DEVELOPMENT OF NOVEL SUSTAINED RELEASE FORMULATIONS FOR OLDER ADULTS WITH SWALLOWING DIFFICULTIES

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Abstract

The older cohort is the fastest growing subsection in the population; they are the major users of medicines and are also more vulnerable to dysphagia which can make safe swallowing of solid oral dosage forms challenging. Tablets and capsules are often modified by crushing tablets or opening capsules and this can be hazardous for slow release dosage forms which reduce the pill burden for these patients but can result in dose dumping and toxicity due to modification. The aim of this study is to understand the practical issues in administering sustained release dosage forms to older adults with dysphagia and to develop novel sustained release dosage forms that are safe to swallow.

A prospective study (Chapter 2) was conducted in secondary care with the focus on administration of sustained release dosage form. There were 49% of sustained release tablets and capsules modified by crushing tablets or opening capsules to facilitate swallowing in older adults with dysphagia. Furthermore, thickened fluids, yogurt and jellies were used as vehicles to deliver modified or whole dosage forms.

Thickened fluids are commonly used to help safety of swallowing thin liquids by dysphagia patients but poorly accepted. An *in vitro* throat model developed for processing liquids was used to provide a systematic understanding and comparison of the flow behaviour of commonly used thickeners under simulated swallowing conditions. Slow *in vitro* oral transit time and cohesive bolus transit with increasing thickening was found for thickened fluids. The processing of jellies for pharmaceutical application in the throat model showed similar findings of oral transit time and bolus length to thickened fluids at high consistencies (honey and spoon thick). Rheological

and textural characterisation of thickened fluids (viscosity, yield stress, firmness, cohesiveness) showed correlation with *in vitro* oral transit time and cohesive transit in the throat model.

Three instant (less than 10 minutes to form from powder when water was added) jellies were developed without requiring heat as a novel DIY dosage form to deliver sustained release microparticles containing gliclazide. Microparticles are useful dosage forms for patients with swallowing difficulties but can be challenging to swallow safely for patients unable to safely swallow thin liquids. The sodium alginate and calcium salts based jellies showed slow *in vitro* oral transit time and cohesive bolus transit in the throat model similar to commercial ready-to-eat jelly products. The jellies enhanced slow release properties of sustained release microparticles containing gliclazide suggesting that they can be effective vehicles to deliver the microparticles for patients with dysphagia.

Overall, this study showed that medicines modification does occur for sustained release dosage forms prescribed to older adults with dysphagia. Jellies showed potential as alternative swallowing aids to thickened fluids which are poorly accepted but commonly used to improve safety of swallowing of fluids by dysphagia patients. Instant jellies were developed without requiring heating with swallowing processing features similar to thickened fluids in the *in vitro* throat model to facilitate delivery of sustained release microparticles safely for dysphagia patients. The novel drug delivery system developed offers a promising solution for medicines administration in patients with dysphagia.

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Dedicated to Pravin, Pushpa, Roshni and Anisha Patel.

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List of Abbreviations

SODF	Solid Oral Dosage Forms
IDDSI	International Dysphagia Diet Standardisation Initiative
VFSS	Videofluoroscopic Swallow Study
FEES	Fiberoptic Endoscopic Evaluation of Swallowing
ADME	Absorption, Distribution, Metabolism, and Excretion
EMA	European Medicines Agency
FDA	Food and Drug Administration
ODT	Orally Disintegrating Tablet
API	Active Pharmaceutical Ingredient
POLYOX	Polyethylene oxide
LVR	Linear Viscoelastic Region
CT	Cambridge Throat
OTT	Oral transit time
BL	Bolus Length
CA	Cerebellar Ataxia
PD	Parkinson’s Disease
CI	Confidence Interval
G’	Storage modulus
G”	Loss modulus
Rad/s	Radian per second
cP	Centipoise
fps	Frames per second
T1	Time taken to reach the epiglottis
T2	Time taken to reach the airway divide

G	α-L-guluronic acid
M	β-D-mannuronic acid
LM	Low Methoxyl
HM	High Methoxyl
HPMC	Hydroxypropyl methylcellulose
CMC	Carboxymethylcellulose
SA	Sodium alginate
CC	Calcium chloride
ADG	3, 6-anhydro-D-galactose
F1	Formulation 1
F2	Formulation 2
F3	Formulation 3
min	Minute
w/v	Weight per volume
g	Gram
mL	Millilitre
mm	Milimetre
g/min	Gram per minute
PB 7.4	Phosphate buffer pH 7.4
SGF	Simulated Gastric Fluid
HCl	Hydrochloric acid
NaOH	Sodium hydroxide
CL	Coating Level
CL16	Coating Level at 16%
CL25	Coating Level at 25%

CL60	Coating Level at 60%
D_{50}	Particle size bellow which 50% of the particles by volume are smaller
h	Hour
UV	Ultraviolet Visible

Chapter 1

INTRODUCTION

Eating and drinking is not only a pleasurable activity but also a necessity for the sustenance of life. Individuals with difficulties in swallowing can make various adjustments if food and drink are difficult to swallow, such as opting for softer food or thickened fluid (Cichero, 2015). Medicines are also significant in maintaining the quality of life of patients, but the most commonly prescribed dosage forms are solid oral dosage forms (SODF). SODF such as tablets and capsules are preferred due to their convenience for patients and cost-effectiveness, but it can be challenging to administer these dosage forms safely and effectively to patients who have difficulties in swallowing. The difficulties patients may encounter in swallowing these dosage forms can sometimes be overlooked. Altering these formulations to facilitate swallowing is not as straightforward as modifying food and drinks and can result in hazardous consequences such as toxicity (Schier, Howland, Hoffman, & Nelson, 2003).

Difficulties in swallowing affect all age spans but are more common in older adults (65 years and over) due to age-related diseases and the natural process of aging (Stegemann et al., 2010; Wilkins, Gillies, Thomas, & Wagner, 2007). Older adults have a greater need for health care resources, compared to younger counterparts due to increased multimorbidities; consequently requiring a greater number of medicines (European Medicines Agency, 2012; Jennifer Kelly, Wright, & Wood, 2012). As the world population is aging and the number of adults over the age of 65 is expected to triple by 2050 to 1.5 billion compared to an estimated 524 million in 2010, the challenges encountered with administering medicines safely and effectively to patients with swallowing difficulties are expected to grow (National Institute on Aging, 2011).

1.1 Deglutition process and dysphagia

In order to understand dysphagia, it is essential first to understand the swallowing process. The oropharyngeal system serves two essential functions: the transport of solid or liquid bolus to the stomach and airway protection (Figure 1-1). The coordinated interactions between swallowing and breathing are fundamental for safe swallowing (Ertekin & Aydogdu, 2003). The process of swallowing is a rapid, synchronized process. It is generally described as three phases; the oral phase, the pharyngeal phase and the oesophageal phase (Table 1-1) (Matsuo & Palmer, 2008).

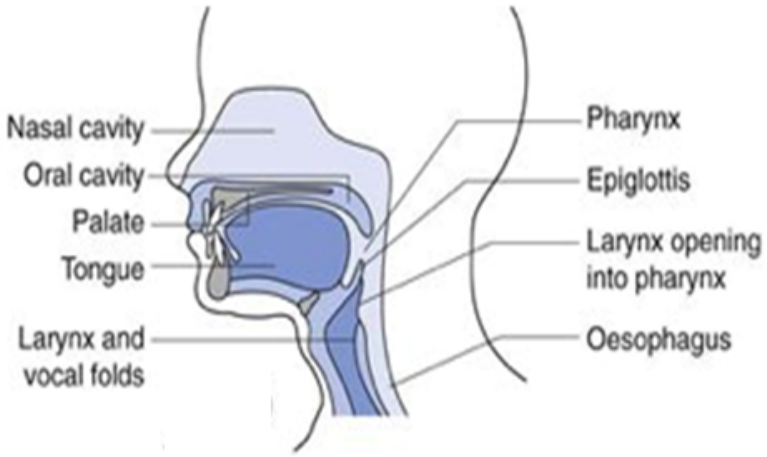


Figure 1-1: Lateral view of the oral cavity and pharynx (reprinted with permission) from Tuleu & Wright, 2013).

Dysphagia is the inability to transfer foods from the mouth to stomach safely and is more specifically defined as the “eating and drinking disorders which may occur in the oral, pharyngeal and oesophageal stages of deglutition” (Royal College of Speech and Language Therapists, 2013). Dysphagia can occur at a single stage of the swallowing process, or simultaneously in more than one stages (Stegemann et al., 2012). It can

be distinguished as two different types based on the location of the swallowing impairment; oropharyngeal and oesophageal dysphagia (Gleeson, 1999; Ratnaike, 2003). Swallowing impairment can be a result of structural or functional impairment such as loss of teeth or weak contraction of the tongue (Matsuo & Palmer, 2008). Oropharyngeal dysphagia can affect the oral phase (forming of bolus) and oral propulsion stage (Ratnaike, 2003). Factors influencing oropharyngeal dysphagia include: xerostomia, drug-induced dysphagia, neurological conditions such as Parkinson's disease and transfer of the bolus in the pharynx before the closure of the airway (Ertekin & Aydogdu, 2003). Oesophageal dysphagia can be caused by mechanical factors such as oesophageal obstruction by ulcers or tumours and neurological causes that affect peristaltic contractions in the oesophagus such as Parkinson's disease (Nelson & Castell, 1988; Ratnaike, 2003).

Table 1-1: The three stages of the swallowing process

Stages	Description
The oral phase (voluntary control)	The bolus transport in the mouth is described as a two-stage process; stage I involves the first bite of food and its transportation to the molar teeth for particle size reduction (Hiiemae et al., 1996). Food is broken down and mixed with saliva to achieve a consistency that is easy to swallow. Stage II involves the movement of the bolus to the back of the oral cavity by the tongue (Hiiemae et al., 1996). The anterior part of the tongue rises to the hard palate while the posterior portion of the tongue lowers to propel the bolus through the fauces into the oropharynx (Matsuo & Palmer, 2008).
The pharyngeal phase (involuntary control)	Before the bolus enters the pharynx, the soft palate elevates, closing the nasopharynx and preventing regurgitation into the nasal cavity (Ertekin & Aydogdu, 2003). The hyoid bone and larynx are also elevated, and the epiglottis is bent backward to help tuck the larynx under the tongue, protecting the larynx's entrance from the bolus entry (Ertekin & Aydogdu, 2003; Matsuo & Palmer, 2008). The bolus is then propelled downwards towards the oesophagus by peristalsis (Chadwick & Jolliffe, 2009).
The oesophageal phase (involuntary phase)	The opening of the upper oesophageal sphincter allows the bolus to enter the oesophagus. The bolus is transported through the oesophagus by peristalsis, and the opening of the lower oesophageal sphincter allows the entry of the food into the stomach (Matsuo & Palmer, 2008).

1.2 Dysphagia as a consequence of aging, age-related diseases and medicines

The cause of dysphagia is often considered as a result of underlying conditions. The causes of dysphagia during infancy, childhood, and adolescence include neurodevelopmental delay and acute infectious causes (Roden & Altman, 2013). In the middle-aged population gastro-oesophageal causes are observed (Roden & Altman, 2013). In older adults, dysphagia is commonly linked to oncological and neurological conditions such as head and neck cancer and stroke (Roden & Altman, 2013).

Dysphagia affects all age spans but is more common in older adults as a result of physiological changes, age-related diseases and side effects of medicines (Aslam & Vaezi, 2013). Dysphagia is reported to occur in 10-32% of older adults in the community (Bloem et al., 1990; Holland et al., 2011; Kawashima, Motohashi, & Fujishima, 2004; Roy, Stemple, Merrill, & Thomas, 2007), 12-47.4% of hospitalised patients (Carrión et al., 2015; Groher & Bukatman, 1986) and as high as 68% of institutionalized older adults in residential care homes (Steele, Greenwood, Ens, Robertson, & Seidman-Carlson, 1997).

Age-related diseases such as stroke, Parkinson's disease, dementia, cancer of the head and neck are frequently cited for causing dysphagia. A prospective based cohort study found that 80% of strokes occurred in older adults over the age of 64 in the UK (Carroll, Murad, & Majeed, 2001). Dysphagia has been reported in 23-81% of patients with stroke (Crary et al., 2013; Gordon, Hewer, & Wade, 1987; Khan, Carmona, & Traube, 2014; Martino et al., 2005; Roden & Altman, 2013; Singh & Hamdy, 2006). The prevalence of Parkinson's disease in over 65's is reported as 1.8%, and 86% of the patients diagnosed with Parkinson's disease are over 60 years of age (European Medicines Agency, 2006; Van Den Eeden, 2003). The prevalence of dysphagia in patients with Parkinson's disease is reported to be over 80% (Altman, Yu, & Schaefer, 2010; Kalf, de Swart, Bloem, & Munneke, 2012; Nilsson, Ekberg, Olsson, & Hindfelt, 1996; Roden & Altman, 2013). The prevalence of dementia has been reported between 4-7% in over 65's (European Medicines Agency, 2006). Dysphagia is reported to occur in up to 70% of patients with advanced dementia (Eggenberger & Nelms, 2004). Cancer of the head and neck is common with advancing age; between 2008 and 2010, 44% of the diagnosed cases of head and neck cancer were in patients

aged 65 and over (Cancer Research UK, 2013). Age-related conditions affect the oral preparatory stage of swallowing and also result in delays in transit of the bolus in the latter phases (Khan et al., 2014; Roden & Altman, 2013).

Medicines can also cause dysphagia as a side effect. Drugs such as anticholinergics, tricyclic antidepressants and sedatives can cause xerostomia (dry mouth) which affects bolus formation and its transportation to the stomach due to lack of lubrication (Balzer, 2000; Gallagher & Naidoo, 2009). Xerostomia is reported to occur in 12-39% of older adults, and it is more commonly a result of increased use of medicines that cause xerostomia rather than aging (Thomson, 2015).

Dysphagia can be caused by the natural process of aging (presbyphagia). Several changes occur in the swallowing process for older adults as a result of aging which are summarised in Table 1-2.

Table 1-2: Effects of aging on the swallowing process

Stages	Description
The oral phase (voluntary control)	The oral preparatory phase is affected by tooth loss and general poor dentition, resulting in an increased number of chew strokes to break food safely (Cichero & Murdoch, 2006). An increase in connective tissue in the tongue and a reduction in masticatory strength results in a reduced tongue driving force, the force necessary to propel the bolus into the pharynx, thus increasing the oral phase duration (Cichero & Murdoch, 2006; Sonies, Parent, Morrish, & Baum, 1988). Rapid ingestion of large quantities of food was observed to be a common problem in older adults for swallowing safely and an increased amount of oral phase residue was noticed post-swallow for older adults (Ekberg & Feinberg, 1991; Tracy et al., 1989).
The pharyngeal phase (involuntary control)	Delays in triggering the swallowing reflex due to more time needed to form a bolus, and an increase in pharyngeal residue post swallowing due to weaker muscle contractions have also been reported in older adults thus there is often a second reflex to clear the residue (Cichero & Murdoch, 2006; Tracy et al., 1989).
The oesophageal phase (involuntary phase)	Alterations in the oesophageal phase due to aging involve slower bolus movement and clearance (Cichero & Murdoch, 2006). Gregersen, Pedersen, & Drewes (2008) found that the peristaltic function of the oesophagus deteriorates after the age of 40, and the oesophagus becomes stiffer with age.

1.3 Diagnosis of dysphagia and the health implications

Swallowing impairment can be investigated through bedside examination or by using instruments. Bedside examination involves observation of the patient during the consumption of a small amount of food or water. This examination is subjective, and signs of coughing, throat clearing, loss of liquid from the mouth and breathlessness are observed as signs of dysphagia (Singh & Hamdy, 2006). The water swallow test includes the patient drinking 90mL of water as they usually would and signs of coughing, a wet or ‘gurgly’ voice post swallowing and an increase in respiratory rate after swallowing is observed for dysphagia (Cichero, Heaton, & Bassett, 2009).

Instruments such as endoscopy and fluoroscopy can also be used to assess dysphagia (Sura, Madhavan, Carnaby, & Crary, 2012). Videofluroscopic Swallow Study (VFSS) has traditionally been used for swallowing assessments. It involves the administration of barium liquid followed by capturing images of its movement in the oropharynx and oesophagus in lateral view (Singh & Hamdy, 2006). VFSS allows observation of entry of the barium into the airway (penetration) or below the true vocal cords (aspiration) (Singh & Hamdy, 2006). Fiberoptic Endoscopic Evaluation of Swallowing (FEES) involves insertion of a tube through the nose to the hypopharynx providing a more anatomical assessment of the pharynx (Campbell-Taylor, 2008; Nacci et al., 2008). A bolus such as water is administered and FEES permits evaluation of the upper airway and upper digestive tract (Nacci et al., 2008).

Swallowing difficulties can have detrimental health implications, including aspiration and penetration (Chadwick & Jolliffe, 2009). Penetration is defined as the passing of the bolus into the airway but not below the vocal cord and aspiration is the passing of the bolus below the vocal cord (Han et al., 2016). Aspiration can result in pneumonia which in severe cases can lead to death (Chen, Golub, Hapner, & Johns, 2009). Swallowing difficulties can also affect medicines adherence, as patients may find swallowing tablets or capsules difficult (Marquis et al., 2013). Dysphagia can also cause malnourishment (due to reduced food intake) and dehydration (due to reduced fluid intake) (Ekberg, Hamdy, Woisard, Wuttge-Hannig, & Ortega, 2002; Strachan & Greener, 2005). Difficulties in swallowing can affect eating and drinking which are social and pleasurable experiences for people. This can cause distress for patients who are unable to enjoy these pleasures and consequently cause patients to feel anxious and isolated (Ekberg et al., 2002). The inability to eat has been reported as a

social handicap that affects not only a patients' physical wellbeing but also their mental wellness (Nguyen et al., 2005).

1.4 Eating and drinking for dysphagic patients

Dietary modification is the mainstay compensatory intervention for dysphagia management (Campbell-Taylor, 2008; Ney, Weiss, Kind, & Robbins, 2009). The aim of food and drink modification is to make the transfer of food and fluid boluses from the oral cavity to the oesophagus easier. A speech and language therapist would generally assess the patient and determine the safety of oral intake.

Texture modified food is graded depending on the level of impairment in the oral preparatory phase, and a speech and language therapist will determine the person's ability to safely swallow food textures and recommend an appropriate texture accordingly (Cichero, 2013). Overall, the bolus needs to be soft for those that have difficulties in chewing food, cohesive to help those unable to manipulate the bolus safely into the pharynx and moist to aid the transport of the bolus during the swallowing process (Cichero, 2015). Although the need for textural adaption is recognised, there is no recommended instrumental ranges for softness (or firmness), cohesiveness and adhesiveness and recommendations are subjective.

There are generally three levels of texture modification depending on dysphagia severity that is commonly described as pureed, mashed or soft (Cichero, 2015). The first level of texture modification is pureed food, which does not require chewing. It is described as cohesive, homogeneous, non-sticky and lump-free (Cichero, 2015; National Dysphagia Diet Task Force & American Dietetic Association, 2002). It is usually recommended for patients with moderate to severe level of dysphagia and

patients that have severe oral phase impairment such as poor tongue control or significant difficulties in chewing ability (Cichero, 2015). Level 2 can be described as ‘mashed or minced’ food. Food in this category requires minimal chewing and can easily form into a bolus. Meats are ground or minced, and sauces, gravy or custard are added to increase the moisture content of the food (Cichero, 2015). It is recommended for patients with mild to moderate dysphagia. Patients who fatigue with chewing or take a longer time to form the bolus or have dry mouth are recommended this modification in food texture. The third consistency is ‘soft’ food that is closest to the regular food and may be prescribed for patients with mild dysphagia, those with a mildly reduced bite or chewing strength or poor dentition (Cichero, 2015).

Thin fluids (e.g. water and beverages) are modified using thickeners (gum or starch based) to increase viscosity allowing better control of the speed and direction of the bolus transiting into the pharynx, providing greater time for the airway to close and preventing spillage into the airway (Campbell-Taylor, 2008; Nicosia & Robbins, 2001; Sura et al., 2012).

Viscosity (resistance to flow) is often described as the salient property for safe-swallowing of fluids. Dysphagia thickening products often have specific quantities of thickeners to add to cold or hot beverages or water resulting in three levels of thickening. Independent of the use of thickening agents, there was no international standard relating to levels of viscosity and descriptors corresponding to the viscosity ranges (Newman, Vilardell, Clavé, & Speyer, 2016). The American National Dysphagia Diet Task Force (2002) developed and classified these consistencies (Table 1-3). The consistency stages are classified by a range of viscosities measured

at $50s^{-1}$ (the shear rate considered to represent the shear rate in the oral cavity during swallowing) for each category of thickness. The shear rate was chosen in the 1960's, a study involving sensory panels was conducted to correlate actual viscosity measurements with perceived viscosity measurements for non-Newtonian fluids (Shama, Parkinson, & Sherman, 1973; Shama & Sherman, 1973). The shear rate was assumed to be a constant, but further investigations provided a wider range of shear rates ($1\text{-}1000s^{-1}$) for fluids and foods using sensory evaluation by healthy volunteers (Shama et al., 1973; Shama & Sherman, 1973). The levels of classification of consistency depends on the severity of dysphagia.

Table 1-3: Consistencies for thickened fluids and the viscosity range measured at $50s^{-1}$ at 25°C (British Dietetic Assocatiaion, 2009; National Dysphagia Diet Task Force & American Dietetic Association, 2002).

Consistency	**Viscosity (cP)**
Stage I, mildly thick; nectar like consistency	51-350
Stage II, moderately thick; honey-like consistency	351-1750
Stage III, extremely thick; spoon-thick consistency	>1750

The differences in levels of thickening and terminology in different countries led to the development of a global standardised framework and were published in November 2015 (International Dysphagia Diet Standardisation Initiative, 2016b). The framework consists of 8 levels associated to consistencies of drink and food Figure 1-2. Liquidised food and moderately thick drink are considered to be equivalent in this framework; similarly pureed food and extremely thick liquid are shown as equivalent in Figure 1-2 as these were determined to be the same in flow characteristics by the International Dysphagia Diet Standardisation Initiative (IDDSI) committee. Transitional foods

(Figure 1-2), such as ice cream and jellies are foods that become easier to chew or swallow with lubrication in the oral cavity and are used for individuals with developmental disabilities (International Dysphagia Diet Standardisation Initiative, 2016b).

Figure 1-2: IDDSI diet framework from The International Dysphagia Diet Standardisation Initiative 2016 @https://iddsi.org/framework/ (International Dysphagia Diet Standardisation Initiative, 2016b).

1.5 Fundamental swallowing parameters

A number of parameters are reported to influence the safe transfer of bolus from the mouth to the stomach (Glassburn & Deem, 1998; Nicosia & Robbins, 2001; Pelletier & Dhanaraj, 2006; Steele & Cichero, 2008). Parameters such as tongue pressure (Nicosia & Robbins, 2001; Steele, Molfenter, Péladeau-Pigeon, Polacco, & Yee, 2014), characteristics of bolus such as viscosity, density, volume and velocity of bolus

transfer are included (Dantas et al., 1990; Sopade, Halley, Cichero, & Ward, 2007; Steele et al., 2014).

1.5.1 Tongue pressure

The tongue plays an essential role in the swallowing function; the muscles in the tongue provides a driving force to the bolus to propel it to the pharynx (Peladeau-Pigeon & Steele, 2017). The amplitude of tongue pressure vary for swallowing different consistencies. Thin liquids (water) are reported to require lower tongue pressure (approximately 15 kPa) for swallowing compared to nectar- and honey-thick fluids (approximately 20 kPa) (Gingrich et al., 2012; Steele et al., 2010, 2014).

The maximum pressure generated by the tongue is believed to decline with age; young adults reportedly apply approximately 80kPa while older adults generate approximately 60kPa (Yoshioka, Ozawa, Yuka, Mukohyama, & Taniguchi, 2004). The tongue strength was reported as significantly lower for healthy older adults showing aspiration (36 kPa) assessed using FEES compared to older adults swallowing safely (42kPa) (Butler et al., 2011) The implications of reduced tongue pressure may increase the risk of aspiration (Peladeau-Pigeon & Steele, 2017).

1.5.2 Bolus characteristics

Individuals with dysphagia require a longer time for swallowing in the oral phase to prevent premature spillage of the bolus into the airway. If the bolus transit is too fast into the pharynx, it can spill into the airway before the complete closure of the airway for safe swallowing (Lundy et al., 1999). A slower transit of bolus to the pharynx can

be achieved by increasing the viscosity of the bolus (Clavé et al., 2006; Dantas et al., 1990).

Thickened fluids have been used in dysphagia management to achieve reduced bolus velocity. Bolus velocity can be reduced by increasing the viscosity of the bolus or reducing the bolus volume (Clavé et al., 2006; Dantas et al., 1990; Tashiro, Ono, Atsuko Tanigome, Kumagai, & Kumagai, 2010). Increasing bolus volume (2.5, 5, 10, 20mL) was observed to increase velocity of the bolus in the pharynx (Ekberg, Olsson, & Sundgren-Borgström, 1988). A study assessed swallowing of thin, nectar-thick and spoon-thick liquids (Resource Thicken Up, a xanthan gum based thickener added to water) using VFSS in 46 patients with brain damage (mean age 48 years) and 46 patients with neurodegenerative diseases (mean age 54 years) (Clavé et al., 2006). The findings showed that patients with brain damage presented aspiration with thin liquids (21.6%) which were significantly reduced to 10.5% with nectar thick liquids and reduced further to 5.3% with spoon-thick liquids. Aspiration was observed in up to 29.7% of neurodegenerative patients swallowing thin liquids; this was reduced significantly to 22.3% with nectar, and less than 3% with spoon-thick liquids (Clavé et al., 2006). Another study assessing swallowing of nectar thick and honey-thick liquids in 711 patients aged 50-95 who have presented aspiration on thin liquids using VFSS found that elimination of aspiration occurred more often with honey-thickened liquids (63%) than nectar thick liquids (53%) (Logemann et al., 2008).

Bolus volume is also reported to influence the safety of swallow. A significant risk of aspiration was reported for bolus volume of 20mL compared to 5, 10 and 15 mL in healthy older adults (61-70 years) (Butler et al., 2010). Higher bolus volumes (2-20mL)

were reported to increase oral retention time and a greater magnitude of structural movement was required for oropharyngeal clearance (Dantas et al., 1990). However, too small a volume (1mL vs 5mL) was also reported more challenging to swallow by stroke patients (Bisch, Logemann, Rademaker, Kahrilas, & Lazarus, 1994).

Although the focus of dysphagia management is modifying the viscosity of liquids, other properties such as cohesion and yield stress of fluids have also been mentioned in literature, albeit scarcely, that might contribute to safe-swallowing. Thin liquids with low cohesion between particles can result in spillage into the airway in dysphasic patients due to the patients' inability to control laryngeal closure (Cichero & Murdoch, 2006; Prinz & Lucas, 1997; Tashiro, Ono, Atsuko Tanigome, Kumagai, & Kumagai, 2010). Yield stress described as the minimum stress required to enable flow is reported as a potentially relevant parameter in safe swallowing, as the yield stress must be surpassed to allow the flow of the bolus (Cho, Yoo, & Yoo, 2012; Steele & Cichero, 2007). Viscosity and yield stress are both linked intrinsically to flow (Payne, Methven, Fairfield, Gosney, & Bell, 2011; Popa Nita, Murith, Chisholm, & Engmann, 2013). As reported earlier, increasing thickening and hence yield stress, requires greater tongue strength to propel the bolus in to the pharynx (Gingrich et al., 2012; Steele et al., 2010, 2014). Bolus density (mass per unit volume) relating to the weight of the fluid has also been described particularly important for swallowing. Density and yield stress of fluids have been linked to increasing solid content (Germain, Dufresne, & Ramaswamy, 2006; Sopade et al., 2007). Dantas et al., (1990) reported barium paste (density of 2.8g/cm^3) showed a slower oral and pharyngeal transit time in healthy subjects compared to liquid barium (density of 1.4g/cm^3).

A study was conducted in eighteen young students (aged 22-25) for sensory analysis of perceived ease of movement of semi-liquid samples (prepared using pregelatinized waxy corn starch as a thickener) in the pharynx, comparing to videomanoflurography (combination of manometry and videoflurography) measurements (Takahashi, Nitou, Tayama, Kawana, & Ogoshi, 2002). A compression test using a texture analyser was used to characterise the semi-liquid samples for hardness, cohesiveness, and adhesiveness. Thickened samples showed an increase in hardness, viscosity and adhesiveness with increasing thickener concentration; however, the cohesiveness of all samples was similar. The study found that increased hardness, viscosity and adhesiveness resulted in perceived difficulty in swallowing and slower bolus transit in the pharynx assessed by videomanoflurography (Takahashi et al., 2002).

1.6 *In vitro* swallowing models

There have been attempts to study the *in vitro* swallowing behavior of fluids and food using less cumbersome and less invasive approaches compared to *in vivo* assessments such as endoscopy. Nicosia & Robbins (2001) used two parallel plates simulate the tongue movement against the palate in order to derive mathematical models to calculate the flow of bolus in the oral cavity. The study found that the time taken to clear half of the bolus in the mouth and the pressure applied by the tongue increased with increasing bolus density and viscosity. Mackley et al. (2013) used an *in vitro* throat model (Figure 1-3) with the geometry of an adult human throat simulating tongue peristalsis, to observe *in vitro* fluid flow behavior. The model consists of a “throat” with static features such as the epiglottis (Mackley et al., 2013). The roller represents the tongue which is activated by releasing a weight attached to the pulley wheel (Mackley et al., 2013). The upper section of the ‘mouth’ in the throat model required a tube which is pushed backward by the moving roller (Mackley et al., 2013).

The study found that the time taken to complete roller motion and the time taken for boluses to move from the epiglottis to the airway divide in the throat model increased with increasing viscosity of the test fluid.

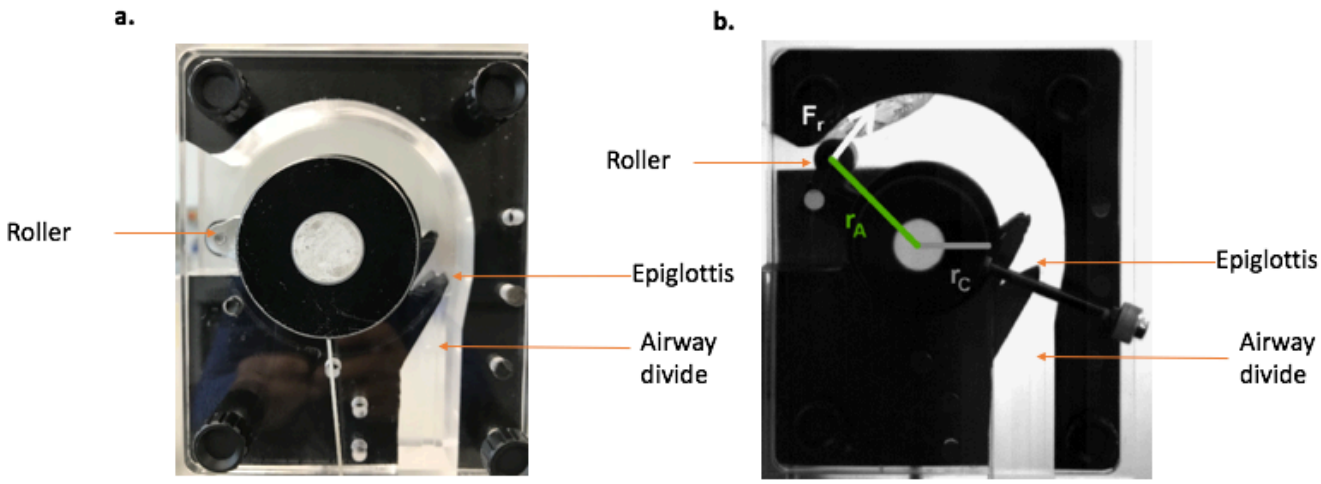


Figure 1-3: a) *In vitro* throat model (Mackley et al., 2013) and b) the modified *in vitro* throat model (reprinted with permission) from Hayoun et al., 2015).

A modified version of this throat model was developed with the addition of a counter weight to equilibrate the weight of the pivoting arm and an initial angular position of the roller (θi = 45°) to better mimic the contact between the tongue and bolus (Hayoun et al., 2015). The study involved processing Newtonian sugar molasses in the throat model and found that an increase in viscosity resulted in higher residual mass in the oral phase and a slower bolus flow. Despite the link of density and viscosity increasing with solid content in thickened fluids, a study on the flow of Resource ThickenUp Clear (xanthan gum thickener) and E-Z- Paque (barium) contrast agent containing 41% higher density than the thickener in this throat model showed that an increase in bolus

density to play a negligible difference in bolus propulsion in the mouth (Mowlavi et al., 2016).

There are other *in vitro* models focusing on the oral processing aspect of swallowing. Woda et al. (2010) developed and validated a mastication simulator to produce food bolus with similar particle sizes compared to expectorated peanuts and carrots from healthy subjects. Parameters such as the number of chewing cycles and duration, temperature control, compression force and saliva addition can be controlled. Size reduction in agar gels was observed using an artificial tongue (silicone rubbers of varying elastic moduli) in between a compression apparatus (metal) to simulate tongue-palate compression (Ishihara et al., 2012). The study found that fracturing of agar gels occured when the deformation (strain) of gels was larger than the artificial tongue and the gels remained intact when the strain of gels was smaller or equivalent to the artificial tongue (Ishihara et al., 2012). More recently, an *in vitro* device focusing on the pharyngeal swallowing process has been developed (Stading et al., 2019). A syringe is used to deliver a bolus into the artificial pharynx made of a polycarbonate-like material (Accura ClearVue), the device can simulate closing of the larynx and a moving epiglottis using a stepper motor, and the upper oesophageal sphincter is modeled using a clamp. The device allows a velocity profile of bolus movement in the pharynx to be obtained (Stading et al., 2019).

Although *in vitro* simulators cannot replace clinical testing as it is difficult to mimic the complicated biophysical reality of swallowing; it can be used to discriminate the flow behavior of different products to aid selection for *in vivo* testing.

1.7 Medicines management in patients with dysphagia

Aspiration or choking risk is a concern for patients unable to safely swallow their medicines. The IDDSI recommends from a texture perspective, individuals who can manage regular food (Level 7, Figure 1-2), soft and bite-sized foods (Level 6, Figure 1-2) and minced and moist foods (Level 5, Figure 1-2) may be able to swallow tablets and capsules safely (International Dysphagia Diet Standardisation Initiative, 2016b). Individuals on lower levels of texture modifications are considered at risk of choking or aspiration to swallow (International Dysphagia Diet Standardisation Initiative, 2016b).

There has been some endeavour to quantify the extent of difficulties in swallowing SODF in older adults. No definition of swallowing difficulties have been provided in literature relating to difficulties in swallowing SODF, however, challenges in swallowing the SODF are usually related to dysphagia. A study conducted in 17 community pharmacies (independents and multiples) in England and Northern Ireland, distributed questionnaires to 792 patients suspected of having swallowing difficulties (Strachan & Greener, 2005). The study found that 60% of patients (aged 60-89) indicated difficulties in swallowing tablets and capsules (Strachan & Greener, 2005). Difficulties in swallowing SODF were observed in 29.5% of hospitalised older adults in France (Fodil et al., 2017). A survey of 540 nurses working mainly in nursing homes for older adults in the UK found that on average 15% of residents had difficulties in swallowing tablets and capsules (Wright, 2002). Schiele et al. (2015) found that patients with stroke-induced dysphagia had increased risk of penetration-aspiration when swallowing SODF together with spoon-thick consistency thickened fluid. Out of 52 patients, 40.2% of patients experienced severe difficulties in swallowing SODF with

spoon-thick water (Schiele et al., 2015). Changing the type and shape (round, oval, oblong and capsule) of the SODF did not modulate the risk of penetration-aspiration (Schiele et al., 2015).

Medicines administration difficulties are ideally addressed by prescribing alternative drug delivery formulations such as liquids when SODF are not suitable. In practice, in order to help patients swallowing their medications, SODF are sometimes administered unlicensed, by splitting, chewing or crushing tablets or opening capsules. Modifying SODF should be the last resort when no licensed alternatives are available (Wright et al., 2006). However, if liquid alternatives are unavailable or are expensive to prescribe then manipulation of SODF is common practice to facilitate ingestion of medicines. The practice of medicines modification is often outside the product license; this places the liability of harm with the prescriber or administrator (nurse or carer) (Barnett & Parmar, 2016).

A study involving a self-administered questionnaire to nursing home nurses found the most common method employed by nurses for medicines administration for patients with swallowing difficulties was obtaining a liquid alternative (88% of nurse respondents), followed by crushing tablets or opening capsules (61% of nurse respondents) (Wright, 2002). Studies in aged-care facilities in Australia and Ireland found that 18-35.1% of residents had medicines modified (i.e., crushing tablets) to facilitate ingestion (Gillicuddy et al., 2016; Mercovich, Kyle, & Naunton, 2014; Paradiso et al., 2002). This practice of modifying medicines was also observed for community-dwelling patients; 68% of 792 patients suspected of having swallowing difficulties, crushed their tablets or opened capsules to release the content to help swallow their

medicines (Strachan & Greener, 2005). A survey into medicines modification for five community pharmacies in Australia found that 10.6% of the 369 patients (ages 18- 60 years plus) modified their medicines (Lau, Steadman, Mak, Cichero, & Nissen, 2015). A questionnaire survey conducted in eleven general practices in Germany, found that 58.8% of the 393 patients (18- 80 years, mean 61.8 years) with swallowing difficulties modified their SODF (Schiele, Quinzler, Klimm, Pruszydlo, & Haefeli, 2013). Observation of medicines administration for 1257 oral doses in 36 drug rounds at a psychiatric hospital in the UK found that 26% of SODF were altered to facilitate swallowing and 44% of these alterations were not authorised by a pharmacist (Haw, Stubbs, & Dickens, 2007). A study in hospitals in Queensland using self-report surverys found 79% (n=31) of hospitals reported medication for adults and children were modified at the bedside, 88% of 73 medications modified were for adults (Nissen, Haywood, & Steadman, 2009).

It is recognised that modification of SODF is common practice to help swallow medicines, but this can be harmful particularly for more complex SODF where the rate and site of drug release must not be altered. For example, modified release formulations such as enteric coated and sustained release formulations are designed to provide either delayed release or extended release of the drug. Enteric coated products are designed to pass through the stomach unaltered and release the drug content within the intestinal tract (Porter, Sackett, & Liu, 2017). Enteric coating is used for many reasons including preventing degradation of acid-labile drugs and stomach irritation. Alteration of these dosage forms can result in reduced drug absorption and efficacy and may irritate the stomach mucosa if the enteric coating is used to reduce irritant effects (Mercovich et al., 2014). Sustained release dosage forms are designed

to release drug content slowly over an extended period to reduce multiple daily dosing for drugs that have short half-lives (Mercovich et al., 2014; Paradiso et al., 2002). These dosage forms contain more drug content than conventional immediate release dosage forms, and altering these formulations can result in the entire drug content being released instantly, having the potential to cause toxicity (Schier et al., 2003). Even for immediate release dosage forms that are designed for immediate disintegration and dissolution after ingestion (mostly in the stomach), modifying these dosage forms may result in alternation of absorption and bioavailability (Dodds Ashley, Zaas, Fang, Damle, & Perfect, 2007; Henney, Fitzpatrick, Stewart, & Runyan, 2008; Lippert, Gbenado, Qiu, Lavin, & Kovacs, 2005; Zafar, Farkouh, Fuster, & Chesebro, 2009). For example, crushed voriconazole tablets showed higher drug absorption compared to the tablets administered intact (Dodds Ashley et al., 2007). Additionally, the loss of drug during crushing and transferring may also lead to subtherapeutic dosing (Manessis et al., 2008; Thong, Manrique, & Steadman, 2018). Furthermore, modification of light-sensitive drugs could compromise the stability of the drug (Paradiso et al., 2002; Root, Tomlin, Erskine, & Lowey, 2011).

Difficulties in swallowing medicines can be challenging for patients prescribed multiple medications. Many older adults are prescribed polypharmacy (average 5 or more medications) to treat multimorbidity (two or more disease states) (Hughes, Cadogan, Patton, & Ryan, 2016; Morin, Johnell, Laroche, Fastbom, & Wastesson, 2018). The pill-burden may complicate adherence particularly in patients with swallowing difficulties. Strachan & Greener (2005) reported that 64% of patients in the community setting admitted to not taking their medication as a result of swallowing difficulties and a study conducted in polypharmacy patients in the community setting (mean age 67

years) reported that 23% of patients with ongoing (9.0%) or past (13.4%) swallowing difficulties did not take their medication (Marquis et al., 2013). Non-adherence with SODF is not just limited to swallowing difficulties. Individuals without swallowing difficulties may have an aversion or anxiety towards swallowing tablets and capsules (Schiele et al., 2013). Individual with previous experience of tablets or capsules stuck in their throat, choking, gagging, repeated swallowing attempts led to 28.2% of 393 of patients fearful of swallowing their medicines (Schiele et al., 2013). Patients experiencing pill swallowing discomfort may go unreported out of embarrassment or feeling that difficulty in swallowing is normal (Llorca, 2011).

1.8 Other physiological changes with aging

Apart from changes in absorption and bioavailability from modifications of medicines, there are also noteworthy physiological changes during ageing affecting therapeutic effects. Pharmacokinetics is a term used to describe physiological processes affecting absorption, distribution, metabolism, and excretion (ADME) of the drug. There are important physiological changes that occur with aging and changes in ADME that will influence the physiological response to the drug treatment (Perrie et al., 2012).

Drug absorption occurs mainly in the small intestine after gastric emptying. Gastric motility is reduced with aging which may result in reduced or delayed drug absorption (Evans, Triggs, Cheung, Broe, & Creasey, 2015). Gastric pH increases with aging as gastric acid production decreases; the increase in gastric pH may affect ionisation and solubility of the drug in the stomach and subsequent drug absorption (Baron, 1963; Lavan, O'Grady, & Gallagher, 2017). For example, a subtherapetic response may be

observed for ketoconazole, a weakly basic drug, which has low solubility at higher pH (Lahner, Annibale, & Delle Fave, 2009).

Drug distribution occurs after drug absorption. The body composition of fat, protein, and water differ from older adults (30:12:54) to younger counterparts (18:16.5:60) (Piug, 1996). Drug distribution is effected by body composition changes. Lipophilic drugs show a higher volume of distribution compared to hydrophilic drugs due to the increase in fat (Klotz, Avant, Hoyumpa, Schenker, & Wilkinson, 1975; Robertson et al., 1989). This can result in increased elimination half-life for liphophilic drugs and therefore a prolonged drug effect and accumulation with the potential for adverse drug events and toxicity (Lavan et al., 2017). For example, diazepam is a lipophilic drug and has a two-fold increase in half-life in older adults and therefore, a reduced dose is required for older adults compared to adult patients (Herman & Wilkinson, 1996). The volume of distribiution decreases for hydrophilic drugs and therefore, a higher plasma concentration of the drug for older adults which can result in toxicity (Lavan et al., 2017). Furthermore, reduced plasma protein levels such as albumin and α-acid glycoprotein may lead to an increase of unbound drug in the plasma which is pharmacologically active increasing the chances of adverse drug events and toxicity (Heuberger, Schmidt, & Derendorf, 2013).

Drug elimination is dependent on liver function for drug metabolism followed by excretion through the kidneys. Changes in drug metabolism in older adults are associated with reduced hepatic blood flow, decreased hepatic function and activities of liver enzymes such as the cytochrome p450 system; this reduces the metabolic elimination of drugs and results in a prolonged half-life of drugs (Abernethy,

Greenblatt, & Shader, 1985; Turnheim, 2003). Higher bioavailability of drugs and reduced metabolic clearance may require dose adjustment to avoid adverse events, for example for drugs such as morphine and verapamil (Eldesoky, 2007; Guay, 2007).

A decline in glomerular filtration rate and renal plasma flow occurs with age which would reduce the rate of clearance for drugs predominantly eliminated by the kidneys such as gentamycin and acyclovir (Eldesoky, 2007; Hilmer et al., 2011; Mühlberg & Platt, 1999).

1.9 Dosage form considerations for dysphagic patients

The shortfall in medicines provision for patient sub-groups such as children and older adults is recognised. In 2007, the Paediatric Regulation was enforced in the European Union to address the lack of appropriate paediatric medicines (European Medicines Agency, 2011b). The objective of this regulation was to improve drug formulations for children aged 0-18 years (European Medicines Agency, 2011b). Guidance released by the European Medicines Agency (EMA) in 2011 for paediatrics stressed that acceptability must be considered in paediatric formulation development and provided guidance on considering the appropriateness of the pharmaceutical dosage form for paediatrics with consideration of dosing frequency, excipients and packaging (European Medicines Agency, 2011b). This guidance was further updated in and released in 2014 (European Medicines Agency, 2013b).

The European Medicines Agency (EMA) also recognized that older adults are the main users of medications and in 2011, the EMA released Geriatric Medicines Strategy with the aim to ensure medicines used by older adults are evidence-based and to improve the availability of information for informed prescribing and use of medications

(European Medicines Agency, 2011a). The Geriatric Expert group was established in 2011 to provide scientific advice of the development and assessment aspects of medicines and released a concept paper outlining the need of a reflection paper on the quality aspects of medicines for older adults (European Medicines Agency, 2013c, 2013a) . The intention was to identify the limitations of licensed pharmaceutical dosage forms in meeting the needs of older adults. Acceptability of dosage forms has been defined as the “overall ability of the patient or caregiver to use a medicinal product as intended or authorized” and acceptability is an important aspect of pharmaceutical dosage form consideration for both paediatric and geriatric patients (Kozarewicz, 2014). The EMA Quality Working Party released a draft reflection paper in 2017 highlighting the distinct needs of older adults for drug products with the reflection of advantages and disadvantages of different dosage form preparations with particular importance to patient acceptance and willingness to take their medication and acceptance by caregivers to administer the medication as authorized (European Medicines Agency, 2017).

Aging is associated with multimorbidity and patients can have disabilities that may affect the handling and use of dosage forms (Stegemann, 2018). Preparations such as buccal or sublingual dosage forms pose a risk for accidental swallowing (European Medicines Agency, 2017). This requires particular attention to patients with impaired cognition and reduced physical capabilities, both associated with aging (Sino, Sietzema, Egberts, & Schuurmans, 2014). Preparations for nasal and inhalation administrations require specific skills for usage which again would be challenging for patients with difficulties in understanding or cognitive impairment (Iwanaga, Sano, & Tohda, 2017). Transdermal patches require reaching the site of administration which

may be challenging for patients with reduced physical capabilities and would also be limiting for patients with polypharmacy, which would require a number of patches to be applied (Kaestli, Wasilewski-Rasca, Bonnabry, & Vogt-Ferrier, 2008). Similarly, rectal and vaginal preparations would be challenging for patients with cognitive difficulties and patients may also feel embarrassed in asking assistance from caregivers to apply these preparations (European Medicines Agency, 2017).

For patients with difficulties in swallowing the obvious route in dosage form development may be to avoid the oral route of administration. However, this is the preferred route of administration across ages and is the most commonly used and convenient for patients (European Medicines Agency, 2017). There are many factors such as size, shape, and density of the medication that can affect the ease at which a patient swallows their medicines and are discussed below (Channer & Virjee, 1986; Perkins et al., 1999).

1.9.1 Tablet and capsule considerations for ease of swallowing

The transit of tablets and capsules through the oesophagus is influenced by many factors; including the size, shape, density and surface characteristics of the dosage form (Channer & Virjee, 1986; Perkins et al., 1999).

The size and shape of the tablets and capsules can influence the ease of its transit through the oesophagus (Overgaard, Højsted, Hansen, & Christrup, 2001). A study by Yamamoto et al. (2013) found that an increase in the size of the tablet requires more effort in swallowing and consequently resulted in an increase in a number of swallows in fourteen male adults (24-33 years) assessed using electromyographic activity and

videofluorographic images. Smaller tablets were found easier and more comfortable to swallow by adults than larger ones and the oesophageal transit time was found to increase with larger tablets assessed using VFSS and patient preference rating (Channer & Virjee, 1986; Overgaard et al., 2001). Oblong and oval tablets transit better through the oesophagus compared to circular tablets, and arched tablets pass through the oesophagus better than flat tablets in adults assessed using VFSS and patient prefererence (Channer & Virjee, 1986, 1985; Hey, Jørgensen, Sørensen, Hasselbalch, & Wamberg, 1982; Overgaard et al., 2001).

Gelatine capsules have been reported to have an adhesive nature and are likely to be more prone to delayed oesophageal transit (Channer & Virjee, 1985; Hey et al., 1982; Osmanoglou et al., 2004). Studies by Perkins et al.,(1994, 1999) found that the oesophageal transit time in healthy adults (50-79 years) of the gelatin capsule was slower than that of an oblong shaped uncoated tablet and a cellulose film-coated tablet. However, contradicting results were found by Channer & Virjee (1986, 1985) who reported that the oesophageal transit of capsules was found to be shorter than uncoated oval tablets in 115 subjects (aged 17-82 years).

A study in the general practice population found that patients with swallowing difficulties preferred tablets over capsules, and round tablets over oval or oblong tablets (Schiele et al., 2013). This contradicts the findings presented in the studies of oesophageal transit of different solid oral dosage forms (Channer & Virjee, 1986, 1985; Hey et al., 1982; Overgaard et al., 2001). The authors speculated that difficulties or discomfort in swallowing oval or oblong tablets or capsules might be due to the tablet or capsule rotating during deglutition (Schiele et al., 2013). A study assessing the

swallowability of medium sized (1-1.5cm diameter) round, oval, oblong tablets and a capsule in older adult patients with dysphagia was assessed using FEES and VFSS in 41 patients found no significant differences between the type and shape of SODF for penetration-aspiration (Schiele et al., 2015). Patient posture has been considered in aiding swallowing of SODF. Postural changes are used as compensatory treatments for oropharyngeal dysphagia. Schiele, Schneider, Quinzler, Reich, & Haefeli (2014) investigated two methods of swallowing SODF, the pop-bottle method for tablets and lean-forward technique for capsules in 151 participants (aged 18-85 years) with 56% of participants reporting difficulties in swallowing SODF. The pop-bottle method involved placing placebo tablets (round, oval, oblong) on the tongue, followed by closing the lips firmly around the opening of a polyethylene terephthalate bottle and swallowing the tablet in a quick suction movement (Schiele et al., 2014). The lean-forward method involved swallowing the capsules in an upright position and tilting the head forward. Participants swallowed the SODF using 20mL of water and rated the ease of swallowing on an 8-point Likert scale (Schiele et al., 2014). The pop-bottle method improved swallowing in 59.7% of patients and the lean-forwad technique improved swallowing for 88.6% of patients (Schiele et al., 2014).

1.9.2 Liquid formulation considerations

Oral liquid dosage forms are advantageous for dosing flexibility and the potential for administration via enteral feeding tubes (European Medicines Agency, 2017). However, in the older adult population, when administrating liquid medicines, patients may experience difficulty in opening the container and shaking the liquid preparation for homogeneity increasing the risk of dose errors and spillages (European Medicines Agency, 2017; Notenboom et al., 2014). The viscosity of liquid formulations is an

important factor to consider for patients with dysphagia particularly if they are at risk of aspiration. In some cases, thickeners may need to be added to aid swallowing for patients with dysphagia, which may pose difficulties for administration to these patients whom dislike thickened fluids (Garcia, Chambers, & Molander, 2005; Murray, Miller, Doeltgen, & Scholten, 2014; Shim, Oh, & Han, 2013). If this is outside the manufacturers recommendations then this could render the medicine as unlicensed (Kelly & Wright, 2009).

