts them in a position of trust with children under 18 or vulnerable adults.
	HEAD OF DEPARTMENT TO DELETE BELOW AS APPLICABLE
	I am satisfied that checks: (1) have been satisfactorily completed (2) have been initiated (3) are not required
	If checks are not required please clarify why below.
	The study does not involve children under 18 or vulnerable adults.
	Chair's Action Recommended: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	A recommendation for Chair's action can be based only on the criteria of minimal risk as defined in the Terms of Reference of the UCL Research Ethics Committee.

PRINT NAME:



SIGNATURE:

DATE:

16/12/15

SECTION B

DETAILS OF THE PROJECT

B1	<p>Please provide a brief summary of the project in <u>simple prose</u> outlining the intended value of the project, giving necessary scientific background (max 500 words).</p> <p>Multiparticulate formulations, which are composed of multiple solid units of small size (pellets, beads or spheroids), are a suitable alternative for the oral administration of medicines to patients that cannot swallow big solid formulations (e.g. tablets or capsules) such as children. Multiparticulates can be coated with a polymeric film which allows taste masking of unpleasant actives, improving palatability. The most important barrier for the development of new multiparticulate formulations is the lack of information regarding their palatability (especially in terms of oral grittiness and mouthfeel) and overall patient's acceptability. Studies in this area are required to enable the development of new medicines that are suitable for such patient populations in need.</p> <p>The aim of this study is to conduct an in-vivo sensory analysis using human taste panels to assess the palatability and acceptability of multiparticulate formulations. The main parameters that will be assessed is the influence of particle size and the presence of polymeric film coating on grittiness perception, overall palatability and acceptability of multiparticulates.</p> <p>Samples will be composed of 500 mg of microcrystalline cellulose pellets (Cellets) of different particle size (below 1mm in all cases), either coated with a polymeric film or uncoated. The drug-free pellets will be given to volunteers pre-dispersed in a small amount of water to aid administration. Participants will have free access to water at all times to help swallow the sample and clean their palate. Palatability of the samples will be assessed using a questionnaire that includes a 5-point hedonic facial scales and additional voluntary participant feedback. The assessment methodology employed in this study has been previously optimised in a preliminary trial conducted by our research team (REC 4612/007).</p> <p>In this study there is no medicine in the particles, they are made of microcrystalline cellulose which is a naturally occurring product that is often used in food and as a bulking agent in tablets. The particles will be manufactured by Glatt under GMP conditions and sourced from Pfizer. Some of the Cellets used in this study will be coated at Pfizer. The coating includes a polymer (Kollicoat Smart Seal 30D, BASF Pharma Ingredients) usually employed for taste masking, a plasticiser (triethyl citrate), an antioxidant (butylated hydroxytoluene) and an anti-tacking agent (talc), commonly used to coat dosage forms. Individual COSHH assessment for each substance have been carried out based on their maximum daily intake. It is completely safe to take the amount of excipients contained within these samples and samples will have no pharmacological effect on the participants.</p> <p>The study is anticipated to provide valuable information regarding the influence of particle size and the presence/absence of polymeric coating on acceptability of multiparticulates which can be used to guide the development of new formulations that are more acceptable to patients.</p>
B2	<p>Briefly characterise in <u>simple prose</u> the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken (max 500 words).</p> <p>Research methodology: Single blind, randomised, sensory evaluation of multiparticulate formulations (Annex 1 – Flow diagram).</p> <p>Inclusion criteria: Healthy male or female adults, able to understand and speak English (Annex 2 – Recruitment advertisement). If smoker, they have to forbear smoking at least one hour before and during all the tests.</p> <p>Exclusion criteria: Antecedent deterioration of taste or smell. Recent dental care. Sensory disorders affecting the mouth or local anaesthetics into the mouth within 24 hours of the study. Swallowing dysfunction.</p> <p>Sample preparation: Placebo formulations (Cellets) will be given to subjects in a ready-to-administer form, pre-suspended in water. Samples will be composed of 500 mg of coated or uncoated Cellets of one of the following particle size fractions: Cellets 200 (200-355 µm), Cellets 350 (350-500 µm), Cellets 500 (500-750 µm) or Cellets</p>

	<p>700 (700-1000 µm). Samples will be weight out and dispersed in water under strict quality measures in a dedicated area under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621; Sejal Ranmal 2074443) and according to standard operating procedures that have been approved by the PI, departmental safety officer and head of department (Annex 3 – Standard Operating Procedures).</p> <p>Experimental protocol: Phase 1 – Crossover study, hedonic scaling. Volunteers will be divided in two groups: <u>Group A</u> will test 3 samples of <u>coated multiparticulates first</u> (in a randomised order) and 3 samples of uncoated multiparticulates later (in a randomised order); whereas <u>Group B</u> will test 3 samples of <u>uncoated multiparticulates first</u> (randomised order) and 3 samples of coated multiparticulates later (randomised order). Thus, each volunteer will test a maximum of 6 samples in this phase. Only the three smallest particle size fractions will be included in this phase (Cellets 200, 350 and 500). Participants will be asked to swallow each sample with the aid of water, but they will be alerted of the possibility to reject one or more samples if they don't feel confident to swallow the sample safely. Immediately after sample ingestion, they will rate the sample using a computerised questionnaire (Qualtrics) with categorical scales (Annex 4 - data collection form). Participants will have free access to water to aid swallowing and/or rinse their palate. An interval of 5 to 10 minutes will be respected between samples.</p> <p>Phase 2 – Direct comparison of sample pairs. Participants will receive coated and uncoated samples of two different particle sizes in pairs. Participants will test 4 different sample pairs in this phase (i.e. 8 samples). A larger particle size fraction (Cellets 700) will be included in Phase 2 if the smaller particles (Cellets 200, 350 and 500) were considered fairly acceptable by the majority of participants on Phase 1. Participants will be asked to swallow each sample with the aid of water, but they will be alerted of the possibility to reject one or more samples. Immediately after sample ingestion, they will rate the samples by direct comparison between samples in each pair using a computerised questionnaire (Qualtrics) Annex 4 - data collection form). Participants will have free access to water to aid swallowing and/or rinse their palate. An interval of 5 to 10 minutes will be respected between each pair of samples.</p> <p>Data processing and analysis: Multisample difference test: rating approach – evaluation by ANOVA with a statistical significance $p=0.05$ and post-hoc analysis [Tukey's honestly significant difference (HSD) test].</p> <p><i>Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).</i></p>
<p>B3</p>	<p>Where will the study take place (please provide name of Institution/department)? If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998?</p> <p>UCL School of Pharmacy, in the pharmacy practice dispensary. Participants will be seated at individual computer stations and screened off from other volunteers.</p> <p>Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test).</p>
<p>B4</p>	<p>Have collaborating departments whose resources will be needed been informed and agreed to participate? <i>Attach any relevant correspondence.</i></p> <p>N/A</p>
<p>B5</p>	<p>How will the results be disseminated, including communication of results with research participants?</p> <p>Once recruited, participants will be assigned individual, anonymous codes only accessible by the researchers. The final results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations. A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. In such cases, an abstract of the overall outcomes will be shared with participants.</p>