The influence of taste of liquids on the ease of swallowing has been investigated. The four main taste sensations traditionally recognised consist of; sweet, sour, salty and bitter (Chee, Arshad, Singh, Mistry, & Hamdy, 2005; Leow, Huckabee, Sharma, & Tooley, 2007). A study by Leow et al. (2007) found that the sour (citrus) taste had the shortest oral bolus preparation time, significantly different from that of sweet (glucose), salty (saline), bitter (quinine) and neutral tastants. However, no significant differences between neutral, salty, bitter tastants for oral preparation times. A combination of sour taste and cold stimuli was found beneficial for patients with oropharyngeal dysphagia by reducing the pharyngeal transit time (Cola et al., 2010). The use of sour tastant (citrus) has also been found to stimulate saliva secretion (Gupta, Epstein, & Sroussi, 2006). Carbonated water has been reported to reduce aspiration penetration risk and improve pharyngeal transit compared to non-carbonated water in 17 adults (18-80 years) with neurogenic dysphagia (Sdravou, Walshe, & Dagdilelis, 2012). Carbonated water is found to chemically stimulate the protective reflexes which protect the airway in healthy adults (Miura, Morita, Koizumi, & Shingai, 2009; Sdravou et al., 2012).

The influence of postural change on ease of swallowing liquids has also been investigated. The chin-down posture (moving the head downwards to touch the chin to the neck) and the head rotation posture is reported to aid narrowing of the laryngeal entrance and provide a posterior shift of the epiglottis, allowing more enhanced protection of the airway (Logemann et al., 2008; Rasley et al., 2013). The head rotation maneuver moves the bolus away from the direction of the head turn while swallowing; this is useful for patients with neurological damage in the pharynx to enable bypass of the effected area during swallowing (Ohmae, Ogura, Kitahara, Karaho, & Inouye, 1998). The chin-down and head rotation posture have been useful compensatory techniques in swallowing liquids and preventing penetration-aspiration in patients with dysphagia (Logemann et al., 2008; Rasley et al., 2013; Solazzo et al., 2012; Terré & Mearin, 2012).

1.9.3 Dispersible and effervescent tablets

Dispersible and effervescent tablets are solid oral tablets that are dispersed in a liquid to form a solution before administration. Similarly to liquid formulations, thickeners may need to be added for patients at risk of aspiration which may render the medicine as unlicensed if it is outside the manufacturers' recommendations. These tablets often require a large amount of water to form a solution. This can be problematic for patients who are fluid restricted, i.e., patients with cardiac disease and for patients with dysphagia who may aspirate with large sip volumes (Butler et al., 2010). These tablets also often contain a large amount of sodium, which can be an issue for patients who require a reduced salt intake, i.e., patients with hypertension (George, Majeed, Mackenzie, Macdonald, & Wei, 2013). Sodium based formulations of effervescent and dispersible nature were found to increase the risk of cardiovascular events;

myocardial infarction, stroke and vascular death compared to standard non-dispersible, non-effervescent and non-soluble formulations of the same drugs (George et al., 2013). A study by Ubeda, Llopico, Sanchez, & Al (2009) found a link between an increase in blood pressure in the elderly and the use of effervescent paracetamol.

1.9.4 Orally disintegrating formulations

Orally disintegrating systems include tablets, films, and wafers (also known as orodispersible strips) (Kathpalia, Sule, Gupte, 2013). The demand for orally disintegrating formulations has increased particularly for the geriatric and paediatric populations who experience difficulties in swallowing SODF (Nagar et al., 2011). The Food and Drug Administration (2008) define orally disintegrating tablets (ODT) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". There have been many orally disintegrating tablets developed for age-related conditions such as Parkinson's disease and Alzheimer's disease (Muramatsu, Litzinger, Fisher, & Takeshita, 2010). A multicenter study by (Nausieda et al., 2005) found that patients with Parkinson's disease preferred ODT of carbidopa-levodopa compared to the conventional tablet formulation.

ODT's have the advantages of requiring a fewer number of swallows, less fluid requirement, reduced muscular effort and swallowing duration (Carnaby-Mann & Crary, 2005). Carnaby-Mann & Crary (2005) investigated the swallowing effectiveness of ODT and conventional tablets. The study found that patients with dysphagia required higher number of swallows to clear the conventional tablet from the oropharynx and more time and larger volume of liquid were required to swallow

conventional tablets compared to ODT. The risk of aspiration, however, was found to be similar for both ODT and conventional tablets (Carnaby-Mann & Crary, 2005). ODT's also have limitations of difficulty in taste masking, the maximum dose that can be incorporated is low and in achieving customized drug release e.g. controlled or delay release (Lopez, Ernest, Tuleu, & Gul, 2015; Venkatesh, Stevens, & Lai, 2012; Walsh et al., 2014).

1.9.5 Chewable tablets

Chewable tablets are tablets that are designed to be mechanically disintegrated by chewing. Chewable tablets are a choice for patients who find swallowing solid oral dosage forms difficult. These are not intended to be swallowed intact and have to be chewed completely before swallowing (Gupta, Chidambaram, & Khan, 2013). However, for older adults with poor dentition and reduced chewability, this would prove difficult (European Medicines Agency, 2017; Liu et al., 2014). There have been reports of adverse events as a result of patients swallowing partially chewed or intact chewable tablets, resulting in intestinal obstruction, ischaemia, and perforations (Gupta et al., 2013). There have also been reports of tooth damage due to hard chewable tablets in older adults (Gupta et al., 2013).

1.9.6 Mini-tablets

Mini-tablets contain a small amount of the required dose and normally have a diameter of 1-4mm in diameter (European Medicines Agency, 2011b; Stoltenberg & Breitkreutz, 2011; Tissen, Woertz, Breitkreutz, & Kleinebudde, 2011; Wen & Park, 2011). Mini-tablets offer many advantages. They offer high drug loading and have good size uniformity, regular shape and a smooth surface (Hadi, Rao, & Firangi, 2012).

Liu, Ghaffur, Bains, & Hamdy (2016) assessed the acceptability of mini-tablets in older adults using a questionnaire in the community setting; 115 patients were shown samples of mini-tablets filled in hard gelatin capsules and patients were asked to provide their opinion on acceptance. Seventeen participants were reported to have swallowing difficulties and twelve reported ongoing difficulties in swallowing SODF (Liu et al., 2016). Participants (dysphagic and non-dysphagic) preferred minitablets over granules and chewable tablets but mini-tablets were less favorable than dispersible and orally disintegrating tablets (Liu et al., 2016). Mini-tablets offer better dosing flexibility compared to granules, however, these dosage forms may result in chewing to aid swallowing and thus not suitable for sustained release dosage forms (van Riet-Nales et al., 2016). However, participants reported that minitablets might be challenging for the visually impaired to use and expressed reservations on taste and concerns about not receiving the full dose when mixing minitablets with food if the meal is not fully consumed (Liu et al., 2016).

1.9.7 Multiparticulate dosage forms

Multiparticulate dosage forms include granules, powders and pellets (maximum size 2.8 mm) that are incorporated into capsules or can be sprinkled onto food or reconstituted to a solution or suspension (Food and Drug Administration, 2012). Multiparticulates can be further processed into conventional tablets, chewable tablets, and orally disintegrating tablets.

In the study by Liu et al. (2014), multiparticulates presented in the form of granules for sprinkling onto food were least accepted by older adults with and without dysphagia compared to minitablets, dispersible tablets, orally disintegrating tablet and chewable

tablets (Liu et al., 2016). Similar to mini-tablets, participants favored the multiparticulates as useful for those with swallowing difficulties (Liu et al., 2016). However, they expressed dislike of multiparticulates at needing to complete a meal for the whole dose and were reserved on mixing the multiparticulates with the food with concerns raised to a potential change in flavor of food (Liu et al., 2016). Adults and older adults recruited in another study also expressed a preference for chewable tablets compared to multiparticulates; multiparticulates were considered more time consuming than chewable tablets for administration (Den Uyl et al., 2010). Acceptability and palatability of coated and uncoated multiparticulate pellets with particule sizes of 200, 350, 500 and 700μm were studied in 61 adults (18-37 years) (Lopez et al., 2018). Acceptability was measured on voluntary consumption of the sample, facial observation, ratings using hedonic scale and the willingness to take multiparticulates daily (Lopez et al., 2018). Palatability is considered to affect acceptability and is the overall appreciation of the dosage form by organoleptic properties such as mouth feel, appearance, smell and taste (Kozarewicz, 2014). Palatability was assessed based on grittiness perception in this study (Lopez et al., 2018). Five hunded milligrams of microcrystalline cellulose pellets were administered with 3mL of spring water and palatability was assessed using a 5-point hedonic scale. The ability to swallow the pellets was 100% for adults assessed by participants not refusing the administration or expelling the placebo pellets. The willingness to take multiparticulates daily was 74% of adults. Smaller sizes and coated pellets were more favoured by adults (Lopez et al., 2018). Grittiness perception received negative scores by 51% of adults (Lopez et al., 2018).

1.9.8 Novel approaches for immediate release dosage form delivery in patients with dysphagia

Several novel technologies have been developed to help patients swallow SODF. Okabe et al. (2008) prepared a dry film formulation that turns into jelly by absorbing a small amount of water or saliva. Drug elution in the mouth was restrained due to gelating layers on either side of the drug-containing layer (Figure 1-4). The oesophagus transit time of the film formulation was found significantly quicker than the gelatin capsules in 10 healthy volunteers (Okabe et al., 2008). This approach may be difficult for patients with xerostomia which is common in older adults (Cassolato & Turnbull, 2003).

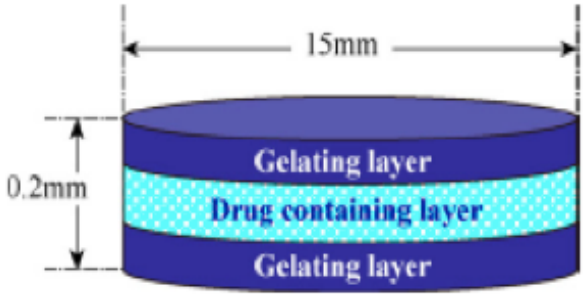


Figure 1-4: Schematic representation of the film formulation (reprinted with permission) (Okabe et al., 2008).

Another approach for easy swallowing is the development of an oral jelly formulation developed for older adults for alendronate sodium hydrate in Japan (Imai, 2013). These dosage forms have an advantage of easy swallowing, taking medicine without water, masking the drug taste and lower risk of accidental ingestion (Imai, 2013). The dosage form comprises of a jelly and air portion, allowing the jelly to be pushed out when opening the package (Imai, 2013).

Innovations have been made in the last two decades in approaches to ease swallowing of medicines, such as inventions aiming at enveloping the dosage form thereby increasing the size with a gel to assist the movement of the dosage form in the throat. Atsuko, Masanori, Takashi, & Mika (2001) developed a swallowing-assistive jelly (Ryukakusan's swallowing aid jelly) using natural polymers such as agar, locust bean gum, pectin, carrageenan and xanthan gum. The jelly negates the use of water for swallowing tablets and capsules. Craig, Wright, Mencarelli, & Rogerson (2006) developed a pre-gel mold comprising hydroxypropylmethyl cellulose (HPMC) and gelatin which envelopes the SODF in water. A *In vivo* study of the swallowing of the pre-gel mold was conducted with the aim to determine whether there is a separation of gel and tablet (participant perception) and visual assessment of swallowing of the tablets with the gel using FEES (Mencarelli, 2009). Pre-spillages of fluid or gel were seen in two participants when swallowed with and without water. Five samples were perceived as fractured and five tablets separated from the gel (Mencarelli, 2009). Another pill enveloping material comprising of corn starch, glycerin, xanthan gum, agar, and carrageenan becomes slippery on contact with saliva or water (Gath, 2016). A lubricating spray for SODF consisting of glycerin, propylene glycol, polyethylene glycol, xanthan gum, carboxymethylcellulose, alginate, carrageenan, and microcrystalline cellulose were developed to facilitate ease of transit of SODF in the oral cavity (David, 2007).

Diamond & Lavallee (2010) described a product called Pill Glide; a flavored spray that requires the patient to coat the back of the mouth and tongue by spraying. This creates a lubricated surface that facilitates ease of swallowing of solid oral dosage forms. Pill

glide was found to reduce medicine taking difficulty in children (6-17 years) assessed using self-reporting diaries with 6-point hedonic scale (Jagani et al., 2016).

Another product developed is the MedCoat, a thin coating (consisting of gelatine, sweeteners and flavoring agents) that the patient applies on the tablet before swallowing. The coating is used to improve the taste of the tablet, and 97.6% of 41 healthy volunteers (ages 18 to 64 years) found it easier to swallow than non-flavored placebo tablets (Uloza, Uloziene, & Gradauskiene, 2010). An acceptability study in children (2-17 years) for MedCoat found that the ability to swallow solid oral dosage forms (tablets and capsules) improved in 66 of 67 children assessed using questionnaires (El Edelbi, Eksborg, & Lindemalm, 2015).

1.10 Sustained release dosage forms

Sustained release dosage forms are dosage forms where there is a sustained release of the active ingredient compared to the release of the active ingredient from immediate release dosage forms administered by the same route (European Medicines Agency, 2013a). Sustained release dosage forms are also known as controlled release, prolonged release, extended release dosage forms and would often have the letters MR, SR, XL and LA in the name of the medicine, for example, Dilzem XL. Conventional immediate release dosage forms are often taken more than once a day; this causes sequential therapeutic Active Pharmaceutical Ingredient (API) blood peaks and troughs for each dose (Allen, Popovitch, & Ansel, 2005). Sustained release dosage forms reduce drug plasma concentration fluctuations thereby reducing the intensity of adverse drug reactions. Sustained release dosage forms are often taken once or twice daily compared to three or four times daily schedule for immediate release dosage forms to achieve the same therapeutic effect. This reduces the

frequency of drug administration subsequently reducing the pill burden, and is beneficial to patients with multimorbidities (Allen et al., 2005). Sustained release dosage forms have been shown to improve patient adherence by switching dosing frequency from twice daily to once daily dosing frequency (Doesch et al., 2010; Doughty, Baker, Jacoby, & Lavaud, 2003; Ingersoll & Cohen, 2008; Portsmouth, Osorio, McCormick, Gazzard, & Moyle, 2005; Souza, Smith, Miller, Doyle, & Ariely, 2008).

Sustained release formulations are conventionally designed as a single tablet or capsule (Liu et al., 2014). Sustained release dosage forms are usually developed as reservoir, monolithic or osmotic delivery systems to control drug release. A reservoir drug delivery system consists of a polymer coating around the core containing the API. Water-insoluble polymers are used for the coating such as ethylcellulose or acrylate and water-soluble components such as sugars, for example lactose or sucrose, or water-soluble polymers such as hydroxypropyl methylcellulose (HPMC) are also employed in the coating (Liu, McConnell, & Pygall, 2011). The water-soluble components dissolve with contact with aqueous fluids, resulting in pores allowing liquid flow and facilitating drug diffusion. This method is commonly used for multiple-unit systems (Liu et al., 2011). Drug release from a reservoir system typically occurs via diffusion and the coating thickness can alter the drug release, for example a thicker coating would result in a slow drug release due to an increase in diffusion path length (Munday & Fassihi, 1989; Ozturk et al., 1990).

A monolithic matrix system for sustained release consists of API dispersed in a matrix (Uhrich, Cannizzaro, Langer, & Shakesheff, 1999). Hydrophillic matrix systems can be

composed of polymers such as HPMC and sodium alginate (Hodsdon, Mitchell, Davies, & Melia, 1995; Siepmann & Peppas, 2012). Upon contact with fluids, a viscous layer is formed around the dosage form, which acts as a barrier for water penetration and drug release from the matrix, and the polymer disentangles from the outer surface (Li, Martini, Ford, & Roberts, 2005; Siepmann, Kranz, Bodmeier, & Peppas, 1999). Drug release is dependent on swelling of the matrix, dissolution of the drug, diffusion and erosion of the viscous layer (Colombo, Bettini, Santi, Ascentiis, & Peppas, 1996; Tahara, Yamamoto, & Nishihata, 1995). A hydrophobic or insoluble matrix system consists of a porous matrix system using water-insoluble polymers such as polyvinyl chloride (PVC) (Desai, Singh, Simonelli, & Higuchi, 1966; Tu, Shen, Mahalingam, Jasti, & Li, 2013). Upon contact with aqueous fluids, API located at the surface of the matrix is released, termed 'burst release' (Allison, 2008; Huang & Brazel, 2001; Narasimhan & Peppas, 1997). Subsequently, the API is released at successively increasing distances from the surface of the matrix through pores (Narasimhan & Peppas, 1997). Drug release is controlled by the initial amount of drug loaded into the matrix, the porosity of the matrix, the length of the pores which is dependent on the size of the matrix and the solubility of the drug (Freiberg & Zhu, 2004; Higuchi, 1963).

An osmotic pump system consists of a semi-permeable membrane, a tablet core containing the API, osmotic agents and a delivery orifice (L. Liu, Khang, Rhee, & Lee, 2000). Osmosis is the movement of water through a semipermeable membrane from a region of high water concentration (a dilute solution) to a region of low water concentration (a concentrated solution) (Raghunathan & Aluru, 2006). Upon contact of the osmotic pump system with aqueous fluids, the surrounding medium permeates the semi-permeable membrane, and the drug is driven out from the delivery orifice in

the membrane (F. Liu et al., 2011). Osmotic agents such as mannitol or sodium chloride may be used for poorly water soluble drugs. A range of polymers are used for the semi-permeable membrane such as cellulose derivatives like cellulose acetate with high water permeability, or polymers such as ethyl cellulose with low water permeability is used depending on the desired dissolution rate (Barzegar-Jalali et al., 2007; L. Liu et al., 2000; Makhija & Vavia, 2003; Verma, Kaushal, & Garg, 2003).

The size of these sustained release dosage forms can be larger than immediate release dosage forms due to the larger drug content and thus are challenging for patients who are struggling to swallow SODF. Modification of these dosage forms by crushing the sustained release dosage form poses a toxicity risk due to the greater API content than conventional immediate release dosage forms. Schier et al., (2003) reported the death of a woman as a result of severe hypotension after administration of crushed sustained-release nifedipine which resulted in dose dumping of the entire nifedipine content designed to be released slowly over a prolonged period.

1.11 Novel approaches for sustained release oral drug delivery for patients with swallowing difficulties

Multiparticulate dosage forms for modified release are easier to swallow than single-unit dosage forms such as tablets, by splitting the full dose into subunits. These were first introduced in the 1950s as pellet-filled capsules (Spansules) (Tiwari, DiNunzio, & Rajabi-Siahboomi, 2011). The pellets are either coated (reservoir system), or used as matrix pellets for modified drug release (Abdul, Chandewar, & Jaiswal, 2010). A crack in the coating can result in loss of modified release properties of that subunit (Abdul et al., 2010). Multiparticulates disperse easily into the gastrointestinal tract as a result of

the small sizes, and display reduced intra- and inter-subject variability compared to single unit dosage forms (Rajabi-Siahboomi, 2017).

There have been other novel approaches of modified release oral dosage form designs to make administration easier for patients who have difficulties in swallowing. El-Gazayerly, Rakkanka, & Ayres (2004) produced a self-sealing chewable tablet of verapamil hydrochloride. Beads were coated with multiple layers and then compressed into a tablet (Figure 1-5).

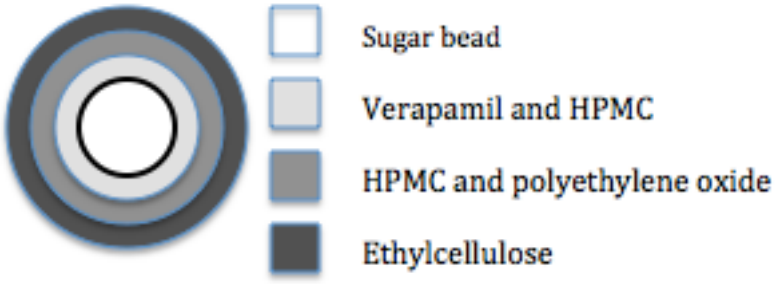


Figure 1-5: Cross-sectional view of the multilayered bead (reprinted with permission) (El-Gazayerly et al., 2004).

The drug was first dissolved in HPMC binder solution and then sprayed to the beads as a first coat. A second coat consisting of a mixture of HPMC and polyethylene oxide (Polyox) was dissolved in alcohol and then sprayed to the drug-containing layer. Polyox was used as a sealant, due to its swelling property when in contact with water. Thus, sealing any cracks that may occur in the coating due to bead compression. The third coating was ethylcellulose for controlled release properties. Lactose and sodium starch glycolate were also dissolved in water and sprayed onto the beads so that once compressed into tablets, the beads can disintegrate into individual units in water. Controlled release properties of this formulation were maintained whether the tablet

was swallowed intact, chewed or crushed due to the sealant layer in the multilayer coating (El-Gazayerly et al., 2004).

Ion-exchange resins have been utilized in suspension form as sustained release preparation for drugs such as morphine sulphate and ambroxol hydrochloride (Bhise, Thenge, Mahajan, Adhao, & Kadam, 2009; Forman et al., 2007). Examples of marketed products include Dyanavel XR (amphetamine extended-release oral suspension) and MST Continus suspension for morphine sulphate (Napp Pharmaceuticals Limited, 2018; Tris Pharma, 2019). Ion-exchange resins are water-insoluble polymeric material containing ionic groups (Y. Raghunathan, Amsel, Hinsvark, & Bryant, 1981). Drug molecules attach through electrostatic interaction onto the ionic groups with the opposite charge (Y. Raghunathan et al., 1981). Drug release occurs when drug molecules are replaced with other ions of the same charge in the gastrointestinal fluid. The exchange capacity of the ion-exchange resin can limit the amount of drug loaded onto the ion-exchange resin; ion-exchange resins for drug delivery are also only suitable for ionizable drugs (Guo, Chang, & Hussain, 2009).

Lipid multi-particulates have also been developed using fatty alcohols, fatty acids and waxes (Feeney et al., 2016; Mu, Holm, & Müllertz, 2013). Lipid-based formulations are used to improve the bioavailability of lipophilic drugs; the presence of lipids mimics more or less fed state of the stomach leading to the secretion of bile salts. Bile salts cause the emulsification of the poorly soluble drug in the gastrointestinal fluid and thus enhances its *in vivo* solubility subsequently increasing the absorption process of the drug resulting in increased bioavailability (Shukla, Chakraborty, Singh, & Mishra, 2011). Sustained release is achieved as a result of the hydrophobic environment

provided by lipids which retard the release of the drug (Shukla et al., 2011). Zmax® (azithromycin) is a marketed product for extended release suspension using this technology (Pfizer, 2017).

In situ gelling oral liquid formulations have been designed for modified release (Itoh et al., 2011; Miyazaki et al., 2009). Miyazaki et al. (2009) described a gel/jelly like formulation that is designed to be administered as a liquid and then forms a gel at a lower pH in the stomach where sustained release occurs. These formulations contain polymers with thermal and ion responsive characteristics (for example, xyloglucan, pectin, gelatin, agar) that undergo gelation in the gastric environment (Itoh et al., 2008, 2011, Miyazaki et al., 2005, 2009). The formulation (gel) remains intact in the stomach for three hours and sustained release occurs over six hours (Itoh et al., 2011). Improved sustained release of paracetamol was found in rats for combinations of methylcellulose with pectin and methylcellulose with alginate in situ gelling formulations (Itoh et al., 2011; Shimoyama et al., 2012).

1.12 Aim of the study

As discussed previously older adults are the major users of medicines and can particularly benefit from sustained release dosage forms in relieving pill burden and side effects commonly associated with immediate release dosage forms. Sustained release dosage forms have been shown to improve medication adherence. However, these dosage forms are conventionally available as tablets and capsules and are challenging to swallow by patients with dysphagia. Modification of sustained release dosage forms can result in toxicity due to larger drug content for prolonged release compared to conventional immediate release dosage forms. There have been novel approaches to navigate sustained release drug delivery for patients with dysphagia

but these have limitations, for example, ionic resin complexes are only suitable for ionisable drugs with low dose and lipid particles are primarily applied to poorly water soluble compounds. In addition, patients with dysphagia may not be able to swallow thin liquids, the consistency of the liquid suspensions and in situ gelling formulations needs to be carefully considered to ensure swallowing safety and patient acceptance.

The aims of this study are to understand the practical issues in administering sustained relase dosage forms in older patients with dysphagia and develop novel sustained release formulations that are safe to swallow and acceptable to these patients. The first part of the study focuses on identifying the extent and nature of problems in swallowing SODF, with a particular interest in difficulties in swallowing sustained release dosage forms in older patients with dysphagia in a secondary care setting. This was followed by determination of rheological, textural and *in vitro* processing properties of products used in dysphagia management, including thickened fluids, jellies and yogurt, to reach an understanding in safe swallowing features of these products. Two types of jellies, free-standing jellies (non-flowing jellies that retain its shape once cut with a spatula) and granular jellies (free-flowing dosage form consisting of granular gels in fluid) were developed without using heat as vehicles for drug delivery. Sustained release microparticles containing the antidiabetic drug gliclazide were developed using fluidised bed coating and incorporated into the jelly vehicles to assess *in vitro* drug release compared to the reference marketed sustained release tablet.

Chapter 2

OLDER ADULTS WITH DYSPHAGIA: ISSUES WITH MEDICINES ADMINISTRATION IN A SECONDARY CARE SETTING

2.1 Introduction

The global trend towards an aging population and the subsequent increase in demand for medicines are well recognized (Department Of Health, 2001; National Institute on Aging, 2011). Older adults have a greater need for health care resources, compared to younger counterparts due to increased comorbidities; consequently requiring a greater number of medicines (European Medicines Agency, 2012; Jennifer Kelly et al., 2012). The oral route is the most convenient for medicines administration. Solid oral dosage forms (SODF) such as tablets and capsules are preferred due to their convenience for patients and cost-effectiveness but it can be challenging to administer these dosage forms safely and effectively to patients who have difficulties in swallowing. Schiele et al. (2015) found that changing type and shape (round, oval, oblong and capsule) of the SODF did not modulate the risk of penetration-aspiration and patients with stroke-induced dysphagia had increased risk of penetration-aspiration when swallowing SODF with spoon-thick consistency thickened fluids. Difficulties in swallowing can lead to modification of SODF by tablet crushing or capsule opening (Table 2-1). Literature available in English relating to medicines modification of SODF in adults and older adults are included in Table 2-1, most of the literature relied on surveys and very few studies depended on direct observation (Fodil et al., 2017; Mercovich et al., 2014; Paradiso et al., 2002; Stubbs, Haw, & Dickens, 2008). Two of the four observation studies (Paradiso et al., 2002; Stubbs et al., 2008) reported on medicine modification in relation to total number of medicines prescribed and patients may have been observed in more than one medicines round. Studies relating to surveys provided a general idea of ongoings of medicines crushing in various institutions as opposed to number of participants (Nissen et al., 2009; Wright, 2002) and a survery by Strachan & Greener (2005) enrolled patients assumed to have

swallowing difficulties, and thus the high prevalence of modification may be noted for these studies.

Table 2-1: Incidence of SODF modification to facilitate swallowing

Study objective	Study setting	Age group	Method	Type and prevalence of modification	Reference
Medicines administration to patients with swallowing difficulties	Nursing homes, UK	Older and young people	Self-administered questionnaires	Crushing tablets or opening capsules (61% of nurse respondents)	(Wright, 2002)
Extent of medicines modification before administration	Residential aged-care facilities, Austrialia	Older adults	Observation	Crushing tablets or opening capsules for 34% of medicines in the aged-care facilities. Modified SODF were mixed with jam, vitamised fruit, custard, or water	(Paradiso et al., 2002)
Difficulties in swallowing SODF in community	Community pharmacies, UK	Older adults (60-89 years)	Survey	Crushing tablet or opening capsules by 68% of 675 patients suspected of having swallowing difficulties	(Strachan & Greener, 2005)
Extent of medicines administration errors in old age psychiatry	Independent psychiatric hospital, UK	Older adults (60-100 years)	Observation	26% of SODF were modified by crushing tablets or opening capsules	(Haw et al., 2007; Stubbs et al., 2008)
Identification of commonly modified medications and method of modification	Hospitals in Queensland, Austrailia	Adult and child	Self-report survey	79% of 97 hospitals modified SODF by crushing tablets and mixing with jam, honey, custard, food, water, juice	(Nissen et al., 2009)
Prevalence of difficulties in swallowing SODF	General practices, Germany	Adults, older adults (18-80 years)	Questionnaire survey	58% of 393 patients modified SODF by splitting and crushing tablets, opening capsules, dissolving in water, chewing and mixing with food	(Schiele et al., 2013)
Observation of medication SODF modification in aged care facilities	Aged care facility, Queensland	Older adults	Observation	18% of 160 older adults modified SODF by crushing tablets or capsule opening and mixing with thickened pear juice and jam	(Mercovich et al., 2014)

Prevalence of dosage form modification	Community pharmacy in Queensland	Adults (18 and over)	Structured interview	10% of 369 patients modified SODF by tablet crushing or capsule opening	(Lau et al., 2015)
Prevalence of dosage form modification	Aged-care facility, Ireland.	Older adults (65 years and over)	Prospective study using drug charts	35% of 111 patients received atleast one modified (tablet crushing or capsule opening) medicine	(Mc Gillicuddy et al., 2016)
Prevalence of dosage form modification	Pharmacy, Jordan, whom experienced	Adults , older adukts (18-90 years)	Interview	27% of 130 outpatient patients whom experienced difficulties in swallowing SODF, modified SODF by cutting or crushing tablets or opening capsule	(Tahaineh & Wazaify, 2017)
Assessment of medication modification	Hospitals in France	Older adults	Observation	110 drugs prescribed and modified from 143 prescriptions in17 geriatric units. Dosage forms were modified by crushing tablets or opening capsules, mixing with water, jellified water, yogurt	(Fodil et al., 2017)

There are very few studies of incidences of dosage form modification conducted in hospital (Table 2-1) where it is expected to be less prevalent considering the greater access to a multidisciplinary team to optimize medicine prescribing and safe administration. For patients with difficulties in swallowing SODF, medicines may be crushed and added with thickeners to aid swallowing or may be crushed and given through enteral feeding tubes (Barnett & Parmar, 2016). Enteral feeding tubes are commonly used for medicines administration for patients that cannot ingest substances orally. In hospitals, feeding tubes are particularly used in the care of the elderly and surgical wards (Salmon et al., 2013). Crushed tablets are administered through enteral feeding tubes when suitable alternatives such as liquids or dispersible tablets are not available, and this is the most common cause of occlusion within the

feeding tube (Bowman, 2007). Instances of requiring SODF modifcation for administration through enteral feeding tubes have been previously reported (Gillicuddy et al., 2016; Paradiso et al., 2002; Wright, 2002).

Although the intent behind the modification of SODF is that the medicines are administered to the patient without the complications of aspiration, modification of dosage forms can be particularly hazardous. Sustained release SODF should not be modified before swallowing and if so it can result in dose dumping and fatalities. Previous studies where SODF modification occurred reported instances of modification of modified release medicines such as oxycodone CR, Paracetamol SR (Mercovich et al., 2014), aminophylline MR, diltiazem MR (Stubbs et al., 2008), morphine SR, nifedipipine CR, felodipine ER, Verapamil SR, Diltiazem CR and lansoprazole EC (Paradiso et al., 2002). Modificatition of these dosage forms can be fatal as reported previously (Schier et al., 2003). There are very few studies that have reported on medicines modification, especially sustained release SODF, in hospitals where multidisciplinary teams in particular pharmacists are easily accessible for advice on medicines modification. Modification of sustained release dosage forms in hospitals can indicate a wider problem with administration of these dosage forms in other environments where specialist advice or timely change of prescription may not be available.

The aim of this chapter was to gain information on the extent and nature of problems in administering SODF, with a particular interest in the administration of sustained release formulations for older adults with swallowing difficulties in a hospital setting and the solutions used to overcome administration difficulties.

The primary objective of this chapter was to gain a better understanding of problems surrounding the use of sustained release dosage forms in older adults with swallowing difficulties.

The secondary objectives of this chapter was to:

- To determine the frequency of prescribing solid oral dosage forms for older adults with swallowing difficulties.
- To determine the frequency of prescribing solid oral dosage forms for administration via the oral route and through the enteral feeding tubes.
- To determine the frequency of prescribing sustained release dosage forms for older adults with swallowing difficulties.
- To determine any changes made in administering or prescribing of sustained release dosage forms in older adults.

2.2 Methods

The study was approved by the NHS South Yorkshire Ethics Committee (REC 14/YH/1105, protocol LMS/PG/NHS/00161) and was conducted in Addenbrookes Hospital, Cambridge, UK throughout two months (between September and November 2014). Data were collected from a total of 22 wards. These included the stroke and rehabilitation unit, respiratory wards, cardiology, and general medicine, medicines for the elderly, diabetes and endocrine, neurology and neurosurgery, surgical wards and the Intensive Care Unit.

In this prorspective study, all patients (over the age of 65) with swallowing difficulties staying in the above wards were identified by ward pharmacists. For this study,

swallowing difficulties were defined using the following criteria which were adapted to help identify patients (Groher & Bukatman, 1986):

- Difficulty in the oral intake or no oral intake
- Frequent choking and excessive coughing
- Need for a diet modified in texture
- Need for non-oral nutritional support
- History of aspiration pneumonia
- Need for individual mealtime supervision
- Patients that are ‘Nil by mouth’
- Refusal of the solid oral dosage form (s)

Informed consent was received for patients who were able to provide informed consent. For patients who were unable to provide informed consent, data were anonymized by the ward pharmacist before analysis.

Data were collected from patients’ medical notes and drug charts using standardized pro forma (Appendix I), including patients’ medical history, any recordings of dysphagia in medical notes and medications that were prescribed for oral or enteral administration. Any changes to the medications prescribed to help facilitate swallowing for the patient, for example, changing to an alternative formulation, modifying solid dosage forms by crushing tablets or opening capsules were also documented. Nurses were approached for clarification on how SODF were administered when it was not clear on the drug chart.

2.2.1 Sample size calculation

Estimation of population proportion was used to calculate the sample size. To enable the calculation of the population proportion, the margin of error equation (Equation 2-1) was used. The margin of error is a measure of accuracy; it provides a limit by which the sample proportion differs from the true population proportion (Utts & Heckard, 2005).

$p \pm Z\sqrt{(pq/n)}$ = margin of error [Equation 2-1]

Where Z in the critical value for a 95% confidence interval is 1.96

p is the expected frequency value, *q* is 1-*p* and n is sample size.

The margin of error was used as 0.05% to provide low error and a reasonable sample size for the study to achieve in this investigation. The primary aim of this study was to determine the incidence of sustained release dosage forms prescribed and administered to older adults with swallowing difficulties. An estimate of the frequency of prescribing these dosage forms to older adults was required as *p*.

The frequency of prescribing sustained release oral medications in older adults with swallowing difficulties is unknown, and therefore, primary care prescription data was used to estimate the frequency of prescribing sustained release medications for the general public (Health and Social Care Information Centre, 2012). Primary care prescription data for medicines prescribed for gastro-intestinal, cardiovascular, central nervous and endocrine systems were selected as diseases relating to these systems are common in the elderly. A frequency of 3.24% of medicines was prescribed as

sustained release dosage forms. Older patients are prescribed on average 5 or more medications (Morin et al., 2018), so it was estimated an average frequency of 16.2% of older adults with swallowing difficulties prescribed sustained release medications. Based on this estimated frequency (*p*) and a margin of error of 0.05%, a sample size of 209 was calculated using Equation 2-1.

2.2.2 Data analysis and evaluation

All data obtained on the proformas were collated on Microsoft Excel and analyzed for frequency of prescribing of dosage forms and dosage form modification. Descriptive statistics were applied.

The appropriateness of modifying dosage forms was evaluated using the NEWT guideline and Handbook of Drug Administration via Enteral Feeding Tubes (Smyth, 2012; White & Bradnam, 2015).

2.3 Results

2.3.1 Patient characteristics

Two hundred and nine participants (42% female and 58% male) with dysphagia were recruited with a median age of 79 years (range 65-100 years). Eighty-four (40%) of these participants had been referred to the Speech and Language therapists and dysphagia was documented in patients' medical notes for ninety-four participants (45%). Table 2-2 shows the number of participants showing difficulties in swallowing according to the criteria used to identify participants.

Table 2-2: Criteria in identifying swallowing difficulty in participants.

Criteria	Number of participants (%)*
Difficulty in oral intake	121 (57.9%)
Diet modified in texture	78 (37.3%)
Need for non-oral nutritional support	48 (22.9%)
Nil By Mouth	48 (22.9%)
Refusal of solid oral dosage forms	10 (4.8%)
Need for individual mealtime supervision	7 (3.3%)
Frequent choking and coughing	3 (1.4%)
History of aspiration pneumonia	1 (0.04%)
Total	316 (150.5%)

- Participants may have more than one indication of dysphagia, and therefore, the total number exceeds 209, % calculated based on 209 patients

2.3.2 Medicines management for patients with swallowing difficulties

A total of 1321 medicines for oral and enteral feed administrations were prescribed (an average of 6.3 medicines prescribed per participant). Of these, 268 medicines were prescribed to 48 participants for administration through enteral feeding tubes, and 1053 medicines prescribed to 161 participants for administration through the oral route.

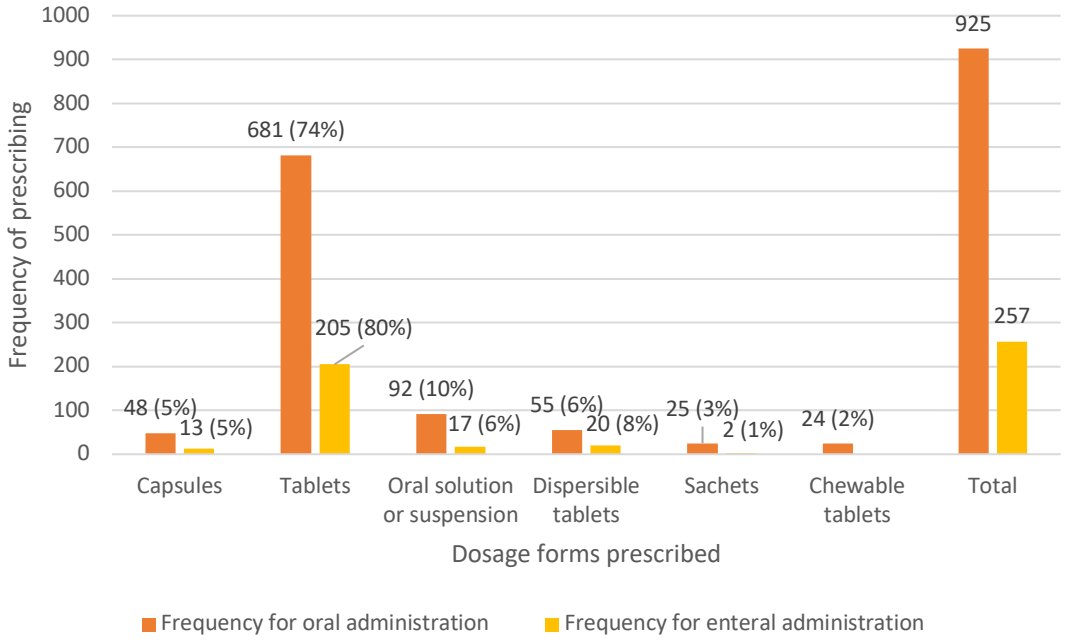
2.3.2.1 Medicines management of immediate release dosage forms

A total of 1182 (90%) of medicines prescribed were immediate release dosage forms. The most commonly prescribed immediate release dosage forms were SODF (tablets and capsules, total 947 cases, 80% of all immediate release medicines prescribed) (Figure 2-1a).

Overall, 71% of immediate release tablets and capsules (518/729) administered to patients taking medicines through the oral route required some form of change to aid swallowing (Figure 2-1b). The most commonly sought change was crushing tablets, followed by changing to alternative dosage forms and chewing tablets and capsules (Figure 2-1b). Tablets and capsules that were crushed or opened for oral administration (n=281) were delivered by either mixing with water (43%, 122/281), thickened fluid (6%, 16/281) or yogurt (51%, 143/281). There were also 17 incidences of swallowing the immediate release tablet or capsule whole with jelly (Hartley's ready to eat free-standing jelly, Hain Daniels Group, UK) to facilitate swallowing.

All of the tablets and capsules prescribed were changed for patients who were administered SODF through enteral tubes; the most common change was tablet crushing followed by changing to alternative dosage forms (Figure 2-1b). Out of 416 incidences of tablet crushing or capsule opening to release contents, only 33% (138/416) for oral and enteral administration were authorized by a pharmacist.

a



b

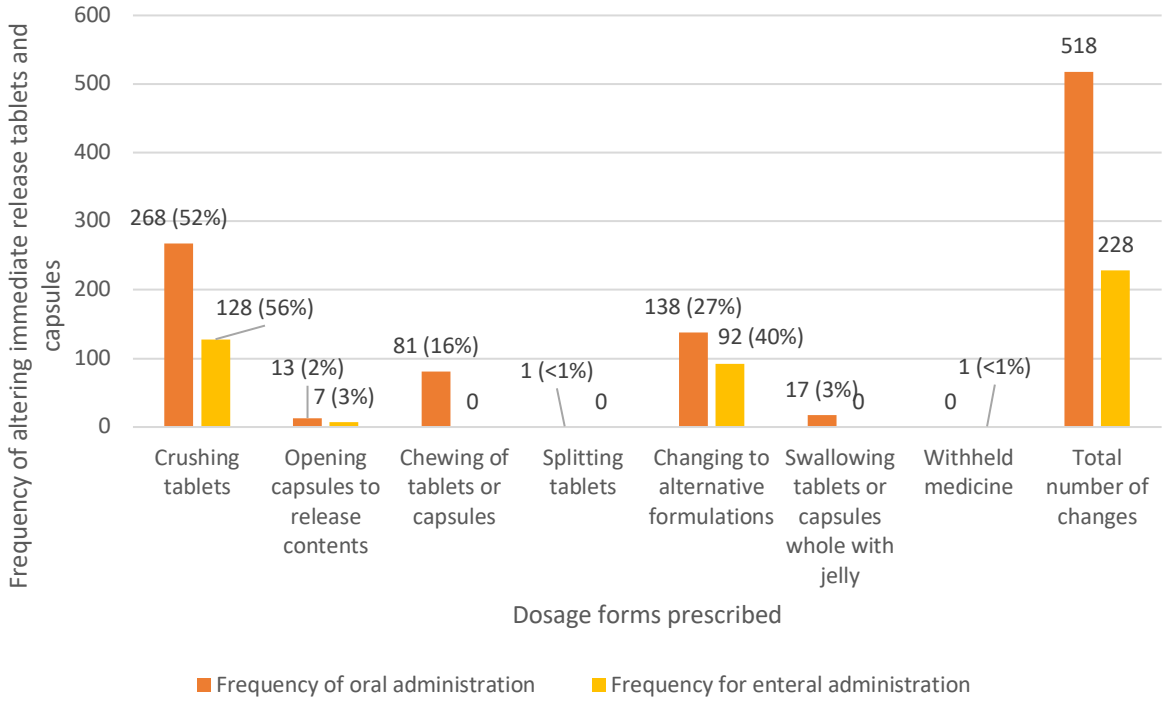


Figure 2-1: a) Most commonly prescribed immediate release dosage forms. b) Modification of immediate release dosage forms for patients with swallowing difficulties. *In the instances where dosage forms were chewed, the capsules were chewed without opening the shell and releasing contents.

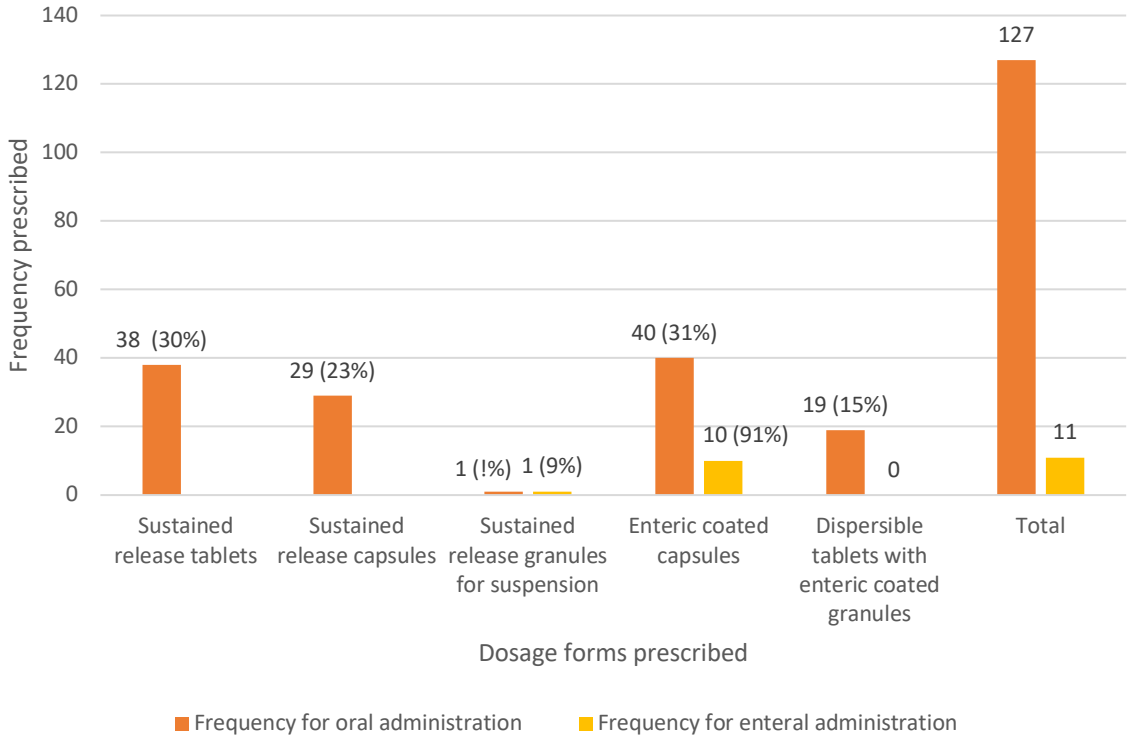
2.3.2.2 Management of modified release dosage forms

There were a total of 138 (69 sustained release and 69 enteric coated; 10% of total medicines prescribed) modified release dosage forms prescribed (Figure 2-2a).

All enteric coated formulations were prescribed to participants in the form of enteric coated capsules or dispersible tablets (Table 2-3). Enteric coated capsules were administered by opening the capsules and releasing contents (14%, 7 of 50 capsules prescribed) and changing to a dispersible tablet for the same drug (24%, 12 of 50 capsules prescribed) (Table 2-3). The rest of the enteric coated capsules and dispersible tablets were swallowed intact.

Figure 2-2b shows that of the 67 sustained-release tablets and capsules prescribed 94% (63/67) were changed or modified for the administration of the medicine. Similarly to immediate release medicines, crushing tablets and opening capsules to release content (33 occasions) were the most common modifications to sustained release formulations. Only 21% (7/33) of this modification to sustained release formulations were authorized by a pharmacist whereby the authorizations were to permit opening capsules for patients to swallow the capsule content whole. There were seven accounts of chewing sustained release dosage forms (6 accounts of chewing capsule contents of Tamsulosin and 1 account of chewing capsule whole with shell for venlafaxine) before swallowing. In 11 cases. Sustained release formulations that were changed to an alternative dosage form were changed to immediate-release tablets or liquids.

a



b

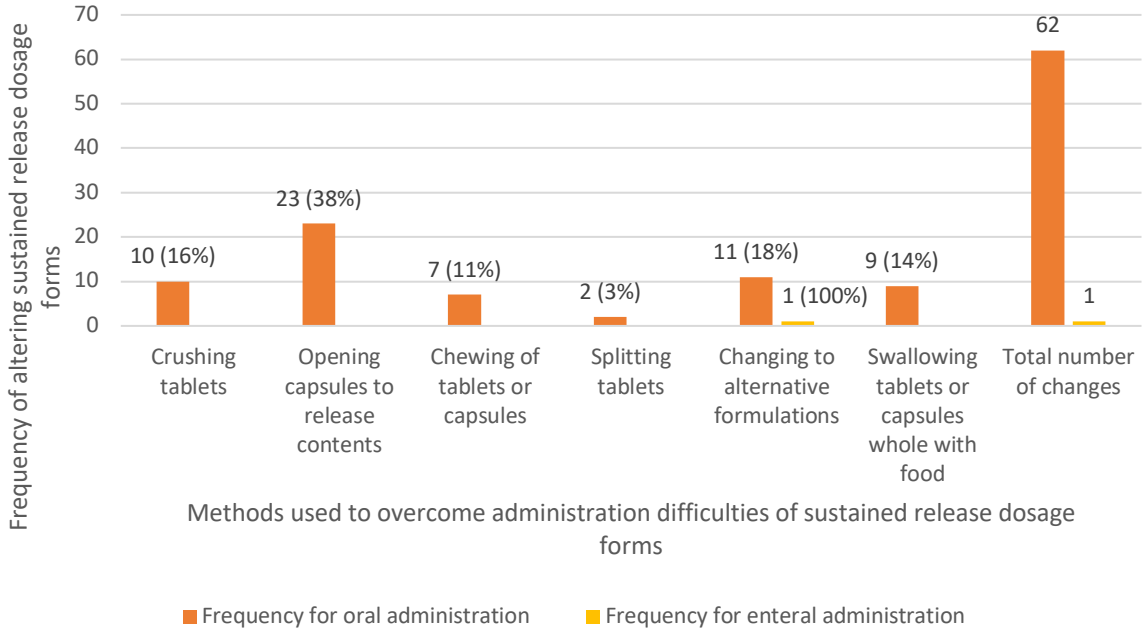


Figure 2-2: a) Type of modified release dosage forms prescribed. b) Modification of sustained release dosage forms.

2.3.2.3 Evaluation of dosage form modification

In total, 50% (538/1083) of tablets and capsules prescribed (including immediate release, sustained release and enteric coated dosage forms) were modified by structural changes, e.g. tablet crushing, opening of the capsule or chewing the dosage form. The most frequent classes of medicines that were structurally modified, administered with food or changed to alternatives were for the treatment of cardiovascular and central nervous system diseases (Table 2-3).

Table 2-3: Disease categories for the most commonly structurally modified medicines.

Disease categories	**Number (%)**
Cardiovascular system	285 (35.2%)
Central Nervous system	258 (31.8%)
Endocrine system	65 (8.03%
Gastrointestinal system	85 (10.5%)
Nutrition	50 (6.2%)
Malignant disease and immunosuppression	3 (0.004%)
Musculoskeletal and joint diseases	7 (0.009%)
Infectious diseases	23 (0.03%)
Respiratory diseases	11 (0.01%)
Total	809 (100%)

A review of guidelines accessible in hospitals in the UK for medicines management for patients with swallowing difficulties or those taking medicines through the enteral feeding tubes showed that 64% (693/1083) of the medicines altered were advised as safe to modify (Smyth, 2012; White & Bradnam, 2015). Licensed alternative formulations were recommended for 18% (194/1083) of medicines modified. There were 9% (97/1083) of medicines modified where tablet dispersal in water was

recommended. This modification may be recommended because the therapeutic outcome may be compromised from a variable amount of Active Product Ingredient (API) being administered (loss of API through crushing and transferring process) or many alternatives are available for medicine such as paracetamol (Mercovich et al., 2014; Paradiso et al., 2002). Modification cases that are contraindicated or permitted with caution are shown in Table 2-4.

Table 2-4: Modifications that are contraindicated or permitted with caution.