B6	<p>Please outline any ethical issues that might arise from the proposed study and how they are be addressed. Please note that all research projects have some ethical considerations so do not leave this section blank.</p> <p>Confidentiality: This study will not be intrusive since minimum personal data will be recorded (contact details, date of birth and gender). Participants will be assigned anonymous codes that are only accessible to the research team, and confidentiality will be maintained throughout the study and when results are disseminated. It will not be possible to identify individual participants from any publications.</p> <p>Participant burden: Test sessions will be restricted to a maximum of 2 hours to reduce burden on participants and minimise fatigue. There is a potential for the participants to suffer from temporary oral discomfort during tasting if the grittiness of the oral suspension is marked, although this is considered to be an unlikely event. If some participants show high discomfort the assessment will be immediately stopped. We have attempted to narrow down the number of samples to taste in order to reduce any inconvenience.</p> <p>Adverse events: The formulations are placebo (do not contain any active pharmaceutical ingredient). The potential for adverse effects, risks or hazards by swallowing of the formulation is therefore negligible. There is a potential for accidental choking while tasting and swallowing of the formulations tested, however this is considered to be a very unlikely event and based on previous experience of our research group. The dose given is considered to be very safe and easy to swallow for adults with no swallowing dysfunction. Participants can refuse ingestion of any of the samples at any point during the study if they feel not capable or not comfortable swallowing the sample.</p> <p>If something should go wrong, first aid will be sought as necessary and the experiment will be stopped. We can seek for medical help on the premises (Dr Kirsten Harvey, MD). If someone complains, the supervisor or a third party (not directly involved in research team) Ms Joanna O'Brien (Institute Manager) can be contacted for further advice.</p> <p>The research team has previous experience in taste assessment studies using the swirl and spit method and sensory evaluations including swallowing of placebo formulations. The methodology employed in this study has been previously optimised in a preliminary trial conducted by our research team (REC 4612/007). The principal investigator has considerable experience of conducting and supervising such studies using volunteer panels including the following research:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Project ID</th> <th style="text-align: left;">Project Title</th> <th style="text-align: left;">Start Date</th> </tr> </thead> <tbody> <tr> <td>0851/001</td> <td>Bitterness-masking Evaluation of Pharmaceutical Excipients</td> <td>09/11/2006</td> </tr> <tr> <td>4612/001</td> <td>Amlodipine palatability assessment study</td> <td>18/03/2013</td> </tr> <tr> <td>4612/002</td> <td>Capsule acceptability study (CAPS): assessing the attributes influencing end-user attitudes</td> <td>28/02/2014</td> </tr> <tr> <td>4612/003</td> <td>Piperaquine Palatability Assessment Study</td> <td>01/03/2014</td> </tr> <tr> <td>4612/004</td> <td>Assessing the palatability of a novel asthma medicine</td> <td>02/02/2015</td> </tr> <tr> <td>4612/005</td> <td>Bitterness assessment of model Active Pharmaceutical Ingredients (APIs)</td> <td>02/02/2015</td> </tr> <tr> <td>4612/006</td> <td>Palatability assessment of three model Active Pharmaceutical Ingredients (APIs) in two platform dispersible tablet formulations</td> <td>16/03/2015</td> </tr> <tr> <td>4612/007</td> <td>Optimisation of research methodology for grittiness assessment</td> <td>16/09/2015</td> </tr> </tbody> </table>	Project ID	Project Title	Start Date	0851/001	Bitterness-masking Evaluation of Pharmaceutical Excipients	09/11/2006	4612/001	Amlodipine palatability assessment study	18/03/2013	4612/002	Capsule acceptability study (CAPS): assessing the attributes influencing end-user attitudes	28/02/2014	4612/003	Piperaquine Palatability Assessment Study	01/03/2014	4612/004	Assessing the palatability of a novel asthma medicine	02/02/2015	4612/005	Bitterness assessment of model Active Pharmaceutical Ingredients (APIs)	02/02/2015	4612/006	Palatability assessment of three model Active Pharmaceutical Ingredients (APIs) in two platform dispersible tablet formulations	16/03/2015	4612/007	Optimisation of research methodology for grittiness assessment	16/09/2015
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SECTION C	DETAILS OF PARTICIPANTS
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C1	<p>Participants to be studied</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">C1a. Number of volunteers:</td> <td>70-80</td> </tr> <tr> <td>Upper age limit:</td> <td>40</td> </tr> <tr> <td>Lower age limit:</td> <td>18</td> </tr> </table>	C1a. Number of volunteers:	70-80	Upper age limit:	40	Lower age limit:	18
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Upper age limit:	40						
Lower age limit:	18						

	<p>C1b. Please justify the age range and sample size:</p> <p>Sample size: N > 20 as this number are within the range of sample size of previous studies regarding taste assessment of medicines with non-trained panels and it is enough to apply statistics.</p> <p>Targeted sample size = 70-80 to allow comparison with a previous study conducted in children in which 71 children volunteers took part.</p> <p>Age range: Taste sensitivity is known to vary with age, therefore "young adults" will be recruited in this study to resemble the paediatric population as closely as possible.</p>
<p>C2</p>	<p>If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the UK Data Protection Act 1998.</p> <p>N/A</p>
<p>C3</p>	<p>Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>How will you ensure that participants in these groups are competent to give consent to take part in this study? If you have relevant correspondence, please attach it.</p>
<p>C4</p>	<p>Will payment or any other incentive, such as gift service or free services, be made to any research participant?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.</p> <p>Participants will be paid £10 per session in cash. This will be paid from the GL account of the PI. Before and during any part of the study, participants will have the option to withdraw if they wish.</p> <p>Please justify the payment/other incentive you intend to offer.</p> <p>This is a thank you gesture for time committed to the project.</p>
<p>C5</p>	<p>Recruitment</p> <p>(I) Describe how potential participants will be identified:</p> <p>Participants will be students and staff at UCL and potentially others outside UCL who receive the advertising email and meet the inclusion/exclusion criteria (healthy adults aged 18 to 40 years).</p> <p>(II) Describe how potential participants will be approached:</p> <p>An email (annex 2) will be circulated using UCL announce to advertise the study. If needed a printed advertisement will also be placed around the School of Pharmacy. Potential volunteers interested in taking part will be invited to contact the research team directly using the contact details in these advertisements.</p> <p>(III) Describe how participants will be recruited:</p> <p>Potential participants who show interest and contact the research team will be provided with a copy of the information sheet for their perusal. They will have at least 24 hours to consider whether or not to take part, and will be invited to ask questions or obtain further information if necessary. Those who decide to participate will then contact the research team to arrange suitable dates and times to undertake the study. Prior to the first session, a member of the research team will orally explain the study and take informed consent from the participant.</p> <p>Attach recruitment emails/adverts/webpages. A data protection disclaimer should be included in the text of such literature.</p>

C6	Will the participants participate on a fully voluntary basis? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	Will UCL students be involved as participants in the research project? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p><i>If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.</i></p> <p>Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?</p> <p>Although stated in the information sheet and consent form, all participants will be reminded that their participation is completely optional and unrelated to the outcomes of their study and that it will not affect their relationship with the research team or with UCL (e.g. teaching matters).</p>	

C7	<p>CONSENT</p> <p>Please describe the process you will use when seeking and obtaining consent.</p> <p>The form attached will be used to obtain informed consent from participants. Those who initially show interest in the study (from the advertisements used) will contact the research team and be provided with the study information sheet. Following consideration, those willing to participate will contact the research team to be recruited onto the study. Prior to the first session, a member of the research team will orally explain the study to the participant, confirm their eligibility and answer any questions if necessary. The researcher will review the consent form with the participant to ensure all of the statements are well understood, and additional time to read the form will be provided if necessary. Two copies of the consent form will be signed, one for the participant and another to be retained by the research team.</p> <p><i>A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.</i></p> <p>In cases where it is not proposed to obtain the participants informed consent, please explain why below.</p>
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C8	<p>Will any form of deception be used that raises ethical issues? If so, please explain.</p> <p>No</p>
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C9	<p>Will you provide a full debriefing at the end of the data collection phase? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If 'No', please explain why below.</p>
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C10	<p>Information Sheets And Consent Forms</p> <p>A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.</p>
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UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE



Sensory evaluation of oral multiparticulate formulations

Participant Information Sheet

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

This study has been approved by the UCL Research Ethics Committee
Project ID Number: REC 4612/010

Principal Investigator: Dr Catherine Tuleu
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5857
Email: c.tuleu@ucl.ac.uk

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

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

Details of the Study

What is the purpose and aim of this project?

The aim of this study is to conduct an in-vivo sensory analysis using human taste panels to assess the palatability and acceptability oral multiparticulates (i.e. pellets, beads or spheroids) of various particle sizes.

The study is anticipated to provide valuable information regarding the influence of particle size on palatability and acceptability of multiparticulates which can be used to guide the development of new formulations that are more acceptable to patients.

The samples tested do not contain any medicine. They are composed of microcrystalline cellulose which is a naturally occurring product that is often used in foods and as a bulking agent in tablets and vitamin supplements.

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 40 years to take part.

If you have problems with the sense of taste or smell or if you have had any recent dental care or if you have any swallowing dysfunction, then unfortunately you will be unable to take part.

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL. You will be asked to commit to 2 sessions of less than 2 hours each.

During each session we will ask you to swallow a small number of samples (8 or less) and then rate the ease of swallowing of the sample, the grittiness of the samples (i.e. rough mouth feel due to the presence of particles), the taste of the sample and the dose (i.e. the amount that you had to take) and other parameters related to palatability and acceptability. You will be asked to rinse your mouth out before and after each test and will be provided with free access to water.

You will be allowed to reject ANY of the samples at any point of the study if you don't feel capable or confident enough to swallow it.

Are there any risks involved?

The samples you will be testing are placebo, this means there is no medicine in their composition.

If the samples you taste/swallow are very gritty, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples and vomit, however this is extremely rare. Nevertheless, a delay of 5 to 10 minutes will be respected between each tested solution to minimise fatigue and discomfort.

If you experience nausea or pain you must alert a member of the team and we will stop the study immediately. The researchers are trained in First Aid and medical doctors will be present to assess the situation. If necessary, we will also contact emergency services.

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

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

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

Who can I contact for more information?

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

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

Ms Joanna O'Brien
Institute Manager
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5814
Email: joanna.o'brien@ucl.ac.uk

Thank you for taking the time to read this information sheet



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

Title of Project: **Sensory evaluation of oral multiparticulate formulations**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): **4612/010**

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

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

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that I should not take part if I have had any dental care or medicinal treatment (except contraceptives) during the 15 days before the tests.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately without penalty.
- consent to the processing of my personal information for the purposes of this research study.
- understand that the information I have submitted will be published as a report and I can request a copy by contacting the researchers. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

Signed:

Date:

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

D1	<p>Have UCL's Risk Assessment Procedures been followed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If No, please explain.</p> <p>There is no significant risk - See annex 5 for UCL risk assessment form.</p>
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D2	<p>Does UCL's Insurer need to be notified about your project before Insurance cover can be provided? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.</i></p> <p>If Yes, please provide confirmation that the appropriate insurance cover has been agreed. Please attach your UCL insurance registration form and any related correspondence.</p>
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D3	<p>Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).</p> <p>This project hold little risk to the research which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.</p>
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D4	<p>Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please describe the nature of the risk or stress and how you will minimise and monitor it.</p> <p>The procedures may cause temporary physical discomfort (exposure to unpleasant mouth feel) during tasting if the test samples are very gritty. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, before and after each test sample, subjects will rinse their mouth with water. The participants will be provided with necessary instruction on properly testing the samples. The level of discomfort may evolve during the study. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the tasting will be immediately stopped.</p>
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D5	<p>Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?</p> <p>If Yes, please explain how you will deal with this.</p> <p>None</p>
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D6	<p>Please describe any expected benefits to the participant.</p> <p>Indirect benefit through contribution to patient care.</p> <p>Participants will contribute to increasing the knowledge of acceptability and in particular grittiness of oral multiparticulate formulations. This will support the development of new formulations for oral administration.</p>
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D7	<p>Specify whether the following procedures are involved:</p> <p>Any invasive procedure(s) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Physical contact <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Any procedure(s) that may cause mental distress <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Please state briefly any precautions being taken to protect the health and safety of the research participants.</p>
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D8	<p>Does the research involve the use of drugs? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please name the drug/product and its intended use in the research and then complete Appendix I</p> <p>Does the project involve the use of genetically modified materials? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, has approval from the Genetic Modification Safety Committee been obtained for work? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please quote the Genetic Modification Reference Number:</p>
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D9	<p>Will any non-ionising radiation be used on the research participant(s)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix II.</p>
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D10	<p>Are you using a medical device in the UK that is CE-marked and is being used within its product indication? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix III.</p>
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CHECKLIST

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

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

Please note that correspondence regarding the application will normally be sent to the Principal Researcher and copied to other named individuals.

3. REC application related to study presented in Chapter 4



IMPORTANT: ALL FIELDS MUST BE COMPLETED. THE FORM SHOULD BE COMPLETED IN PLAIN ENGLISH UNDERSTANDABLE TO LAY COMMITTEE MEMBERS.
SEE NOTES IN STATUS BAR FOR ADVICE ON COMPLETING EACH FIELD. YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.

APPLICATION FORM

SECTION A		APPLICATION DETAILS		
A1	Project Title: Improving palatability of oral multiparticulate formulations using oral gels as suspending media			
	Date of Submission: 09/09/2016	Proposed Start Date: 26/09/2016		
	UCL Ethics Project ID Number: 4612/011	Proposed End Date: 31/03/2016		
	If this is an application for classroom research as distinct from Independent study courses, please provide the following additional details: Course Title: _____ Course Number: _____			
A2	Principal Researcher			
	<i>Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.</i>			
	Full Name: Dr Catherine Tuleu	Position Held: Reader in Pharmaceutics		
	Address: UCL School of Pharmacy 29-39 Brunswick square London WC1N 1AX	Email: c.tuleu@ucl.ac.uk		
		Telephone: 0207 753 5857		
Fax: 0207 753 5942				
Declaration To be Signed by the Principal Researcher <ul style="list-style-type: none"> ▪ I have met with and advised the student on the ethical aspects of this project design (<i>applicable only if the Principal Researcher is not also the Applicant</i>). ▪ I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: N/A <ul style="list-style-type: none"> ▪ I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the Data Protection Act 1998. My Data Protection Registration Number is: Z6364106/2016/08/45 ▪ I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements. ▪ I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee. ▪ I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate hazards to the participant. ▪ I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee. ▪ I will undertake to provide notification when the study is complete and if it fails to start or is abandoned. 				

SIGNATURE:

DATE:

A3	Applicant(s) Details (<i>If Applicant is not the Principal Researcher e.g. student details:</i>)	
	Full Name: Felipe Lopez	
	Position Held: Phd Student	
	Address: UCL School of Pharmacy 29-39 Brunswick square London WC1N 1AX	Email: felipe.lopez.13@ucl.ac.uk
		Telephone: 07784353745
		Fax: N/A

Full Name: N/A		
Position Held: N/A		
Address: N/A		
	Email: N/A	
	Telephone: N/A	
	Fax: N/A	

A4	Sponsor/ Other Organisations Involved and Funding
	a) Sponsor: <input checked="" type="checkbox"/> UCL <input type="checkbox"/> Other Institution
	If your project is sponsored by an Institution other than UCL please provide details: N/A
	b) Other Organisations: If your study involves another organisation, please provide details. Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request. N/A
c) Funding: What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? If study is funded solely by UCL this should be stated, the section should not be left blank. UCL	

A5	Signature of Head of Department [or Chair of the Departmental Ethics Committee]
	<i>(This must not be the same signature as the Principal Researcher)</i>
	A. I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it. I am satisfied that <i>(please highlight as appropriate):</i>
	(1) Data Protection registration:
	• has been satisfactorily completed <input checked="" type="checkbox"/>
	• has been initiated <input type="checkbox"/>
	• is not required <input type="checkbox"/>
	(2) a risk assessment:
	• has been satisfactorily completed <input checked="" type="checkbox"/>
	• has been initiated <input type="checkbox"/>
(3) appropriate insurance arrangements are in place and appropriate sponsorship [funding] has been approved and is in place to complete the study. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
(4) a Disclosure and Barring Service check(s):	
• has been satisfactorily completed <input type="checkbox"/>	
• has been initiated <input type="checkbox"/>	
• is not required <input checked="" type="checkbox"/>	
Links to details of UCL's policies on the above can be found at: http://ethics.grad.ucl.ac.uk/procedures.php	
**If any of the above checks are not required please clarify why below.	

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

B. Having read the 'criteria of minimal risk' as defined on page 3 of our Guidelines at: <http://ethics.grad.ucl.ac.uk/forms/guidelines.pdf> I recommend that this application should be considered by the Chair of the UCL REC.