API	Dosage form	Frequency prescribed	Modified by crushing or chewing (frequency)	Recommendations in guidelines
Alendronic acid	Immediate release tablets	16	10	Do not crush, can irritate. Use oral solution or zoledronic acid (administered once yearly) (Smyth, 2012)
Nitrofurantoin	Immediate release tablets	1	1	Do not crush, can irritate. Use oral suspension(Smyth, 2012)
Tamsulosin	Capsules with slow release granules	24	15 (capsule opened to release contents, granules chewed by 6 participants)	Contents of the capsule may be mixed with cold water and swallowed whole, but not suitable for patients unable to follow instructions on not to chew (Smyth, 2012)
Alfuzosin	Slow release tablet	1	1	Do not crush, use standard release immediate release tablets which can be crushed or dispersed in water (Smyth, 2012).
Felodipine	Slow release tablet	6	1	Do not crush, change to amlodipine tablets (Smyth, 2012)
Venlafaxine	Capsule with slow release granules	2	1 (capsule shell chewed)	Contents of capsules can be released and given with smooth food such as yogurt. Granules must be swallowed whole, not suitable for patients unable to follow instructions on not to chew (Smyth, 2012).
Slow sodium	Slow release tablet	2	1	Should be swallowed whole and not chewed (HK Pharma Limited, 2015).
Melatonin	Slow release tablet	1	1	Do not crush or chew. Use immediate release dosage forms (Smyth, 2012).
Omeprazole	Capsule with enteric-coated granules	19	11 (4 capsule shell chewed and 2 capsules	Can open the capsule and swallow contents with water, fruit juice,

			contents chewed).	apple sauce or non-carbonated water. Enteric-coated granules should not be chewed (AstraZeneca UK Limited, 2015).
Lansoprazole	Capsule with enteric-coated granules	31	4 (1 capsule shell chewed and 1 capsule content chewed).	Can open the capsule, contents must be swallowed whole (Consilient Health Ltd, 2012)

2.4 Discussion

The findings in this study show that tablets and capsules are commonly prescribed by physicians for older adults with dysphagia in a hospital. Tablet crushing or opening capsules is a commonly used method for administration to patients with swallowing difficulties despite the availability of the multidisciplinary team such as speech and language therapists for assessment of dysphagia and pharmacists for easily accessible medicines advice for alternative dosage forms in a secondary setting (Fodil et al., 2017; Haw et al., 2007; Gillicuddy et al., 2016). It was expected that the incidence of tablet crushing and capsule opening would be low considering the access to specialist advice and the availability of guidelines but our findings showed 49.7% of tablets and capsules for immediate and modified release were structurally modified for patients with dysphagia via administration through the oral route and enteral feeding tube . There are limited studies reporting on overall incidence of modification of SODF in hospital, a previous study hospital reported 26% of medicines modification in a psychiatric unit for older adults, a lower incidence compared to our findings possibly due to the fact that our study is conducted only in patients with dysphagia (Haw et al., 2007; Stubbs et al., 2008).

Although alternative dosage forms such as solutions or suspensions are available for most medicines, these are expensive, and thus, tablets and capsules are prescribed and modified to facilitate swallowing. For example, the antibiotic metronidazole tablet costs £1.70 per pack whereas the liquid suspension version of the drug would cost £32.93 per pack (Joint Formulary Committee, 2019a). Lajoinie, Kassai, & Terry (2014) evaluated the cost-savings if oral liquid dosage forms were substituted with SODF for children over two years. The study found the total cost of dispensing oral liquid dosage forms for one week was £8,307 and £11,697 respectively for hospital and community charges and substitution of these to SODF would have cost £4,951 and £8,550 for hospital and community respectively. Prescribing the SODF would have accounted for 60% and 73% of the cost for liquid dosage forms. The concern with modification of SODF is that dosage forms may be modified without careful consideration and authorization, and this can lead to harm. A study in a psychiatric hospital found 44% of dosage form modifications by crushing tablets, or opening capsules were unauthorized by pharmacists, and another study in a hospital in France found 48% of modifications were contraindicated assessed using local guidelines (Fodil et al., 2017; Stubbs et al., 2008). In some cases, advisory labels affixed on medicines boxes contain the words “swallow the dosage form whole” for enteric and sustained release medication or drugs with unpleasant taste (Joint Formulary Committee, 2019c); if the practice of modification is introduced for medicines with this labeling in the hospital by staff, it may inadvertently lead to this practice being continued at home by patients or carers despite label warnings.

Modification of immediate release dosage forms, such as crushing tablets, may lead to faster absorption and thus higher bioavailability; on the other hand this may lead to

sub-therapeutic API levels due to loss of API through the process of altering and transferring the manipulated dosage forms (Dodds Ashley et al., 2007; Manessis et al., 2008; Thong et al., 2018). Although altering immediate release dosage forms with a wide therapeutic window is considered of low risk, there are instances where this may not be appropriate. For example, altering dosage forms of APIs that are light sensitive may lead to degradation before administration (Root et al., 2011); modifying cytotoxic or hormonal medicines with carcinogenic and teratogenic potential can be hazardous due to risk of contact and inhalation of particles and thus posing health and safety risks for those modifying and administering these medicines (Haywood & Glass, 2007; Root et al., 2011). Alendronic acid and nitrofurantoin are both contraindicated for crushing and administration through the enteral feeding tube due to possible oesophageal or stomach irritant effects (Smyth, 2012; Root et al., 2011)

Enteric coated dosage forms are designed to pass through the stomach intact and release the drug in the intestine; crushing these formulations would reduce efficacy or cause stomach irritation (Haywood & Glass, 2007; Root et al., 2011). Modifying enteric coated dosage forms for drugs that degrade in acidic conditions can reduce efficacy. This can be detrimental for example when proton pump inhibitors such as omeprazole or lansoprazole are used to protect the stomach from bleeding when non-steroidal inflammatory drugs are used. Lansaprazole is available as oral dispersible tablets which are more suitable for swallowing difficulties but despite this, capsules were prescribed. Omeprazole is also available as a dispersible tablet, but capsules were prescribed. This may be due to the patient prescribed the capsules prior to admission due to cost considerations. Omeprazole (Losec MUPS) for example, costs £9.30 per pack compared to the capsules which are £0.75 per pack (Joint Formulary Committee,

2019b). Flexible dosage forms are dosage forms that can be administered in more than one manner such as dispersal in water or swallowing the dosage form intact and have been developed to offer an alternative to patients with difficulties in swallowing (Liu & Shokrollahi, 2015; World Health Organization, 2012). In this study enteric coated capsules were opened to release the granules and in some cases these enteric coated granules were chewed for omeprazole and lansoprazole, which may be a result of oral grittiness ('rough feeling in the mouth') if the pellets were large leading to chewing (Lopez et al., 2016). It has been previously reported that there is a low perception of grittiness for particle sizes 90-263 μm (Lopez et al., 2016) and lansoprazole and omeprazole granules in capsules are reportedly 750-1400μm and 1000-2000 much larger than this size range (Liu & Shokrollahi, 2015). The enteric coated granule sizes in dispersible tablets are 352μm and 180-253μm for lansoprazole and omeprazole respectively, indicating better acceptance and suitability for these patients (Liu & Shokrollahi, 2015).

Despite that it being widely known that sustained release dosage forms should not be crushed (Root et al., 2011; Schier et al., 2003), this study showed a surprisingly high proportion of sustained release SODF (tablets and capsules) prescribed to patients with swallowing difficulties and only a small number of these were authorized for modification before administration. It has been previously reported that prescribers are more likely to consider allergies and medical history as important considerations than swallowing problems, in contrast to nurses, who are at the forefront of medicines administration and are more likely to ask about patients swallowing ability (Nguyen, Lau, Steadman, Cichero, Dingle, 2014).

Sustained release formulations are designed to release the drug slowly over time and are often prescribed to minimalize side effects due to fluctuation in plasma drug concentration observed with immediate release dosage forms, or to provide optimal control over symptoms to improve disease management, for example, breakthrough symptoms such as pain and control of blood pressure. It is well known that structurally modifying any sustained release dosage form can be harmful since it often contains a greater API content than immediate release dosage forms to reduce dosing frequency; modifying this results in immediate release of the dose and can cause toxicity. The majority of the sustained release dosage forms (tablets and capsules) were modified by crushing the tablets or opening the capsules to release content to enable swallowing rather than changing the dosage form to liquids such as immediate release suspensions. Swallowing granules whole may be challenging for patients unable to follow instructions, and this is worth considering before permitting this practice. The maximum size of granules or pellets incorporated into capsules is 2.8mm recommended by the FDA for sprinkling which is greater than the 263μm reported for grittiness perception (Food and Drug Administration, 2012; Lopez et al., 2016). Particle size of extended release products labelled for use by sprinkling on apple sauce or pudding were analysed and found to range from 277 to 1485μm (Nagavelli et al., 2010). Marconati, Lopez, Tuleu, Orlu, & Ramaioli (2019) found pellets of 891.5μm in size were considered more difficult to swallow compared to 325.3μm by healthy adult volunteers and the pellets, irrespective of the size, were easier to swallow dispersed in polymer solutions (xanthan gum and carboxymethyl cellulose solutions) compared to water. The study found water-thin vehicles were not effective for oral transport of multiparticulates and left residue of multiparticulates in the mouth (Marconati et al., 2019). Changing to alternative formulations or drugs, for example, immediate release

liquid formulations would obviate the advantages of taking sustained release formulations. This can result in losing sustained release properties and increasing dosage frequency or pill burden. The opening of capsules to swallow the sustained release granules could result in off-label use; however, even if this is permitted by the prescriber or pharmacist, then it is stressed that the granules are not chewed, which could result in dose dumping. Structurally modifying these formulations by crushing, chewing can result in toxicity due to dose dumping and is perilous to introduce this practice to patients who may continue this practice upon discharge. There has been a previous case report on patient death as a result of crushing slow release nifedipine (Schier et al., 2003). There were incidences of modification of sustained release dosage forms in this study without authorization which could have lead to patient harm. Previous studies on medicines modification have also reported on modification of sustained release SODF occurring in aged-care facilities and hospital (Haw et al., 2007; Mercovich et al., 2014; Paradiso et al., 2002). Despite the widely acknowledged fact by health professionals that sustained release SODF should not be modified, modification of these dosage forms has been and still is occurring in practice. This indicates the need for serious attention towards handling medicines for patients with swallowing difficulties, the need for routine training for administrators on managing medicine administration and the need for more suitable dosage forms to be designed that provide sustained release and are easy to swallow.

The NEWT guidelines by Smyth, 2012 is based on theoretical, anecdotal and practical information from various sources particularly anecdotal reports for medicines administration and the Handbook of Enteral feeding by White & Bradnam (2015) is based on information from pharmaceutical companies and pharmacist research for

medicines administration. These guidelines are used in hospitals in the UK (UKMI, 2011) and since the modifications of SODF are likely to be unlicensed, it is a useful tool in recognizing whether the modification may be harmful or not from previous cases. Evaluation using these resources showed that 9% of SODF were contraindicated or recommended to proceed with caution. Previous studies reported that 4-48% of alterations were contraindicated (Fodil et al., 2017; Mercovich et al., 2014; Paradiso et al., 2002; Stubbs et al., 2008). As reported in previous studies, drugs prescribed for the central nervous system and cardiovascular system were modified the most due to swallowing difficulties (Fodil et al., 2017; Gillicuddy et al., 2016; Stubbs et al., 2008).

SODF modified in this study were administered with water, thickened fluid or yogurt, and in a few cases, swallowed whole using Hartley's jelly as a swallowing aid. Using thickening agents may alter drug release; previous *in vitro* studies in simulated gastric fluid showed thickened fluids and yogurt could reduce drug release from crushed tablets of warfarin and carbamazepine (Manrique-Torres et al., 2014).

This study reports cases of medicines alterations that could have resulted in harm to the patient. Pharmacists were involved in the study who have provided feedback in cases inappropriate modification took place. This led to training by clinical pharmacists to the nurses administrating the medicines on their wards and guidance of medicines that should not be modified developed by the Pharmacy department was provided where required as a reminder for safe medicines administration. Although greater safety of administration of medicines is expected in hospitals, the practice of modifying dosage forms is a strategy being used by health care professionals and patients to

facilitate swallowing and also in some cases the practice occurred without authorization. It is clear from this study that more appropriate dosage forms are needed for older adults to prevent this practice particularly for sustained release dosage forms where modification can result in toxicity. Swallowing aids such as jellies that alter shape during swallowing maybe useful as drug administration vehicle to alleviate the instant of chewing, for example granules, and their swallowing safety in dysphagia patients needs to be understood.

2.5 Conclusions

This study found unauthorized medicines modification in secondary care to be common practice despite the availability of specialist advice. Modifying SODF during hospitalization may result in the same practice being adopted by patients once discharged despite that warning labels may be affixed onto dosage form packages after dispensing advice to swallow the medicines whole. This is a risky practice and unauthorized medicines modification also occurred for sustained release medicines which can result in toxicity. The findings reinforce the need for safer, accessible and easier to swallow sustained release dosage forms to provide better medicines for patients with dysphagia in the future.

Chapter 3

SAFE SWALLOWING FEATURES OF THICKENERS, JELLIES AND YOGURT OBSERVED IN AN *IN VITRO* MODEL

3.1 Introduction

Dysphagia is the inability to safely transfer fluids or food boluses from the oral cavity to the oesophagus and diet modification is the mainstay of compensatory intervention for dysphagia management (Campbell-Taylor, 2008; Ney et al., 2009). Thin fluids (e.g., water and beverages) are modified using thickeners (gum or starch based) for patients with dysphagia to improve swallowing safety (Garcia, Chambers IV, Clark, Helverson, & Matta, 2010). Although the exact mechanism is unknown, it is thought that thickened fluids increase viscosity allowing better control of the speed and direction of the bolus transiting into the oropharynx, providing greater time for the airway to close and preventing spillage into the airway (Campbell-Taylor, 2008; Nicosia & Robbins, 2001; Sura et al., 2012).

Thickened fluids are widely used in dysphagia management, but acceptance for these products is low due to grainy textures from starch-based thickeners and stickiness from gum-based thickeners (Garcia, Chambers, et al., 2005; Murray et al., 2014; Shim et al., 2013). Starch-based thickeners are described to have an undesirable grainy and 'lumpy' texture, and these products are physically unstable and can continue to increase in viscosity or thicken over time (Cichero, 2013; Lotong, Chun, Chambers IV, & Garcia, 2003; Matta, Chambers IV, Garcia, & Helverson, 2006). On the other hand, they can become thinner when mixed with saliva due to digestion by amylase present in the oral cavity (Lotong, Chun, Chambers, & Garcia, 2003). Gum based thickeners are reported to have an undesirable stickiness; they are more physically stable over time (keeping constant viscosity) but need to be shaken vigorously during mixing (Lotong et al., 2003; Matta et al., 2006). Starch added to water swells, forming a

swollen structure of starch granules whereas gum-based thickeners form a mesh of entanglement of polymer chains (Cichero, 2013).

Viscosity is often described as the salient property for safe-swallowing of fluids. Although the focus of dysphagia management is modifying the viscosity of liquids, other rheological and textural properties such as cohesion and yield stress of fluids have also been mentioned in literature, albeit scarcely, that might contribute to safe-swallowing. Thin liquids with low cohesion between particles can result in spillage into the airway in dysphasic patients due to inability to control laryngeal closure (Cichero & Murdoch, 2006; Prinz & Lucas, 1997; Tashiro, Ono, Atsuko Tanigome, Kumagai, & Kumagai, 2010). An increase in thickener concentration is known to increase viscosity and yield stress (Payne, Methven, Fairfield, Gosney, et al., 2011; Popa Nita et al., 2013). Yield stress described as the minimum stress required to enable flow is reported as a potentially relevant parameter in safe swallowing (Cho et al., 2012; Payne et al., 2011). A study was conducted in eighteen young students (aged 22-25) for sensory analysis of perceived ease of movement of semi-liquid samples (prepared using pregelatinized waxy corn starch as a thickener) in the pharynx, comparing to videofluoroscopy measurements (Takahashi et al., 2002). A texture analyser was used to characterise the semi-liquid samples for hardness, cohesiveness, and adhesiveness. Thickened samples showed an increase in hardness and adhesiveness with increasing thickener concentration; however, the cohesiveness of all samples was similar. The study found that increased hardness resulted in perceived difficulty in swallowing and slower bolus transit (Takahashi et al., 2002).

The present study uses the *in vitro* throat model presented by Mackley et al. (2013) which is designed for processing of liquids to compare dysphagia thickened fluids (starch and gum-based thickeners) to jellies and yogurt for pharmaceutical application (Chapter 1, Section 1.6). Patient acceptability for thickened fluids is found to be low. A study testing acceptability by using 9-point hedonic scales for overall liking, taste and texture of thickened fluids in healthy volunteers found the rating reduced for increased thickening for overall liking and ratings were mostly below average for nectar-thick and honey-thick fluids (Jane Mertz Garcia, Chambers, Chacon, & Di Donfrancesco, 2015). A retrospective audit of medical records of adults diagnosed with dysphagia showed only 56.5% of patients complied with thickened fluids consumption (Shim et al., 2013). and thus these products were compared to potentially more palatable swallowing aids, jellies, and yogurts which were used as alternative swallowing aids (Chapter 2). There is very little scientific evidence on the safety of swallowing of these alternative swallowing aids (Sonoi et al., 2016). However, jellies that are made from gums are commonly used in Japan and are recommended as a transitional food product that change in texture, for example break down quickly in the oral cavity and become easier to swallow (International Dysphagia Diet Standardisation Initiative, 2016b). A study conducted in postoperative cancer patients has found that jellies are safer than nectar-thick thickened fluids to swallow (Sonoi et al., 2016). A study was conducted examining the efficiency of intervention methods to prevent aspiration in twenty-five patients with Parkinson's disease (PD) and 23 patients with degenerative cerebellar ataxia (CA) (Nagaya, Kachi, Yamada, & Sumi, 2004). Thirteen PD patients and seven CA patients showed aspiration without intervention. Three interventions were used; changing food form to using jelly, chin-down posture and supraglottic swallow techniques. The study found that changing to

jelly was effective and resulted in no aspiration observed in all PD patients and five CA patients (Nagaya et al., 2004). The two CA patients that showed aspiration after jelly intervention were patients whose feeding was severely impaired and were at the end stage of the progressive disease (Nagaya et al., 2004). Kumagai, Tashiro, Hasegawa, Kohyama, & Kumagai (2009) studied the velocity spectrum in the pharynx measured using ultrasonic pulse Doppler method for yogurt, water and thickener solutions and found that the maximum velocity of water was thrice that of yogurt. The velocity spectra for water and thin fluids showed the velocity spectra distributed over a wider range than yogurt and more viscous thickened fluids suggesting cohesive and thus safer bolus flow for yogurt and thickened fluids with increasing concentration (Kumagai et al., 2009).

The aim of this chapter is to compare the acceptability of jellies and thickened fluids commonly used for dysphagia management, to characterize rheological, texture and *in vitro* processing properties of thickened fluids and to compare these with alternative products used for dysphagia patients such as jellies and yogurts.

The primary objective of this study is to compare the processing behaviour of thickened fluids to jellies and yogurt in the *in vitro* throat model.

The secondary objectives of this study are to:

- Compare the acceptability of thickened fluids and jellies in healthy adults
- Compare the rheological, textural and *in* vitro processing properties of thickened fluids with jellies and yoghurt

3.2 Materials and methods

3.2.1 Materials

Three commercial thickeners, five commercial jellies, and a smooth yogurt were purchased and are shown in Table 3-1 with the main ingredients. Within the thickeners, Thick & Easy® (referred to as Thick & Easy in this chapter) is starch-based; Resource® ThickenUp™ Clear (referring to Resource Clear in this chapter) is xanthan gum-based, and Nutilis Powder contains a mixture of starch and gums. Three of the commercial jellies (Hartley's, Vimto and Peppa pig) are firm, homogeneous and retain a free-standing structure when left on a plate; whereas the Ryukakusan jellies (both for adults and children) are in a granular form (non-homogeneous in texture) and can flow on a plate.

Table 3-1: Products used in the study.

Product		**Main ingredients**	**Manufacturer**
Thickeners	Thick & Easy®	Modified starch	Fresenius Kabi, Ireland
	Resource® ThickenUp™ Clear	Xanthan gum	Nestle Health Science, Switzerland
	Nutilis Powder	Modified starch, xanthan gum, tara gum, guar gum	Nutilis, The Netherlands
Jellies	Hartley's strawberry ready-to-eat jelly	Locust bean gum, xanthan gum, gellan gum	Hain Daniels Group, UK
	Vimto ready-to-eat jelly	Carrageenan, locust bean gum	Caterers choice Ltd., UK
	Peppa pig ready-to-eat jelly	Gelatine	Heaven made foods Holt Ltd., UK
	Ryukakusan "magic" jelly for adults	Agar	Ryukakusan, Japan
	Ryukakusan "magic" jelly for children	Agar	Ryukakusan, Japan
Yogurt	Ski strawberry yogurt	Milk, rice starch, sugar, lemon juice, carrot concentrate, guar gum, milk calcium concentrate	Nestle, Switzerland

3.2.2 Preparation of test samples

Each commercial thickener was prepared using the lowest amount of powder within the manufacturer recommended range in deionized water, corresponding to three levels of thickening (Table 3-2). The thickening levels comply with the American National Dysphagia Diet guideline recommendations for use in patients with different stages of dysphagia according to the disease severity, with stage 3 being the most severe (National Dysphagia Diet Task Force & American Dietetic Association, 2002) (Chapter 1, Table 1-3). To be able to process the three free-standing jellies (Hartley's, Vimto and Peppa pig) for the *in vitro* swallowing test, they were manually chopped (using a spatula) to particles of 4mm diameter.

Table 3-2: Amount of thickeners added to deionized water (100ml) for each level of thickening.

Product	Level of thickening	Thickener content in deionized water % (w/v)
Thick & Easy	1	4.5
	2	6.75
	3	9
Resource Clear	1	1.2
	2	2.4
	3	3.6
Nutilis Powder	1	2
	2	4
	3	6

3.2.3 Particle size distribution and acceptability study of jellies and thickened fluid

The study was approved by the University of Hertfordshire Ethics Committee (LMS/PGR/UH/02759). Twelve healthy volunteers provided informed consent to participate in the study. Participants with swallowing difficulties or any allergies or restrictions with the ingredients of the test products were excluded from the study.

Participants were given jellies that were firm enough to retain a free-standing structure (Hartley's, Vimto and Peppa pig gelatin jellies) and were asked to chew the jellies (if they needed to) until they felt it was ready to swallow the bolus and to expel the bolus just before swallowing. The chewing time was not assessed as the aim of this investigation was to measure particle size once the bolus was deemed ready to swallow. The temperature of the expelled boluses was measured using a digital thermometer (Fisher Scientific, traceable pocket-size thermometer) immediately after the expulsion of the first three boluses for each jelly product. The particle sizes of randomly selected 20 particles for each product for each participant were measured using a digital calipher (DML 150mm, Digital Micrometers Ltd). Boluses of similar particle sizes for each product from different participants were mixed together and used for further testing.

After the particle size distribution study, participants were provided with a questionnaire (Appendix II) to assess the acceptability of the Hartley's, Vimto, Peppa Pig and Ryukakusan's adult jellies and Thick & Easy stage 3 thickener, in a randomized sequence. The Thick & Easy stage 3 was prepared as described in Section 3.2.2. Participants were asked to swallow a spoonful of each product and were

asked to answer the questionnaire regarding the acceptability of the product straightaway after each swallowing. Participants used water to rinse their mouths after consuming each product. Questions included rating ease of swallowing and stickiness of the product using a 5-point Likert scale (1 being very easy to swallow or not sticky at all and 5 being extremely difficult to swallow or extremely sticky), whether there was any residue felt in the mouth or throat, whether samples required chewing and whether consistency changed in the mouth prior to swallowing. Participants were also asked which product they preferred and disliked the most.

3.2.4 *In vitro* performance in the "Cambridge throat" ("CT") model

The "Cambridge Throat" (CT) model was used to understand the *in vitro* swallowing of the thickeners, jellies, and yogurt. The "CT" model is a static mechanical model designed to simulate the physiological anatomy and dimensions of the human throat (Mackley et al., 2013). A five-milliliter test sample was held within a 25mm dialysis tube attached to the top of the perpex mouth of the "CT" model, representing the mouth (Figure 3-3). The thickeners were used as prepared according to Table 3-2; the Ryukakusan jellies (adults and children) were used as directly taken out from package, and the three free-standing jellies (Hartley's, Vimto and Peppa pig) were processed both as manually chopped samples (dry jellies), and participant chewed samples (chewed jellies) as shown in Section 3.2.2 and 3.2.3. Five replicates were processed for each sample.

In the "CT" model, the tongue action is represented by a roller which has an attached weight (190g) held by a pin. When the pin is released, the weight provides a constant torque which causes the roller to apply a constant pressure (approximately 0.1 bar) on

the bolus through the tubing (Mackley et al., 2013). The roller movement ends just before the area representing the epiglottis, and the samples then flow under gravity, reaching a diversion of the model cavity representing the airway divide (Figure 3-1). An iPhone 6S camera was used to capture images of the flow of test samples within the throat model at 30fps. The retrieved images were used to calculate the oral transit time (OTT) and bolus length (BL) at airway divide of the test sample. The position of the bolus in the tubing was previously described by Mowlavi et al. (2016) by measuring the angel θ between the roller and the horizontal direction. At the initial position (before the pin was released), the roller was held at an angle θ_0 = 45°; at the end of the roller movement, the roller reached its final position at θ_f = 165° (Figure 3-1) (Mowlavi et al., 2016). The OTT is defined as the time taken for the roller to move from its initial position (θ_0) until reaching θ_{end} = 120° (Figure 3-1) (Mowlavi et al., 2016). Image J (Fiji) was used to calculate BL at airway divide by capturing the first image in which the bolus front can be seen to reach the airway divide. Using this image, the BL was measured as the length of the bolus from bolus front to bolus tail (Figure 3-2a). In cases where the bolus tail cannot be clearly seen, the BL was measured from the end of the dialysis tubing as the bolus tail to the bolus front (Figure 3-2b).

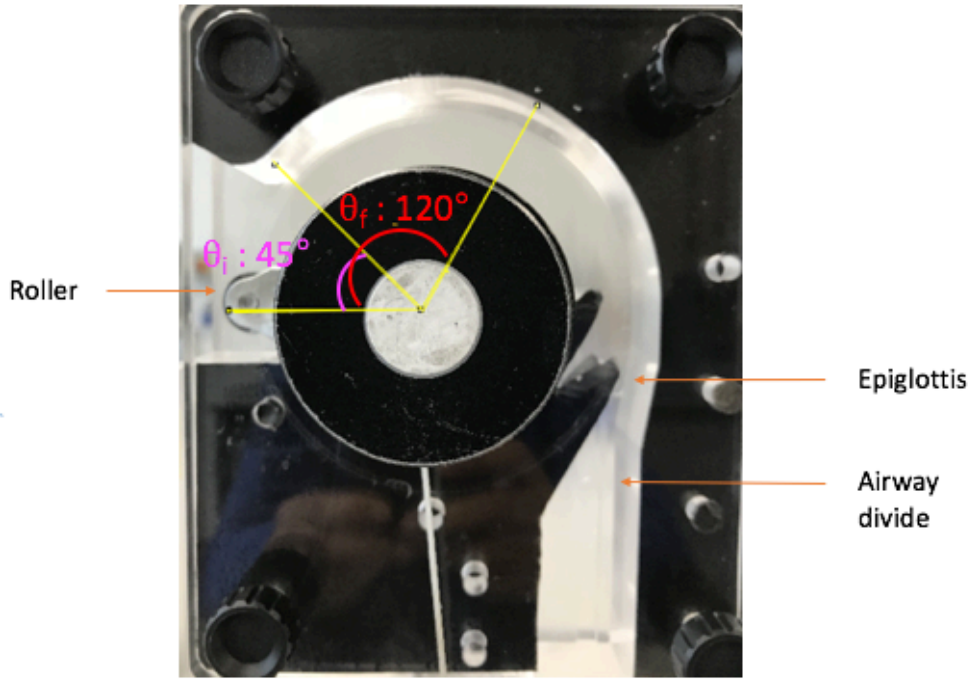


Figure 3-1: CT throat model with measured angles.

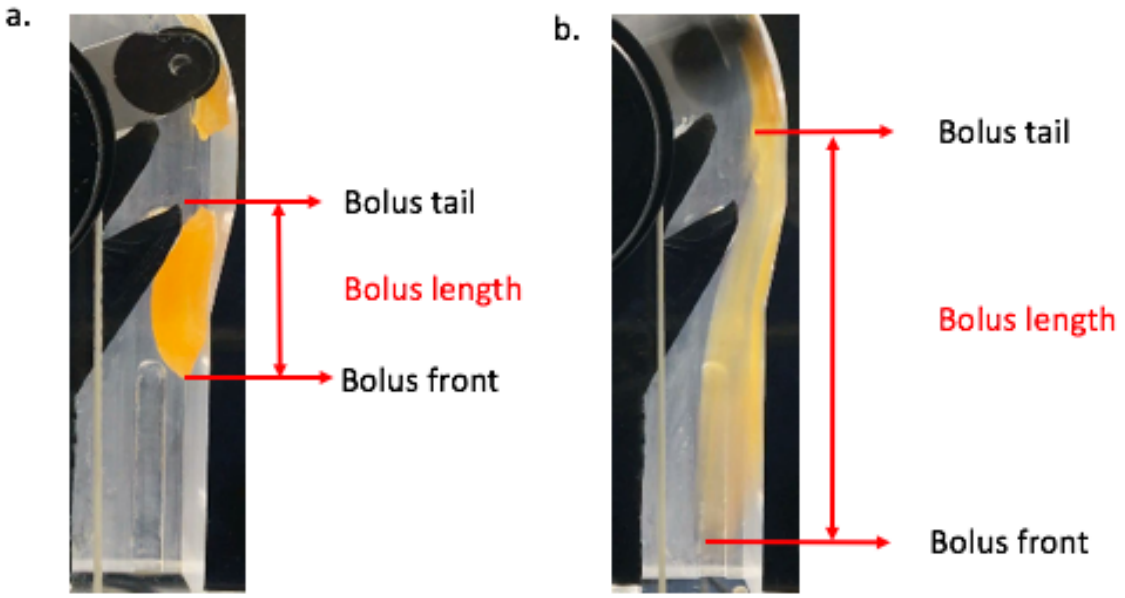


Figure 3-2: a) Bolus length measurement for boluses with the bolus tail and front. b) An example bolus length measurement for boluses where bolus tail is not clearly defined.

3.2.5 Rheological and textural characterization

Rheological and textural characterisation was carried out for all products listed in Table 3-1. The preparation of samples were as described in Section 3.2.2 and 3.2.3. A TA 1500 EX controlled–stress rheometer (TA instruments) was used to obtain steady shear apparent viscosity and oscillatory viscoelastic data. Measurements were carried out at 25°C using parallel plate geometry (diameter: 40mm, gap 650mm) for all experiments. For each sample, oscillatory stress sweep (torque 0.01-10,000 micro N.m at a frequency of 10 rad/s), frequency sweep (0.1 to 100rad/s) and steady-state rate sweep (0.01-100/s) were carried out in triplicate. Apparent viscosity was determined at a shear rate of $50s^{-1}$ during a steady state rate sweep, and yield stress was determined as the linearity limit of G' from stress (amplitude) sweeps.

Texture characteristics (cohesiveness, surface adhesion and firmness) were evaluated using back extrusion tests on a Texture Analyser (TA.XT. *Plus,* Stable Microsystems) applying a 5kg load cell. An extrusion disc (35mm) was positioned centrally over the sample container containing 100ml of the sample; the disc penetrates the sample to 20mm at 0.5mm/s test speed. The maximum force (g) used to reach this depth is taken as a measurement of firmness or hardness. The maximum negative force (when the probe is drawn up at a speed of 0.5mm/s) is an indication of cohesiveness. Surface adhesion was determined by drawing the disc at a speed of 0.5mm/s towards the sample; the disc is then held on the surface of the sample for 30 seconds and pulled away at 2mm/s. The force (g) for withdrawal of the disc from the sample is the indication of surface adhesion (adhesiveness). The measurements were carried out at room temperature with triplication for all samples.

3.2.6 Data analysis

Prism Graphpad (Version 7.0) was used to assess if the data relating to ease of swallowing and stickiness scores from participant questionnaires was normally distributed using the Shapira-Wilk test and normal distribution was rejected ($p<0.05$). The Kruskal Wallis test was applied to determine significant differences for ease of swallowing, stickiness scores between the stage 3 thickened fluid and jelly products, significant differences were noted if $p \leq 0.05$.

Prism Graphpad (Version 7.0) was used to obtain Pearson correlation coefficient for OTT and BL against rheological (apparent viscosity and yield stress) and textural parameters (cohesiveness, firmness, and adhesiveness) of thickened fluids. Five repetitions were performed for *in vitro* swallowing tests (OTT and BL) and triplicates for rheological and textural measurements. To calculate the correlation, three results were selected randomly for OTT and BL from the five repetitions to match the three results of the rheological and textural measurements. This was repeated ten times to obtain ten random combinations, and an average correlation coefficient was obtained using the mean value of the ten combinations. Correlation coefficient was graded according to Table 3-3.

The OTT and BL were presented as a mean ± confidence interval (CI). CI was calculated at 95% confidence using Equation 3-6:

$$\text{Mean} \pm 1.96 \left(\sigma/\sqrt{n}\right) \qquad \text{[Equation 3-6]}$$

Prism Graphpad (Version 7.0) was used to assess if the data relating to OTT times and BL was normally distributed using the Shapira-Wilk test and normal distribution was rejected ($p<0.05$). The Mann Whitney U test was applied to determine significant differences for OTT and BL between stages of thickening for each thickened fluid product and between dry jellies and participants boluses, significance differences were noted if $p \leq 0.05$.

Table 3-3: Correlation coefficient classification (Mukaka, 2012).

Classification	**Correlation coefficient (R)**
Very high positive or negative correlation	±0.9 - ±1
High positive or negative correlation	±0.7 - ±0.9
Moderate positive or negative correlation	±0.5 - ±0.7
Low positive or negative correlation	±0.3 - ±0.5
Negligible correlation	0.0 - ±0.3

3.3 Results

3.3.1 Participant demographics

Twelve participants took part in the acceptability study (5 females and 7 males) of age range 29-44 years (mean 30 years).

3.3.2 Particle size distribution of jelly boluses and acceptability of different products

The mean temperatures of the jelly boluses after chewing and immediately after expelling were 24.6 ± 1.9 °C, 25.2 ± 1.9°C and 21.0 ± 2.9°C for Hartley's, Vimto and Peppa Pig jellies respectively, similar to room temperature (21.1 ± 0.2°C) at the time

of the test. The particle sizes (mean ± SD) for the expelled jelly boluses were 7.2 (± 3.5) mm, 6.9 (± 3.6) mm and 4.3 (± 0.8) mm for Hartley's, Vimto and Peppa Pig jellies respectively. Peppa pig gelatin-based jelly was only measured for boluses from 9 participants due to a change of consistency to liquid after chewing in some paticipants' expelled samples.

All participants commented that the thickened fluid was the product they liked the least (Table 3-4), citing 'sticky' (5 participants), 'granular' (4 participants) and 'unpleasant' (4 participants) as reasons for disliking the product. The majority of participants (9/12) liked Hartley's jelly as their favorite product for being "soft" (6 participants) and "smooth" (9 participants).

Participants rated thickened water (Thick & Easy stage 3) as more difficult to swallow ($p<0.05$) and sticky ($p<0.05$) compared to jellies. Sixty-seven percent (8) of participants felt residue left in their throat and mouth during swallowing of the thickened water (Table 3-4). There was no significant difference in ease of swallowing or stickiness between jelly products. All participants needed to chew the free-standing commercial jellies (Hartley's, Vimto and Peppa pig) and only two participants needed to chew the Ryukakusan jelly for swallowing.

Table 3-4: Participant responses on acceptability aspects of products.

Acceptability aspects	Hartley's jelly	Vimto jelly	Peppa pig (gelatin-based) jelly	Ryukakusan swallowing aid	Thick and easy stage 3
Ease of swallowing (mean score and range)	1.3 (1-2)	1.1 (1-2)	1.6 (1-3)	1.3 (1-2)	3 (1-5)
Residue felt in the mouth (% (number) of participants)	17 (2)	8 (1)	16 (2)	0 (0)	83 (10)
Residue felt in the throat (% (number) of participants)	17 (2)	8 (1)	33 (4)	25 (3)	67 (8)
Participants needing to chew jellies to enable swallow (% (number) of participants)	100 (12)	100 (12)	100 (12)	17 (2)	0 (0)
Stickiness of products (mean score and range)	1.4 (1-2)	1.4 (1-2)	1.8 (1-3)	1.2 (1-2)	3.3 (2-5)
No. of participants noticing a change in consistency of product in the mouth	0	0	4	0	0

3.3.3 Viscosity and *in vitro* swallowing of thickeners

The commercial thickeners were prepared using the manufacturer recommended concentrations to reach expected stages of thickening according to the American National Dysphagia Diet guideline (National Dysphagia Diet Task Force & American Dietetic Association, 2002). The expected apparent viscosity range (measured at 50 S^{-1}) for each stage of thickening are marked in Figure 3-5 using the colour boxes. However, the actual apparent viscosity of the thickeners measured in the rheological test showed differences to the expected stages of thickening (Figure 3-3). Resource Clear (xanthan gum-based) showed consistently low viscosity even at stage 2 and 3 concentrations. Thick & Easy (starch-based) showed higher viscosity than the

expected viscosity range at thickening stages 1 and 2, and the viscosity was also in the high end of the expected range for stage 3. Interestingly, Nutilis Powder (a mixture of starch and gum-based thickener) showed viscosity within the expected range at all three thickening stages.

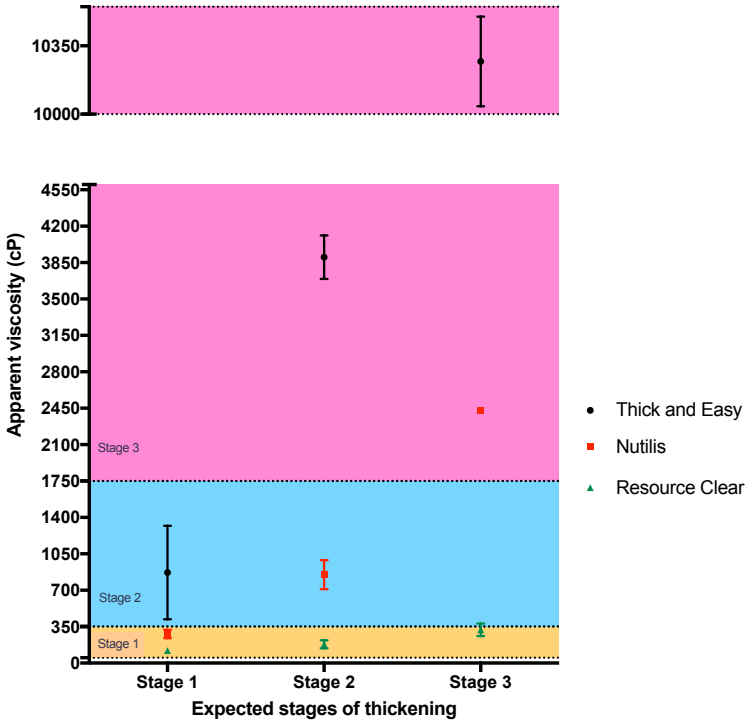


Figure 3-3. A comparison of expected to actual stages of thickening for the commercial thickeners.

Figure 3-4 shows images of the thickeners during the *in vitro* swallowing process in the "CT" and Figure 3-5 shows the oral transit time (OTT) and bolus length (BL) at airway divide for each expected stages of thickening. For all three thickeners, OTT increased with incremental increase in thickening (Figure 3-5a) and BL at airway divide decreased for each incremental increase of thickening (Figure 3-5b). Table 3-5a shows statistical differences in OTT and BL between stages of thickening for each thickener. OTT and BL showed significant differences between different stages of thickening at stages, 1, 2 and 3 for all thickeners except Resource Clear (xanthan

gum-based) at stages 2 and 3. Table 3-5b shows the comparison between different thickeners at each stage. At stage 1, Resource Clear and Thick & Easy did not show a significant difference in OTT between each other, but both showed a significant difference to Nutilis Powder. There is no significant difference between the thickeners at stage 2 in OTT. At stage 3, all thickeners shown significant differences in OTT to each other, with a ranking order of Thick & Easy > Nutilis Powder > Resource Clear. For BL, there was no significant difference between the thickeners at stages 2 and 3; however, at stage 1 a significant difference was detected with a ranking order of Thick & Easy > Resource Clear >Nutilis Powder.

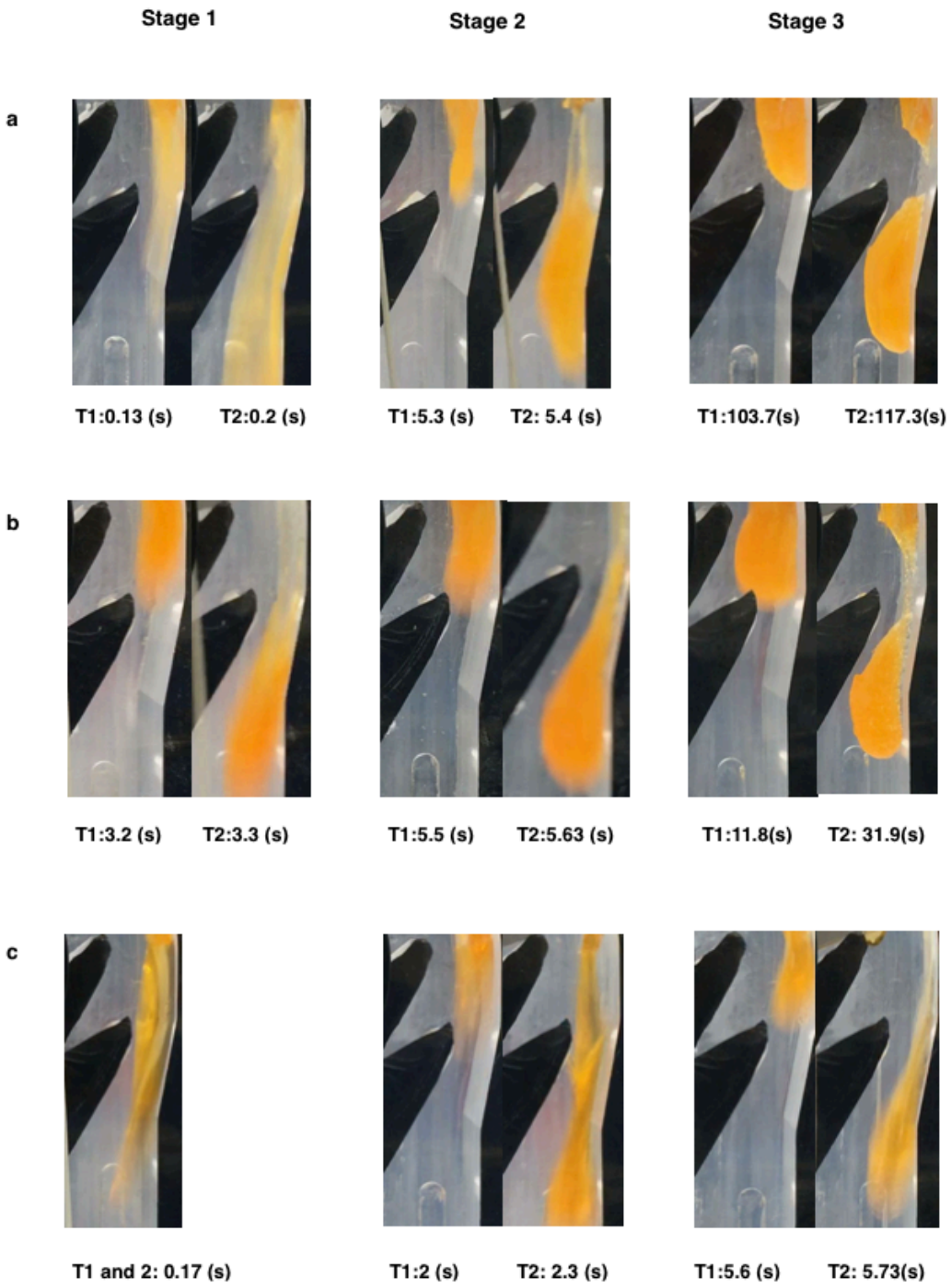


Figure 3-4. Images of stages 1, 2 and 3 thickened fluids of a) Thick & Easy, b) Nutilis Powder and c) Resource Clear at T1 (time taken for the bolus to reach epiglottis) and T2 (time taken for the bolus to reach airway divide).

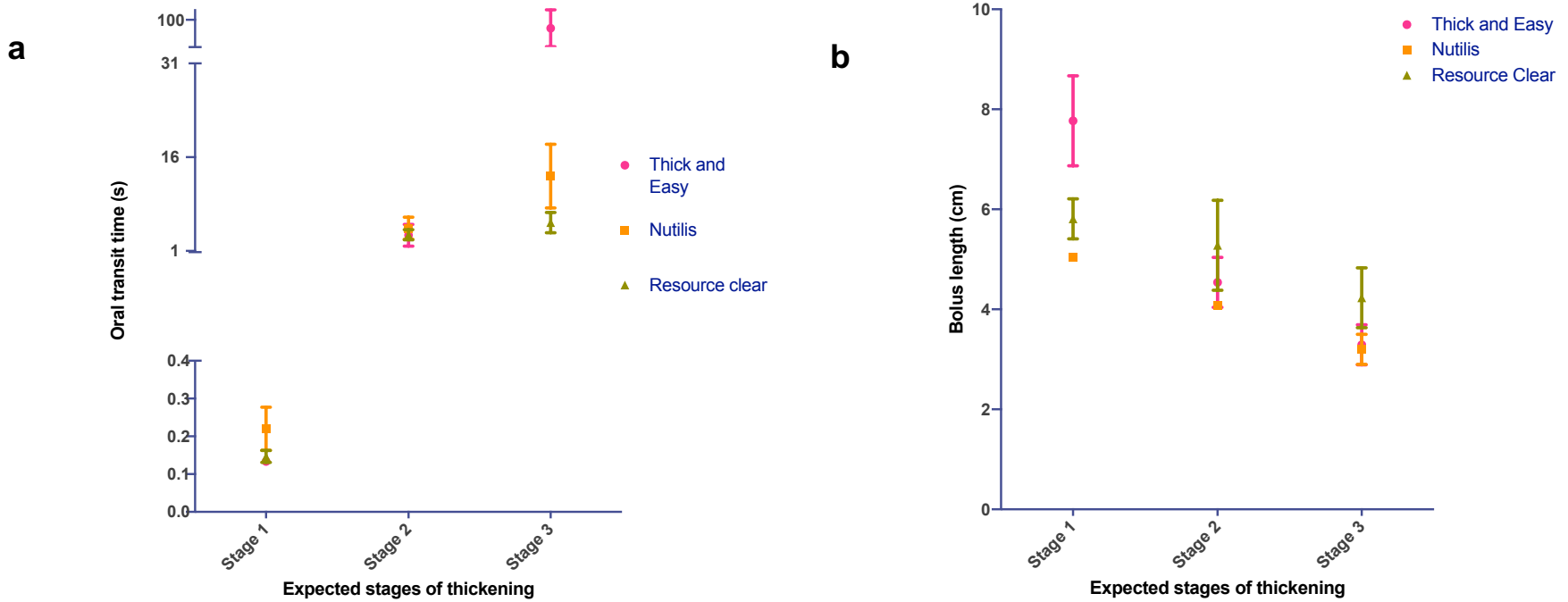


Figure 3-5. Oral transit time (a) and bolus length (b) at airway divide of commercial thickeners at each expected stages of thickening.

Table 3-5: A comparison of statistical differences in OTT and BL (a) between stages of thickening for each thickener (b) between different thickeners at each stage (significance was marked as * $p \leq 0.05$ and ** $p \leq 0.01$).

(a)

Product	**Comparison stages**	**p-value for OTT**	**p-value for BL**
Thick & Easy	1 and 2	0.0079**	0.0079**
	2 and 3	0.0079**	0.0079**
Resource Clear	1 and 2	0.0079**	0.0079**
	2 and 3	0.1508	0.2778
Nutilis Powder	1 and 2	0.0079**	0.0079**
	2 and 3	0.0159*	0.0079**

(b)

Products	**Comparison stages**	**p-value for OTT**	**p-value for BL**
Thick & Easy and Nutilis Powder	1	0.0079**	0.0079**
	2	0.7937	0.2857
	3	0.0079**	>0.9999
Thick & Easy and Resource Clear	1	0.4444	0.0159*
	2	0.8413	0.5000
	3	0.0079**	0.952
Nutilis Powder and Resource Clear	1	0.0238*	0.2857
	2	0.5159	0.2143
	3	0.0159*	0.1508

3.3.4 Rheological and textural characterisations

Three representative oscillatory frequency sweeps are shown in Figure 3-6 for stage three thickening of commercial thickeners. The commercial thickeners all show the same characteristic features; *G'* dominance over G" within the frequency range tested and a decline in complex viscosity (|η*|) over the frequency range. A greater magnitude in G' and G" is shown for Thick & Easy (Figure 3-8a), followed by Nutilis (Figure 3-6b) and Resource clear (Figure 3-6c).

The response to the steady state rate test of the thickener products at different stages of thickening is shown in Figure 3-7. All three commercial thickeners showed shear thinning behavior and an increase in apparent viscosity was observed with each incremental stage of thickening.

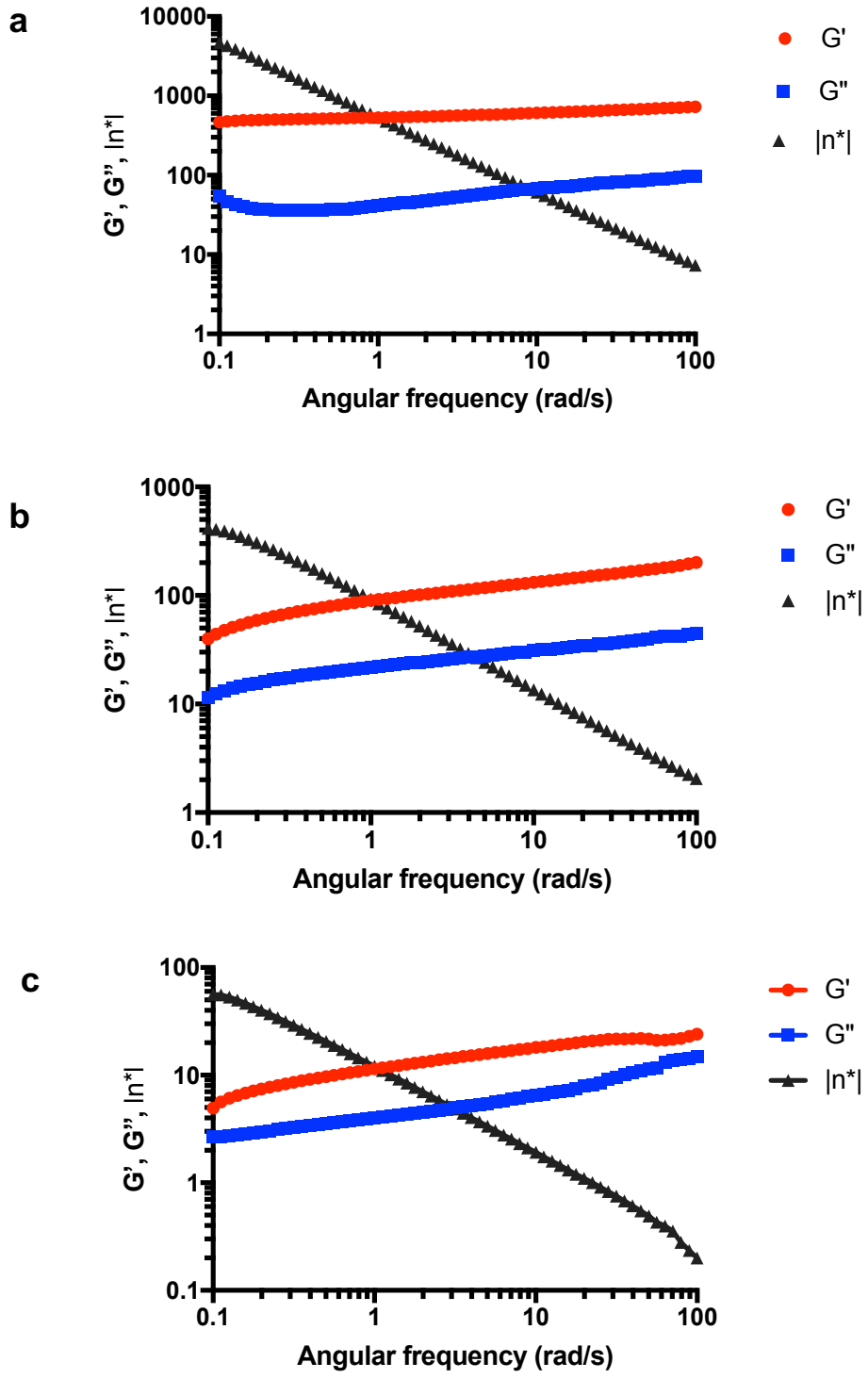


Figure 3-6: Oscillattory frequency sweeps for a. Thick & Easy; b. Nutilis; c. Resource Clear at stage 3 thickening.

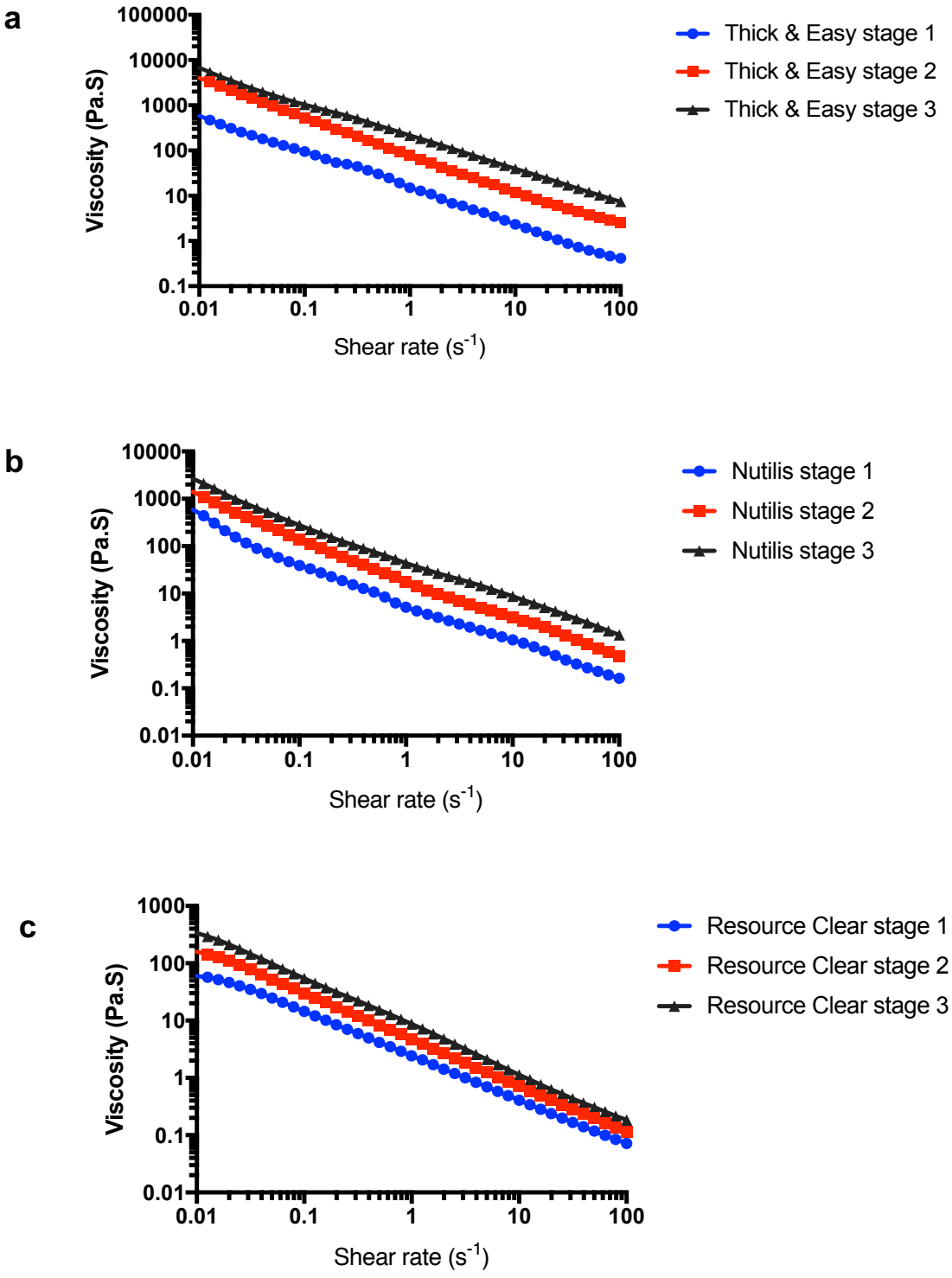


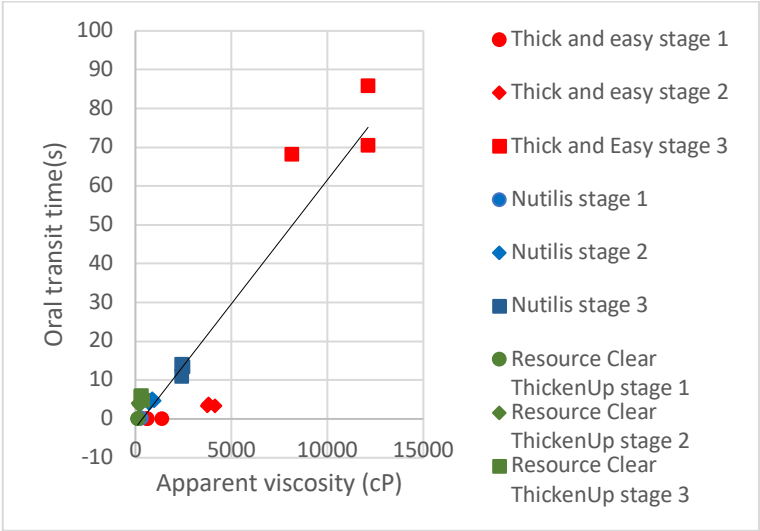
Figure 3-7: Apparent viscosity as a function of shear rate for a. Thick & Easy; b. Nutilis; c. Resource Clear at three stages of thickening.

Very high or high positive correlations were found between OTT and some of the rheological and textural properties of thickeners, including apparent viscosity, yield stress, cohesiveness and firmness (Table 3-6, Figure 3-8). Adhesiveness showed negligible correlation with OTT. Moderate negative correlations were found between BL and cohesiveness, adhesiveness and firmness; while low confidence in the correlation between BL and apparent viscosity and yield stress was observed (Table 3-6, Figure 3-9).

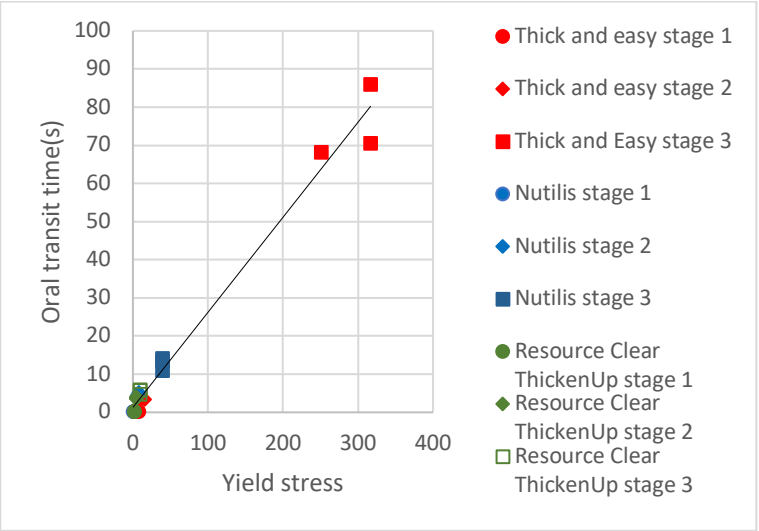
Table 3-6: Pearson's correlation coefficients between OTT, BL and rheological/textural parameters.

Parameters	Correlation with OTT		Correlation with BL	
	R	**Correlation**	**R**	**Correlation**
Apparent viscosity	0.89	High positive	-0.52	Moderate negative
Yield stress	0.95	Very high positive	-0.52	Moderate negative
Cohesiveness	0.87	High positive	-0.66	Moderate negative
Adhesiveness	0.07	Negligible	-0.54	Moderate negative
Firmness	0.78	High positive	-0.66	Moderate negative

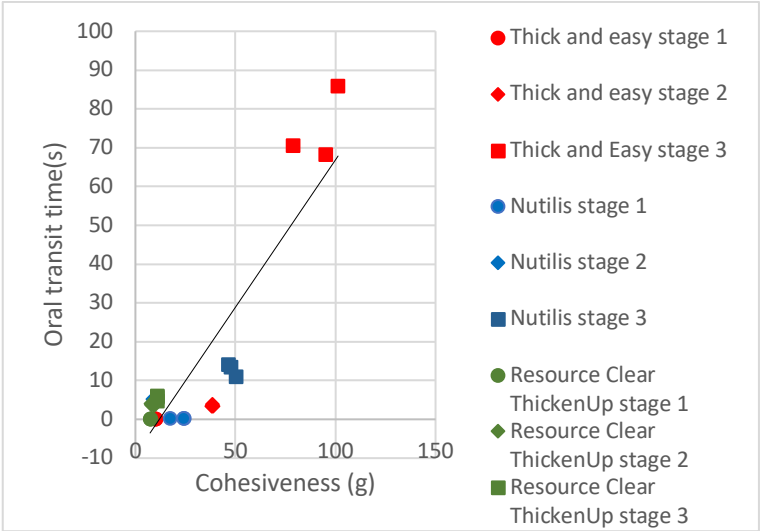
a


Oral transit time(s)
Apparent viscosity (cP)
Thick and easy stage 1
Thick and easy stage 2
Thick and Easy stage 3
Nutilis stage 1
Nutilis stage 2
Nutilis stage 3
Resource Clear ThickenUp stage 1
Resource Clear ThickenUp stage 2
Resource Clear ThickenUp stage 3

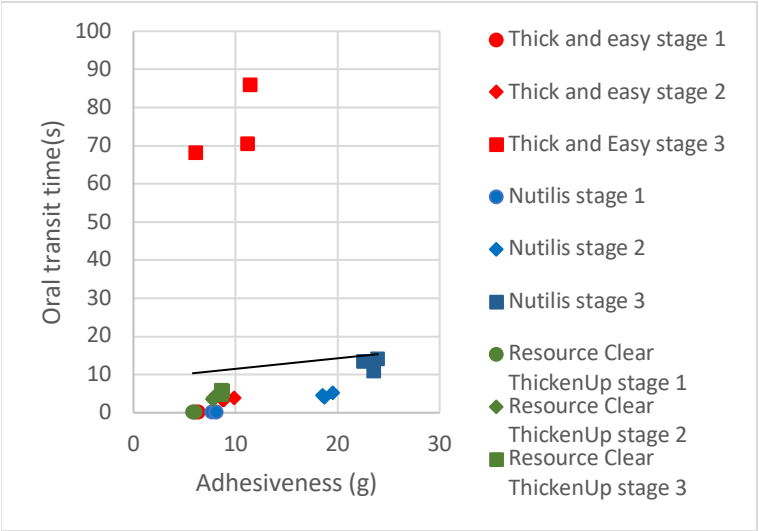
b


Oral transit time(s)
Yield stress
Thick and easy stage 1
Thick and easy stage 2
Thick and Easy stage 3
Nutilis stage 1
Nutilis stage 2
Nutilis stage 3
Resource Clear ThickenUp stage 1
Resource Clear ThickenUp stage 2
Resource Clear ThickenUp stage 3

c


Oral transit time(s)
Cohesiveness (g)
Thick and easy stage 1
Thick and easy stage 2
Thick and Easy stage 3
Nutilis stage 1
Nutilis stage 2
Nutilis stage 3
Resource Clear ThickenUp stage 1
Resource Clear ThickenUp stage 2
Resource Clear ThickenUp stage 3

d


Oral transit time(s)
Adhesiveness (g)
Thick and easy stage 1
Thick and easy stage 2
Thick and Easy stage 3
Nutilis stage 1
Nutilis stage 2
Nutilis stage 3
Resource Clear ThickenUp stage 1
Resource Clear ThickenUp stage 2
Resource Clear ThickenUp stage 3

e

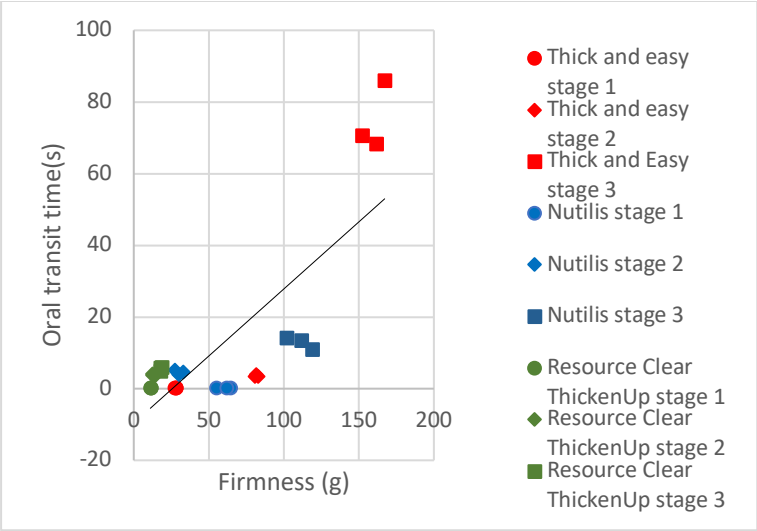
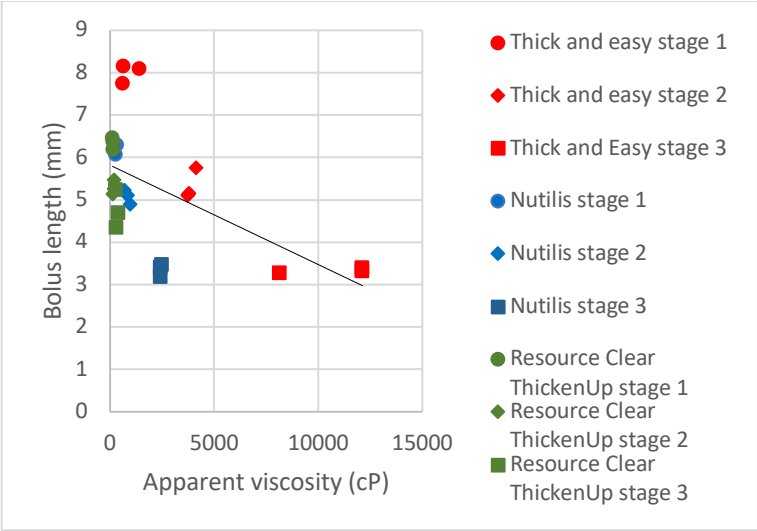
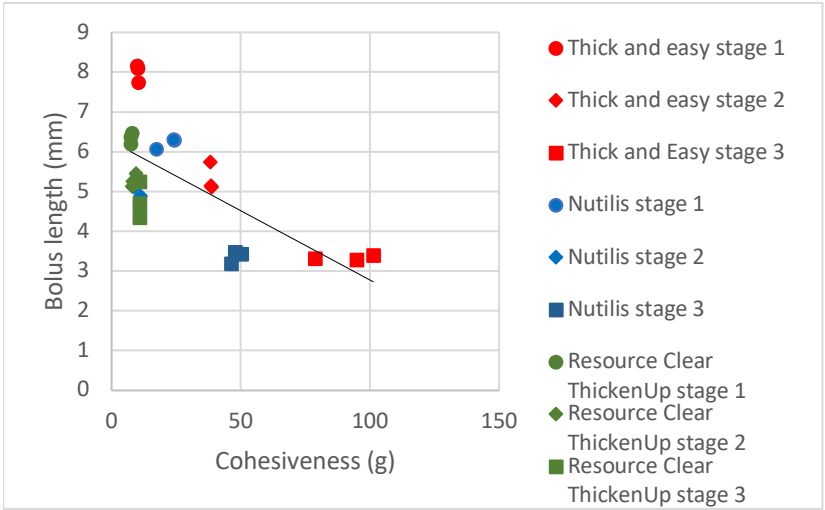


Figure 3-8: Correlation graphs between OTT and a) apparent viscosity, b) yield stress, c) cohesiveness, d) adhesiveness and e) Firmness.

a



b



c

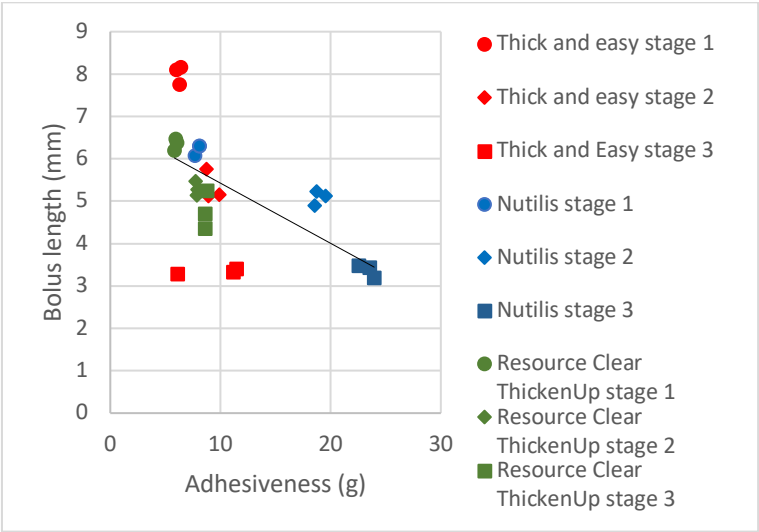


Figure 3-9: Correlation graph between bolus lengths and a) apparent viscosity, b) cohesiveness, c) adhesiveness.

3.3.5 *In vitro* swallowing of jellies and yogurt

Figure 3-10 and 3-11 shows the transit of jellies and yogurt in the "CT" model. Figure 3-12 shows the OTT and BL at airway divide for jellies and yogurt in comparison to Nutilis Powder which showed the expected level of thickening at stages 1, 2, and 3. The OTT of manually chopped (dry) jellies (Hartley's, Vimto and Peppa Pig) were significantly longer than chewed boluses of the same jelly (Table 3-7). The dry jellies showed much slower transit than stage 3 Nutilis Powder. The OTT of the chewed jellies and the free-flowing Ryukakusan jellies (for adults and children) are comparable to stage 2 Nutilis Powder. Ski yogurt showed similar OTT to stage 3 Nutilis Powder.

The BL at airway divide did not show a significant difference between dry and chewed jellies for Hartley's, Vimto and Peppa Pig jellies (Table 3-7). All jelly boluses had BL between the BL of stage 2 and 3 Nutilis Powder; however, larger variations (bigger confidence intervals) were observed for BL of jelly samples. Ski yogurt showed longer bolus BL than the jelly samples, with the mean value bigger than the CI range of the BL of stage 1 Nutilis Powder.

Figure 3-(13-15) show data from the oscillatory frequency sweep and steady-state rate sweep rheological tests. The mechanical spectra showed G' dominance over G" for all jellies. Ski yogurt shows more dependence of moduli on the frequency (Figure 3-13f). Shear-thinning rheology was observed for the jellies and yogurt (Figure 3-15).

Figures 3-(16-18) show the rheological and textural properties of jelly boluses compared to thickened fluids. Most rheological and textural properties of jellies, including apparent viscosity, yield stress, firmness and cohesiveness, were comparable to stage 1-2 thickened fluids, except for Peppa pig jelly which showed firmness and cohesiveness similar to stage 3

thickened fluids. Adhesiveness for jellies was similar to stage 1 and 2 thickened fluids (comparable to Thick & Easy and Resource clear).

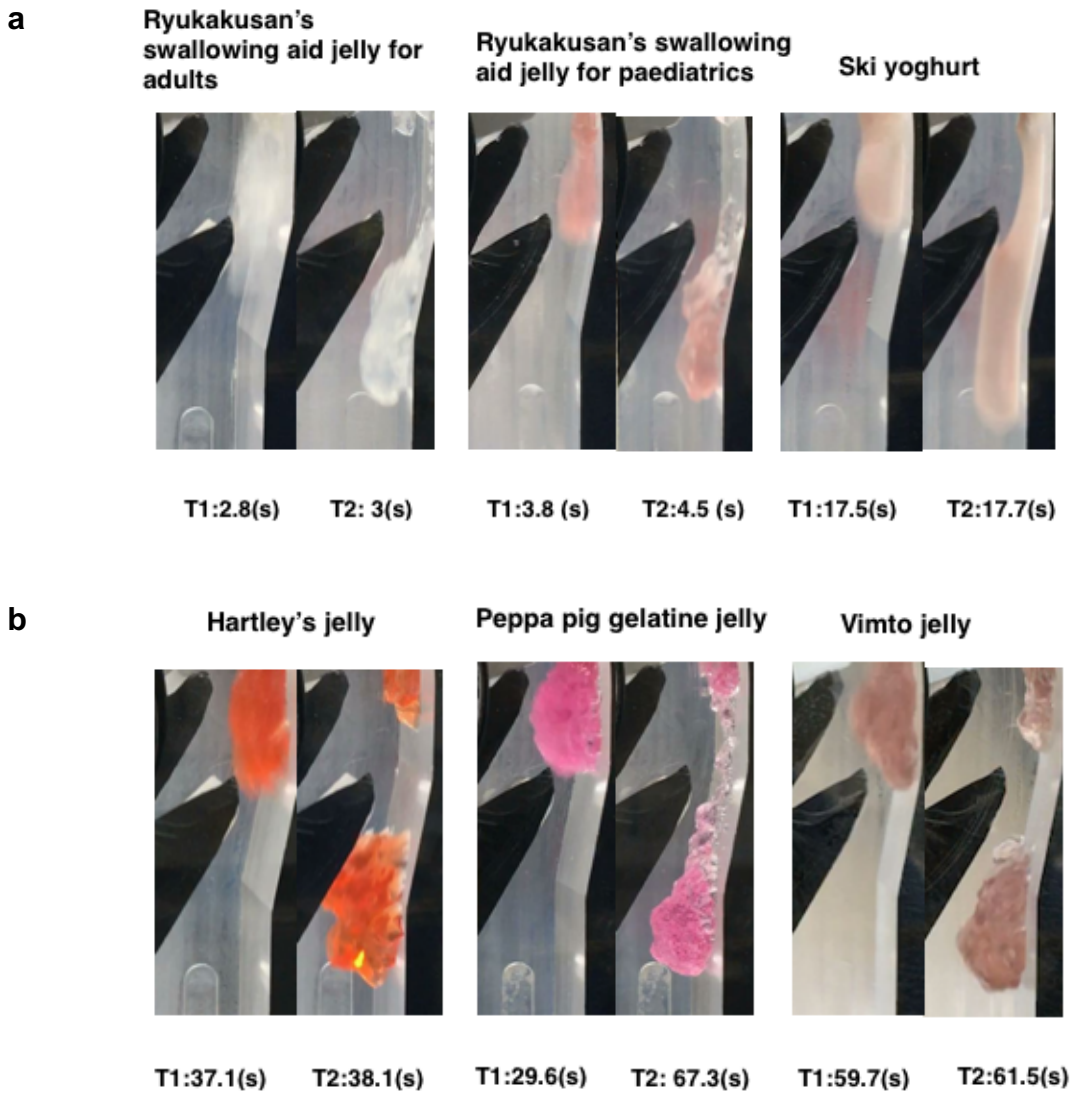


Figure 3-10: Transit of jellies and yogurt in the Cambridge Throat towards the epiglottis (T1) and airway divide (T2) for a) Ryukakusan jellies and yogurt and b) dry jellies.

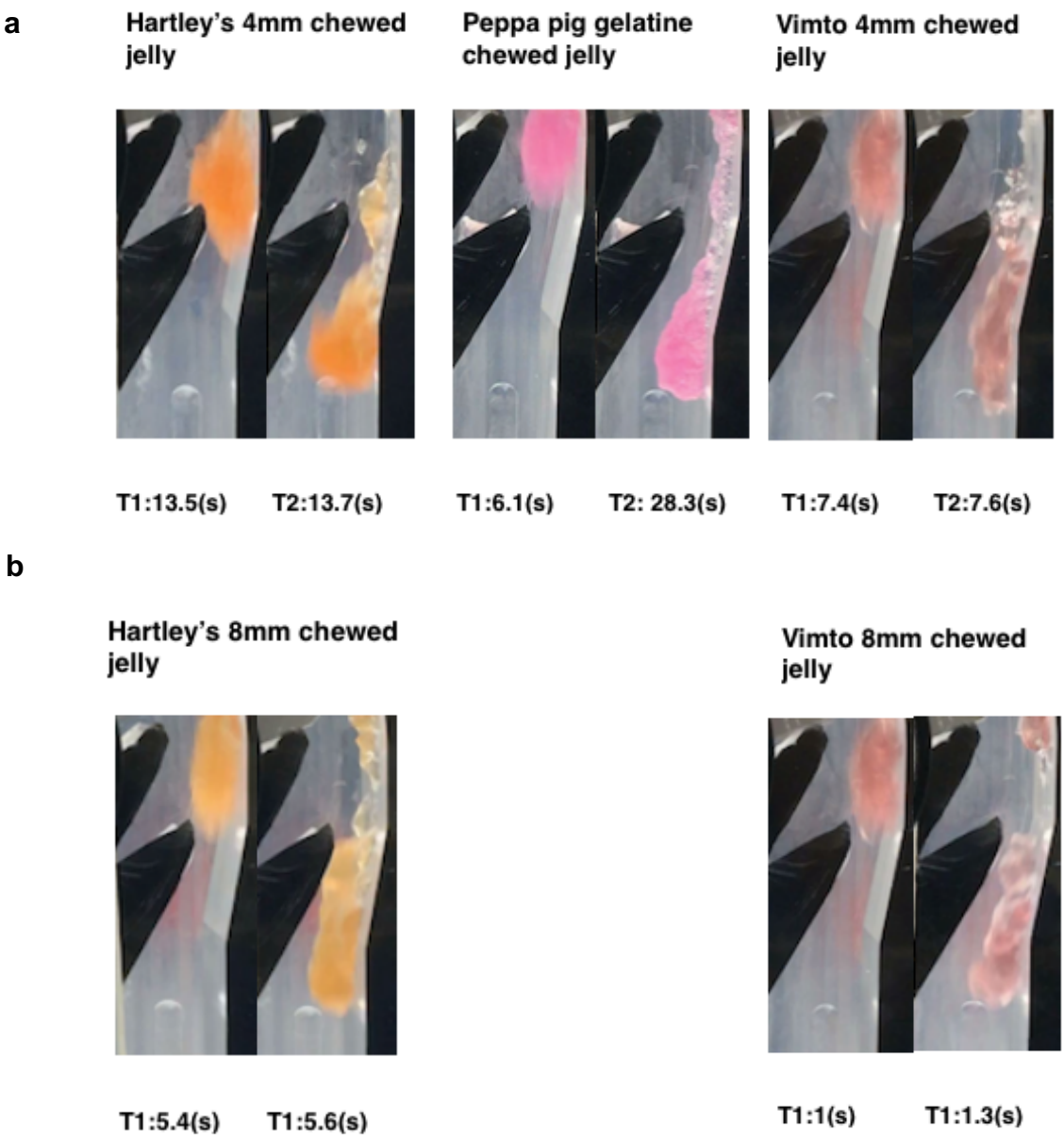


Figure 3-11: Transit of participants' jelly boluses in the Cambridge Throat towards the epiglottis (T1) and airway divide (T2) for a) 4mm particle size b) 8mm particle size.

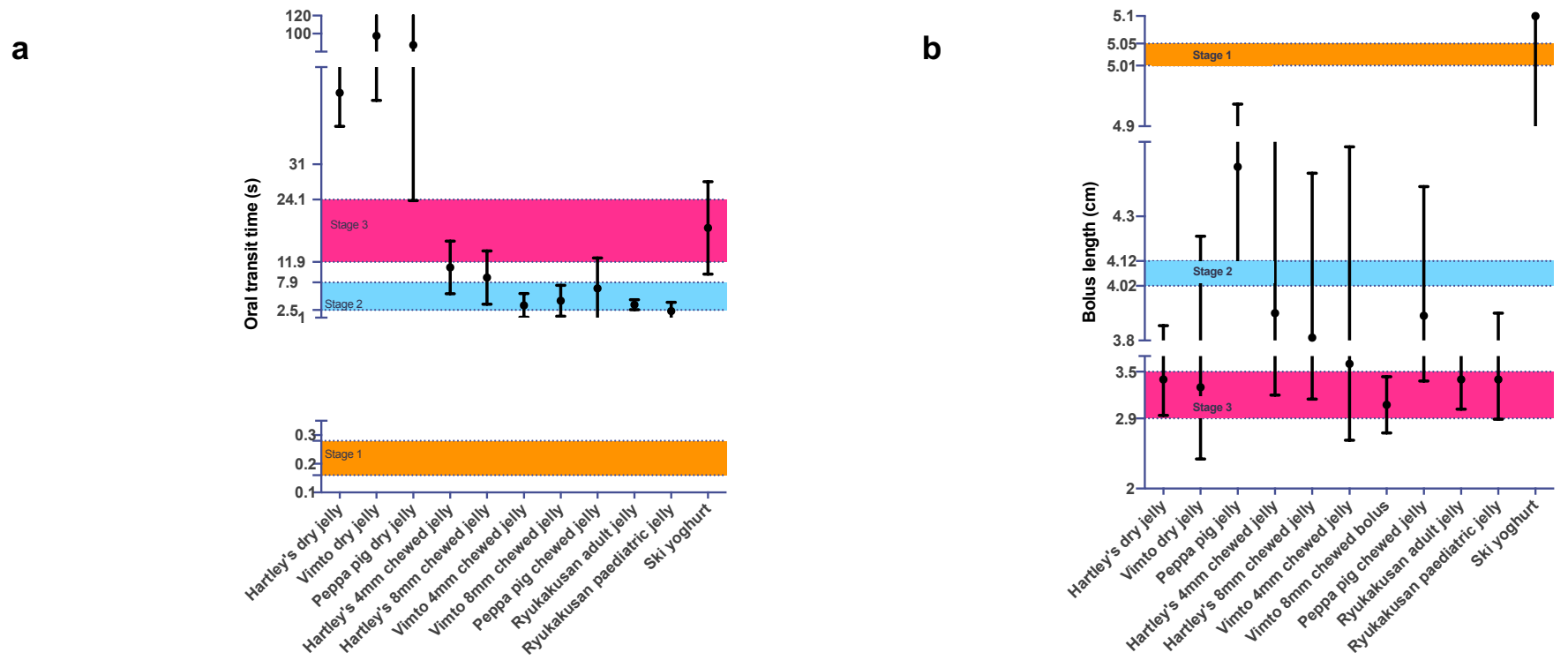


Figure 3-12: The OTT (a) and BL (b) at airway divide for jellies and yogurt. The coloured boxes represent the confidence interval range for the thickener Nutilis Powder at stages 1, 2, and 3 for comparison.

Table 3-7: A comparison of statistical differences in OTT and BL between dry and participant bolus jellies (significant differences was marked as *).

Product	Comparison boluses	p-value for OTT	p-value for BL
Hartley's	Dry jelly vs. participants bolus	0.0159*	0.8413
Vimto	Dry jelly vs. participants bolus	0.0079**	0.6905
Peppa pig	Dry jelly vs. participants bolus	0.0079**	0.6905

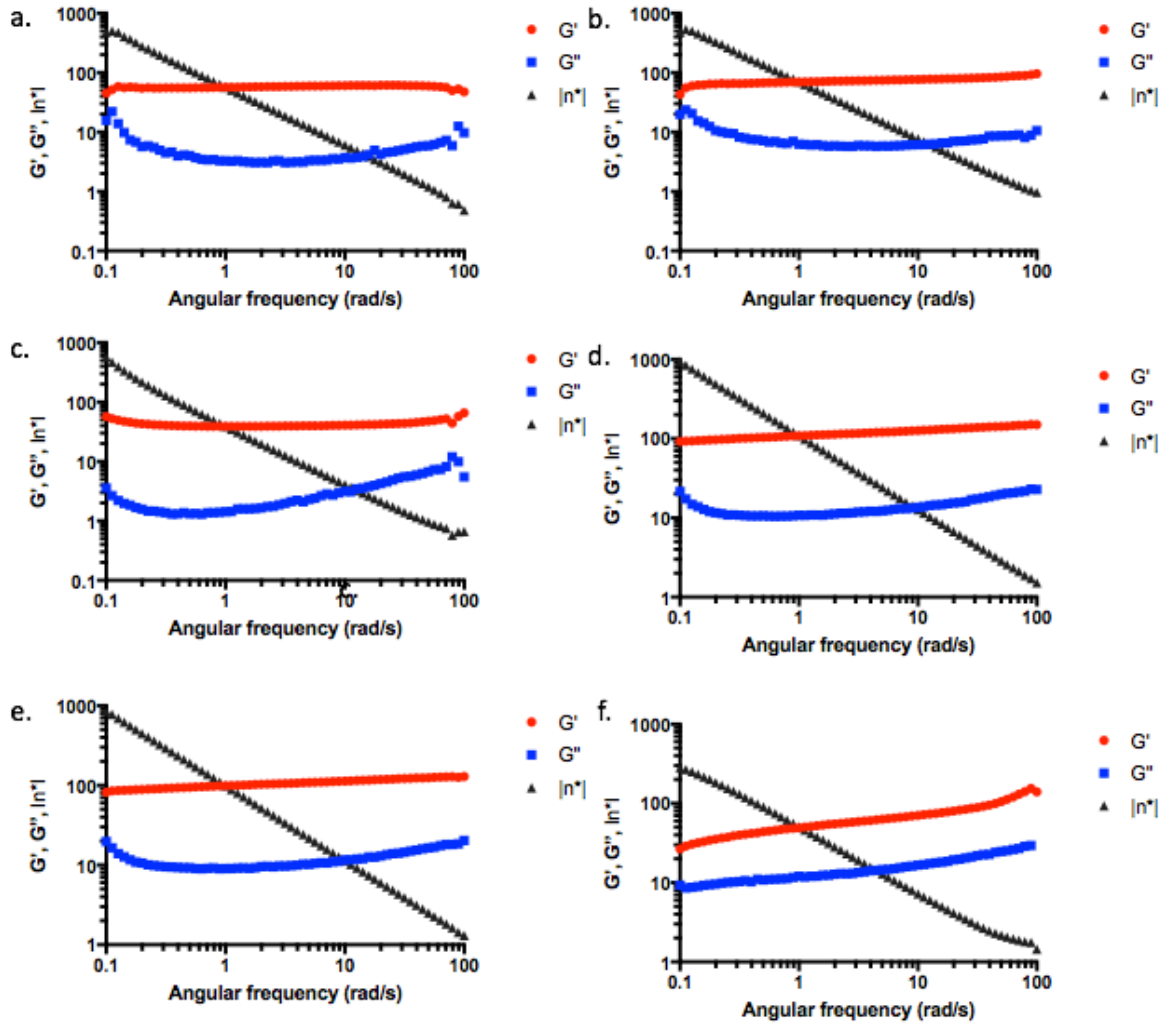


Figure 3-13: Oscillatory frequency sweeps for (a) Hartley's jelly, (b) Vimto jelly, (c) Peppa pig (gelatin-based) jelly, (d) Ryukakusan jelly for adults, (e) Ryukakusan jelly for paediatrics and (f) Ski yogurt.

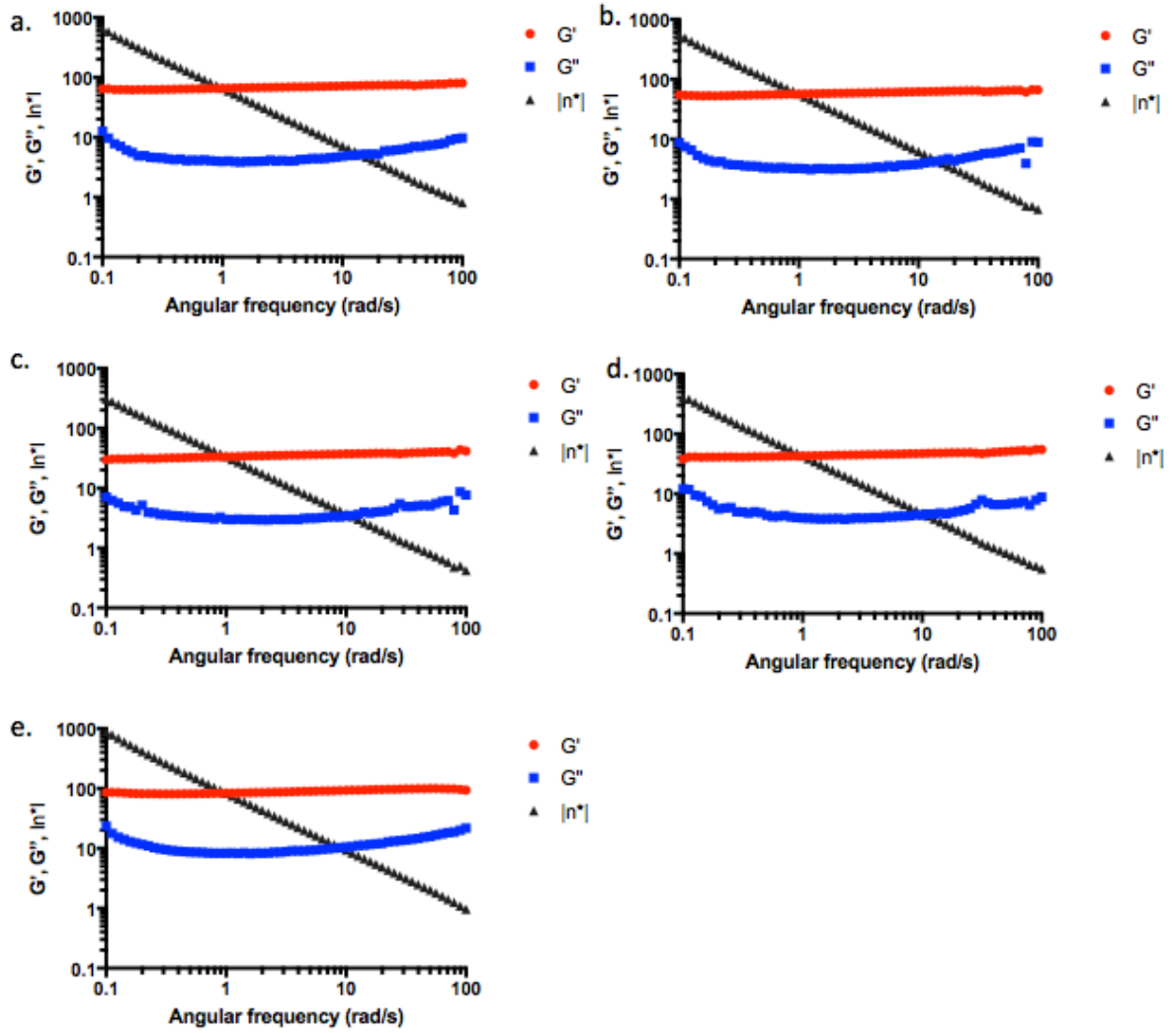


Figure 3-14: Oscillatory frequency sweep for participants' boluses: a) Hartley's small particles b) Hartley's large particles. C) Vimto small particles d) Vimto large particles and e) Peppa pig gelatine bolus.

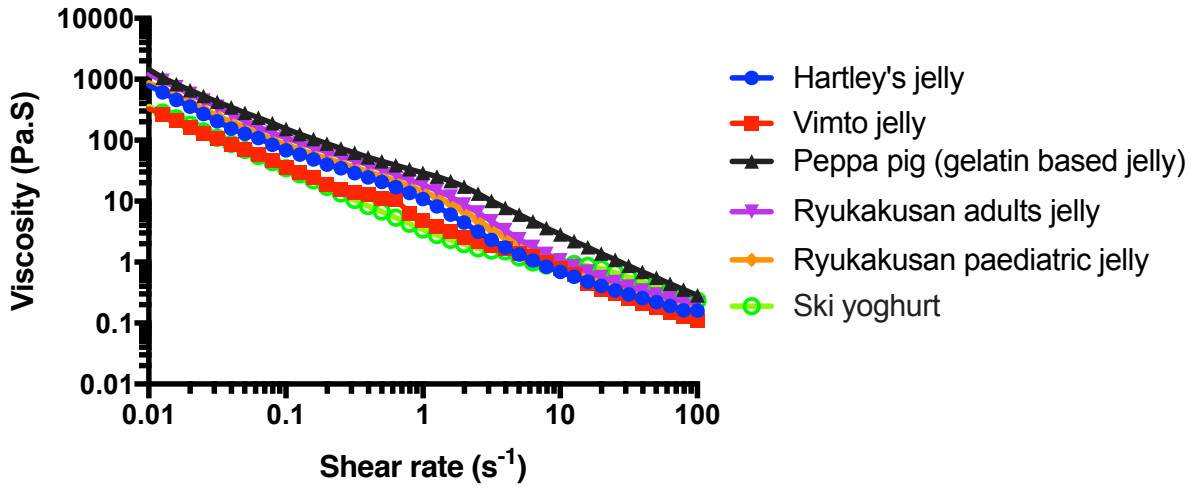


Figure 3-15: Apparent viscosity as a function of shear rate for dry jellies and yogurt.

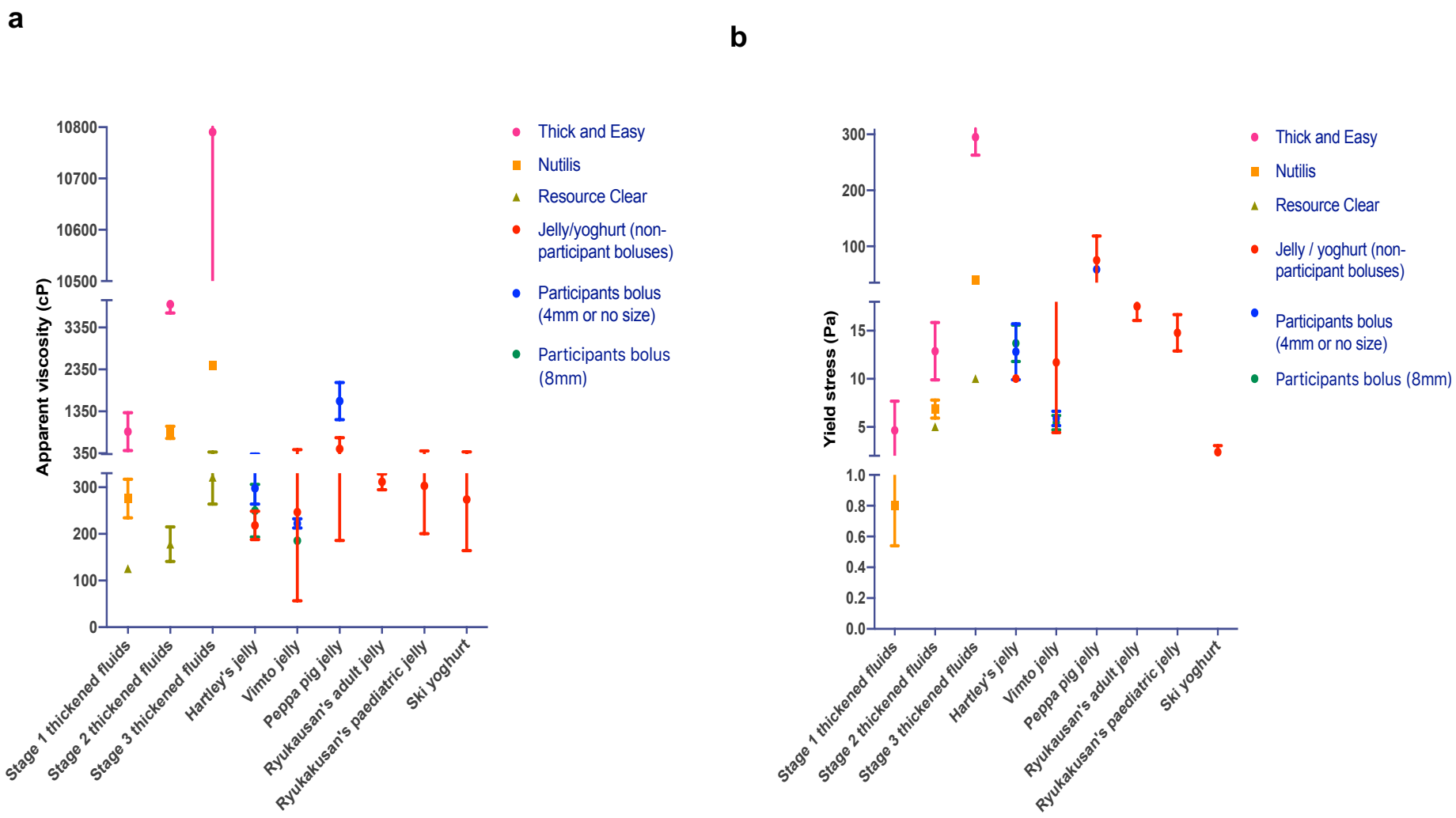


Figure 3-16: Comparison of apparent viscosity (a) and yield stress (b) between thickened fluids, jellies and yogurt.

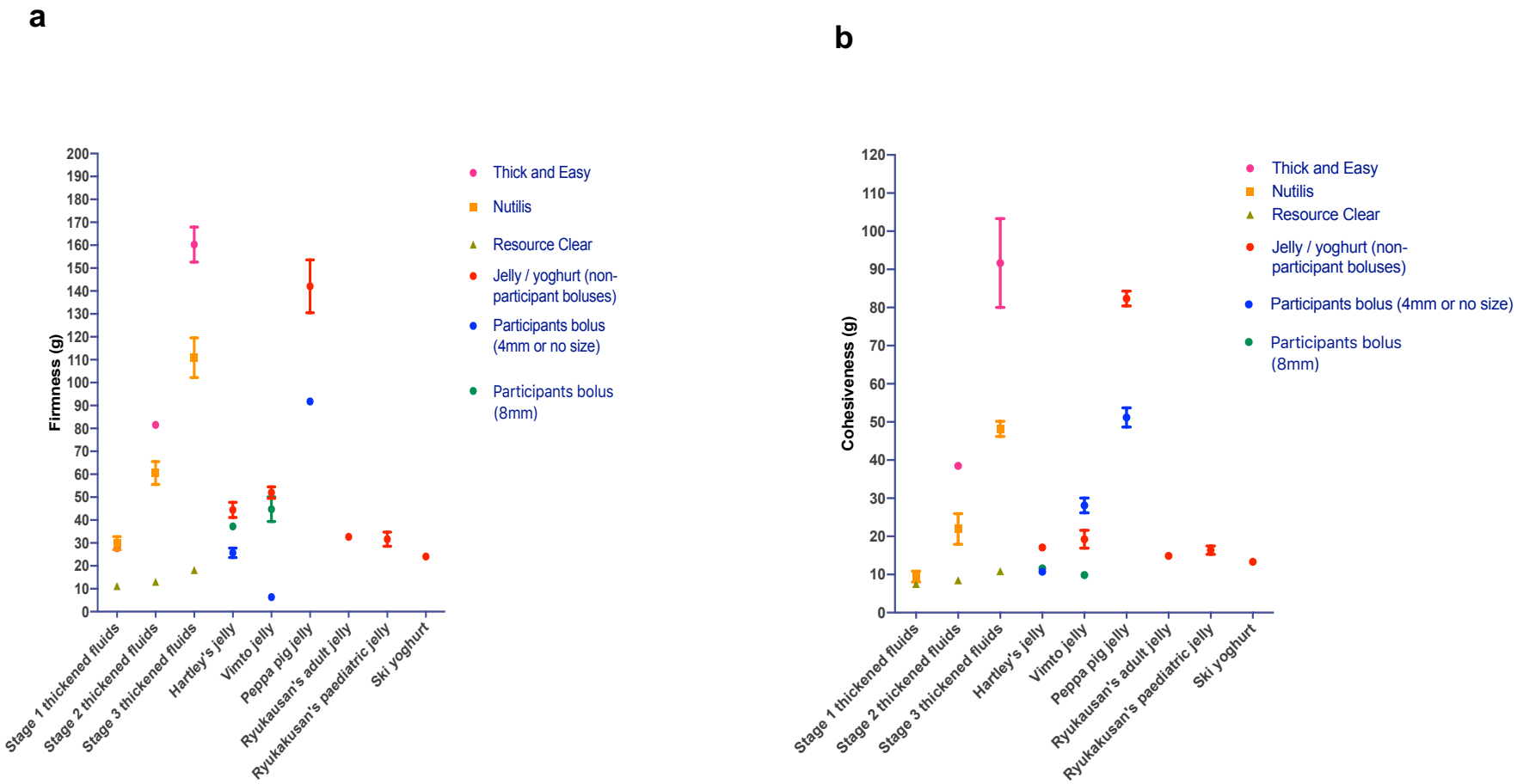


Figure 3-17: Comparison of firmness (a) and cohesiveness (b) between thickened fluids, jellies and yogurt.

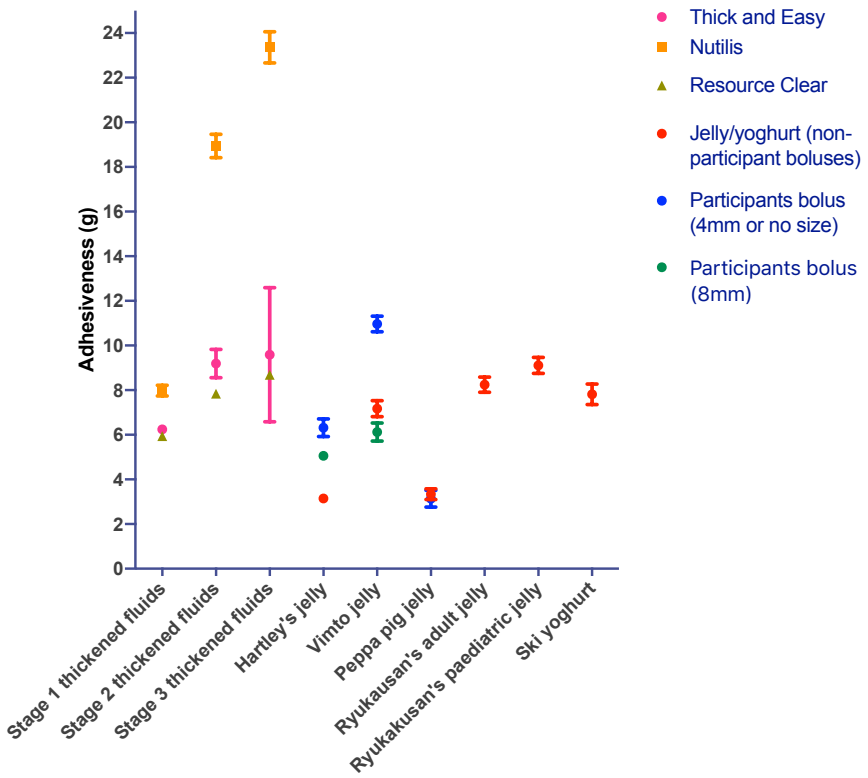


Figure 3-18: Comparison of adhesiveness between thickened fluids, jellies and yogurt..