Yes No

PRINT NAME:

SIGNATURE:

DATE:

SECTION B **DETAILS OF THE PROJECT**

B1	<p>Please provide a brief summary of the project in <u>simple prose</u> outlining the intended value of the project, giving necessary scientific background (max 500 words).</p> <p>Multiparticulate formulations, which are composed of multiple solid units of small size (pellets, beads or spheroids), are a suitable alternative for the oral administration of medicines to patients that cannot swallow big solid formulations (e.g. tablets or capsules) such as children and patients with dysphagia.</p> <p>Previous studies conducted by our research team demonstrate that textural aspects (i.e. oral grittiness perception) limit palatability and acceptability of this type of formulation. We propose that oral gels prepared with gelling agents commonly used in food industry (e.g. xanthan gum and carboxymethylcellulose) could be used to administer multiparticulates with improved organoleptic properties.</p> <p>The aim of this study is to conduct an in-vivo sensory analysis using an untrained human taste panel to assess palatability and acceptability of multiparticulates dispersed in oral gels of varying consistency.</p> <p>Samples will be composed of microcrystalline cellulose pellets (Cellets; http://cellets.com/) dispersed in oral suspending media composed of varying amounts of xanthan gum (which forms highly shear thinning gels) or carboxymethylcellulose (which forms poorly shear thinning gels). Volunteers will be asked to swallow less than 8 samples in any individual session (less than 2 hours per session).</p> <p>Participants will be asked to give feedback of various palatability parameters (e.g. mouthfeel and taste) using computerised scales. The methodology employed in this study has been previously optimised by our research team in a preliminary sensory evaluation approved by UCL Research Ethics Committee (REC 4612/007).</p> <p>Analysis of results will indicate the type of gelling agent and its concentration that is most successful in "masking" the gritty feeling of multiparticulates, and improve overall palatability and acceptability of this type of formulation.</p>
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B2	<p>Briefly characterise in <u>simple prose</u> the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken (max 500 words).</p> <p>Research methodology:</p> <p>Single blind, randomised, sensory evaluation of multiparticulate formulations (Annex 1 – Flow diagram).</p> <p>Inclusion criteria:</p> <p>Healthy male or female adults, able to understand and speak English (Annex 2 – Recruitment advertisement). If smoker, they have to forbear smoking at least one hour before and during all the tests.</p> <p>Exclusion criteria:</p> <p>Antecedent deterioration of taste or smell. Recent dental care. Sensory disorders affecting the mouth or local anaesthetics into the mouth within 24 hours of the study. Swallowing dysfunction.</p> <p>Sample preparation:</p> <p>Suspending media will be prepared by dispersion of gelling agents in water (in the range of 0.25 to 1.5% w/v gelling agent/water) and continuous mixing until gel formation is achieved. The gelling agents used will be food grade or pharmaceutical grade suitable for human consumption. The amounts of gelling agents used are within the ranges used in food products. Placebo formulations (Cellets) will be given to subjects in a ready-to-administer form, pre-suspended in oral suspending media.</p> <p>Samples will be prepared under strict quality measures in a dedicated area under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621; Sejal Ranmal 2074443) and according to standard operating procedures that have been approved by the PI and the departmental safety officer; Annex 3 – Standard Operating Procedures).</p> <p>Experimental protocol:</p> <p>Participants will be asked to swallow the whole sample, but they will be alerted of the possibility to reject one or more samples if they don't feel confident to swallow the sample safely. Immediately after sample ingestion, they will rate the sample using a computerised questionnaire (Qualtrics) with categorical scales (Annex 4 - data collection form). Participants will have free access to water to aid swallowing and/or rinse their palate.</p> <p>The study will be conducted in two sessions to minimise participants fatigue and discomfort. In each sessions, participants will receive a sample of multiparticulates dispersed in water first (control) followed by 6 samples of multiparticulates dispersed in different suspending media. An interval of 5 to 10 minutes will be respected between samples.</p> <p>Crossover study, volunteers will be divided in two groups: Group A will test samples of the smaller multiparticulates during the first session and samples of larger multiparticulates in the second session; whereas Group B will test samples of the larger multiparticulates first and samples of smaller multiparticulates later.</p> <p>Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).</p>
B3	<p>Where will the study take place (please provide name of Institution/department)?</p> <p>If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country?</p> <p>Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998?</p> <p>UCL School of Pharmacy, in the pharmacy practice dispensary. Participants will be seated at individual computer stations and screened off from other volunteers.</p> <p>Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test).</p>
B4	<p>Have collaborating departments whose resources will be needed been informed and agreed to participate?</p> <p>Attach any relevant correspondence.</p> <p>N/A</p>

B5	<p>How will the results be disseminated, including communication of results with research participants?</p> <p>Once recruited, participants will be assigned individual, anonymous codes only accessible by the researchers. The final results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations. A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. In such cases, an abstract of the overall outcomes will be shared with participants.</p>
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B6	<p>Please outline any ethical issues that might arise from the proposed study and how they are to be addressed. Please note that all research projects have some ethical considerations so do not leave this section blank.</p> <p>Confidentiality: This study will not be intrusive since minimum personal data will be recorded (contact details, date of birth and gender). Participants will be assigned anonymous codes that are only accessible to the research team, and confidentiality will be maintained throughout the study and when results are disseminated. It will not be possible to identify individual participants from any publications.</p> <p>Participant burden: Test sessions will be restricted to a maximum of 90 minutes to reduce burden on participants and minimise fatigue. There is a potential for the participants to suffer from temporary oral discomfort during tasting if the grittiness of the oral suspension is marked, although this is considered to be an unlikely event. If some participants show high discomfort the assessment will be immediately stopped. We have attempted to narrow down the number of samples to taste in order to reduce any inconvenience.</p> <p>Adverse events: The formulations are placebo (do not contain any active pharmaceutical ingredient). The potential for adverse effects, risks or hazards by swallowing of the formulation is therefore negligible. There is a potential for accidental choking while tasting and swallowing of the formulations tested, however this is considered to be a very unlikely event and based on previous experience of our research group. The dose given is considered to be very safe and easy to swallow for adults with no swallowing dysfunction. Participants can refuse ingestion of any of the samples at any point during the study if they feel not capable or not comfortable swallowing the sample.</p> <p>If something should go wrong, first aid will be sought as necessary and the experiment will be stopped. We can seek for medical help on the premises (Dr Kirsten Harvey, MD). If someone complains, the supervisor or a third party (not directly involved in research team) Ms Joanna O'Brien (Institute Manager) can be contacted for further advice.</p> <p>The research team has previous experience in taste assessment studies including studies which involved swallowing of placebo multiparticulate formulations. The methodology employed in this study has been previously optimised in a preliminary trial conducted by our research team (REC 4612/007 and REC 6062/001). The principal investigator has extensive experience of conducting and supervising such studies using volunteer panels.</p>
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SECTION C	DETAILS OF PARTICIPANTS
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C1	<p>Participants to be studied</p> <table border="1" style="margin-left: 20px;"> <tr> <td style="padding: 2px;">C1a. Number of volunteers:</td> <td style="text-align: center;">30</td> </tr> <tr> <td style="padding: 2px;">Upper age limit:</td> <td style="text-align: center;">40</td> </tr> <tr> <td style="padding: 2px;">Lower age limit:</td> <td style="text-align: center;">18</td> </tr> </table> <p>C1b. Please justify the age range and sample size:</p> <p>Sample size: N > 20 as this number are within the range of sample size of previous studies regarding taste assessment of medicines with non-trained panels and it is enough to apply statistics.</p> <p>Age range: Taste sensitivity is known to vary with age, therefore "young adults" will be recruited in this study to resemble the paediatric population as closely as possible.</p>	C1a. Number of volunteers:	30	Upper age limit:	40	Lower age limit:	18
C1a. Number of volunteers:	30						
Upper age limit:	40						
Lower age limit:	18						