3.4 Discussion

The study was conducted to compare processing behaviour in an *in vitro* throat model which was originally designed for processing of liquids and to compare bolus characteristics of thickened fluids to alternative swallowing aids; jellies and yogurt for pharmaceutical application. Thickened fluids are known to improve the safety of swallowing fluids and are also used to administer solid oral medicines (Bisch, Logemann, Rademaker, Kahrilas, & Lazarus, 1994; Clavé et al., 2006; Inamoto et al., 2013). Chapter 2 from this thesis showed thickened fluids are not the only vehicles used to administer medicines, jellies and yogurt were also used but the swallowing safety of jellies and yogurt is less studied than thickened fluids.

The *in vitro* throat model used in this study to evaluate the swallowing process does not account for chewing, in particular for jellies that need chewing before swallowing. The particle size distribution of jellies after chewing and bolus temperature were determined in healthy volunteers. This information was used to manually fragment jellies to represent chewing and process jelly products and thickening agents in the *in vitro* throat model. Firmer foods tend to have smaller particle sizes after chewing compared to softer foods and this is observed with Hartley's and Vimto jelly having similar mean particle size distribution compared to Peppa pig gelatin based jelly which has a higher firmness value (from the texture analysis data) and was chewed to much smaller mean particle sizes (Chen, Khandelwal, Liu, & Funami, 2013).

The temperature of expelled boluses was also measured to indicate the extent of change in bolus temperature after chewing relevant for the *in vitro* testing of jellies. A change (increase) in temperature during chewing may change the jelly texture and

gelatin is recognized to have a melt-in-mouth effect (Karim & Bhat, 2008). A previous study reported that the average oral residence time of strawberry jellies of varying firmness was between 3-5 seconds (Chen & Lolivret, 2011). In this study, there was no considerable increase in bolus temperature when the bolus was deemed ready to swallow, likely due to the short oral resident time in healthy volunteers. The manually fragmented jellies were thus processed at room temperature for the *in vitro* tests.

Although thickeners (gum or starch based) are commonly used to increase viscosity of thin liquids (water and beverages) to aid safe swallowing in patients with dysphagia, previous reports show that acceptability of thickened fluids is low (Garcia, Chambers, et al., 2005; Murray et al., 2014; Shim et al., 2013). All participants in this study showed displeasure with Thick & Easy stage 3 thickened water compared to jelly products. Starch-based thickeners such as Thick and Easy have been reported to have a grainy texture, and starch flavour which suppresses other flavours, while gum-based thickeners have been reported to have an undesirable stickiness (Lotong et al., 2003; Matta et al., 2006). For patients with dysphagia where the time required for swallowing may be longer, this can be undesirable. Acceptability studies for foods are normally conducted by obtaining consumer ratings on appearance, taste, texture, and overall acceptability of a product (Garcia, Chambers, Chacon, & Di Donfrancesco, 2015). Acceptability of dosage forms has been defined as the “overall ability of the patient or caregiver to use a medicinal product as intended or authorized” and acceptability is an important aspect of pharmaceutical dosage form consideration (Kozarewicz, 2014). This study shows jellies as potentially better accepted to use as delivery vehicles for dosage forms than thickened fluids.

The volunteers in this small scale pilot study were not trained sensory panellists; however, their feedback can be valuable in indicating preference of using these products as medication swallowing aids and to guide formulation development for acceptable liquid or semi-solid oral medicines for patients with dysphagia. The participants found that Thick & Easy stage 3 was more difficult to swallow and there were no significant differences in ease of swallowing of jellies. Feelings of residue in the throat after consuming Thick & Easy stage 3 was experienced by more participants compared to jellies; residue for patients with dysphagia can increase the risk of aspiration or choking sensation (Clavé et al., 2006; Rofes, Arreola, Mukherjee, Swanson, & Clavé, 2014; Vilardell, Rofes, Arreola, Speyer, & Clavé, 2016). This indicates that jellies might potentially be more suited for patients with weak muscular contractions such as older patients, as weak contractions could lead to choking or sensation of product lodged in the throat (Cichero & Murdoch, 2006; Tracy et al., 1989).

There has been considerable emphasis on dysphagic patients consuming thickened fluids of the correct consistency due to concerns regarding the consumption of too thin or thick consistency both of which may result in penetration-aspiration due to spillage in the airway or residue in the pharynx (Steele et al., 2015). In this study, the thickened fluids were prepared according to manufacturers guidelines; however, the apparent viscosity at $50s^{-1}$ used to determine the stages of thickening does not correspond to the expected stage of thickening. For example, Resource clear (gum-based thickener) thickened to expected stages 1, 2 and 3, showed measured apparent viscosity corresponding to stages 1, 1 and 2. Thick and Easy (starch-based thickener) exceeded expected levels of thickening, although there is no upper limit for stage 3

(the viscosity range is >1750cP), the apparent viscosity for the starch-based thickener was five times greater than this minimum value. Interestingly, Nutilis, a mixture of starch and gum thickener met expected levels of thickening. It has been previously reported that both starch and gum-based thickeners prepared using manufacturers' recommendations do not always fall within the viscosity range for the National Dysphagia Diet Task Force guidelines and starch thickeners tend to continue to thicken over time and less change is observed for gum-based thickeners (Cho & Yoo, 2015; Garcia, Chambers IV, Matta, & Clark, 2005; Pelletier & Dhanaraj, 2006). Numerous factors can affect the viscosity of thickened fluids including the media used for example, water and juice, the thickening time, type of thickening agent and solid content, which might contribute to the variation of the resultant apparent viscosity compared to manufacturers' recommendations (Garcia, Chambers, et al., 2005; Sopade et al., 2008)

The movement of thickened fluids in the *in vitro* throat model showed slower and more cohesive (reduced bolus length) transit with incremental stages of thickening. Each incremental level of thickening involved increased solid content of the thickening agent. The most critical concern with difficulties in swallowing is to prevent penetration-aspiration caused by food or drinks entering into the airway. The important feature of the safe swallowing is the closure of the airway to enable the passing of food to the oesophagus and not the trachea (Logemann, 2007). Penetration-aspiration can occur both at the oral stage and pharyngeal stage. If the bolus transit is too fast, for example, thin fluids such as water require greater agility to maneuver in the oral cavity and the pharynx, the fast oral transit and lack of cohesion between particles can result in premature spillage into the airway particularly for patients requiring longer pharyngeal

closure times, where their airways may not have sufficiently closed when bolus arrives or during transit in the pharynx (Crary & Groher, 2003; Dantas et al., 1990; Tashiro et al., 2010). Additionally, the bolus needs to transit cohesively (as one homogeneous bolus without fragmentation) in the pharynx to prevent spillage into the airway (Newman et al., 2016).

Although there is a lack of clinical evidence for texture modified food and drinks for dysphagia management, the reduced bolus velocity of thickened fluids has been linked with swallowing safety (Painter, Le Couteur, & Waite, 2017; Steele et al., 2015). Several studies have reported that increasing viscosity of the bolus resulted in reduction of aspiration-penetration observed in patients with dysphagia (Kuhlemeier, Palmer, & Rosenberg, 2001; Leonard, White, McKenzie, & Belafsky, 2014; Logemann et al., 2008; Painter et al., 2017; Rofes et al., 2014; Troche, Sapienza, & Rosenbek, 2008; Vilardell et al., 2016). Rofes et al. (2014) reported a significant increase in bolus transit time between the glossopalatal junction and upper esophageal sphincter when the viscosity of a 5mL thin-liquid bolus was increased to spoon-thick for patients with oropharyngeal dysphagia. Troche et al. (2008) reported that increasing bolus viscosity resulted in a significant reduction in OTT. Similarly, Dantas et al., (1990) and Reimers-neils, Logemann, & Larson (1994) reported an increase in oral and pharyngeal transit time for viscous paste boluses compared to low-viscosity liquid bolus in healthy subjects.

The finding of slow bolus transit in the *in vitro* model with increasing thickening level was consistent with previous *in vitro* studies using similar *in vitro* throat models (Mackley et al., 2013; Mowlavi et al., 2016). Different commercial thickeners showed

different degree of reduction in the velocity of bolus transit. Xanthan gum-based thickeners have been previously reported to influence the reduction in the *in vitro* OTT the least (Mackley et al., 2013; Mowlavi et al., 2016). This is particularly notable at stage 3 possible due to the greater shear thinning nature of xanthan gum compared to starch, resulting in low viscosity at $50s^{-1}$ (the shear rate believed to represent oral processing) (Cho & Yoo, 2015; Kumagai, Tashiro, Hasegawa, Kohyama, & Kumagai, 2009; Vickers et al., 2015; Waqas, Wiklund, Altskar, Ekberg, & Stading, 2017). Starch-based thickeners have shown higher apparent viscosity at $50s^{-1}$ and consequently showed longer oral transit times particularly at stage 3. This could increase the risk of post-deglutitive residue in the pharynx with the potential to cause penetration-aspiration if the airway is not closed. Residue associated with starch-based thickeners has been reported previously particularly in patients with reduced muscle strength and reduced ability for bolus propulsion such as older adults (Clavé et al., 2006; Rofes et al., 2014; Vilardell et al., 2016). Interestingly Nutilis, a thickener which is a mixture of xanthan gum and starch showed intermediate OTT compared to xanthan gum or starch used independently, owing to its moderate apparent viscosity at $50s^{-1}$ complying the National Dysphagia Diet Task Force & American Dietetic Association, (2002) standard for all three thickening levels.

The association between cohesion of bolus flow and safety of swallowing is less well understood in comparison to bolus viscosity. Kumagai et al. (2009) studied the relationship between the velocity of polysaccharide based thickeners, including xanthan gum, through the pharynx by using the ultrasonic pulse Doppler method. The polysaccharide solutions velocity distributed over a narrower range with increasing concentration indicating more cohesive bolus flow. Nakauma, Ishihara, Funami, &

Nishinari (2011) performed acoustic analysis of the transit of xanthan gum solutions in the pharynx and found that the acoustic balance for swallowing sounds shifted to a higher frequency indicating xanthan gum flows as one coherent bolus. The cohesive nature of the flow of xanthan gum boluses compared to starch can be further supported by its extensional flow behavior. Starch-based thickeners stretched heterogeneously; this led to premature filament breakage whereas xanthan gum solutions showed homogeneous deformation and extended filament thinning (Mackley et al., 2013). Mackley et al. (2013) also reported that xanthan gum showed a higher extensional viscosity compared to starch at $50s^{-1}$ shear rate. The differences in extensional flow behavior may be explained by the differences in the microstructure of xanthan gum and starch solutions. Xanthan gum solutions show a mesh-like network while starch solutions show swollen starch granules (Waqas et al., 2017). Boluses with low extensional viscosity may result in bolus fragmentation in the pharynx and subsequently result in penetration-aspiration.

In this study, the extensional flow behavior may be reflected in the BL at the airway divide. Generally, increasing thickener concentration resulted in a decrease in BL indicating cohesive bolus transit, supporting previous *in vivo* findings (Kumagai et al., 2009; Nakauma et al., 2011). At lower thickening stages, xanthan gum based thickener showed shorter BL at the airway divide compared to the starch-based thickener, supporting the higher extensional viscosity reports of xanthan gum-based thickeners (Hadde & Chen, 2019; Waqas et al., 2017). Xanthan gum and starch-based thickener showed similar efficiency *in vivo* in safety of swallowing at spoon-thick thickening assessed using videofluoroscopy; however xanthan gum was more

effective at lower thickening levels (nectar-thick) in reducing penetration-aspiration compared to starch-based thickeners (Leonard et al., 2014; Vilardell et al., 2016).

The swallowing process is complex involving coordinated contractions of muscles. The *in vitro* throat model used in this study mimics the oral phase by using the roller to represent tongue peristalsis and unlike muscle contractions found in the pharynx in humans. The pharynx (located after the 120° angle and before the airway divide in Figure 3-3) in the throat model is static. The flow of bolus along a wall will induce given shear stress. The more solid-like behavior of the thickened fluid compared to thin liquids results in a reduced shear strain and hence slower transit speed. The wall shear rate was assumed as $50s^{-1}$ in this *in vitro* throat model simulating that in the oral cavity *in vivo* (Hadde, 2017; Mackley et al., 2013). The *in vitro* model has limitations, for example, it does not simulate the chewing process, the interaction of food with mucosal surfaces, the conditions operating in the oral cavity such as the mixture of the food with saliva, the tongue surface contact with the bolus during peristalsis and the extensional shearing of foods that occur in the mouth. Although the *in vitro* model over simplifies the swallowing process and the throat model cannot replace *in vivo* studies, it is a useful tool to compare the oral transit of fluids and has been consistent with reports of increasing oral transit time with increasing thickening. It is also a useful tool in comparing how the fluids transit in a static pharynx, i.e., participants with weak muscular movement, and whether the fluids move cohesively or loosely (as indicated by BL at airway divide in the *in vitro* thorat model) where more control may be required to direct the bolus.

In the rheological test, all products showed a G' dominance over G" indicating solid-like behaviour; it is clear from the frequency dependency of Thick & Easy compared to Nutilis and Resource clear that these are structurally different products, with Thick & Easy having a stronger gel structure (modulus are more independent of frequency compared to the other two products) (Zhang, Daubert, & Foegeding, 2005). Shear thinning rheology was observed for each incremental thickening of fluids as reported in previous studies (Mackley et al., 2013; Payne, Methven, Fairfield, & Bell, 2011). The shear-thinning feature of the thickened fluids is believed to prevent uncontrolled spillover due to higher viscosities at lower shear rates (Mowlavi et al., 2016).

This study showed a correlation between rheological and textural parameters with parameters that were measured using the *in vitro* throat model, i.e. oral transit time and bolus length measured in the airway divide. Firmness is the ability of the material to withstand stress, cohesiveness is the intermolecular attraction between like molecules, or the unity of particles throughout a mass and adhesion is the molecular interactions with dissimilar molecules, or the interaction between two interfaces (Marshall, Bayne, Baier, Tomsia, & Marshall, 2010). The yield stress is the point at which reversible elastic deformation ends and irreversible deformation occurs and viscosity is the internal friction of the fluid. All of the parameters; viscosity, yield stress, cohesiveness, firmness related to the structural integrity of the material. An increase in the concentration of thickener understandably increased apparent viscosity, cohesiveness, yield stress, and firmness and showed correlations to *in vitro* OTT and BL.

Although the central focus for dysphagia food and drink management has been viscosity, other physical properties can also be influential for safe swallowing such as cohesiveness and yield stress, both properties influenced by the binding force between the particles in a bolus (Marcotte & Hosha, 2015; Steele et al., 2015). Rheological and textural parameters such as firmness, cohesiveness, and adhesiveness of food have also been given importance for food management for dysphagia by the National Rehabilitation Center for Persons with Disabilities Japan (2015). However, the effect of properties other than viscosity is not widely studied. Tsukada, Taniguchi, Ootaki, Yamada, & Inoue (2009) found an increase in firmness, cohesiveness, and adhesiveness with an increase in agar solid content corresponding to an increase in oral ejection time in healthy subjects. Funami, Ishihara, Nakauma, Kohyama, & Nishinari (2012) compared the sensory properties of polysaccharide gels and acoustic analysis for swallowing performance and found that gels that were scored higher in sensory cohesiveness also showed a shorter transit time in the pharynx, indicating the bolus transiting as one 'coherent' bolus. However, high cohesiveness is associated with residue in the pharynx in older adults with post-stroke dysphagia (Momosaki, Abo, & Kobayashi, 2013). In this study, parameters of cohesiveness, yield stress, firmness, and viscosity was found to have high correlations to OTT, while low correlations were found for adhesiveness. Only moderate correlations were obtained between these parameters and BL. It was expected that all the parameters associated with structural integrity (viscosity, yield stress, cohesiveness, firmness) would show a strong association with bolus length.

The *in vitro* swallowing behavior of jellies and yogurt were tested in this study due to the findings in Chapter 2 as both were used as vehicles for medicine management in

dysphagic patients. The confidence intervals of Nutilis stages one to three were taken forward to compare with our alternative swallowing aid products since Nutilis showed consistent thickening with expected stages. There is limited literature on the safety of swallowing of jellies and yogurts. The transit of the Ski yogurt in the *in vitro* model showed the spread of yogurt across the pharynx wall (as indicated by the long bolus length when reached the airway divide), which was also observed for stage 1 thickened fluids. However, the oral transit of yogurt in the *in vitro* model was comparable to stage 3 thickened fluids. This is in agreement with Kumagai et al. (2009) reported yogurt to have similar velocity spectra in the pharynx to higher thickening concentrations and as a lower risk of aspiration than water, due to the reduced velocity spectra, which is believed to aid safe swallowing.

The term jelly is often used interchangeably with gels which form a three- dimensional matrix interlocking solvent (Satyanarayana, Kulkarni, & Shivakumar, 2011). The dry jellies showed slow transit, and the participant boluses which were lubricated by saliva were faster in the *in vitro* transit as expected. The BL was similar for dry and chewed jellies showing cohesiveness in the flow. Ryukakusan jellies are presented as free-flowing granular jellies (Tsuji, Uchida, Fukui, Fujii, & Sunada, 2006). This product is used in Japan as a swallowing aid (Tsuji et al., 2006). Tablets and capsules are added to a layer of jelly and then covered further with more jelly before being swallowed. The cohesive nature of the jelly bolus (shorter BL at air way divide) could help to reduce spillage into the airway, which could be the reason that aspiration-penetration is reduced when jellies were swallowed by patients with oesophageal cancer (Sonoi et al., 2016). These findings indicate jellies to have similar safety features to thickened fluids stages 2 and 3, consistent with a study comparing the safety of swallowing of

thin, nectar thick, stage three thickened water and jelly in 42 oesophageal cancer patients (mean age 68 years), and 43 control hospitalised patients (mean age 69 years). Puree consistency and jelly were the safest to swallow, laryngeal penetration was not observed for patients taking puree consistency and occurred in only one patient for jelly (Sonoi et al., 2016). The safety of puree consistency and jelly was considered a result of easy flow of the bolus from the pharynx to the oesophagus and a lower chance of flow into the trachea before transiting to the pharynx. This is consistent with the findings of the current study of a more cohesive flow (shorter BL) of jellies and stage 3 thickened fluids compared to thinner liquids (stage 1 and 2 thickened fluids). However, starch-based thickeners, such as at the puree consistency reported above, transited too slowly which may increase the risk of residue.

A comparison of rheological and texture parameters of jellies and thickeners showed parameters such as apparent viscosity, firmness, cohesiveness, yield stress and adhesion of jellies to be similar to stage 1 or 2 thickened fluids but safety features (slow transit, cohesive bolus flow) closer to stage 3. Rheological characterization showed that jelly products have stronger gel network compared to thickened fluids (a greater magnitude of G', which was dominant over G" over a frequency range), which may explain structural integrity in the throat model and thus shorter bolus length. Yogurt showed a greater dependency of G' over the frequency range, indicating a weaker structure and hence the spreading of flow across the pharynx. Thickened fluids, jellies and yogurt are all produced differently. Thickened fluids involve entanglement of polymers (for xanthan-gum based thickeners), jellies including the Ryukakusan jelly involve heating followed by cooling to form an ordered structure and yogurt is the coagulation of protein (Atsuko et al., 2001; Sandoval-Castilla, Lobato-

Calleros, Aguirre-Mandujano, & Vernon-Carter, 2004). A set of rheological and textural parameters that contribute to safety of swallowing for thickened fluids did not influence the processing of jellies and yoghurt in the throat model. It is speculated that it would be easier to deform an ordered structure (as in jellies after fragmentation or chewing) than entangled composition (such as in thickened fluid) during oral processing, which may have resulted in lower apparent viscoisity at the shear rate relevant to oral processing, cohesiveness, firmness, yield stress of jellies compared to stage three thickened fluids.

This is the first study to systematically compare thickeners composed of different materials with a focus on BL to indicate cohesive bolus movement in addition to OTT which was investigated in previous studies (Hayoun et al., 2015; Mackley et al., 2013; Mowlavi et al., 2016). This is also the first study to investigate products other than liquids for the processing in the *in vitro* throat model for pharmaceutical application. The rheological and textural parameters showed a correlation for thickened fluids, however, this study showed that these parameters may not be appropriate in predicting the movement of other products in the “CT” model due to structural differences. The *in vitro* throat model is a useful tool to compare the OTT and BL of jellies, yogurt and thickened fluids and further investigation would be required to establish a *in vitro-in vivo* correlation for the processing of these products.

3.5 Conclusions

Acceptability of jellies was better than thickened fluid. Although viscosity has been used as an indicator for the safety of swallowing of fluids and has been the central focus for dysphagia product development, a more holistic approach using rheological

and textural parameters is needed. Our study has shown that viscosity is not the only feature contributing to the safety of swallowing; cohesiveness, yield stress, firmness are also factors that influenced transit time and bolus length (an indicator of cohesiveness) of flow of thickened fluids.

Jellies showed similar safety features as thickened fluids; slow transit and cohesive bolus flow, which prevents premature spillage. There was greater variability in the processing of some jelly products and a further investigation is required to correlate *in vitro-in* vivo results. The *in vitro* throat model proved to be a useful tool in evaluating the processing behavior of thickened fluids, jellies, and yogurt, to assess whether the bolus moves as a unit mass or cohesively and can be used in the future as a tool to help the selection or design of safe food or drink for patients with dysphagia.

Chapter 4

DEVELOPMENT OF INSTANT JELLIES WITH SAFE SWALLOWING FEATURES IN AN *IN VITRO* THROAT MODEL TO USE AS DRUG ADMINISTRATION VEHICLES TO PATIENTS WITH DYSPHAGIA

4.1 Introduction

It is well recognised that patients with dysphagia find solid oral dosage forms (SODF) difficult to swallow (Fodil et al., 2017; Schiele et al., 2015; Strachan & Greener, 2005; Wright, 2002). However, patients still consume food and drinks in a modified form to allow safe swallowing. SODF such as tablets and capsules are commonly prescribed and although liquid alternatives are available for many of these SODF these still can be challenging to swallow for patients with dysphagia whom are unable to safely swallow fluids. Liquid dosage forms sometimes require further modification by using thickened fluids to ease swallowing which may pose difficulties for patients whom dislike the thickened fluids (Garcia, Chambers, & Molander, 2005; Murray, Miller, Doeltgen, & Scholten, 2014; Shim, Oh, & Han, 2013). Countries such as Japan include jellies in their dysphagia diet. Jellies made from gelatin are recognised to potentially cause aspiration due to a change in consistency from a gel to liquid at body temperature (National Rehabilitation Center for Persons with Disabilities Japan, 2015). However jellies made from other polysaccharides such as carrageenan are recognised to hold together in the oral phase mitigating aspiration risks (International Dysphagia Diet Standardisation Initiative, 2016a). Chapter 3 showed that jellies were better accepted and presented similar safety features of cohesive bolus flow in the pharynx and reduced oral transit, similar to stage three thickened fluids performance in the *in vitro* throat model.

Jellies are potentially useful for drug administration to dysphagia patients, however, jellies require heating to form which can affect drug stability. Jellies presented in pre-prepared form with water can also affect drug stability. An instant (jelly forming in less than 10 minutes) preparation for safe-to-swallow jelly that would not require heating to

form the jelly for older adults with swallowing difficulties would obviate drug stability issues with heating storage in ready-made jellies.

4.1.1 Gelation

The terms gel and jelly is often used interchangeably, and their distinction is not clear by definition. Both ‘gel’ and ‘jelly’ can be traced back to the Latin term ‘gelare’ meaning to ‘congeal’, suggesting the idea of a liquid congealed in a semisolid material, elastic and retaining liquid characteristics (Satyanarayana et al., 2011). Martin (1993) describes gels as “a solid or semisolid system of at least two constituents, consisting of a condensed mass enclosing and interpenetrated by a liquid.” A matrix rich in the liquid is often called a jelly or gel, and when the liquid is removed, it is called xerogel (Martin, 1993). There is no literature information on the difference between gels and jellies, but a qualitative or an objective description of a food jelly is ‘will quiver, not flow…a product with a texture so tender that it cuts easily with a spoon, yet so firm that the angles produced retain their shape; a clear product that is neither syrupy, gummy, sticky or tough; neither is it brittle and yet it will break” (Bourne, 2002; Goldthwaite, 1909).

The process of gelling involves an association between segments of polymers or proteins in a dispersion so that a three-dimensional network is formed (Saha & Bhattacharya, 2010). The greater the regions of association or junction zones, the more rigid the gel (Saha & Bhattacharya, 2010). Gels can be classified as physical or chemical gels; Chemical gels involve covalent cross-linkage between polymers swollen in a solvent. Physical gels are formed by the physical association of polymer chains in water through hydrogen bonding, cation-mediated cross-linking and hydrophobic interactions (Saha & Bhattacharya, 2010).

4.1.3 Existing swallowing aids and instant jellies

Chapter 2 and 3 show that food jellies have better acceptability and are used as swallowing aids for medicine administration in older patients with dysphagia. An instant jelly dosage form would be useful for patients with dysphagia. There are a number of literature on use of sodium alginate-calcium gelation for capsule shell, film formation, *in situ* gels and gel beads (Al-Kassas, Al-Gohary, & Al-Faadhel, 2007; P. Aslani & Kennedy, 1996; Pafisa Aslani & Kennedy, 2006; Blandino, Macias, & Canter, 1999; Kubo, 2003; Miyazaki, Kubo, & Attwood, 2000; Pawar, Lalitha, & Ruckmani, 2015). There are also patents in using sodium alginate-calcium gelation to form jelly without heating which are summarised in Table 4-1.

Table 4-1: A summary of patents for instant jellies and swallowing aids.

Inventor and year	**Target product**	**Ingredients**	**Method for jelly formation**	**Time reported for jelly formation**
(Yasushi, Kentaro, Yoshida, & Yuichi, 2016)	Jelly containing foaming bubbles	Sodium alginate, tribasic calcium phosphate, bicarbonate, organic acid (citric acid, malic acid, tartaric acid), a polymer compound (egg white)	Sodium alginate, sodium carbonate, calcium phosphate mixed together. Acidic component added.	Not reported
(Masumoto, Yuichi, & Nakamura, 2016)	Instant foaming solid jelly dessert powder	Sodium alginate, calcium sulfate, calcium sequestering agent, sodium hydrogen carbonate or organic acid, egg white	Not reported	Not reported
(Hong et al., 2012)	Sodium alginate jelly powder and application	Sodium alginate, calcium carbonate, sodium hexametaphosphate (or sodium tripolyphosphate, or sodium pyrophosphate), citric acid	Dissolve these ingredients and add juice, stir and place 1.5-2 hours for jelly formation.	1.5-2 hours

In the *in vitro* studies described in Chapter 3 both the free-standing jellies (Hartley's, Vimto, Peppa pig) and granular jelly that flows (Ryukakusan's jelly) showed promise showing slow oral transit time and cohesive bolus transit in the pharynx. Instant jellies that do not need heating to form and show these consistencies (free-standing and granular) could be useful as medication delivery systems. There are patents attempting to produce these type of instant jellies; however, the consistency of the resultant jellies and their safe swallowing features are not clear.

This study aims to develop instant free-standing and granular jellies that resemble closely to commercial jellies (i.e. wobbly for free-standing jellies) and do not require heat to form. The jellies will be used as a vehicle to safely administer medicines to older patients with dysphagia and may benefit other patient groups who find it difficult to swallow SODF such as children. The safe to swallow features of these instant jellies will be evaluated using the *in vitro* "Cambridge Throat" ("CT") model and textural and rheology properties, compared to commercial products.

The primary objective of this study is to form an instant (less than 10 minute formation time) free-standing and granular jelly that requires no heat.

The secondary objectives of this study are to:

- Compare the textural and rheological profile of developed jellies with commercial jelly products.
- Assess the processing of the developed jellies in the CT model and compare the processing behaviour to commercial jelly products.

4.2 Materials and methods

4.2.1 Materials

Gelling agents used in this study are listed below in Table 4-2.

Table 4-2: Gelling agents used in this study.

Gelling agent	Grade and supplier
Sodium alginate	Protanol GP 1740, FMC Biopolymer, UK
Gellan gum	Low acyl gellan gum, CP Kelco, UK
	High acyl gellan gum, CP Kelco, UK
Pectin	HM pectin pure, CP Kelco, UK
	LM pectin pure, CP Kelco, UK
Carrageenan	Kappa, CP Kelco, UK
	Iota, CP Kelco, UK
	Lamda, CP Kelco, UK
Guar gum	B&V, Italy
Locust bean gum	Genu GUM type RL-200Z
	CP Kelco, UK
Gum tragacanth	Thew Aarnott, UK
Gum karaya	Thew Aarnott , UK
Gum ghatti	Thew Aarnott, UK
Gum arabic	Thew Aarnott, UK
Agar	Special Chem, UK
Xanthan gum	Keltrol
	CP Kelco, UK
	Keltrol advanced performance CP Kelco, UK
Maize starch	Roquette, UK
Egg protein	Bodybuilding Warehouse, UK
Soya protein	Pro-Fit SI90, Roquette, UK
Whey protein	Simplesse Microparticulated whey protein, Roquette, UK
Pea protein	Cel-Fit QM3, Roquette, UK
Hydroxypropyl methyl cellulose	E5 Methocel, Premium LV, Colorcon litd, UK
Polyethylene oxide	Sentry Polyox WSR N10 LEO NF, Colorcon Ltd, UK

Dicalcium phosphate dihydrate and calcium carbonate were purchased from Sigma Aldrich, UK. Citric acid, calcium chloride was purchased from Fischer Scientific UK. Hartley's ready to eat jelly (locust bean gum, xanthan gum, gellan gum), Hain Daniels Group, UK, Vimto's ready to eat jelly (carrageenan, locust bean gum), Caterers Choice Litd, UK and Peppa pig ready to eat jelly (gelatin), Heaven Made foods Hold

Ltd, UK was used in this study. Ryukakusan “magic jelly” (agar based) was purchased from Ryukakusan, Japan. Ski yogurt (milk, rice starch, sugar, lemon juice, carrot concentrate, guar gum, milk calcium concentrate) from Nestle, Switzerland was used in this study. Nutilis Powder (starch, xanthan gum, tara gum, guar gum), Nutilis, Netherlands was used in this study. Harrogate still bottled water was purchased from a local supplier, and deionised water was prepared using a water purification system (Purite Select Analyst A80 system, Purite Ltd, UK) at the University of Hertfordshire, UK.

4.2.2 Summary of developing instant jellies

Instant jellies for this study are jellies that form in less than 10 minutes. There were two important factors predominantly considered for developing Instant jellies; one was time to form the jellies which were considered at the early stages of development and secondly, testing these jellies in an *in vitro* throat model to ensure safe swallowing. Rheological and textural properties were also investigated to compare with existing commercial jelly products.

A summary of steps to develop two forms of instant jellies; a free-standing jelly and granular jelly is shown in Figure 4-1.

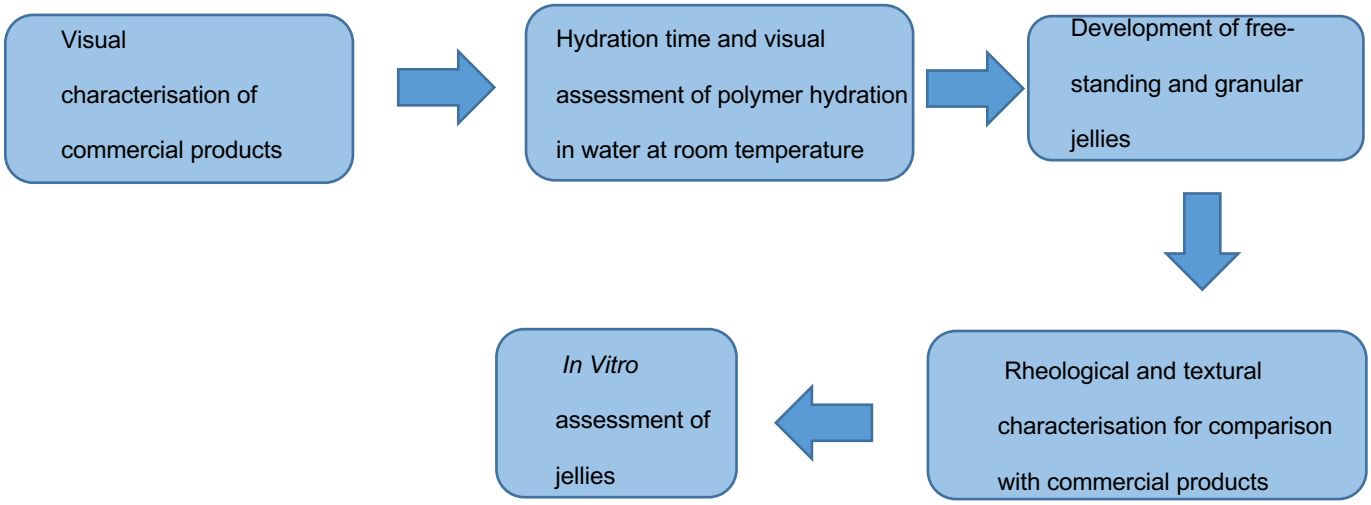


Figure 4-1: Summary of steps in jelly development.

4.2.3 Visual assessment of commercial jellies and thickened fluids

In order to visually characterise the products formed during jelly development, visual criteria of assessment were formed to distinguish differences between thickened fluid, granular jelly and free-standing jellies. Products were assessed for:

1. Flow when the container is inverted
2. Granular gels immersed in fluid
3. Homogeneous consistency
4. Cuts easily with a spatula, but firm enough that the angles produced retain its shape (Goldthwaite, 1909)
5. Quivers or wobbles when held on a spatula
6. Smooth surface

Nutilis, Hartley's ready-to-eat jelly, Ryukakusans 'magic' jelly for adults was used to assess these visual characteristics.

Table 4-3 and Figure 4-2 shows the visual assessment of commercial products used for development of vehicles. There are clear differences between stage 1 and stage 3 thickened fluids (Nutilis), the first easily flowing with inversion of the container and the latter not flowing at all. The granular (Ryukasuan's) jelly has granular gels in fluid and flows, and the free-standing jelly (Hartley's) does not flow, retains its shape when cut with a spatula and wobbles.

Table 4-3: Visual assessment of commercial products.

Criteria	**Stage 1 or 2 thickened fluid**	**Stage 3 thickened fluid**	**Granular jelly**	**Free-standing jelly**
Flow when the container is inverted	√	x	√	x
Granular jelly with fluid.	x	x	√	x
Homogeneous consistency	√	√	X	√
Cuts easily with a spatula, but firm enough that the angles produced retain its shape	x	x	x	√
Quivers or wobbles when held on a spatula	x	x	x	√
Smooth surface	√	x	x	√

Figure 4-2: Visual appearance of products scooped with a spatula.

4.2.4 Initial scoping study: polymer hydration times

Polymers listed in Table 4-2 were added slowly to 20mL deionised water and were mixed using a cylindrical magnetic stirrer at 180rpm at room temperature. A range of concentrations of polymers (0.15, 0.5, 1, 2, 3, 4% w/v) were tested. Hydration time

was determined as the time taken for the polymer to fully dissolve or disperse. The end product after hydration was determined using the criteria in Section 4.2.3 and characterised against the most closely resembled commercial product, e.g. thickened fluid, free-standing or granular jellies

Polymers that form gels with ions (sodium alginate, low acyl gellan gum, carrageenan (kappa and iota) and low methoxy pectin at 0.5% w/v were dissolved in 10mL deionised water and mixed with calcium chloride aqueous solution (0.5% and 2% w/v).

4.2.5 Development of free-standing jellies

Sodium alginate and dicalcium phosphate dihydrate were added to 20mL deionised water and stirred at 180rpm using a cylindrical magnetic stirrer until the mixture was hydrated. Citric acid powder was then added to this mixture and allowed to mix for 30 seconds before leaving this mixture to set for 5 minutes (Figure 4-3).

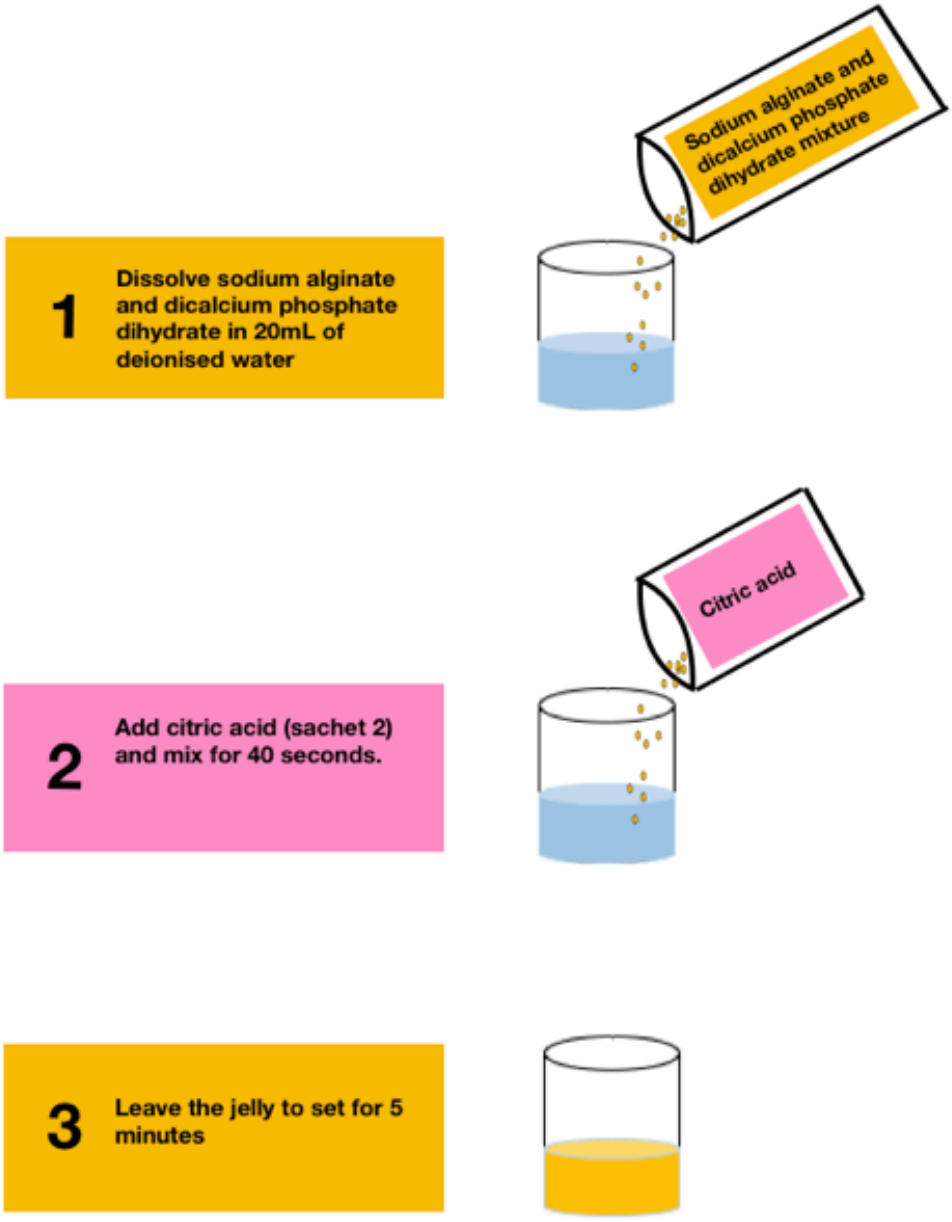


Figure 4-3: Summary of sodium alginate free-standing jelly steps.

Free-standing jellies were developed using sodium alginate (0.5, 1% w/v), dicalcium phosphate dihydrate (0.1, 0.2, 0.3, 0.4, 0.5, 1% w/v) and citric acid (1, 2, 3, 4, 5, 10% w/v). The jellies were assessed using the visual criteria outlined in Section 4.2.3. Any

residual water was measured by pouring all residual water from the jelly container into a measuring cylinder.

Further experiments were conducted to improve jelly hydration time using Formulation 1 (F1) - sodium alginate 0.5% w/v, dicalcium phosphate dihydrate 0.4% w/v and citric acid 2% w/v. For this different stirring methods involving shaking the beaker, stirring with a rod, were investigated. Guar gum was used as an additional polymer to sodium alginate to improve jelly formation time, residual water and visual appearance using F1. Guar gum was selected due to its short hydration time (less than 10 minutes) assessed in Section 4.2.4.

Three ratios of sodium alginate to guar gum (75:25, 50:50 and 25:75) were investigated. The maximum total polymer concentration was kept at 1% w/v to achieve good hydration time. The concentration of dicalcium phosphate dihydrate was calculated in proportion to sodium alginate. The composition of the three polymer ratios used are shown below:

75: 25 sodium alginate to guar gum: 0.75% w/v sodium alginate, 0.25% w/v guar gum, 0.6% w/v dicalcium phosphate dihydrate, 3% w/v citric acid

50:50 sodium alginate to guar gum: 0.5% w/v sodium alginate, 0.5% w/v guar gum, 0.4% w/v dicalcium phosphate dihydrate and 2% w/v citric acid.

25:75 sodium alginate to guar gum: 0.25% w/v sodium alginate, 0.75% w/v guar gum, 0.2% w/v dicalcium phosphate dihydrate and 1% citric acid.

The resultant jellies were assessed using the visual analysis criteria (4.2.3). Other polymers that showed short hydration times (less than 10 minutes) assessed in Section 4.2.4 were investigated in the same way as guar gum including egg white protein, LM pectin, maize starch, polyethylene oxide, HPMC, carrageenan (kappa) and low-acyl gellan gum, at 50:50 ratio.

The volume (15, 20 and 25 mL) and hardness of water used for jelly formation were varied and any changes in visual assessment (Section 4.2.3) and time taken for jelly to form were determined. Harrogate still bottled water (soft water 98g calcium carbonate/L) and tap water (very hard, 358g calcium carbonate/L) were used as alternatives to deionised water to determine the effect of water hardness on jelly formation.

4.2.6 Development of granular jellies

Sodium alginate and calcium chloride were used to develop granular jellies that flow. Sodium alginate of varying concentrations (0.1, 0.2, 0.5, 1, 1.5, 2, 2.5% w/v) was dissolved in 10mL deionised water using a cylindrical magnetic stirrer at 180rpm. The resultant solution was added to 10mL calcium chloride solution (0.1, 0.2 and 0.3% w/v of calcium chloride in 10mL deionised water) (Figure 4-4). The mixture was then mixed for 5 seconds using a spatula.

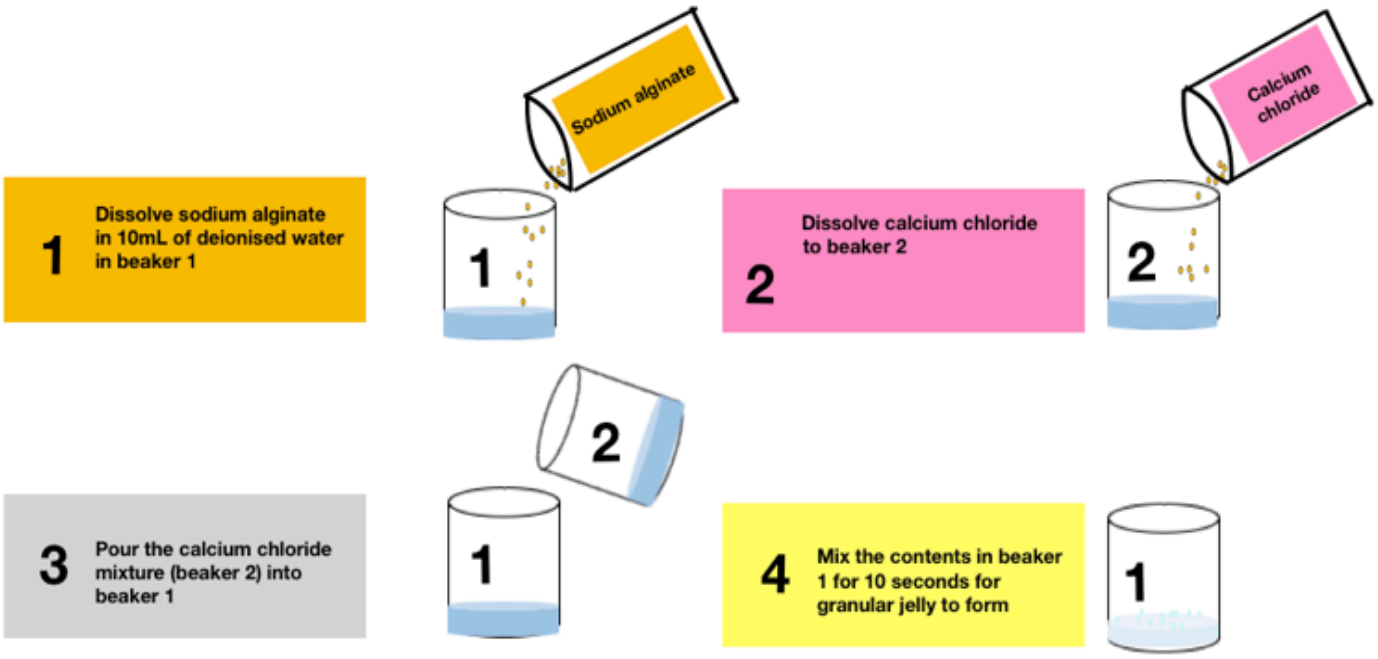


Figure 4-4: Summary of granular jelly formation.

Formulation 2 (F2) containing sodium alginate 2% w/v and calcium chloride 0.3% w/v was selected for further investigation. Additional polymers (egg protein, LM pectin, guar gum, maize starch, polyethylene oxide, hydroxyl propyl methyl cellulose, kappa carrageenan, and low acyl gellan gum) were added to F2 to determine the time for the jelly formation and for assessment against the visual criteria (Section 4.2.3). Three ratios were investigated with additional polymers at 75:25, 50:50 and 25:75.

The maximum total polymer concentration with additional polymers for F2 was kept at 1% w/v to achieve good hydration time. The concentration of calcium chloride was calculated in proportional to sodium alginate. The composition of the three polymer ratios used are shown below:

1. 75:25 sodium alginate to other polymer: 0.75% w/v sodium alginate, 0.25% w/v other material and 0.11% w/v calcium chloride
2. 50:50 sodium alginate to other polymer: 0.5% sodium alginate, 0.5% other material and 0.075% calcium chloride. Low acyl-gellan gum was also trialled with 0.15% calcium chloride.
3. 25:75 sodium alginate to other polymer: 0.25% w/v sodium alginate, 0.75% w/v other material and 0.0375% w/v.

The additional polymer was added using two approaches:

Method A: Additional polymer and sodium alginate were mixed together and dissolved in deionised water.

Method B: Additional polymer and calcium chloride were mixed together and dissolved in deionised water.

Polymers such as LM pectin, kappa carrageenan, and low-acyl gellan gum were only added using method A due to the interaction between calcium and these polymers.

4.2.7 Rheological and textural characterisation of free-standing and granular jellies

Commercial jellies (Hartley's, Peppa pig and Vimto jelly) and the developed free-standing and granular jellies (F1 – F3, Table 4-4) were characterized using texture analyzer and rheometer.

Table 4-4: Formulation and composition.

Formulation	Jelly and composition
F1	Free-standing: Sodium alginate (0.5% w/v), dicalcium phosphate dihydrate (0.4% w/v) and citric acid (2% w/v).
F2	Granular jelly: Sodium alginate (2% w/v) and calcium chloride (0.3% w/v)
F3	Granular jelly: Sodium alginate (0.5% w/v), low acyl gellan gum (0.5% w/v) and calcium chloride (0.15% w/v).

A TA 1500 EX controlled–stress rheometer (TA instruments) was used to obtain steady shear apparent viscosity and oscillatory viscoelastic data. Measurements were carried out at 25°C using parallel plate geometry (diameter: 40mm, gap 650mm) for all experiments. For each sample, oscillatory stress sweep (torque 0.01-10,000 micro N.m at a frequency of 10 rad/s), frequency sweep (0.1 to 100rad/s) and steady-state rate sweep (0.01-100/s) were carried out.

For texture analysis, the gel strength test was used for free-standing jellies and the back extrusion test was applied for granular jellies. These tests gave comparison of the developed “instant” jellies to commercial ready-made jellies. The gel strength test used is a penetration test and is useful for determining gel characteristics before chewing. The gel strength test was used for free-standing jellies to determine the firmness and adhesiveness of gels and compare with commercial jellies. A Texture Analyser (TA.XT. *Plus,* Stable Microsystems) with an attached cylindrical (P/0..5)

probe was used to depress 4mm into spherical jellies gel of diameter 4.5cm and height 2cm. Texture characteristics (cohesiveness, surface adhesion and firmness) were evaluated using back extrusion tests on a Texture Analyser (TA.XT. *Plus,* Stable Microsystems) applying a 5kg load cell. The same test conditions were applied as described in Chapter 3, Section 3.2.5. The measurements were carried out at room temperature with triplication for all samples.

4.2.8 *In vitro* characterisation of jellies using the "CT" model

F1-3 (Table 4-4) were tested in the CT model. The free-standing (F1) jellies were manually chopped to 4mm pieces to account for chewing. A 5mL sample of each was placed carefully with a spatula into the dialysis tubing attached in the CT model.

In the "CT" model was used as described in Chapter 3, Section 3.2.4

4.3 Results

4.3.2 Initial scoping: polymer hydration times

Polymers that hydrated under 10 minutes are presented in Table 4-5. Ten minutes was selected as the maximum time for full hydration; this is due to the consideration of convenience for patient preparation. Materials taking longer than 10 minutes to hydrate where gum ghatti, karaya, Arabic, tragacanth, carrageenan iota, carrageenan lamda, pea protein, soya protein, whey protein, locust bean gum, xanthan gum, HM pectin (with and without sucrose), LM pectin with calcium chloride, carboxymethyl cellulose and agar. Low-acyl gellan gum, sodium alginate, guar gum and maize starch showed hydration times under 5 minutes at the concentrations investigated. Kappa carrageenan, high-acyl gellan gum, LM pectin, HPMC, polyethylene oxide showed hydration times that extended to over 5 minutes but less than 10 minutes.

Sodium alginate and low-acyl gellan gum both showed potential with calcium salts in forming jelly-like structures. Sodium alginate-dicalcium phosphate dihydrate formed jellies that met the full criteria for free-standing jellies. Sodium, alginate (0.5-1.5% w/v)-calcium chloride combinations (0.5-1.5% w/v) at high concentrations also formed a free-standing structure but do not meet all visual assessment criteria for free-standing jellies. The jellies did not quiver, did not retain the angles once cut with a spatula and a rubbery, string like texture was observed once the jelly was cut. This combination at low concentration range showed potential to form granular jellies. Low-acyl gellan gum (0.15-0.5% w/v) – calcium chloride (0.5-2% w/v) also formed gels with a free-standing structure but do not meet all visual assessment criteria for free-standing jellies. The jellies did not quiver, did not retain angles once cut with a spatula and a rubbery, string like texture was observed once the jelly was cut. In addition, the low-acyl gellan gum crosslinked with calcium salt gels showed large volume of residual water (8-13mL) and thus were not investigated further.

Table 4-5: Materials with hydration times under 10 minutes.

Material	**Concentration w/v (%)**	**Time taken to hydrate (min)**	**Visual assessment of end product**			
			Thickened fluid stage 1 or 2	**Thickened fluid stage 3**	**Ryukakusan jelly**	**Free-standing jelly**
Carrageenan (kappa)	1-4	4-8	√* (2)	√*		
Low acyl gellan gum	0.15-1	2-4	√* (2)	√*		
High acyl gellan gum	0.5-1	4-6		√		
Guar gum	1-4	1-3	√ (1)			
Maize starch	1-4	1-3	√ (1)			
Egg protein	0.5-1.5	3-7	√ (2)			
LM pectin	0.5	9	√ (1)			
HPMC	0.5	8	√ (1)			
Polyethylene oxide	0.5	9	√ (1)			
Sodium alginate	0.5-2	1-5	√ *(1, 2)			
Sodium alginate and calcium chloride	-*	4-8			√*	√**
Sodium alginate and dicalcium phosphate dihydrate	-*	6-9				√

Low acyl gellan gum and calcium chloride **	-*	6-9	√**
Low acyl gellan gum and dicalcium phosphate dihydrate	*		√**

*Properties vary depending on the concentrations used.

**Formed a free-standing structure but did not meet the full visual assessment criteria

4.3.3 Development of free-standing jellies

As shown in Section 4.3.2 (Table 4-5), sodium alginate-dicalcium phosphate dihydrate formed the most promising free-standing jelly structure and was investigated further by varying the concentrations of the ingredients. The visual appearance, gel strengths and adhesion of the developed jellies were compared with commercial products. A variation of gel strengths was observed for the commercial jellies (Table 4-6) ranging from 13g to 30g and adhesion ranging from 3g to 6g.

Table 4-6: Gel strength and adhesiveness of commercial jellies.

Commercial ready-made jelly	Gel strength (g)	Adhesion (g)
Hartley's jelly	13.36±1.5	2.8±0.6
Vimto jelly	27.78±1.09	6.071±0.28
Gelatine peppa pig jelly	29.34±0.28	4.079±0.18

An increase in citric acid concentration increased gel strength of the resultant jellies until 4% w/v citric acid was utilised (Table 4-7). A decline in gel strength was observed with further increase in citric acid concentration. Additionally increasing citric acid concentration to above 2% w/v increased hydration time; therefore sample number 2 was selected to further evaluate the effect of changing dicalcium phosphate dihydrate concentration on jelly formation. An increase in dicalcium phosphate dihydrate concentration also resulted in an increase in gel strength; furthermore, a concentration lower than 0.4% w/v did not result in the formation of jelly and a concentration of 1% w/v resulted in a rigid gel not fulfilling jelly criteria (Table 4-7). In comparison sample 10 showed quicker hydration time and higher gel strength than sample 2 and thus taken for further evaluation. An increase in sodium alginate concentration from 0.5% w/v to 1% w/v increased gel strength but again the resultant jelly was rigid. An

increase in hydration time was observed for all incremental increase in the concentration of the ingredients and due to an increase in hydration time above 10 minutes, no further concentration increase was investigated after sample 12. No clear pattern was observed for adhesiveness with changes in the concentration of the ingredients; however, the adhesiveness of the alginate jellies were generally lower than commercial jellies. Table 4-7 shows a green highlight for the promising jelly sample selected by taking into consideration texture analysis results, residual water and final jelly formation time (relevant columns highlighted).

Table 4-7: Development of sodium alginate and dicalcium phosphate dihydrate jellies (triplicate samples).

Sample number	Sodium alginate (% w/v)	Dicalcium phosphate dihydrate (% w/v)	Citric acid (% w/v)	Time taken to hydrate (min) magnetic stirrer method	Final jelly formation time after setting (5 min)	Visual assessment		Texture analysis Gel strength		
						Whether or not free-standing jelly formed	Other information	Residual water (mL)	Gel strength (g)	Adhesiveness (g)
1	0.5	0.5	1	8	13	x	Does not retain shape	4	2.8±0.8	0.3±0.05
2	0.5	0.5	2	7	12	√	Slight quiver	7	10.6±0.3	1.03±0.2
3	0.5	0.5	3	11	16	√	Very slight quiver	6	14.3±0.6	1.3± 0.3
4	0.5	0.5	4	14	19	√	Very slight quiver	8	12.7±2.3	1.8±0.05
5	0.5	0.5	5	12	17	√	Very slight quiver	8	3.2±0.6	0.4±0.04
6	0.5	0.5	10	13	18	x	Doesn't retain shape	8	0.2±0.06	0.9±0.3
7	0.5	0.1	2	4	9	x	Doesn't retain shape	8	0.2±0.1	0.7±0.2
8	0.5	0.2	2	5	10	x	Doesn't retain shape	8	1.9±0.5	1.02±0.0.4
9	0.5	0.3	2	5	10	x	Doesn't retain shape	9	3.7±0.6	0.6±0.07
10	0.5	0.4	2	6	11	√	Quivers	6	12.3±1.5	0.9 ±0.2
11	0.5	1	1	6	11	x	no quiver	5	12.3±1.5	0.9±0.2
12	1	0.5	1	14	19	√	Firm, very slight quiver	4	55.2±3.8	0.77±0.18

Sample 10 showed the quickest hydration time out of samples that met the visual assessment criteria, and showed gel strength and adhesiveness similar to Hartley's jelly. Hydration time for this jelly sample 10 (Table 4-7, Figure 4-10a) was thus tested using shaking the beaker method gave an overall jelly preparation time of 6 minutes (hydration time 1 minute, jelly formation 6 minutes), stirring using a glass rod resulted in 2 minutes hydration time 7 minutes for jelly formation.

The effect of variation of the volume and hardness of water on jelly formation is shown in Tables 4-8 and 4-9. A reduction in water volume from 20 mL to 15 mL increased the gel strength of the jelly and time taken to form the jelly. An increase in the volume of water to 25 mL resulted in a weak gel that did not retain its shape, with low firmness. Soft (bottled water) and hard (tap) water increased the time to form the jelly and gel strength compared to deionised water.

Table 4-8: The effect of variation in water volume for the jelly formation (sample 10).

Volume of water	**Jelly formation time after setting (5 min)**	**Jelly formed**	**Gel strength (g)**	**Adhesion (g)**
15ml	17	√	20.7±2.9	0.99±0.83
25ml	9	x	1.9±1.3	0.39±0.105

Table 4-9: The effect of water hardness on the jelly formation.

Water hardness	**Jelly formation time after setting (5 min)**	**Jelly formed**	**Gel strength (g)**	**Adhesion (g)**
Soft	15	√	12.3±1.5	0.9±0.2
Very hard	18	√	14.3±0.6	1.3± 0.3

All variations of sample 10 using different volumes and hardness of water showed G' dominance over G" (Figure 4-5). Both G' and G" reduced with using 25ml of deionised water (Figure 4-5b) indicating lesser elastic properties for a greater volume of deionised water. The magnitude of G' increased at low frequency for sample 10 jelly developed using less volume (15mL) of deionised water (Figure 4-5c). Both G' and G" increased for soft and hard water prepared jellies (Figure 4-5d and e).

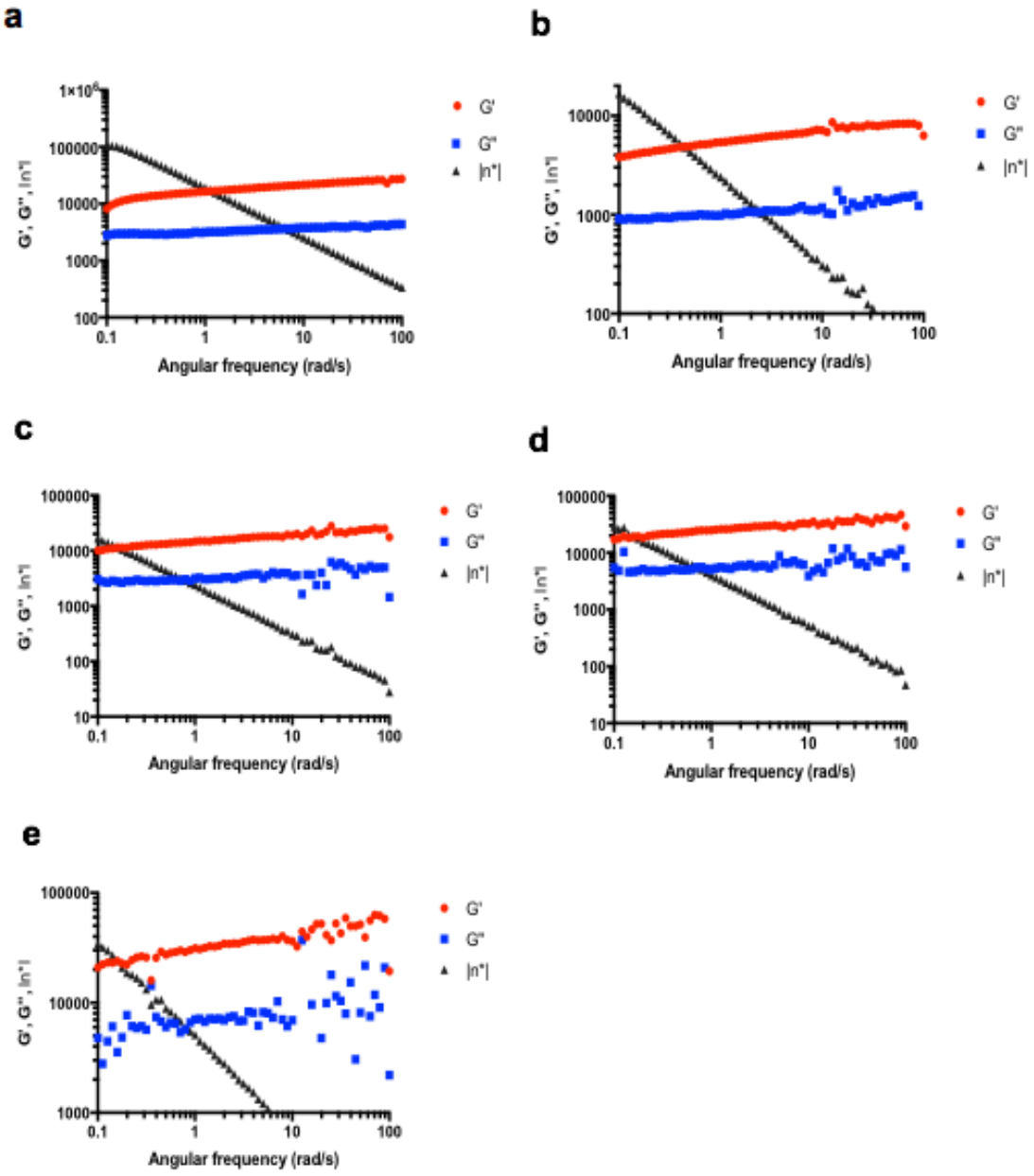


Figure 4-5: G' and G" represented as a function of frequency for a) Sample 10 sodium alginate dicalcium phosphate dihydrate b) sample 10 formed in 25ml of deionised water, c) sample 10 formed in 15ml of deionised water, d)sample 10 formed using soft water, e) sample 10 formed using hard water.

Additional materials that showed hydration times under 10 minutes for free-standing jelly development were guar gum, polyethylene oxide, HPMC and low-acyl gellan gum (Table 4-10, Figure 4-16). Egg protein, LM pectin, carrageenan kappa resulted in substantial preparation time. Low-acyl gellan gum combination was quick to prepare but resulted in a lot of residual water (Table 4-10, Figure 4-6).

Gel strength was comparable to sodium alginate-dicalcium phosphate dihydrate jelly (sample 10) after the addition of guar gum, polyethylene oxide and kappa carrageenan (Table 4-11). Polyethylene oxide jellies showed considerably lower gel strength or firmness than the sodium alginate-calcium phosphate jelly (sample 10).

Table 4-10: Development of sodium alginate and dicalcium phosphate dihydrate jellies with the additional polymer at 50:50 ratio.

Sample number	Additional polymer	Time taken to hydrate (min) Shaking beaker method	Jelly formation time after setting (5 min)	Visual assessment		
				Jelly formed	Other information	Residual water (mL)
13	Egg protein	>15	NA	x	clumps	NA
14	LM pectin	>15	NA	x	clumps	NA
15	Guar gum	1	6	√	Wobbly, pale yellow	3
16	Maize starch	>15	NA	x	clumps	NA
17	HPMC	4	9	√	Wobbly, transparent	7
18	Polyethylene oxide	3	8	√	Wobbly, transparent	7
19	Carrageenan (kappa)	>15	NA	x	clumps	NA
20	Low-acyl gellan gum	50 secs	5 minutes 50 seconds	√	Wobbly, transparent	9
21	High-acyl gellan gum	>15	NA	x	clumps	NA

Table 4-11: Gel strength and adhesiveness of free-standing jellies.

Sample number	Additional polymer	Gel strength (g)	Adhesiveness (g)
15	Guar gum	11.1±0.4	1.9± 0.9
17	HPMC	16.1±0.3	1.3±0.3
18	Polyethylene oxide	0.8±0.3	0.3±0.1
20	Low-acyl gellan gum	13.1±0.5	0.4±0.0.05

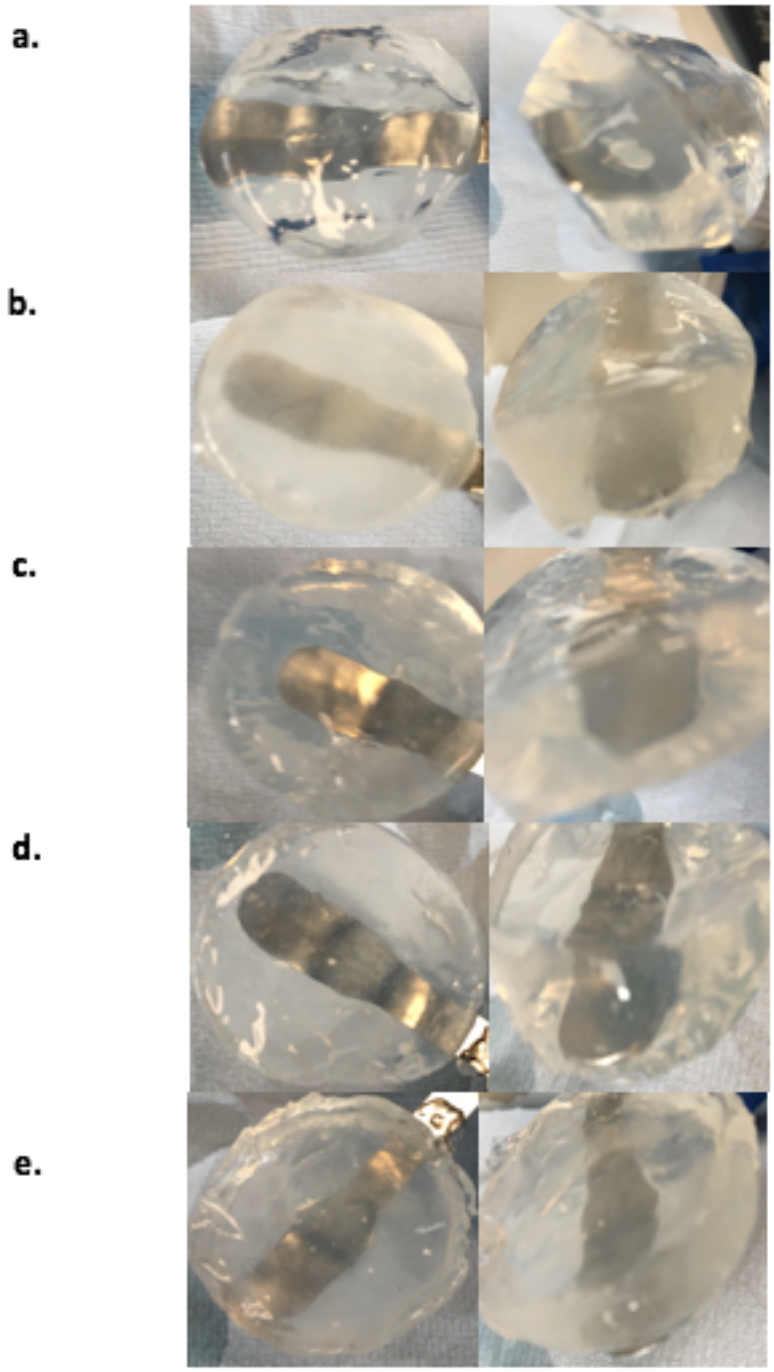


Figure 4-6: a) Sodium alginate jelly, (sample 10) b) Sodium alginate and guar gum jelly (sample 15, F1) c) Sodium alginate and HPMC jelly (sample 17) 50:50 ratio d) Sodium alginate, polyethylene oxide jelly, 50:50 ratio (sample 18), and sodium alginate, low-acyl gellan gum jelly, 50:50 ratio (sample 20).

A comparison of the frequency dependence of G' and G" of sodium alginate- guar gum jelly (F1, sample 15, Figure 4-7c) to commercial products (Hartley's and Vimto jellies, Figures 4-7a and b shows a greater magnitude of G' and G" for sodium alginate-guar gum jelly and a lower magnitude of G' and G" to sample 10 (sample without guar gum, Figure 4-5a). The finding indicates greater structural strength compared to commercial products.

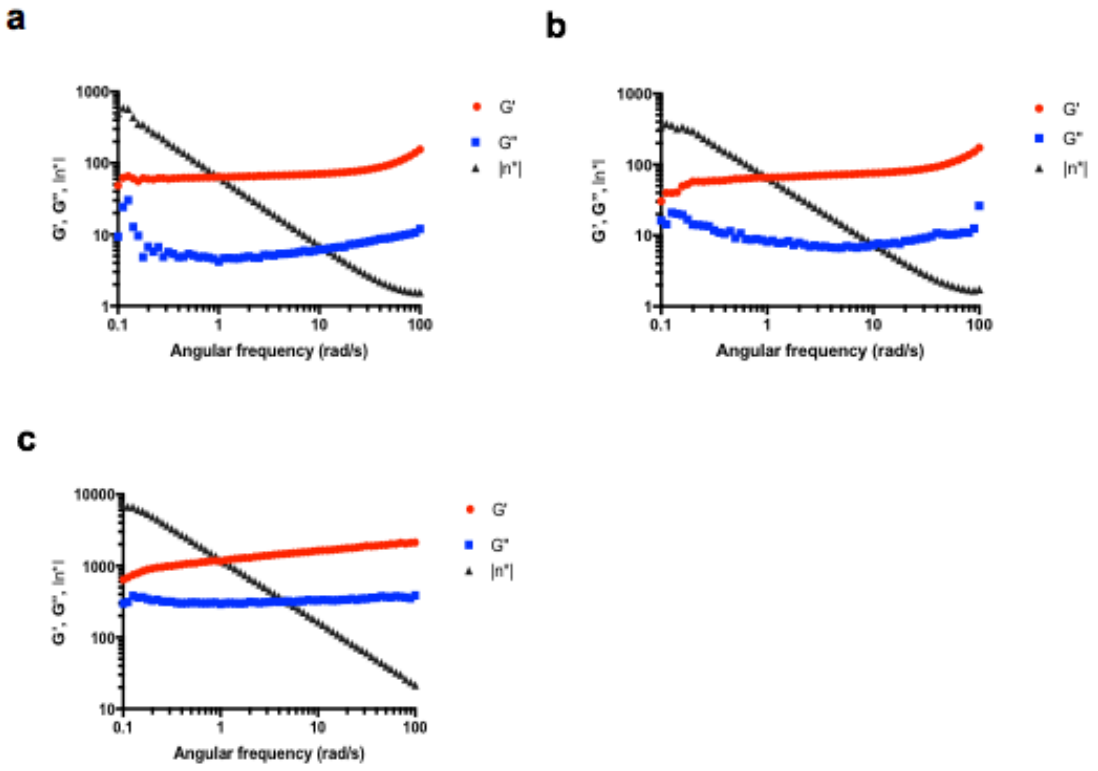


Figure 4-7: Frequency dependence of G' and G" for a) Hartley's, b) Vimto jellies and c) F1 (sample 15).

4.3.4 Granular jelly formation

Sodium alginate, dicalcium phosphate dihydrate and citric acid were not appropriate for the granular jelly formation as a free-standing jelly begins to form over a short period of time. Sodium alginate and calcium chloride combination formed granular jellies at low concentrations. Low concentrations of sodium alginate (0.1-2.5w/v)and calcium chloride (0.1-0.3 %w/v) were trialled to form a granular jelly and the majority formed a thickened fluid. Granular jelly was formed using sodium alginate 2% w/v and calcium chloride 0.3% w/v (F2, Figure 4-13) and further increase in concentration of sodium alginate resulted in little flow. Back extrusion results for F2 showed considerable increase in firmness (238.7±22.2g) compared to Ryukakusan jelly for adults (32.7g ± 0.2g), low cohesiveness of 5.29±0.09g compared to the Ryukakusan jelly (14.89 ± 0.03g) and slightly greater surface adhesiveness 13.73±1.2g compared to the commercial product (8.24 ± 0.3).

Adding some of the additional polymer to F2 kept the jelly appearance meeting the visual criteria for granular jellies, including polyethylene oxide, HPMC, carrageenan kappa and low acyl gellan gum (Table 4-12). Time taken to hydrate and visual assessment (columns highlighted in Table 4-12) were used to select jellies that met the criteria (highlighted rows in green in Table 4-12). Low acyl gellan gum was the additional polymer that had the quickest jelly formation (F3). All materials that were successful as additional polymers for forming granular jelly were added using Method A by mixing the additional polymer with sodium alginate and dissolving together. Table 4-13 shows the results of texture analysis of granular jelly formed with additional polymers which were more comparable in firmness to Ryukakusan jelly for adults with

sample 55 (F3) (highlighted green) showing the closest resemblance in firmness, cohesiveness and adhesiveness.

Table 4-12: Sodium alginate-calcium chloride jelly development with other polymers.

Sample number	Additional material	Method of adding additional material	Time taken to hydrate	Visual assessment	
				Ryukakusan jelly	Reasons
Ratio 75 sodium alginate: 25 other material					
43	Egg protein	A	14	x	Thickened fluid stage 1, granular gels not formed
44		B	8	x	Thickened fluid stage 1, granular gels not formed
45	LM pectin	A	14	x	Thickened fluid stage 1, granular gels not formed
46	Guar gum	A	5	x	Very watery, and no granular gels, sludge-like
47		B	4	x	Mostly water
48	Maize starch	A	>15	x	Mostly water
49		B	5	x	Thickened fluid
50	Polyethylene oxide	A	8	√	Large granular gels

51		B	6	x	Sludge like
52	HPMC	A	8	√	Large granular jellies
53		B	7	x	Sludge like
54	Carrageenan (kappa)	A	14	√	Large granular jellies
55	Low-acyl gellan gum	A	6	√	Large granular jellies
Ratio 50 sodium alginate: 50 to other material					
56	Polyethylene oxide	A	12	x	Fluid, granular gels not formed
57	HPMC	A	13	x	Fluid, granular gels not formed
58a	Low-acyl gellan gum with 0.075% calcium chloride	A	9	x	Sludge like with few granular jellies.
58b	Low-acyl gellan gum with 0.15% calcium chloride	A	9	√	Granular jelly formed
59	Kappa carrageenan	A	13	√	Granular jelly formed
Ratio 25 sodium alginate: 75 other material					
60	Polyethylene oxide	A	>20	x	Clumps
61	HPMC	A	>20	x	Clumps

62	Low-acyl gellan gum	A	11	x	Sludge like but few granular jellies formed
63	Kappa carrageenan	A	>20	x	Clumps

Table 4-13: Textural characteristics (back-extrusion tests) after addition of polymers (method A) for granular jelly.

Sample number	**Additional polymers**	**Firmness**	**Cohesiveness**	**Adhesiveness**
	Ratio 75 sodium alginate: :25 other material			
50	Polyethylene oxide	27.5±3.5	6.4±0.4	6.1±0.1
52	HPMC	30.6±4.1	5.9±0.1	6.05±0.6
55	Low-acyl gellan gum	28.4±1.4	16.05±0.3	10.5±0.69
	Ratio 50 sodium alginate: :50 other material			
58b	Low-acyl gellan gum	28.9±1.4	14.2±2.7	6.7±0.1

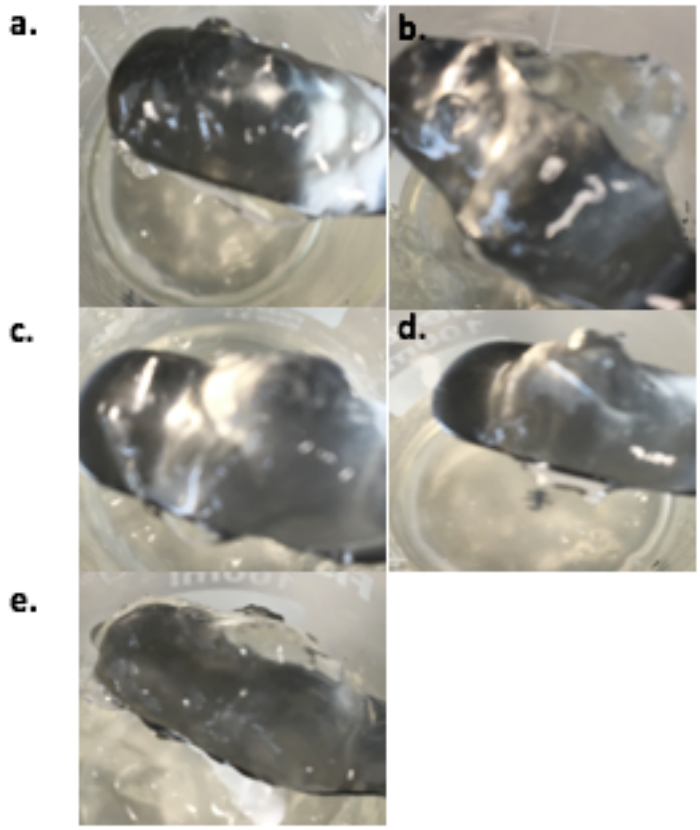


Figure 4-8: a) Sodium alginate 2% calcium chloride 0.3% w/v (sample 41, F2). b) Sodium alginate 75 parts: polyethylene oxide 25 parts granular jelly (sample 50) c) Sodium alginate 75 parts: HPMC 25 parts granular jelly (sample 52) d) Sodium alginate 75 parts: Low-acyl gellan gum 25 parts granular jelly (sample 55, F3) e) Sodium alginate 50 parts: Low-acyl gellan gum 50 parts granular jelly (sample 58b).

The frequency dependency of moduli for sample 41 (F2, sodium alginate and calcium chloride) and 58 (F3, sodium alginate, low acyl gellan gum (50:50 ratio) and calcium chloride) is shown in Figure 4-9. A frequency dependence profile for sodium alginate and calcium chloride showed a greater magnitude of G' and the difference with G", indicating a stronger network (Figure 4-9b) compared to Ryukakusan jelly for adults (Figure 4-9a). Sodium alginate-low acyl granular gel showed G' dominance over G". The profile is similar to Ryukasun's jelly for adults frequency spectre (Figure 4-9c).

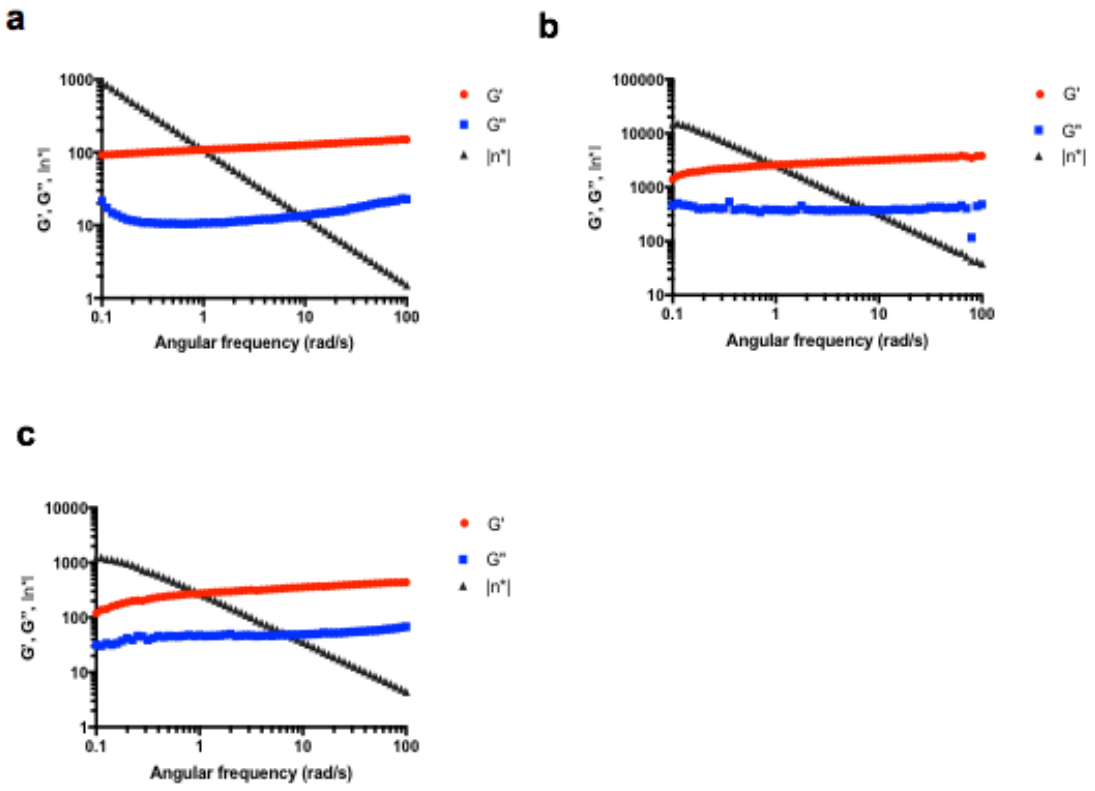


Figure 4-9: Frequency dependence of G' and G" for a) Rukakusan jelly for adults, b) sodium alginate and calcium chloride granular jelly (F2, sample number 41) and c) sodium alginate-low acyl gellan gum granular jelly (ratio 50:50) (F3, sample number 58).

The response to the steady state rate test of promising jellies (F1-3; sample numbers 15, 41, 58) is shown in Figure 4-10. All the jellies showed shear-thinning rheology. A much greater apparent viscosity for all shear rates was observed for sodium alginate granular jelly (F2, sample number 41).

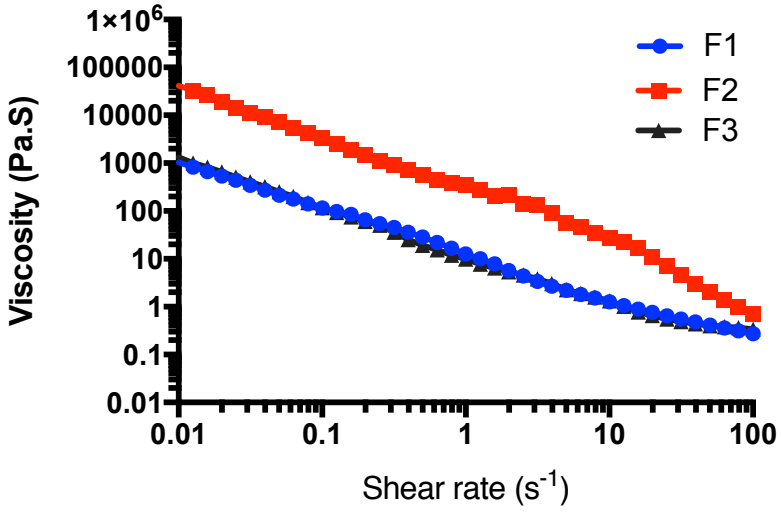


Figure 4-10: Apparent viscosity as a function of shear rate for promising jellies (F1, 2 and 3).

4.3.5 *In vitro* processing of "instant" jellies

Figure 4-11 shows the transit of F1, 2 and 3 in the *in vitro* 'CT' model. All three jellies showed fast transit (Figure 4-12a) comparable to stage 2 thickened fluids and cohesive bolus movement comparable to stage 3 and 2 thickened fluids (Figure 4-12b).

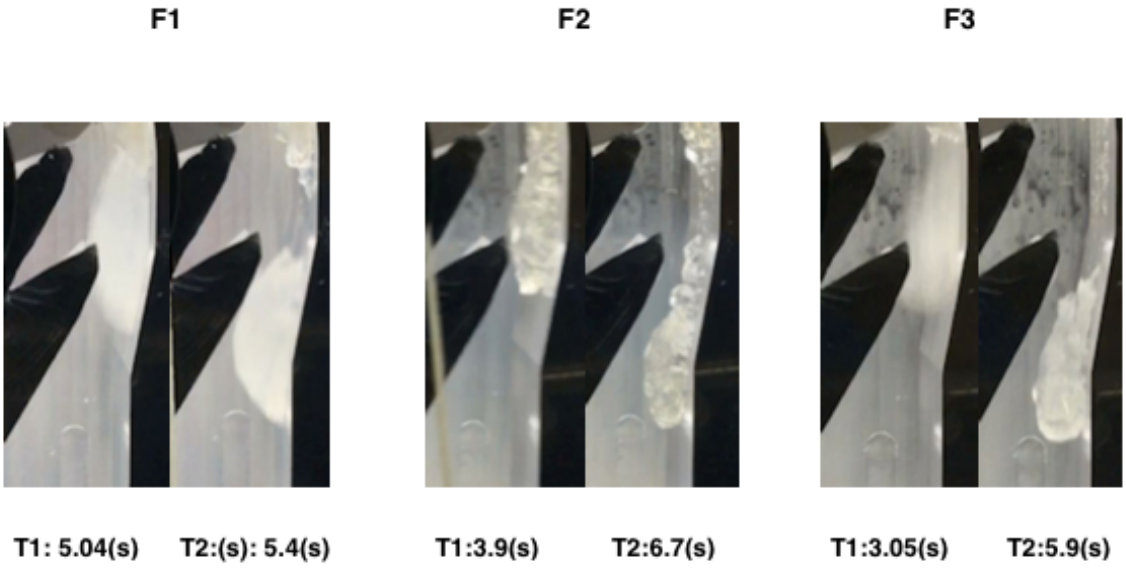


Figure 4-11: : Transit of participants bolus jellies in the Cambridge Throat towards the epiglottis (T1) and airway divide (T2) for a) F1; sodium alginate- guar gum free standing jelly, (manually chopped) b) F2; sodium alginate granular jelly, c) F3; sodium alginate-low-acyl gellan gum granular jelly.

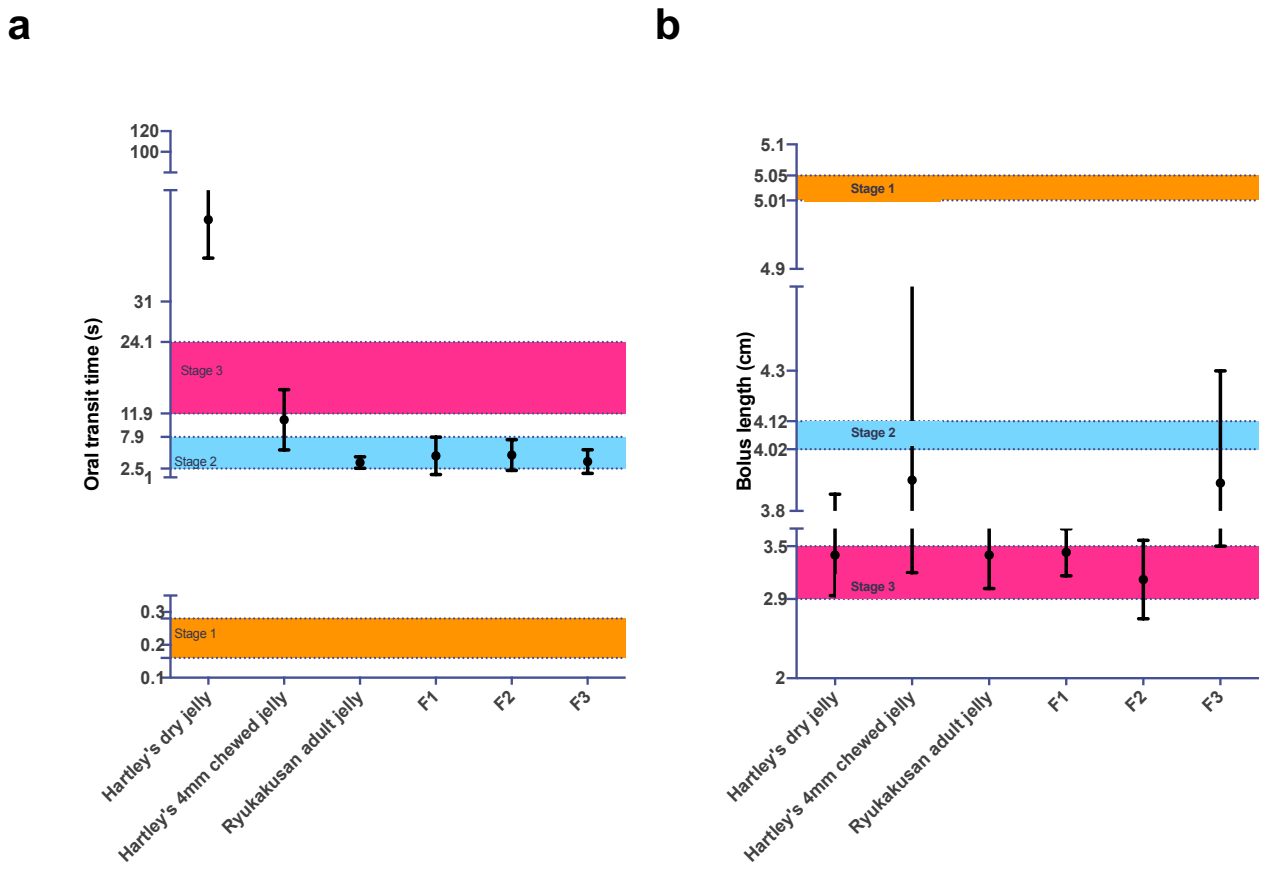


Figure 4-12: The OTT (a) and BL (b) at airway divide for jellies. The coloured boxes represent the confidence interval range for the thickener Nutilis Powder at stages 1, 2, and 3 for comparison.

4.4 Discussion

The purpose of this study was to develop jelly formulations that take less than 10 minutes to form without requiring heat in order to present a sachet product that patients can add to water and form a jelly for medication administration. The time of less than 10 minutes was chosen for patient convenience, a jelly that requires a lot of preparation time may not be accepted by the patient. A number of materials have met this hydration criteria including carrageenans (kappa), guar gum, gellan gum, sodium alginate, maize starch, egg protein, LM pectin, which all have good water-binding properties. Water binding occurs by hydrogen bonding with hydroxyl groups on guar

gum and sodium alginate, charged carboxyl groups and hydroxyl groups on low methoxy pectin, negatively charged sulphate groups and hydrogen bonding with kappa carrageenan (Fisher, 2009; Tripathy & Das, 2013; Vaclavik & Christian, 2008; Venugopal, 2011). Hydrogen bonding occurred between water and charged amino acid groups on egg protein(Zayas, 1997). Longer hydration times were expected for other materials such as locust bean gum, gum ghatti, gum tragacanth and agar which are known to be partially soluble or not soluble in cold or room temperature water (Dakia, Blecker, Robert, Wathelet, & Paquot, 2008; López-Franco, Higuera-Ciapara, Goycoolea, & Wang, 2009). Differences in hydration times were observed for LM and HM pectins as expected, due to the carboxylic acid and hydroxyl groups on the LM pectin allowing hydrogen bonding with water molecules.

Generally, in rank order for carrageenans, lamda>iota>kappa are expected to dissolve in room temperature deionised water from quickest to slowest. Lamda carrageenan is highly sulphated, consists of hydroxyl group and is void of hydrophobic 3,6 anhydro-D- galactose subunits (ADG). Kappa carrageenan contains the ADG subunits as a repeating unit and has fewer sulphate groups. Iota carrageenan is expected to be intermediate and more hydrophilic than the kappa carrageenan due to the presence of 2-sulphate which also counteracts the ADG group. However, the kappa carrageenan showed quicker hydration in this study as the product was presented as a sodium salt form of the sulphated group increasing is water solubility (CP Kelco, 2001).

Most of the materials formed thickened fluids which occurs due to entanglement of polymer chains (Saha & Bhattacharya, 2010). Sodium alginate showed potential to

form jellies as reported previously (Hong et al., 2012; Masumoto et al., 2016; Yasushi et al., 2016). Low-acyl gellan gum also showed potential for jellies using the same method but showed greater residual water possibly due to greater binding with calcium and stronger gel contractions resulting in syneresis. Syneresis of water is when the unbound water is expelled from the gel matrix (Banerjee & Bhattacharya, 2011). Gellan gum has reported to form brittle texture and therefore is commonly blended with other polymers to form softer, elastric textures, brittle gels are reported to be susceptible to syneresis compared to elastic gels (Mao, Tang, & Swanson, 2000; Valli & Clark, 2009). Two different methods of introducing calcium crosslinking ions were used to prepare free-standing jellies and granular jelly. Calcium chloride is commonly used for sodium alginate gelation, however, calcium chloride is highly water soluble in cold water (40% w/v) compared to dicalcium phosphate dihydrate (0.02% w/v) which results in an instantaneous reaction between alginate and calcium (Draget, 2009; Helgerud, Gåserød, Fjæreide, Andersen, & Larsen, 2009; Lee & Mooney, 2012). Calcium chloride was used for the free standing jelly but the rapid interaction can result in the inhomogeneous distribution of calcium due to a sharp gelling zone forming at the surface and decrease towards the center of the gel (Helgerud et al., 2009). This resulted in a rubbery and string-like texture inside the jelly and didn't retain angles once cut with the spatula. Since dicalcium phosphate dihydrate is less soluble in cold water than calcium chloride, the low solubility allows the dicalcium phosphate dihydrate and sodium alginate to be mixed and added together to the deionised water for *in situ* gelation (Helgerud et al., 2009). Controlled release of calcium ions was achieved by a change of pH using citric acid for the free-standing jelly. The citric acid in the formulation helps to dissolve the calcium phosphate which is less soluble in neutral pH, thereby increasing the presence of calcium ions (Draget, 2009).

The firmness of supermarket jellies was tested to compare with the free-standing jelly formulation to maintain similarity of the ease of chewing. An increase in firmness was observed with increasing calcium concentration or citric acid concentration. An increase in calcium or sodium alginate concentration is expected to increase the firmness of the sample as a result in increased binding between G units of sodium alginate and calcium ions (Lee & Mooney, 2012). Sodium alginate and calcium gels are known to retain water through hydrogen bonds, and during gel contraction, release water known as syneresis (Draget, 2009). Greater residual water was observed with increasing citric acid (which would increase calcium content) or calcium content.

The volume of water for jelly preparation was altered considering potential instances whereby patients and health care professionals may accidentally use a different volume than advised. As expected, an increase in volume resulted in softer jellies as a result of the lower concentration of gelling agent and calcium, and a reduction in volume increased firmness of the jellies. An increase in water hardness increased the firmness of the jellies and the time for jelly formation. Water hardness is normally expressed in terms of the concentrations of calcium and magnesium ions in water as equivalent to calcium carbonate (Rubenowitz-Lundin & Hiscock, 2005). An increase in these ions which contribute to gel formation of alginates is expected to increase the firmness of the gels. This was further reinforced with the frequency spectra. A greater magnitude of G' and dominance over G" was observed throughout the frequency range showing an increase in the concentration of calcium ions resulted in a stronger gel network. The presence of these ions also delays the hydration time of alginate as clumps started to form. The effect of water volume and hardness indicates the need

for the correct volume and type of water to be used in jelly formation. It would be recommended that the correct volume of deionised water is supplied with the sachet containing dry materials of the jelly which would increase the cost of the dosage form, however, it is expected that a safe-to-swallow sustained release dosage form would have long-term cost benefits by reducing pill burden, facilitating compliance with dosage form administration, reduced missed doses, reducing subtherapeutic dosing and better therapeutic management.

Additional polymers were added to improve time for the jelly formation and reduce residual water. Guar gum improved the time for jelly formation and reduced residual water. The use of multiple gelling agents is believed to reduce syneresis (Banerjee & Bhattacharya, 2011). Guar gum is known to increase the viscosity of solutions at low concentrations, due to intermolecular chain interaction or entanglement which enhances viscosity (Mudgil, Barak, & Khatkar, 2014). Guar gum is used for controlling water migration in bakery products due to its water binding properties (Ward, Hanway, & Ward, 2005). However, more residual water was observed with using HPMC and polyethylene oxide in the jelly composition. The reasoning for more residual water with HPMC and polyethylene oxide may be due to the lower water binding of HPMC and polyethylene oxide. HPMC has ether groups preventing intermolecular association with water (BeMiller, 2019). The ethylene oxide units in polyethylene oxide prevent intermolecular association with water (Graham, 1992). Low-acyl gellan gum also showed larger residual water; this may be a result of an excess of calcium in the jelly and the interaction between calcium and low-acyl gum potentially resulting in gel contraction and extruding liquid out of the jelly.

A different method approach was used for forming the granular jelly. The sodium alginate- dicalcium phosphate dihydrate method results in a non-flowing, free-standing jelly formed over a short time and was not appropriate for granular jelly. Sodium alginate and calcium chloride at low concentrations formed a granular jelly. The sodium alginate-calcium chloride trials for very low concentrations of both component only resulted in a thickened fluid with none, or a low number of granular gels. Increasing the concentrations provided granular jelly, but increasing it further, resulted in a jelly with little flow. Sodium alginate-calcium chloride showed a much larger firmness compared to Ryukakusan's granular jelly. This combination met the visual criteria for granular jelly; however, the greater firmness of the granular jelly compared to the commercial product, Ryukakusan jelly. However, the "instant" granular jelly was less firm than Thick and Easy stage 3 (Chapter 3). Chapter 3 showed that firmness did not influence the safety of swallowing features that were observed in the *in vitro* throat model for jelly. Further development of this granular jelly with other polymers showed much lower firmness which may be due to the lower amount of sodium alginate and calcium chloride used and loosening of the structure of sodium alginate-calcium chloride formed jelly. The presence of other polymers may be entangled with the sodium alginate and restricting cross-linkage with calcium ions.

Frequency spectre showed a greater magnitude of G' and G" sodium alginate-calcium chloride granular jelly (F2) compared to Ryukakusan's granular jelly, reinforcing the greater firmness observed using the texture analyser due to greater proportions of the polymer and calcium ions. The greater magnitude of G' and G" for the F3 compared to the Ryukakusan 's granular jelly yet similar firmness to commercial products show

potential for *in vivo* studies in retaining cohesive bolus during peristaltic contractions in the pharynx.

There were clear differences in hydration time between mixing methods using a magnetic stirrer at a low speed, shaking by hand and mixing with a rod. Mixing with a magnetic stirrer provided agitation at the bottom of the beaker, and thus results of jelly formation were much slower. The speed was kept very slow to simulate the potential difficulties in hand movement older patients may have. Shaking of the beaker by hand and glass rod provided quicker jelly formation time potentially due to greater agitation and that the agitation was throughout the fluid which helps homogenous hydration of the polymer.

The three jellies (F1, 2 and 3) that met the visual criteria for free-standing jellies and granular jellies and were the quickest to prepare were selected for *In vitro* testing using the CT model. Although gels and jellies are used interchangeably, the visual criteria were used to mimic commercial jelly products in terms of overall appearance. The reason for this consideration is that patients whom are already familiar with jellies from the supermarket and enjoy these products as dessert are likely to accept the jellies as dosage forms. Thickened fluids which are safer to swallow than thin water are not well accepted (Garcia, Chambers, et al., 2005; J. Murray et al., 2014; Shim et al., 2013), Japan includes jelly in the dysphagia diet and have jellies as swallowing aids to help swallow tablets and capsules intact without needing water for swallowing (International Dysphagia Diet Standardisation Initiative, 2016a; National Rehabilitation Center for Persons with Disabilities Japan, 2015; Tsuji et al., 2006). Japan also has a marketed oral immediate release jelly dosage form for Donepezil for Alzeimer's disease (Aricept

oral jelly) to help patients with swallowing difficulties (Elsai, 2009). Although the focus of this thesis is developing an instant jelly dosage form for older adults, jellies may be beneficial for the younger cohort and for patients with a psychological aversion to swallowing SODF. Previous incidences of children choking with jelly were associated to aspiration related to konjac-based jellies which are known to swell (Seidel & Gausche-Hill, 2013). However, Kluk & Sznitowska (2014) observed 83% of children (2-3 years) were able to swallow five or ten 2-3mm minitablets with jelly on a spoon, although only 57% of children were capable of swallowing without prior chewing.

The jellies selected for *in vitro* testing showed similar safety features of slow transit and coherent bolus movement as observed for commercial jellies in Chapter 3. Although this drug delivery vehicle was developed for older adults, jellies are also useful as swallowing aids for children (Kluk & Sznitowska, 2014).

The free-standing jelly and granular jelly are prepared differently, and there is an influence of water volume and hardness. These considerations affect the design and selection of the final jelly product presentation, the deionised water needs to be provided and the polymer powder needs to be provided and then prepared by the patient or administrator of the dosage form. The free-standing jelly requires the addition of powders from two sachets, one sachet for the polymers and one sachet for the citric acid, in addition to providing the deionised water. The granular jelly would requires deionised water to be provided, and one sachet of powder for polymer and calcium chloride solution. The granular jelly would be more challenging to prepare and likely to be bulky. The preparation of these jellies and ease of preparation may be facilitated with bespoke packaging design.

There has been an increase in development of novel administration designs for paediatrics (Lopez et al., 2015; Walsh, Bickmann, Breitkreutz, & Chariot-Goulet, 2011). For example, dose sipping technology (XStraw^{TM}) is a ready-to-use pre-dosed straw containing granulated dosage form (Raumedic, n.d.; Walsh et al., 2011). The straw containing a filter (controller) is placed in a drink, and the end-cap is taken off and the drink with the full dose is swallowed through the straw. The product is for thin fluids and therefore not useful for the jelly formulations developed in this study. Packaging containers for jellies in Japan include a single serve type, which is a container with a jelly, a stick type which involves squeezing the jelly from the packaging container and an air-extruded type packaging which comprises of a jelly and air portion which allows smooth discharge of the jelly (Imai, 2013). A bespoke packaging design may reduce having different containers and packages and may facilitate preparation of the jellies with ease. A potential package for F1, for example, having a small central container attached with a small tube of sodium alginate and guar gum and another separate small tube with citric acid on one side of the container. The central container can be rotated and the relevant tube can be pressed to dispense the powder into the central container. The central container can be shaken to mix the powder contents with deionised water. The top of the container can then be opened using a peel or lid and the jelly can be pushed out on the patients hand or the jelly can be consumed using a spoon. For F2, using the same principle, the centralised container can include the polymer in one tube and a calcium chloride solution in the other tube and pressure can be applied on the tubes to release the relevant powders in order to prepare the jelly.

4.5 Conclusions

Two forms of jelly were developed, a free-standing jelly and two granular jellies using sodium alginate. The sodium alginate jellies developed in this study form relatively quickly without the requirement of heat and showed promise as swallowing aids for patients with dysphagia in the *in vitro* throat model. The jellies showed slow oral transit times and cohesive bolus movement in the pharynx, the safety features that were observed for stage 3 thickened fluids in Chapter 3. The developed jellies (F1 anf F2) also showed reduced variability in the *In vitro* model compared to the commercial jelly products but this would need further investigation and validation using *in vivo* studies. The jellies would, however, require a supply the correct volume of deionised water to ensure that the desired consistency is formed and would require a bespoke packaging design to ease preparation of jellies for patients.