C2	<p>If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the UK Data Protection Act 1998.</p> <p>N/A</p>
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C3	<p>Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>How will you ensure that participants in these groups are competent to give consent to take part in this study? <i>If you have relevant correspondence, please attach it.</i></p> <p>N/A</p>
C4	<p>Will payment or any other incentive, such as gift service or free services, be made to any research participant? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.</p> <p>Participants will be paid £10 in cash for volunteering. This will be paid from the GL account of the PI. Before and during any part of the study, participants will have the option to withdraw if they wish.</p> <p>Please justify the payment/other incentive you intend to offer.</p> <p>This is a thank you gesture for the time committed to the project.</p>
C5	<p>Recruitment</p> <p>(I) Describe how potential participants will be identified:</p> <p>Participants will be students and staff at UCL and potentially others outside UCL who receive the advertising email and meet the inclusion/exclusion criteria (healthy adults aged 18 to 40 years).</p> <p>(II) Describe how potential participants will be approached:</p> <p>An email (annex 2) will be circulated using UCL announce to advertise the study. Potential volunteers interested in taking part will be invited to contact the research team directly using the contact details in these advertisements.</p> <p>(III) Describe how participants will be recruited:</p> <p>Potential participants who show interest and contact the research team will be provided with a copy of the information sheet for their perusal. They will be allowed sufficient time to consider whether or not to take part, and will be invited to ask questions or obtain further information if necessary. Those who decide to participate will then contact the research team to arrange suitable dates and times to undertake the study. Prior to the first session, a member of the research team will orally explain the study and take informed consent from the participant.</p> <p><i>Attach recruitment emails/adverts/webpages. A data protection disclaimer should be included in the text of such literature.</i></p>
C6	<p>Will the participants participate on a fully voluntary basis? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Will UCL students be involved as participants in the research project? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.</i></p> <p>Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?</p> <p>Although stated in the information sheet and consent form, all participants will be reminded that their participation is completely optional and unrelated to the outcomes of their study and that it will not affect their relationship with the research team or with UCL (e.g. teaching matters).</p>

C7	<p>CONSENT</p> <p>Please describe the process you will use when seeking and obtaining consent.</p> <p>The form attached will be used to obtain informed consent from participants. Those who initially show interest in the study (from the advertisements used) will contact the research team and be provided with the study information sheet. Following consideration, those willing to participate will contact the research team to be recruited onto the study. Prior to the first session, a member of the research team will orally explain the study to the participant, confirm their eligibility and answer any questions if necessary. The researcher will review the consent form with the participant to ensure all of the statements are well understood, and additional time to read the form will be provided if necessary.</p> <p><i>A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.</i></p> <p>In cases where it is not proposed to obtain the participants informed consent, please explain why below.</p> <p>N/A</p>
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C8	<p>Will any form of deception be used that raises ethical issues? If so, please explain.</p> <p>No</p>
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C9	<p>Will you provide a full debriefing at the end of the data collection phase? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If 'No', please explain why below.</p> <p>N/A</p>
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C10	<p>Information Sheets And Consent Forms</p> <p>A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.</p>
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Improving palatability of oral multiparticulate formulations using oral gels as suspending media

Participant Information Sheet

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

This study has been approved by the UCL Research Ethics Committee
Project ID Number: REC 4612/011

Principal Investigator: Dr Catherine Tuleu
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5857
Email: c.tuleu@ucl.ac.uk

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

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

Details of the Study

What is the purpose and aim of this project?

The aim of this study is to conduct an in-vivo sensory analysis using human taste panels to assess the palatability and acceptability oral multiparticulates (i.e. pellets, beads or spheroids) dispersed in various suspending media.

The study is anticipated to provide valuable information regarding the influence of different suspending media on palatability and acceptability of multiparticulates which can be used to guide the development of new formulations that are more acceptable to patients.

The samples tested do not contain any medicine. They are composed of naturally occurring products (microcrystalline cellulose, carboxymethyl cellulose and xanthan gum) that are often used in foods and in tablets and vitamin supplements.

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 40 years to take part.

If you have problems with the sense of taste or smell or if you have had any dental care or if you have any swallowing dysfunction, then unfortunately you will be unable to take part.

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL. You will be asked to commit to two sessions of 90 minutes each.

During the trial we will ask you to swallow a small number of samples (8 or less) and then rate the ease of swallowing of the sample, the grittiness of the samples (i.e. rough mouth feel due to the presence of particles), the taste of the sample and the sample volume (i.e. the amount that you had to take) and other parameters related to palatability and acceptability of the sample. You will be asked to rinse your mouth out before and after each test and will be provided with free access to water.

You will be allowed to reject ANY of the samples at any point of the study if you don't feel capable or confident enough to swallow it.

Are there any risks involved?

The samples you will be testing are placebo, this means there is no medicine in their composition.

If the samples you taste/swallow are very gritty, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples and vomit, however this is extremely rare. Nevertheless, a delay of 5 to 10 minutes will be respected between each tested solution to minimise fatigue and discomfort.

If you experience nausea or pain you must alert a member of the team and we will stop the study immediately. The researchers are trained in First Aid and medical doctors will be present to assess the situation. If necessary, we will also contact emergency services.

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

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

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

Who can I contact for more information?

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

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

Ms Joanna O'Brien
Institute Manager
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5814
Email: joanna.o'brien@ucl.ac.uk

Thank you for taking the time to read this information sheet

UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE



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

Title of Project: **Improving palatability of oral multiparticulate formulations using oral gels as suspending media**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): **4612/011**

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

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

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that I should not take part if I have had any dental care or medicinal treatment (except contraceptives) during the 15 days before the tests.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately without penalty.
- consent to the processing of my personal information for the purposes of this research study.
- understand that the information I have submitted will be published as a report and I can request a copy by contacting the researchers. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

Signed:

Date:

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

D1	<p>Have UCL's Risk Assessment Procedures been followed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, please explain.</p> <p>There is no significant risk - See annex 5 for UCL risk assessment form.</p>
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D2	<p>Does UCL's Insurer need to be notified about your project before insurance cover can be provided? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies, the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.</i></p> <p>If Yes, please provide confirmation that the appropriate insurance cover has been agreed. Please attach your UCL insurance registration form and any related correspondence.</p> <p>N/A</p>
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D3	<p>Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).</p> <p>This project holds little risk to the researchers, which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.</p>
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D4	<p>Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please describe the nature of the risk or stress and how you will minimise and monitor it.</p> <p>The procedures may cause temporary physical discomfort due to exposure to unpleasant samples if the test samples are very unpalatable. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, before and after each test sample, subjects will rinse their mouth with water. The participants will be provided with necessary instruction on properly testing the samples. The level of discomfort may evolve during the study. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the tasting will be immediately stopped.</p>
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D5	<p>Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?</p> <p>If Yes, please explain how you will deal with this.</p> <p>None</p>
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D6	<p>Please describe any expected benefits to the participant.</p> <p>Indirect benefit through contribution to patient care.</p> <p>Participants will contribute to increasing the knowledge of palatability and acceptability testing and, in particular, how to improve organoleptic properties and acceptance of oral multiparticulate formulations. This will support the development of new formulations for oral administration.</p>
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D7	<p>Specify whether the following procedures are involved:</p> <p>Any invasive procedure(s) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Physical contact <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Any procedure(s) that may cause mental distress <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Please state briefly any precautions being taken to protect the health and safety of the research participants.</p> <p>The study is divided in two sessions and the number of samples is kept to a minimum in each session to minimise fatigue and discomfort. Before and after each test sample, subjects will rinse their mouth with water and will have free access to water during the study. The participants will be provided with necessary instruction on properly testing the samples. Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the tasting will be immediately stopped.</p>
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D8	<p>Does the research involve the use of drugs? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please name the drug/product and its intended use in the research and then complete Appendix I</p> <p>N/A</p> <p>Does the project involve the use of genetically modified materials? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, has approval from the Genetic Modification Safety Committee been obtained for work? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please quote the Genetic Modification Reference Number: N/A</p>
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D9	<p>Will any non-ionising radiation be used on the research participant(s)?</p> <p style="text-align: center;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix II.</p>
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D10	<p>Are you using a medical device in the UK that is CE-marked and is being used within its product indication?</p> <p style="text-align: center;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix III.</p>
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CHECKLIST

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

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

Please note that correspondence regarding the application will normally be sent to the Principal Researcher and copied to other named individuals.

4. REC application related to study presented in Chapter 5



IMPORTANT: ALL FIELDS MUST BE COMPLETED. THE FORM SHOULD BE COMPLETED IN PLAIN ENGLISH UNDERSTANDABLE TO LAY COMMITTEE MEMBERS.
SEE NOTES IN STATUS BAR FOR ADVICE ON COMPLETING EACH FIELD. YOU SHOULD READ THE ETHICS APPLICATION GUIDELINES AND HAVE THEM AVAILABLE AS YOU COMPLETE THIS FORM.

APPLICATION FORM

SECTION A		APPLICATION DETAILS		
A1	Project Title: Taste assessment of excipients for dispersible tablets			
	Date of Submission: 24/02/2017	Proposed Start Date: 15/03/2017		
	UCL Ethics Project ID Number: 4612/015	Proposed End Date: 15/09/2017		
	If this is an application for classroom research as distinct from Independent study courses, please provide the following additional details:			
	Course Title: N/A	Course Number: N/A		
A2	Principal Researcher Please note that a student – undergraduate, postgraduate or research postgraduate cannot be the Principal Researcher for Ethics purposes.			
	Full Name: Dr Catherine Tuleu	Position Held: Reader in Pharmaceutics		
	Address: UCL School of Pharmacy 29-39 Brunswick square London, WC1N 1AX	Email: c.tuleu@ucl.ac.uk		
		Telephone: 0207 753 5857		
		Fax: 0207 753 5942		
Declaration To be Signed by the Principal Researcher				
<ul style="list-style-type: none"> ▪ I have met with and advised the student on the ethical aspects of this project design (<i>applicable only if the Principal Researcher is not also the Applicant</i>). ▪ I understand that it is a UCL requirement for both students & staff researchers to undergo Disclosure and Barring Service (DBS) Checks when working in controlled or regulated activity with children, young people or vulnerable adults. The required DBS Check Disclosure Number(s) is: N/A <ul style="list-style-type: none"> ▪ I have obtained approval from the UCL Data Protection Officer stating that the research project is compliant with the Data Protection Act 1998. My Data Protection Registration Number is: Z6364106/2017/02/70 ▪ I am satisfied that the research complies with current professional, departmental and university guidelines including UCL's Risk Assessment Procedures and insurance arrangements. ▪ I undertake to complete and submit the 'Continuing Review Approval Form' on an annual basis to the UCL Research Ethics Committee. ▪ I will ensure that changes in approved research protocols are reported promptly and are not initiated without approval by the UCL Research Ethics Committee, except when necessary to eliminate apparent immediate hazards to the participant. ▪ I will ensure that all adverse or unforeseen problems arising from the research project are reported in a timely fashion to the UCL Research Ethics Committee. ▪ I will undertake to provide notification when the study is complete and if it fails to start or is abandoned. 				

SIGNATURE:

DATE:

A3	Applicant(s) Details (<i>If Applicant is not the Principal Researcher e.g. student details:</i>)	
	Full Name: Felipe Lopez	
	Position Held: PhD Student	
	Address: UCL School of Pharmacy 29-39 Brunswick square London, WC1N 1AX	Email: felipe.lopez.13@ucl.ac.uk Telephone: 07784353745 Fax: N/A
	Full Name: N/A	
	Position Held: N/A	
	Address: N/A	Email: N/A Telephone: N/A Fax: N/A

A4	Sponsor/ Other Organisations Involved and Funding
	a) Sponsor: <input checked="" type="checkbox"/> UCL <input type="checkbox"/> Other Institution
	b) Other Organisations: If your study involves another organisation, please provide details. Evidence that the relevant authority has given permission should be attached or confirmation provided that this will be available upon request. N/A

If your project is sponsored by an institution other than UCL please provide details: The study is sponsored by the Centre for Doctoral Training (CDT) in Targeted Therapeutics and Formulation Sciences. The Applicant is currently doing a PhD at UCL School of Pharmacy which is funded by the CDT.

c) Funding: What are the sources of funding for this study and will the study result in financial payment or payment in kind to the department or College? If study is funded solely by UCL this should be stated, the section should not be left blank. The study is funded by the Applicants' PhD scholarship, given by the CDT in Targeted Therapeutics and Formulation Sciences.

A5	Signature of Head of Department [or Chair of the Departmental Ethics Committee]
	(This must not be the same signature as the Principal Researcher)
	A. I have discussed this project with the principal researcher who is suitably qualified to carry out this research and I approve it.
	I am satisfied that (please highlight as appropriate):
	(1) Data Protection registration:
	• has been satisfactorily completed <input checked="" type="checkbox"/>
	• has been initiated <input type="checkbox"/>
	• is not required <input type="checkbox"/>
	(2) a risk assessment:
	• has been satisfactorily completed <input checked="" type="checkbox"/>

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

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

• has been satisfactorily completed	<input type="checkbox"/>
• has been initiated	<input type="checkbox"/>
• is not required	<input checked="" type="checkbox"/>

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

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

B. Having read the 'criteria of minimal risk' as defined on page 3 of our Guidelines at: <http://ethics.grad.ucl.ac.uk/forms/guidelines.pdf>
I recommend that this application should be considered by the Chair of the UCL REC.

Yes No

PRINT NAME:

SIGNATURE:

DATE:

SECTION B

DETAILS OF THE PROJECT

B1	<p>Please provide a brief summary of the project in <u>simple prose</u> outlining the intended value of the project, giving necessary scientific background (max 500 words).</p> <p>Palatability is a critical property of an oral formulation which influences patient acceptability and thus have an impact on patient compliance with a drug regime. Palatability, as the overall sensation of a product in the mouth, is composed of various factors including taste, mouthfeel, smell and even appearance.</p> <p>Dispersible tablets are a suitable formulation for paediatric patients and those with swallowing difficulties. These tablets disintegrate in water within seconds, forming an easy-to-swallow suspension. The choice of excipients within dispersible tablets is critical to ensure appropriate palatability.</p> <p>The objective of this study is to evaluate the taste and mouth feel acceptability of 1g excipients (commonly used for the preparation of dispersible tablets) dispersed in 10 ml of water. Mixture of excipients will be prepared by blending dry powders together, to resemble the combination of excipients that would be present within a dispersible tablet formulation. Powders will be dispersed in water immediately before tasting.</p> <p>The widely used "swirl and spit" method will be used for tasting of the samples, in which participants swirl a small volume of the test sample in their mouth for some seconds before spitting it out. Then, participants will rate the samples using categorical scales (to rank several attributes such as taste, mouth feel and overall acceptability).</p> <p>In this study there is no medicine in the samples, they are just made of lactose, mannitol, microcrystalline cellulose and other substances commonly used as a bulking agent in tablets and vitamin supplements. It is completely safe to take the amount of these substances within these samples and it will have no pharmacological effect on the participants.</p> <p>The study is anticipated to provide valuable information about the taste and mouth feel of various excipients which can be used to guide the development of new formulations that are more acceptable to patients</p>
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B2	<p>Briefly characterise in <u>simple prose</u> the research protocol, type of procedure and/or research methodology (e.g. observational, survey research, experimental). Give details of any samples or measurements to be taken (max 500 words).</p> <p>Research methodology:</p> <p>Single blind, randomised, taste assessment of suspensions (Annex 1 – Flow diagram).</p> <p>Inclusion/exclusion criteria:</p> <p>Healthy young adults 18-40 years old. Volunteers must:</p> <ul style="list-style-type: none"> - Be considered generally healthy & on no regular medication - Not have active mouth ulcers or bleeding gums during the previous 24 hours - Not have contraindications to receiving medication - Be non-smokers (abstinent for past 3 months) <p>If prior to the study, any of the volunteers believe that they have developed a medical condition (e.g. a cold) that may have an impact on their ability to taste they will be excluded from the study.</p> <p>Sample preparation:</p> <p>Samples will be reconstituted immediately before testing by adding 1 g of powder to 10 ml of water, then shaking until an homogeneous suspension is achieved. Powder blends will be previously prepared by mixing dry powders together in clean glass bottles. Then 1g samples of powders will be placed into individually labelled vials and kept in a locked cupboard until the tasting day. Samples will be prepared under strict quality measures in a dedicated area under the supervision of a registered UK pharmacist (GPhC registration: Dr. Catherine Tuleu 2052621) and according to standard operating procedures that have been approved by the PI and the departmental safety officer; Annex 3 – Standard Operating Procedures).</p> <p>Experimental protocol:</p> <p>Participants will be asked to swirl the sample in the mouth for approximately 20 seconds and then spit out the sample into a receptacle provided. Participants will be alerted of the possibility to reject one or more samples (without the need to provide any reason for rejection of the sample). Immediately after sample expectoration, they will rate the sample using a questionnaire with categorical scales (Annex 4 - data collection form). Participants will have free access to water and unsalted crackers to rinse their palate between samples. An interval of 5 to 10 minutes will be respected between samples to minimise discomfort. Participants will be asked to commit to two sessions, lasting less than 1 hour each. Participants will receive a maximum of 9 samples to test in each individual session.</p> <p><i>Attach any questionnaires, psychological tests, etc. (a standardised questionnaire does not need to be attached, but please provide the name and details of the questionnaire together with a published reference to its prior usage).</i></p>
B3	<p>Where will the study take place (please provide name of Institution/department)? If the study is to be carried out overseas, what steps have been taken to secure research and ethical permission in the study country? Is the research compliant with Data Protection legislation in the country concerned or is it compliant with the UK Data Protection Act 1998?</p> <p>The study will take place at UCL School of Pharmacy, in a dedicated room. Participants will be seated at individual stations and screened off from other volunteers.</p> <p>Environment: Calm, daylight, aired and odourless (to avoid any influence on the sensory part of the test)</p>
B4	<p>Have collaborating departments whose resources will be needed been informed and agreed to participate? Attach any relevant correspondence.</p> <p>N/A</p>