Chapter 5

SUSTAINED RELEASE COATING OF MICROPARTICLES AND THE EFFECTS OF INTEGRATING INTO "INSTANT" JELLIES ON *IN VITRO* DISSOLUTION

5.1 Introduction

Solid oral dosage forms (SODF), particularly conventional immediate release dosage forms are popularly prescribed, however as described in Chapter 1, these dosage forms have limitations compared to sustained release dosage forms. Sustained release dosage forms exist predominantly as tablets and capsules and can be challenging to swallow by patients with swallowing difficulties. Novel approaches such as multiparticulate dosage forms which involve splitting the full dose into subunits were first introduced in the 1950's as pellet-filled capsules (Spansules) (Tiwari et al., 2011). Multiparticulates obviate the challenges associated with swallowing SODF (e.g. tablets) and are also less likely to be chewed compared to mini-tablets due to its size and are therefore more suitable for patients with dysphagia. However, taking multiparticulates alone without a delivery vehicle can be challenging to these patients. For example, patients with dysphagia may not be able to swallow thin fluids to help administer the pellets or granules and thickened fluids for administration of multiparticulates may not be acceptable to patients therefore more palatable and safe-to-swallow delivery vehicles are needed.

5.1.1 Sustained release multiparticulates

Multiparticulates disperse easily into the gastrointestinal (GI) tract as a result of the small sizes, and display reduced intra- and inter-subject variability compared to single unit dosage forms and less likelihood of dose dumping due to the spread of the units in the GI tract (Rajabi-Siahboomi, 2017). Active pharmaceutical ingredients (API) can be included within a granule using processes such as extrusion spheronisation. The API can also be layered onto an inert core. The inert core for extended release is

typically sugar spheres or microcrystalline cellulose (Sidwell, Hansell, Rane, & Rajabi-Siahboomi, 2017). Sugar cores or pellets which contain 62.5-91.5% dried sucrose are widely available but have limitations. Sucrose has high osmolality, and any presence of residual moisture after the manufacturing process can result in drug dissolution in the residue water during storage as a result of osmotic pressure (Kállai et al., 2010; Sidwell et al., 2017). In addition, sucrose may be unsuitable for patients with sugar restrictions (Kállai et al., 2010). Microcrystalline cellulose is insoluble in water and thus advantageous as the inert core for sustained drug release (Kállai et al., 2010). Microcrystalline cellulose although widely used does have disadvantages such as drug adsorption on its surface which can affect bioavailability of drugs (Al-Nimry, Assaf, Jalal, & Najib, 1997; Okada, Nakahara, & Isaka, 2011).

5.1.2 Sustained release coating of multiparticulates

Film coating consists of a dry, outer material (thin membrane) on the surface of the dosage form to achieve specific benefits; for sustained release, it is to allow the drug to release slowly from the dosage form for an extended period (Skalsky & Stegemann, 2011). Film formers normally comprising of polymers are important components in the coating (Skalsky & Stegemann, 2011). The coating can be applied in aqueous dispersions or polymer solutions using organic solvents. Water or aqueous dispersions are more popular due to environmental and toxicity concerns regarding the use of organic solvents (Lecomte, Siepmann, Walther, MacRae, & Bodmeier, 2004; Ozturk et al., 1990). Coating with aqueous solutions involves the process of continued solvent evaporation, droplets of coating solution are allowed to build up on the substrate and continued solvent evaporation results in immobilization of polymers due to continued solvent loss (Lecomte et al., 2004; Porter, Sackett, & Liu, 2017).

The coating process for polymer dispersions involves the atomization of the coating solution or dispersion into small droplets using spray atomization. The polymer particles pack closely onto the surface of the inert core or substrate and move closer during water evaporation during drying due to the cohesive forces between the polymers which coalesce to form a homogeneous film (Eckersley & Rudin, 1994; Lecomte et al., 2004). The minimum film forming temperature is the temperature above which a homogeneous film is formed, and the product temperature is normally kept 10°C above the minimum film forming temperature during coating (Eckersley & Rudin, 1994; Skalsky & Stegemann, 2011). Curing after the coating process is also applied to promote coalescence of the film (Felton, 2013).

Polymers used in coatings are classified according to their origin as natural, synthetic and semi-synthetic. Natural polymers, for example, include alginate and pectin (Abletshauser, Schneider, & Rupprecht, 1993; Semdé, Amighi, Devleeschouwer, & Moës, 2000). Methacrylic acid and co-polymers are example of synthetic polymers (Savage & Rhodes, 1995) and semi-synthetic polymers include ethylcellulose (S. C. Porter, 1989), hydroxypropyl methylcellulose (HPMC) (Wan & Lai, 1991), cellulose acetate (Shivanand & Sprockel, 1998).

Multiparticulate sustained release dosage forms are usually designed as a reservoir drug delivery system. A reservoir drug delivery system consists of a polymer coating, around the core containing the API and water-insoluble polymers such as ethylcellulose or acrylate are typically used for the coating (Liu et al., 2011). Water-soluble components such as lactose or sucrose, or HPMC are also used as pore

formers to facilitate drug release (Liu et al., 2011). Drug release from a reservoir system typically occurs via diffusion and the coating thickness can alter the drug release, for example a thicker coating would result in a slow drug release due to an increase in diffusion path length (Munday & Fassihi, 1989; Ozturk et al., 1990).

Apart from film-forming polymers, other common components of coating include a plasticizer, an anti-tacking agent, pore formers to provide aqueous channels for drug release (Porter et al., 2017). Plasticizers are used to lower the minimum film forming temperature by weakening the intermolecular attractions between the polymer chains, increasing flexibility (Felton, 2013). Common plasticizer examples are citrate esters such as triethyl citrate, glycol derivatives such as propylene glycol and even water (Okarter & Singla, 2000). Anti-tacking agents are used to preventing agglomeration of the pellets during the coating process (Wan & Lai, 1993); typical examples include talc and magnesium stearate (Wan & Lai, 1993).

Water soluble additives or pore formers may be added to increase the rate of drug release from the sustained release coating. Typical water-soluble low-molecular additives include sucrose, lactose, calcium phosphate, sodium chloride which leach out from the coating layer into the aqueous media forming pores during dissolution. High molecular weight pore formers include polyvidone, HPMC which hydrates in aqueous media forming channels for drug release (Tang, Chan, & Heng, 2005).

5.1.2.1 Fluidised bed coating

Fluidised bed processing has been around since the late 1960s and the technology is widely used for coating multiparticulates (Kuntz, Weisbrod, Chakraborty, & Skalsky,

2017). Inert cores used for coating are usually 100 μm and above; particles smaller than this size are cohesive and agglomerate during coating, resulting in poor film formation (Werner, Jones, Paterson, Archer, & Pearce, 2007b).

Fluidised bed coating can be configured to top spray, bottom spray, and tangential spray. The top spray process is mainly used for drying, spray granulating and may also be used for core material manufacture by solution or suspension layering (Jones, 1994). The nature of an open vessel for top spraying results in the non-uniform coating and thus this process is not preferred for film coating (Jones, 1994). Tangential spray involves a rotating disc and spraying of liquid concurrently with the flow of the inert core, commonly used for dry powder layering (Jones & Rajabi-Siahboomi, 2017).

The bottom spray was introduced in 1959, at the University of Wisconsin by Dr. Dale Wurster (Jones & Godek, 2017). Hence the technique is known as the Wurster system. The Wurster system is the most popularly used for coating for sustained release due to the specially designed air distribution plate and nozzle location (Teng & Qiu, 2010). The air distribution plate is specially designed with large holes around the center, small holes outside the center (Figure 5-1a). At the center of the air distribution plate is a nozzle, and surrounding this is a partition, or the Wurster column (Figure 5-1b). There is a gap between the column and the air distribution plate, allowing particles to be drawn towards the center of the plate where the nozzle is located and accelerated in the gap (Cheng & Turton, 2000). The coating solution or suspension is sprayed upward from the nozzle. As the particles move upwards in the spray zone, they are decelerated in the chamber outside the Wurster column and the process continues in a loop. The process allows more uniform film formation than the top spray process

due to the recurring flow of substrates through the spray zone (Jones & Rajabi-Siahboomi, 2017).

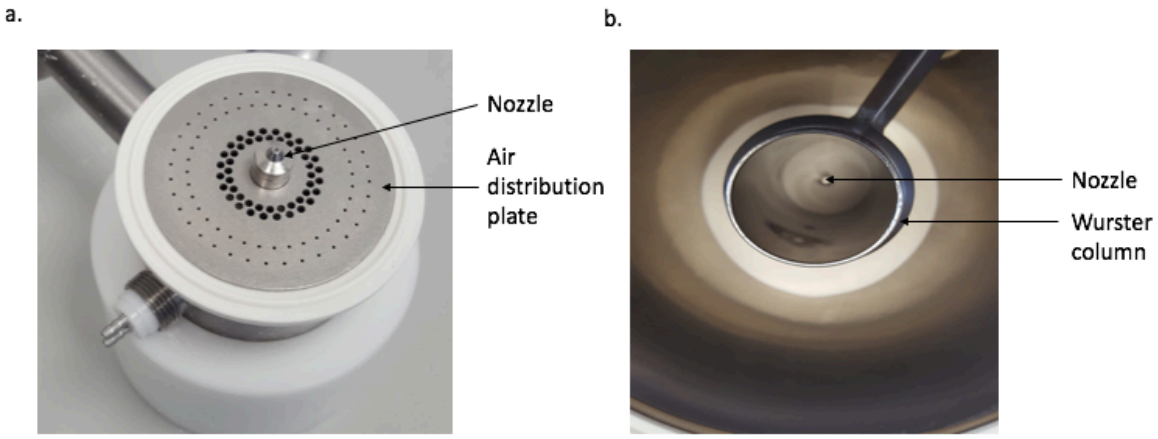


Figure 5-1: Image of (a) the air distribution plate and nozzle and (b) image of the Wurster column and nozzle.

5.1.2.2 Coating processing variables

Fluidised bed coating involves control of spray rate, atomization air pressure, inlet air temperature, inlet air volume, product temperature and curing to ensure product quality and consistency (Cheng & Turton, 2000; Maa, Nguyen, & Hsu, 1996; Shah, Mehta, Aware, & Shetty, 2017) (Table 5-1).

Table 5-1: Processing variables for fluid bed coating.

Processing variable	Effect of variable
Spray rate	The spray rate is the rate of liquid coating application to the substrate. If the spray rate is too high, agglomeration can occur (S. K. Singh, Reddy, & Khan, 1996). Too low spray rate results in too few droplets and drying of the sprayed coat before coalescing (Singh et al., 1996).
Atomisation air pressure	Atomisation air pressure is important in controlling droplet size distribution and velocity, This helps to prevent overwetting and spray drying (Werner, Jones, Paterson, Archer, & Pearce, 2007a). An increase of this parameter would increase volume and velocity of air passing through the nozzle reducing the air-droplet size, leading to spray drying and subsequently incomplete coating due to the prevention of coalescence of polymer (Werner et al., 2007a). Too little pressure can lead to agglomeration as a result of larger spray droplets bridging between particles (Werner et al., 2007a)
Inlet temperature	This is the temperature of the air before it enters the product chamber. The inlet temperature is set low compared to drying, a high inlet temperature can result in agglomeration during coating due to increased polymer stickiness or film softening (Teng & Qiu, 2010).
Air volume	Too high air volume can result in particles trapped in the filter housing, and too low can result in overwetting of particles passing through the spray area due to insufficient drying (Teng & Qiu, 2010).
Product temperature	The product temperature needs to be above the minimum film-forming temperature to allow coalescence of polymer to avoid discontinuous porous films (de Oliveira, Freire, & Coury, 1997). Higher temperatures allow enhanced mobility of particles and faster drying. However too high temperature can result in drying of the atomized droplets before reaching the inert cores (de Oliveira et al., 1997). An increase in the inlet temperature and air volume can increase the product temperature whilst an increase in spray rate can decrease the product temperature (Jones & Godek, 2017).
Curing	Coated particles are cured to allow further evaporation of water and complete polymer coalescence (Williams & Liu, 2000). The curing temperature should exceed the minimum film forming temperature but not the glass transition temperature (the

temperature at which the film changes from hard and brittle to elastic and soft), beyond which the polymer coating would become soft, and sticky and may result in agglomeration (Williams & Liu, 2000).

5.1.3 Gliclazide

Gliclazide (Figure 5-2) is a second generation sulfonylurea used for the treatment of type II diabetes mellitus. Gliclazide is a weak acid (pKa 5.8) and reported to have poor water solubility (55 μg/mL) (Allaboun, Alkhamis, & Almomani, 2003; Skripnik, Riekes, Pezzini, Cardoso, & Stulzer, 2017). Gliclazide is formulated as immediate release and sustained release tablets. The immediate release tablets can be taken once to twice daily, and the sustained release tablet is taken once in the morning with breakfast (Joint Formulary Committee, 2019d).

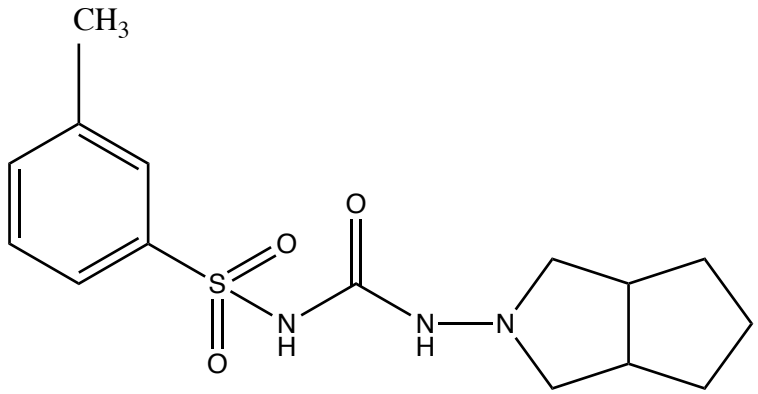


Figure 5-2: Chemical structure of gliclazide (Al-Kassas et al., 2007).

Diabetes is reportedly a growing health burden in older adults and almost one-third of over-65's in the US are reported to have diabetes (Kirkman et al., 2012; Narayan, Boyle, Geiss, Saaddine, & Thompson, 2006). Modification of sustained release

gliclazide may lead to hypoglycemia which can subsequently result in coma (Joint Formulary Committee, 2019d). Gliclaizde is not the first line treatment for diabetes in the UK and was selected as a model drug for this study for proof of concept. Absorption of gliclazide was not considered for this study.

The aims of this study are therefore to develop sustained release microparticles for gliclazide and integrate the sustained release microparticles into the “instant” jellies as delivery vehicles and test the influence of jellies using *in vitro* dissolution.

The primary objective of this study was to develop sustained release microparticles for gliclazide with a dissolution profile similar to the reference marketed product (Diamicron).

The secondary objective of this study was to integrate the microparticles into the developed instant jellies to gain an understandaing of the potential influence of the jellies on drug release from sustained release microparticles.

5.2 Materials and Method

5.2.1 Materials

Gliclazide was purchased from Sinobio Chemistry Co Ltd, China. Diamicron sustained release 30mg tablets manufactured by Servier (pack size 56) were ordered from AAH pharmaceuticals, UK. Microcrystalline cellulose microspheres (Cellets 100) was obtained from IPC Process-Centre GmbH & Co, Germany, Eudragit NM30D (Poly(ethyl acrylate-co-methyl methacrylate) was purchased from Evonik AG, Germany. Magnesium stearate was ordered from Acros Organics, Belgium. Talc was

purchased from Imerys Talc, Italy. Hydroxypropyl methylcellulose (Methocel E5) was ordered from Colorcon, UK. Silicon dioxide (Aerosil 200 Pharma) was purchased from Evonik AG, Germany.

Sodium alginate (Protanol GP 1740) was kindly gifted by FMC Biopolymer, UK. Low acyl gellan gum (Kelcogel F) was gifted by CP Kelco, UK and guar gum was gifted by B&V, Italy. Calcium chloride and citric acid were purchased from Fischer Scientific, UK and dicalcium phosphate dihydrate was purchased from Sigma Aldrich, UK.

5.2.2 Drug layering and sustained release coating of microparticles using fluidised bed

Gliclazide was layered onto microcrystalline cores (Cellets 100) using a fluidized bed coater with Wurster insert (Mini-Glatt, Glatt GmbH, Germany). Gliclazide was milled for two hours using a mini ball mill (160g of gliclazide with 60 x 10mm, 19 x 20mm and 24 x 10mm mini balls at 450 rpm) (Copley Scientific). Gliclazide suspension for drug layering was prepared by dissolving HPMC (1% w/v) in water and the milled gliclazide (10%w/v) was then added into the HPMC solution, followed by adding talc (1.9% w/v) to form a suspension.

The batch size for the drug layering was 100g (Cellets 100 starting core) and the process followed parameters shown in Table 5-2.

The sustained release coating dispersion was prepared by dispersing talc (7.5% w/v) in water using a magnetic stirrer and the resultant dispersion was homogenized at 10,100 rpm for 20 minutes (Silverson L4RT, Silverson Machines, UK). The talc dispersion was added to Eudragit NM (30%) dispersion (7.5% w/v) and stirred using

a magnetic stirrer for 20 minutes. The final coating dispersion was sieved using a 250 µm mesh sieve before the coating process (Table 5-2) to remove any aggregates.

Small aliquots (1.5g) of magnesium stearate was added every 15 minutes throughout the coating process into the fluidized bed coater through an external feeding port. Silicon dioxide (1g) was added into the coating chamber and allowed to mix for 20 minutes before the coated microparticles were collected and cured in the oven at 40°C for 24 hours.

Table 5-2: Processing parameters for drug loading and polymer coating are shown.

Processing conditions	**Drug layering**	**Sustained release coating**
Amount of starting material (g)	100g	100g
Nozzle size (mm)	0.5	0.5
Inlet air temperature (°C)	70 - 80	30-35
Product temperature (°C)	40 – 45	18-20
Atomization pressure (bar)	2	1.5
Fluidisation air velocity (m^3/hr)	18 ±0.5	18 ± 0.5
Spray rate (g/min)	2-2.5	1.8-2
Weight gain (%)	50	16, 25, 40

After curing, the sustained release microparticles were weighed and placed in a sieve shaker with meshes placed in order of 710µm, 255µm, 250µm, 180µm, 125µm and 90µm and shaken at 70 amplitude for 10 minutes. The portion of sustained release micropellets in the size range of 125-250µm were weighed and the percentage yield was calculated (Equation 5-1). The sze of 125-250µm was selected for non-agglomerates of the sustained release micropellets which was confirmed with light microscopy.

Percentage yield = $\frac{\text{Weight of coated microparticles in } 125-250\mu\text{m size range}}{\text{Intiail weight of microparticles before coating}}$x100 [Equation 5-1]

5.2.3 Light microscopy and particle size measurement by laser diffraction

Coated microparticles were observed for morphology and aggregation using light microscopy (GXCAM-5, 0.5x CCD adapter, GT vision ltd. the UK). The sample was mounted onto slides before observation using objective lens PL 5/0.2 and a magnification of 50.

Particle size measurements of the sustained release microparticles were made using a Sympatec HELOS/RODOS (Sympatec GmbH, Germany) using R5 lens. The cellets 100 and sustained release microparticles were depressed with compressed air at 2.0 bar pressure to obtain particle size measurements. The average particle size was described as D_{50} to correspond to the particle size bellow which 50% of the particles by volume are smaller.

5.2.4 Incorporation sustained release microparticles into jellies

Three jellies were prepared, formulations 1-3 according to Chapter 4 (Section 4.2.7, Table 4-3) . Preparation of jellies containing coated gliclazide microparticles at coating level 25% (CL25) are shown below.

Formulation 1 (F1; free-standing jelly): Dry powder mixture of sodium alginate (0.5% w/v), guar gum (0.5% w/v), coated microparticles (0.71% w/v) and dicalcium phosphate dihydrate (0.4% w/v) were added to 20mL of deionized water and mixed

using a spatula. The concentration of the ingredients indicates the concentration in the final jelly formulation. The mixture was stirred until the polymer was dissolved and particles dispersed. Citric acid powder (2% w/v) was then added to the above dispersion and mixed for 30 seconds before leaving the jelly to set for 5 minutes.

F1 was also manually fragmented to 4mm pieces using a spatula to account for chewing for dissolution testing.

Formulation 2 (F2; granular jelly): Dry powder mixture of sodium alginate (2% w/v) and coated microparticles (0.71% w/v) were added to 10mL of deionized water and mixed using a spatula. The concentration of the ingredients indicates the concentration in the final jelly formulation. The mixture was stirred until the polymer was dissolved. Calcium chloride aqueous solution (0.3% w/v) was then added to the above dispersion and stirred for 10 seconds until a granular jelly consistency was obtained.

Formulation 3 (F3; granular jelly): Dry powder mixture of sodium alginate (0.5% w/v), low-acyl gellan gum (0.5% w/v) and coated microparticles (0.71% w/v) were added to 10mL of deionized water and mixed using a spatula. The concentration of the ingredients indicates the concentration in the final jelly formulation. Calcium chloride solution (0.15% w/v) was added to the above dispersion stirred for 10 seconds until a granular mix was obtained.

5.2.5 Ultraviolet-visible spectroscopy analysis of gliclazide

A standard Ultraviolet-Visible (UV) calibration curve for gliclazide in phosphate buffer pH 7.4 (PB 7.4); 50mL of 0.2M of potassium dihydrogen orthophosphate and 39.5 mL of 0.2M sodium hydroxide (NaOH) were mixed and diluted to 200mL with water) and

Simulated Gastric Fluid (SGF); 250mL of 0.2M sodium chloride and 425mL of 0.2M hydrochloric acid (HCl) were mixed and diluted to 1000mL with water) (British Pharmacopoeia, 2018a, 2018b). Gliclazie test solutions (0.0016 to 0.053mg/mL were prepared by diluting a stock solution (0.067mg/mL) of gliclazide in dissolution media PB 7.4 or SGF. A UV-spectrophotometer (T80; PG Instruments Ltd., UK) was used to analyse each sample with buffer media PB 7.4 and SGF used as blank at 226nm wavelength. Absorbances obtained for each known concentration were plotted to obtain a calibration curve covering the dissolution concentrations (5% - 200% of drug release).

The influence of jellies on gliclazide UV absorbance was investigated by dissolving the three jellies (prepared as described in Section 5.2.4 but without the sustained release microparticles) in 900mL of PB 7.4 and a UV spectra scan (400-190nm) is performed using UV-spectrophotometer (T80; PG Instruments Ltd., UK). Each component of the jellies (sodium alginate, guar gum, dicalcium phosphate dihydrate, citric acid) was also dissolved separately in 900mL PB 7.4 and UV spectra scans performed.

5.2.6 Determination of solubility of gliclazide

The equilibrium solubility of gliclazide was determined using the shake-flask method. A series of aqueous solutions with pH levels ranging from 1-12 were prepared using serial dilutions of 0.1M HCl (pH 1-7) and 1M NaOH (pH 13-8) with deionized water. The pH was measured using a pH-electrode (WTW inoLab pH 720 with WTW pH-electrode SenTix 42, WTW GmbH; Germany) before and after addition of excess amount of gliclazide. After the addition of gliclazide, the pH level of the solutions was

adjusted using HCl (0.1M or 1M) and NaOH (0.1M or 1M) and measured every 24 hours to maintain the desired pH. The sample was left on the shaker (Roller Mixer SRT9, Stuart, manufactured in PRC) with amplitude 16 mm and frequency 20 min^{-1}) for a total of 72 hours. Two-milliliter samples were taken from each solution at different pH levels and centrifuged (MiniSpin Plus, Eppendorf AG, Hamburg) at 14500 rpm for 15 min. Aliquots of 1mL or 0.1mL of the supernatant were placed in 25mL or 100mL volumetric flask and made to volume using PB 7.4. The concentration of dissolved gliclazide was determined at 226nm using UV-spectroscopy (T80; PG Instruments Ltd., UK). Measurements were made in triplicates.

5.2.7 Dissolution testing of coated gliclazide microparticles with and without jellies

All dissolution tests were conducted in triplicate using apparatus II dissolution with a paddle rotation speed of 100rpm (DIS 6000, paddle apparatus NE4-COP, Copley Scientific, UK). The dissolution tests were performed in 900mL PB 7.4 or SGF for 14 hours at 37°C. UV-spectrophotometer (PG Instruments Ltd., UK) at wavelength 226nm was used for detection of released gliclazide.

Commercial gliclazide SR 30mg tablet (Dimicron, Servier) was used as a reference for dissolution testing. Dissolution testing was carried out using the coated sustained release gliclazide microparticles (equivalent to 30mg of gliclazide) at varying coating levels (CL16, CL25, and CL60). Milled gliclazide, a physical mixture of milled gliclazide and Cellets 100, and gliclazide layered Cellets 100 were also tested for drug release. Coated gliclazide microparticles at CL25 were incorporated in the three jelly F1-3 (prepared as described in Section 5.2.4) and tests for drug release in PB 7.4. Placebo

jellies were prepared without the sustained release microparticles and subjected to dissolution testing to obtain baseline dissolution profiles. Drug release from jellies containing the microparticles was calculated by deducting the jelly baseline absorbance from the total UV absorbance value at each sample time points. In an alternative method, placebo jellies were placed in the dissolution bath with PB 7.4 and SGF and were allowed to dissolve completely. Coated gliclazide microparticles (CL25) was then placed in the dissolution bath for drug release testing. The UV absorbance of the placebo jelly solutions were auto-zeroed before dissolution testing began for coated microparticles.

The pH change of the dissolution media PB 7.4 during dissolution testing of placebo jellies was measured using an ELIT PH2011 pH electrode (NICO2000 Ltd, UK.) and recorded using NICO2000 software and 6-channel pH monitor (NICO2000 Ltd, UK).

5.2.8 Data analysis

The similarity factor is used to determine the closeness between two dissolution profiles; this was calculated using Equation 5-2 (Food and Drug Administration, 1997).

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

[Equation 5-2]

Where n corresponds to the number of time points and R_t corresponds to drug release of Diamicron reference at time t, and T_t corresponds to drug release of the test product at time t. The closeness of the dissolution profile is indicated when f_2 is between 50 and 100.

Prism Graphpad (version 7.0) was used to assess normality of dissolution profiles; normal distribution was rejected ($p<0.05$). The Mann-Whitney U test was applied to compare significant differences between dissolution profiles and significance differences was noted for $p \leq 0.05$.

5.3 Results

5.3.1 Light microscopy and particle size distribution

Successful drug layering and coating processes were achieved for the microparticle coating using a fluidised bed coater. The yields for polymer coatings at coating levels (CL) CL16, CL25 and CL60 were 99.5%, 99.0% and 79.0% respectively and agglomerates (sieve fractions above the size of 250μm confirmed using light microscopy) was 0.5%, 1.0% and 21.0% respectively. It can been seen that at higher coating level (CL60), particles started to agglomerate during coating.

A representative light microscopy image of coated microparticles at CL25 is shown in Figure 5-3; mostly spherical particles with smooth surfaces is observed. The D_{50} of the coated microparticles at CL25 were 198μm ± 4.3 and for Cellets 100 were 160.33 ± 2.1 μm.

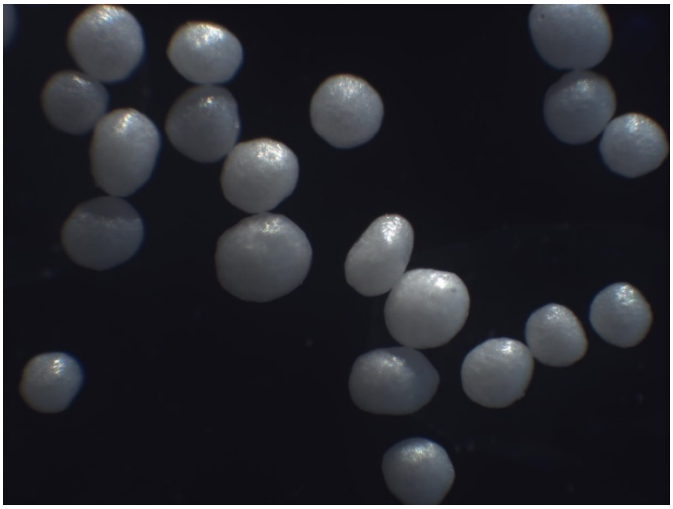


Figure 5-3: Light microscopy results of sustained release CL25.

5.3.2 Calibration curve and solubility profile of gliclazide

A representative calibration curve is shown for gliclazide in PB pH 7.4 (Figure 5-4a), and good linearity was obtained (R^2=0.9997). The equilibrium solubility of gliclazide shows that the solubility is dependent on pH and increases with increasing pH level from pH 6 (Figure 5-4b).

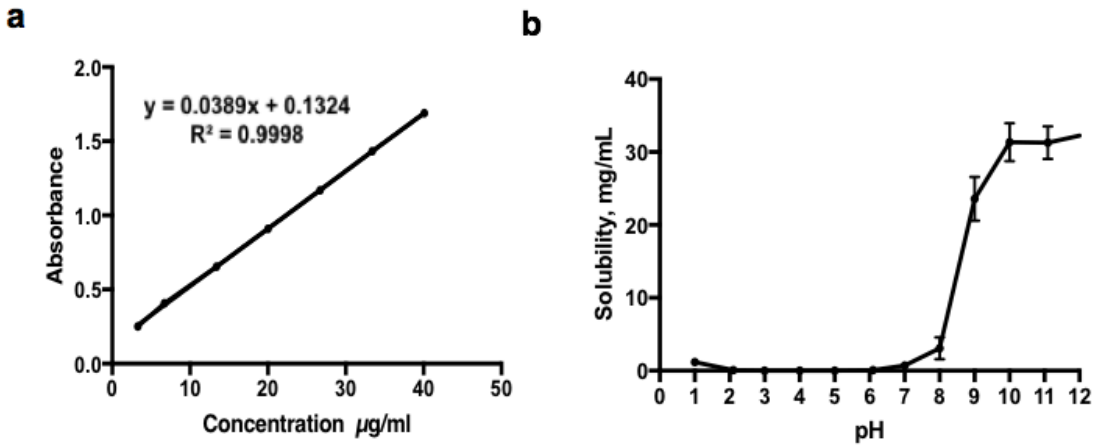


Figure 5-4: Graphical representation of a) Calibration of gliclazide in PB 7.4 (n=3), b) equilibrium solubility of gliclazide at different pH levels (n=3).

5.3.3 Gliclazide release from sustained release microparticles

Figure 5-5 shows the drug release profile for coated microparticles at coating levels CL16, CL25 and CL60, milled gliclazide, gliclazide Drug Layered (DL) Celles 100, a physical mixture of gliclazide and Cellets 100 and Diamicron in PB 7.4. The dissolution of milled gliclazide, drug layered Cellets and physical mixture of milled gliclazide and Cellets showed similar dissolution profiles. A ranking order of drug release is DL Cellets 100 > gliclazide > physical mixture of gliclazide and Cellets 100 > CL16 > CL25 > Diamicron > CL60. Microparticles at coating level CL16 showed a much faster drug release than Diamicron (f_2 18.5, $p<0.0001$) while at CL60 (f_2 23.3, $p<0.0011$) showed a much slower drug release than Diamicron. Coated microparticles at CL25 showed a f_2 value of 54.2 ($p=0.6653$) to Diamicron, demonstrating equivalent drug release according to Food and Drug Administration (FDA) guideline (Food and Drug Administration, 1997).

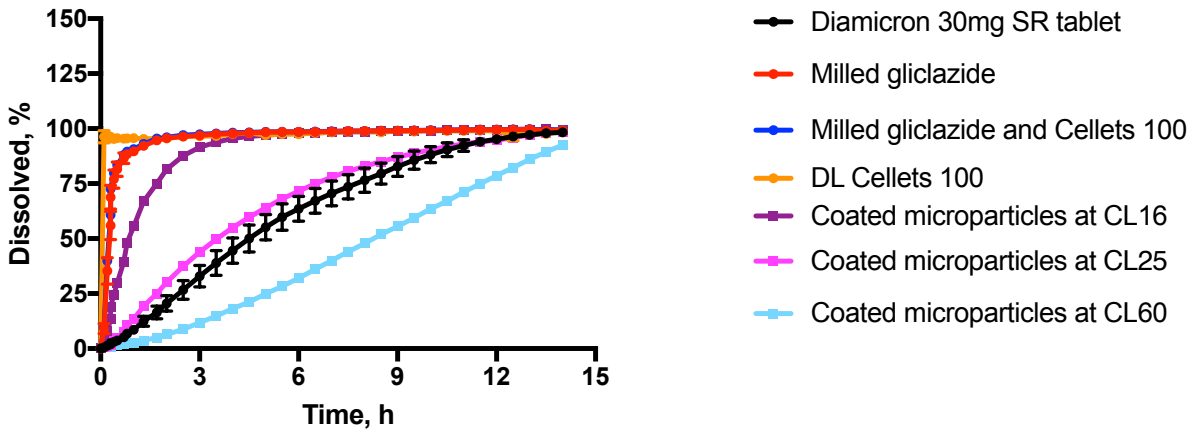


Figure 5-5: A comparison of drug release for commercial reference tablet Diamicron, milled gliclazide, physical mixture of milled gliclazide and Cellets, DL Cellets, and coated microparticles at CL16, CL25 and CL60 in PB 7.4 (n=3).

5.3.4 Gliclazide release from sustained release microparticles incorporated in jellies

UV spectrum scans of placebo F1 in PB 7.4 showed a peak in the same UV wavelength expected for gliclazide (226nm) (Figure 5-6a), and citric acid was found to be the main ingredient in F1 to contribute to this peak (Figure 5-6b). The absorbance for gliclazide appeared without interference from F2 and 3 (Figure 5-6c and 5-6d).

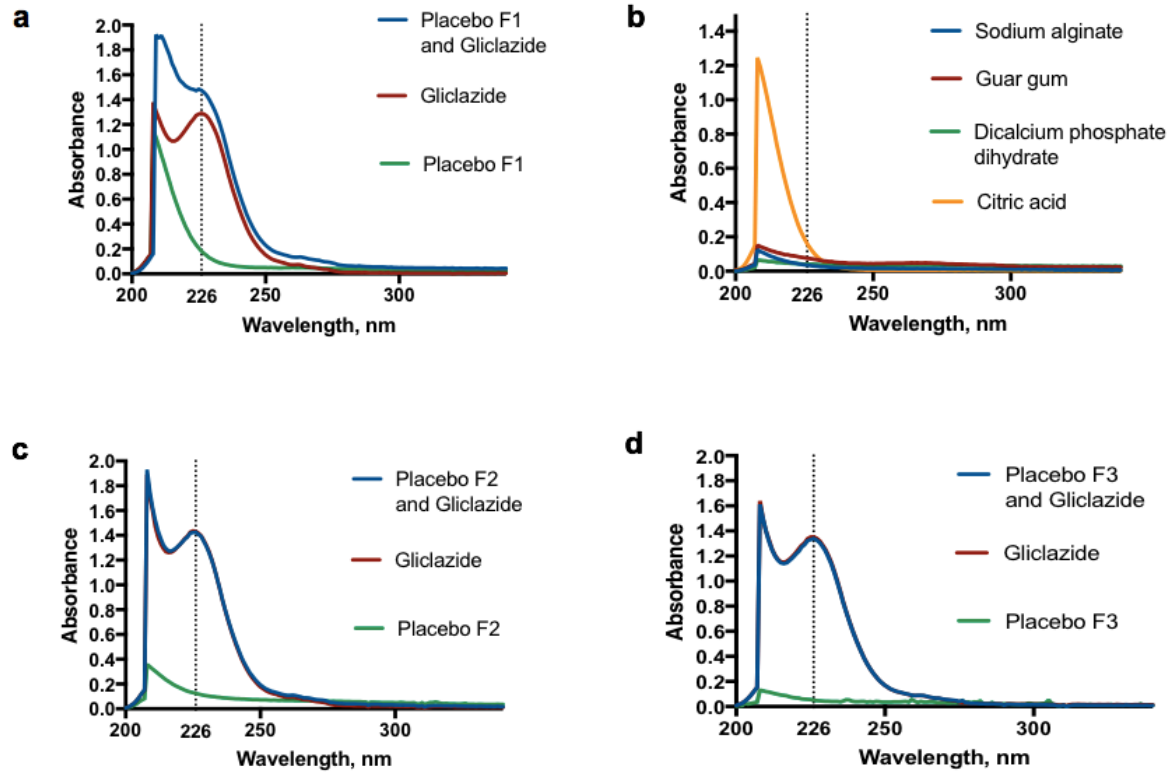


Figure 5-6: UV spectra scans for glicllazide, placebo jellies and mixture of gliclazide and placebo jelly for a) Placebo F1, b) the excipients contributing to peak in placebo F1, c) Placebo F2 and d) Placebo F3, in PB 7.4.

Figure 5-7 showed drug release from coated gliclazide microparticles at coating level CL25 incorporated into jellies. Dissolution profiles of the microparticles incorporated in jellies show much slower release compared to microparticles without jellies. A ranking order of drug release was CL25 > Diamicron> F3> F2> F1 small subunits > F1 intact. The similarity factor between drug release of CL25 and the three

formulations and between F1 intact and fragmented are shown in Table 5-3. Drug release for CL25 and F1 (intact and fragmented), F2 showed significant differences. No significant differences were found for drug release for CL25 and F3. F1 intact and fragmented showed f2> 50 demonstrating equivalent drug release (Table 5-4) (Food and Drug Administration, 1997). Monitoring of pH changes during the dissolution test of placebo jellies without microparticles shows that pH level of the dissolution media decreased considerably with F1 from pH 7.4 to 7.0 and no apparent changes were noticed for F2 and 3 (Figure 5-8).

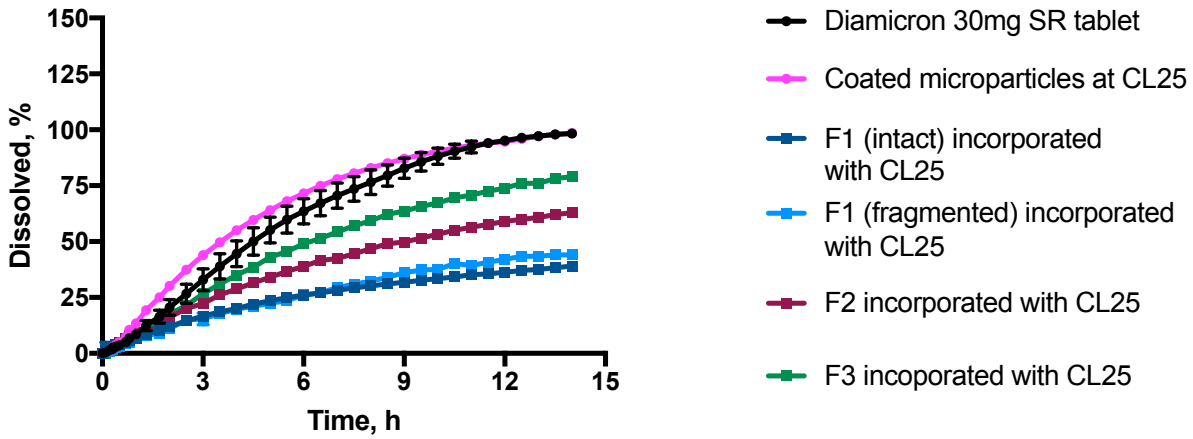


Figure 5-7: A comparison of drug release for Diamicron, coated microparticles at CL25 and F1-3 incorporated with CL25 in PB 7.4 (n=3).

Table 5-3: A comparison of similarity factor and statistical differences between drug release for CL25 and F1-3 (significance was marked as * $p \leq 0.05$ and ** $p \leq 0.01$).

Comparison	**Similarity factor**	**p-value**
CL25 and F1	19.9	<0.0018**
CL25 and fragmented F1	20.4	<0.0004**
CL25 and F2	27.4	0.0425*
CL25 and F3	38.4	0.0623
F1 intact and fragmented	84.4	0.2523

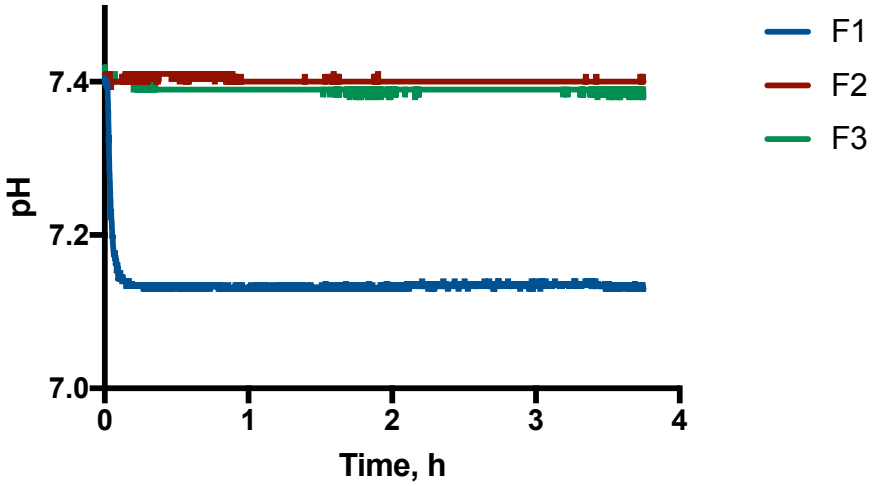


Figure 5-8: The effect of jelly dissolution on the pH level of PB 7.4

Figure 5-9 shows gliclazide release from microparticles CL25 after placebo jellies were dissolved in the dissolution media (PB 7.4) before dissolution test commenced. Similar to microparticles incorporated into the jellies for dissolution testing, slower dissolution rates were noted compared to microparticles alone (without jellies). Significant differences were observed for placebo F1 and placebo F2 compared to drug releases for CL25 (without jellies) (Table 5-4), at ranking order for drug release, CL25 > Diamicron > dissolved placebo F3> dissolved placebo F2> dissolved placebo F3. For each jelly, there is an increase in release rate from coated microparticles in PB 7.4 with pre-dissolved jelly compared to microparticles incorporated into jelly before dissolution testing; however, the difference was not significant (Figures 5-7 and 5-9).

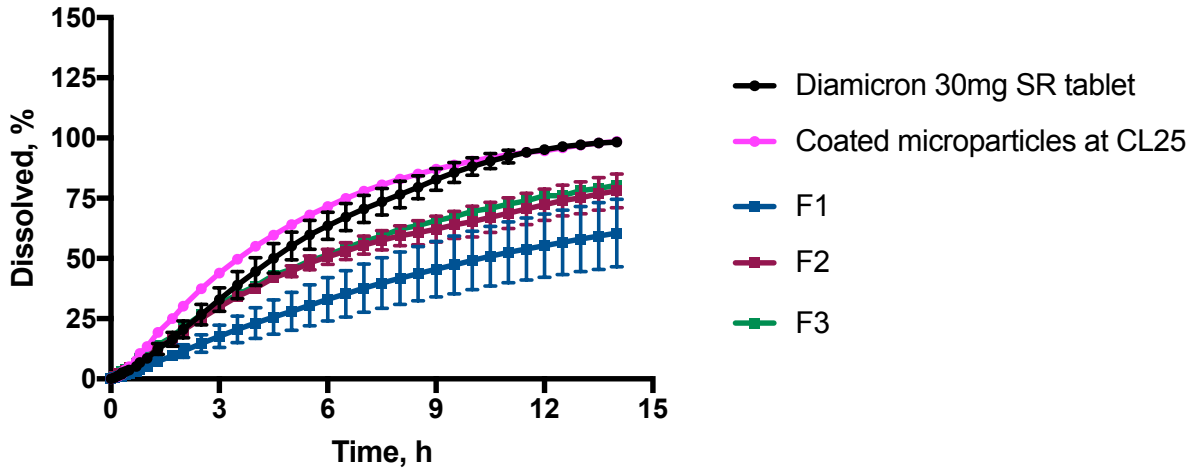


Figure 5-9: A comparison of drug release for Diamicron, coated microparticles at CL25 and CL25 after placebo F1-3 were dissolved in the media (PB 7.4) before testing (n=3).

Table 5-4: A comparison of similarity factor and statistical differences between drug release for CL25 and placebo F1-3 (significance was marked as * $p \leq 0.05$ and ** $p \leq 0.01$).

Comparison	Similarity factor	p-value
CL25 and placebo F1	23.9	<0.0018**
CL25 and placebo F2	36.5	<0.0425*
CL25 and placebo F3	40.3	0.0623

Figure 5-10 shows gliclazide release from microparticles CL25 after placebo jelly formulations were dissolved in the dissolution media SGF. There is no significant difference in drug release profiles for gliclazide release from CL25 alone and after placebo F1-3 were dissolved. Drug release in SGF was lower than in PB 7.4 (Figure 5-9).

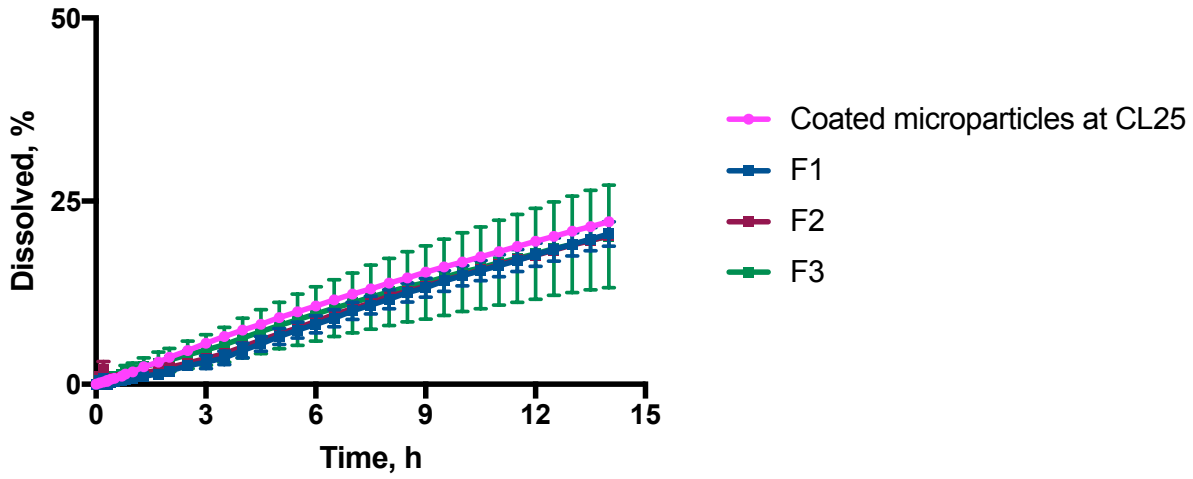


Figure 5-10: A comparison of drug release for coated microparticles at CL25 and CL25 after placebo F1-3 were dissolved in the media (SGF) before testing (n=3).

5.4 Discussion

The sustained release coated microparticles showed low aggregation at coating levels 16% and 25%; increased aggregation was noted with increased coating level (60%). Larger particles are expected to elutriate up in the fluidised bed column at a slower velocity than smaller particles, the slower velocity of particle movement for higher coating level (60%) may have resulted in greater proximity between the particles and thus liquid binding amongst the particles during coating (Iley, 1991). Light microscopy showed mostly spherical particles with a smooth coating surface at 25% coating level which is desirable for achieving uniform dissolution characteristics. The average particle size produced for coating level at 25% was less than 200 µm. Reports on perceptibility by adults of micropellets in gels prepared with carboxymethyl cellulose or carbomer, suggests that pellet sizes less than 350 µm are imperceivable or have low perception in the oral cavity regardless of the polymer concentrations (Kluk & Sznitowska, 2014). Another study tested acceptability of gels of HPMC containing

MCC Cellets in adults and found that oral grittiness (rough mouthfeel) increased with increasing particle size; the study concluded that particles below 263 μm showed low perception of grittiness (Lopez et al., 2016). Increasing viscosity of the gel also reduced perceived grittiness (Lopez et al., 2016). A rough mouth feel of the coated microparticles can result in poor patient acceptability; the prepared sustained release gliclazide are much smaller than the threshold size described in these studies, indicating they will likely have good patient acceptability.

The solubility of gliclazide increased with increasing pH due to the weakly acidic nature of gliclazide (pKa 5.8) (Jondhale, Bhise, & Pore, 2012). Higher pH levels result in greater ionisation of gliclazide and thus an increase in solubility is observed (Skripnik 2016). The solubility data also showed that a slight change in pH level in the range of pH 6-10 will result in a large difference in the solubility of gliclazide.

The Food and Drug Administration (1997) guidance advises three dissolution media to be tested for BCS class II drugs (applicable to gliclazide as a poorly water soluble drug). In this study only one dissolution media (phosphate buffer pH 7.4) was used for the primary dissolution tests considering the low solubility of gliclazide at low pH levels such as pH 4.5 and pH 1.2 relevant to simulated fed and fasted stomach conditions. No official dissolution test was recorded in the pharmacopeia at the time of this study for sustained release gliclazide dosage forms; therefore the dissolution method recommended for immediate release formulations was taken forward to attain an indication on comparative dissolution profiles of coated microparticles with and without incorporation into jellies.

Gliclazide layered onto Cellets showed rapid release and almost superimposed dissolution results to milled gliclazide indicating that the sustained release coating is the only contributor to differences observed in dissolution for varied coating thickness levels. Coating thickness is known to influence the rate of dissolution. Diffusion from a sphere is described by Fick's law of diffusion (Laghoueg, Paulet, Taverdet, & Vergnaud, 1989). The drug release is determined by surface area, thickness of the transport barrier such as the film coat and the concentration gradient between the drug concentration on the substrate surface and the surrounding medium. The thickness of the film coat determines the length for drug diffusion pathway, thinner coats result in a faster dissolution and thicker coats result in slower dissolution, as observed in this study in drug release from coated microparticles of different coating levels (Ozturk et al., 1990).

The potential influence of jellies on gliclazide UV detection was determined. Citric acid (used in F1) is reported to absorb and produce broad UV bands due to the presence of unionised or ionised carboxyl groups. The presence of this jelly influenced the UV absorption of gliclazide (Krukowski, Karasiewicz, & Kolodziejski, 2017). This influence was mitigated by obtaining a baseline dissolution profile of the placebo jelly to account for the increase in UV absorbance during dissolution testing of sustained release microparticules.

Retardation of gliclazide dissolution was observed through the entire dissolution duration in phosphate buffer media when the microparticles were incorporated into the jelly formulations. The jelly formulations were prepared using sodium alginate cross-linked with calcium. The jelly formulations immersed in phosphate buffer result in ion-

exchange between sodium in the phosphate buffer media and calcium in the jelly matrix, a process which loosens the structure of the gel network and over time to facilitate the dissolution of the jellies (Bajpai & Sharma, 2004; Voo, Ooi, Islam, Tey, & Chan, 2016). In this study, the jelly formulations were observed to completely dissolve within two hours. The jelly matrices are expected to provide an additional barrier for drug release possibly through a combination of drug diffusion through the jelly network and jelly dissolution/erosion similar to hydrophilic matrix systems for sustained drug release. For this reason, alginate is used for encapsulation of drugs for controlled release drug delivery (Voo et al., 2016). Manrique-Torres et al. (2014) found retardation of atenolol, amlodipine, carbamazepine, and warfarin with the use of gum and starch-based thickening agents. Slower dissolution was observed with greater thickening, indicating greater entanglement network or solid-like behavior impairing drug release (Manrique-Torres et al., 2014).

The extent of drug release retardation by the three jellies was different; at pH 7.4, the rank order of drug release from incorporated microparticles was F3> F2> F1. This can be linked to the different preparation methods and jelly compositions especially the amount of calcium salt in the jelly formulation. F1 has the highest calcium salt concentration and showed slowest drug release, due to a higher level of ion exchange between sodium (in the phosphate buffer) and calcium (in the jelly) being required for jelly dissolution. In addition, previous reports show that an increase in calcium concentration resulted in slower drug release from calcium alginate beads due to an enhanced structural network, reduced water intake and subsequently greater drug entrapment (Bajpai & Sharma, 2004; Pawar et al., 2015; Voo et al., 2016). It has been previously reported with increasing cross-linkage of alginate with calcium, water

uptake decreases (Bajpai & Sharma, 2004). The jellies prepared with lower calcium concentration (F2 and 3) showed lower magnitude of G' (Chapter 4) indicating weaker gel structure and internal crosslinking, thus allowing faster gliclazide release from incorporated microparticles.