B5	<p>How will the results be disseminated, including communication of results with research participants?</p> <p>Once recruited, participants will be assigned individual, anonymous codes only accessible by the researchers. The final results of the study may be anonymously reported and disseminated in peer reviewed scientific journals, internal reports and conference presentations. A statement is included in the patient information sheet inviting participants to contact the research team should they wish to know the results of the study. In such cases, an abstract of the overall outcomes will be shared with participants.</p>
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B6	<p>Please outline any ethical issues that might arise from the proposed study and how they are addressed. Please note that all research projects have some ethical considerations so do not leave this section blank.</p> <p>Confidentiality: This study will not be intrusive since minimum personal data will be recorded (contact details, age and gender). Participants will be assigned anonymous codes that are only accessible to the research team, and confidentiality will be maintained throughout the study and when results are disseminated. It will not be possible to identify individual participants from any publications.</p> <p>Participant burden: Test sessions will be restricted to a maximum of 1 hour to reduce burden on participants and minimise fatigue. There is a potential for the participants to suffer from temporary oral discomfort during tasting if the taste of the oral suspension is marked, although this is considered to be an unlikely event. If some participants show high discomfort the assessment will be immediately stopped. We have attempted to narrow down the number of samples to taste in order to reduce any inconvenience.</p> <p>Adverse events: The formulations are placebo (do not contain any active pharmaceutical ingredient). The potential for adverse effects, risks or hazards by swirl and spit of the samples is therefore negligible. There is a potential for accidental choking while tasting, however this is considered to be a very unlikely event based on previous experience of our research group. The dose given is very safe, well below the Maximum Daily Intake of each substance. If something should go wrong, first aid will be sought as necessary and the experiment will be stopped.</p> <p>The research team has previous experience in taste assessment studies, including studies which involved swallowing of placebo multiparticulate formulations in adults and children.</p>
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SECTION C	DETAILS OF PARTICIPANTS
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C1	<p>Participants to be studied</p> <table border="1" style="margin-left: 20px;"> <tr> <td style="padding-left: 20px;">C1a. Number of volunteers:</td> <td style="text-align: center;">24</td> </tr> <tr> <td style="padding-left: 40px;">Upper age limit:</td> <td style="text-align: center;">40</td> </tr> <tr> <td style="padding-left: 40px;">Lower age limit:</td> <td style="text-align: center;">18</td> </tr> </table> <p>C1b. Please justify the age range and sample size:</p> <p>Sample size: Previous studies in our research group have demonstrated that sample size of 20-25 volunteers is large enough to detect significant differences between samples. Since the aim of this study is to identify "good samples" and differentiate them from "bad samples", a sample size of 24 is considered sufficient to achieve the aim while minimising exposure to volunteers to a minimum.</p> <p>Age range: Taste sensitivity is known to vary with age, therefore "young adults" will be recruited.</p>	C1a. Number of volunteers:	24	Upper age limit:	40	Lower age limit:	18
C1a. Number of volunteers:	24						
Upper age limit:	40						
Lower age limit:	18						

C2	<p>If you are using data or information held by a third party, please explain how you will obtain this. You should confirm that the information has been obtained in accordance with the UK Data Protection Act 1998.</p> <p>N/A</p>
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C3	<p>Will the research include children or vulnerable adults such as individuals with a learning disability or cognitive impairment or individuals in a dependent or unequal relationship? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>How will you ensure that participants in these groups are competent to give consent to take part in this study? <i>If you have relevant correspondence, please attach it.</i></p> <p>N/A</p>
C4	<p>Will payment or any other incentive, such as gift service or free services, be made to any research participant?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes, please specify the level of payment to be made and/or the source of the funds/gift/free service to be used.</p> <p>Participants will be paid £5 per session in cash. This will be paid from the GL account of the PI. Before and during any part of the study, participants will have the option to withdraw if they wish.</p> <p>Please justify the payment/other incentive you intend to offer.</p> <p>N/A</p>
C5	<p>Recruitment</p> <p>(I) Describe how potential participants will be identified:</p> <p>Participants will be students and staff at UCL and potentially others outside UCL who receive the advertising email and meet the inclusion/exclusion criteria (healthy adults aged 18 to 40 years).</p> <p>(II) Describe how potential participants will be approached:</p> <p>An email (annex 2) will be circulated using UCL announce to advertise the study. If needed a printed advertisement will also be placed around the School of Pharmacy. Potential volunteers interested in taking part will be invited to contact the research team directly using the contact details in these advertisements.</p> <p>(III) Describe how participants will be recruited:</p> <p>Potential participants who show interest and contact the research team will be provided with a copy of the information sheet for their perusal. They will have at least 24 hours to consider whether or not to take part, and will be invited to ask questions or obtain further information if necessary. Those who decide to participate will then contact the research team to arrange suitable dates and times to undertake the study. Prior to the first session, a member of the research team will orally explain the study and take informed consent from the participant.</p> <p><i>Attach recruitment emails/adverts/webpages. A data protection disclaimer should be included in the text of such literature.</i></p>
C6	<p>Will the participants participate on a fully voluntary basis? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Will UCL students be involved as participants in the research project? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>If yes, care must be taken to ensure that they are recruited in such a way that they do not feel any obligation to a teacher or member of staff to participate.</i></p> <p>Please state how you will bring to the attention of the participants their right to withdraw from the study without penalty?</p> <p>Although stated in the information sheet and consent form, all participants will be reminded that their participation is completely optional and unrelated to the outcomes of their study and that it will not affect their relationship with the research team or with UCL (e.g. teaching matters).</p>

C7	<p>CONSENT</p> <p>Please describe the process you will use when seeking and obtaining consent.</p> <p>The form attached will be used to obtain informed consent from participants. Those who initially show interest in the study (from the advertisements used) will contact the research team and be provided with the study information sheet. Following consideration, those willing to participate will contact the research team to be recruited onto the study. Prior to the study, a member of the research team will orally explain the study to the participant, confirm their eligibility and answer any questions if necessary. The researcher will review the consent form with the participant to ensure all of the statements are well understood, and additional time to read the form will be provided if necessary.</p> <p><i>A copy of the participant information sheet and consent form must be attached to this application. For your convenience proformas are provided in C10 below. These should be filled in and modified as necessary.</i></p> <p>In cases where it is not proposed to obtain the participants informed consent, please explain why below.</p> <p>N/A</p>
C8	<p>Will any form of deception be used that raises ethical issues? If so, please explain.</p> <p>No</p>
C9	<p>Will you provide a full debriefing at the end of the data collection phase? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If 'No', please explain why below.</p> <p>No</p>
C10	<p>Information Sheets And Consent Forms</p> <p>A poorly written Information Sheet(s) and Consent Form(s) that lack clarity and simplicity frequently delay ethics approval of research projects. The wording and content of the Information Sheet and Consent Form must be appropriate to the age and educational level of the research participants and clearly state in simple non-technical language what the participant is agreeing to. Use the active voice e.g. "we will book" rather than "bookings will be made". Refer to participants as "you" and yourself as "I" or "we". An appropriate translation of the Forms should be provided where the first language of the participants is not English. If you have different participant groups you should provide Information Sheets and Consent Forms as appropriate (e.g. one for children and one for parents/guardians) using the templates below. Where children are of a reading age, a written Information Sheet should be provided. When participants cannot read or the use of forms would be inappropriate, a description of the verbal information to be provided should be given. Please ensure that you trial the forms on an age-appropriate person before you submit your application.</p>

UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE



Taste assessment of excipients for dispersible tablets

Participant Information Sheet – Information for parents/carers

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

This study has been approved by the University College London (UCL) Research Ethics Committee
Project ID Number: REC 4612/015

Principal Investigator: Dr Catherine Tuleu
Department of Pharmaceutics
UCL School of Pharmacy
29/39 Brunswick Square
London, WC1N 1AX
Tel: 020 7753 5857
Email: c.tuleu@ucl.ac.uk

Would you like to participate in a study about taste of medicines?

We would like to invite you to participate in this research project. Taking part is voluntary; it is up to you to decide whether or not to take part, and choosing not to will not disadvantage you in any way.

If you do decide to take part, you will still be free to withdraw at any time without the need to give a reason.

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

What is the purpose of this study?

The aim of this study is to assess taste and overall liking of dispersible tablet formulations (i.e. powders dispersed in water). The powders used are commonly used to prepare dispersible tablets (i.e. tablets which disperse in water within seconds). The aim is to identify what you like, what you don't like and what is "acceptable" for you.

The study is anticipated to provide valuable information regarding taste and mouth feel of excipients (i.e. substances with no pharmacological effect used to make medicines). This information can be used to guide the development of new medicines that are more acceptable to patients.

The samples tested **do not contain any medicine**. They are composed of lactose, mannitol, cellulose and other substances that are often used in tablets and vitamin supplements.

8

Who can take part in this study?

We are looking for young healthy adults aged between 18 and 40 years to take part.

If you have smoked in the past three months or if you have problems with the sense of taste or smell or if you have had any recent dental care, then unfortunately you will be unable to take part.

What will happen if I agree to take part?

The study will take place in the consultation rooms of the pharmacy practice dispensary at UCL. You will be asked to commit to **2 sessions of less than 1 hour each**.

During the trial we will be given samples of powders dispersed in water. You will be asked to put the sample in your mouth, swirl it around for about 20 seconds and then spit it out. Then you will be asked to rate various attributes, such as taste and mouth feel, using scales. You will be asked to rinse your mouth out before and after each test and will be provided with free access to water.

You will be allowed to reject ANY of the samples at any point of the study.

Are there any risks involved?

This study uses powders and liquid that contain **no medicine**. They are composed of lactose, mannitol, cellulose and other substances that are often used in tablets and vitamin supplements.

If you are **lactose intolerant**, it is advised that **you don't take part** in this study. If in doubt, please contact the research team using the contact details provided below.

If the samples that you taste are very unpalatable, there is potential to suffer from temporary oral discomfort. Some sensitive participants may gag in response to the samples, however this is extremely rare. A break of 5 to 10 minutes will be respected between each tested sample to minimise discomfort.

If you experience nausea or pain, you must alert a member of the team and we will stop the study immediately. If necessary, we will also contact emergency services.

What happens after?

The lead researcher will report information found from the study. This will allow other people in research to read about this study as the results may appear in specific magazines (i.e. scientific journals).

If the study is published or presented to a wider audience, your anonymity will be respected (your name will never be made public). All data will be collected and stored in accordance with the Data Protection Act 1998.

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

What if I have any questions?

If you have any questions or worries at all, feel free at any time to contact us using the contact details provided below.

Contact details: Felipe Lopez
Tel: 07784353745
Felipe.lopez.13@ucl.ac.uk

Thank you for taking the time to read this information sheet



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

Title of Project: **Taste assessment of excipients for dispersible tablets**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): **4612/015**

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

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

Participant's Statement

I

- have read the notes written above and the information sheet, and understand what the study involves.
- understand that I should not take part if I have had any dental care or medicinal treatment (except contraceptives) during the 15 days before the tests.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately without penalty.
- consent to the processing of my personal information for the purposes of this research study.
- understand that the information I have submitted will be published as a report and I can request a copy by contacting the researchers. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.

Signed:

Date:

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

D1	<p>Have UCL's Risk Assessment Procedures been followed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, please explain.</p> <p>There is no significant risk - See Annex 5 for UCL risk assessment form.</p>
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D2	<p>Does UCL's Insurer need to be notified about your project before insurance cover can be provided? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>The insurance for all UCL studies is provided by a commercial insurer. For the majority of studies, the cover is automatic. However, for a minority of studies, in certain categories, the insurer requires prior notification of the project before cover can be provided.</p> <p>If Yes, please provide confirmation that the appropriate insurance cover has been agreed. Please attach your UCL insurance registration form and any related correspondence.</p> <p>N/A</p>
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D3	<p>Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research participants).</p> <p>This project hold little risk to the researchers, which has been risk assessed (see annex 5). Standard operating procedures as well as working sheets reviewed by the School safety officer are also included.</p>
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D4	<p>Will these participants participate in any activities that may be potentially stressful or harmful in connection with this research? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please describe the nature of the risk or stress and how you will minimise and monitor it.</p> <p>The procedures may cause temporary physical discomfort due to exposure to unpleasant samples if the test samples are very unpalatable. The potential discomfort is minimal and not greater than that ordinarily encountered in daily life. In order to minimise the discomfort, before and after each test sample, subjects will rinse their mouth with water. The participants will be provided with necessary instruction on properly testing the samples.</p> <p>The level of discomfort may evolve during the study, reason why the number of samples tested by a single individual has been restricted to a maximum of 9 samples in each individual session (n.b. previous work from our research team suggest that up to 18 samples is acceptable in a session of 2 hours). Risk will be continuously monitored by asking participants how they feel between samples. If participant report any distress, the tasting will be immediately stopped.</p> <p>Previous studies conducted by our research group in adults confirm the safety of the procedures involved in this research.</p>
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D5	<p>Will group or individual interviews/questionnaires raise any topics or issues that might be sensitive, embarrassing or upsetting for participants?</p> <p>If Yes, please explain how you will deal with this.</p> <p>None</p>
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D6	<p>Please describe any expected benefits to the participant.</p> <p>Indirect benefit through contribution to patient care.</p> <p>Participants will contribute to increasing the knowledge of palatability and acceptability testing and, in particular, how to improve organoleptic properties and acceptance of oral multiparticulate formulations. This will support the development of new formulations for oral administration.</p>
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D7	<p>Specify whether the following procedures are involved:</p> <p>Any invasive procedure(s) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Physical contact <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Any procedure(s) that may cause mental distress <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>Please state briefly any precautions being taken to protect the health and safety of the research participants.</p>
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D8	<p>Does the research involve the use of drugs? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please name the drug/product and its intended use in the research and then complete Appendix I</p> <p>N/A</p> <p>Does the project involve the use of genetically modified materials? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, has approval from the Genetic Modification Safety Committee been obtained for work? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If Yes, please quote the Genetic Modification Reference Number: N/A</p>
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D9	<p>Will any non-ionising radiation be used on the research participant(s)?</p> <p style="text-align: center;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix II.</p>
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D10	<p>Are you using a medical device in the UK that is CE-marked and is being used within its product indication?</p> <p style="text-align: center;"><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If Yes, please complete Appendix III.</p>
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CHECKLIST

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

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

Please note that correspondence regarding the application will normally be sent to the Principal Researcher and copied to other named individuals.

5. Set-up of facilities for acceptability studies