Another potential reason for the slow drug release from F1 is the inclusion of guar gum in the jelly composition. Galactomannans such as guar gum are reported to increase the entrapment efficiency of drug and thereby to enhance sustained release (Pawar et al., 2015). In addition, F1 was shown to lower the pH of dissolution media during jelly dissolution (due to the presence of citric acid in the jelly composition), which would further explain the retarded release of gliclazide considering its pH-dependent solubility. The pH level of the dissolution media maintained the same level during the dissolution of F2 and 3.

It was postulated that smaller subunits of F1 in the fragmented jelly to account for chewing was expected to increase gliclazide release by reducing the diffusion pathway in contrast to gliclazide release from intact jelly. However, dissolution of gliclazide in the unfragmented F1 and smaller subunits of fragmented F1 showed similar drug release. It was reported that reducing droplet sizes of xanthan gum thickening agent resulted in faster atenolol release in simulated gastric acid (Manrique, 2015). However, in this study, drug release from the fragmented and intact F1 may be predominantly based on dissolution of the jelly rather than diffusion of fluids and drug through pores in the jelly matrix. Since the dissolution of jellies in phosphate buffer pH 7.4 is ion-exchange mediated there may not be a significant difference in the dissolution of fragmented jelly compared to intact jelly F1, resulting in similar drug

release. This similarity of drug release in intact and fragmented jellies indicates that chewing may not impair the gliclazide release from microparticles incorporated in F1; however, it needs to be taken into caution that chewing might cause impairment to the coating of the sustained release microparticles and increase drug release. This effect needs to be investigated in future studies, possible mitigation strategies if chewing of microparticles does occur is presenting the jelly in a smaller easy to swallow size.

Dissolution testing of coated gliclazide microparticles in dissolution media containing dissolved jellies showed slower drug release compared to the sustained release microparticle alone without jelly. This could be due to the increase in the viscosity of the dissolution media and decrease in media pH in the case of F1. However the extent of drug release retardation was lower in dissolved jellies than microparticles incorporated in intact jelly, although the difference in drug release was not statistically significant. Gliclazide release from coated microparticles with and without jellies were very low in simulated gastric fluid. This was predominantly due to the low solubility of gliclazide at low pH levels.

Gliclazide release from microparticles incorporated in jellies, especially F1, was slower compared to drug release form Diamicron; this can be rectified by using lower coating thickness beneficial for cost saving during production. This study has shown sodium alginate-calcium jellies decreased gliclazide release from sustained release microparticles in phosphate buffer medium. However the extent of this release deduction needs further investigation in dissolution media that better simulate the *in vivo* small intestinal fluids than phosphate buffer, for example using bicarbonate buffers that have lower buffer capacity. This would allow better comparison with the

reference product Diamicron and subsequently provide insight into *in vivo* performance of the novel drug delivery systems. The dissolution apparatus II is limited in reproducing fluid mechanics *in vivo*. The influence of hydrodynamics varies according to the position of the dosage form in the vessel and the paddle speed is set to 50rpm to allow discrimination power between drug release profiles (Armenante & Muzzio, 2001). The dissolution of jelly is likely to vary with varying shear rates and hence the absorption of gliclazide may vary in patients. This would require further investigation *in vivo*. Furthermore, varying of chewing patterns for jelly 1 may also result in variation in dissolution *in vivo* but this requires further investigation of whether the extent chewing would influence gliclazide dissolution.

Dissolution testing in this study using UV detector has provided an insight on potential influences for drug dissolution such as slower drug release with jelly vehicles. However, a more accurate quantification for gliclazide is required using HPLC and the acceptability, palatability and ease of swallowing of the developed instant jellies for needs further investigation *in vivo.*

5.5 Conclusions

Sustained release gliclazide microparticles were developed and “instant” jellies were used as delivery vehicles. All three jelly formulations contributed to decreased drug release from the sustained release microparticles, with F1 (free-standing jelly) showing the greatest effect on drug release retardation compared to F2 and 3 (granular jellies). F1 showed similar drug release between intact jelly and fragmented jelly indicating chewing will not affect drug release from incorporated microparticles. The decrease in drug release from sustained release microparticles in jellies could

reduce the coating level required and thus achieving cost saving in production. The novel drug delivery system using “instant” jellies incorporating sustained release microparticles offer a promising solution for medication administration in patients with dysphagia.

Chapter 6

GENERAL DISCUSSION

The safe administration of tablets and capsules in patients with dysphagia can be challenging and medicines modification (tablet crushing and capsule opening) is sometimes used to facilitate administration (Paradiso et al., 2002). Older patients are often prescribed multiple medicines (Hughes et al., 2016; Morin et al., 2018) and can benefit from sustained release dosage form to reduce pill burden, however, medicines modification of sustained release dosage forms can be dangerous and result in toxicity (Schier et al., 2003). The aim of the study was to understand the practical issues in administering sustained release dosage forms in older patients and develop novel sustained release dosage forms that are safe to swallow and acceptable to these patients.

Existing literature explored medicines modification and the occurrence of sustained release dosage form modification was recognised, however, the extent of modification occurring for these dosage forms was not reported (Fodil et al., 2017; Mc Gillicuddy et al., 2016; Paradiso et al., 2002; Stubbs et al., 2008). The study of medicines modification (Chapter 2) focused on difficulties in administering sustained release dosage forms to older adults with dysphagia. The study highlighted that sustained release dosage forms are prescribed to patients with dysphagia (10% of medicines prescribed) and were modified by tablet crushing or capsule opening to aid swallowing (49%). The population is aging and prescribing and incidences of modification of sustained release dosage forms in this cohort may grow. The study also showed swallowing aids were sometimes used to facilitate swallowing of modified dosage forms such as thickened fluids, yogurt and jellies. There were also cases of swallowing the dosage form whole with jelly. This study was designed as a prospective study involving medicines charts to enable data to be obtained across wards and relied on

the nurses input on details of medicines modification, in hindsight, an observation study may have given first-hand insight into the clinical situation.

Swallowing aids such as thickened fluids, yogurt and jelly were used in the medicines modification study but whilst there was literature supporting improvement of safety of swallowing with thickened fluids (Clavé et al., 2006; Logemann et al., 2008) there was little or no information for jellies and yogurt (Nagaya et al., 2004; Sonoi et al., 2016). An *in* vitro throat model was used to assess processing of these products and compare findings with rheological and textural characteristics of the thickened fluids, jellies and yogurt to determine if there are universal parameters that can predict *in vitro* performance (oral transit time and bolus length). At the time of this study, previous literature used the throat model for the processing of thickened fluids (Hayoun et al., 2015; Mackley et al., 2013; Mowlavi et al., 2016). This was the first study that explored application of the *in vitro* throat model for processing of semi-solids for pharmaceutical application and the first study that considered the combination of *in vitro* oral transit time and bolus length in the airway divide as *in vitro* markers of velocity and cohesiveness of bolus transit. Previous studies showed, an increase in oral transit time was observed with increased thickening (Clavé et al., 2006; Dantas et al., 1990; Tashiro et al., 2010). *In vitro* processing of thickened fluids in this study showed increase in oral transit time and reduced bolus length in the airway divide with increasing thickening indicating slow and cohesive bolus transfer as important considerations for safety of swallowing. Increasing in oral transit time and reduced bolus length correlated with viscosity, yield stress firmness and cohesiveness of thickened fluids. Jellies paralleled processing findings in the *in* vitro throat model of honey and spoon thick thickened fluids for oral transit time and reduced bolus length

but show lower viscosity, yield stress, firmness and cohesiveness instrumental values compared to the thickened fluids. The rheological and textural characterisation of products used in this study cannot be used to predict *in vitro* processing behaviour, the throat model did however, show potential in differentiating the processing behaviour of different products. The *in vitro* throat model is a static model whereas the *in vivo* swallowing mechanism is complex, for example, peristaltic contractions in the pharynx help to move the bolus towards the oesophagus (Chadwick & Jolliffe, 2009), which cannot be simulated using the *in vitro* model. Further investigation is needed into the correlation between *in vivo* and *in vitro* results and possibly calibrate the *in vitro* throat model accordingly. A acceptability study (Chapter 3) conducted in healthy volunteers using 5-point likert scale for rating showed commercial free-standing and granular jellies were found easier to swallow than thickened fluids in healthy volunteers and the *in vitro* findings for jellies showed potential for jellies to be assessed further *in vivo* for safety of swallowing.

The findings from the *in vitro* study and medicines modification led to development of instant jellies (forms in less than 10 minutes) to use as vehicles for the administration of sustained release microparticles for older adults with dysphagia. Sodium alginate and calcium salts were the primary components used to develop free-standing and granular jellies without heat. The combination of sodium alginate and calcium salt is listed in existing patents (Hong et al., 2012; Masumoto et al., 2016; Yasushi et al., 2016) but the quality of the final products and safety of swallowing is unknown. The combinations of sodium alginate and calcium salt jellies were assessed according to a visual criteria for commercial products, any residual water due to gel contractions and time taken for final product to form. The jellies were compared using texture and

rheological analysis to mimic the properties of commercial jelly products which are familiar to patients as desserts or used as swallowing aids for tablets and capsules in Japan (Tsuji et al., 2006) and in our clinical study (Chapter 2). The final jellies developed in this study mimicked the behaviour of commercial jellies (slow oral transit and cohesive bolus movement) in the *in vitro* throat model. The study found variation in water hardness and volume can compromise jelly formation in terms of quality and time for the jelly to form which would result in additional costs of providing deionized water for the dosage form. The jellies require multiple sachets of components which may be challenging and bulky for patients, however, this may be mitigated using bespoke packaging. These additional costs however, may be less than the costs incurred for missed doses, subtherapeutic dosing as a result of swallowing difficulties and manipulation of dosage forms.

The jellies developed in Chapter 4 were used as a delivery vehicle for sustained release microparticles for older adults with swallowing difficulties. Simply mixing microparticles with existing commercial jellies may compromise the jelly performance for swallowing and would not allow integration of the microparticles sufficiently into the jelly structure for complete and safe delivery. Although microparticles were not favoured by patients due to potential impact on taste when consuming with meals and the use of mini-tablets poses the risk of chewing due to sensation of grittiness reported in sizes above 263 μm (Liu et al., 2016; Lopez et al., 2016). The sustained release microparticles (198μm) developed in this study were smaller than the reported sizes for grittiness (above 263 μm) to reduce the risk of chewing (Kluk & Sznitowska, 2014; Lopez et al., 2016). The sustained release microparticles developed using cellet 100 and coated with gliclazide and sustained release coating consisting of Eudragit NM

and talc using fluid bed technology for model drug gliclazide showed similar drug release compared to the marketed reference drug Diamicron in phosphate buffer pH 7.4. The jellies however, sustained gliclazide release further. Sodium alginate and calcium combination is previously reported to retard drug release (Bajpai & Sharma, 2004; Pawar et al., 2015; Voo et al., 2016) and this study validated these findings with increasing sustained release observed with increased calcium concentration. The free-standing jelly was expected to show faster gliclazide release upon fragmentation to account for chewing, similar to the findings by (Manrique, 2015). However, both chewed and whole forms of the free-standing jelly showed similar drug release profiles potentially due to ion-mediated dissolution (Bajpai & Sharma, 2004; Voo et al., 2016). This study was a proof-of-concept and requires further investigation with biorelevant dissolution media that better simulates the *in vivo* small intestine fluids such as bicarbonate buffers and there is also a requirement of more accurate quantification of gliclazide with HPLC to eliminate potential influence of jelly. The jellies integrated with sustained release microparticles offer a novel platform for drug delivery for patients with swallowing difficulties. A further investigation is however required for patient acceptability and palatability for these jelly dosage forms similar to previous acceptability and palatability study performed by Lopez et al. (2018).

6.1 Final conclusions

The study found challenges in administration of sustained release dosage forms for patients with swallowing difficulties and hazardous practices of administration by crushing tablets and opening capsules to facilitate administration. The developed jellies showed similar safety features to thickened fluids in the *in vitro* throat model but requires validation from *in vivo* studies. The jellies with sustained release

microparticles can be potentially useful platform of dosage forms for older adults with swallowing difficulties and may also be suitable for paediatrics.

6.2 Future work

The swallowing process is much more complex than the static throat model used in this study and a correlation needs to be established between *in vivo* and *in vitro* throat model to provide validation for results that are obtained from the *in vitro* throat model and for further investigation using the developed jellies with integrated microparticles. The throat model is designed for liquids and jelly products did show variable results, this would require further investigation *in vivo,* particularly the effect of chewing variability on cohesive bolus transit and safety of swallowing for the free-standing jelly.

A acceptability and palatability study is required for the instant jelly with sustained release microparticles to establish whether older patients would accept these dosage forms. A acceptability study is also required for preparation of the dosage form and ease of use of potential packaging options. The ease of swallowing *in vivo* needs to be investigated for the developed jellies. Although the focus of this thesis is older adults, these dosage form may be potentially useful for the paediatric population.

Further studies into *in vitro* drug release in biorelevant media would be worthwhile for *in vivo* predictions and better quantification of gliclazide drug release is required using HPLC to eliminate potential jelly influences in quantifying gliclazide using UV. The *in vitro* dissolution study showed chewing may not effect dissolution of gliclazide but the effect of chewing of jellies and microparticles needs further investigation *in vivo.*

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Appendices

Appendix I

AN INVESTIGATION INTO THE USE OF MODIFIED RELEASE MEDICATIONS IN OLDER ADULTS WITH SWALLOWING DIFFICULTIES

Research protocol: An investigation into the use of modified release medications in older adults with swallowing difficulties

An investigation into the use of modified release medications in older adults with swallowing difficulties

Research Protocol

Version 4.0
31st October 2014

UH Protocol number: **LMS/PG/NHS/00161**

REC reference: **14/YH/1105**

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SYNOPSIS

Title	An investigation into the use of modified release medications in older adults with swallowing difficulties
Chief Investigator	Miss Simmi Patel– University of Hertfordshire
Principal Investigator	Mr. Narinder Bhalla- Cambridge University Hospitals NHS Foundation Trust.
Aim	The aim of this study is to determine the extent and nature of problems with administration of modified release oral medications in older adults with swallowing difficulties and how these problems are solved in practice.
Objectives	• To find out the frequency of prescribing modified release medications for older adults with swallowing difficulties. • To find out if any changes are made in administering or prescribing of modified release medication in this patient population. • To analyse the problems associated with changes that are made with modified release medications to aid administration for older adults with swallowing difficulties. • To determine the types of modified release oral medication and the disease categories that causes the most concerns for administration of modified release medications in older adults with swallowing difficulties.
Setting	Secondary care- Cambridge University Hospitals NHS Foundation Trust.
Sample size estimate	A sample size of 209 was calculated using a population proportion estimate.
Eligibility criteria	• Patients must be aged 65 or over • Patients with swallowing difficulties • Medicines reconciliation must be complete.
Summary of method	This is a prospective study using medical notes and drug charts to collect information on the use of modified release oral medications in older adults with swallowing difficulties. A data collection pro forma will be used to determine

	whether the patient is prescribed any modified release medications, whether this has been changed to an alternative to manage administration in patients with swallowing difficulties, whether this medication has been manipulated (i.e. crushed tablets or opened capsules) or whether there are any other methods used to make medicines easier to swallow such as mixing with foods.
Duration of study	The duration of this study is six months
Outcome measures	• The frequency of prescribing modified release medications for older adults with swallowing difficulties • The frequency of changing modified release medications to alternative medications to aid administration for older adults with swallowing difficulties. • The frequency of modification of modified release medications to aid administration for older adults with swallowing difficulties.

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STUDY BACKGROUND INFORMATION AND RATIONALE

1. Introduction

The proportion of older adults (aged 65 and over) in the population is rising; it has been estimated that the world population of adults aged 60 and over will be 2 billion by 2050 and by 2035, 23% of the UK population will be 65 or over (1,2). Older adults tend to have a greater need for health and social care compared to their younger counterparts and account for 50% of prescribed medicines (3,4). Older adults are the major users of medication, particularly as they are commonly on multiple medications due to comorbidities. One of the challenges faced with administering medication to older adults is swallowing difficulties, which is more prevalent in older adults than the younger cohort. It has been reported that swallowing difficulties occur in 11% of older adults amongst the general population, 12% in hospitalised older adult patients and 68% of institutionalised older adult patients (5–7). This problem is expected to become more widespread as the population ages.

2. Healthy swallowing process

The process of swallowing (also known as deglutition) is a rapid and synchronised process and it is generally explained in terms of three phases; the oral phase, the pharyngeal phase and the oesophageal phase (8).

The oral phase involves chewing food and mixing it with saliva to form a pellet (9). This pellet of food is then propelled towards the pharynx. Before the pellet of food enters the pharynx, the larynx is closed so that the pellet of food does not enter into the lungs. After the movement of the pellet of food through the pharynx (the pharyngeal phase), it enters the oesophagus and is moved towards the stomach through contractions (the oesophageal phase) (10).

3. Swallowing difficulties

Swallowing difficulties are defined as the "eating and drinking disorders which may occur in the oral, pharyngeal and oesophageal stages of deglutition" (11). It is more likely to occur in older adults compared to their younger counterparts because of the natural process of ageing, age-related diseases and certain medications (12).

The natural process of ageing can cause swallowing difficulties. This can be caused by poor dentition, and decline in neuromuscular function and muscle mass. This can affect the break down of food to form a pellet and its propulsion during the oral phase. Delays in all three phases of the swallowing process can be observed in older adults (13).

Diseases such as stroke, Alzheimer's disease, Parkinson's disease and other dementia syndromes increase in prevalence with age and are known to cause swallowing difficulties (12,14). It has been reported that the prevalence of swallowing difficulties can affect up to 81% of stroke patients, 70% of patients with Alzheimer's disease and 87 % of patients with Parkinson's disease (15,16).

Medicines can also impair the swallowing process, particularly medicines that cause dry mouth, oesophageal injuries, central nervous system depressants (also referred to as tranquilisers and sedatives), and antipsychotics (13). Although these medications are not specifically used in just the elderly, they are frequently prescribed for older adults. Antipsychotics cause symptoms that mimic Parkinson's disease, one of the symptoms of which includes swallowing difficulties. Medicines that cause dry mouth, for example, sedatives can affect the formation of the pellet of food, reducing its cohesiveness and this can result in residue being left during the swallowing process (17).

Swallowing difficulties can result in severe health implications, including malnourishment, aspiration (when food travels through the respiratory tract) and choking. Aspiration may also lead to pneumonia which in severe cases can lead to death (9,18).

4. Medicine administration in patients with swallowing difficulties

The oral route for adminstering medications is the most popular as it is more convenient for patients. However, it is particularly popular amongst older adults as it can be packaged into dossette boxes to ensure older adults, particularly those on multiple medicines, remember to take their medicines (19).

It is challenging to administer medications through the oral route to patients with swallowing difficulties and there have been studies on medicine administration for patients with swallowing difficulties. Wright (2002) utilised questionnaires for nurses working mainly in nursing homes for older adults in the UK. The report revealed that the most common method employed for medicines administration in patients with swallowing difficulties were to obtain a liquid alternative (88%), followed by crushing or opening capsules (61%) (19). Strachan & Greener (2005) distributed questionnaires to patients in 17 community pharmacies (independents and multiples) in England and Northern Ireland, 68% of patients with swallowing difficulties revealed the need to open a capsule or crush tablets to help swallow their medicine (20). Another study by Stubbs, Haw, & Dickens (2008) looked at the frequency of authorised and unauthorised drug modification, for older patients in a mental health hospital. Medication administration during ward rounds were observed, and found that in 26% of administrations, tablets or capsules were crushed or opened to aid administration, and only 56% of the tablets crushed or capsules opened were authorised on the drug chart (21).

There are concerns regarding the safety and clinical risks associated with medicines administration to patients with swallowing difficulties. As mentioned in the studies related to medicines administration for patients with swallowing difficulties, the common practice is to crush tablets or open capsules to help swallow the medication. There are many factors to consider when modifying medications; the stability of the drug can be altered due to light, heat and water sensitivity, which can result in the degradation of the drug before its administration. Medications are often formulated with specific properties, crushing tablets and opening capsules can change what happens with the drug in the body from what is expected. This can compromise therapeutic outcomes and can cause toxicity (19,21).

Feeding tubes are commonly used for medicines administration for patients that cannot ingest substances orally. In hospitals, feeding tubes are particularly used in the care of the elderly and surgical wards (22)**.** Generally, liquids or dispersible tablets are sought for administration via enteral feeding tubes. Crushed tablets are also administered through enteral feeding tubes when suitable alternatives are not available, however, this is the most common cause of occlusion within the feeding tube (23)**.**

A consensus guideline was developed for medicines management of adults with swallowing difficulties. The guideline recommends that suitable alternatives such as liquid formulations should be sought when solid oral medications cannot be administered, however, not all patients can swallow liquids and often thickeners have to be added to aid swallowing. Modifying medications, for example, by crushing tablets or opening capsules should be the last resort when licensed alternatives are not available (25).

5. Modified release oral medications

Modified release medications are medicines that have a specific structure, such as a special coating or use of a matrix that breaks down slowly to allow drugs to be released over an extended period of time. These medications often have the letters 'MR', 'SR', 'XL', and 'LA' after their name, for example, Dilzem XL (19).

These medications offer three main advantages. They allow less frequent administration of medicines that would require multiple dosing due to the release of drug over a longer period of time compared to conventional immediate release dosage forms. Sustained release of the drug can also provide optimal control over symptoms and improve disease management, particularly in terminal diseases where breakthrough symptoms are concerned. Modified release medications also reduce side effects of drugs compared to conventional oral medications; the sustained release of drug ensures that drug levels do not go beyond the safety limits and thus reduce adverse effects.

Modified release oral medicines often have more drug content than conventional immediate release oral tablets and capsules to allow release of the drug for a longer period of time. Manipulating these formulations can result in immediate release of the drug content and result in toxicity. The consensus guidelines on medicines management for adults with swallowing difficulties, recommends that modified release medications should not be modified, i.e. crushed, opened, chewed or sucked (25).

Modified release oral medications are particularly beneficial for older adults. Older adults tend to have multiple diseases and on average take more than five medications (14). The use of modified release medications reduces the pill burden for these patients and also offers reduced side effects as well as better disease management (14,26). However, these medications are usually large and pose difficulties to administer in patients with swallowing difficulties. In practice, they may be switched over to a liquid dosage form, or to a conventional immediate release tablet or capsule and modified but then the patient would not be able to benefit from the advantages of modified release medications.

It is important to gain information of the extent and nature of problems of administering modified release medications to older adults with swallowing difficulties, and the solutions used by health professionals in practice to overcome administration difficulties of modified release medications. This information could lead to the development of novel modified release medications that are suitable for older adults with swallowing difficulties and could guide best practice for management of administration of modified release medications in older adults with swallowing difficulties.

STUDY OBJECTIVES AND PURPOSE

Aim

The aim of this study is to determine the extent and nature of problems with administration of modified release oral medications in older adults with swallowing difficulties and how these problems are solved in practice.

Primary objective

To gain a better understanding of the problems surrounding the use of modified release oral medications in older adults with swallowing difficulties.

Secondary objective

- To find out the frequency of prescribing modified release medications for older adults with swallowing difficulties.
- To find out if any changes are made in administering or prescribing of modified release medication in this patient population.
- To analyse the problems associated with changes that are made with modified release medications to aid administration for older adults with swallowing difficulties.
- To determine the types of modified release oral medication and the disease categories that causes the most concerns for administration of modified release medications in older adults with swallowing difficulties.

STUDY DESIGN

Study Configuration

This is a prospective study using medical notes and drug charts to collect information on the use of modified release oral medications in older adults with swallowing difficulties.

Study Management

The Chief Investigator (Simmi Patel) will be completing this project as part of a PhD programme of study, and will collect the data. The principal investigator (Narinder Bhalla) will lead the project and ensure that it is completed successfully and to the highest of standard. The academic supervisors of this project will oversee the project and ensure it is of high academic quality.

Duration of the Study and Participant Involvement

The study duration is anticipated to be six months (commencing from August 2014).

A member of the direct care team (clinical pharmacists on ward) will identify eligible participants. Participants' medical notes will be checked and their clinicians may be approached to find out whether the participant has the capacity to provide informed consent. For participants who can provide informed consent (no indication of lack of capacity to consent documented in the medical notes or communicated by the participants clinician), a member of the direct care team will approach the eligible participant and provide a patient information sheet (Appendix 2). Verbal consent will be sought from eligible participants by the member of the direct care team for the participants' details (patients ward and patients' name) to be passed onto the chief investigator (CI). The CI will then approach the participant, explain the study and obtain informed consent. Verbal authorisation for details to be passed onto the CI will be recorded in the medical notes by a member of the direct care team that approached the potential participant. Participants that are interested in the study will be asked to provide written consent for the chief investigator to collect non-identifiable data from the participants' medical notes and drug charts and they will not be approached during the data collection.

For participants that cannot provide consent (lack of capacity recorded in the medical notes or if the participants clinician has verbally communicated patients lack of capacity to consent) then the information required for the data collection pro forma, which is non-identifiable and anonymous, will be provided to the researcher by the pharmacist.

Enrolment will commence after Ethical approval, and after obtaining an honorary contract from Addenbrooke's hospital, Cambridge.

End of the Study

The end of the data collection period of the study will be after data is collected from 209 eligible patients.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment of Participants

The study setting is based in secondary care, in Addenbrookes' hospital, Cambridge. Clinical pharmacists will identify patients over 65's with swallowing difficulties on all wards using the criteria outlined below (6):

- Difficulty in oral intake or no oral intake
- Frequent choking and excessive coughing
- Need for a diet modified in texture
- Need for non-oral nutritional support

- History of aspiration pneumonia
- Need for individual mealtime supervision

Clinical pharmacists will identify wards with eligible patients. For all wards involved for data collection, participants that can provide informed consent will be approached by clinical pharmacists or speech and language therapists and will be provided with a participant information sheet (Appendix 2). Verbal consent will be sought from potential participants for their details (patients' ward and patient name) to be passed to the CI who will then approach the participant, explain the study and obtain informed consent. Informed consent for the CI to collect non-identifiable data from the patients' medical notes and drug charts will be recorded on a consent form (Appendix 3).

Anonymous, non-identifiable data necessary to complete the data collection pro forma will be provided to the researcher for participants that cannot provide informed consent (documentation of lack of capacity in medical notes or verbally communicated by participants clinician to the member of the direct care team involved in identifying the participant).

Inclusion Criteria

- Patients must be aged 65 or over
- Patients with swallowing difficulties
- Medicines reconciliation must be complete.

Exclusion Criteria

- No exclusion criteria.

Expected Duration of data collection from patients

Data will be collected from patients' drug chart and medical notes until the standard data collection pro forma is complete for that patient.

Withdrawal of data collection from patients

Patients will not be approached during data collection, but there may be circumstances whereby a health professional in the patients direct care team may ask to discontinue data collection. These requests will be respected and data collection will cease for that patient.

Informed consent

Clinical pharmacists will be involved in identifying eligible participants. Participants that can provide informed consent (no documentation of lack of capacity in medical notes or communicated by participants clinician) will be approached and provided with a patient information leaflet. Verbal consent will be sought for their details (patients' ward and patient name) to be passed onto the CI. The CI will then explain the study to the participants. Participants will be given time to consider whether they would like data to be collected from their medical notes and drug charts, and written consent will be

sought later in the day by the CI (Appendix 3). Only after consent is provided, will data be collected from the medical notes and charts.

For participants that are unable to provide informed consent (lack of capacity documented in medical notes, or communicated by the participants clinician), data required for the data collection pro forma (anonymous and non-identifiable) will be provided to the CI.

METHODOLOGY

This is a prospective study using medical notes and drug charts to collect information on the use of modified release oral medications in older adults with swallowing difficulties. For patients that can provide informed consent (no indication of lack of capacity documented in the medical notes or verbally communicated by patients' clinician), drug charts of patients will be viewed to determine whether the patient is prescribed any modified release medications, whether these have been changed to an alternative to manage administration in patients with swallowing difficulties, whether this medication has been manipulated (i.e. crushed tablets or opened capsules) or any other methods used to make the medicine easier to swallow (for example, mixing with food). If this information is not clear on the drug chart then questions may be asked to nurses looking after the patient for further clarification. Patients' medical notes will be used to determine the reason for admission, and patients' current condition(s). For patients that lack the capacity to provide informed consent, data necessary for the completion of the data collection pro forma, which is anonymous and non-identifiable, will be provided by the member of the direct care team (clinical pharmacist) identifying the participant to the CI. All data will be recorded on a standardised data collection pro forma (Appendix 1).

The steps that will be taken during the data collection period is summarised in the flow chart (Figure 1) below.

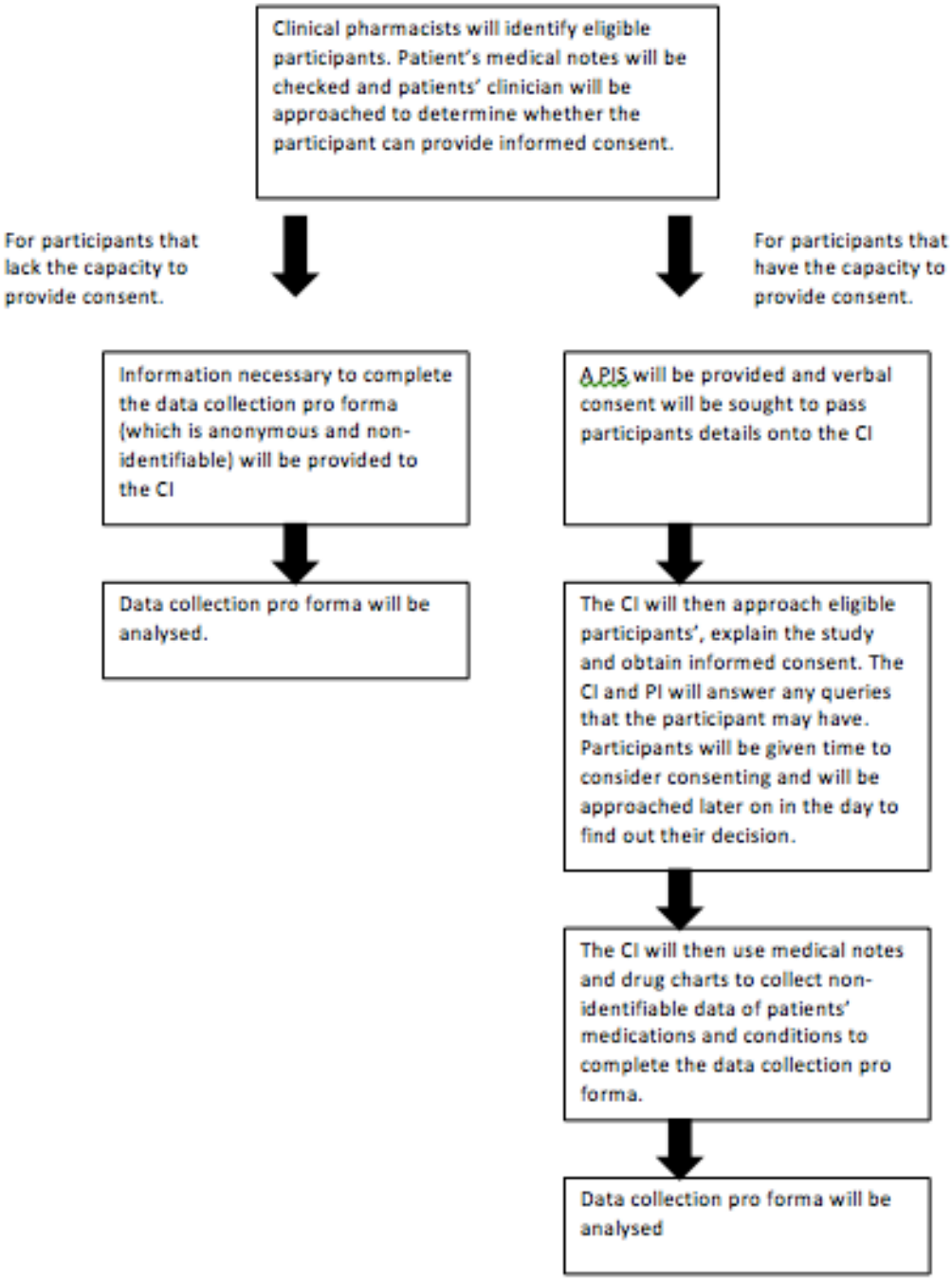

Figure 1: Flow chart of research methodology

Sample Size and Justification

A sample size was calculated to determine how many patients would need to be recruited to provide a representative sample of older adults with swallowing difficulties that are prescribed modified release medications. An estimation of population proportion was thus made using the margin of error equation:

$p \pm Z\sqrt{(pq/n)}$ = margin of error

Where Z is the critical value for 95% confidence level is 1.96.
p is the expected frequency value
q is 1-*p*
Margin of error is a measure of accuracy; it provides a limit by which the sample proportion differs from the true population proportion (27). For this calculation, a margin of error of 5% was used.

The expected frequency value in this study is the frequency of prescribing modified release medications in older adults with swallowing difficulties. This value is not reported and thus, primary care prescription data for 2012 were used to calculate how often modified release medications were prescribed (Table 1)(28). Primary care data for drugs prescribed for the gastro-intestinal system, cardiovascular system, central nervous system and endocrine system were selected, as diseases relating to these systems are common in the elderly.

Table 1: Frequency of prescribing modified release oral medications

Disease category	Total items prescribed (thousands)	Modified release oral medications prescribed (thousands)	Frequency of prescribing modified release oral medications (%)
Gastro-intestinal system	83900.107	1485.816	1.77
Cardiovascular system	300647.907	24350.911	8.10
Central Nervous system	180133.396	9629.898	5.34
Endocrine system	691332.124	5277.845	0.76
Total	**1256013.534**	**40744.47**	**3.24**

The value of 3.24% is the frequency of items prescribed in primary care to patients of all ages. Older adults are prescribed on average 5 or more medications so it is estimated an average of 16.2% (5 x 3.24%) chance of older adults with swallowing difficulties prescribed with modified release medications (14). Based on an estimated frequency of 16.2%, data will be collected from a total of 209 patients.

There is no data available on the prescribing frequency of modified release medications in older adults with swallowing difficulties. Thus, the sample size was calculated by using primary care data instead of secondary care and on the general public instead of older adults with swallowing difficulties. However, data collection from 209 patients' medical notes and drug charts is practical to achieve within the six month data collection period and can provide representative information of the problems associated with using modified release medications for older adults with swallowing difficulties in a clinical setting.

Data Collection and Analysis

A pilot study will first be conducted; data will be collected from 10 patients and the information gained from the pilot study will be used to determine whether there are any deficiencies in the design of the data collection pro forma. If there are no changes to be made to the data collection pro forma, then results from the pilot study will be included in the data collection.

The standard data collection pro forma (Appendix 1) will be used to collect information of patients' medical background, patients' medications and more specifically, whether modified release medications are prescribed and if there are any changes to this to help the patient swallow their medication. Nurses looking after patients may be approached if this information is not clear on patients' drug chart and medical notes. Patient identifiable data will not be collected, and thus information collected will be anonymous.

Data collected on the pro forma will be analysed to determine the frequency of prescribing modified release medications in patients with swallowing difficulties, any problems associated with changes to modified release medications, and which modified release drugs are of most concern for patients with swallowing difficulties.

ETHICAL AND REGULATORY ASPECTS

Ethics Committee and Regulatory Approvals

This study will not commence until approval by the Research Ethics Committee (REC). If any amendments need to be made that requires REC approval, the changes will only be implemented once the revised version has been approved by the REC. Minor protocol amendments for logistical or administrative changes may be implemented immediately; and the REC will be informed.

Person- identifiable data will not be collected in this study, and data will not be collected until consent is gained for the patients' data to be collected and for the CI to use patients' medical notes and drug charts to collect data. Data collection on the pro forma will be anonymous.

Informed consent and participant information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The CI who will be obtaining consent and the participant shall both sign and date the Consent form before the person can participate in the study.

QUALITY ASSURANCE & AUDIT

Insurance and Indemnity

Insurance and indemnity for study participants and researcher is covered by the insurance underwriters from the University of Hertfordshire.

Study Data

Data collection pro forma's will be stored in the Chief Investigators' locked drawer in a locked office at the University of Hertfordshire. Monitoring of study data shall include confirmation of consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

Record Retention and Archiving

The chief investigator will maintain records and documents for 2 years after completion of data collection, until the completion of the PhD programme of study.

Statement of Confidentiality

Personal identifiable data will not be collected during this study. Data generated as a result of this study will be available for inspection on request by the University of Hertfordshire representatives, the REC and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results from this work will be published in peer reviewed journals as well as presentation to appropriate conferences and used within the final PhD thesis.

STUDY FINANCES

Funding Source

This study is funded as part of the Chief Investigator's PhD research by the University of Hertfordshire.

Participant Stipends and Payments

Neither participants nor staff at the pharmacies will be paid to participate in the study. Participants will not be identified in any publications.

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Data collection pro forma

University of Hertfordshire

Data collection pro forma

(Version 4.0: 31st October 2014)

Patient details		
Age:	Gender:	Ethnicity:

Medical background	
Existing diseases/conditions	**Reasons for admission**

Swallowing difficulties (please tick the appropriate box, or if 'other', then please give reasons)					
New □ **Pre-existing** □					
Identified via:		**Criteria for swallowing dysfunction:**			
Medical notes		Enteral feeding tube/ Non oral nutritional support		Need for a diet modified in texture	
SALT team		Refusal of solid oral dosage form(s)		Frequent choking and excessive coughing	
Nurse		Nil By Mouth		History of aspiration pneumonia	
		Difficulty in oral intake		Need for individual mealtime supervision	
Other:		Other:			

Medications					
Controlled release oral formulation Newly prescribed □ Prescribed before admission □			**Other medications**		
Generic name	**Brand name**	**Dose and frequency**	**Generic name**	**Brand name**	**Dose and frequency**
Total number of CR oral medications			**Total number of medicines**		

Medicines modification					
Controlled release oral formulations			**Other oral dosage forms**		
Has the controlled oral formulation structure been modified: Yes □ No □ Has the controlled release oral formulation been changed to an alternative formulation Yes □ No □ **If yes to any of the above questions, please provide more detail below:**			Has the solid oral dosage form structure been modified Yes □ No □ Has the solid oral dosage form been changed to an alternative formulation Yes □ No □ **If yes to any of the above questions, please provide more detail below:**		
Drug	**Form of modification/Alternative formulation**	**Modification authorised by pharmacist (Yes/No)**	**Drug**	**Form of modification/alternative formulation**	**Modification authorised by pharmacist (Yes/No)**
Any other methods used to help swallow medicines (please provide further details below):					

Participant Information Sheet

Participant Information Sheet

(Version 4: 31st October 2014)

Title of Study: "An investigation into the use of modified release medications in older adults with swallowing difficulties**"**

Invitation to take part

You are invited to take part in the above study, however before you decide to take part, it is important to understand this research and what it involves. The information sheet provides you with a brief explanation of what will happen during the study and will provide you with information on all aspects that the study will cover. Please take the time to read the leaflet provided and feel free to ask questions and discuss it with the pharmacist and principal investigator. Please take your time and decide whether or not you would like to be a part of this study.

Thank you for taking the time to read this leaflet.

What is the purpose of the study?

Swallowing difficulties is common in older adults (patients 65 years and over) and this can make swallowing medicines such as tablets and capsules difficult. Difficulties in swallowing tablets and capsules can be particularly difficult for a special group of medicines called modified release medicines or slow release medicines. These medicines have a special structure that releases drug over a long period of time. To accommodate for the slow release over a long period of time they have more drug content then normal tablets and capsules and are typically larger in size. These medicines provide many advantages, they allow medicines to be taken less frequently, provide better symptom control and reduce the risk of side effects.

The purpose of this study is to determine if there are any difficulties with swallowing slow release medicines. The information gained from this study will be used to develop slow release medicines that are easier for patients to swallow.

Why have I been invited?

You have been invited because the pharmacist has identified you as a patient over the age of 65 that may have difficulties in swallowing tablets or capsules.

Do I have to take part?
No, it is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time, and without giving a reason. If you decide not to take part, or to withdraw from the study at a future date, this will not affect you or the standard of care you receive.

What will happen if I decide to take part?

If you decide to take part in the study you will be asked to provide consent for the researcher to collect information of the medicines you are prescribed from your drug chart and information of any diseases/conditions that you have from your medical notes. All information collected will not be identifiable and will be anonymous.

What are the possible disadvantages or risks of taking part?

There are no disadvantages or risks with taking part in this study. The data collected from your medical notes and drug charts will be anonymous, and you will not be approached during data collection.

The data collected during this study will be stored in a secure and confidential way. Data collection sheets will be stored in a locked cabinet in a locked office in the Department of Pharmacy, University of Hertfordshire.

What are the possible benefits of taking part?

There is no direct benefit, but the data collected from this study will highlight problems with these medicines in practice and the information may help in developing guidelines for medicines management for modified release medicines for patients with swallowing difficulties. The data collected in this study will also be used to develop novel modified release medicines for older adults with swallowing difficulties.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. Please contact the Patient Advice and Liaison Service (PALS) to make complaints.

Telephone number: 01223 216 756
Email: pals@addenbrookes.nhs.uk
Fax: 01223 256 170
Postal address: Box 53, Cambridge University Hospitals, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0QQ

Offices are located in the information centre, just inside the main entrance of the hospital. The centre is wheelchair accessible.

Will my participation in the study remain confidential?

All information collected during the course of this research is non-identifiable and therefore anonymous.

What do I have to do?

To take part in the study you need to let the researcher know that you are happy to do so and sign a consent form.

Can I withdraw from the study if I want to?

Yes, your participation is voluntary and you can withdraw from the study at any time. Any withdrawal from this study will not affect you, or your care, in any way.

What will happen to the results of this study?

The results of the study will be published in the researchers PhD thesis, medical journals and will be presented at conferences. There is no possibility that any individual person could be identified in any report or article that is published.

Who is organising this research?

I am undertaking this research as part of my PhD study. The research is organised by Department of Pharmacy in the University of Hertfordshire.

Who has reviewed the study?

The South Yorkshire REC and the Research and Development team at Addenbrooke's hospital has reviewed this research.

Contact for further information

If you wish to ask any questions about this study before providing consent, please contact the chief investigator or the principal investigator who would be pleased to help you:

Chief investigator: Miss Simmi Patel, PhD candidate
University of Hertfordshire, Department of Pharmacy
College Lane, Hatfield, AL10 9AB

Tel: 07926938266
E-mail: s.4.patel@herts.ac.uk

Principal investigator : Mr. Narinder Bhalla, Consultant pharmacist in medicines safety.
Cambridge University Hospitals NHS Foundation Trust
Hills Road, Cambridge, CB2 0QQ.
Tel: 01223217487
E-mail: narinder.bhalla@addenbrookes.nhs.uk

Consent form

University of Hertfordshire

Consent form
(Version 4.0: 31st October 2014)

Title of study: "An investigation of the use of modified release medications in older adults with swallowing difficulties"

REC ref: **14/YH/1105**

Name of Researcher: Miss. Simmi Patel

Name of Participant: **Please initial box**

1. I confirm that I have read and understood the information sheet version number 4.0 dated (31st October 2014) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected. ☐
3. I agree my medical notes can be accessed to obtain relevant information for this research. ☐
4. I understand data collected in the study may be looked at by authorised individuals from the University of Hertfordshire where it is relevant to my participation in the study. I give permission for these individuals to collect, store, analyse, and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
5. I agree to take part in the above study ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix II

A STUDY OF PARTICLE SIZE DISTRIBUTION OF SAFE-SWALLOW BOLUSES OF COMMERCIAL JELLIES

Participant information sheet

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

1 **Title of study**

A study of the particle size distribution of safe-swallow boluses of commercial jellies

2 **Introduction**

You are being invited to take part in a study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether you wish to take part. The University's regulations governing the conduct of studies involving human participants can be accessed via this link:

http://sitem.herts.ac.uk/secreg/upr/RE01.htm

Thank you for reading this.

3 **What is the purpose of this study?**

Food is normally broken down and mixed with saliva to achieve a consistency that is safe to swallow. The purpose of this study is to determine the particle size reduction of jelly once it is formed into a bolus in the mouth to enable *in* vitro studies in a model designed to replicate the swallowing process (the Cambridge Throat model). The study will generate useful information in the safety of swallowing jellies for patients with dysphagia (swallowing difficulties).

4 **Do I have to take part?**

It is completely up to you whether you decide to take part in this study. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you must complete it. You are free to withdraw at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect any treatment/care that you may receive (should this be relevant).

5 **Are there any age or other restrictions that may prevent me from participating?**

This study will involve swallowing a spoonful of commercial jellies and water thickened with a commercial thickener. Participants with difficulties in swallowing will be excluded from the study. Please check the ingredients below for any allergies or any personal

reasons that you may not be able to swallow these products. The commercial products contain the following ingredients:

Gelatine, Locust Bean Gum, Xanthan Gum, Gellan Gum, modified maize starch, agar, maltodextrin, citric acid, glucose-fructose syrup, hydrogenated maltose syrup, sugar, potassium citrates, calcium lactate flavourings and colourings: carmine, anthocyanins, beetroot red, stevia, gardenia, erythritol.

6 **How long will my part in the study take?**

If you decide to take part in this study, you will be involved in it for *30 minutes.*

7 **What will happen to me if I take part?**

If you decide to take part in the study you will be asked to provide consent to participate in the study. The study will also involve swallowing a spoonful of three different commercial jellies and water thickened with a commercial thickener and you will be required to fill in a short questionnaire and rate the ease of swallowing of these products.

Following this, you will be asked to chew the commercial food jellies that required chewing for swallowing and to spit out once you feel it is ready to be swallowed.

8 **What are the possible disadvantages, risks or side effects of taking part?**

There are no disadvantages or risks with taking part in this study. Your identity will be assigned a code number and you will not be identified in any reports or publications generated by the study.

9 **What are the possible benefits of taking part?**

There is no direct benefit, but the data collected from this study will help in determining the particle sizes that are deemed safe to swallow for these products and further analysis of the boluses will help us understand mechanical properties of safe-to-swallow jelly boluses.

10 **How will my taking part in this study be kept confidential?**

All information collected about you will be kept strictly confidential. Data generated during this study will be retained in accordance with the University of Hertfordshire's policy on academic integrity. Each participant will be assigned a code number to ensure anonymity.

12 **What will happen to the data collected within this study?**

Data collected in this study will be used in a PhD thesis, it may be published in scientific journals and presented at scientific conferences at a later date. No participants will be identified in any reports or publications.

12.2 The data collected will be stored in hard copy by SImmi Patel, University of Hertfordshire and stored in a locked cupboard for a year, after which time it will be destroyed under secure conditions;

13 **Will the data be required for use in further studies?**

The data will not be required for further studies.

14 **Who has reviewed this study?**

This study has been reviewed by University of Hertfordshire Health and Human Sciences Ethics Committee with Delegated Authority (ECDA)

The UH protocol number is LMS/PGR/UH/02759

15 **Factors that might put others at risk**

There are no anticipated risks for this study.

16 **Who can I contact if I have any questions?**
If you would like further information or would like to discuss any details personally, please get in touch with me, in writing, by phone or by email: My name is Simmi Patel and I am a PhD researcher in the Department of Pharmacy, University of Hertfordshire. My telephone number is 07926938266 and email: s.4.patel@herts.ac.uk.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University's Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

Consent form

UNIVERSITY OF HERTFORDSHIRE
ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS
('ETHICS COMMITTEE')

FORM EC3
CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

……..…
of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as a postal or email address]*

…..……
hereby freely agree to take part in the study entitled 'A study of particle size distribution of safe-swallow boluses of commercial jellies'

……..

(UH Protocol number LMS/PGR/UH/02759)

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, how the information collected will be stored and for how long, and any plans for follow-up studies that might involve further approaches to participants. I have also been informed of how my personal information on this form will be stored and for how long. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed, and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 In giving my consent to participate in this study, I understand that voice, video or photo-recording will take place and I have been informed of how/whether this recording will be transmitted/displayed.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

Signature of participant……..…Date……

Signature of (principal)
investigator……Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

……

Questionnaire

Date		
Participant number		
Gender (*please circle*)	Female	Male
Age	years	

1	Have you experienced any difficulties in swallowing foods previously?	Yes	No	Unsure
	If YES, what was the food item?			
	How old were you when you experienced difficulty in swallowing the particular food?			
2.	Have you experienced any difficulties in swallowing any medications (tablets or capsules)?	Yes	No	Unsure
	Have you ever had to crush your tablets or open capsules and release contents to enable swallowing of medication	Yes	No	Unsure

Please swallow a spoonful of Jelly or thickened water as you normally would and answer the following questions. Please rinse your mouth with water before swallowing a spoonful of each product.

Jelly 1 (please rate the ease of swallowing) (1 being not difficult at all and 5 being extremely difficult)				
1	2	3	4	5
Did you feel any residue in your throat during swallowing				
Yes	No	Unsure		
Did you have to chew the sample before swallowing (please circle)				
Yes	No	Unsure		
If yes, please rate the effort required to chew the sample (1 being not at all and 5 requiring most effort)				
1	2	3	4	5
How sticky did you feel the jelly was (adhering to the tongue or palate or coating the palate)				
1	2	3	4	5
Did the product melt in the mouth (changing from gel to liquid? Please circle the appropriate answer				
Yes	No	Unsure		

Jelly 2 (please rate the ease of swallowing) (1 being not difficult at all and 5 being extremely difficult)				
1	2	3	4	5
Did you feel any residue in your throat during swallowing				
Yes	No	Unsure		
Did you have to chew the sample before swallowing (please circle)				
Yes	No	Unsure		
If yes, please rate the effort required to chew the sample (1 being not at all and 5 requiring most effort)				
1	2	3	4	5
How sticky did you feel the jelly was (adhering to the tongue or palate or coating the palate)				
1	2	3	4	5
Did the product melt in the mouth (changing from gel to liquid? Please circle the appropriate answer				
Yes	No	Unsure		

Jelly 3 (please rate the ease of swallowing) (1 being not difficult at all and 5 being extremely difficult)				
1	2	3	4	5
Did you feel any residue in your throat during swallowing				
Yes	No	Unsure		
Did you have to chew the sample before swallowing (please circle)				
Yes	No	Unsure		
If yes, please rate the effort required to chew the sample (1 being not at all and 5 requiring most effort)				
1	2	3	4	5
How sticky did you feel the jelly was (adhering to the tongue or palate or coating the palate)				
1	2	3	4	5
Did the product melt in the mouth (changing from gel to liquid? Please circle the appropriate answer				
Yes	No	Unsure		

Thickened water (please rate the ease of swallowing) (1 being not difficult at all and 5 being extremely difficult)				
1	2	3	4	5
Did you feel any residue in your throat during swallowing				
Yes	No	Unsure		
Did you have to chew the sample before swallowing (please circle)				
Yes	No	Unsure		
If yes, please rate the effort required to chew the sample (1 being not at all and 5 requiring most effort)				
1	2	3	4	5
How sticky did you feel the thickened water was (adhering to the tongue or palate or coating the palate)				
1	2	3	4	5
Did the product melt in the mouth (changing from gel to liquid? Please circle the appropriate answer				
Yes	No	Unsure		

Which product did you prefer the most and why:

Which product did you least like and why: