In vitro models for the formulation of easy-to-swallow products

Marco Marconati

Principal supervisor: Dr Marco Ramaioli
Second supervisor: Dr Alasdair Campbell

Submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy in Chemical and Process Engineering
April 2019
Statement of Originality

This thesis and the work to which it refers are the results of my own efforts. Any ideas, data, images or text resulting from the work of others (whether published or unpublished) are fully identified as such within the work and attributed to their originator in the text, bibliography or in footnotes. This thesis has not been submitted in whole or in part for any other academic degree or professional qualification. I agree that the University has the right to submit my work to the plagiarism detection service TurnitinUK for originality checks. Whether or not drafts have been so-assessed, the University reserves the right to require an electronic version of the final document (as submitted) for assessment as above.

Marco Marconati
Summary

Cerebrovascular and neurodegenerative diseases are clinical conditions increasingly observed in geriatric populations. A common symptom of these pathologies is represented by the increased difficulty with food manipulation and intake. Developing food products, dietary supplements and oral medications for this set of patients requires an improved understanding of the interplay between bolus rheology, tongue coordination and lubrication of the oral cavity and their effect on the resulting ease of swallowing.

This study employs an in vitro model experiment to elucidate the role of bolus rheology and to describe the oral swallowing dynamics in presence of suspended particles, to mimic swallowing of solid oral dosage forms.

The model was first used to test viscoelastic liquids to validate the hypothesis that elasticity can contribute to a smoother bolus flow in the transition between the oral and the pharyngeal phase of swallowing. In this respect, the experimental results confirmed the effectiveness of thin viscoelastic liquids. These consistently led to a measurable reduction in bolus fragmentation at the ejection from the in vitro oral cavity without however significantly delaying the overall oral transit time. Conversely, model thick elastic liquids noticeably increased the measured oral transit times and led to an increased quantity of post-swallow residues. These results suggests the existence of an optimum range of rheological properties in vitro to secure the best balance between bolus fragmentation and bolus velocity. This finding, if confirmed in vivo could help designing novel products with elastic properties for a better management of swallowing disorders.

Attention was then dedicated to the study of the alterations to the in vitro swallowing dynamics resulting from the presence of suspended tablets and multiparticulates. This topic was developed in relation to the peculiar needs of paediatric and geriatric populations that require a high dose flexibility and often show a reduced acceptance towards large solid oral dosage forms. Based on the theoretical results reported for simpler peristaltic flow, the study aimed at quantifying the additional pumping effort required for swallowing single and multiple tablets as a function of their physical attributes. in vitro tests confirmed that model-tablets with a larger cross section in the direction of swallowing consistently delayed the bolus flow. The viscosity of the suspending vehicle was also an important
factor: thicker liquid media were able to ensure a smoother flow *in vitro*, even for large solid oral dosage forms. This finding confirms the effectiveness of thickened liquids as suspending vehicles for the oral administration of tablets and capsules.

The importance of the suspending vehicle rheology was further highlighted with a combined *in vitro* and sensory study that considered the swallow-ability of placebo multiparticulates. The *in vitro* model provided a higher discrimination ability among the different formulations. This helped to clarify the results obtained from the 30 untrained healthy volunteers recruited for the sensory tests. Whilst confirming its utility, the study also pointed out some of the limitations of the *in vitro* model that consistently over-predicted the viscosity for smooth swallowing, compared to the *in vivo* data. This led to the development of a novel experimental setup, inspired by the functionality of the tongue, and capable of tackling a significant number of the limitations observed for previous *in vitro* studies of swallowing. This three dimensional model, can handle liquid boli spanning a wide range of consistencies and the soft robotic actuation can also be tailored to provide insights on the role of poor tongue coordination. The availability of this model allows to greatly extend the kinematic and dynamic comparison with clinical data and can allow for a more in-depth investigation of the role of oral lubrication in the bolus transport.
Acknowledgements

This research project was completed under the sponsorship of Nestlé Health Science. I would like to acknowledge the continuous supervision and guidance of Dr Marco Ramaioli and Dr Alasdair Campbell. Special thanks also go to Dr Jan Engmann and Dr Adam Burbidge who provided valuable advice and an endless number of inputs throughout the whole duration of the project.

I am extremely obliged to all the co-authors and collaborators I had the privilege to work with. The excellent training provided by Dr Robert Lloyd was crucial for the successful hand-over of the in vitro model at the beginning of this project.

The contribution of Dr Felipe Lopez, Dr Mine Orlu and Professor Catherine Tuleu from UCL was fundamental to dive into the world of pharmaceutical formulations and instrumental to obtain a valuable set of sensory data to validate the in vitro model.

I would like to extend my deepest gratitude to Dr Vincent Mathieu and Professor Isabelle Souchon for wonderfully hosting me at INRA and for the precious support that they provided with the co-authorship of my review article.

I must also acknowledge the help of Dr Brigitte Watzke with COMSOL Multiphysics during my stay at NRC (which requires some more thanks to Dr Jan Engmann).

This acknowledgement section would not be complete without mentioning the contribution from all the students that I had the opportunity to supervise during these three years. Their commitment was instrumental to test new ideas that enabled important developments of this study. In this regards, I cannot thank Dr Silvia Pani enough for her role of co-supervision and for sharing her extensive knowledge on diagnostic ultrasounds.

To conclude, I must not forget to express my gratitude to the Erasmus+ program that allowed me to meet some truly extraordinary people and undoubtedly gifted me with the best memories of the whole doctorate.
## Contents

**Statement of originality**  

**Summary**  

**Acknowledgements**  

### 1 Introduction  

1.1 Motivation and Objectives  

1.2 Outline of the thesis  

### 2 Anatomy and physiology of deglutition  

2.1 Introduction  

2.2 The physiology of the oropharynx  

2.2.1 Respiration  

2.3 Normal swallowing  

2.3.1 The preparatory and oral phases of swallowing  

2.3.2 The pharyngeal phase of swallowing  

2.3.3 The esophageal phase of swallowing
2.4 Dysphagia

2.4.1 Diagnostic imaging for the assessment of the swallowing function

2.4.2 Managing dysphagia

2.5 In vivo studies of the kinematics and the dynamics of swallowing

2.5.1 Tongue strength and coordination

2.6 Properties of the food bolus

2.7 Bolus rheology

2.7.1 Food thickeners for the management of dysphagia

2.7.2 Bolus density

2.7.3 Bolus volume

2.8 Conclusions

3 In vitro and in silico models of swallowing

3.1 Introduction

3.2 Mechanical properties of relevant tissues

3.3 Salivary lubrication

3.4 Swallowing motor control

3.5 In vitro and in silico models of human swallowing

3.5.1 In vitro and in silico models of the oral phase of swallowing

3.5.2 In vitro and in silico models of the pharyngeal phase of swallowing

3.5.3 In vitro and in silico models of the esophageal phase of swallowing

3.6 Conclusions
4 Viscoelastic and extensional properties of liquids

4.1 Introduction ................................................................. 78
4.2 Materials and Methods .................................................. 79
  4.2.1 Rheological characterization ..................................... 80
4.3 Results ................................................................. 86
  4.3.1 Shear rheology ....................................................... 86
  4.3.2 Extensional rheology ............................................... 90
  4.3.3 In vitro swallowing tests ......................................... 97
4.4 Conclusions .......................................................... 104

5 Swallowing of solid oral dosage forms .................................. 107

5.1 Introduction .......................................................... 108
  5.1.1 Materials ............................................................ 111
  5.1.2 Methods ............................................................. 115
  5.1.3 Results and discussion ........................................ 116
  5.1.4 Conclusions ......................................................... 130

6 Swallowing of multiparticulates .......................................... 133

6.1 Introduction .......................................................... 134
  6.1.1 Materials and Methods .......................................... 135
  6.1.2 Results and discussion ........................................ 138
  6.1.3 Conclusions ......................................................... 144
7 A soft robotic tongue to study human swallowing

7.1 Design and fabrication

7.1.1 Palate and pharynx

7.1.2 Tongue design

7.1.3 Structure of the control algorithm

7.1.4 Definition of the swallowing pattern

7.1.5 Doppler velocimetry

7.1.6 Palatal pressure characterization

7.1.7 Mechanical tests and interfacial characterization

7.1.8 FE simulations

7.1.9 Bolus properties

7.1.10 In vitro swallowing of Newtonian and shear thinning liquids

7.2 Results

7.2.1 Mechanical and interfacial properties of the soft pneumatic tongue

7.2.2 Numerical simulations of the inflation of the soft tongue

7.2.3 In vitro swallowing tests

7.2.4 Modifications to the swallowing sequence

7.3 Conclusions

8 Conclusions
8.1.1 Reviewing the in vitro and in silico models of swallowing based on motor control ........................................ 177
8.1.2 Behaviour of viscoelastic liquids during swallowing .............................................................................. 178
8.1.3 Design of tablets and multiparticulate formulations for improved swallow-ability .............................. 179
8.1.4 Shear thinning vehicles ease administration of multiparticulates ......................................................... 180
8.1.5 A novel soft robotic model to study swallowing ...................................................................................... 181
8.2 Limitations and future work ...................................................................................................................... 182
8.3 List of contributions .................................................................................................................................. 183
8.3.1 Poster presentations .............................................................................................................................. 183
8.3.2 Oral presentation ...................................................................................................................................... 184
8.4 Publications ................................................................................................................................................ 184
8.4.1 Conference proceedings ....................................................................................................................... 184
8.4.2 Journal articles ....................................................................................................................................... 184
8.5 Co-supervision of MEng and MSc students .............................................................................................. 185

A Theoretical model of the in vitro peristaltic simulator ................................................................................ 186
A.1 Rotational dynamics ................................................................................................................................. 186
A.2 Viscous dissipation .................................................................................................................................... 189
A.3 Annular flow in infinitely long shells ......................................................................................................... 190
A.3.1 Assumptions .......................................................................................................................................... 190
A.3.2 Derivation .............................................................................................................................................. 191
List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Advantages and disadvantages of current imaging techniques with respect to the description of the bolus flow during swallowing.</td>
<td>23</td>
</tr>
<tr>
<td>2.2</td>
<td>Reference nomenclature and consistency levels of thickened drinks suggested by the 2002 National Dysphagia Diet (NDD) and the 2009 Japanese guidelines (1).</td>
<td>32</td>
</tr>
<tr>
<td>2.3</td>
<td>Consistency levels and nomenclature of thickened drinks proposed by the International Dysphagia Diet Standardization Initiative (IDDSI) (2).</td>
<td>32</td>
</tr>
<tr>
<td>3.1</td>
<td>List of <em>in vitro</em> and <em>in silico</em> studies of the oral phase of swallowing.</td>
<td>55</td>
</tr>
<tr>
<td>3.2</td>
<td>List of <em>in vitro</em> and <em>in silico</em> studies of the pharyngeal phase of swallowing.</td>
<td>59</td>
</tr>
<tr>
<td>3.3</td>
<td>List of <em>in vitro</em> and <em>in silico</em> studies of the esophageal phase of swallowing.</td>
<td>69</td>
</tr>
<tr>
<td>4.1</td>
<td>Average results of the IDDSI flow test over three repeats. Standard deviation in brackets.</td>
<td>87</td>
</tr>
<tr>
<td>4.2</td>
<td>Steady shear viscosity: fitting parameters for PL (Eq. 4.8) and Ellis models (Eq. 4.9).</td>
<td>88</td>
</tr>
<tr>
<td>4.3</td>
<td>Capillary break-up time $t_c$, extensional relaxation time $\lambda_c$ and surface tension $\sigma_S$ of the liquids tested. Standard deviation in brackets.</td>
<td>95</td>
</tr>
</tbody>
</table>
### 4.4 Post-swallow residues, characteristic oral transit time (FO), time for bolus ejection (TO-FO) and angular velocity of the roller at FO from in vitro tests. The amount of post-swallow residues is normalized with respect to 1.19 % w/w TUC (Nectar-thick). Average values over three repeats, standard deviation in brackets.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>Post-swallow residues, characteristic oral transit time (FO), time for bolus ejection (TO-FO) and angular velocity of the roller at FO from in vitro tests. The amount of post-swallow residues is normalized with respect to 1.19 % w/w TUC (Nectar-thick). Average values over three repeats, standard deviation in brackets.</td>
<td>99</td>
</tr>
</tbody>
</table>

### 5.1 Summary of the solid oral dosage forms used in the in vitro experiments to model swallowing of a single solid oral dosage form.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Summary of the solid oral dosage forms used in the in vitro experiments to model swallowing of a single solid oral dosage form</td>
<td>113</td>
</tr>
</tbody>
</table>

### 5.2 Characteristic in vitro oral transit times measured obtained for swallowing of a single spherical tablets in a 1.09 Pa s liquid carrier (glycerol). Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2</td>
<td>Characteristic in vitro oral transit times measured obtained for swallowing of a single spherical tablets in a 1.09 Pa s liquid carrier (glycerol). Average values and standard deviation from three repeats.</td>
<td>120</td>
</tr>
</tbody>
</table>

### 5.3 Characteristic oral transit times at 2 N load in different suspending vehicles for tablets with different AR and an equivalent volume to a d=10 mm sphere. Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3</td>
<td>Characteristic oral transit times at 2 N load in different suspending vehicles for tablets with different AR and an equivalent volume to a d=10 mm sphere. Average values and standard deviation from three repeats.</td>
<td>124</td>
</tr>
</tbody>
</table>

### 5.4 Characteristic in vitro oral transit times for mono-dispersed solids (φ=0.08 v/V) in a 1.09 Pa s Newtonian liquid carrier. Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4</td>
<td>Characteristic in vitro oral transit times for mono-dispersed solids (φ=0.08 v/V) in a 1.09 Pa s Newtonian liquid carrier. Average values and standard deviation from three repeats.</td>
<td>128</td>
</tr>
</tbody>
</table>

### 6.1 Particle size and density of the cellulose pellets. Average values and standard deviation over three repeats.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Particle size and density of the cellulose pellets. Average values and standard deviation over three repeats.</td>
<td>136</td>
</tr>
</tbody>
</table>

### 6.2 Description of the sensory and in vitro assessment of the swallowing tasks.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2</td>
<td>Description of the sensory and in vitro assessment of the swallowing tasks.</td>
<td>138</td>
</tr>
</tbody>
</table>

### 6.3 Measured sedimentation time of cellulose pellets in the different liquid vehicles.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3</td>
<td>Measured sedimentation time of cellulose pellets in the different liquid vehicles.</td>
<td>139</td>
</tr>
</tbody>
</table>

### 7.1 List of parameters chosen to simulate the oral phase of swallowing with the in vitro model.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>List of parameters chosen to simulate the oral phase of swallowing with the in vitro model.</td>
<td>153</td>
</tr>
</tbody>
</table>

### 7.2 Shear viscosity and IDDSI categorization for the liquid boli tested. Whenever relevant, brackets are used to report the standard deviation from repeats.

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2</td>
<td>Shear viscosity and IDDSI categorization for the liquid boli tested. Whenever relevant, brackets are used to report the standard deviation from repeats.</td>
<td>160</td>
</tr>
</tbody>
</table>
7.3 Young’s modulus (E) and contact angle (CA) of Eco-Flex 00-30 with added sorbitan monooleate (Span® 80). ....................................................... 162

7.4 Transit times from video recordings of the experiment at different in vitro swallowing condition. Standard deviation from three repeats in brackets. ........................................... 168

7.5 Peak velocities from Doppler US measurements at different in vitro swallowing condition. Standard deviation from three repeats in brackets. ........................................... 168

7.6 Ratio of ejected bolus mass relative to the injected bolus mass as a function of the in vitro swallowing condition: first swallow, repeated swallows and % variation for water pre-wetted swallows against the first swallow. Standard deviation from three repeats in brackets. ...................................................... 172

C.1 comparison between the peak velocities measured by Doppler US with those obtained through image analysis at the instant the roller transits in front of probe A or probe B. ................................................................. 205
List of Figures

2.1 Schematic illustration of the main anatomical structures of the human pharynx. ......................................................... 9

2.2 Schematic illustration of the three phases of swallowing: oral phase (a), pharyngeal phase (b) and esophageal phase (c). .................. 11

2.3 Top view of the epiglottis with the vocal folds closed (left) and open (right). Figure adapted from Crary (3). .................. 13

2.4 Lateral and posterior view from a X-ray computed tomography scan of a healthy patient swallowing a 10 mL Nectar-thick barium bolus. Figure adapted from Inamoto et al. (4). 14

2.5 Videofluoroscopy swallowing study (VFSS) of a healthy subject drinking an opaque liquid through a straw. The different tissues are visualized with different shades of grey depending on X-ray absorbance. Figure adapted from Leonard and Kendall (5). ........................................... 17

2.6 Endoscopy provides visual inspection of the oropharynx, especially useful to quantify the amount of post-swallow residues around the epiglottis. Colorants are commonly added to the liquid bolus to enhance image contrast (5). 19
2.7 Lateral MRI images of a healthy volunteer swallowing 5 mL of thickened pineapple juice in supine position. Acquisition speed of approx. 24 frames per second \cite{6}. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . \hspace{1em} 20

2.8 Multislice computed tomography (CT) provides a three dimensional visualization of swallowing with a temporal resolution of approximately 10 frames per second \cite{7}. \hspace{1em} 20

2.9 Ultrasound imaging can be used observe the the motion of the tongue during swallowing and track the position of the bolus (in red). Figure adapted from Mowlavi et al. \cite{8}. \hspace{1em} 21

2.10 The laryngeal prosthesis proposed by Debry et al. has a specially designed cap that allows for the patient to breathe and drink fluids, significantly reducing the risk of aspiration \cite{9}. \hspace{1em} 23

2.11 Kinematic data obtained from Tasko et al. who tracked the position of pellets attached to the tongue \cite{10}. \hspace{1em} 25

2.12 Steele et al. used Electromagnetic Mid-sagittal Articulography (EMMA) with transducer coils located on the tongue blade, body and dorsum to study the motion pattern of tongue during discrete and sequential water swallows. Statistically significant differences were found on the study population of 34 healthy individuals \cite{11}. \hspace{1em} 26

2.13 The Iowa Oral Performance Instrument (IOPI) can been used to measure isometric tongue pressure and tongue applied pressure during dry swallows \cite{12}. \hspace{1em} 28

2.14 Hori et al. \cite{13} developed an array of transducers to study the lingual-palatal pressure during swallowing. \hspace{1em} 29
2.15 Palatal pressure profiles recorded by Hori et al. during a healthy swallow of 4 mL of barium sulphate suspension (40% w/w). Data were obtained using a 5 channel sensor sheet placed on the palate (right) (14). . . . . . . 29

2.16 Classification of foods and drinks proposed under the framework of the International Dysphagia Diet Standardization Initiative (IDDSI) (2). . . . 33

3.1 Mowlavi et al. used an in vitro model experiment, at imposed stresses, to study the oral swallowing dynamics. Visual comparison between in vivo ultrasound images and in vitro tests with thick Newtonian boli was also provided by the authors (5). . . . . . . . . . . . . . . . . . . . . . . . . . . 51

3.2 Swallowing simulator, developed by Noh et al. to replicate the oropharyngeal sequence of swallowing at imposed strains. The flow of liquid and semisolid boli was visualized through VFSS (15). . . . . . . . . . . . . . . 51

3.3 Schematics of the pharyngeal peristalsis simulator, operating at imposed strains, developed by De Loubens et al. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 51

3.4 Schematics of the elastohydrodynamic model proposed by Mathieu et al. to evaluate the pharyngeal lubrication at imposed strains (cylinder rotational speed) and stresses (contact force) (16). . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 52

3.5 Prototype and structural Finite Element (FE) simulation of a soft polydimethylsiloxane (PDMS) tongue proposed by Lu et al. The organ can elongate and bend due to the differential stresses generated at the interface of upon inflation of embedded sets of air chambers (17). . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 52

3.6 Visual comparison presented by Ho et al. to assess the effect of salivary lubrication (slip and no-slip) when simulating swallowing of a Honey-thick bolus in a reclined position against in vivo CT data (18). . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 72

3.7 Soft robotics applications to swallowing. Schematics of the swallowing robot used to simulate esophageal peristalsis by Dirven et al. (19). . . . . . . 73
4.1 Schematics of the in vitro experiment used to replicate the oral phase of swallowing. .......................... 86

4.2 Steady shear viscosity for aqueous solutions of TUC and cereal extract (a) and PEO (b). Average values and error bars from three repeats. The corresponding fitting parameters of are listed in Table 4.2. .......................... 88

4.3 Oscillatory shear tests at 1% strain for aqueous solutions of TUC (a) and cereal extract (b). Storage ($G'$) and Loss ($G''$) moduli are illustrated with filled and open markers respectively. Visible crossover frequencies are indicated with an arrow. Average values and error bars from three repeats. .......................... 89

4.4 Oscillatory shear tests at 1% strain for aqueous solutions of 1 to 5% w/w PEO. Storage ($G'$) and Loss ($G''$) moduli are illustrated with filled and open markers respectively. Visible crossover frequencies are indicated with an arrow. Average values and error bars from three repeats. .......................... 89

4.5 Capillary thinning for TUC and cereal extract solutions: row a) 0.3 % w/w Cereal extract, b) 1 % w/w Cereal extract, c) 1.19 % w/w TUC (Nectar-thick), d) 2.35 % w/w TUC (Honey-thick), e) 3.48 % w/w TUC (Pudding-thick). Times are normalized with respect to the capillary break-up time. .......................... 91

4.6 Capillary thinning for PEO solutions: row a) 1 % w/w PEO, b) 3 % w/w PEO and c) 5 % w/w PEO. Times are normalized with respect to the capillary break-up time. .......................... 92
4.7 Comparison between two different procedures used to analyse the CaBER results for 3.48 % w/w TUC (Pudding consistency) and cereal extract highlighting the approximations stemming from using the midpoint filament diameter (laser micrometer) versus the more accurate use of the minimum diameter (full filament shape analysis from the video recordings). Diameters are normalized with respect to the post-stretch midpoint diameter $D_0$. .......................................................... 93

4.8 Profiles of the capillary thinning for aqueous solutions of TUC, cereal extract (a) and 1 to 5 % w/w PEO (b). Average values from five repeats. Diameters are normalized with respect to the post-stretch midpoint diameter $D_0$. .......................................................... 95

4.9 Values of apparent extensional viscosity as a function strain for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats. .......................................................... 96

4.10 Values of apparent extensional viscosity as a function of the strain rate for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats. .......................................................... 96

4.11 Ratio of extensional to zero shear viscosity for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats. .......................................................... 97

4.12 Roller angular velocity from in vitro experiments for TUC, cereal extract (a) and PEO (b) solutions. Average values and maximum deviation from three repeats. .......................................................... 98

4.13 Screenshots from the in vitro experiment. From left to right the instant of bolus front out (top row) and tail out (bottom row) for TUC and cereal extract solutions: a) 1.19 % w/w TUC (Nectar-thick), b) 2.35 % w/w TUC (Honey-thick), c) 3.48 % w/w TUC (Pudding-thick), d) 0.3 % w/w Cereal extract and e) 1 % w/w Cereal extract. .......................................................... 100
4.14 Screenshots from the *in vitro* experiment. From left to right the instant of bolus front out (top row) and tail out (bottom row) for solutions of increasing PEO concentration: a) 1% PEO, b) 2% PEO, c) 3% PEO, d) 4% PEO and e) 5% PEO. ................................. 100

4.15 Calculated strain at the bolus ejection from the *in vitro* oral cavity. .......... 101

4.16 Normalized bolus length for aqueous PEO solutions. Square and triangular markers identify the time of bolus front out (FO) and tail out (TO) respectively. Average values and maximum deviation from three repeats. 102

4.17 Calculated $De$ (bars) and $Er$ (triangles) at the bolus ejection from the *in vitro* oral cavity. ................................. 104

5.1 Different shapes of model-solid oral dosage forms were considered by the study. Ellipsoids are identified by their aspect ratio (AR), defined with the ratio between the equatorial and the azimuthal semiaxes. In the figure: oblate (i.e. flattened) spheroid of AR=0.25, b) sphere AR=1, c) prolate spheroid of AR=1.5, d) prolate spheroid of AR=2.5, e) prolate spheroid of AR=3.5, f) capsule size 3. The arrow points at the direction of swallowing. 111

5.2 Schematics of the *in vitro* setup. ........................................ 115

5.3 Screenshots from the *in vitro* experiments using a 2 N load, a 1.09 Pa s Newtonian liquid carrier and single spherical tablets having different diameters. The pictures in the third and fourth columns are respectively taken when the bolus front leaves the membrane (FO) and when the tail of the bolus leaves the membrane (TO). ................................. 117

5.4 Roller velocity profiles for model spherical tablets of d=4.8, 6.4, 8.0 and 10 mm using a 2 N load and a 1.09 Pa s Newtonian liquid carrier. Theoretical curves are obtained using Eq. A.39. ................................. 118
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>Roller velocity profiles for model spherical tablets of d=6.4, 8 and 10 mm at 2.7 N (a) and 4 N (b) load suspended in a 1.09 Pa s Newtonian liquid carrier. Theoretical curves are obtained using Eq. A.39.</td>
</tr>
<tr>
<td>5.6</td>
<td>Effect of tablet shape using a 2 N load in a 1.09 Pa s Newtonian liquid carrier: roller angular velocity for oblate, spherical, and prolate tablets of identical volumes to that of a d=8 mm (a) and d=10 mm sphere (b). Theoretical curves are obtained using Eq. A.39.</td>
</tr>
<tr>
<td>5.7</td>
<td>Effect of the carrier liquid vehicle viscosity at 2 N load when considering <em>in vitro</em> swallowing of oblate (AR&lt;1) and prolate (AR&gt;1) spheroidal tablets. Theoretical curves are obtained using Eq. A.39 for a tablet diameter of 10 mm.</td>
</tr>
<tr>
<td>5.8</td>
<td>Angular distance between the bolus tail and the centre of mass of spherical solid oral dosage forms using a 1.09 Pa s Newtonian liquid carrier at respectively 2 N (a), and 2.7 N (b) applied force.</td>
</tr>
<tr>
<td>5.9</td>
<td>Roller angular velocities for experiments at constant volume fraction of suspended solids ($\phi=0.08 v/V$) suspended in a 1.09 Pa s Newtonian liquid vehicle. The applied force was changed from 2 N (a) to 2.7 N (b) and 4 N (c). Theoretical angular velocity profiles are obtained from Eq. A.41.</td>
</tr>
<tr>
<td>5.10</td>
<td>Screenshots from the <em>in vitro</em> experiment using a 2 N load and multiple spherical tablets (d=4.8 mm, $\phi=0.08 v/V$) suspended in a 1.09 Pa s Newtonian liquid carrier. Tablets moving towards the bolus tail are circled.</td>
</tr>
<tr>
<td>6.1</td>
<td>Shear viscosity as a function of shear rate for the different hydrocolloids.</td>
</tr>
<tr>
<td>6.2</td>
<td>Shear stress as a function of shear rate for the different hydrocolloids.</td>
</tr>
<tr>
<td>6.3</td>
<td><em>In vitro</em> oral transit time (bars) and sensory attribute of ease of swallowing (markers). Upward pointing bars identify conditions in which clogging was observed and the <em>in vitro</em> model could not complete the swallowing test.</td>
</tr>
</tbody>
</table>
6.4 Relative amount of *in vitro* post-swallow residues (bars) and sensory scores for residual particles (markers). Upward pointing bars identify conditions in which clogging was observed and the *in vitro* model could not complete the swallowing test. ................................. 143

6.5 Qualitative comparison of the solid residues left after *in vitro* swallowing of Cellets® 200 in aqueous solutions of XG and CMC. ................................. 144

7.1 Schematics of the *in vitro* soft robotic setup comprising the peristaltic actuator inspired by the human tongue (light red). ................................. 149

7.2 Longitudinal cross section of the pneumatic actuator inspired by the tongue. 150

7.3 Chronogram of the swallowing sequence of the *in vitro* model. ................................. 153

7.4 The pneumatic actuation can be adjusted to mimic loss of lingual coordination. In the example above, the delay for inflation of the anterior chamber $t_A$ was set to a) $-0.2$ s, b) 0 s, c) $+0.2$ s. In all cases $t_P$ is equal to 0.5 s. The bolus is not introduced to better visualize the deformed shape of the tongue. ................................. 154

7.5 Characteristic shape and size of the specimen used for tensile tests. The gauge length is 25 mm. ................................. 158

7.6 Force-distance curves from repeated uni-axial stretch of mould-cased silicone rubber (Ecoflex 00-30) specimens. ................................. 161

7.7 Stress-strain curves from uni-axial tensile tests for mould cased silicone rubber (Ecoflex 00-30) specimens with added surfactant (Span® 80). The mechanical response is well-fitted by the Yeoh model (Eq. 7.2). ................................. 162

7.8 Three dimensional FE simulation of tongue actuation: a) undeformed configuration, b) inflation of the posterior part of the tongue, c) start of the swallowing sequence, d) inflation of the anterior air chamber. ................................. 164
7.9 Deformation of the posterior wall of the pneumatic tongue for negative applied pressures to the actuator. Parallel lines are drawn to visualize the curvature. ........................................ 165

7.10 Screenshots from in vitro swallowing tests with an IDDSI Level 2 glycerol-water solution. The tip of the Doppler probe is visible on the left. .......... 165

7.11 Screenshots from in vitro swallowing tests with an IDDSI Level 2 TUC. The tip of the Doppler probe is visible on the left. ...................... 166

7.12 Examples of Doppler waveforms from in vitro tests with aqueous solutions of glycerol and TUC, of similar consistencies (IDDSI Level 2). ........... 167

7.13 Absolute value of inflation pressure of the pneumatic tongue during the in vitro swallowing sequence for dry swallows and tests with a glycerol-water solution with IDDSI consistency Level 4. ........................................ 169

7.14 Absolute pressure during in vitro swallowing measured at the anterior, median and posterior palate for glycerol-water (a, c and e) and TUC solutions (b, d and f) of increasing IDDSI level consistency (rows from top to bottom: Level 2, Level 3 and Level 4). ........................................... 171

7.15 Oral transit times from video recordings of the experiment for different time delays of bolus propulsion ($t_A$). The thickest TUC solution (IDDSI Level 4) was used as a model liquid bolus. .................. 174

7.16 Doppler velocity profiles from in vitro swallowing experiments for different time delays of bolus propulsion ($t_A$). The thickest TUC solution (IDDSI Level 4) was used as a model liquid bolus. .................. 175

A.1 Geometry of the field of motion. ........................................ 187

A.2 Geometry of the field of motion for an annular flow. .................. 192
B.1 The bolus volume was scaled to maintain the same bolus length when the width of the membrane was reduced from 23 mm (c) to 19 mm (b) and 15 mm (a).

B.2 Roller angular velocities for a 1.05 Pa.s Newtonian bolus (a) and a 4% w/w aqueous solution of PEO ($M_W 10^6$ g/mol) (b). Experiments were run at two load configurations (2 and 4 N) for different values of membrane width (15, 19 and 23 mm).

C.1 Schematics of the *in vitro* setup with highlighted the position of the two Doppler probes used to measure the bolus velocity during swallowing. The probes are both inclined 50° towards the local tangent.

C.2 Examples of Doppler waveforms recorded during *in vitro* swallowing tests with a $\eta=0.03$ Pa.s Newtonian bolus under an applied load of 4 N. Snapshots from the simultaneous video recordings show a good match with the characteristic features of the US spectra.
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALE</td>
<td>Arbitrary Lagrangian-Eulerian</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>AR</td>
<td>Aspect ratio</td>
</tr>
<tr>
<td>ASTM</td>
<td>American Society for Testing and Materials</td>
</tr>
<tr>
<td>CMC</td>
<td>Carboxymethylcellulose</td>
</tr>
<tr>
<td>CA</td>
<td>Contact Angle</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>FDA</td>
<td>Food Drug Administration</td>
</tr>
<tr>
<td>FE</td>
<td>Finite Element</td>
</tr>
<tr>
<td>FO</td>
<td>Bolus Front Out</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>fps</td>
<td>Frames per Second</td>
</tr>
<tr>
<td>FSS</td>
<td>Full Scale Span</td>
</tr>
<tr>
<td>GPJ</td>
<td>Glossopalatal Junction</td>
</tr>
<tr>
<td>IB</td>
<td>Immersed Boundary Method</td>
</tr>
<tr>
<td>IDDS</td>
<td>International Dysphagia Diet Standardization Initiative</td>
</tr>
<tr>
<td>INRA</td>
<td>Institut National de la Recherche Agronomique</td>
</tr>
</tbody>
</table>
Chapter 0. List of Abbreviations

IOPI Iowa Oral Performance Instrument
LES Lower Esophageal Sphincter
LST Line Spread Test
MPS Moving Particle Semi-implicit method
MRE Magnetic Resonance Elastography
MRI Magnetic Resonance Imaging
NDD National Dysphagia Diet
NRC Nestlé Research Centre
OSA Obstructive Sleep Apnoea
PAS Penetration-Aspiration Scale
PDMS Polydimethylsiloxane
PEO Polyethylene Oxide
PIV Particle Imaging Velocimetry
PL Power-Law
PSD Particle Size Distribution
SAOS Small Amplitude Oscillatory Shear
SD Standard Deviation
SG Specific gravity
SPH Smoothed Particle Hydrodynamics
TO Bolus Tail Out
TUC ThickenUp™ Clear
UES Upper Esophageal Sphincter
US Ultrasound
VESS Videoendoscopy Swallowing Study
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFSS</td>
<td>Videofluoroscopic Swallowing Study</td>
</tr>
<tr>
<td>XG</td>
<td>Xanthan Gum</td>
</tr>
</tbody>
</table>
List of Symbols

\( c \)  
Speed of sound

\( C \)  
Concentration

\( d \)  
Tablet diameter

\( d_n \)  
\( n^{th} \) percentile of the particle size distribution

\( D \)  
Diameter of the capillary thread

\( De \)  
Deborah number

\( E \)  
Young modulus

\( E \)  
Elasticity number

\( f \)  
Frequency

\( F \)  
Applied load

\( F_d \)  
Drag force

\( g \)  
Gravitational acceleration

\( G \)  
Shear modulus

\( G' \)  
Storage modulus

\( G'' \)  
Loss modulus

\( I \)  
Moment of inertia

\( K \)  
Flow consistency index

\( k \)  
Size ratio of the suspended solid and the bolus
$L$ \quad Length

$L_B$ \quad Bolus length

$m$ \quad Mass

$M_w$ \quad Weight average molecular weight

$W_B$ \quad Width of the *in vitro* oral cavity

$n$ \quad Flow behaviour index

$Oh$ \quad Ohnesorge number

$P$ \quad Pressure

$p$ \quad Statistical significance for the Kruskal-Wallis test

$R^2$ \quad Coefficient of correlation

$R_B$ \quad Bolus radius

$r_A$ \quad Radius of the bolus trajectory

$r_A$ \quad Radius of the pulley

$Re$ \quad Reynolds number

$t$ \quad Time

$Tr$ \quad Trouton ratio

$v$ \quad Velocity

$V_B$ \quad Bolus volume

$Wi$ \quad Weissenberg number

$\Delta \alpha$ \quad Relative angular position of the particle to the roller

$\beta$ \quad Corrective factor to the drag force

$\delta$ \quad Corrective factor to the moment of inertia

$\gamma$ \quad Shear strain

$\dot{\gamma}$ \quad Shear rate
\begin{itemize}
\item $\varepsilon$ \hspace{1cm} Strain
\item $\eta$ \hspace{1cm} Shear viscosity
\item $\eta_a$ \hspace{1cm} Apparent shear viscosity viscosity
\item $\eta_a^{ext}$ \hspace{1cm} Apparent extensional viscosity
\item $\theta$ \hspace{1cm} Roller angle
\item $\dot{\theta}$ \hspace{1cm} Angular velocity
\item $\ddot{\theta}$ \hspace{1cm} Angular acceleration
\item $\lambda$ \hspace{1cm} Relative elongation
\item $\lambda_c$ \hspace{1cm} Relaxation time for the extensional flow
\item $\nu$ \hspace{1cm} Poisson ratio
\item $\rho$ \hspace{1cm} Density
\item $\sigma_S$ \hspace{1cm} Surface tension
\item $\sigma_{ij}$ \hspace{1cm} $i,j^{th}$ element of the Cauchy stress tensor
\item $\varphi$ \hspace{1cm} Insonation angle
\item $\phi$ \hspace{1cm} Volume fraction of the suspended solids
\end{itemize}
Chapter 1

Introduction

Swallowing is a critical physiological function driven by an integrated series of sensory stimuli and operated under the coordinated action of more than twenty-five pair of muscles. Cerebrovascular, neurological and congenital disorders can severely impair normal swallowing functions, leading to a significant deterioration to the quality of life (5; 20). A great number of clinical studies have been devoted to identify the best treatments and compensatory remedies to a range of swallowing impairments (5; 21; 22). Alterations to the bolus viscosity through the use of thickening agents represent a clinically proven method to manage swallowing disorders. However, this approach still lacks mechanistic understanding, which hinders further improvements.

The role of rheology is not limited to the in-mouth behaviour of the liquid bolus, but is also relevant for sensory stimulation and aroma release of foods (23; 24). The persistence of aroma and taste is heavily conditioned by the amount of post-swallow residues that coat the oral and pharyngeal cavity (25; 26). Furthermore, bolus rheology must also be considered in the administration of solid oral dosage forms. Therefore, a comprehensive understanding of the swallowing mechanism is needed to support the design of a wide range of food and pharmaceutical products.
Simplified models for human swallowing have been proposed and could be used for a more cost effective pre-screening of novel recipes and formulations. Such pre-screening systems could lead to more effective clinical trials, accelerating the development of novel liquid and solid formulations for dysphagic patients.

1.1 Motivation and Objectives

This study moves from considering three key aspects that have not yet been comprehensively investigated in the field of medical literature and pharmaceutical formulation design (Chapter 2).

The effect of bolus rheology on the dynamics of swallowing has been studied in vivo, but the mechanisms at stake are not quantitatively understood. In particular, only few and sparse results are currently available in the literature for viscoelastic liquids (Chapter 4).

An equally wide gap relates to the oral delivery of solid dosage forms. Whilst it is known that palatability significantly conditions the compliance of patients to an oral drug therapy, the importance of tablet size, shape and suspending vehicle rheology has not yet been studied and understood quantitatively in relation to the ease and safety of swallow (Chapter 5 and 6).

Finally, a review of current and past model experiments of swallowing pointed out remarkable oversimplifications with respect to the geometry of the bolus field of motion, the motor control strategy and the role of oral lubrication (Chapter 3). This motivates the interest towards the development of a more reliable model of swallowing that can also be used as a testing base for the development of new formulations (Chapter 7).

This work therefore aimed at shedding lights on these three areas by:

- deepening the understanding on the role of rheological properties of liquid foods in the dynamics of human swallowing, with particular focus on viscoelastic liquids and on the role of extensional properties;
investigating the alterations to the normal swallowing dynamics in presence of suspended particles, representative of the ingestion of oral solid medications and multiparticulate formulations;

• reviewing the limitations of current and past experimental models of swallowing available in the literature and introducing a novel experimental setup combining a realistic three dimensional geometry and a sufficient number of degrees of freedom to enable the simulation of different swallowing disorders.

The experimental approach of the thesis is based on the use of in vitro experiments inspired by the physiology of the oropharyngeal phase of swallowing. This enables to investigate in a quantitative, consistent, and more controlled way the impact of bolus rheology, compared to clinical investigations.

1.2 Outline of the thesis

This thesis starts with an introduction of the physiology of swallowing. The normal deglutition process is reviewed in light of the contemporary and past studies presented in the literature. The process of swallowing is described following the ideal path of a food bolus from the mouth to the final esophageal transport, in a sequence that starts with voluntary movements which then become entirely involuntary. Alterations to the normal sequence are then discussed, as well as the techniques used to assess swallowing disorders. The approaches and compensatory strategies used to improve the quality of life of patients affected by dysphagia are then reviewed. Alterations to bolus properties are reviewed with particular focus on the interplay between bolus rheology and swallowing.

In Chapter 3 in vitro and in silico models of swallowing are critically described to identify the gaps and the points that have not yet been addressed. This chapter is part of a published review article(27).

Following this background section, the outputs of the current research project are then
presented. The experimental approach used by this study primarily relies on the use of an in vitro model of swallowing, originally introduced by Mackley et al. (28) and later improved by Hayoun et al. (29) and Mowlavi et al. (8). This in vitro model, used throughout Chapter 4 to 6, replicates the peristaltic motion of the bolus during the early stages of swallowing and allows to quantitatively study the swallowing dynamics for a wide set of bolus models.

Tests with the in vitro simulator aimed at characterizing the oral dynamics of complex viscoelastic liquids. A summary of the results obtained in this set of experiments is reported in the form of a draft article in Chapter 4.

The following chapters (Chapter 5 and Chapter 6) consider instead the effect of suspended particles in the liquid bolus on the in vitro swallowing dynamics. This set of experiments is of practical importance for oral delivery of solid formulations (tablet and capsules), especially in geriatric and paediatric patients. Both these chapters have been published in pharmaceutical journals (30; 31). Chapter 5 examines the in vitro swallow-ability of single and multiple tablets, varying their size and shape. A combined in vitro and sensory study, result of a collaboration with the UCL School of Pharmacy, is then proposed in Chapter 6 to investigate the swallowing attributes for novel multiparticulate formulations, suspended in different liquid vehicles. In this chapter the limitations of the first in vitro setup are discussed and put in relation to the results from the sensory studies.

Chapter 7 proposes a completely novel soft robotic experiment to address some of the gaps in the state of the art of in vitro models and to tackle the limits of the simple peristaltic simulator used in the previous chapters.

Finally, the main contributions of this thesis are summarized in Chapter 8. The thesis terminates with a discussion of the main limitations of the study and few suggestions for future research opportunities.

For the sake of space and time, other than confidentiality constraints, this thesis only presents a limited amount of the whole set of data collected during the doctorate. In
particular, no reference is made to the experiments with the pharyngeal coating simulator developed by Mathieu et al. at the GMPA of INRA Thiverval-Grignon (16). Similarly, in vitro test considering the swallow-ability of infant paracetamol suspensions, carried out for GSK Nyon, are not discussed here. Reference to some other activities are included in Appendix B and C.
Chapter 2

Anatomy and physiology of deglutition

This introductory chapter provides the reader with a general overview on the physiology of normal and impaired swallowing along with the approaches commonly used to clinically assess the swallowing performance. Compensatory techniques, based on alterations to bolus properties, are discussed in relation to the current clinical practice. In this regard, attention is drawn to the use of food thickeners for the management of swallowing disorders. The rheology of thickened products is presented while discussing the different behaviour of starch and gum-based formulations. Two important gaps in the recent medical literature are identified: the lack of studies considering viscoelastic boli and the scattered results about the effect of solid oral dosage forms on the normal swallowing dynamics. These represent key aspects addressed in the following chapters.
2.1 Introduction

The anatomy of the human oral cavity, pharynx and upper digestive tract has long been studied (32). The swallowing process and its controlling mechanisms are well reviewed in the medical literature (32). In healthy individuals, swallowing of solids and liquids represents an activity that is generally accomplished with limited effort (32). Precise timing and neurologic control is necessary to coordinate the transport of the food bolus, while protecting the airway against food aspiration and penetration (5; 21). Difficulties with food manipulation and ingestion are increasingly observed in elderly and studies reveal that the incidence of swallowing disorders in nursing homes can commonly reach 40% of the total number of patients hospitalized (33). Dysphagia profoundly deteriorates the quality of life, by strongly limiting the variety of food, drinks and oral solid medications that can be safely swallowed (5; 34). Management of dysphagia requires a patient-centred approach considering a broad spectrum of compensatory techniques, such the adjustment of posture during eating, surgical interventions and, in the most extreme cases, enteral feeding (5).

Over the past years clinical studies have revealed the paramount role of food texture and rheology in the perceived ease of swallowing, triggering the attention of a wide and heterogeneous community of researchers whose activity is well synthesized by the growing number of articles dealing with textural modifications in the management of dysphagia (35; 36; 22). A wide number of *in vivo* studies has focused, in particular, on the role of bolus rheology leading to the general conclusion that thicker solutions promote safer swallows at the expense of an increased quantity of post-swallow residues in the oral and pharyngeal cavities (35; 22; 5; 37; 38). The use of food thickeners has long been proposed to support nutrition and hydration for dysphagic patients. However, the underlying mechanisms that explain the effectiveness of thickened products is still debated. The increasing oral transit time with increasing bolus viscosity led some researchers to state that a slower bolus flow can partially compensate lags in the actuation of the swallowing motor control. This hypothesis is however challenged by other works that were not able to
find any significant increase in the duration of the swallowing sequence when considering highly shear thinning liquids. In this case, the better bolus perception and control on the tongue is key to avoid premature spillage before triggering the swallowing sequence (38).

The currently adopted texture and rheology of structured products and thickened beverages is however still lacking a sound mechanistic justification. The interplay between bolus properties, tongue coordination and lubrication of the oral cavity is not quantitatively understood.

Classical techniques such as videofluoroscopy (VFSS), videoendoscopy (VESS) and manometry have extensively been used to study swallowing disorders (39). Recent advances in microelectronics have also allowed for less invasive in vivo measurements of parameters such as tongue pressure, pattern and position during swallowing (39). Progress in medical imaging has also led to a higher temporal and spatial resolution of novel techniques for the assessment of the biomechanics of swallowing, such as magnetic resonance imaging (MRI) and X-ray computed tomography (CT) (40; 41; 4; 42).

Nonetheless, sensory and clinical evaluation of swallowing do not always converge to similar results due to the different methodologies and approaches considered by different studies. The availability of alternative techniques to in vivo measurements could allow for a more detailed understanding of swallowing. In this respect, In vitro experiments and in silico, or computational, models could also provide a valuable support during the design of clinical studies, aiming at tailoring food and drink properties to the specific needs of different classes of patients.

### 2.2 The physiology of the oropharynx

Food oral processing begins in the oral cavity, a hollow space that extends from the lips anteriorly, to the palatoglossal arch posteriorly (Fig. 2.1). The volume of the oral cavity is defined as the maximum amount of liquid that can be held in mouth. As such, it is subject to a certain intrapersonal variability. Alsanei et al. indicated a volume of 78±20
2.2 The physiology of the oropharynx

Figure 2.1: Schematic illustration of the main anatomical structures of the human pharynx.

mL for younger individuals (22-65 years) and 56±16 mL for elderly, with also significant gender-based differences (43). The superior part of the oral cavity is characterized by a rigid structure composed of alveolar ridges, the hard palate, that posteriorly leads to the soft palate and terminates with the palatine uvula (Fig. 2.1).

The tongue constitutes the inferior boundary of the oral cavity and has a paramount role in food oral processing and swallowing: the tongue assists the mastication, contributes to modulating speech, transports the bolus during the first stages of deglutition and collects tactile and taste stimuli (44). Mechanical stimuli are captured by mechanoreceptors that are sensitive to different strains and to the frequencies of applied forces (45). The tongue is a non-bony muscular structure with a high steric mobility that extends for an average total length of approximately 6 to 10 cm from the lips to the oropharynx (45 44). The anterior portion of the tongue is anchored to the floor of the mouth by the lingual fraenum, while, at the opposite end, the root of the tongue terminates with the vallecula, leading to the epiglottis (Fig. 2.1). The superior part of the tongue is referred to as dorsum, whilst the tip is called apex (Fig. 2.1). The superior and posterior surface of the tongue is lined with a stratified mucosa that provides physical and chemical protection with its multi-layered and keratinized epithelial surface.

The oral cavity posteriorly leads to the pharyngeal cavity via the Glossopalatal Junction (GPJ), also referred to as fauces or isthmus of fauces. The throat, or pharynx,
Chapter 2. Anatomy and physiology of deglutition

is divided into three parts: the nasopharynx, the oropharynx and the laryngopharynx (Fig. 2.1). The nasopharynx is the superior part of the throat and on its back sits the pharyngeal tonsils. The nasopharynx is lined in ciliated mucous membrane or pseud stratified columnar ciliated epithelium like most of the respiratory tract. Conversely, the lower oropharynx and the laryngopharynx (Fig. 2.1) are instead lined by a non-keratinized stratified squamous epithelium: the same tougher tissue that lines the oral cavity. The glottis separates the pharynx from the tracheal cartilages and supports the vocal folds. The pharynx can deform during swallowing: in its passive state its resting length is approximately 12 to 14 cm (in adults) while it contracts, following the laryngeal elevation, to shorten the distance that the bolus has to travel during swallowing (46). Directly above the glottis sits a cartilaginous leaf-shaped structure, the epiglottis, which bends down in normal swallowing to guide the bolus downward to the esophagus. This passive movement is initiated by the motion of the hyoid bone and is preceded by the up-swing of the soft palate that seals the nasopharynx. The pharynx terminates with the esophageal cricopharyngeal muscle, also referred to as Upper Esophageal Sphincter (UES) that leads to the esophagus. Here peristaltic contractions guide the bolus for, a length of between 18 to 25 cm, to the stomach (47).

2.2.1 Respiration

During normal breathing, air flows from the anterior nares through the nasal cavities to the posterior nares (or choanae) and the nasopharynx. After crossing the oropharynx, the flow of air passes through the laryngeal aperture to a cartilaginous structure called the larynx, which lies anterior to the laryngopharynx and is suspended by muscles attached to the hyoid bone which itself is suspended between the jaw, tongue, and sternum by suprahyoid and infrahyoid musculature. Vocal folds are the ultimate barrier to access the trachea and the aperture between them allows modulation of voice tone in speech. The normal respiratory cycle is interrupted during deglutition. This normally occurs at the expiratory phase of the respiratory cycle (48). The short period of apnoea, that commonly
2.3 Normal swallowing

The swallowing process is articulated into three subsequent stages: 1) the oral phase, 2) the pharyngeal phase and 3) the esophageal phase (Fig. 6.3). These three phases, commonly described separately, are however deeply interlinked under tight neurologic control (32). The overall process, involves the movements of more than 25 pairs of intrinsic and extrinsic muscles (5), starting from the first preparatory phase, in which the food bolus is chewed and wetted with saliva, until the latter esophageal phase, in which the peristaltic motion induced by sphincters ultimately guides the bolus downward to the stomach.

2.3.1 The preparatory and oral phases of swallowing

The first phase of deglutition consist in the intake and preparation of the food or liquid bolus. This phase is voluntary and its duration is highly dependent upon on the number of chewing cycles needed to form the bolus when eating solid and semisolid foods. The oral preparatory phase is characterized by the progressive reduction in particle size of
solid foods due to mastication (44). In this phase the incorporation of saliva softens and moistens the food particles. The tongue shapes the chewed solid food into a cohesive bolus.

In the case of liquid sips, coordination between tongue, lip, and cheek muscles’ movements is necessary to hold the bolus and prevent it from prematurely spilling into the pharynx (23). When the bolus is deemed ready to be swallowed, the oral phase of swallowing is initiated. The existence of a swallowing threshold, in terms of bolus texture has long been debated. Studies have linked the swallow-ability of foods and liquids to the particle size of chewed food, wettability with saliva, rheology and other textural attributes of the bolus (50). During the oral phase of swallowing the bolus is transported from the oral cavity through the fauces to the upper part of the pharynx. In case of thin liquids, the process is usually accomplished within 0.5 seconds (51). The motion is assisted by the contraction of the cheek muscles, which prevent the bolus from exiting the front of the oral cavity. Subsequently, the tongue tip is raised to seal the anterior oral cavity whilst the bolus is held against the hard palate. Breathing is then inhibited. This is followed by a retraction of the tongue that leaves the bolus posteriorly unconfined and free to flow into the oropharynx. The soft palate is then swept-up, as to seal the nasopharynx. The motion of the tongue, induces an upward and forward movement of the hyoid bone leading to an upward translation and contraction of the larynx. As the larynx rises, the cartilaginous epiglottis progressively covers the top of the airway, completing an elaborate system of airway protection that allows the bolus to be directed toward the esophagus rather than into the trachea (32).

2.3.2 The pharyngeal phase of swallowing

The pharyngeal phase begins with the bolus front entering the oropharynx. The oral and pharyngeal phases overlap as the bolus passes through the GPJ. The duration of the pharyngeal phase depends on the volume of the swallowed bolus and on the clinical condition of the patient. Power et al. measured average values of approximately 0.6
2.3. Normal swallowing

Figure 2.3: Top view of the epiglottis with the vocal folds closed (left) and open (right). Figure adapted from Crary [3].

seconds in healthy subjects, while significantly longer transit times were observed in post stroke patients [51]. Molfenter and Steele in their review of temporal variability of events in the recent dysphagia literature reported instead values spanning between 0.3 to 1.2 s [52].

As the bolus enters the pharynx, the hyoid bone continues its superior and anterior excursion whose total duration spans between 0.8 and 1.4 s [52]. This induces an upward movement of the larynx that results in shortening the pharynx, reducing the distance that the bolus has to cover on its way to the esophagus. It was shown that the pharynx shortens by about 40% of its original rest length during deglutition [53]. Moreover, laryngeal elevation and contraction helps to induce a slight negative gauge pressure (approx. -20 kPa for a 10 mL water sip [51]) in the region of GPJ that drags the bolus downward preventing reflux [54]. Additional protection against bolus entrance into the trachea is provided by the partial occlusion of the vocal folds and the complete down tilting of the epiglottis (Fig. 2.3).

The particular geometry of the zone between the epiglottis and the esophagus might cause the bolus to unevenly split before merging again at the entrance of the esophagus [32]. This phenomenon has recently been observed by three dimensional imaging techniques (Fig. 3.6). The extent of intra personal variability and head posture in relation to the bolus asymmetry in the oropharynx and laryngopharynx have however not yet been
Chapter 2. Anatomy and physiology of deglutition

2.3.3 The esophageal phase of swallowing

The final phase of swallowing initiates with the relaxation of the UES that is followed a sudden reduction in the pressure measured laryngopharynx pressure. This is followed by the onset of a first peristaltic wave whose pressure amplitude ranges from 5 to 25 kPa, depending on the subject gender, age, volume of bolus and type of monomeric probe used \(^{(23)}\). In the esophagus, muscular contractions guide the bolus to the Lower Esophageal Sphincter (LES). The speed of peristalsis is limited to few centimetres per second and the velocity of the bolus is much reduced compared to the initial phases of swallowing. After the bolus has entered the UES, the larynx is brought back to its normal resting position and length, and the muscles controlling the soft palate are relaxed. Respiration is again restored after a period of apnoea that varies from 0.75 to 1.25 seconds in healthy subjects.
2.4 Dysphagia

Alterations in the normal movement of bolus from the oral cavity to the stomach due to abnormalities in the structures critical to swallowing, or in their movement, are categorized under the clinical name of dysphagia. Swallowing disorders manifest with a broad range of symptoms and their severity ranges from mild cases of unpleasant eating and drinking, to the need for nasogastric or gastronomy tube feeding. The incidence of swallowing disorders is particularly high in elderly, affecting between 15 to 22% of patients aged 50 or above in the United States (33). The prevalence of dysphagia is even higher in nursing homes, where typically more than 40% of the residents are reported to have feeding difficulties (33). Physiological, anatomical, motoric and sensory alterations to the normal swallowing function also affect people with neurological disorders, such as Parkinson’s disease, Amyotrophic Lateral Sclerosis (ALS) and gastrointestinal and cardiopulmonary diseases, including gastroesophageal reflux and chronic obstructive pulmonary disease (5). Moreover, dysphagia also represents an aftermath of traumatic brain injuries, stroke, laryngeal carcinoma, and radioactive treatment (5).

Dysphagia can lead to bolus penetration and aspiration. The former refers to small amount of liquid bolus entering the glottis with residues usually accumulating in proximity of the vocal folds. The occurrence of penetration can be perceived by the patient and who may trigger protective measures such as coughing or choking to expectorate the foreign material from the glottis. Conversely, aspiration takes place when the bolus is able to flow through the vocal folds and is therefore able to move downward in the trachea to sit in the lower lobe of the lungs (5). Aspirated bolus may support the growth of bacteria leading to aspiration pneumonia: a condition that often represents a serious life-threatening disease,
especially in individuals affected by other co-morbidities (5). The risk of aspiration and penetration is not limited to the duration of swallowing, as food residues accumulated in the piriform sinus can subtly leak in the glottis. Shaker et al. reported that the threshold of water holdup in the piriform sinuses reaches volumes of up to 1.8 mL in elderly, while 40% lower volumes were found in younger individuals (55).

2.4.1 Diagnostic imaging for the assessment of the swallowing function

Recent progress in the field of medical imaging and in sensor design has allowed for a more quantitative assessment of the characteristic variables involved in deglutition. By manipulating what is swallowed, how it is swallowed, and the patient position, clinicians can complete a comprehensive assessment of the patient swallowing ability (56).

Videofluoroscopy Swallowing Study

The benchmark of medical imaging of the pharynx is videofluoroscopy (Videofluoroscopy Swallow Study or VFSS), a technique that has been in use since the 70s (42). VFSS is a dynamic radiographic examination at the acquisition speed up to 30 frames per second (fps) of fluoroscopic images in subjects eating or swallowing radio opaque materials, such as suspensions of barium sulphate. The opaqueness of barium swallows appear black in videofluoroscopy images, as opposed to the light grey of negative contrast substances, such as air (Fig. 2.5). Tissues and bony structures appear as shades of grey (darker than air) depending on their density (Fig. 2.5).

The radiation dose for swallowing examination is on the order of 1.05 mSV during a 5-minute exposure (42): a value approximately 20 times lower than the maximum yearly amount limit suggested by the Ionizing Radiations Regulations (57). The time resolution of VFSS can be a limiting factor as videofluoroscopy can only be expected to capture events with durations of 0.03 s or longer (39). The stack of images generated during a
2.4. Dysphagia

Figure 2.5: Videofluoroscopy swallowing study (VFSS) of a healthy subject drinking an opaque liquid through a straw. The different tissues are visualized with different shades of grey depending on X-ray absorbance. Figure adapted from Leonard and Kendall [5].

VFSS can be used to qualitatively assess the integrity of the pharyngeal structures and the occurrence of penetration or aspiration. Often, however, VFSS cannot resolve the events involved in airway closure due to the poor image contrast between the different soft tissues [3].

The event of penetration or aspiration of a bolus is commonly quantified during VFSS using the Penetration Aspiration Scale (PAS), developed by Rosenbek et al. [56]. Following this classification, the results of videofluoroscopy analysis are given a score from 1, in case of successful competition of the swallowing task, to 8 in case the material is irreversibly aspirated below the vocal folds [56].

Coupling VFSS data with image analysis tools can give additional useful quantitative data to track the spatial coordinates and shape of bolus and bony structures. In this case lead markers, that appear as black spots in VFSS images, are often used to ease the identification of reference lengths and points such as the hyoid bone or molars [5] (Fig. 2.5). The information that can be extracted from videofluoroscopy tests is limited to a two dimensional projection. However, simultaneous imaging of the lateral (mid-sagittal) and antero-posterior projections can be performed to better resolve the flow of bolus around the epiglottis, any asymmetry in the larynx, and the presence of bolus residues in the piriform sinus and in the vallecula.

There is not an univocal protocol for VFSS, but Crary [3] listed a common sequence
approach that begins with an initial small quantity (<5 mL) of a *Mildly-thick* barium suspension and, based on the response of the patient, the consistency and the volume can then be consequently adjusted. The importance of using a range of different bolus textures and volumes during a VFSS cannot be overstated \(^3\). Consequently, a wide range of different viscosities for suspensions of barium sulphate have been developed and are available to the practitioners. In particular cases, solid foods coated with barium can also be considered as an option \(^3\). The volume of the bolus for VFSS is not standardized, although values of 5 and 10 mL are frequently used in the literature \(^22\).

**Fiberoptic endoscopic evaluation of swallowing**

Videoendoscopy swallowing examination (VESS) is a more recent technique, compared to VFSS, with imaging capability focused on the pharynx. The basic equipment required for an endoscopic swallowing study include a flexible fibre optic endoscope, a light source and a camera to record the videos. The endoscope is passed through one nostril and gives a view from the top of the pharynx downward (Fig. 2.3). The fibre optic probe is generally well tolerated by patients and its presence does not induce any reported significant interaction with the normal swallowing mechanism \(^39\). Like VFSS, the endoscopic procedure is a dynamic study that, when recorded, provides a reliable examination of pharyngeal swallowing function. Moreover, endoscopy provides a superior inspection of pharyngeal anatomy, laryngeal closure patterns, dryness, and secretions compared with VFSS. Another advantage of endoscopy is that any fluid can be used, for swallowing tasks, provided there is enough image contrast to distinguish the bolus from the epithelium. To that extent a small amount of dye or colorant can be effectively used to ease the visualization of the bolus residues (Fig. 2.6).

The potential of endoscopy for assessing the biomechanics of swallowing is however rather limited by the reduced field of view. Abnormal tongue motor patterns are not directly assessable by endoscopy, nor is it possible to appreciate the movement of the hyoid bone and the cartilaginous tissues. For these reasons VFSS remains far more suitable to describe
Figure 2.6: Endoscopy provides visual inspection of the oropharynx, especially useful to quantify the amount of post-swallow residues around the epiglottis. Colorants are commonly added to the liquid bolus to enhance image contrast (5).

the kinematics of the events during swallowing. Endoscopy and videofluoroscopy are thus better seen as complementary tests rather than alternatives (5).

Computed tomography and magnetic resonance imaging

Computed aided Tomography (CT) and Magnetic Resonance Imaging (MRI) are complementary techniques used to diagnose traumatic injuries and diseases. MRI scanners provide a detailed imaging of internal organs and soft tissues, while CT has a higher contrast resolution of bony structures and blood vessels. The working principle of the two types of scanners is remarkably different: while MRI is based on the encoding of magnetic resonance signal from water protons present in tissues, CT uses X-ray radiation.

Real-time visualization of swallowing has only recently taken benefit from MRI and CT. A noticeable enhancement in the level of detail and image quality, with respect to the standards of VFSS imaging, can be achieved by MRI (Fig. 2.7). Recent advances in terms of acquisition speed make MRI scanners an appealing alternative to VFSS when studying the kinematics of soft tissues during swallowing (6). On the other hand, the design of current MRI scanners only allows for swallowing examination in a supine position which clearly does not reflect the normal eating posture and might also pose unnecessary hazards when scanning the swallowing of dysphagic volunteers. Moreover, there is a significant cost associated with the purchase and maintenance of current high-speed MRI scanners that substantially pose a limit to their widespread use.
Figure 2.7: Lateral MRI images of a healthy volunteer swallowing 5 mL of thickened pineapple juice in supine position. Acquisition speed of approx. 24 frames per second (6).

Figure 2.8: Multislice computed tomography (CT) provides a three dimensional visualization of swallowing with a temporal resolution of approximately 10 frames per second (7).

The applicability of CT in the dynamic examination of human swallowing has also recently been proposed (58). The technique shares some of the drawbacks of VFSS and adds a significantly higher radiation exposure to the patient. Preliminary results are however promising to support the kinematic description of the flow of bolus through the pharynx. The current limitations of the setup developed by Fuji et al. still sit in the limited temporal resolution of the detector (10 fps), and the particular reclined position of the patient during the CT scan (Fig. 2.8) (7).
2.4. Dysphagia

Ultrasound imaging can be used observe the motion of the tongue during swallowing and track the position of the bolus (in red). Figure adapted from Mowlavi et al. [8].

Ultrasound imaging

Ultrasound (US) in swallowing assessment can provide visualization of soft tissues, such as muscles and internal organs, without some of the drawbacks of VFSS and videoendoscopy. US imaging can be proficiently used extract data on the early phases of swallowing, but is however not a widely used technique to diagnose swallowing disorders, due to the fact that the field of view in the pharynx is limited by the presence of the larynx [59]. Diagnostics ultrasounds typically use frequencies in range from 2 to 40 MHz to create real-time 2D images of soft tissues such as muscles, internal organs and blood flow [59]. Doppler imaging, a function embedded in most modern diagnostic ultrasound machines, also allows to record the velocity distribution in liquids. As an imaging technique, diagnostic ultrasound have a limited spatial resolution due to the fact the sound waves do not reflect beyond tissue-fluid interface and therefore the upper palate can only be visualized when there is direct lingual contact, or when a fluid with sufficient sound wave reflective properties fills the oral cavity [39]. Observation of tongue motion is the most common ultrasonography application in swallowing evaluation and Shawker et al. were among the first to make use of ultrasound probes to describe the variation of tongue height in the oral cavity during deglutition of a 5 mL water bolus [60] (Fig. 2.9).
Power and limitations of current diagnostics

Medical imaging examinations allow the practitioner to obtain a better picture for the diagnosis of swallowing disorders. Whilst VFSS and VESS remain the most widely used tools in current clinical practice, new techniques, such as CT and MRI have also been introduced. The potential use of these tools to map the bolus position during swallowing leads to important developments in the understanding of the bolus fluid dynamics. The advantages of CT and MRI in terms of sterical accuracy are however partially cancelled out by the limits of these techniques, that sit in the rigid and unnatural swallowing position that has to be assumed by the patient. The low time resolution also represents a strong limit of the current CT scans. A good balance between image resolution of the soft organs and acquisition speed is often offered by US. The possibility of extracting kinematic data from Doppler spectra represents a key advantage to describe the internal bolus velocity distribution. The drawbacks of the technique is essentially related to its limited field of view that does not allow to get any meaningful information about the bolus flow through the pharynx. Well-established diagnostic techniques such as VFSS and VESS both share advantages and disadvantages with respect their application into the description of the bolus transit during and after swallowing (Table 2.1). Therefore, it is clear that more than one technique should be used to obtain a more comprehensive picture of the swallowing dynamics.

2.4.2 Managing dysphagia

Compensatory approaches to improve the quality of life of dysphagic patients currently mainly consist of changes to food habits and eating posture. Variations in food habits include controlling the size of sips and adjusting textural attributes of food through the use of pureed and minced foods and thickened liquids. Alterations to taste and temperature of food were also found to affect oral awareness in patients with mild forms of dysphagia (61, 62, 63). The eating posture can be adjusted to improve bolus flow, commonly by lowering the head towards the chest prior to swallowing (56).
Table 2.1: Advantages and disadvantages of current imaging techniques with respect to the description of the bolus flow during swallowing.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFSS</td>
<td>Acquisition speed</td>
<td>Bi-dimensional projection</td>
</tr>
<tr>
<td></td>
<td>Different body postures possible</td>
<td>Requires image contrast agents</td>
</tr>
<tr>
<td></td>
<td>Post-swallow residues</td>
<td></td>
</tr>
<tr>
<td>VESS</td>
<td>Different body postures possible</td>
<td>Limited FOV (glottis)</td>
</tr>
<tr>
<td>CT</td>
<td>Three dimensional domain</td>
<td>Fixed body position</td>
</tr>
<tr>
<td>MRI</td>
<td>Three dimensional domain</td>
<td>Low acquisition speed</td>
</tr>
<tr>
<td></td>
<td>Excellent resolution of soft tissues</td>
<td>Requires image contrast speed</td>
</tr>
<tr>
<td></td>
<td>Good resolution of soft tissues</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Different body postures possible</td>
<td>Bi-dimensional projection</td>
</tr>
<tr>
<td></td>
<td>Doppler capability</td>
<td>Limited FOV (oral cavity)</td>
</tr>
</tbody>
</table>

Figure 2.10: The laryngeal prosthesis proposed by Debry et al. has a specially designed cap that allows for the patient to breathe and drink fluids, significantly reducing the risk of aspiration (9).

The implantation of surgical prosthesis in particularly severe clinical cases of dysphagia has also been attempted: an artificial larynx has been developed and tested in vivo by Debry et al. (9). This device, schematically illustrated in Fig. 2.10, represents an important step towards the improvement of the quality of life in patients that underwent total laryngectomy. The particular design of the device allows for normal feeding and breathing through the pharynx with a minimal risk of aspiration.
2.5  *In vivo* studies of the kinematics and the dynamics of swallowing

Diagnostic imaging, combined with other techniques, such as manometry and electromyography (EMG), have been widely used to characterize the trajectories of tissues, the activation patterns of muscles and the time dependent shape of organs during human swallowing [39].

2.5.1 Tongue strength and coordination

The high mobility of the tongue plays a paramount role in food oral processing as is responsible for bolus manipulation and propulsion during the first stages of swallowing. From the physiological point of view, the tongue is composed of both intrinsic and extrinsic muscles: the former are not connected to bones and are responsible for the modulation of lingual gestures. Extrinsic muscles that originate from the skeletal structure of maxilla are instead used to control protrusion, retraction and side-to-side movement of the tongue. Full coordination of the intrinsic and extrinsic muscular activity gives the tongue a high number of degrees of freedom, necessary to shape and hold the bolus before initiation of the deglutition reflex.

Kinematics of tongue motion

The complete description of the kinematics and the dynamics of tongue movement during swallowing has not gained, in the literature, an extensive amount of attention. A few studies have considered the tongue movement in the specific application of logopedics as to investigate the effect of tongue shape on the amplitude and frequency of the vocal sound emitted [64; 65]. However, it has been proved that speech and swallowing, although sharing certain common peripheral structures, require a rather different coordination and muscle activation pattern [64]. Indeed a higher degree of variability in the lingual ges-
2.5. *In vivo* studies of the kinematics and the dynamics of swallowing

Figure 2.11: Kinematic data obtained from Tasko *et al.* who tracked the position of pellets attached to the tongue (10).

In *in vivo* studies of the kinematics and the dynamics of swallowing, particular attention was paid to the position of the tongue and jaw during swallowing. Tasko *et al.* (10) conducted an experiment where they tracked the position of six small pellets attached to the tongue and jaw during water swallows. The authors reported that females exhibit smaller tongue displacements than males. They also suggested that the maximal amplitude of the tongue displacement is correlated with the size of the swallowed bolus. In all cases, the highest deformation velocities were recorded in the posterior part of the dorsum of the tongue (200 mm/s) while 50% lower values were reported in proximity of the apex (10; 61) (Fig. 2.11).

VFSS or VESS do not allow to precisely track the rapid movement of the tongue during the oral phase of swallowing. Instead, the motion of the tongue has been traced either using electromagnetic techniques (upon incorporation of magnetic pellet markers (11)) and diagnostic ultrasounds (59). Using ultrasounds, Stone and Shawker (67) described a tongue movement sequence during swallowing that initiates with a forward protrusion of the tongue followed by a rapid upward movement, palatal contact, and slow forward motion till returning to the rest position.

Further studies, considering an increased number of participants, indicated the presence of a high degree of intrapersonal variability in tongue movement during swallowing. Tasko *et al.* studied the kinematics of tongue motion of 12 healthy volunteers by tracking the positions of six small pellets attached to the tongue and jaw during water swallows (10). The authors highlighted the fact that females exhibit smaller tongue displacements than males. They also suggested that the maximal amplitude of the tongue displacement is correlated with the size of the swallowed bolus. In all cases, the highest deformation velocities were recorded in the posterior part of the dorsum of the tongue (200 mm/s) while 50% lower values were reported in proximity of the apex (10; 61) (Fig. 2.11).
Figure 2.12: Steele et al. used Electromagnetic Mid-sagittal Articulography (EMMA) with transducer coils located on the tongue blade, body and dorsum to study the motion pattern of tongue during discrete and sequential water swallows. Statistically significant differences were found on the study population of 34 healthy individuals (11).

Steele et al. (11) used an electromagnetic technique (EMMA), to track the swallowing-related movements of markers located midline on the anterior, middle, and posterior parts of the tongue for a subset of 34 healthy adults. The authors identified a common modulation of the tongue movement in which the anterior regions of the tongue display greater displacement in the horizontal plane, while the more posterior regions of show instead larger displacements in the vertical plane (11). Further, the authors also provided a comparison between signals recording in the case of single and multiple water swallows, which in itself represents an important element of novelty with respect to other past and contemporary works. Results in this case showed that the coordination necessary to complete sequential swallowing tasks was significantly greater than the case of single swallows (11). The authors showed that higher peak velocities and longer movement durations were recorded for multiple water swallows compared to a single sip. Multiple swallows also occurred with slightly smaller amplitude of tongue displacements (Fig. 2.12). Furthermore, movement variability among individuals was significantly greater in the single swallow condition than in sequential swallows. This somehow reduces the extent of applicability of traditional studies based on the analysis of single discrete swallows.

Medical literature also provides evidence of changes in tongue movements during swal-
In vivo studies of the kinematics and the dynamics of swallowing

lowing with age, however, such differences appear to be only restricted to the domain of movement duration, with slower movements, but similar tongue displacements observed in older, healthy, volunteers (5; 61). Unsurprisingly, a greater variability in the duration and amplitude of tongue movements, in comparison to healthy individuals, is observed in patients affected by neurogenic dysphagia (5). Detailed studies aiming at describing the kinematics of the tongue in dysphagic patients have however not yet appeared.

Dynamics of tongue motion

The quantification of tongue strength has been carried out with specific pressure transducers or ad hoc instruments (Fig. 2.13 and Fig. 2.14). The ability to generate tongue-palate pressure has emerged as a measure of considerable clinical and research interest in the field of dysphagia over the past two decades (5). Key to this interest is that the strength of the tongue, measured during maximum isometric tongue-palate pressure tasks, appears to decline with age (68). Most importantly, reduced tongue strength has also been observed in adults with dysphagia (5). How such changes impact tongue movements, and the extent to which they contribute to the functional changes during swallowing, remains however still unquantified (12). A popular tool to measure the maximum isometric tongue pressure was the Iowa Oral Performance Instrument (IOPI). This device uses a small air filled chamber placed between the dorsum of the tongue and the upper palate (Fig 2.13). Variations in the bulb air pressure, upon palatal tongue compression are recorded by the instrument. The IOPI was initially conceived to determine the relationship between tongue muscle weakness and speech motor control, but subsequently its use has been extended to the evaluation of the swallowing function too. Studies with the device gave scattered values of maximum isometric tongue pressure among the test-populations, with the gender also constituting a relevant variable. Alsanei, considering a large subset of 106 healthy volunteers, has indicated a range of maximum tongue pressures spanning between 10 to 80 kPa, with an average value of 35±10 kPa (12). In the same study, the author also indicates higher pressures (48 kPa) for younger individuals.
Figure 2.13: The Iowa Oral Performance Instrument (IOPI) can be used to measure isometric tongue pressure and tongue applied pressure during dry swallows (12).

The maximum isometric tongue pressure only gives a value of muscular strength, however the dynamic evolution of tongue pressure during swallowing is also of relevant interest as it could be linked to a series of characteristic events occurring during swallowing (13). A number of studies made use of the IOPI to obtain the pressure peak values on the rigid palate during a single wet and dry swallows. This approach has however been questioned by Hori et al. who stated that the insertion of the IOPI probe into the oral cavity prevents evaluation of physiologically natural swallowing kinetics (13). Furthermore, they highlighted the fact that the standardization of measurement point had been insufficient because of the hand-held measuring probe tip design.

Cross comparing studies using different measuring devices, Redfearn has recently indicated a range of maximum applied pressures during swallowing spanning between 1 and 43.5 kPa (69).

Such a wide range can also be viewed under the possible variations to the location of the pressure measurement device. It has been indicated that the maximum applied pressure in different points of the tongue is not identical and, accordingly to Ono et al., higher pressures were measured on the anterior part of the tongue (70).

Hori et al. therefore developed a new setup of specially designed array force sensors with a geometry that could be better integrated during normal swallowing (13) (Fig. 2.14).

The same authors compared the temporal sequence among tongue pressure, supra-hyoid...
2.5. *In vivo* studies of the kinematics and the dynamics of swallowing

Figure 2.14: Hori *et al.* [13] developed an array of transducers to study the lingual-palatal pressure during swallowing.

Figure 2.15: Palatal pressure profiles recorded by Hori *et al.* during a healthy swallow of 4 mL of barium sulphate suspension (40% w/w). Data were obtained using a 5 channel sensor sheet placed on the palate (right) [14].
EMG muscle activity and VFSS measurement during a 4 mL barium swallow both in presence and absence of the force sensors on 15 healthy young volunteers \((14)\). Results showed no significant variations in the recorded duration and delay of events with and without the 5 channel sensor sheet. The time-evolution of the palatal pressure at the front-most position was characterized by either one (monophasic) or two peaks (biphasic) \((\text{Fig. 2.15})\). The tongue pressure was initially generated in the central and middle (anterior-median) region of the tongue to then progressively move to the posterior-median region \((14)\). Readings from the pressure transducers quickly reached their peaks at the onset of swallowing, and then gradually decreased before disappearing almost simultaneously on each of the 5 measuring points located on the hard palate. Values of pressure from the non-median sensors were similar, confirming the sagittal axial symmetry of bolus propulsion. The maximum values of the pressure waves in the order of 18 kPa for the front-most sensor \((14)\). This value, compared to that presented by Alsanei \((12)\) confirms the fact that a consistent functional reserve, with respect to the maximum isomeric pressure, is present, even in case of effortful swallowing. The same conclusion was also drawn by Steele \((74)\) who found that the value of functional reserve is uncorrelated with age.

### 2.6 Properties of the food bolus

Medical research shows that food structure has a paramount role on the ease and safety of swallowing \((72)\). An additional knowledge of food texture is highly desirable for dysphagia specialists, as dietary modifications represent currently one of the most effective recognized compensatory approaches to dysphagia.

In this regard, research in food science, has led to the development of several \textit{in vitro} models to study the oral preparatory phase of swallowing for different bolus textures \((73)\). However, the challenge of fully modelling the path of solid food breakdown has been the subject of several reviews in the past and is still far from being fully addressed \((74)\, (75)\). The existence of a swallowing threshold in terms of bolus particle size, wettability
or bolus cohesion is still debated (74; 75; 76).

Understanding bolus structure at the instant of swallow can help towards designing more effectively novel food and pharmaceutical products.

With this respect, limiting the analysis to liquid formulations allows for a significant simplification of the problem due to the higher bolus homogeneity and the shorter duration of the preparatory phase of swallowing. Studying the swallowing dynamics of structured liquids is also particularly relevant for the management of dysphagia, because thin liquids are prone to be aspirated.

While the structural attributes of solid and semisolid foods are often described in terms of force-displacement (77), rheology and tribology are also commonly used to characterize viscous and viscoelastic foods (78; 79). Several studies have focused on the rheology of texture-modified products used for dysphagia management. In this regard Xanthan gum-based (XG) thickeners proves to be more shear thinning than modified starch-based thickeners and show a significantly higher pH and temperature stability (28; 80; 81; 82). The need for categorization of the product consistency led to the definitions of a few different standards (36; 1). The qualitative description of texture-modified foods relies on extensive sensory tests and seldom allows for direct comparison between different products in terms of measurable rheological properties. In the literature, the level of viscosity for liquid formulations is often referred to the classification published in 2002 by the National Dysphagia Diet (NDD) standardization initiative (83). Under the NDD framework four different consistency levels of thickened liquids are proposed, depending on the shear viscosity at the reference shear rate of 50 s$^{-1}$ (1). Following the NDD standardization, in 2009 similar guidelines were introduced in Japan with minor alterations to the range of viscosities. Other countries have different legal requirements in relation to dysphagia thickeners, that most often do not explicitly refer to quantitative values of viscosity or shear rates (1). To date, there is no yet a worldwide agreement on such categorization, nor the shear rates at which the value of viscosity should be reported (84). This lack of shared agreement has led to the development of various techniques to characterize
Table 2.2: Reference nomenclature and consistency levels of thickened drinks suggested by the 2002 National Dysphagia Diet (NDD) and the 2009 Japanese guidelines (1).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin</td>
<td>η_a at 50 s^{-1}</td>
<td>Less mildly thick</td>
</tr>
<tr>
<td>Nectar-like</td>
<td>0.001-0.05 Pa s</td>
<td>Mildly thick</td>
</tr>
<tr>
<td>Honey-like</td>
<td>0.051-0.35 Pa s</td>
<td>Moderately thick</td>
</tr>
<tr>
<td>Spoon-thick</td>
<td>&gt;1.751 Pa s</td>
<td>Extremely thick</td>
</tr>
</tbody>
</table>

Table 2.3: Consistency levels and nomenclature of thickened drinks proposed by the International Dysphagia Diet Standardization Initiative (IDDSI) (2).

<table>
<thead>
<tr>
<th>Consistency descriptor</th>
<th>Residual hold-up IDDSI flow test</th>
<th>IDDSI Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin</td>
<td>&lt; 1 mL</td>
<td>0</td>
</tr>
<tr>
<td>Slightly thick</td>
<td>2-4 mL</td>
<td>1</td>
</tr>
<tr>
<td>Mildly thick</td>
<td>4-8 mL</td>
<td>2</td>
</tr>
<tr>
<td>Moderately thick</td>
<td>8-10 mL</td>
<td>3</td>
</tr>
<tr>
<td>Extremely thick</td>
<td>10 mL</td>
<td>4</td>
</tr>
</tbody>
</table>

bolus consistency. Among these, the Line Spread Test (LST) is commonly used as a quick and inexpensive semi-quantitative way to correlate the thickness of thickened drinks with the diameter of the pond of liquid spread over a flat surface (83). Although useful at bedside, similar tests cannot provide a sufficient indication of product thickness nor enable for a sound quantitative comparison between different products. In this regard, for instance, the results obtained with the LST are strongly dependant upon inertia and the wetting properties of the liquid. This lack of a worldwide agreement has led to the recent establishment of the International Dysphagia Diet Standardization Initiative (IDDSI), an organization created with the precise aim of developing an internationally recognized set of procedures and standards in the management of dysphagia. The framework of IDDSI proposes an eight-level classification of the consistency of foods and drinks (Fig. 2.16). Thickened beverages are classified via the residual holdup in a standard 10 mL luer slip tip syringe discharging under gravity (2) (Table 2.3).

Although useful, all the above categorizations still oversimplify the rheological problem that excludes information about yield stress, shear behaviour, viscoelasticity and thixotropy.
Sensory studies comparing different food thickening agents report significant variations in the perceived viscosity, depending on the shear behaviour \((85; 80)\). The viscoelastic properties of liquids are also expected to influence the ease of swallow \((86)\). In this regard, \textit{in silico} methods have already highlighted that both shear and extensional flow occur as the bolus gets compressed between the tongue and the palate and during the pharyngeal phase of swallowing \((87)\). To which extent these properties might be important during swallowing is however still to be comprehensively investigated \textit{in vivo}.

In general, the properties of a liquid bolus can differ from those of the pre-swallowed liquid due to dilution with saliva, interaction of hydrocolloids with saliva, enzymatic transformations and temperature gradients. Furthermore the boundary conditions during bolus flow have to be carefully specified in order to account for salivary lubrication.

This complexity has been neglected by past and contemporary \textit{in vitro} and \textit{in silico} models of swallowing, which, so far, have idealized the liquid bolus as either a Newtonian or a simple power-law (PL) fluid. A PL model can represent well the steady shear rheology of Xanthan gum (XG) solutions over the range of shear rates expected during \textit{in vivo} swallowing \((50-300 \text{ s}^{-1})\), but are not adequate to describe the shear rheology of starch-
based thickeners or other types of gums (88). Newtonian models, on the other hand, only apply to water and sucrose syrups: certainly liquids not representative of the common diet of dysphagic patients.

2.7.1 Food thickeners for the management of dysphagia

Food thickeners are widely used to manage dietary needs of dysphagic patients (38). These products are mostly based on hydrocolloids such as modified starch or gums (38). The thickening effect produced by different hydrocolloids depends both on the intrinsic properties of the polymer and on the chemical and physical properties of the solvent.

Starch-based thickeners

Starch is the broad name given to two polymers of glucose, namely Amylose and Amylopectin, found in the chloroplast of plant cells and in the endosperm of grains. The difference among the two starch polymers is essentially due to their constitutional isomery: Amylose chains are linear (α-1-4 bonds) while Amylopectin has a more complex branched structure. In both cases, polymer chains have a molecular weight typically below 1 MDa. In its raw form, starch finds limited use in the food industry: raw starch requires elevated temperature and shear to be brought into solution, produces cohesive, rubbery pastes when heated above the gelatinization temperature, and a gel when the pastes are cooled (retrogradation) (84).

Raw starch can be modified to enhance hydration and improve thermal and pH stability (84). Modified starch are widely used in the food industry as thickeners, stabilizers, gelling agents and emulsifier (89). These products are obtained from raw starch following chemical processing such as hydroxypropylation, acylation and esterification. Physical and enzymatic treatments of raw starches are also widely used. Thermal treatments are employed to produce pre-gelatinized starch making it water-soluble at ambient temperature. Maltodextrins are instead obtained from enzymatic hydrolysis of starch (83).
When used as a food thickener, solutions of pre-gelatinized starch exhibit a progressive build-up of viscosity in time due to the progressive hydration and change of polymer conformation \((84)\). The rheological profile of starch-based thickeners is also affected by the residence time in mouth, due to the enzymatic action of salivary \(\alpha\)-amylase that hydrolyses the \(\alpha\)-1,4-glycosidic bonds. In addition to the physical dilution with saliva, this can cause the bolus to thin below a consistency deemed adequate for safe swallowing in patients affected by dysphagia \((90)\). Further drawbacks of modified starch-based thickeners include the opaque appearance and the grainy texture of the thickened product \((38; 22)\).

**Gum-based thickeners**

Gums are a class of polysaccharides commonly used as food excipients and stabilizers of colloidal suspensions and emulsions in culinary and dairy products. Gum-based thickeners offer significant benefits over classical modified-starch products which include amylase resistance and lower degree of tixotropicity and lower reported amount of post-swallow residues, compared to starch-based thickeners \((22)\).

Among the gums approved as food additives, Xanthan gum (XG, or excipient E415) has been extensively used in a wide range of products. XG is a biopolymer of glucose produced by aerobic bacterial fermentation of *Xanthomonas Campestris* in a concentrated sucrose solution. Its molecular structure is more complex than that of both Amylose and Amylopectin and its average molecular weight is typically an order of magnitude higher than that of raw starch \((91)\). Concentration of XG as low as 0.5% w/w are commonly used for sauces, salad dressings and seasoning, while solutions up to 1.5% w/w XG typically achieve a *Pudding-like* consistency for dysphagia dietary supplements \((92)\). Viscosity build-up of XG solution is due to the hydration of polymer chain and the generation of sterical entanglements \((28)\). This is opposed to the overlap of swollen granules that drives the viscosity increase of modified starch solutions \((28)\). As a result, XG is a more effective thickener per unit mass: comparable levels of product consistency to that of starch-based thickeners are obtained with half the amount of XG-based thickeners \((93; 89)\). Moreover
aqueous solutions of XG are optically clear and have a smoother texture compared to starch-thickened products (89).

XG solutions exhibit a characteristic rheological profile with a pronounced shear thinning behaviour and a very little frequency dependence of the dynamic moduli, typical of entangled polymer systems.

On the contrary, aqueous solutions of modified starch typically show a mild shear thinning behaviour and increasing values of $G’$ and $G”$ with frequency, consistently with the different polymer structure (83).

Gellan gum has also recently been proposed as an alternative to XG, sharing a similar shear thinning profile and the desirable resistance to the enzymatic hydrolisation of $\alpha$-amylase with the additional advantage of gellan gum being an even more effective thickener per unit mass, compared to XG (94).

Finally, other gums, such as guar and locust gum are also used as thickening agents in commercial products for the management of dysphagia. However they provide a lower thermal and pH stability than XG (89). These polysaccharide show a mildly shear thinning and a thixotropic behaviour and are generally used in conjunction to XG and maltodextrins (95).

**Model thickeners and other thickening agents**

Besides starch and gums, other liquids and hydrocolloids can also be used as thickening agents for food and pharmaceutical applications. Some of these products have interesting rheological properties that make them appealing replacements of complex thixotropic products in relation to the applications presented in the following chapters.

Carboxymethyl cellulose is a cellulose derivative widely used as a thickening and binding agents for gravies, fillings, and sauces. It has a less shear thinning behaviour than XG and guar gum with a viscosity that significantly decreases at low pH and in presence of electrolytes (96). Glycerol is instead a thick and dense (SG=1.25 and $\mu$=1.4 Pa.s (97))
liquid commonly employed as a food preservative and widely used as an humectant in pharmaceutical formulations including syrups and oral suspensions (97). Glycerol can be used as a thickener due to the high solubility in water, the clear appearance and the high viscosity. Aqueous solutions of glycerol are Newtonian with a density function of the weight fraction of the components of the binary mixture and the volume contraction of mixing (97). Glycerol solutions are more easily prepared and have a longer shelf life than molasses which makes them a better alternative for Newtonian boli to be tested in vitro.

Finally, polyethylene-oxide (PEO) is a water-soluble polymer mostly used as a binder for cosmetic products, including skin creams, toothpastes and personal lubricants (frequently combined with glycerol). Aqueous solutions of PEO are characterized by a relevant viscoelastic behaviour that increases with the polymer concentration and has been well-documented in the literature. This makes PEO an excellent model to test the effect of viscoelasticity during swallowing using an in vitro model.

2.7.2 Bolus density

Whilst it is clear that alterations to bolus rheology produce some quantitative variations in the swallowing dynamics, it is not clear whether similar conclusions can be drawn with respect to the bolus density. Discriminating the effect of bolus density is not easily attainable in VFSS tests, given the fact that radio opaque solutions are considerably denser than typically water-based thickened liquid solutions (8).

The relative importance of inertia and viscosity can however be quantified by the ratio of their associated stresses, expressed by the Reynolds number ($Re$). Burbidge et al. first discussed the existence of an inertia-dominated regime and a viscous-dominated regime in the oropharyngeal phase of swallowing. The point at which the transition between the two occurs depends on the rheology of the fluid (23).

For Newtonian boli, an increase in the bolus viscosity accelerates the transition to the viscous regime with a growth of viscous stresses at the expenses of the bolus velocity. As
a result, the importance of bolus density on the swallowing dynamics becomes marginal for thick enough liquid boli. This conclusion, already drawn from numerical simulations (53; 98), has also been proven *in vitro* by Mowlavi *et al.*

### 2.7.3 Bolus volume

A few number of *in vivo* studies have discussed the change in the swallowing dynamics resulting stemming from an alteration in the sip volume. The careful control of bolus size is a recognized method to manage dysphagia. In the case of healthy adults, the typical volume of a liquid sip was reported between 10 to 12 mL (99; 12). Other authors instead reported higher values (up to 25 mL for men and 20 mL for women) (53). This gender-specific effect could be explained in terms of the different capacity of the oral cavity (53). Alterations to the swallowing sequence with respect to the size of the bolus have been measured both in terms of timings and displacements of the structures traversed by the bolus. Whilst reviewing the temporal variability in the dysphagia literature, Molfenter and Steele found that the duration of the hyoid movement is positively correlated with the volume of bolus (52). Moreover Butler *et al.* also showed a positive correlation between the duration of the swallowing apnoea in healthy individuals and the volume of the bolus, no matter its consistency (100).

### 2.8 Conclusions

Swallowing represents an extremely complex physiological process that exhibits a strong degree of interpersonal variability. In this regards, attempts to model the whole or part of the swallowng function require to consider the functionality of the oral tissues and the gometry of the oropharynx.

Medical imaging is extensively used in the diagnosis of swallowing disorders and new techniques such as CT and MRI could allow to study in greater detail the flow of a liquid
2.8. Conclusions

A large number of clinical studies in dysphagia literature have been devoted to the investigation of the parameters that can influence and ease bolus transport. Whilst clinical evidence promotes the use of thickened products for the daily management of dietary requirements in dysphagic populations, the mechanisms of action of thickened liquids remain still debated. The swallowing performance of gum-based thickeners is reported superior to modified starches due to the better temperature and enzymatic resistance, the more palatable texture and the higher zero shear viscosity that allows a better perception and control of the bolus in mouth prior to swallowing. The highly shear thinning behaviours of XG thickened liquids also allows for a less effortful bolus transport during swallowing.

The extensional properties of liquids have only marginally been considered by recent dysphagia literature. This leaves room for further research and promote the use of experimental models of swallowing for a more thoughtful understanding of the interplay between rheology and swallowing. The power and limitations of these models are reviewed in the next chapter while a model in vitro experiment to understand the impact of extensional viscosity on swallowing is presented in Chapter 4.
Chapter 3

In vitro and in silico models of swallowing

In vitro and in silico experiments represent attractive complements to the in vivo investigations because they allow varying parameters independently, which is key to understand the effect of different food and drink properties and to adapting them to different needs. The aim of this chapter is to critically examine the current state of the art in the computational and in vitro studies of human swallowing, pointing out their strengths and limitations. Models have helped to clarify the role of bolus rheology in the oral phase of swallowing and the importance of salivary coating in the pharyngeal bolus flow. Few areas of improvements were identified: 1) the use of more realistic geometries and mechanical properties representing the relevant tissues, 2) the need to consider the role of salivary lubrication and 3) the demand for testing a more comprehensive set of food boli. Further clinical studies should also focus on identifying the most realistic motor control strategy to mimic human swallowing.
3.1 Introduction

The complexity of the swallowing process has called for in vitro and in silico simplifications both in terms of geometry, physiology and bolus properties. These simplifications have not always been critically discussed and have only rarely been validated against in vivo results. This review is introduced by a synthetic description of bolus and tissue properties to highlight their astounding level of complexity. In vitro and in silico models are reviewed separately for the oral, pharyngeal and esophageal phases of swallowing. The last section comments on the capabilities and the limitations of these in vitro and in silico models and suggests the future directions for their improvement.

3.2 Mechanical properties of relevant tissues

The biomechanical properties of the connective and epithelial tissue involved in the bolus transit have a paramount role in ensuring the correct functionality of the swallowing process. Moreover, muscular tone and surface properties of the mucosa can significantly condition the efficiency of bolus transport. Previous studies aimed at characterizing the mechanical properties of oral and pharyngeal tissues with ex vivo tests in animals with similar digestive and associated metabolic processes to humans (101). These tests are typically carried out by indentation, torsion and suction and aim at mapping the stress-strain behaviour of the material with a constitutive law (102). For sufficiently small applied stresses, linear elasticity can be assumed, leading to considerable simplifications in the description of the structural dynamics of the problem. In the case of isotropic and incompressible materials, the problem reduces to the determination of a single parameter represented by the Young’s modulus (E).

In general however, the constitutive model that governs the stress-strain response of tissues can seldom be simplified with a constant elastic modulus, due to the significant hardening followed by muscle activation (101, 103). This is well illustrated by Duck et al. who measured nearly a 10-fold increase in the elastic modulus of the tongue when
contracted, with respect to the values measured at rest. In this regard, Shibata et al. report average values of Young’s modulus spanning between 10 kPa at rest to 60 kPa during active muscular contraction. Aside from the increased stiffness due to muscular activation, a strain hardening response of the physiological tissues is also commonly observed at higher applied stresses. In these conditions, a correction to linear elasticity is offered by hyperelastic models that can describe the stress-strain behaviour in terms of the derivative of the strain energy density.

An additional characteristic of muscular and epithelial tissues is their viscoelasticity. Non-invasive diagnostic tools such as Magnetic Resonance Elastography (MRE) have enabled the *in vivo* quantification of the viscoelasticity of the tongue and the palate in its passive state during normal and assisted breathing. MRE was also used to quantify the anisotropy of muscular fibres that leads to tongue hardening in patients affected by Obstructive Sleep Apnoea (OSA). Using MRE Cheng et al. reported values of shear storage modulus of about 2.7 kPa for the tongue and slightly lower values for the soft palate when measured in their relaxed state during normal breathing. When considering the lingual tissues in their active state other studies reported a 5-fold increase in the storage modulus (from 1.5 to 8.8 kPa), a behaviour that closely follows the increase in Young’s modulus. Cheng et al. did not report a significant difference in magnitude between the measured storage and loss moduli. This finding indicates the relatively high importance of the energy dissipation followed by the shear deformation of the tissues.

Cartilaginous structures such as the larynx and the epiglottis have not yet been comprehensively described in terms of mechanical properties. Some studies managed to correlate the rigidity of connective tissues with the quantity of collagen. Measurements *ex vivo* in rabbits indicate values of Young’s modulus of the epiglottis in the order of 0.25 MPa for strain up to 20%.

Concerning the assumption of tissue incompressibility, the data available suggest values of Poisson ratios close to 0.5 for predominantly muscular structures. Conversely, cartilaginous structures, such as the epiglottis and the larynx, exhibit a higher compressibility.
due to the more complex structure made up of collagen chains bounded by proteins (110). The assumption of incompressibility applies to the tongue and the body of the pharynx, being predominantly comprised by multiple muscular tissues (111; 110). The structure of these two organs is not supported by a skeletal system but the musculature itself acts both for support and actuation. A significant anisotropy then stems from the directional orientation of muscular fibres within the tongue. The deformability of the pharynx together with the properties of the mucosa have comprehensively been described in relation to the condition of pharyngeal collapse, observed in patients affected by obstructive sleep apnoea (OSA) (101; 110).

Correctly capturing the structure of the oral mucosa lining the pharynx is particularly important in view of modelling its interaction with the bolus. The epithelial tissue is composed of a rigid non-keratinized layer supported over highly vascularized connective tissues that provide a viscous damping effect, particularly important to protect palate and cheeks against wear during mastication. The mucosa is therefore a highly anisotropic and viscoelastic material whose mechanical properties have not yet been fully characterized. A recent review by Chen et al. comprehensively examined the structure and mechanical models of pharyngeal mucosa reporting the broad spectrum of Young’s moduli reported in the literature, that span between 0.1 to 19 MPa (101).

3.3 Salivary lubrication

Saliva is a complex slightly acidic biological fluid that plays an essential role in food oral processing (112; 113). Saliva is needed to 1) moisten and lubricate the oral tissues, 2) clear food debris and bacterial products from the oral cavity, 3) buffer the acids produced by bacteria, 4) initiate the digestion of starches (114). The degree of oral lubrication significantly contributes to the oral perception of foods (115; 116). The role of saliva is also instrumental for bolus preparation before swallowing (50).

The influence of mucosa properties on the friction between bolus and oral cavity is greatly
Chapter 3. *In vitro and in silico* models of swallowing

Influenced by the degree of salivary lubrication of the epithelium (115; 117). A permanent thin layer of saliva is adsorbed on the oral and pharyngeal mucosa. The thickness of this pellicle was reported in the range between 30 and 100 nm, depending on the surface roughness of the underlying tissues (113). Measurements carried out on normal subjects and patients with salivary hypofunction indicated values of salivary thickness of ranging from approximately 5 µm on the hard palate to 25 µm on the tongue dorsum (118), consistently with its significantly coarser surface roughness (119).

The composition of saliva is mainly made up of water (>99% w/w) (120; 112) while the physical and chemical properties of saliva are significantly affected by the concentration of mucins: large proteins (0.5-20 10^6 g/mol) composed of an amino acid backbone with chains of sugar residues (24; 114). Enzymes are also present in saliva. Salivary amylase, for instance, initiates the hydrolysis of the α-1-4 bonds of amylose (i.e. starch) to oligo- and di-saccharides. The characteristic kinetics of salivary α-amylase depends on the spatial configuration of the form of starch considered (114). The composition of saliva has a paramount role in determining its rheological and tribological properties (114; 121; 122; 112; 113). Entanglements between mucins give saliva a mildly shear thinning rheology (114; 121; 122; 112). Saliva is also characterized by a high elongational viscosity. Ratios of elongational to shear viscosity higher than 100 are reported in the literature (121).

The role of salivary lubrication, in relation to food oral processing, has been the subject of an increasing number of studies in the literature (123; 113).

The tribological properties of saliva have been studied in relation to the sensation of creaminess, smoothness and astringency (75). Attempts to measuring a salivary coefficient of friction have recently included soft elastomeric substrates to simulate a more faithful contact pair that accounts for the deformability of biological tissues (115; 122).

Different studies however give often inconsistent results, as it was shown that the properties of human saliva greatly depended on the method of stimulation, pH, donor and the way the biological samples are processed before experiments (124; 114; 113). The interaction of the salivary lubricating layer with soft tissues results in a further reduction of the
friction coefficient that can be described coupling the in terms of elastohydrodynamics \((125)\). Values of friction coefficient two orders of magnitude lower than those obtained for water were reported for mechanically stimulated whole human saliva in the boundary lubrication layer \((122)\).

Measurements of wettability of the oral and pharyngeal mucosa are rarely attained \textit{in vivo} and information on contact angles and adhesiveness still relies on \textit{ex vivo} or animal data \((114)\). The surface tension of mucous was described in relation to the magnitude of pressures required to separate mucosal surfaces that come into contact during airway collapse in patients affected by OSA \((126)\). Further relevant studies considered the mucoadhesion in the esophagus for pharmacology and tablet design. \textit{In vitro} experiments have been set up to quantify the adhesion and detachment force of tablets against a simplified model of esophageal mucosa lined with artificial saliva \((127)\).

**Salivary secretion**

Salivary secretion is a reflex mostly stimulated by chemical and mechanical stimuli \((114)\) and the parotid, submandibular and sublingual glands are the main secretion centres of saliva. The largest of the three is the parotid, located in front and below (antero-inferior) the ear. Submandibular salivary glands are located within the lower mandible, and their salivary ducts open beside the lingual frenulum. The sub-lingual glands are located beneath the floor of the mouth and account for more than 60% of the total flow rate of saliva when stimulated by taste or chewing \((128)\). Other than the three main salivary glands, there are many other minor secretion centres located throughout the oral cavity, such as the Von Ebner glands \((114)\). The rate of production of saliva varies significantly among individuals and the type of stimuli received. The mean flow rate of unstimulated saliva reported in the literature is in the order of \(0.4\pm0.25\) mL/min \((24)\). A consistent decrease in the measured salivary flow rate was observed for elderly individuals. The extent of this reduction was reported of about 38% both for unstimulated and stimulated saliva \((113)\). Moreover, changes in salivary composition were also highlighted with age.
In their recent review paper Xu et al. report that saliva from elderly donors shows a higher ionic concentration and a thicker consistency that limits the water retention capacity of mucin and leads to oral dryness (113). Insufficient salivation (xerostomia) can lead to discomfort while swallowing together with a measurable increase in post-swallow residues (129).

3.4 Swallowing motor control

Capturing the dynamics of swallowing in a model is a complex task because of the complex time-dependant field of motion and the fluid-structure coupling. The sequence of movements and the spatial reconfiguration of the pharynx during swallowing has to ensure efficient bolus transport and full protection of the airway against aspiration. The central nervous system is responsible for the initiation and the coordination of the swallowing process through a sensory feedback from the oral and the pharyngeal cavities (130; 131; 132). Both reflexive (or automic) and volitive (voluntary) behaviours concur to control swallowing (133). Wong et al. showed that the trajectory of the hyoid bone and the extent of larynx elevation in different subjects are adapted to maximize airway protection (134).

From an engineering perspective, four main alternative swallowing control scenarios can be envisaged: 1) imposed displacements (with no control), 2) imposed forces (with no control), 3) feed-forward control adapting the applied forces or displacements to the bolus characteristics perceived before the swallow, 4) feedback control during swallowing, adapting forces or displacements.

In vitro and in silico approaches to modelling swallowing have so far simplified the in vivo motor control either by considering an imposed kinematics (also known as displacement or strain control) or by prescribing stresses (force control). Modern diagnostics has made it reasonably easy to measure the displacement of the tissues involved in swallowing and this has induced some authors to impose the measured displacements in their in vitro and in silico models, assuming implicitly that these displacements are constant regardless of the
properties of the fluid being swallowed. On the contrary, in a prescribed force (or stress) model, the bolus dynamics is directly influenced by the properties of the bolus being swallowed. Consistently with an imposed-stress flow, in vivo ultrasound observations by Mowlavi et al. showed an increase in oral transit time with increasing viscosity (8). Other in vivo studies also found different swallowing patterns when consuming solid foods compared to drinks (131). More complex, feed-forward or feedback control loops should also be considered. Some evidence supporting a feedback control was obtained applying anaesthesia to the larynx, as this was found to induce laryngeal penetration, and tracheal aspiration (131, 135).

### 3.5 In vitro and in silico models of human swallowing

#### 3.5.1 In vitro and in silico models of the oral phase of swallowing

The transport of a liquid bolus from the mouth to the pharyngeal cavity is preceded by the coordinated movement of the tongue, lips and cheek muscles, necessary to hold the bolus preventing it from prematurely spilling into the pharynx and to separate the bolus into multiple sips (23). A quantitative understanding of the condition for liquid bolus spillage is of particular importance in patients with poor tongue coordination. In vivo studies have already proved how thicker fluids can promote sensory awareness and allow a better bolus control in the mouth. This last aspect has not yet been investigated in vitro, despite presenting some similarity with the classical, well-known problem of sloshing. In the past, some anatomically sound applications of computational methods have been reported to simulate air flow through the oral cavity to study speech production and to investigate syndromes such as the OSA (136, 65), while other studies have been dedicated to modelling food breakage in the oral cavity during mastication (137).
Bolus containment in the oral cavity has been considered by Nicosia et al., using a two-dimensional domain that replicates simple lingual gestures against the hard palate during swallowing \(^{138}\). In this study, forced oscillations were applied to a time variant function describing the tongue dorsum shape. Sloshing of an equivalent bolus volume of 5 mL was simulated in the case of three different levels of thickness for Newtonian liquids of respectively 0.01, 0.1 and 1 Pa.s. Outcomes of the study proved more contained sloshing amplitudes and frequencies when considering thicker liquids, that translates into an easier bolus containment compared to thinner boli. The authors were able to tackle the computational issues stemming from modelling free surfaces under large deformations by using an Arbitrary Lagrangian Eulerian (ALE) method.

Few models for the bolus propulsion in the oral cavity have previously been described building on the availability of \textit{in vivo} palatal pressure measurements. Theoretical estimations of shear rates associated with the squeezing action of the tongue against the palate during the oral phase of swallowing have been provided by Nicosia et al. \(^{139}\). Their approach finds roots in studies considering the sensory perception of different viscous fluids between tongue and palate \(^{78}\). The squeezing action of the tongue was idealized with a pair of circular undeformable parallel plates in between sits a viscous Newtonian bolus. The radius of these plates was chosen to match the area of the tongue dorsum, with an initial gap set to host a 3 mL bolus. A uniform pressure distribution between 7 and 33 kPa, based on contemporary \textit{in vivo} data, was applied to the bottom plate to mimic the squeezing action of the tongue against the palate. The physical properties of model Newtonian liquid solutions were investigated, varying the density (SG between 1 and 3) and the viscosity (\(\eta\) between 0.001 and 100 Pa.s). A non-slip condition was applied at the fluid-solid interface and the time required to clear half the gap between the plates was identified as a descriptive parameter of the study. The authors showed that the effect of liquid density on the predicted squeezing time is important only for viscosity lower than approximately 0.1 Pa.s, while the inertial effects become negligible at viscosity larger than 1 Pa.s. Squeeze-flow time is inversely proportional to the applied tongue pressure and the authors predicted higher maximum shear rates for thinner liquids.
The boundary condition originally chosen by the authors neglected the presence of a salivary layer. As saliva interposes between the bolus and tissues, part of the velocity gradient can be supported within the thin layer of lubricating fluid \textsuperscript{(139)}. This effect can be accounted for by a wall-slip condition. The introduction of wall slip leads to a significant decrease in the shear rates, in particular for thinner liquids \textsuperscript{(139)}.

The studies above are however limited to the domain of Newtonian fluids, while most food products and texture modified foods used in the management and assessment of dysphagia exhibit a significantly more complex rheological behaviour. Oral spreading of dairy products was considered both \textit{in vitro} and \textit{in silico} by Mossaz \textit{et al.} \textsuperscript{(140)}. The authors investigated the evolution of the spreading area of yogurt and cottage cheese, described through a Herschel-Bulkley model, between a parallel plate geometry to model the tongue compression against the hard palate. The model considered constant-speed squeezing of the bolus between the plates (between 5 mm/s and 30 mm/s) to a prescribed maximum strain, whilst in-line monitoring the applied force. This was followed by a second phase of compression at constant force (F=1-10 N). Coherently with results from Finite Element simulations (FE), \textit{in vitro} tests show that the lower the squeezing speed, the greater the spreading area for the same instantaneous compression force. Alterations to the surface finishing of the plates only led to variations in the size of the spreading area during the constant force compression phase. The effect of partial slip at the wall was investigated \textit{in silico} leading to a significant reduction in the compression force required to obtain the same bolus strain. However, both salivary lubrication and tissue elasticity remained unaddressed. Moreover the transition between the regime of imposed strain to imposed stress was not investigated in depth.

In an attempt to more comprehensively simulate the bolus transport in the oral phase of swallowing, Mackley \textit{et al.} \textsuperscript{(28)} proposed an \textit{in vitro} device, whose geometry was meant to approximate the tongue-induced peristaltic motion in the oropharyngeal cavity. The setup is conceptually similar to a peristaltic pump with the single degree of freedom represented by the angle of rotation. The liquid bolus is confined within a dialysis tube attached to the palate of the model while the tongue propulsion is modelled by the squeezing action
of a roller driven by an external load. The bolus is therefore driven by imposing a force rather than a displacement. The measured \textit{in vitro} transit times increased with increasing concentration of the thickener, above a threshold concentration of about 3%, which corresponds to a \textit{Nectar-thick} consistency for the commercial thickeners considered in the study \cite{28}. This finding follows the experimental observation that thicker fluids flow less rapidly in the oropharynx, hence confirming the imposed-force approach considered by the study. Using the same \textit{in vitro} model, the authors also attempted to characterize the interaction between the bolus and epiglottis highlighting the occurrence of bolus splitting with increasing bolus viscosity. In this case however, a meaningful comparison with \textit{in vivo} data was not reported to validate the findings.

In a subsequent study, Hayoun \textit{et al.} \cite{29} improved the original design of Mackley \textit{et al.} and proposed a theory capable of predicting the \textit{in vitro} bolus velocity profiles from 1) the viscosity of the Newtonian liquid tested and 2) the applied force to the roller. The authors were able to provide a qualitative comparison between \textit{in vitro} experiments and \textit{in vivo} ultrasound data when swallowing molasses. The authors categorized two regimes of bolus dynamics: one dominated by the rotational inertia and the other one driven by bolus viscosity. An extension of their study to non-Newtonian liquids considered the shear thinning behaviour of aqueous solutions of a commercial thickener and provided a quantitative \textit{in vivo} validation. \cite{8}. Furthermore, the authors were able to prove the negligible effect of bolus density for viscous boli in the \textit{in vitro} swallowing dynamics by comparing the results obtained with water based solutions (SG=1) against standard barium sulphate liquids used in videofluoroscopy study (SG=1.4). These studies therefore contributed significantly to bridge the gap between physical measurable properties (bolus volume, density and shear viscosity) with the bolus velocity, and therefore oral transit time, in a geometry that still retains a degree of similarity with the human oral cavity. Although these studies proposed an \textit{in vivo} validation, the clinical data lacked measurement of the tongue pressures.

Recently, Redfearn and Hanson \cite{69} proposed an \textit{in vitro} model to characterize the squeezing action of the tongue against the hard palate at the initiation of the oral phase of
3.5. *In vitro* and *in silico* models of human swallowing

Figure 3.1: Mowlavi *et al.* used an *in vitro* model experiment, at imposed stresses, to study the oral swallowing dynamics. Visual comparison between *in vivo* ultrasound images and *in vitro* tests with thick Newtonian boli was also provided by the authors (8).

Figure 3.2: Swallowing simulator, developed by Noh *et al.* to replicate the oropharyngeal sequence of swallowing at imposed strains. The flow of liquid and semisolid boli was visualized through VFSS (15).

Figure 3.3: Schematics of the pharyngeal peristalsis simulator, operating at imposed strains, developed by De Loubens *et al.*
Chapter 3. *In vitro and in silico models of swallowing*

Figure 3.4: Schematics of the elastohydrodynamic model proposed by Mathieu *et al.* to evaluate the pharyngeal lubrication at imposed strains (cylinder rotational speed) and stresses (contact force) (16).

Figure 3.5: Prototype and structural Finite Element (FE) simulation of a soft polydimethylsiloxane (PDMS) tongue proposed by Lu *et al.*. The organ can elongate and bend due to the differential stresses generated at the interface of upon inflation of embedded sets of air chambers (17).
swallowing. This bi-dimensional model is operated imposing fixed displacements and monitoring both the pressure and velocity distribution along the bolus during the oral transit. The bolus velocities presented by Redfearn et al. are however lower than the in vivo measurements reported by Mowlavi et al. 

A model experiment to study the force required to clear the bolus from the oral cavity to the pharynx through the GPJ was recently proposed by Ng et al., using a slip extrusion test in which model liquid and gels are extruded in a plastic bag pulled through a pair of rollers at constant speed (141). The authors found a good correlation between measured deformation, slip resistance, and hardness and viscosity of the different samples. However, clinical implications of a similar testing method were not presented by the authors: the speed of bolus transport is limited to 20 mm/s and the deformation of the plastic membrane used to mimic the oral cavity occurs symmetrically without considering the rigidity of the hard palate.

Insights on the modelling of lingual gestures

The tongue has a fundamental role in ensuring bolus containment and propulsion. Models of tongue pressure patterns during the oral phase of swallowing are available in the literature and the mobility of the tongue has been the subject of a variety of in vivo and in vitro studies, not just limited to its action during swallowing. Talking robots have long been under development at Waseda University in Tokyo. The latest evolution of the original prototype was able to control the movement of a rubber tongue with seven degrees of freedom, three for the tip, two for the blade and the remaining two in the body (142). Another mechanical device, inspired by the motion of the tongue, and actuated through tendons was developed by Kawamura and co-workers. But it is only recently that advances in robotics allowed for the development of manipulators particularly suitable to replicate motion of unstructured tissues, able to compress, elongate, and bend in multiple directions simultaneously similarly to an octopus tentacle (143). These characteristics, that started to get exploited for grippers and soft manipulators, are attractive
when considering the design of an artificial tongue. Unlike conventional robots moved by imposed linear and angular displacements of rigid links, the kinematics of soft robots is governed by inflation and deflation of air chambers embedded in a support material characterized by high deformability. Recent studies focused on the development of a soft robotic tongue actuated under inflation of six internal air chambers embedded in a sandwich of elastomeric layers. The size of the prototype conserves the general proportions of the human tongue while simplifying its overall shape (Fig. 3.5). Separate control of the air pressure in the different chambers allows to replicate simple lingual gestures, such as tongue protrusion, bending and twist. Structural simulations, run using a commercial software, allowed to validate the in vitro kinematics by tracking the position of different markers on the tongue tip (17). However, to date, multimodal bending, required to mimic tongue propulsion during the oral phase of swallowing, cannot yet be simulated by the device. Moreover, the dynamic response of the device was not investigated.

In silico models of the oral phase of swallowing

Structural and acoustic grid methods have been employed to study the motion of the tongue and speech production (65), but these become inadequate and computationally expensive when dealing with swallowing. Classical FE simulations based on a Lagrangian approach to represent the liquid domain cannot cope with very the large deformations at the interface, such as those observed during bolus flow. On the other hand, Eulerian methods used to simulate the air-liquid interfaces are also of limited applicability, due to the numerical diffusion arising from the advection term in the momentum balance. Methods based on an ALE frameworks are potentially able to give useful insights in the computational model of bolus flow. However, they appear to be computationally expensive and still unable to fully model high deformation of the liquid domain (144).
### Table 3.1: List of *in vitro* and *in silico* studies of the oral phase of swallowing.

<table>
<thead>
<tr>
<th>REF</th>
<th>Bolus model</th>
<th>Measurement</th>
<th>Methodology</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(138)</td>
<td>Newtonian liquids ( \eta = 0.01, 0.1 \text{ and } 1 \text{ Pa.s.} )</td>
<td>Condition for bolus spillage under prescribed lingual gestures.</td>
<td>2D FE simulation with imposed wall displacements.</td>
<td>Thicker liquids avoid premature spillage in the pharynx under sloshing.</td>
</tr>
<tr>
<td>(140)</td>
<td>Commercial yogurt and cottage cheese modelled as Herschel-Bulkley fluids.</td>
<td>Bolus spreading area in a squeezing flow between two parallel plates.</td>
<td><em>In vitro</em> model with imposed strain and stress.  Numerical FE simulation with imposed wall displacements.</td>
<td>Thicker boli spread less and the spreading area is inversely proportional to the applied strain.</td>
</tr>
<tr>
<td>(139)</td>
<td>Newtonian liquids ( \eta = 0.01, 0.1 \text{ and } 1 \text{ Pa.s.} )</td>
<td>Time required for oral clearance and shear rates as a function of bolus density and viscosity.</td>
<td>Mathematical model with imposed stresses.</td>
<td>Slip boundary condition reduces the time required for oral clearance and shear rates at the wall.</td>
</tr>
<tr>
<td>(29)</td>
<td>Newtonian liquids ( \eta = 0.006-1.2 \text{ Pa.s.} )</td>
<td>Oral transit time and velocity supported by a predictive model.</td>
<td><em>In vitro</em> model with imposed stresses.</td>
<td>Oral transit times increase with bolus volume and viscosity.</td>
</tr>
<tr>
<td>(8)</td>
<td>Newtonian liquids ( \eta = 0.006-1.2 \text{ Pa.s.} ) and barium sulphate and commercial gum-based thickener.</td>
<td>Oral transit time and velocity supported by a predictive model.</td>
<td><em>In vitro</em> model with imposed stresses.</td>
<td>Negligible inertial effects of bolus at high viscosity.</td>
</tr>
<tr>
<td>(30)</td>
<td>Newtonian liquids ( \eta = 1.05 \text{ Pa.s and } \eta = 0.03 \text{ Pa.s as vehicles for oral solid dosage forms.}</td>
<td>Oral transit time, bolus tail velocity and relative position of the tablets within the bolus.</td>
<td><em>In vitro</em> model with imposed stresses.</td>
<td>Tablet size and shape affect oral transit time.</td>
</tr>
</tbody>
</table>
More recently, mesh-less methods have been employed to give a better visualization of fluid splashes and large transformations, that are not optimally captured with FE methods. The conceptual idea behind particle methods is that a fluid could be represented as an ensemble of calculation points (i.e. particles). Each fluid particle represents a small domain of fluid containing parameters of local pressure and velocity. The calculation points, unlike classical mesh-based FE methods, are allowed to move in space as a result of their kinetic attributes. Following the trajectory of the particles in a Lagrangian framework suppresses the numerical instability caused by the presence of advection terms in the conservation equations, and gives a realistic representation of flow phenomena, especially in the case of splashing and sloshing. The set of governing equations of fluid flow are described as the interaction between the reference particle and its neighbours, and thus the computational grid is not required.

By date, the two most widely used particle methods for flow characterization are the Moving Particle Semi-implicit method (MPS) and the Smoothed Particle Hydrodynamics.
3.5. *In vitro and in silico models of human swallowing*

(SPH). Conceptually, both models share a similar structure, despite having appeared in two remarkably different frameworks.

The MPS method was originally developed by Koshizuka *et al.* and is of relevant use to model free surfaces of incompressible fluids (146). The fundamental equations of conservation of mass and momentum in the case of a non-compressible fluid are expressed in a Lagrangian form and are discretized as particle interaction models. Every particle of the model interacts only with surrounding particles within a certain radial distance. A kernel function is defined to account for neighbour interactions between particles and algebraic operations, defined on scalar and vectors, are approximated. The interfacial properties are considered using a continuum surface force model, which adds a force proportional to curvature of the interface on the free surface, calculated on two density functions.

Smoothed Particle Hydrodynamics (SPH) is a technique alternative to MPS that can be used for fluid dynamics simulations in the presence of high surface deformations. Originally developed for astrophysics simulations, the SPH method has been used to simulate free surface flow and solid-laden liquid flows (147, 148). In particular, SPH simulations have been extensively used in computer graphics to obtain realistic rendering of moving liquid interfaces. Like the MPS, the SPH is a Lagrangian mesh-free method that discretizes the conservation equation using particles. Using both the SPH and MPS conceptions, any quantity of particle can be approximated by the direct summation of the relevant quantities of its neighbouring particles. However, differently from the MPS algorithm, the SPH governing equations are that of compressible fluids and therefore require to be closed by an equation of state. Moreover the gradients and divergence terms of the conservation equations are computed through the differentiation of the kernel function that has therefore to be continuous, and is thereby characterized by a more complicated mathematical definition in respect of the MPS.

Meshless methods have already been used to study the oral and pharyngeal phases of swallowing. Ho *et al.* (98) performed a structural analysis of the tongue, palate, and oropharynx using a FE model implemented in ArtiSynth, an open source software specif-
ically designed for biomechanical simulations (149). In the study the authors considered the bolus transit with a SPH model for which the fluid bolus consisted of just below 400 particle elements, roughly corresponding to a simulated swallow of 1.3 mL. The boundary conditions were expressed by dummy particles lining the surface of the solid organs, enforcing a non-penetration constraint. The authors did not properly justify the choice of their boundary conditions, as the use of such boundary particles can allow slip in the tangential direction. The effect of gravity was not accounted for as the main aim of the researchers was to demonstrate that the SPH method is stable enough to withstand the squeezing flow deformations imposed by the motion of the tissues.

Later, Farazi et al. used SPH to obtain a much more realistic visualization of a liquid bolus swallow (150). The simulations made use of more than 2500 particles simulating swallowing of 20 mL of two Newtonian liquids of different consistencies: water ($\eta=0.001$ Pa.s) and a Nectar-thick bolus ($\eta=0.01$ Pa.s). A no-slip boundary condition was applied at the liquid-solid interface. The three dimensional model of the oropharyngeal cavity was built based on a symmetrical reconstruction of the anatomical structures from 2D videofluoroscopy images. The kinematics of the organs was instead modelled on VFSS, thus giving the study clinically sound timings. The structural FE simulation was implemented with the same freeware software used by Ho et al. A one-way fluid structure interaction was used for the combined FE/SPH simulations. The authors however suggested that the approach could be extended to consider a full two ways coupling. Unfortunately, the study does not provide any quantitative results aside from the qualitative conclusion that an increase in bolus viscosity results in a slower swallowing dynamics. This leaves significant space for further validation of particle methods to geometries and boundary conditions relevant for the oral phase of swallowing.
3.5.2 \textit{In vitro} and \textit{in silico} models of the pharyngeal phase of swallowing

Significant rapid alterations to the bolus field of motion occur in the pharyngeal phase of swallowing. This begins with the bolus front passing through the GPJ and conventionally terminates when the bolus front enters the UES. This stage of swallowing is characterized by relevant and rapid alterations to the geometrical domain of the bolus field of motion, following the triggering of the complex series of mechanisms held in place to protect the airway.

Table 3.2: List of \textit{in vitro} and \textit{in silico} studies of the pharyngeal phase of swallowing.

<table>
<thead>
<tr>
<th>REF</th>
<th>Bolus model</th>
<th>Measurement</th>
<th>Methodology</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>Jelly samples of different hardness.</td>
<td>Bolus transit time and position as a function of time.</td>
<td>3D FE simulation with imposed deformations of the pharynx, prescribed initial velocity of bolus and wall friction.</td>
<td>Soft boli deform more in the region of the epiglottis.</td>
</tr>
<tr>
<td>25</td>
<td>Newtonian liquids with $\eta$ between 0.026 and 0.4 Pa.s.</td>
<td>Experimental and theoretical values of thickness and composition of the pharyngeal coating.</td>
<td>Mathematical model and \textit{in vitro} experiments. Imposed kinematics fixed geometry.</td>
<td>The thickness of the salivary layer and the viscosity ratio with the food bolus affect the residue coating on the pharyngeal mucosa.</td>
</tr>
<tr>
<td>26</td>
<td>Newtonian liquids with $\eta=0.005$ and $\eta=0.05$ Pa.s.</td>
<td>Values of thickness and composition of the pharyngeal coating.</td>
<td>Mathematical model. Imposed kinematic constraint on peristaltic wave velocity.</td>
<td>Velocity, viscosity ratio and deformability of the mucosa all influence the thickness of the liquid coating.</td>
</tr>
<tr>
<td>REF</td>
<td>Bolus model</td>
<td>Measurement</td>
<td>Methodology</td>
<td>Conclusions</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>[152]</td>
<td>Water and two shear thinning PL liquids (K=30 and 4.5, n=0.17 and 0.63 respectively). Three volumes of boli 2, 5 and 10 mL.</td>
<td>Bolus velocity and conditions for bolus aspiration in simulated swallowing abnormalities.</td>
<td>3D FE simulation with Eulerian grid for bolus flow. Imposed motion of the pharyngeal walls and fixed initial acceleration of the bolus.</td>
<td>Bolus velocity in the pharynx increases with its volume and is not strongly dependent on the liquid rheology. Small boli lead to post swallow aspiration.</td>
</tr>
<tr>
<td>[144]</td>
<td>Water $\eta=0.001$ Pa.s and SG=1.</td>
<td>Leading edge position of collapse of a water column and visual assessment of the swallowing behavior in a 2D geometry.</td>
<td>3D MPS simulation with imposed wall displacements.</td>
<td>Highlighted and tackled issues at modelling structural mechanics with particle methods.</td>
</tr>
<tr>
<td>[28]</td>
<td>Water, 1% XG and two commercial starch- and gum-based thickeners.</td>
<td>Transit times and effect of the epiglottis.</td>
<td>In vitro model with imposed force.</td>
<td>Increased oral transit times with viscosity and increased bridging in proximity of the model epiglottis.</td>
</tr>
</tbody>
</table>
### 3.5. *In vitro and in silico models of human swallowing*

<table>
<thead>
<tr>
<th>REF</th>
<th>Bolus model</th>
<th>Measurement</th>
<th>Methodology</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>[98]</td>
<td>1.3 mL of water-thin and honey-thick Newtonian liquids ($\eta=0.001$ and 10 Pa.s, SG=1).</td>
<td>Qualitative swallowing behaviour.</td>
<td>3D SPH numerical simulation with imposed wall displacements.</td>
<td>SPH can handle liquid structure coupling in the pharynx. Water-thin bolii leave the oral cavity with a greater velocity.</td>
</tr>
<tr>
<td>[154]</td>
<td>Newtonian liquid ($\eta=0.0025$ and SG=1) and a PL thickener (K=5.6 n=0.276)</td>
<td>Velocity and force distribution in a control region close to the epiglottis.</td>
<td>3D MPS simulation with imposed wall displacements.</td>
<td>Thickened bolii had lower maximum velocity in the pharynx and flow with a narrower velocity distribution.</td>
</tr>
<tr>
<td>[155]</td>
<td>Shear thinning liquid K=20.5, n=0.39 and SG=1.8.</td>
<td>Velocity and shear rate in an axial symmetric domain.</td>
<td>Immersed boundary axial-symmetric simulation with imposed wall displacements and inlet pressure.</td>
<td>Channeling occurs at the walls in for high peristaltic wave pressures. A combined shear and extensional flow is observed in the pharynx.</td>
</tr>
<tr>
<td>[150]</td>
<td>Water and a $\eta=0.01$ Pa.s liquid.</td>
<td>Numerical stability of the coupling between structural domain and liquid domain.</td>
<td>3D SPH simulation with imposed wall displacements.</td>
<td>Water-like bolii escape the oral cavity with greater velocity than the nectar-like bolii.</td>
</tr>
<tr>
<td>[145]</td>
<td>Dry swallow.</td>
<td>Movement of the epiglottis following activation pattern of muscles during swallowing.</td>
<td>3D MPS numerical simulation with imposed wall displacements.</td>
<td>High friction coefficient between tissues can limit the motion of the epiglottis.</td>
</tr>
<tr>
<td>REF</td>
<td>Bolus model</td>
<td>Measurement</td>
<td>Methodology</td>
<td>Conclusions</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>[80]</td>
<td>Aqueous solutions of a commercial thickener $\eta=0.16$-0.95 Pa.s at 50-10$^{-1}$.</td>
<td>Bolus transit times between two markers in a vertical plane.</td>
<td><em>In vitro</em> model with imposed stresses.</td>
<td>Longer pharyngeal transit times and higher pharyngeal residues with increasing bolus viscosity.</td>
</tr>
<tr>
<td>[156]</td>
<td>Newtonian liquid $\eta=0.002$ Pa.s</td>
<td>Time variant particle density in a control region close to the epiglottis and average bolus velocity.</td>
<td>3D MPS simulation with imposed wall displacements</td>
<td>Maximum bolus velocity at the GPJ. The shape of the epiglottis is key to avoid liquid penetration.</td>
</tr>
<tr>
<td>[87]</td>
<td>PL liquid with K=11, n=0.32 and SG=1.8.</td>
<td>Velocity and shear rate in an axial symmetric domain.</td>
<td>Immersed boundary axial-symmetric simulation with imposed wall displacements.</td>
<td>The bolus is subject both to extensional and elongational stresses.</td>
</tr>
<tr>
<td>[18]</td>
<td>Water and glucose solutions ($\eta=0.0012$-$0.01$-$0.057$ Pa.s and SG=1-1.3)</td>
<td>In line measurement of the thickness of the coatings resulting from bolus flow.</td>
<td><em>In vitro</em> elastohydrodynamic model. Combined imposed displacements and contact force.</td>
<td>Mucosa stiffness, bolus viscosity, salivary flow rate and speed of peristalsis affect the thickness of pharyngeal coating.</td>
</tr>
</tbody>
</table>
The coordination of this series of events is of primary importance to ensure safe bolus transport, but undoubtedly poses significant challenges for \textit{in vitro} simulations. Nonetheless, a few experimental studies considering simplified geometries have been presented and can give quantitative insights of the bolus flow in the pharynx. A comprehensive list of the publications dealing with both \textit{in vitro} and \textit{in silico} models of the pharyngeal phase of swallowing is reported in Table 3.5.2.

Noh et al. have attempted to replicate realistically the physiology of the human oropharynx with the principal aim to develop a training tool for practitioners. The original prototype was actuated by 16 servo motors through wire assemblies (157). The swallowing process was successfully reproduced \textit{in vitro} and assessed by VFSS (Fig. 3.2). A range of barium impregnated foods (custard pudding and rice) were tested during the VFSS in presence of artificial saliva to simulate oral lubrication (15). Experiments showed that, for the same imposed kinematics there were significant differences in swallow efficacy, depending on the consistency of the model boli considered. Thicker barium solutions left more post-swallow residues than thin boli: 62\% of the total initial swallowed volume remained in the oral cavity and above the epiglottis after completion of the swallowing mechanism, compared to just 10\% in case of thin liquids. Moreover, the \textit{in vitro} transit time required for swallowing thick boli was considerably longer than that of thin liquids (3.5 s versus 0.2 s for thin barium suspensions). The figures obtained for pharyngeal transit times were however still unrealistically long compared to any \textit{in vivo} observation. This highlights the noticeable difficulties encountered while relying on the sole adaptation of the \textit{in vitro} motor pattern to accommodate a few of the degrees of freedom that characterize the \textit{in vivo} biomechanics of swallowing.

Later improvements to the original prototype led the authors to include actively controlled degrees of freedom with torque sensors on each joint that can reproduce human muscle stiffness and can actively respond to the external force applied by the users. Sensors embedded in the tongue and pharynx allow the evaluation of trainees’ proficiency during assigned airway management tasks (such as insertion of endoscopic probes and nasogastric feeding tubes). However there have not yet been attempts to simulate swallowing with
this new-generation model.

An *in vitro* study of pharyngeal phase of swallowing is ongoing at the Chalmers University of Technology (Gothenburg, Sweden). The model consists of a pumping system that approximates the geometry of the pharynx as a tube of constant elliptical cross section. The device has a movable flap to mimic the action of the epiglottis in order to consider the breathing-swallowing relationship. The flow of liquid bolus is monitored by a Doppler US to yield a spatial description of the flow field. However, only few experimental results have been disseminated so far (158).

A more anatomically realistic model of the pharynx has been only recently presented by a French medical company active in the development and manufacturing of laryngeal implants (9; 159; 160). The *in vitro* model, used as a testing base for laryngeal prosthesis, replicates the motor pattern of the laryngeal sphincters, pharyngeal shortening and active epiglottis down-fold while also considering the activation and relaxation of the UES (161). A set of linear actuators are used to impose displacements to nodal points via steel wires: an approach that finds roots in the original swallowing robot by Noh *et al.* (15). The geometry of the model is based on a CT scan and the prototype is mould-casted in silicone rubber. Visual qualitative inspection and dynamic information from pressure transducers of the swallowing performance was investigated for thick liquids, but the role of formulation rheology was not comprehensively investigated by the authors.

The pharyngeal phase of swallowing was also studied *in vitro* by Hadde who considered aqueous solutions of a commercial thickener in a range of shear viscosities at 50 −1 spanning between 0.16 to 0.95 Pa.s (80). The pharyngeal transit time was simply defined as the interval required for the bolus to cross two markers separated by a distance of 5 cm on a vertical plane. The author showed that this pharyngeal time indicator was correlated with bolus apparent viscosity at 50 −1. The experiments demonstrated that the mass of residues in the oral cavity is directly proportional to the shear viscosity. Unrealistically long transit times were however recorded: increasing the value of shear viscosity, at 50 −1, from 0.46 to 0.80 Pa.s led to a 10-fold increase in the experimental oral transit times.
In vitro and in silico models of human swallowing

(From approx. 90 ms to more than 1 s). Moreover, experimental results also showed that decreasing the bolus volume (from 5 to 2 mL) led to significantly longer oral transit times: a trend that does not find any equivalent in vivo. The author attributed the result to the neglected role of oral lubrication in vitro and suggested the introduction of a lubricating fluid to better bridge in vivo observations with in vitro experiments (80).

In this regard, some theoretical considerations and experimental methods were proposed to tackle the role of salivary coating in pharyngeal transport. In particular, De Loubens et al. focused on the thickness of bolus coating left behind by pharyngeal peristalsis and proposed the use of lubrication theory to describe the variations of pharyngeal coatings with salivary flow rate (26). The authors idealized the most occluded region of the peristaltic wave during the pharyngeal peristalsis with a forward roll coating process at constant speed. The model considered a couple of counterrotating rigid cylinders rotating at the tip velocity of 0.2 m/s. The two rollers are separated by a small adjustable gap where the liquid bolus gets squeezed (Fig. 3.3). Results show that the flow rate of thick glucose solutions ($\eta < 0.5$ Pa.s) was a function of the lubricating layer (water) used to mimic saliva (25).

More recently, Mathieu et al. extended the model presented by De Loubens et al. investigating the elastohydrodynamic of the pharyngeal phase of swallowing (16). The authors improved the original in vitro setup of De Loubens et al. introducing a deformable gelatine coating to mimic wettability and deformability of the pharyngeal mucosa (Fig. 3.4). Furthermore, a fixed contact force between the rollers was imposed in place of the fixed gap configuration originally considered by De Loubens et al.. Theoretical considerations of a similar elastohydrodynamic problem were provided by De Loubens et al. (26). It was found that varying the stiffness of the mucosa did not strongly condition the measured bolus flow rate. The thickness and the rate of dilution of the coatings were however found to be a decreasing function of bolus viscosity and of the rotational velocity of the rollers. This conclusion was used to provide an interpretation of in vivo data of aroma release that demonstrate a decrease in the measured aroma peak intensity for increasing bolus viscosity (162).
qualitative observations suggest its importance (26). Similarly tests with shear thinning liquids were not performed, although potentially relevant, given the reported wide range of shear rates found in the gap between the rollers (0-1000 s\(^{-1}\)).

Understanding the magnitude of the shear rates during swallowing is of primary importance to design liquid and pureed products, as most food thickeners used to manage dysphagia have a shear thinning rheological behavior. Meng et al. (163) used the finite volume approach to simulate the flow of Newtonian (\(\eta =0.001\) and 0.150 Pa.s) and PL liquids through a time-variant axial symmetric geometrical domain of the pharynx. Time dependent radial displacements and pressure gradients were imposed to simulate opening of the UES and tongue applied pressure.

Maximum shear rates obtained from the simulation in the region proximal to the UES were in the order of 300 \(\text{s}^{-1}\) in case of water-thin liquids, whilst much lower values were obtained in case of thicker liquids. Furthermore, the authors showed that the oral transit time for a bolus volume of 1 mL increased with the liquid consistency (163).

Salinas-Vazquez et al. applied an immersed boundary method (IBM) to model the time variant shape of the pharynx of Meng et al. (155). IBM uses a fixed Eulerian mesh to solve the Navier-Stokes equations of the fluid domain whilst a non-stationary Lagrangian mesh models the fluid-solid boundaries within the Eulerian grid. Interpolation via a kernel function is then used to exchange the dynamic information between the meshes to force the no-slip condition at the solid-liquid interface.

The peristaltic movement was imposed using a fixed axial velocity of the pharynx surface, whilst the radial velocity was derived from the time variant positions of the wall surface used by Meng et al. The effect of different pressure gradients was investigated. A non-uniform axial pressure distribution was needed for the simulation to correctly converge without the occurrence of reflux. The authors investigated the flow topology for a PL liquid, indicating the existence of a narrow central stream of relatively low shear rates ranging between 20 to 50 \(\text{s}^{-1}\), axially surrounded by a region where the velocity gradients are as high as 200 \(\text{s}^{-1}\). In case of non-Newtonian fluids, the authors thereby concluded
3.5. *In vitro* and *in silico* models of human swallowing

that the liquid flow rate in close proximity to the walls was higher than that in the central region of the pharynx (155).

Less idealized geometries of the field of motion have also been considered by other authors. Mizunuma *et al.* (151) first developed a three dimensional Lagrangian grid model of the flow of a semisolid bolus through a 3D model of the oropharyngeal cavity. Tissues were simplified as isotropic materials with constant shear and bulk moduli, taken from previous literature data (151). Salivary lubrication was accounted for by using a frictional coefficient between the bolus and the structural mesh. Numerical results, not complemented by *in vivo* data, showed that, increasing the consistency of the semisolid bolus resulted in a velocity reduction in proximity of the posterior wall of the pharynx. The study however oversimplified the kinematics of the pharyngeal walls, including discontinuous transitions between the movements (145). The work of Mizunuma *et al.* was then extended to liquid boli with different consistencies by Sonomura *et al.* who conveyed a number of significant results out of their simulation study, some of them were directly compared to *in vivo* VFSS (152). Sonomura *et al.* were able to overcome some of the limitations of Mizunuma *et al.*, using a refined mesh made of solid elements, in place of shell elements, to better cope with large mesh deformations. Additionally, they made use of ALE methods to better simulate the movement of a food bolus flow. The authors made an attempt to more realistically investigate the oral phase of swallowing by introducing a certain degree of mobility of the posterior dorsal part of the tongue. They studied some abnormal swallowing situations, with an epiglottis left in its upward position for the whole duration of the liquid swallow, or prematurely raised in the final moments of the pharyngeal phase (152). The way the anatomical structures were manipulated is essentially similar to what was already done by Mizunuma *et al.* with imposed nodal displacements to specific points in the structural mesh, at fixed instants of time within the duration of the simulated swallowing (0.8 s). Differently from Mizunuma *et al.*, the liquid bolus was initially held on the tongue and subject to a constant body force acceleration of 2.2 m/s², a value not justified by the researchers, that was maintained throughout the duration of the oral phase of swallowing. The dorsum of the tongue was then raised to squeeze the
bolus into the oropharynx under a constant acceleration. The computational model did not consider friction between the organ walls and the bolus. A simple slip velocity boundary condition was chosen to simulate the lubricating saliva layer covering the pharyngeal mucosa, in place of the frictional coefficient considered by Mizunuma et al. In silico simulations considered three different bolus volumes (2, 5, and 10 mL) and three level of consistency: water and two PL liquids, already used for VFSS by Nishinari et al. (164). Simulations predicted higher bolus velocities for the thinnest consistency. For larger boli the flow around the epiglottis was found to be relatively smooth and continuous with a low amount of residues on the vallecula and the piriform sinus. Conversely, a decrease in the volume of the bolus led to the occurrence of pooling that might induce secondary liquid aspiration in case of abnormal swallows.

Despite the noticeable effort and the positive comparisons obtained between in silico results and in vivo VFSS and US Doppler velocimetry analyses, the model of Sonomura et al. (152) still did not justify the choice of using a slip condition at the wall, artificially introduced to model saliva coating. Moreover, the approach based on imposed displacements to the organs remains questionable when comparing the swallowing performance of liquid formulations of different rheological properties.

Osada et al. used MPS to model swallowing of non-Newtonian liquids within in a three dimensional geometry obtained from MRI and CT scans (154). Simulations considered PL boli and show a narrower velocity distributions for the thickened boli than for water. Furthermore, the integration of particle transfer of momentum and pressure in the region of the epiglottis gave additional support to the theory that thickened liquids flow in a more regular pattern (154).

To improve the interactions between the liquid bolus and the walls, Kikuchi et al. (156) verified the applicability of an Hamiltonian MPS method to describe hyper-elastic deformations and derived corresponding wall boundary conditions. The motion of organs is generated by imposing fixed displacements to groups of particles within the organs. The contact pairs between the walls was instead modelled with penalty functions (156). The
structural coupling between organs was discussed with particular emphasis on the down
fold of the epiglottis. The friction coefficient was varied to represent that of a dry throat
and a well-dispersed saliva coating. The authors presented a study to qualitatively com-
pare simulations of a 6 mL water bolus with VFSS data [156]. A good agreement with
in vivo observations was claimed by comparing the variations of brightness in the VFS
images and the simulated bolus flow within the same control region close to the epiglottis.
Values of shear rate as high as $300^{-1}$ were calculated, at the entrance of the pharynx and
in the region leading to the esophagus. The authors found that the maximum velocity of
the bolus is of the order of 0.5 m/s and is reached at the end of the oral phase. Results
showed also a temporary decrease in the bolus velocity at the beginning of the pharyngeal
phase. However, the model still neglects fluid-structure interaction and the overall system
was assumed to be at constant pressure whilst in vivo measurements during swallowing
show a gradient of pressures in the laryngopharynx, following the laryngeal elevation and
the relaxation of the UES [100].

The role of salivary lubrication in the pharyngeal phase of swallowing was recently con-
sidered in silico by Ho et al. [18]. By confronting the in silico model with in vivo
real time X-ray computed tomography the authors claimed a better similarity achieved
while neglecting the role of salivary lubrication (Figure 3.6). This conclusion is however
still based on an imposed kinematic to follow a pre-determined activation pattern of the
organs, which oversimplifies the in vivo motor control.

Table 3.3: List of in vitro and in silico studies of the esophageal phase of swallowing.

<table>
<thead>
<tr>
<th>REF</th>
<th>Bolus model</th>
<th>Measurement</th>
<th>Methodology</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>[165]</td>
<td>Newtonian and PL liquids $n=0.5$, 1 and 1.5</td>
<td>Pressure and velocity distribution in axial symmetric domain with sinusoidal waves.</td>
<td>Mathematical model. Imposed wall displacements.</td>
<td>Shear thinning liquids are more easily transported by peristalsis.</td>
</tr>
<tr>
<td>REF</td>
<td>Bolus model</td>
<td>Measurement</td>
<td>Methodology</td>
<td>Conclusions</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>(166)</td>
<td>Jeffrey fluid</td>
<td>Pressure velocity and temperature distribution in axial symmetric domain with sinusoidal waves.</td>
<td>Mathematical model. Imposed wall displacements.</td>
<td>Bolus transport and thermal conduction is affected by the viscoelastic properties of the liquid bolus.</td>
</tr>
<tr>
<td>(167)</td>
<td>Dry swallow.</td>
<td>Description of the synthesis and control algorithm of a soft-robotic peristaltic actuator.</td>
<td>Time imposed pressure distribution to a set of pneumatic actuators.</td>
<td>Feasibility study to demonstrate the potential of a soft actuator mimicking primary peristalsis.</td>
</tr>
<tr>
<td>(168)</td>
<td>Dry swallow.</td>
<td>Measured peristaltic wave trajectory by articulography.</td>
<td>In vitro model. Time imposed pressure distribution to a set of pneumatic actuators.</td>
<td>Feasibility study to demonstrate the potential of a soft actuator mimicking primary peristalsis.</td>
</tr>
<tr>
<td>(169)</td>
<td>Aqueous solutions of a commercial starch based thickener $\eta=0.450-3$ Pa.s.</td>
<td>Measured pressure profile during bolus transit.</td>
<td>In vitro model. Time imposed pressure distribution to a set of pneumatic actuators.</td>
<td>Maximum intra-bolus pressure increases more than linearly with bolus viscosity measured at 50 1/s.</td>
</tr>
<tr>
<td>(170)</td>
<td>Newtonian bolus $\eta=0.01$ Pa.s V=1 mL</td>
<td>Pressure and velocity distribution from axial symmetric model esophageal peristalsis.</td>
<td>Immersed boundary simulation. Imposed longitudinal and radial fibre displacements embedded in a multi-layered esophageal model.</td>
<td>Coordination of circumferential and longitudinal muscles affects bolus transport and intra-bolus pressure.</td>
</tr>
</tbody>
</table>
3.5. *In vitro and in silico models of human swallowing*

The final phase of swallowing initiates with the relaxation and opening of the UES that is followed by an increase in upper pharyngeal pressure (100) and a sudden reduction in laryngopharynx pressure. In the esophagus ring-like progression of muscular contractions guide the bolus to the LES.

*In vitro* models have already been presented to simulate conceptually analogous problems. In these applications, peristalsis is induced by imposing wall displacements through rollers or pneumatic actuators (172).

Shape memory alloys, actuated by an electrical current were used to replicate the basic...
Figure 3.6: Visual comparison presented by Ho et al. to assess the effect of salivary lubrication (slip and no-slip) when simulating swallowing of a *Honey-thick* bolus in a reclined position against *in vivo* CT data (18).

<table>
<thead>
<tr>
<th>Slip</th>
<th>CT</th>
<th>No-slip</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Slip Image" /></td>
<td><img src="image2" alt="CT Image" /></td>
<td><img src="image3" alt="No-slip Image" /></td>
</tr>
</tbody>
</table>

- **Airway**
- **Simulated Bolus**
- **CT Bolus**
features of esophageal peristalsis in animals (173). Chen et al. developed a pressure operated actuator capable of generating a periodical peristaltic wave to study the esophageal flow of a liquid bolus (174). The artificial esophagus is composed of a series of inflatble chambers made of a soft elastomer that are inflated and deflated accordingly (Fig. 3.7). In total, the air pressure in 48 chambers can be manipulated to generate primary and secondary peristaltic contractions along the 20 cm length of the tube (174).

Tests were run with aqueous solutions of a commercially available starch-based thickener with viscosity ranging between 0.1 and 5.4 Pa.s at the shear rate of $50^{-1}$ (168). The pressure distribution within the bolus was evaluated by manometry and the authors observed a general increase in the intra-bolus pressure with increasing bolus consistency.

Follow-up publications by the same authors focused on the issue of inflation control and shape of the peristaltic wave, but it is not clear whether the proposed in vitro model considered the different muscle activation patterns in the distal zone of the esophagus, nor if the imposed radial displacement is a good assumption in respect of the longitudinal fibre contraction observed in vivo. Furthermore, the structure and wettability of the mucosa were not described by the authors.

Computational studies of the esophageal phase of swallowing have mainly considered the approximations used in the description of peristaltic flows. Analytical expressions for the stream function, axial velocity and pressure gradient could be obtained both for Newtonian and non-Newtonian liquids under the approximation that the amplitude of the
peristaltic wave is much smaller than the wavelength. Shapiro et al. studied the peristaltic flow of a viscous liquid in an infinite tube by imposing a sinusoidal wall displacement (175). They performed the analysis under the assumption of a long wavelength and discussed the phenomena of liquid reflux and trapping during peristalsis. Later, Li and Brasseur studied the peristaltic flow of viscous Newtonian liquid through finite length tube and they discussed the importance of the length of the tube (176). The same authors extended the analysis to arbitrary wave shapes and wavenumbers in tubes of finite length showing that the extent of retrograde motion of fluid particles is much greater for single waves than train waves (177).

Models of peristaltic pumping for PL liquids have also been presented suggesting an easier transport of shear thinning liquid (178, 179, 165). The flow of viscoelastic liquids, modelled through Jeffrey constitutive equations has also been studied and a coupled fluid-dynamic and thermal simulation was presented by Tripathi et al. under the hypothesis of small wavelengths (166).

Computational models of peristalsis in the presence of suspended solids were proposed through the use of an IB method imposing prescribed wall displacements (180). A model of esophageal transport, considering more realistic circular and longitudinal muscle contractions was proposed by Kou et al. (170). The modelled esophagus was considered as a multi-layered deformable tube with embedded muscular fibres. Results for different activation pattern of the longitudinal and circumferential muscles show that coordination between lumen closure and esophageal shortening has an important effect on the intra-bolus pressure pattern. The role of mucosa stiffness in bolus transport was also highlighted in a following study by the same authors who, based on their simulations, speculate that a stiffened mucosa might lead to a significant backward bolus transport (46).
3.6 Conclusions

The growing interests towards food oral processing and swallowing has led to the introduction and development of a wide number of *in vitro* and *in silico* models. The mechanistic understanding derived from these models provides explanations for a range of *in vivo* observations such as the evolution of tongue pressure and the effect of bolus viscosity on the kinetics of aroma release. The valuable contribution of these swallowing models has also allowed researchers to clarify the role of bolus density with respect to bolus viscosity. Moreover, comparing different liquid formulations proved the effectiveness of gum based thickeners in the management of dysphagia.

Despite these relevant results, both *in vitro* and *in silico* models still present significant limitations that need to be addressed. The common assumption of quasi 2D or axial symmetry remains hard to justify and a more accurate reconstruction of the region around the epiglottis seems advisable to correctly predict the quantity of post swallow residues and the conditions for bolus penetration. In terms of bolus models, most studies still consider simple viscous liquids with little insights into the flow of thin liquids and viscoelastic liquids. The role of oral and pharyngeal lubrication is most often neglected, as well as the elastohydrodynamics of the tongue against the palate and of other tissues experiencing contacts. The physical properties of the epithelium itself have only been characterized in terms of mechanical deformability without sufficient attention to its wetting properties and their dependence on the salivary coating. While the role of salivary lubrication for liquid bolli has not yet been comprehensively understood *in vivo*, studies on oral tribology could serve as a basis to underpin the potentiality of *in vitro* and *in silico* models for the oral and pharyngeal transport of semisolid bolii. The incorporation of the salivary lubrication as a single friction coefficient or as a wall-slip velocity should be more appropriately justified and tailored to match relevant *in vivo* data.

Despite such limitations, *in vitro* and *in silico* models suggest interesting areas for future research. Most of the *in vitro* and *in silico* studies in the literature impose displacements to the bolus, probably because these are easier to measure from *in vivo* diagnostics. Only
few consider swallowing imposing stresses, despite some clinical evidence supporting this approach. More complex scenarios, such as a feed-forward or a feedback control have not been considered in *in vitro* and *in silico* models. Although some evidence already exists in support of these more complex scenarios, further clinical results are needed to better understand the control strategy. Recent advances in medical instrumentation should also be used to further compare quantitatively *in vivo* data with models, further increasing the confidence in *in vitro* and *in silico* predictive approaches.
Chapter 4

Viscoelastic and extensional properties of liquids

Textural modifications represent a common compensatory technique to manage swallowing disorders. The shear rheology of thickened products has been well characterized however only few studies so far have considered the potential role of the extensional properties of the liquid bolus during swallowing. This chapter proposes an in vitro model to describe the role of the extensional properties of liquids on the oral phase of swallowing. The study combines steady shear, SAOS and capillary breakage extensional rheometry with an in vitro experiment to characterize the oral transport of a commercial XG-based thickener and two model elastic liquids. Bolus velocity and bolus length were extracted from in vitro experiments using image analysis tools and related to shear and extensional properties of the boli. Theory shows that the extensional properties do not influence the dynamic of the oral transit, dominated by inertia and, to a lower extent, by the shear thinning behaviour. Conversely, in vitro results suggest that the extensional properties affect the transition from the oral to the pharyngeal phase of swallowing, where thin, viscoelastic liquids reduce uncontrolled splashing and lead to lower post-swallow residues. This suggests the potential benefit of liquid formulations with a moderate elasticity in the management of dysphagia.
Chapter 4. Viscoelastic and extensional properties of liquids

4.1 Introduction

The impact of alterations of bolus viscosity to the ease to swallow and mouthfeel has been the subject of several studies in the literature, sometimes with contrasting results (37; 2; 72; 22).

Investigation of flow behaviour of highly complex fluids has not yet been fully exploited by present and past studies with only few exceptions (181; 86; 182). Whilst it is well accepted that both shear and extensional flows occur during swallowing (182; 183; 184; 155), the importance of the elastic properties has only recently been subject of research. The attribute of bolus cohesiveness, as a main contributor to triggering swallowing, was put in relation to the elongational properties of fluids (24; 185). However, the significance of this attribute has not yet been comprehensively investigated in dysphagic patients. Sensory tests comparing Newtonian and constant viscosity elastic fluids (Boger) on dysphagic subjects seem to suggest an improvement in the swallow-ability when introducing an elastic component. Additional studies are however needed to confirm these findings, as similar differences were not appreciated by the control group (181; 86).

Nystrom et al. stated that the superior performance of gum-based thickeners for dysphagia management, compared to starch based thickeners, can be directly related to the difference in terms of extensional viscosity (86). At similar level of consistency, the authors found that commercial Xanthan gum (XG) based thickeners have a considerably higher extensional viscosity than starch based counterparts (86). The same conclusion was also drawn by Hadde and Chen who studied the capillary break-up of commercial XG and starch-based thickeners (182).

Moving from these results, the current investigation proposes the use of an in vitro model, previously developed in (29; 8; 30), to clarify the role of extensional properties in a geometry relevant for the oral phase of swallowing. The study is completed by a full rheological characterization of the liquid matrices both in shear and extensional flow.
4.2 Materials and Methods

This study considers three different model liquid bolii. First, aqueous solutions of a commercial thickener (Resource® ThickenUp™ Clear, Nestlé Health Science), in the following TUC, were chosen to provide a reference relevant to commercial products used in the management of dysphagia. The composition of TUC includes Xanthan gum, that is the main thickening agent, maltodextrin and potassium chloride. Three concentrations of TUC were tested: the lowest thickening level consistency (*Nectar-thick*) was prepared adding 100 mL of deionized water to 1.2 g of TUC (1.19 % w/w). This corresponds to a Level 2 (or mildly thick) liquid under the IDDSI framework. The dosage of TUC was doubled and tripled in the same amount of water for *Honey* (2.4 g/100 mL or 2.35 % w/w) and *Pudding* (3.6 g/100 mL or 3.48 % w/w) consistency. Starch-based products were not considered in the study due to their inferior performance as food thickeners, significant tixotropicity and lower extensional viscosity (186, 182).

Aqueous solutions of polyethylene oxide (PEO, CAS 25322-68-3, average molecular weight \( M_W = 10^6 \) g/mol) were used to study the effect of liquid elasticity. PEO is a polymer commonly used as a binder for pharmaceutical products, but not commonly used for food applications. Nonetheless PEO was included in the study to represent a model system characterized by relevant and well-studied extensional properties (187). For this study, aqueous solutions of 1 to 5% w/w PEO were prepared in deionized water with the polymer left hydrating overnight in sealed containers under magnetic stirring.

Finally, an edible cereal extract with significant extensional properties was also considered in the study. Frozen samples of this cereal extract were provided by Nestlé Research (Lausanne, CH). The total dry matter was approximately 0.3 and 1 % w/w for the low and high concentration samples respectively. Prior to the rheological characterization and *in vitro* tests, the samples were thawed in a refrigerator at 4 °C for 12 hours, then left to equilibrate at ambient temperature for 4 hours.
4.2.1 Rheological characterization

The rheological measurements included tests in steady shear, small amplitude oscillatory shear (SAOS) and extensional flow.

Measurements of shear viscosity were taken in triplicate, at 22 °C, with a Paar Physica UDS 200 controlled stress rheometer (Anton Paar GmbH, Graz, Austria). The flow curves were obtained in rate range of shear rates between 0.1 to 500 reciprocal seconds using a cone and plate geometry (d=75 mm α=2°). Viscosity measurements during the step ramps were taken imposing a steady state condition.

Dynamic characterization of the samples in frequency was carried out in the range of frequencies between 0.1 and 10 Hz. These measurement were taken at low strains (γ =1%), after checking that this was within the linear viscoelastic range.

Additionally the IDDSI flow test [2] was run in triplicate at the temperature of 22 °C. This consists in measuring the volume of fluid discharged through the orifice of standard eccentric luer slip tip 10 mL syringe (BD, Franklin Lakes, NJ, USA) in a fixed amount of time (10 s). Depending on the residual liquid hold-up from the initial 10 mL filling level, liquid samples are categorized in four levels of increased thickness. The liquid is classified Level 0 if the syringe is completely empty in 10 s, Level 1 if the remaining liquid volume is between 1 and 4 mL, Level 2 if between 4 and 8 mL and Level 3 if more than 8 mL are left. Liquids thicker than Level 3 do not flow at all through the orifice of the syringe in the prescribed amount of time and are better characterized with the other methods proposed by IDDSI [2].

The extensional properties of the liquids were measured by capillary break-up rheometry using a HAAKE CaBER 1 (Thermo Electron, Karlsruhe, Germany). Five repeats were taken per each sample at the test temperature of 22 °C. The instrument measures the transient evolution of the midpoint diameter of the capillary bridge generated by the rapid separation of two circular plates that axially constrain the liquid sample. The initial separation between the two plates of diameter 6 mm was set at $h_0=3$ mm. This gives
an initial aspect ratio of 0.5, value that limits the initial curvature of the liquid column resulting from the combined effect of gravity ($g$) and surface tension ($\sigma_S$) \cite{188, 189}. The liquid sample was injected between the plates using a 1 mL syringe. The experiment was triggered 60 s after loading the sample, to avoid shear preconditioning effects \cite{190}.

A rapid (50 ms) linear strike of 10 mm in the plate separation (to $h_f=13$ mm) is imposed to drive the filament thinning. As the capillary thread thins, its midpoint diameter is measured with a near infra-red laser micrometer with a with a beam thickness of 1 mm and a resolution of 20 µm. High-speed videos of the experiment were taken at 1000 frames per second to record the shape evolution of the capillary thread using a Phantom V1612 high-speed camera (Vision Research, Wayne, NJ) with a telecentric TC16M012 f/18 lens (Opto Engineering, Mantova, Italy). The resulting image resolution was approx. 9.6 µm/pixel.

The cylindrical elements of fluids at the axial mid-plane plate are subject to a strain expressed by Eq. 4.2.

$$\varepsilon = -2 \ln \frac{D_{mid}}{D_0} \quad (4.1)$$

Where $D_{mid}$ is the instantaneous filament midpoint diameter and $D_0$ is the post-stretch midpoint diameter of the filament.

The filament necking, driven by capillarity, is opposed by viscous, inertial and elastic terms. The relative importance of these contributions depends on the rheological and physical properties of the sample, other than the characteristic size of the filament \cite{191}.

The relative importance between viscosity and surface tension forces is quantified through the Ohnesorge number, $Oh = \eta / (\rho \sigma_S 0.5 D_{mid})$, where $\eta$ is the shear viscosity, $\rho$ the liquid density and $\sigma_S$ the surface tension \cite{192, 193}.

The theory for the time evolution of slender fluid filaments, in the limit of vanishing inertial terms was presented by Renardy \cite{194}. Analytical solutions have been presented for simple constitutive models. For instance, in the case of Newtonian fluids, the visco-capillary
force balance predicts a linear rate of decay of the midpoint diameter, function of the capillary velocity, defined as the ratio of surface tension and shear viscosity. Conversely, for an upper convected Maxwell model (UCM) the elasto-capillary force balance predicts an exponential diameter decay in time with a characteristic time scale $\lambda_c$ (Eq. 4.3). The value of this constant was linked to the longest shear relaxation mode in shear for aqueous polyethylene-oxide solutions (189).

\[
D_{\text{mid}} \sim \frac{\sigma_S}{\eta} (t_c - t) \tag{4.2}
\]

\[
D_{\text{mid}} \sim \frac{3}{\sigma_S} \sqrt{\frac{D_0^2}{\sigma_S}} \exp \left( -\frac{t}{3\lambda_c} \right) \tag{4.3}
\]

The apparent extensional viscosity of the liquid sample in the elasto-capillary regime is defined by the ratio of the normal stress difference $\sigma_{zz} - \sigma_{rr}$, that drives the filament elongation, and the strain rate $\dot{\varepsilon}$ (Eq. 4.4).

\[
\eta_{\text{app}}^{\text{ext}} = \frac{\sigma_{zz} - \sigma_{rr}}{\dot{\varepsilon}} \tag{4.4}
\]

The instantaneous strain rate for a cylindrical element of fluid is given by Eq. 4.5 and is a constant, equal to $2/(3\lambda_c)$, for ideal elastic liquids (192; 193).

\[
\dot{\varepsilon} = -\frac{2}{D_{\text{mid}}} \frac{dD_{\text{mid}}}{dt} \tag{4.5}
\]

Further neglecting the axial curvature effects, and assuming that the viscoelastic stresses equal the capillary pressure, Eq. 4.4 can be rearranged in the form of Eq. 4.6 (192; 193).

\[
\eta_{\text{app}}^{\text{ext}} = \frac{2\sigma_S / D_{\text{mid}}}{\dot{\varepsilon}} \tag{4.6}
\]

In the case of non slender liquid filaments the analysis of the self-similar solution proposed
by Papageorgiou (195) and summarized by Mckinley (192), leads to the introduction of a corrective factor in Eq. 4.6. The value of this prefactor, that accounts for the axial variations in the filament shape during visco-capillary thinning, is approximately equal to 0.43 for Newtonian liquids (193).

The value of surface tension was measured using a Wilhelmy plate-equipped Kruss ST10 surface tensiometer (KRÜSS GmbH, Hamburg, Germany). Five repetitions were taken per each sample.

The *in vitro* model of swallowing

An *in vitro* experiment was used to compare the characteristic oral transit time and bolus shape in conditions relevant to oral swallowing.

The experimental setup simplifies the *in vivo* peristaltic motion induced by the tongue during the oral phase of swallowing in a quasi-two-dimensional geometry.

The *in vitro* experiment effectively decouples the two physiological functions of tongue propulsion and bolus containment during the oropharyngeal phase of swallowing. The peristaltic wave is generated by the motion of a roller that squeezes the liquid bolus contained inside a thin and freely deformable polyethylene membrane (Figure 4.1). The bolus is loaded into the membrane from the anterior opening and is initially held in position by gravity. The trajectory of the bolus follows a constant curvature path that mimics the geometry of the oropharynx. The posterior end of the plastic membrane is open and the bolus is ejected as the roller stops. The bolus volume used throughout the experiments was 6 mL. *In vivo*, this value corresponds to an adult mouthful of 10 mL (8).

The experimental setup allows to adjust the propulsive force for bolus flow to mimic variation in tongue pressure applied by different individuals (Figure 4.1). The study here presented only considers an applied load of 2.0 N, which corresponds to an applied pressure to the bolus tail of approximately 11 kPa (29). Previous studies using the same setup showed good agreement between *in vivo* ultrasound measurements and *in vitro* results.
using this load configuration (29; 8).

The experiment is triggered by releasing a pin that initially holds the roller supporting arm at rest. Lateral images of the bolus flow are taken using a high-speed camera (model ac1920-155 µm, Blaser, Isny im Allgäu, Germany). Measurements of the injected bolus mass, the amount of bolus ejected after every in vitro swallow, and the quantity of residues left inside the plastic membrane are taken for each experimental run. The percentage of bolus residues was computed by the ratio between the amount of post-swallow residues left in the plastic membrane and the initial bolus mass.

Image analysis techniques were used to extract the angular position of the roller. After data filtering, numerical differentiation was used to compute the bolus angular velocity. Theoretical predictions are derived from the Lagrangian equation of motion of the mechanical system considering the viscous dissipation of the bolus as a modified Poiseuille drag flow, as detailed in Appendix A. The theory simplifies the bolus as a straight tube of length $L_B$ and radius $R_B = 5$ mm in which the mean velocity is considered equal to the instantaneous tangential velocity of the roller. The latter being given by the product of angular velocity of the shaft, $\dot{\theta}$, and length of the roller supporting arm, $r_A$. In the case of Newtonian liquids, the drag force assumes the form of Eq 4.7 in which the constant $\beta$ is independent both of the aspect ratio of the bolus and the applied force to the system and has a value of 3.23 (8).

$$F_d = \beta 8\pi \eta L_B \dot{\theta} r_A$$ (4.7)

In the case of shear thinning liquid, the above equation was corrected introducing simple models of constitutive equations to map the shear-stress relation which included PL (Eq. 4.8) and Ellis models (Eq. 4.9).

$$\eta_a = K \dot{\gamma}^{n-1}$$ (4.8)
4.2. Materials and Methods

\[ \eta = \frac{\eta_0}{1 + \left| \frac{\tau_0}{\tau} \right|^{\alpha-1}} \]  

(4.9)

Where \( \eta_0 \), \( \alpha \), and \( \tau_0 \) are the constants of the Ellis model.

Introducing the PL model in the Navier-Stokes equation under the assumptions reported in A.3.1 ultimately leads to the following expression for the viscous force (196):

\[ F_d = 2\pi \beta K R_B^{1-n} \left( \frac{3n+1}{n} \right)^n (\dot{\theta} r_A)^n L_B \]  

(4.10)

where \( n \) is the flow behaviour index, \( K \) the flow consistency index and \( R_B \) the bolus radius.

Conversely, in the case of the Ellis model the drag force is computed iteratively as the model is implicit in the shear rate.

Although idealized, this approach has been shown to offer remarkably good correlation with previous experiments (29; 8). Furthermore, the theoretical analysis also allows for a more straightforward understanding of the role of fluid rheology in terms of energy loss by the system.

The rotational parameters of the device, such as the inertia of the rotating assembly and the friction of the bearing, are characterized with experiments without fluids.

The video recordings of the experiments served also to track the instantaneous position of the bolus leading edge. Profiles of normalized bolus length along the trajectory and at the outlet of the plastic membrane were calculated from the relative position of bolus front and roller position. The variation in the bolus length (strain: \( \varepsilon_{Bolus} \)) during the ejection from the plastic membrane was characterized for the different liquids. Furthermore, the ratio between bolus elongation and the time required for complete bolus ejection (strain rate: \( \dot{\varepsilon}_{Bolus} \)) was also computed.
Chapter 4. Viscoelastic and extensional properties of liquids

4.3 Results

The set of liquids considered in this study was designed to cover a wide range of product consistencies. This was first qualitatively evaluated through the IDDSI flow test: the results are listed in Table 4.1. For all the liquid products, the discharged volume decreases with increasing polymer concentration. Concentrations of PEO above 3% resulted in a noticeable amount of residual liquid hold-up in the syringe. Hardly any outflow was measured in the 10 s test time for concentrations of PEO above 4% w/w. The thinnest TUC solution (1.19 % w/w TUC) was classified as IDDSI Level 2, while more concentrated TUC solutions (2.35 % w/w TUC and 3.48 % w/w TUC) are both classified under IDDSI Level 3. Higher concentrations leading to level 4 were not considered in this study. Results are in agreement with the levels anticipated on the package and measured in other studies (93, 197). Samples of cereal extract were characterized as IDDSI Level 1 and Level 2 respectively.

4.3.1 Shear rheology

Rheological measurements in steady shear showed a shear thinning behaviour for all products, although with specific differences. Solutions of TUC in deionized water showed a pronounced shear thinning behaviour that is well-fitted by a power law model in the range of shear rates considered (Table 4.2). In line with previous studies (198), the aqueous solu-
Table 4.1: Average results of the IDDSI flow test over three repeats. Standard deviation in brackets.

<table>
<thead>
<tr>
<th>Liquid sample</th>
<th>Remaining volume</th>
<th>IDDSI level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.19 % w/w TUC (Nectar-thick)</td>
<td>4.9 (0.3)</td>
<td>Level 2</td>
</tr>
<tr>
<td>2.35 % w/w TUC (Honey-thick)</td>
<td>8.3 (0.2)</td>
<td>Level 3</td>
</tr>
<tr>
<td>3.48 % w/w TUC (Pudding-thick)</td>
<td>8.9 (0.2)</td>
<td>Level 3</td>
</tr>
<tr>
<td>0.3 % w/w Cereal extract</td>
<td>2.9 (0.3)</td>
<td>Level 1</td>
</tr>
<tr>
<td>1 % w/w Cereal extract</td>
<td>5.3 (0.2)</td>
<td>Level 2</td>
</tr>
<tr>
<td>1% w/w PEO</td>
<td>2.2 (0.3)</td>
<td>Level 1</td>
</tr>
<tr>
<td>2% w/w PEO</td>
<td>7.0 (0.2)</td>
<td>Level 2</td>
</tr>
<tr>
<td>3% w/w PEO</td>
<td>9.5 (0.2)</td>
<td>Level 3</td>
</tr>
<tr>
<td>4% w/w PEO</td>
<td>9.9 (0.1)</td>
<td>Level 3</td>
</tr>
<tr>
<td>5% w/w PEO</td>
<td>10.0 (0.1)</td>
<td>Level 4</td>
</tr>
</tbody>
</table>

Dilutions of PEO are less shear thinning than TUC and have a visible high viscosity plateau at low shear rates that increases with polymer concentration (Fig. 4.2a and 4.2b).

The flow curves of the cereal extracts are intermediate between TUC and PEO, being slightly more shear thinning than PEO but less than the gum-based thickener (Fig. 4.2a and 4.2b). The Ellis model (Eq. 4.9) fits well the flow curves of the PEO and the cereal extract solutions in the range of shear rates considered (Table 4.2). The model captures well the low shear rate Newtonian plateau and the onset of the shear thinning region (Fig. 4.2b and 4.2a), as demonstrated by the high $R^2$ values reported in Table 4.2.

Comparing the flow curves with the IDDSI classification highlights that the thickest cereal extract solution and the 2% PEO (both IDDSI Level 2) have a similar shear viscosity at the shear rate of 100 reciprocal seconds. TUC Pudding (3.48 % w/w TUC) has also a very similar viscosity at 100 reciprocal seconds. The thinnest cereal extract solution and the 1% PEO solution, both IDDSI Level 1, have the same shear viscosity at 50 reciprocal seconds.

The result of the small amplitude frequency sweeps within the linear viscoelastic regime is illustrated in Fig. 4.3 and 4.4. TUC solutions show a dominant storage modulus ($G'$) over the loss modulus ($G''$) in the range of frequency considered. The shear moduli of TUC solutions do not exhibit a strong frequency dependence: a behaviour that is consistent with previous results from Mackley et al. (28). In the case of PEO and cereal extract, $G''$ dominates the first part of the mechanical spectra with crossover occurring at higher
Chapter 4. Viscoelastic and extensional properties of liquids

Figure 4.2: Steady shear viscosity for aqueous solutions of TUC and cereal extract (a) and PEO (b). Average values and error bars from three repeats. The corresponding fitting parameters are listed in Table 4.2.

Table 4.2: Steady shear viscosity: fitting parameters for PL (Eq. 4.8) and Ellis models (Eq. 4.9).

<table>
<thead>
<tr>
<th>Liquid sample</th>
<th>K (Pa.s^n)</th>
<th>n (-)</th>
<th>η_0 (Pa.s)</th>
<th>τ_0 (Pa)</th>
<th>α (-)</th>
<th>R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.19 % w/w TUC</td>
<td>1.82</td>
<td>0.28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.99</td>
</tr>
<tr>
<td>2.35 % w/w TUC</td>
<td>4.12</td>
<td>0.20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.99</td>
</tr>
<tr>
<td>3.48 % w/w TUC</td>
<td>5.81</td>
<td>0.23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.99</td>
</tr>
<tr>
<td>0.3 % w/w Cereal extract</td>
<td>-</td>
<td>-</td>
<td>0.62</td>
<td>0.43</td>
<td>2.24</td>
<td>0.98</td>
</tr>
<tr>
<td>1 % w/w Cereal extract</td>
<td>-</td>
<td>-</td>
<td>5.68</td>
<td>7.60</td>
<td>3.90</td>
<td>0.99</td>
</tr>
<tr>
<td>1% w/w PEO</td>
<td>-</td>
<td>-</td>
<td>0.07</td>
<td>11.67</td>
<td>1.68</td>
<td>0.98</td>
</tr>
<tr>
<td>2% w/w PEO</td>
<td>-</td>
<td>-</td>
<td>0.39</td>
<td>23.99</td>
<td>2.24</td>
<td>0.96</td>
</tr>
<tr>
<td>3% w/w PEO</td>
<td>-</td>
<td>-</td>
<td>3.22</td>
<td>22.83</td>
<td>2.07</td>
<td>0.99</td>
</tr>
<tr>
<td>4% w/w PEO</td>
<td>-</td>
<td>-</td>
<td>10.37</td>
<td>27.11</td>
<td>2.08</td>
<td>0.99</td>
</tr>
<tr>
<td>5% w/w PEO</td>
<td>-</td>
<td>-</td>
<td>31.12</td>
<td>35.32</td>
<td>2.11</td>
<td>0.98</td>
</tr>
</tbody>
</table>
4.3. Results

Figure 4.3: Oscillatory shear tests at 1% strain for aqueous solutions of TUC (a) and cereal extract (b). Storage ($G'$) and Loss ($G''$) moduli are illustrated with filled and open markers respectively. Visible crossover frequencies are indicated with an arrow. Average values and error bars from three repeats.

Figure 4.4: Oscillatory shear tests at 1% strain for aqueous solutions of 1 to 5% w/w PEO. Storage ($G'$) and Loss ($G''$) moduli are illustrated with filled and open markers respectively. Visible crossover frequencies are indicated with an arrow. Average values and error bars from three repeats.
frequencies. The characteristic relaxation time at crossover is in the order of 0.2 s for the thickest PEO solution: a comparable value to that of the thinnest solution of cereal extract.

4.3.2 Extensional rheology

The extensional properties of the samples were studied by capillary break-up. Fig. 4.5 and Fig. 4.6 report snapshots of the necking profiles. For the liquids considered in this study, the filament break-up times span a range between 0.1 and 3.5 s (Table 4.3). The video recordings of the capillary break-up allow to appreciate the different regimes of filament thinning. This dynamic process is driven by capillarity and resisted by viscous, elastic and inertial forces. In the case of Newtonian liquids the capillary thinning experiment is driven by viscosity only and the liquid bridge takes the shape of a hourglass. In this case, the filament diameter decreases linearly in time and the break-up time is relatively short (199). Conversely, elastic fluids thin with an approximately cylindrical capillary, whose radius exponentially decreases in time (199). This last behaviour is well-matched by the cereal extract solutions (Fig. 4.8a). The relaxation time for the extensional flow can be computed as the inverse of the gradient and is of the order of 0.05 to 0.15 s (Table 4.3). A similar elastic capillary thinning is also observed for the aqueous solutions of 2 and 3% PEO. However, at higher polymer concentrations, the viscous drainage gives a more significant contribution to the first portion of the filament thinning dynamics. This effect can qualitatively be appreciated by comparing the filament shape in Fig. 4.6b and c. In particular, results for the 5% PEO show a distinctive long time decay of the filament axial curvature (Fig. 4.8b).

In the case of TUC, the dynamics of filament break-up for is complicated by the combined effect of the elastic contribution and the shear thinning rheology. In the viscous dominated regime, this results in an acceleration of filament break-up as opposed to less shear thinning liquids. In this case, a spectrum of relaxation times, rather than a single one would be more appropriate in the description of the extensional flow (192; 199).
Figure 4.5: Capillary thinning for TUC and cereal extract solutions: row a) 0.3 % w/w Cereal extract, b) 1 % w/w Cereal extract, c) 1.19 % w/w TUC (Nectar-thick), d) 2.35 % w/w TUC (Honey-thick), e) 3.48 % w/w TUC (Pudding-thick). Times are normalized with respect to the capillary break-up time.
Additionally, when the filament shape loses its symmetry due to due to drainage, the midpoint laser micrometer does not allow computing accurately the extensional rate. This happens, for instance, with the thickest TUC solution (Fig. 4.6). In this case, high speed video recordings allow to correctly identify the diameter of the filament. To this extent, the videos are analysed using ImageJ (v1.51j8). A threshold limit in the grayscale pixel level is chosen to outline the edges of the filament, these outline pixels are then mapped to find the instantaneous minimum filament diameter in the thread. The extent of this correction for the thickest TUC solution (i.e. 3.48 % w/w TUC) is quantitatively illustrated in Fig. 4.7. The profiles based on the midpoint filament diameter lead to an under prediction of the relaxation time. When the filament shape is more symmetric the laser micrometer readings do not require correction, as shown for the thickest cereal extract sample in Fig. 4.7.

Inertial forces affect the dynamics of capillary thinning only for low viscosity fluids, for which the Ohnesorge number falls into the inertio-visco-capillary regime ($Oh \lesssim 0.2$).
4.3. Results

Figure 4.7: Comparison between two different procedures used to analyse the CaBER results for 3.48% w/w TUC (Pudding consistency) and cereal extract, highlighting the approximations stemming from using the midpoint filament diameter (laser micrometer) versus the more accurate use of the minimum diameter (full filament shape analysis from the video recordings). Diameters are normalized with respect to the post-stretch midpoint diameter $D_0$.

(192, 193). This condition was only observed for the thinnest PEO solution where visible oscillations in the shape of the filament were generated following the rapid acceleration and deceleration at the beginning of the stretching profile.

The apparent transient extensional viscosity of the fluids tested was calculated using Eq. 4.6. The measured value of surface tension are rather similar for all the fluids and show only a weak dependence on concentration (Table 4.3). The calculated values of apparent extensional viscosity are given in Fig. 4.9a as a function of strain. The profiles for the different liquids tested illustrate the difference between TUC and the other viscoelastic solutions. The weak strain dependence of the TUC solutions is compatible with a dominant visco-capillary thinning dynamics that is also highlighted by the more rapid terminal breakage of the filament, compared to the other liquids tested. Instead, the strain hardening behaviour of the PEO and cereal extract solutions confirms the more important contribution of elasticity during the transient filament break-up, typical of elastic fluids (Fig. 4.9b). Results for TUC and PEO are close to the values reported in the literature.
The values of apparent extensional viscosity of the cereal extracts are within the range of 2 to 4% PEO (Fig. 4.9a and 4.9b).

The increase in extensional viscosity with strain observed for the cereal extracts and the PEO solutions follows a similar exponential growth in the elasto-capillary regime. Furthermore, Fig. 4.9a and Fig. 4.9b do not highlight a strong relationship between the maximum attainable strain and the polymer concentration for filament diameters above the laser resolution. This is in contrast with Arnolds et al. that reported a noticeable increase in the maximum attainable strain with increasing PEO concentration due to a bead-on-a-string instability in the final phases of filament break-up (187).

The exponential diameter decay of the cereal extract solutions occurs at approximately constant strain rates within the elasto-capillary regime of the filament thinning. This is illustrated in Fig. 4.10a with the clustering of data point around a narrow range of extensional rates, characteristic of each different solution. The theoretical value of the strain rate of the extensional flow can be computed as $2/(3\lambda_c)$ (199, 193). The values of $\dot{\varepsilon}$ in Fig. 4.10a are consistent with those obtained from the relaxation times measured from the filament diameter decay. In the case of PEO, a good agreement is also found between the measured relaxation times for the extensional flow and the scaling rule with polymer concentration $C$, proposed by Arnolds et al. and expressed by $\lambda_c \sim C^{4/3 \pm 1/3}$ (187).

The extensional viscosity of TUC does not exhibit a strong strain rate dependence, in agreement with the less elastic and the shear thinning rheology of the these samples. In this regard, other studies also reported a slight extensional thinning behaviour for thicker aqueous solutions of TUC (181).

The transient Trouton ratio ($Tr$), was computed as the ratio of extensional to the zero shear viscosity, or flow consistency index $K$ (Table 4.2) (199). The cereal extract solutions show higher Trouton ratios than TUC for comparable IDDSI consistency, thus confirming the significantly higher elasticity of the former.
A decrease in $Tr$ is observed increasing the concentration of PEO (Fig. 4.11b). This trend is in agreement with the sharper increase of zero shear viscosity with polymer concentration that effectively compensates the increase in extensional viscosity \cite{187}. The value of $Tr$ for thick PEO solutions, such as 4 and 5% PEO, is close to the theoretical limit of 3 typical of Newtonian fluids. The same observation applies to the cereal extract solutions that exhibit a similar decrease in the values of $Tr$ with increasing polymer concentration.
Figure 4.9: Values of apparent extensional viscosity as a function of strain for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats.

Figure 4.10: Values of apparent extensional viscosity as a function of the strain rate for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats.
4.3. Results

![Graph](image)

Figure 4.11: Ratio of extensional to zero shear viscosity for TUC, cereal extract (a) and PEO (b) solutions. Average values from five repeats.

4.3.3 *In vitro* swallowing tests

Swallowing tests with the *in vitro* simulator gave quantitative information on the swallow-ability of the samples in terms of oral transit velocity and amount of residues. In the analysis of the results two key events were identified: bolus front out (FO-front out) and bolus tail out (TO-tail out). FO represents the time at which the front of the bolus exits the plastic membrane, which plays the role of the oral cavity in the *in vitro* model. Instead TO is the moment when the roller impacts the stopper, the peristaltic actions stops, and the tail of the bolus progressively clears the oral cavity. Screenshots taken from *in vitro* experiments at bolus FO and TO out are illustrated in Fig. 4.13 and 4.14.

The roller velocity profiles give an account of the relative importance of liquid rheology during the oral phase of swallowing (Fig. 4.12a and 4.12b). Whenever the viscous dissipation in the bolus becomes vanishingly small, the roller velocity profile assumes the shape of straight line. The angular acceleration in this case is constant and only dependent upon the inertia of the system, mimicking the tongue inertia. The dynamics is also almost insensitive to the bolus mass and viscosity \((29)\). Conversely, whenever viscous dissipation is sufficiently high, the system evolves towards constant values of angular velocity after a first -brief- inertial phase in which angular velocity linearly increases with time. The existence of an inertial and a viscous regime has been previously discussed by Hayoun *et al*.
Figure 4.12: Roller angular velocity from *in vitro* experiments for TUC, cereal extract (a) and PEO (b) solutions. Average values and maximum deviation from three repeats.

* al. who compared the kinematic data for different solutions of Newtonian liquids (29). In the case of shear thinning liquid with the transition from the inertial to the viscous regime depends on the shear rates generated during the bolus flow. An example is illustrated in Fig. 4.12a where the experimental velocity profiles are plotted until the moment in which the bolus front exits the plastic membrane (FO). Experiments with the thicker solution of PEO result in values of angular velocity approaching an asymptote, while TUC solutions always evolve within the inertial regime, regardless of the thickener concentration. This behaviour is remarkably well captured by the theoretical model that only considers shear viscosity, neglecting elasticity.

In between the extremes situation of 5% PEO and TUC *Nectar-thick*, the set of experiments with 1 to 4% PEO gives significant insights on the importance of elastic properties during swallowing. Solutions for the 3% and 4% PEO show a two folds difference in apparent shear viscosity measured at 50 reciprocal seconds. Whilst the former evolve always within the inertial regime, the latter shows a strong effect of the viscous dissipation on the bolus dynamics. A threshold shear rate to compare the effect of viscosity cannot however be univocally defined as the maximum shear rates generated during swallowing are a strong function of the shear rheology of the bolus.

The mass of post-swallow residues left in the plastic membrane was measured after each
Table 4.4: Post-swallow residues, characteristic oral transit time (FO), time for bolus ejection (TO-FO) and angular velocity of the roller at FO from in vitro tests. The amount of post-swallow residues is normalized with respect to 1.19 % w/w TUC (Nectar-thick). Average values over three repeats, standard deviation in brackets.

<table>
<thead>
<tr>
<th>Liquid sample</th>
<th>Residues (-)</th>
<th>FO (s)</th>
<th>TO-FO (s)</th>
<th>( \dot{\theta} ) at FO (RAD/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.19 % w/w TUC</td>
<td>1.00 (0.07)</td>
<td>0.30 (0.01)</td>
<td>0.09 (0.01)</td>
<td>8.96 (0.24)</td>
</tr>
<tr>
<td>2.35 % w/w TUC</td>
<td>1.16 (0.19)</td>
<td>0.31 (0.01)</td>
<td>0.09 (0.01)</td>
<td>8.71 (0.33)</td>
</tr>
<tr>
<td>3.48 % w/w TUC</td>
<td>1.22 (0.11)</td>
<td>0.32 (0.01)</td>
<td>0.09 (0.02)</td>
<td>8.70 (0.11)</td>
</tr>
<tr>
<td>0.3 % w/w Cereal extract</td>
<td>0.78 (0.13)</td>
<td>0.32 (0.01)</td>
<td>0.09 (0.01)</td>
<td>8.57 (0.14)</td>
</tr>
<tr>
<td>1 % w/w Cereal extract</td>
<td>1.11 (0.19)</td>
<td>0.35 (0.01)</td>
<td>0.09 (0.02)</td>
<td>7.61 (0.08)</td>
</tr>
<tr>
<td>1% w/w PEO</td>
<td>1.21 (0.18)</td>
<td>0.30 (0.01)</td>
<td>0.08 (0.01)</td>
<td>9.12 (0.22)</td>
</tr>
<tr>
<td>2% w/w PEO</td>
<td>1.59 (0.16)</td>
<td>0.33 (0.01)</td>
<td>0.08 (0.02)</td>
<td>8.92 (0.11)</td>
</tr>
<tr>
<td>3% w/w PEO</td>
<td>1.84 (0.09)</td>
<td>0.38 (0.01)</td>
<td>0.09 (0.02)</td>
<td>7.15 (0.15)</td>
</tr>
<tr>
<td>4% w/w PEO</td>
<td>2.34 (0.17)</td>
<td>0.52 (0.01)</td>
<td>0.12 (0.02)</td>
<td>4.76 (0.13)</td>
</tr>
<tr>
<td>5% w/w PEO</td>
<td>2.67 (0.23)</td>
<td>1.01 (0.05)</td>
<td>0.23 (0.03)</td>
<td>2.10 (0.20)</td>
</tr>
</tbody>
</table>

The residues of the different fluids, normalized with respect to the average residue left by TUC Nectar (i.e. 1.19 % w/w TUC), are reported in Table 4.4. The quantity of residues always increases with polymer concentration. This behaviour is evident in the case of PEO and, to a lesser extent, cereal extract. In the case of TUC the residue increases less rapidly when the concentration is higher than 2.35 % w/w. The low concentration, cereal extract sample induced the lowest amount of residues, compared to TUC Nectar while the thickest cereal extract solution led to a comparable amount of residues to the intermediate and thickest TUC.

The in vitro model also allows measuring the evolution with time of the bolus shape. Both the transit time and the shape of the bolus depend strongly on the liquid considered. The loss of confinement occurring at the exit of the plastic membrane represents the transition from the oral to the pharyngeal phase of swallowing. During this transition, it is instructive to analyse the bolus length.

Screenshots captured at bolus front out (FO) and tail out (TO) show a noticeable expansion (elastic recoil) in the case of concentrated PEO solutions, as shown by the evolution of the bolus deformation during the interval between front out (FO) and tail out (TO) (Fig. 4.13 and 4.14).

The bolus ejection from the in vitro oral cavity is followed by an increase in bolus length.
Chapter 4. Viscoelastic and extensional properties of liquids

Figure 4.13: Screenshots from the \textit{in vitro} experiment. From left to right the instant of bolus front out (top row) and tail out (bottom row) for TUC and cereal extract solutions: a) 1.19 \% w/w TUC (\textit{Nectar-thick}), b) 2.35 \% w/w TUC (\textit{Honey-thick}), c) 3.48 \% w/w TUC (\textit{Pudding-thick}), d) 0.3 \% w/w Cereal extract and e) 1 \% w/w Cereal extract.

Figure 4.14: Screenshots from the \textit{in vitro} experiment. From left to right the instant of bolus front out (top row) and tail out (bottom row) for solutions of increasing PEO concentration: a) 1\% PEO, b) 2\% PEO, c) 3\% PEO, d) 4\% PEO and e) 5\% PEO.
4.3. Results

101

Figure 4.15: Calculated strain at the bolus ejection from the *in vitro* oral cavity.

for both cereal extract and TUC solutions (Fig. 4.15). However, as the concentration of polymer is increased, images reveal a bolus expansion and shortening (die swell).

Moving from the lowest to the highest concentration of cereal extract results in a three-fold decrease in the ejection strain when the bolus leaves the *in vitro* palate (Fig. 4.15).

PEO solutions were used as a model material to show the effect of a very high viscoelasticity. As the PEO concentration is increased, a noticeable die swell occurs at the outlet (Fig. 4.14). This is illustrated quantitatively in Fig. 4.16 where a clear shortening of the bolus is visible for concentrations above 3 % PEO.

Comparing the results for fluids with similar IDDSI classification highlights some relevant differences in the bolus shape. While all Level 1 liquids show a similar degree of strain at ejection, the Level 2 cereal extract solution showed a more compact bolus shape, compared to both 2% PEO and 1.19 % TUC (*Nectar-thick*). The slightly higher shear and extensional viscosity of the cereal extract solution may account for this experimental observation. Moving to higher IDDSI Levels makes comparison between the transit dynamics and bolus elongation from different liquids less straightforward, and the role of rheology is amplified.

Overall, a mild die swell results in a compact bolus shape characterized by a low bolus elongation and absence of fragmentation (splashing). This would be a desirable condition
Figure 4.16: Normalized bolus length for aqueous PEO solutions. Square and triangular markers identify the time of bolus front out (FO) and tail out (TO) respectively. Average values and maximum deviation from three repeats.
in vivo to promote a smoother and more controlled bolus flow through the pharynx. However, excessive die swell is associated to a slower flow, because of the associated higher shear viscosity. This could become a potential hazard in vivo, if thick elastic boli spend more time in the pharynx, potentially compromising the airway protection mechanisms.

Die swell has long been studied in continuous processes such as polymer extrusion and blow moulding and several theoretical and semi-empirical equations have been proposed to model the ratio of extrudate to die diameter (swelling ratio) \( \frac{200}{201} \frac{202}{} \). That depends on the ratio between the first normal stress difference and the shear stress calculated at the wall of the die \( \frac{200}{} \). The Deborah and Weissenberg numbers \( De \) and \( Wi \) are common dimensionless quantities used in the study of viscoelastic flows \( \frac{203}{} \). Although conceptually different, in the case of transient flows where one length scale determines the dynamics of the flow, they assume a similar definition, based on the ratio between the relaxation time of the polymer, \( \lambda \), and a time scale relevant to the flow \( \frac{203}{} \). In the study of continuous polymer extrusion, it was shown that the swelling ratio increases with \( Wi \), while the position of the maximum die swell is controlled by the elasticity number \( E \), defined as the ratio between \( Wi \) and the Reynolds number \( Re \) \( \frac{201}{202} \).

Despite the difference between a continuous extrusion process and the present system, the theory of die swell still allows us to interpret some of the in vitro results. An approximate expression of \( De \) for the in vitro model here considered can be calculated with the ratio of the extensional relaxation time \( \lambda_e \) and the time required for bolus ejection \( (De = \frac{\lambda_e}{(t_{TO} - t_{FO})}) \). Increasing the polymer concentration results in higher values of \( \lambda_e \) and longer times required for bolus ejection (Table 4.3 and 4.4). Their ratio \( De \) scales with the bolus elongation at ejection. For PEO, results show that the calculated values of \( De \) increase more than linearly with polymer concentration (Fig. 4.17). For the same polymer, a threshold \( De \) for uprising of die swell can be identified: at higher polymer concentrations (>3 % w/w, \( De \approx 0.5 \)) the swollen bolus remains coherent and is slowly dragged downward by gravity leaving an increased quantity of residues.

The numerical value of the Deborah number is however not capable of self-describing the occurrence of die swell when cross comparing different products. Thin PEO and TUC
Chapter 4. Viscoelastic and extensional properties of liquids

Figure 4.17: Calculated $De$ (bars) and $Er$ (triangles) at the bolus ejection from the *in vitro* oral cavity.

solutions have a similar highly elongated bolus shapes with values of $De$ consistently below 0.4. The least concentrated cereal extract solution, despite having a comparable bolus elongation to PEO and TUC, has double the value of $De$.

Inertia significantly affects the position of maximum die swell, which is delayed downstream at higher extrusion rates. The Elasticity number $E$ allows us to remove the inertial contribution and to directly relate compare the elastic and viscous time-scales. Low values of $E$ were found for thin liquids (Fig. 4.17). $E$ significantly increases with the concentration of PEO thus confirming the existence of a threshold for the dominance of die swell. The value of $E$ remains comparably low for TUC, confirming its not pronounced swelling (Fig. 4.15).

4.4 Conclusions

This chapter relates the effect of the extensional properties of viscoelastic liquids to the dynamics of the oral phase of swallowing. Different viscoelastic liquids were tested and a mathematical model was used to predict the experimental bolus velocity profiles from
the liquid rheology. Higher shear thinning liquids were transported with a speed that is independent of the shear rheology. With fluids showing higher viscosity at shear rates around 100 reciprocal seconds, the *in vitro* oral transport is conditioned by the steady shear viscosity, but not by the viscoelastic properties in the range considered in this study.

Both the commercial thickener and the cereal extract solutions show a comparable, fast, oral dynamics in agreement with their highly shear thinning viscosity. This conclusion remarks that the increased safety of swallowing achieved through alterations in bolus viscosity with highly shear thinning liquids is not linked to the rapidity of the oral transport. Conversely, the less shear thinning behaviour of PEO led to a sluggish viscous-dominated dynamics for polymer concentrations above 3% w/w. A similar behaviour will be expected for starch-thickened solutions.

The extensional properties of the viscoelastic liquid boli played a significant role during bolus ejection from the *in vitro* oral cavity. Liquids of similar shear viscosity but different extensional properties show a different bolus shape and elongation. This is the case, for instance, of the thinnest PEO and cereal extract solutions: in the latter case the bolus shape remained more compact. This effectively limited the fragmentation and splashing observed for thin PEO solutions.

When compared against TUC, the solutions of cereal extract always showed a more controlled bolus flow at the outlet followed by a general decrease in the amount of left-over residues.

Tests with PEO allowed to investigate the limits of elastic behaviour: a significant elastic recoil was observed at high PEO concentrations. This was also associated with a significant delay in the bolus ejection. This observation led us to consider the existence of an optimal threshold for safe swallowing both in terms of shear and extensional viscosities: in this regard, thick and elastic liquids should be avoided not to compromise the airway protection mechanism *in vivo*. These findings suggest the importance of a holistic characterization of the rheology of food thickeners, since it may condition the residues, the oral transit time and the shape of the bolus at the transition between the oral and the
pharyngeal phase of swallowing.

The next two chapters extend the *in vitro* model to study the bolus dynamics in presence of suspended solids and the mitigating effect of the bolus rheology to ensure a smooth flow of model tablets and multiparticulates, which is key to develop easy-to-swallow formulations in the pharmaceutical industry. The limits of the *in vitro* model in terms of flow domain, role of salivary lubrication and force measurement will be addressed in the final experimental chapter of the thesis that considers the development of a novel soft robotic device to simulate the oral swallowing dynamics.
Chapter 5

Swallowing of solid oral dosage forms

The previous chapter considered the benefits of elastic fluids for the developments of easy-to-swallow liquid formulations. Thin elastic liquids were proposed as an alternative to current gum-based thickeners to ensure a smoother bolus transit from the oral cavity to the pharynx. The following two chapters aim instead to understand how the presence of solid oral dosage forms affects the oral swallowing dynamics. This is key to develop oral drug delivery systems for paediatric and geriatric populations that ensure both the combined requirements of dose flexibility and ease of swallowing.

In this chapter the dynamics of swallowing was investigated in vitro for model tablets, varying their size and shape. The rheological problem was simplified with respect to Chapter 4 by considering only Newtonian liquids.

In vitro swallowing tests for single model-tablets remarked a strong effect of the volume of the medication with respect to the duration of oral transit, with elongated tablets flowing faster than spherical tablets. However, the geometrical properties of the solid oral dosage forms did not significantly affect the bolus dynamics when the cross section of the tablet was lower than 40% of that of the bolus. Results also show the mitigating role of the suspending vehicle viscosity with thicker liquids ensuring a smoother flow of large tablets.

These findings and this approach could pave the way for a better design of solid oral medications to address the special needs of children or patients with swallowing disorders and could help designing more successful sensory evaluations and clinical studies.
Chapter 5. Swallowing of solid oral dosage forms

5.1 Introduction

Tablet size and shape of can significantly condition the compliance of patients to a prescribed drug therapy \textsuperscript{(201)}. In clinical conditions of oropharyngeal dysphagia the swallowing threshold has to be carefully considered by both the practitioner and the caregiver \textsuperscript{(205; 206; 207)}.

Solid oral dosage forms could become trapped in the larynx folds, leading to a potential risk of choking and triggering local inflammations, esophagitis, and ulceration \textsuperscript{(208)}. Although oral liquid formulation and novel solid oral dosage forms, such as orodispersible and mucoadhesive tablets, have been developed and commercialized, capsules and tablets still remain the most common oral drug delivery forms, by virtue of the longer stability of the active pharmaceutical ingredient (API) and the higher standardization of the tableting process \textsuperscript{(209; 210)}. multiparticulates can be also designed in a range of particle sizes offering dose flexibility while retaining the advantages of conventional solid oral dosage forms \textsuperscript{(211)}. Moreover, multiparticulate formulations have potential to be better tolerated by patients than conventional tablets \textsuperscript{(212; 213; 207)}. However, further research is needed to shed light on the optimal way of administering multiparticulates to patients: acceptability of multiparticulate administration potentially depends on palatability and rheology of the suspending liquid carrier \textsuperscript{(214)}.

The practice of dispersing crushed tablets into thickened liquids, jelly, or food, can however change significantly the pharmacokinetics and bioavailability of some solid oral dosage forms \textsuperscript{(215; 216; 217; 218; 219)}.

Size and shape are deemed the most important reasons that limit acceptability of classical solid oral dosage forms \textsuperscript{(208; 220)}. Aspiration and choking during the oropharyngeal phase of deglutition become increasingly common with increasing the size of solid oral dosage forms \textsuperscript{(221)}. Studies revealed that the level of acceptability of an oral medication, albeit dependent upon the age subset, is greatly reduced when its diameter is above 8 mm \textsuperscript{(222)}.

It has also been shown that size is a major player in determining the esophageal transit
time, smaller tablets flowing faster (222, 223, 205). Concerning the dynamics of the pharyngeal phase of swallowing, no significant variations were observed when swallowing small enough solid oral dosage forms (d=2 mm) compared to the case of swallowing homogeneous liquids (221). There is however a comparable lack of studies on the effect of size of tablets on the duration of the oral phase of swallowing. The role of tongue propulsion in the first stages of deglutition was briefly discussed by Yamamoto et al. while investigating the behavioural performance of pill swallowing in 12 subjects. In their report, the authors speculated that the difference in flow rate between tablets and liquid vehicle may be the cause for the failure of the first swallowing attempt, leading the patient to take further sips to correctly transfer the oral medication from the oral cavity to the esophagus (223). Hey et al. also found that administration of solid oral prescriptions in a single swallow might more easily leave the tablet lag the pharynx, while taking an identical solid dose while drinking 100 mL of water effectively reduces the transit time of the tablet. The difficulty in tablet swallowing and the delay in their organogastric transit is much accentuated by the potential inability of some patients to drink larger amount of water or drinks in large sips (206).

Other than size, particle shape is also very important factor to be considered in tablet design. Previous reports suggest that prolate (i.e. axially elongated) tablets are easier to swallow and have faster esophageal transit times than oblate (i.e. flattened) for the same delivered dose of medication (225, 220, 205) and capsules are generally preferred to tablets (226). On the other hand, it was also observed that more elongated tablets and capsules have a greater tendency to adhere and stick to the esophageal epithelium than biconvex and less elongated tablets, hence increasing the risk of irritating the esophageal mucosa (227). Behavioural tests seem however to suggest the preference of panellists towards oblong shapes which has not yet been mechanistically explained in terms of oral dynamics.

Factors such as density and surface coating were also among the factors considered to study the swallowability and the esophageal transit of tablets and capsules (205). Channer and Virjee showed that the esophageal transit time of capsules size 0, measured with the
patients in a standing position, noticeably decreased when increasing their filling density (228) while Kasashi et al. found no statistical significant difference in the oral transit times in respect of the density for small (0.24 mL) and medium sized (0.60 mL) capsules (229). In general, several reports have proved tablet coating improves the acceptability in patients (205). Hey et al. were among the first to demonstrate that small coated oval tablets are swallowed more easily than uncoated oval tablets when consumed with an equal volume of water (225). The type of film coating can also greatly affect the tendency for solid oral formulations to adhere to the esophageal epithelium as reported in several in vitro studies (227; 205). Furthermore, coating also can affect other factors that contribute to patient acceptance, such as palatability and smell. The latter being a factor of paramount acceptance of solid oral dosage forms in children, as several aids have been developed ranging from in situ coating for tablets to lubricating flavoured gels containing glycerol to be applied to the back of the mouth prior to taking the medication (230).

Lopez et al. highlighted the need for quantitatively assessing the ease of swallowing of novel types of solid oral dosage forms, such as mini-tablets and granulates, that specifically aim at optimally tailoring the dose of API to paediatric and adolescent patients’ body weight or age (213). Oral liquid formulations indeed constitute the most widely used oral forms in paediatrics (205). Preliminary clinical studies showed a non-significant difference in acceptability in new-borns between a 15% glucose syrup and a single mini-tablet of d=2 mm (231). In the report however the volume and rheology of the suspending liquid vehicles was not discussed in relation to that of the syrup. Other clinical studies showed that small tablets (d=3 mm) can be easily swallowed by children from 2 to 6 years of age (232). A study involving 124 children aged 6 to 11 years, also demonstrated a high acceptability towards ingestion of a flat round tablet of d=7 mm, especially upon training (233). Swallowing performance of multiple tablets in children has been the subject of a few studies, as reviewed by Mistry & Batchelor (207). It was shown that the acceptable number of tablets per unit dose depends both on the diameter of the tablet and the age of the patient (207; 234). Improvement in children compliance when taking mini-tablets
5.1. Introduction

Figure 5.1: Different shapes of model-solid oral dosage forms were considered by the study. Ellipsoids are identified by their aspect ratio (AR), defined with the ratio between the equatorial and the azimuthal semiaxes. In the figure: oblate (i.e. flattened) spheroid of AR=0.25, b) sphere AR=1, c) prolate spheroid of AR=1.5, d) prolate spheroid of AR=2.5, e) prolate spheroid of AR=3.5, f) capsule size 3. The arrow points at the direction of swallowing.

was achieved dispersing the tablets into flavoured liquids jelly, as proposed by Jagani et al. (235) and Kluk et al. (234). In regard to the optimal dose and volume of the solid prescription Hayakawa et al. showed that the ease of swallowing of multiple tablets as a unit dose decreases with their increasing number (212). In particular administration of a single conventional tablet of d=8 mm was perceived easier to swallow than an identical mass of 10 mini-tablets (212).

This study aims to present a method to quantitatively assess the role of the physical properties solid oral dosage forms primarily highlighting the importance of their size, shape and number in the oral dynamics of swallowing. The approach follows the use of the same in vitro model of the oral cavity presented in Chapter 4. Alterations to the experimental procedure there described are presented.

5.1.1 Materials

Different sizes and shapes of hard particles, representative of solid oral dosage forms, were considered to compare the relative difference in the measured in vitro oral transit time and bolus velocity. The effect of size for different solid oral dosage forms was studied using calibrated polypropylene spheres (The Precision Plastic Ball Company Ltd, Addingham, UK) of diameter ranging from 4.8 to 10 mm and smooth surface finishing. By using those model shapes the degree of freedom of initial particle orientation in respect of
the bolus was removed, allowing for generalization of the results. More realistic model shapes of pharmaceutical tablets were instead used to assess the impact of the solid oral medication geometry on the oral flow. These consisted of ellipsoids of revolution with volumes comparable to either a 8 mm or a 10 mm sphere (Table 5.1). To this extent, elongated particles were designed and 3D printed by UV curing (ProJect™MJP 3600, 3D Systems Inc., San Diego, CA, USA). The shape of both flattened (i.e. oblate) and elongated (i.e. prolate) spheroids was consistently described through their aspect ratio (AR), defined by the ratio of polar and equatorial semiaxis (Fig 5.1). Density was measured by gas pycnometry (AccuPyc pycnometer 1330, Micrometrics Instrument Corp., Norcross, GA, USA) for both spherical and elongated tablets, obtaining values of \( \rho_S = 850 \pm 50 \text{ kg m}^{-3} \) and \( 1100 \pm 50 \text{ kg m}^{-3} \) respectively. The impact of tablet density in the oral swallowing dynamics was not considered an important experimental variable as previous in vivo studies already proved \(^{229}\). Similarly, the specific density of different liquid vehicles was tested in vitro without showing any significant variation in the bolus velocity \(^8\).

Moreover, in order to further explore the dynamics of swallowing of elongated solid oral dosage forms, empty hydroxypropylmethyl cellulose (HPMC) capsules size 00 and size 3 were purchased from Bulk Powders (Sports Supplements Ltd, Colchester, Essex, UK) and filled with sucrose so that their density would match that of the spherical beads \( \rho_S = 850 \pm 50 \text{ kg m}^{-3} \). The volume of a \( d=8 \text{ mm} \) sphere is comparable to a size 3 capsule and the volume of a \( d=10 \text{ mm} \) sphere is almost double. A much bigger size 00 capsule was considered as a limiting case, given that it is the maximum capsule size recommended by the Food and Drug Administration \(^{208}\).

To assess the dynamics of the bolus in presence of multiple tablets, experiments were also run with several mono-dispersed spheres. In this set of tests, the number of solid oral medications was varied while maintaining constant the solid volume fraction of \( \phi = 0.08 \text{ v/V} \), corresponding to the dose of a single \( d=10 \text{ mm} \) spherical tablet.

Newtonian suspending liquid vehicles were considered in this study. Complex liquids were
Table 5.1: Summary of the solid oral dosage forms used in the *in vitro* experiments to model swallowing of a single solid oral dosage form.

<table>
<thead>
<tr>
<th>Tablet shape</th>
<th>Characteristic size (d or L x H)</th>
<th>Tablet to bolus cross section</th>
<th>Volume</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>d=4.8 mm</td>
<td>15 %</td>
<td>0.06 mL</td>
<td>50 mg</td>
</tr>
<tr>
<td>Sphere</td>
<td>d=6.4 mm</td>
<td>28 %</td>
<td>0.13 mL</td>
<td>120 mg</td>
</tr>
<tr>
<td>Sphere</td>
<td>d=8 mm</td>
<td>44 %</td>
<td>0.27 mL</td>
<td>240 mg</td>
</tr>
<tr>
<td>Sphere</td>
<td>d=10 mm</td>
<td>68 %</td>
<td>0.52 mL</td>
<td>460 mg</td>
</tr>
<tr>
<td>Oblate spheroid</td>
<td>12.7 x 3.2 mm</td>
<td>28 %</td>
<td>0.27 mL</td>
<td>310 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>10.5 x 6.9 mm</td>
<td>33 %</td>
<td>0.27 mL</td>
<td>310 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>14.7 x 5.9 mm</td>
<td>24 %</td>
<td>0.27 mL</td>
<td>310 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>18.4 x 5.3 mm</td>
<td>19 %</td>
<td>0.27 mL</td>
<td>310 mg</td>
</tr>
<tr>
<td>Capsule size 3</td>
<td>15.5 x 5.8 mm</td>
<td>22 %</td>
<td>0.27 mL</td>
<td>280 mg</td>
</tr>
<tr>
<td>Oblate spheroid</td>
<td>15.8 x 3.9 mm</td>
<td>42 %</td>
<td>0.52 mL</td>
<td>610 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>13.1 x 8.7 mm</td>
<td>52 %</td>
<td>0.52 mL</td>
<td>610 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>18.4 x 7.4 mm</td>
<td>37 %</td>
<td>0.52 mL</td>
<td>610 mg</td>
</tr>
<tr>
<td>Prolate spheroid</td>
<td>23.1 x 6.6 mm</td>
<td>30 %</td>
<td>0.52 mL</td>
<td>610 mg</td>
</tr>
<tr>
<td>Capsule size 00</td>
<td>32.5 x 8.5 mm</td>
<td>49 %</td>
<td>0.95 mL</td>
<td>900 mg</td>
</tr>
</tbody>
</table>
not tested in order to reduce the number of degrees of freedom and build a more sound understanding of the role of tablet size and shape on the dynamics of swallowing. The viscosity of the vehicle was varied to assess the importance of this parameter in the oral transport of solid oral dosage forms. Glycerol (Sigma-Aldrich, CAS Number 56-81-5) was used as a model thick liquid carrier to simulate the administration of tablets in thickened liquids or jelly: a common practice in nursing homes \(^{(216, 217)}\). A number of tests were also carried out using a thinner orange juice from concentrate (Tesco Stores Ltd., Welwyn Garden City, Hertfordshire, UK), a thin Newtonian liquid vehicle often used to mask the bitter taste of tablets. In both cases traces of a red dye (0.02 % w/w) were added to enhance the image contrast. The density of the two liquids were measured using a graduated cylinder obtaining values of \( \rho_L = 1250 \pm 20 \text{ kg m}^{-3} \) and \( 1040 \pm 30 \text{ kg m}^{-3} \) for glycerol and orange juice respectively. The liquid volume used in the experiments was 6 mL, consistently with previous studies \(^{(29)}\) and comparable to \textit{in vivo} values reported in the literature \(^{(12, 234)}\). All the experiments were performed at \( 22 \pm 1 \degree \text{C} \) and, at this temperature, the viscosity of the two liquid vehicles, both Newtonian, measured in compliance to ISO standard 3219 with a controlled stress rheometer (Model UDS 200, Paar Physica, Germany), was \( \eta = 1.09 \pm 0.050 \text{ Pa s} \) and \( \eta = 0.03 \pm 0.01 \text{ Pa s} \).

The experimental setup used to study the oral phase of swallowing is introduced in Chapter 4 and its theoretical description is given in Appendix A. Variability of tongue applied pressure among individuals was accounted for by adjusting the weight driving the rotation of the pivoting arm. In this study roller driving forces \((F)\) of 2, 2.7, and 4 N were used, corresponding to applied torques of 57, 73 and 108 mNm respectively. These driving forces generated maximum pressures on the bolus tail of approximately 11, 15, and 21 kPa, consistently with \textit{in vivo} data from the literature \(^{(29)}\). Results from the same \textit{in vitro} model were successfully validated against \textit{in vivo} ultrasound measurements with thickened fluids \(^{(8)}\) and the swallowing simulator matched well the \textit{in vivo} bolus dynamics when applying a force of 2 N.
Figure 5.2: Schematics of the *in vitro* setup.

### 5.1.2 Methods

The different solid oral dosage forms listed in Table 5.1 were first incorporated into the suspending liquid carrier and subsequently the bolus was pushed manually into the membrane through its anterior opening. The initial position of the tablets in the bolus is essentially dictated by buoyancy as the density of the solids is lower than that of the suspending liquid vehicle. Solids were located centrally within the bolus cross section in order to avoid direct contact with the walls of the membrane. Moreover, non spherical tablets and capsules were consistently aligned with the longitudinal axis of the bolus, in order to present their smallest cross section in the direction of swallowing (Fig. 5.1).

The relative position of the solid oral dosage forms within the bolus was quantified by the difference ($\Delta \theta$) of the angular positions of the bolus tail and of the tablet, as schematically illustrated in Fig. 5.2. Decreasing $\Delta \theta$ indicated that the tablet was slower than the liquid carrier and moved towards the tail of the bolus, while constant $\Delta \theta$ indicated that it moved at the same velocity as the rest of the bolus.

$$\Delta \theta = \theta_{tablet} - \theta_{roller}$$

Three repeats, in randomized order, were taken per each set of experimental variables to
assess the variability and robustness of the *in vitro* setup to external disturbances, such as slight variations in the initial position of the solid oral dosage forms within the liquid bolus, or minor differences in the shape of the PE membranes.

### 5.1.3 Results and discussion

The experiments aimed at understanding the effect of solid oral dosage size, shape and number on the oral swallowing dynamics while varying the external applied force.

*In vitro* swallowing of single tablets

The effect of tablet size on the dynamics of the mechanical system was initially investigated. The applied force and the initial position of the spherical tablet were consistent in all experiments, as illustrated in Fig. 5.3 and the characteristic oral transit time was extracted from the experimental video recordings, marking the frame at which the front of the peristaltic flow left the plastic membrane (front out-FO) and the instant at which the roller hit the stopper leading the tail of the bolus to exit the plastic membrane (tail out-TO). Average values and standard deviations were computed based on three repetitions of each experiment, as listed in Table 5.2.

From the snapshots in Fig. 5.3 and the data listed in Table 5.2 it can be seen that larger solid oral dosage forms had a slightly delayed FO and TO with respect of smaller spherical tablets. More generally, the delay between these events both depended on the size of solid oral dosage forms and on the applied load to the system. The range of values for the characteristic *in vitro* swallowing listed in Table 5.2 well compares with the typical values of oral transit times reported in the literature when considering swallow of homogeneous thickened fluids. When considering administration of solid oral dosage forms only a few references are found in the literature: Kasashi *et al.* provide slightly longer oral transit times (1.14-2.23 s), based on videofluoroscopy assessment of capsule swallowing (229), while EMG recordings from Yamamoto *et al.* show a two fold increase in the swallowing
5.1. Introduction

Figure 5.3: Screenshots from the *in vitro* experiments using a 2 N load, a 1.09 Pa s Newtonian liquid carrier and single spherical tablets having different diameters. The pictures in the third and fourth columns are respectively taken when the bolus front leaves the membrane (FO) and when the tail of the bolus leaves the membrane (TO).
Figure 5.4: Roller velocity profiles for model spherical tablets of d=4.8, 6.4, 8.0 and 10 mm using a 2 N load and a 1.09 Pa s Newtonian liquid carrier. Theoretical curves are obtained using Eq. A.39.

duration when taking a large d=9 mm biconvex tablet compared to the water control (223), but a less insignificant increase for smaller tablets.

The velocity profiles obtained after numerical differentiation of the time dependent roller angular positions are plotted in the following figures until bolus front out (FO), consistently to the approach followed by Hayoun et al. (29).

The results obtained with different solid oral dosage forms shapes and sizes were compared to the theoretical predictions obtained considering the system dynamics and the drag force defined in Eq. A.39 and illustrated in the charts with thin solid lines.

Variations in the driving load applied to the mechanical device strongly conditioned the bolus dynamics, as discussed by Hayoun et al. (29). The combined effect of applied force and size for spherical solid oral dosage forms is illustrated in Fig. 5.4 and Fig. 5.5: experiments at low applied forces (2 N) were characterized by an inertial regime, in which the angular velocity was almost linearly increasing in time, followed by a viscous regime,
where the drag force became predominant and effectively equilibrated the inertial force, leading to asymptotic values of bolus velocity (Fig. 5.4). By contrast, experiments at higher applied loads only showed the inertial regime.

The relative importance of the additional drag force induced by the presence of swallowed solids is also dependent upon the external load applied to the system. Experiments in the lowest load configuration (2 N) showed a moderate decrease of swallowing velocity and longer oral transit time increasing the diameter of the suspended spherical solids. Small solid oral dosage forms were also found not to significantly alter the system dynamics, compared with the solid-free case presented by Hayoun et al., as can be appreciated from the profiles reported in Fig. 5.4 and 5.5.

Conversely, tests with significantly bigger model tablets seem to suggest the onset of an anticipated viscous regime of significantly low angular velocity than the asymptotic values reached in clear liquid. This is especially visible at low applied forces, as illustrated in Fig. 5.4. Conversely, at the highest load (4 N), no significant effect of the tablet diameter was observed, although the in vitro transit time of the biggest sphere was still slightly slower than the others (Fig. 5.5). In the case of an intermediate load (2.7 N), results showed a comparably slow dynamics of the d=10 mm spherical solid, when compared to
Table 5.2: Characteristic *in vitro* oral transit times measured obtained for swallowing of a single spherical tablets in a 1.09 Pa s liquid carrier (glycerol). Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Applied load</th>
<th>Tablet diameter</th>
<th>Bolus FO</th>
<th>Bolus TO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 N</strong></td>
<td>4.8 mm</td>
<td>0.58 (0.03) s</td>
<td>0.73 (0.02) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>0.61 (0.04) s</td>
<td>0.78 (0.04) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>0.64 (0.03) s</td>
<td>0.82 (0.02) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>0.97 (0.17) s</td>
<td>1.27 (0.18) s</td>
</tr>
<tr>
<td><strong>2.7 N</strong></td>
<td>4.8 mm</td>
<td>0.45 (0.02) s</td>
<td>0.58 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>0.46 (0.02) s</td>
<td>0.59 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>0.47 (0.01) s</td>
<td>0.60 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>0.53 (0.03) s</td>
<td>0.66 (0.03) s</td>
</tr>
<tr>
<td><strong>4 N</strong></td>
<td>4.8 mm</td>
<td>0.34 (0.02) s</td>
<td>0.43 (0.03) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>0.34 (0.02) s</td>
<td>0.43 (0.02) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>0.33 (0.02) s</td>
<td>0.43 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>0.38 (0.01) s</td>
<td>0.48 (0.02) s</td>
</tr>
</tbody>
</table>

The examination of the relative motion of the tablet within the suspending liquid vehicle was considered in light of the study of peristaltic model flows and the experimental observation of Yamamoto *et al.* (223) that commented on the different flow rate between liquid and solid portions of the swallowed bolus. The angular distance between the position of the roller and the position of the centre of mass of the tablet was quantified through the value of $\Delta \theta$. This parameter, not being directly comparable to a specific theoretical formulation for the field of motion here considered, leads to a more qualitative interpretation, compared to the much more quantitative information obtained instead from the roller velocity profiles. Nonetheless, the typical average profiles of $\Delta \theta$ reported, as a
function of the tablet size and applied load, in Fig. 5.8, give some coherent results. The profiles show good consistency of initial positioning of the beads, that were always placed in proximity to the bolus front with the sole exception of the largest spherical tablet, that instead was positioned slightly rearward in order to limit the occurrence of liquid leaking before triggering the experiment. For a low applied force of 2 N, Fig. 5.8 indicates that both the 6.4 and the 8 mm spherical tablets did not move significantly within the bolus, as the initial angle was preserved throughout the bolus trajectory. Conversely, a significant reduction in $\Delta \theta$ was observed in both the d=4.8 mm and d=10 mm spheres that lagged toward the tail of the bolus. This results somehow confirms that small objects are less efficiently transported by peristalsis, as indicated in previous works in that field (180; 236). On the other hand, the relative backward motion of the biggest sphere, unexplained in terms of simple peristaltic transport, is instead driven by the friction with the wall membrane. In this case the liquid carrier, under the imposed squeezing action of the roller, was able to flow cross the free portion of the bolus unoccupied by the solid oral dosage form lagging the spherical tablet behind. Increasing the external applied load did not lead to significant changes in the tablet relative position: the smallest solid still slides backwards, whist no noticeable variations in relative position in respect of the bolus tail are observed for both the intermediate size spherical tablets (d=6.4 and the d=8 mm).

Based on these in vitro observations, the backward motion of the smallest, or largest solids might limit the active volume of liquid available to wash them out during the pharyngeal and esophageal phase of swallowing and also cause them to be more easily perceived in vivo by the contracted part of the tongue propelling the bolus. Following this hypothesis, the extent of mechanical solicitation on the tongue apex and dorsum will also be dependent upon the size and density of the solid oral prescription and the level of its surface finishing. The lack of comparable videofluoroscopy images does currently not allow to confirm this claim, although the conclusion from Yamamoto et al., seems to suggest that the difference between tablet and liquid vehicle velocity might indeed lead to the need for repeated swallows to effectively wash the tablet down the pharynx (223).

The effect of shape was considered comparing results of spherical, oblate (flattened) and
proule (elongated) solid oral dosage forms (Fig. 5.6). The orientation of the solids in respect of the longitudinal axis of the bolus was always maintained throughout the oral trajectory. The corresponding theoretical velocity profiles were in this case computed considering the cross sectional radius of the tablet in the direction of swallowing as $R_i$ in Eq. A.39.

The effect of tablet shape on the bolus dynamics was more significant when the mechanical system was operated under low applied forces, as already observed when discussing the role of size for spherical solid oral dosage forms. In this condition, the tablet and capsule geometries were found to affect more significantly the dynamics of larger solid oral dosage forms (Fig. 5.6). The set of data from in vitro swallowing at constant volumetric dose of solid oral medications (equivalent to that of a d=10 mm sphere) showed that there was a correlation between the cross sectional area of the swallowed solid and the rapidity of bolus transport through the oral cavity (Fig. 5.6). As the cross section of the tablet fell below 40% of that of the bolus, the effect of shape for spheroids became less and less important (Fig. 5.6a). Naturally, the increased wall interaction observed when running experiments with the largest spherical tablet likely resulted in further dissipation phenomena. Yet, the velocity profile of that solid oral dosage form was nearly identical to that of a size 00 capsule, whose volume is noticeably larger than the sphere (Fig. 5.6b). This consideration highlights the importance of optimally choosing the solid oral dosage shape in the delivery of oral medications.

When considering the set of data from experiments with tablets of equivalent volume to that of a d=8 mm sphere, it was found that the change in cross section did not lead to significant variations in bolus dynamics. The role of tablet shape became therefore marginal. This observation is in good agreement with the clustering of the velocity profiles observed in Fig. 5.6.

Increasing the driving force applied to the roller led to a faster bolus dynamics that was not strongly conditioned by the tablet shape, in that case the oral transit times obtained for the elongated tablets (AR 3.5) were similar to those of spherical tablets of identical volume.
Moreover, the theoretical velocity profiles consistently over-predicted the experimental data of spheroidal solids. This highlights the necessity for more accurate models to account for particle shape, as the model of Eq. A.39 does not account for the length of the solid oral dosage form in the direction of swallowing, but only considers its cross sectional radius. In vivo the preference of patients towards different shapes of tablets was comprehensively discussed by Overgaard et al. over a sample population of 331 volunteers (226). Based on the evaluation scheme proposed by the authors, a higher preference towards strongly arched circular shapes was preferred over oblong shapes for small tablets (approx. volume of 0.16 mL), while for medium and large tablets (approx. 0.5 and 0.95 mL), oblong and oval shapes were preferred over the flat circular. In particular, for the biggest size subset, thick oval shapes (i.e. prolate ellipsoid with low aspect ratios) were generally indicated as difficult to swallow, which is consistent to the poor performance observed in vitro.

The high viscosity of glycerol is close to that of oral paediatric formulations, such as paracetamol suspensions (237). Thickened liquids and jelly have also been used to aid pill and mini-tablet swallowing in geriatric and paediatric patients (234; 207). In order to assess the feasibility of using the proposed in vitro tests to characterize a wider range of liquid carriers, a concentrated orange juice was also considered. The viscosity of this carrier is considerably lower than that of glycerol but still approximately 30 times higher than water. The effect of the rheology of the liquid carrier was assessed using the largest tablets and in the lowest load configuration (2 N) to better capture the effect of tablet elongation, as highlighted by the precedent trials in glycerol. Results show a noticeable decrease in the characteristic oral transit times (Table 5.3). The observation is consistent with the findings of Mowlavi et al. who assessed the role of viscosity using diluted glycerol solutions and a commercial food thickener (8). Comparing the different liquids in terms of their rheology, the authors demonstrated the transition from an inertial regime, characterized by a linearly increasing bolus angular velocity during swallowing, to a viscous regime of asymptotic values of bolus velocity. Consistently to this finding, the velocity profiles obtained with orange juice, illustrated in Fig. 5.7, remarkably differ from those of Fig. 5.6 b. The low viscous dissipation calculated in case of the concentrated juice predicts
Table 5.3: Characteristic oral transit times at 2 N load in different suspending vehicles for tablets with different AR and an equivalent volume to a d=10 mm sphere. Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Liquid vehicle</th>
<th>Tablet AR</th>
<th>Bolus FO</th>
<th>Bolus TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>0.25</td>
<td>0.67 (0.09) s</td>
<td>0.92 (0.05) s</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.69 (0.06) s</td>
<td>0.95 (0.10) s</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>0.65 (0.04) s</td>
<td>0.87 (0.04) s</td>
</tr>
<tr>
<td>Orange juice</td>
<td>0.25</td>
<td>0.31 (0.03) s</td>
<td>0.43 (0.02) s</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.39 (0.09) s</td>
<td>1.59 (0.35) s</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>0.31 (0.02) s</td>
<td>0.42 (0.02) s</td>
</tr>
</tbody>
</table>

an almost linear velocity profile not significantly dependent on the diameter of the tablet considered. Besides, experiments with concentrated juice demonstrated a stronger impact of tablet elongation compared to the weak effect observed with glycerol. Comparing the values listed in Table 5.3 with the velocity profiles Fig. 5.7 shows comparable transit times for the most elongated (AR 3.5) and the flattest (AR 0.25) tablets. Conversely, longer transit times, higher variability and lower bolus velocities were registered for the spheroidal tablet of largest cross section (AR 1.5). A visual analysis of the corresponding tests helps to identify the cause for a similar behaviour in terms of tablet friction against the sidewalls. Tablet shapes with smaller cross sections were found less likely to lag behind the liquid vehicle therefore avoiding direct contact with the sidewalls. Conversely, tablets of large cross section (AR 1.5) pinch against the membrane. This results in a non-monotonic roller angular velocity profile and considerably longer TO times, as reported in Table 5.3

**In vitro** swallowing of multiple tablets

The relevant change in the measured *in vitro* oral dynamics was assessed when swallowing several tablets as a single unit dose. In these experiments the amount of liquid vehicle was kept consistent with the previous trials and the number of tablets was varied, according to their diameter, to deliver approximately an identical cumulative volume of solid oral medications. Beside a realistic volume fraction of solid oral medications of $\phi=0.08$ v/V, corresponding to a dose of 460-500 mg/6 mL, using the *in vitro* model also allowed
5.1. Introduction

Figure 5.6: Effect of tablet shape using a 2 N load in a 1.09 Pa s Newtonian liquid carrier: roller angular velocity for oblate, spherical, and prolate tablets of identical volumes to that of a d=8 mm (a) and d=10 mm sphere (b). Theoretical curves are obtained using Eq. A.39.

Figure 5.7: Effect of the carrier liquid vehicle viscosity at 2 N load when considering in vitro swallowing of oblate (AR<1) and prolate (AR>1) spheroidal tablets. Theoretical curves are obtained using Eq. A.39 for a tablet diameter of 10 mm.
Figure 5.8: Angular distance between the bolus tail and the centre of mass of spherical solid oral dosage forms using a 1.09 Pa s Newtonian liquid carrier at respectively 2 N (a), and 2.7 N (b) applied force.

considering the effect of pushing the volume fraction to $\phi=0.15 \, \text{v/V}$ (920-960 mg/6 mL).

Average velocity profiles at $\phi=0.08 \, \text{v/V}$, obtained from three repetitions for the different diameters and applied forces, are plotted in Fig. 5.9. The corresponding characteristic transit times reported in Table 5.4. The oral dynamics at low volume fraction of suspended solids was not strongly conditioned by the size of the spherical tablets when the system was operated under higher applied loads (2.7 and 4 N). Decreasing the applied force to the mechanical system led to an increase in the oral transit time with the volumetric dose of suspended solids $\phi$ for the tablet diameters here considered. In particular, driving the system with a more physiologically representative 2 N load resulted in velocity profiles that quickly reached a steady state where the viscous dissipation quantitatively equilibrated the applied force (Fig. 5.9a).

Tests with a higher volume fraction of suspended solids, not presented in this thesis, showed a more accentuated viscous dissipation leading to a lower steady state velocity and a faster onset of the steady state, in particular for smaller tablets (238). This suggests that the fluid-solid interaction in presence of multiple beads increased significantly the drag force, hence leading to a reduction in the measured bolus velocity. This finding is somehow confirmed by the increased duration and area of the EMG bursts registered in


Figure 5.9: Roller angular velocities for experiments at constant volume fraction of suspended solids ($\phi=0.08 \, \text{v/V}$) suspended in a 1.09 Pa s Newtonian liquid vehicle. The applied force was changed from 2 N (a) to 2.7 N (b) and 4 N (c). Theoretical angular velocity profiles are obtained from Eq. A.41.
Table 5.4: Characteristic in vitro oral transit times for mono-dispersed solids ($\phi=0.08$ v/V) in a 1.09 Pa s Newtonian liquid carrier. Average values and standard deviation from three repeats.

<table>
<thead>
<tr>
<th>Applied load</th>
<th>Tablet diameter</th>
<th>Number of tablets</th>
<th>Bolus FO</th>
<th>Bolus TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 N</td>
<td>4.8 mm</td>
<td>9</td>
<td>0.69 (0.04) s</td>
<td>0.91 (0.04) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>4</td>
<td>0.76 (0.07) s</td>
<td>1.01 (0.08) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>2</td>
<td>0.75 (0.08) s</td>
<td>0.99 (0.09) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>1</td>
<td>0.97 (0.17) s</td>
<td>1.27 (0.18) s</td>
</tr>
<tr>
<td>2.7 N</td>
<td>4.8 mm</td>
<td>9</td>
<td>0.48 (0.02) s</td>
<td>0.68 (0.03) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>4</td>
<td>0.54 (0.04) s</td>
<td>0.73 (0.06) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>2</td>
<td>0.50 (0.02) s</td>
<td>0.68 (0.03) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>1</td>
<td>0.53 (0.03) s</td>
<td>0.66 (0.03) s</td>
</tr>
<tr>
<td>4 N</td>
<td>4.8 mm</td>
<td>9</td>
<td>0.35 (0.01) s</td>
<td>0.47 (0.02) s</td>
</tr>
<tr>
<td></td>
<td>6.4 mm</td>
<td>4</td>
<td>0.36 (0.02) s</td>
<td>0.47 (0.03) s</td>
</tr>
<tr>
<td></td>
<td>8 mm</td>
<td>2</td>
<td>0.45 (0.02) s</td>
<td>0.65 (0.03) s</td>
</tr>
<tr>
<td></td>
<td>10 mm</td>
<td>1</td>
<td>0.38 (0.01) s</td>
<td>0.48 (0.02) s</td>
</tr>
</tbody>
</table>

vivo when swallowing multiple tablets, indicating the need for effortful swallows (223).

The increase in apparent liquid carrier viscosity predicted through the Krieger-Dougherty model (Eq. A.41) led to a slower theoretical dynamics, as can be appreciated comparing the results presented in Fig. 5.9 with those of Fig. 5.4 and Fig. 5.5. A good agreement between experimental results and theoretical values was found at low suspended solids volume fraction, however the theoretical model was incapable to capture the effect of particle size on the dynamics of the system. The experiments demonstrated that this effect was more significant at low applied forces or when the suspended phase volume fraction was increased.

Image analysis revealed that when the size of the solid oral dosage was reduced, they
moved towards the tail of the bolus. This effect is qualitatively illustrated in Fig. 5.10 where clustering of suspended solids in proximity of the roller can be observed. The build-up of solids close to the roller resulted in a concentration gradient that limits the applicability of Eq. A.41, justifying the gap between experimental data and theory. More sophisticated theoretical models are therefore needed to account for both the effect of solid oral dosage form size and dose. Particle image velocimetry could be used to study the bolus flow pattern, and numerical simulations, accounting for the full fluid-particle and particle-particle interaction, should be considered to model more accurately the dynamic system.

In vivo, it can be speculated that the apparent backward motion of tablets, flowing towards the tip of the tongue, might lead the patient to interrupt the swallow or to masticate the tablets, instead of swallowing them whole. Studies in children show that the occurrence of chewing increases with the administrated amount of mini-tablets, as already demonstrated by Kluk et al. \(^{(234)}\). In another study, that compared the ease of swallowing of mini-tablets (d=3 mm) in respect of a conventional tablets (d=8 mm), few of the healthy young participants were able to swallow 10 mini-tablets with a single sip of water \(^{(212)}\). The result led the authors to conclude that there is an optimal number of tablets above which the perceived attribute of ease of swallow with respect to conventional tablets deteriorates \(^{(212)}\). This highlights the need for understanding the bolus internal fluid dynamics in presence of multiple suspended particles that is key to support the design of novel solid oral medications that are easier to swallow.

With respect to tablet size, in vivo data from the literature does not currently allow us to complement the in vitro observations, as comparable videofluoroscopy swallowing studies aiming at describing the dynamics of pill swallowing are scarce. In one of these studies Kasashi et al. compared the effect of size for two different gelatine capsules (size 1 and size 4) and density \((\rho_S=690 - 1370 \text{ kg m}^{-3})\) together with the patients’ head position during swallowing \(^{(229)}\). Their results indicate patient’s preference towards swallowing smaller capsules that, irrespective of their density, lead to a statistically significant reduction in the oral transit time of the solid medication. The authors therefore suggest that the oral
transit time may be effectively used to establish swallowing preferences in patients \(^{(229)}\). Numerous other sensory have shown how the attribute of ease of swallowing for single tablets consistently increases, decreasing the size of the solid oral dosage forms \(^{(205)}\). This observation is confirmed by the present experimental study that shows the negligible impact of small tablets on the oral swallowing dynamics (Fig.5.4).

Sensory trials with mini-tablets (d<4 mm) showed a higher acceptability in children and new-borns than other conventional types of oral delivery medications (i.e. syrup) \(^{(205, 231, 207)}\). This conclusion should however be put in relation to the viscosity of the different liquid vehicles used for tablet administration as it highly conditions the palatability and grittiness perception \(^{(205, 214)}\). Therefore, examination of oral transit of similar solid oral dosage forms against liquid oral medicines would greatly benefit from a solid \textit{in vitro} testing base.

An interesting future direction is to extend the \textit{in vitro} experiment to consider also the pharyngeal and esophageal phases of swallowing which would enable one to assess more holistically the impact of tablet formulation on all stages.

Finally, modelling the complex physics of salivary lubrication and wall interaction, although outside the aim of the present study, could constitute an important development in view of a more comprehensive description of wall friction and adhesion with the oral mucosa, following notable examples of \textit{in vitro} works dealing with tablet adhesion to the esophagus \(^{(239)}\).

### 5.1.4 Conclusions

This study investigated the effect of single and multiple suspended solids in a peristaltic flow of a Newtonian liquid relevant for the oral phase of swallowing, to improve the understanding of the mechanical phenomena governing pill swallowing. The effect of tablet size, shape, volume fraction, and applied force were studied in a controlled and consistent way using an \textit{in vitro} model experiment. Results at low to medium applied
loads demonstrated that the dynamics of the bolus in presence of small, single spherical tablets did not exhibit significant variations with respect to the theoretical predictions in absence of any suspended solids. Conversely, the flow was more consistently slowed down when testing larger spherical tablets, especially at low driving forces. Increasing the applied driving force reduced the effect of the diameter of the swallowed solid and speeded up the dynamics.

The relative position between solid oral dosage forms and roller was also studied and it was found that small spherical solids steadily moved towards the tail of the bolus, whilst slightly bigger tablets (d=6.4 and d=8 mm) conserved their initial position relative to the bolus tail. Further increasing in the cross sectional diameter of the spherical tablet increased its friction against the in vitro oral cavity, ultimately causing the solid to lag behind the bolus. In vivo, it can be speculated that increased proximity with the tongue apex might result in a stronger perception of the presence of the solid oral medication.

The effect of solid oral dosage shape was considered using spheroids of different aspect ratios but identical volumes to those of two calibrated spherical tablets (0.27 and 0.52 mL). Experiments show that using solids with smaller cross sections speeded up the dynamics of the bolus. This effect was only appreciable for the largest tablets and under low roller applied force, but it is accentuated with low viscosity liquid carriers.

While the role of suspending vehicle rheology was not the focus of the study, In vitro tests showed that the swallowing dynamics was more affected by the tablet shape for thin suspending vehicles. In this regard, glycerol ensured a smoother bolus transit than orange juice even in the case of large spherical tablets.

In the case of single tablets, the simple theoretical model proposed gives reasonably good predictions for small particles, but fails to capture the complex phenomena occurring when considering larger solid oral dosage forms, hence demonstrating the importance of considering in vitro experiments.

The in vitro oral phase of swallowing was significantly slowed down when considering
multiple suspended solids. Varying the size of the solid oral prescription changes their ability to pack: while larger tablets tended to align in the direction of flow, smaller tablets could also pack more closely in the width of the bolus. These differences limit the applicability of existing theories, in particular at higher volume fractions of suspended solids and provide further evidence supporting the use of *in vitro* experiments. In this regard, Chapter 6 proposes a further extension of the study to consider the alterations to the swallowing dynamics caused by the presence of fine suspended solids (multiparticulates) in the bolus. The study also proposes more comprehensive investigation of the effect of bolus rheology and is complemented by a parallel sensory trial carried out at the UCL School of Pharmacy.
Chapter 6

Swallowing of multiparticulates

This chapter extends the *in vitro* experiment to consider swallowing of fine multiparticulates suspended in liquid vehicles of different rheology. Water and two hydrocolloids, with a different shear thinning behaviour, were considered as suspending vehicles. The suspended solid phase consisted of cellulose pellets of two different average sizes. *In vitro* results were compared against sensory tests, organized by the UCL School of Pharmacy. These panel tests considered the attributes of ease of swallowing and post-swallow residues from 30 young healthy volunteers. Both *in vivo* and *in vitro* tests reported smoother and easier swallows for smaller multiparticulates. Besides, water thin liquids appeared not optimal for complete oral clearance of the solids. The sensory study did not highlight significant differences between the levels of thickness of the hydrocolloids. Conversely, more discriminant results were obtained from *in vitro* tests, suggesting that a minimum critical viscosity is necessary to enable a smooth swallow, but increasing too much the carrier concentration affects swallowing negatively. These results highlight the important interplay of particle size and suspending vehicle rheology and the meaningful contribution that *in vitro* methods can provide to pre-screening multiparticulate oral drug delivery systems before sensory evaluation.
6.1 Introduction

 multiparticulates have recently been presented as alternatives to conventional solid oral dosage forms. The superior dose flexibility and the better palatability of multiparticulates are key to tailor the needs of specific sets of patients (211; 212; 213; 207). However, further research is needed to shed light on the optimal way of administering multiparticulates to patients: acceptability of multiparticulate administration can depend also on the rheology of the suspending liquid carrier (214). Thicker fluids are known to ease swallowing of tablets and capsules (240; 207; 234). The rheological properties of a pharmaceutical liquid vehicle require special attention as these will have an impact on several critical quality attributes, such as suspendability, palatability (including appearance, taste and mouth-feel), ease of swallowing and drug bioavailability. In this regard, viscosity modifiers or thickening agents are an essential excipient in the development of liquid vehicles for the administration of medicines. Example of hydrocolloids frequently used as thickening agents include xanthan gum and cellulose derivatives like methylcellulose, hydroxypropyl cellulose and carboxymethyl cellulose (89). The link between rheology and texture or mouth-feel perception has been extensively studied (especially in food products) (241). Thicker liquids have been reported to facilitate swallowing and reduce the risk of bolus penetration-aspiration in patients with swallowing disorders. Nonetheless, there is insufficient evidence to support precise delineation of viscosity boundaries related to such clinical outcomes (22). Viscosity measurements taken at shear rates of 50 s$^{-1}$ correlate with initial thickness perception and are commonly used as a reference value to compare between samples (211, 212, 21). However, higher shear rates, function of bolus rheology, have been indicated for the pharyngeal and esophageal phases of swallowing (87, 165).

In this regard it is important to determine the amount of oral and pharyngeal residues to ease swallowing and ensure thoughtful delivery of the drug. In this context, in vitro models of swallowing have recently become available and could be used to understand the end user acceptability of oral dosage forms and to complement the findings obtained from the human panel studies. In vitro models make simplifications of the swallowing
physiology and allow to understand the effect of the physical properties of a bolus on its flow (158; 27).

However, the quantitative understanding derived from \textit{in vitro} models requires \textit{in vivo} validation due to the multifactorial nature of texture perception and palatability. Therefore, sensory tests remain indispensable tools to evaluate specific product attributes and/or overall acceptability (214).

Hedonic tests on untrained volunteers are key to determine the degree of liking of different product alternatives and allow to identify the drivers for formulation design. Along with the development of the product, more targeted analytical testing with trained panellists are normally performed to finalize the product taste and appearance. Results from hedonic tests can be corrupted by the multiple perception of different textural and taste attributes and are influenced by personal preference. In this regard \textit{in vitro} methods may allow to interpret the trends obtained from unclear panel results to define the directions for product development.

This study combines and compares the results obtained from an independent hedonic test with those obtained an \textit{in vitro} model when considering the oral administration of fine multiparticulates suspended in three different liquid vehicles.

### 6.1.1 Materials and Methods

**Materials**

Cellulose pellets (Cellets® 200 and Cellets® 700) provided by Pharmatrans Sanaq AG (Basel, Switzerland) were considered as model multiparticulates. Particle size and sphericity were measured in triplicates by dynamic image analysis using a QICPIC/R02 (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Particle density was measured by gas pycnometry using a MicroMeritics 1305 multi-volume pycnometer (Micromeritics Instrument Corp., Norcross, USA). Results from optical and physical measurements are listed in
Table 6.1: Particle size and density of the cellulose pellets. Average values and standard deviation over three repeats.

<table>
<thead>
<tr>
<th>Product name</th>
<th>(d_{50})</th>
<th>(d_{90})</th>
<th>Sphericity</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellets® 200</td>
<td>325.3 (0.1) µm</td>
<td>358.8 (0.2) µm</td>
<td>0.874 (0.003)</td>
<td>1470 (40) kg m(^{-3})</td>
</tr>
<tr>
<td>Cellets® 700</td>
<td>891.2 (0.1) µm</td>
<td>970.1 (0.3) µm</td>
<td>0.902 (0.002)</td>
<td>1340 (60) kg m(^{-3})</td>
</tr>
</tbody>
</table>

Table 6.1

Water and two hydrocolloids were considered as suspending vehicles. In order to study the importance of the suspending vehicle’s rheology liquids with different shear thinning behaviours were tested. Aqueous solutions of Xanthan gum (XG) were chosen as model highly shear thinning vehicles. Instead, sodium carboxymethyl-cellulose (CMC) was used to obtain mildly shear thinning solutions. Elastic liquids, such as the PEO solutions, previously considered in Chapter 4, were not included in this study not to increase the number of degrees of freedom. This choice allows to obtain a more targeted set of sensory data that considers the role of shear viscosity only. For the experiments XG (Xantural 180) was supplied by CP Kelco (Leatherhead, UK) and CMC (Blanose 7HF-PH) was instead provided by Ashland (Covington, USA). The aqueous solutions of XG and CMC were prepared in DI water at room temperature. The study considered three different concentration per each of the two hydrocolloids: 0.25, 0.5 and 1% for the gum and 0.5, 1 and 1.5% for the carboxymethyl cellulose salt. For sensory evaluation, a 0.1% vanillin was added to mask any potential taste and smell of the polymers. The flavouring ingredient was supplied by Sigma-Aldrich (Irvine, UK).

Rheological characterization

Shear tests of the liquid samples were preformed at 22°C using a HAAKE RheoStress 600 rheometer (Thermo Fisher Scientific, Waltham, USA) equipped with a cone and plate geometry \((d=60\,mm,\alpha=2°)\). Flow curve were run in triplicates in the range of shear rates between 0.01 and 1000 reciprocal seconds.

Sedimentation of cellulose pellets in the aqueous vehicles was quantified by time taken
for an homogeneous suspension to completely clarify the top 1/3 of a 50 mL filled sample holder (diameter of 30 mm and height of 115 mm) provided by Techno Plastic Products (Trasadingen, Switzerland). The concentration of Cellets (250 mg of solids in 3 mL of vehicle) was kept consistent throughout the sedimentation tests and equal to that used during the sensory evaluation and the \textit{in vitro} tests.

**The \textit{in vitro} swallowing model**

The experimental setup used to study the oral phase of swallowing has been introduced in Chapter 3. Cellets were first suspended in the carrier liquid and the suspension was then manually injected into the membrane through its anterior opening. To mimic the tongue, an elastomeric roller with a Young’s modulus of \( E = 25 \) kPa was used. The modulus was determined with uniaxial compression tests at low strain \((\gamma = 0-10\%)\).

Consistently with the results presented in Chapter 3, this study uses a roller driving force of 2 N.

During the experiments with multiparticulates, the roller movement was triggered within 60 seconds from the initial bolus loading to mitigate the effect of particle sedimentation. After each experiment the amount of liquid and solid residues left in the \textit{in vitro} oral cavity was recorded. Four repeats, in randomized order, were taken per each set of experimental variables to assess the variability and robustness of the \textit{in vitro} setup.

**Sensory tests**

The sensory study comprised a total of 30 volunteers, 9 men (age 22.4 ± 3.9 years) and 21 women (age 25.2 ± 4.8 years). The volunteers were not diagnosed with dysphagia and had no history of swallowing difficulties \((243)\). Ethical approval was obtained from UCL Research Ethics Committee (Project ID: 4612-011).

The participants were divided into six subgroups and three sessions were organized for
sensory evaluation. In each session, the volunteers were offered the six hydrocolloid solutions, water and vanillin-flavoured water in randomized order.

The particle size of the Cellets was not varied within the same daily session. A control test in absence of multiparticulates was run to assess the baseline score for the different liquid solutions. Each participant was asked to rate the attribute ease of swallowing using a 5-point hedonic scale (1-extremely easy to 5-extremely difficult) and the attributes presence of oral residue based on a 5-point magnitude scale (1-not perceptible to 5-extremely perceptible). Furthermore, anecdotal feedback of the participants was also registered. Descriptive statistics are presented as mean±SD. A Kruskal-Wallis test was used to identify statistically significant differences among the set of data collected. Significance was set at p<0.01 with 95% confidence level.

Samples for sensory tests were prepared individually, by mixing 250 mg of cellulose pellets in of 3 mL of liquid vehicle. The suspension was handed to the volunteers with a spoon. The same volume of liquid and weight fraction of Cellets used throughout the in vitro experimental campaign was also considered during the sensory tests.

### 6.1.2 Results and discussion

The role of suspending vehicle rheology was initially assessed considering control trials in absence of solids. The sensory evaluation showed a noticeable decrease in the attribute of ease of swallowing (p<0.001) moving from water to the hydrocolloids and when the viscosity of the liquid vehicles was increased (Fig. 6.3).

XG hydrogels were slightly easier to swallow than CMC hydrogels, differences between
Table 6.3: Measured sedimentation time of cellulose pellets in the different liquid vehicles.

<table>
<thead>
<tr>
<th>Liquid vehicle</th>
<th>Sedimentation time Cellets® 200</th>
<th>Sedimentation time Cellets® 700</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>&lt;0.5 min</td>
<td>&lt;0.5 min</td>
</tr>
<tr>
<td>0.5% CMC</td>
<td>10.5 (0.6) min</td>
<td>3.34 (0.6) min</td>
</tr>
<tr>
<td>1% CMC</td>
<td>&gt;30 min</td>
<td>22.0 (1.1) min</td>
</tr>
<tr>
<td>1.5% CMC</td>
<td>&gt;30.0 min</td>
<td>&gt;30.0 min</td>
</tr>
<tr>
<td>0.25% XG</td>
<td>&gt;30.0 min</td>
<td>15.5 (0.8) min</td>
</tr>
<tr>
<td>0.5% XG</td>
<td>&gt;30.0 min</td>
<td>&gt;30.0 min</td>
</tr>
<tr>
<td>1.5% XG</td>
<td>&gt;30.0 min</td>
<td>&gt;30.0 min</td>
</tr>
</tbody>
</table>

Figure 6.1: Shear viscosity as a function of shear rate for the different hydrocolloids.

both sets of hydrogels were statistically significant (p<0.018). An almost linear correlation was found between the average scores given by the volunteers and the concentration of hydrocolloids in water. These results are in line with previous publications that report more effortful swallows with increasing hydrocolloid concentration (211). A previous study also indicates that cellulose-based thickeners were perceived slightly more viscous than XG-based thickeners (85). On the other hand, XG hydrogels were reported more slimy than to other cellulose or starch-based thickeners (85; 80). These results are consistent with the pronounced shear thinning behaviour of XG (Fig. 6.1).

In support of the sensory findings, in terms of ease of swallowing, the in vitro experiments highlighted an increased duration of the time required for bolus transit moving from
water to the hydrogels. A positive correlation between the measured *in vitro* oral transit time and the CMC concentration was observed. Conversely, tests with XG showed no significant variations with respect to concentration (Fig. 6.3).

The healthy volunteers also rated the differences among the liquids in terms of after-swallow feel. Results indicate a minor increase in the amount of residues ($p < 0.025$) when swallowing hydrogels, compared to water. *In vitro*, the amount of oral residues after each experimental run was found to be dependent upon concentration and type of vehicle considered. Water boli left no significant residual mass in the *in vitro* oral cavity whilst a significant portion of the initial bolus mass was not ejected when testing thick vehicles. The amount of residues increased with the concentration of the solutions and was significantly higher for CMC than for XG solutions at the highest concentrations considered (Fig. 6.4). When considering vehicles with similar viscosity in the range of shear rates considered important during swallowing (50-300 reciprocal seconds (22)), similar results, in terms of residual mass, were obtained for the thickest gum solution (1% XG) and the low to intermediate thickness of the CMC vehicles.

A good overall correlation between *in vitro* and sensory results is outlined in terms of increased swallowing difficulty and oral transit time as the viscosity level increased. Anec-

---

**Figure 6.2:** Shear stress as a function of shear rate for the different hydrocolloids.


6.1. Introduction

Figure 6.3: *In vitro* oral transit time (bars) and sensory attribute of ease of swallowing (markers). Upward pointing bars identify conditions in which clogging was observed and the *in vitro* model could not complete the swallowing test.

dotal feedbacks collected during the panel tests remark, in a few occasions, the noticeable increase in the swallowing effort required for the thick polymer solutions. In particular, the feedback from 4 volunteers quoted the thickest CMC sample as being very viscous, difficult to swallow and leading to persistent residues in the mouth after swallowing.

Results from the panel tests also show that swallowing of multiparticulates was considered more difficult for increasing particle size. An average score of 2.36 was attributed to the smaller multiparticulates (Cellets 200), compared to 2.91 for the larger Cellets 700 (*p*<0.001). Irrespectively of the size of the particles, multiparticulates dispersed in polymeric hydrogels were easier to swallow by approximately 0.50 points than multiparticulates dispersed in water (*p*<0.001).

Despite the contrasting shear thinning behaviour of XG and CMC, the sensory results of the 5-point scales did not indicate a significant difference between the hydrocolloids, which proved effective in facilitating oral delivery of the multiparticulate formulations. Both sets of hydrogels received comparable scores for ease of swallowing (2.52 for XG and 2.49 for the CMC vehicles). However, the average swallowing score for the thickest CMC solutions (1 and 1.5%) was less significantly modified by the presence of multiparticulates.
compared to XG.

Aside from worsening the swallowing experience, administration of multiparticulates in water also leads to a gritty sensation followed by a feeling of incomplete clearance of particles from the mouth. The feeling of residual particles in the mouth increased with increasing size of the multiparticulates. Panellists rated an average score of 1.67 for Cellets 200 and 2.14 for Cellets 700 (p<0.001). However, the use of polymeric hydrogels reduced the feeling of particles in the mouth after swallowing by approximately 0.5 points on average as compared to water (p<0.001). No significant differences were found in the scores for residual particles between XG and CMC hydrogels. Similarly, scores for particle residues were not strongly correlated with the concentration of the polymers.

Anecdotal comments from the volunteers reveal that XG hydrogels were slightly superior multiparticulate carriers than CMC. In the presence of Cellets 200, swallowing of the thinnest XG solution was associated to drinking water whilst the 0.5% XG vehicle was reported viscous, but still easy to swallow and not much persistent in the mouth after the first swallow. Conversely, some participants reported difficulty when swallowing micro-particulates in CMC. Complaints also came from the higher effort required to clear the mouth from residues. This latter aspect might be linked to the higher stress required to shear CMC at the shear rates relevant to the oral phase of swallowing (Fig. 6.2).

The in vitro experiments in the presence of suspended particles led to a general increase in the measured oral transit time and amount of post swallow residues. Thicker liquid vehicles facilitated in vitro swallowing of multiparticulates. In vitro experiments also highlighted the importance of particle suspendability. Mechanical jamming (clogging) was observed whenever the suspended particle size was increased and the rheology of the vehicle was unable to prevent a rapid sedimentation. This was always experienced with water for both the particle sizes tested. Hydrocolloids allowed instead a smooth bolus flow with the smallest particles (Cellets 200). However, only the two thickest XG and CMC solutions allowed us to run the in vitro experiment when the average particle size of the suspended phase was increased to 970 µm (Cellets 700). Among the two hydrocolloids,
shorter sedimentation times were registered for CMC (Table 6.3), consistently with the higher zero shear rate viscosity of XG (Fig. 6.1).

The in vitro results are consistent with the sensory results, since participants stated that larger amounts of Cellets remained in the oral cavity when swallowing samples in thinner vehicles. Some volunteers explicitly mentioned the fact that thin vehicles seemed unable to effectively suspend the solid particles. As a result, solids were left behind the liquid bolus during swallowing. On the other hand, thicker vehicles were perceived as more effective to disperse and transport the intake of multiparticulates. Consistently with the perceived decrease in the ease of swallow, in vitro transit times increased with increasing particle size. In this respect, XG performs better in vitro than CMC, although a smoother bolus flow was observed with CMC. This is reflected in the larger SD observed for XG samples in Fig. 6.3. The amount of post-swallow residues (liquid and solid) left in the in vitro oral cavity increased with the particle size of the multiparticulates (Fig. 6.4). Above the critical viscosity required to avoid particle sedimentation and clogging, the carrier
viscosity does not bring a benefit. Visual inspection of the plastic membranes from the in vitro experiment seems consistent with the hypothesis that thinner vehicles leave more residual particles behind (Fig. 6.5). Accordingly, this could compensate for the increase in post-swallow residues with the viscosity of the vehicles, observed in absence of suspended particles (Fig. 6.4). A positive correlation between the in vitro residues (Fig. 6.4) and the perceived ease of swallowing (Fig. 6.3) is also visible when considering the effect of the vehicle concentration, particularly without particles and with the smallest particles. This would be consistent with a higher total residue left in the oral cavity as a result of the perceived increased swallowing difficulty with more concentrated carriers.

6.1.3 Conclusions

Both the in vitro model and the sensory tests outlined that water-thin vehicles were not optimal for Cellets palatability and oral transport. A critical viscosity threshold for smooth swallowing was observed both in vivo and in vitro. In vivo, above this thresh-
old, differences between vehicles were not significant for healthy volunteers, who rated all samples, on average, on the positive side of the scale. However, analysis of the anecdotal feedback suggested that samples of medium consistency (i.e. 0.50% XG and 1.00% CMC) were preferred. Preference for smaller multiparticulates was also expressed by the volunteers, both in terms of ease of swallowing and lower amount of post-swallow residues.

The *in vitro* results showed that smaller particles eased bolus transport and reduced residues. Particle suspendability was also a key factor. The residues measured in the *in vitro* test were able to discriminate formulations, even when sensory tests did not indicate a clear difference. In this regard, clear examples were obtained with Cellets 200, both when comparing different CMC concentration and CMC vs XG. Given the pharmaceutical interest for new solid oral formulations, targeting the special needs of infants and elderly, the *in-vitro* approach presented in this chapter could help screening novel formulations and help designing more targeted *in vivo* studies before running *in vivo* investigations.

While this research activity confirms the positive contribution that *in vitro* swallowing tests can give to complement sensory studies, some key differences between the *in vitro* results and the sensory test were found, due to the rigid geometrical constraints of the *in vitro* setup. For instance, a higher critical hydrocolloid concentration was required for a smooth *in vitro* swallowing with Cellets 700, when compared to the sensory results. This difference calls for a further development of the *in vitro* model to better bridge the gap with *in vivo* results. In the next chapter the development of a novel, more faithful, *in vitro* model of swallowing is presented. Some preliminary results with this improved model are then discussed, following swallowing tests with Newtonian and shear thinning liquids.
Chapter 7

A soft robotic tongue to study human swallowing

The previous chapters studied the oral swallowing dynamics through the use of a mechanical device that approximates the propulsive action of the human tongue during swallowing with the peristaltic motion induced by a roller. Results allowed to interpret the role of bolus viscosity during swallowing and led to establish the importance of the physical attributes of solid oral dosage forms. However, few limitations of the setup appeared when testing water thin-liquids in presence of suspended solids, where a significantly higher threshold for swallowing was measured \textit{in vitro} as opposed to the sensory data (Chapter 6). This last experimental chapter proposes the development of radically novel, more faithful \textit{in vitro} model of swallowing to reproduce the essential features of the oral phase of swallowing. The review work presented in Chapter 3 laid the bases for the definition of the key design requirements for this novel \textit{in vitro} model of swallowing. Bolus control and propulsion are ensured via a soft pneumatic actuator, embedded the three dimensional geometry of the oropharynx. The design of this pneumatic actuator, with two separate inflatable chambers, is inspired by ultrasound images of the tongue, taken during swallowing. An actuation sequence including up to four steps allows both to contain the bolus and to induce a peristaltic propulsion to direct the bolus toward the back of the model oral cavity. Altering the duration of the steps, allows simulating a lack of muscle coordination resulting in swallowing disorders. The bolus velocity and pressures are measured during \textit{in vitro} swallowing via Doppler velocimetry and palatal pressure transducers. The apparatus provides physiologically valid pressures and liquid oral transit times and has been operated successfully with
liquids with different consistencies. Preliminary tests with Newtonian and shear thinning liquids show an increase in the palatal pressures upon increasing bolus consistencies, while bolus rheology and the coordination of the peristaltic contractions can both influence the bolus velocity distribution.

This pneumatic actuator inspired by the human tongue and these preliminary findings can stimulate further research to investigate the role of bolus rheology and a reduced coordination on the swallowing performance, contributing to developing personalized solutions to swallowing disorders.

Several in vitro models of swallowing have been proposed. These models are simplifying strongly human anatomy, use rigid materials, and excluding few cases, neglect the role of lubrication. Only by removing these simplifications one can truly assess their effect on the swallowing process and improve the understanding of this important physiological process.

Recent technological developments in robotics led to the development of manipulators with an increased number of degrees of freedom, able to compress, elongate, and bend in multiple directions simultaneously. These characteristics make them suitable to simulate the behaviour of muscle hydrostats, such as the tongue, that is able to hold and shape the bolus and guide it to the pharynx. Different actuation mechanisms, based on the use of advanced materials, such as electroactive polymers, shape memory alloys or nanocomposites have been proposed. The speed of response to stimuli, and the poor mechanical properties have however been identified as limitations. Classical pneumatic actuation offers instead the advantage of easier design and control, fast response and comparably low costs. Soft manipulators are generally using materials with Young’s moduli, E, of the order of $10^4$-$10^9$ Pa. By the careful design of a network of cavities embedded in a polymeric matrix, different deformed configurations can be attained.

Despite the relative ease of manufacturing of soft manipulators, the use of materials such as PDMS, rubber, or other elastomeric polymers, can present significant challenges
when simulating the mechanical response, which include the long term performance under fatigue (143). Despite these limitations, few applications of soft robotics to mimic the biomechanics of human swallowing have been proposed. A soft pneumatic model of the esophagus was introduced by Chen and Dirven at Massey University (New Zealand). The apparatus is capable of generating and tracking periodical peristaltic waves to study the esophageal flow of a liquid bolus (169; 167; 252; 253; 19).

More recently, a soft bodied prototype to mimic specific tongue gestures, without considering swallowing has also been considered (17).

This study uses soft robotics to understand bolus propulsion during the oral phase of swallowing and the transition into the pharynx. A soft inflatable tongue was developed to constrain and move the bolus within a three dimensional cavity representing the geometry of the human oropharynx.

Finite element (FE) simulations were run to support the design of the robotic tongue. The surface properties were also tailored to reproduce the wettability of oral tissues.

Videos were recorded during the in vitro swallows to follow the instantaneous position of the liquid bolus. Simultaneous measurements of palatal pressures were taken for comparison with in vivo data reported in the literature and Doppler ultrasound spectra were also acquired to characterize the bolus velocity.

### 7.1 Design and fabrication

#### 7.1.1 Palate and pharynx

The design of the palate and pharynx is based on a 3D geometry used to characterize the fluid dynamics of aerosols (254). The lower part of oral cavity of the model was modified to include the soft actuator inspired by the human tongue. The oropharynx was 3D printed in VeroClear™ using an Objet 260 Connex 3 printer (Stratasys Inc., Eden Prairie,
Figure 7.1: Schematics of the in vitro soft robotic setup comprising the peristaltic actuator inspired by the human tongue (light red).

MN). The material used by the printer is optically clear to allow for video recording of the experiment.

### 7.1.2 Tongue design

Platinum-catalysed silicone rubber was used to mould-cast the pneumatically actuated tongue. Smooth-On Ecoflex™ 00-30 was purchased from Bentley Advanced Materials (London, UK). This material has already been widely used for soft robotic applications, due to the high elongation at break, moreover, its mechanical properties have already been characterized (253 167). Although Ecoflex™ is available in a range of different hardnesses, a previous study indicates a good match between the stiffness of the pharynx and that of silicone rubber for a rated shore hardness of 30 (scale 00) (161). The same shore hardness grade was also already chosen by Chen and Dirven in the design and manufacturing of their pneumatically operated esophagus (167 101).

The preparation of the silicone rubber followed the indications from the supplier. An equal amount by weight of the two components was poured into a glass beaker and thoroughly
mixed. The mixture was then transferred to a conical flask for degassing under vacuum. The liquid was finally poured into the moulds where it was allowed to cure at ambient temperature for 8 to 10 hours. The silicone rubber tongue was mould casted to similar values of length and width measured in vivo \(^{256}\). The moulds were 3D printed in PLA (Polysmooth from Polymaker, Shanghai, China) using an Ultimaker 3 (Ultimaker BV, Geldermalsen, The Netherlands). An isopropanol polisher (Polymaker, Shanghai, China) was used to obtain a smoother surface finishing of the moulds to ease demoulding.

A good wettability of the silicone rubber tongue is required to approximate the role of the adsorbed salivary pellicle in vivo. The surface of the human tongue was reported hydrophobic and weakly polar \(^{119}\). However, salivary adsorption, caused by electrostatic interaction with the polar substrate makes the tongue significantly more hydrophilic with a reported contact angle of about 50° \(^{119}\). Different techniques for surface treatment to reduce hydrophobicity in PDMS have been proposed \(^{257, 258}\). UV treatment or O\(_2\) plasma oxidation are commonly used treatments to reduce the strong hydrophobicity of PDMS \(^{259, 260}\). These treatments are however not permanent due to the progressive diffusion of crosslinked polymer chains from the bulk to the treated surface \(^{261, 257}\). The hydrophobic recovery is more rapid for soft silicones due to the higher mobility of short silicon chains \(^{262}\).

For the peculiar needs of this project, it was decided to add non-ionic surfactants to the bi-component mixture to reduce the contact angle of aqueous solutions onto the final silicone moulded part. Samples of silicone rubber with concentrations of sorbitan monooleate (Span® 80, CAS:1338-43-8) between 0.5 and 2% w/w were tested.
Two air cavities are contained within the soft actuator (Fig. 7.2). Their inflation and deflation allows the soft actuator to perform the two key lingual functions: 1) bolus containment prior to swallowing and 2) propulsion during swallowing.

The inflation of the posterior air chamber controls the initial bolus containment. Instead, the anterior air chamber induces the bolus propulsion during the oral phase of swallowing that is completed by re-inflation of the posterior chamber to clear-up the residues.

The anterior air chamber has a novel trapezoidal cross section (Fig. 7.2) that induce a preferential direction in bolus propulsion by guaranteeing that the contact with the palate extends progressively from the anterior to the posterior of the tongue. The final design of the internal chambers was refined through structural FE simulations using the hyperelastic material module in COMSOL Multiphysics 3.5a (COMSOL Inc., Stockholm, Sweden).

7.1.3 Structure of the control algorithm

The control algorithm used to actuate and time the inflation of the air chambers and the initial bolus injection was implemented in Arduino IDE v1.8.7 (Arduino AG, Chiasso, Switzerland).

The pneumatic system that controls the deformation of the soft tongue is regulated via two solenoid valves and a rotary vane vacuum pump. Two relays control the actuation of the three-way solenoid valves type G356A002SBA8 (ASCO Numatics Sirai Srl, Bussero, Italy).

The maximum inflation pressures are adjusted with a pair of needle valves, set at different apertures. This allows for modulating independently the inflation pressure of the two air chambers using a single compressed air supply, regulated at 50 kPa. A pair of pressure transducers is used to monitor the air pressure evolution in the chambers and to ensure that the actuation is reproducible across different swallowing experiments.
The actuation sequence starts by inflating the posterior air chamber to ensure bolus containment. A syringe pump model NE-501 (ProSense BV, Oosterhout, The Netherlands) then injects the liquid bolus through a 4 mm circular orifice located on top of the hard palate. The input to start and stop the pumping cycle is provided through an Arduino Uno board (Arduino AG, Chiasso, Switzerland). The volume of bolus used throughout the study was set to 10 mL. This represents a value comparable to a natural sip size in adults and is also an amount of liquid frequently used in videofluoroscopy swallowing studies.

After bolus loading, at time t=0, suction generated by a rotary vane vacuum pump induces a rapid deflation of the posterior air chamber, which is followed by the inflation of the anterior one to squeeze the bolus against the hard palate. The combined deflation/inflation of the two air chambers peristaltically guides the bolus towards the pharynx. Finally, a rapid re-inflation of the posterior air chamber, with the anterior still fully inflated, enables to clear the bolus tail from the palate. After, both chambers are deflated to return to the initial undeformed configuration.

The setup gives flexibility in the definition of a swallowing pattern in order to simulate the lack of tongue coordination stemming from different sets of swallowing disorders. The duration of the swallowing sequence can be adjusted by varying the delay between the deflation of the posterior chamber and the inflation of the anterior chamber ($t_A$) as well as the delay before the second inflation of the posterior cavity ($t_P$). An example is reported in Fig. 7.4 where the delay for the inflation of the anterior chamber was changed from -0.2 to +0.2 s.

The chosen values of the parameters for this preliminary study are inspired by the duration of the swallowing sequence reported by Tasko et al. and are listed in Table 7.1.

A Basler RGB camera (model ac1920-155 µm, Basler, Isny im Allgäu, Germany) was used to record the bolus transit at 100 frames per second. The amount of bolus discharged from the pharynx was also weighted to evaluate the mass of post-swallow residues.
Figure 7.3: Chronogram of the swallowing sequence of the \textit{in vitro} model.

Table 7.1: List of parameters chosen to simulate the oral phase of swallowing with the \textit{in vitro} model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus volume</td>
<td>V</td>
<td>10 mL</td>
</tr>
<tr>
<td>Time for inflation of the anterior air chamber</td>
<td>$t_A$</td>
<td>100 ms</td>
</tr>
<tr>
<td>Time for re-inflation of the posterior air chamber</td>
<td>$t_P$</td>
<td>500 ms</td>
</tr>
<tr>
<td>Inflation pressure anterior air chamber</td>
<td>$P_A$</td>
<td>25 kPa</td>
</tr>
<tr>
<td>Inflation pressure posterior air chamber</td>
<td>$P_P$</td>
<td>10 kPa</td>
</tr>
<tr>
<td>Deflation pressure posterior air chamber</td>
<td>$P_{vac}$</td>
<td>-20 kPa</td>
</tr>
</tbody>
</table>
Figure 7.4: The pneumatic actuation can be adjusted to mimic loss of lingual coordination. In the example above, the delay for inflation of the anterior chamber $t_A$ was set to a) -0.2 s, b) 0 s, c) +0.2 s. In all cases $t_P$ is equal to 0.5 s. The bolus is not introduced to better visualize the deformed shape of the tongue.
Clinical studies showed that the kinematics and dynamics of tongue motion is subject to a high degree of interpersonal variability both in terms of duration and amplitude of tongue movement. Unsurprisingly, that variability is further amplified by neurogenic dysphagia which adversely affect tongue coordination (5). Some authors have proposed a general categorization of the swallowing pattern based on the tongue position prior to swallow, distinguishing among dipper and tipper swallows (263). Others identified slightly a more consistent behaviour for sequential swallows, compared to single swallows, that show greater horizontal displacements for the anterior part of the tongue and a greater modulation of the posterior (11). In general, it was found that females exhibit smaller tongue displacements than males and that the amplitude of tongue displacement is correlated by bolus size. Highest velocities were recorded in the posterior part of the dorsum of the tongue (200 mm/s) while 50% lower values were registered in proximity of the apex of the tongue (10; 61).

The dynamics of tongue motion has been studied with pressure transducers in vivo. Results are however scattered due to the technology used adding to patient variability. Redfearn, comparing the maximum palatal pressures from ten studies, reports a range that spans between 1 to 43.5 kPa, with a median of 13.6 kPa (69). The variability of in vivo data and approaches for the characterization of tongue motion requires to introduce in vitro models with multiple degrees of freedom. In this regard, the model here presented allows to adjust the inflation pressures of the two air chambers (P_A, P_P), the vacuum pressure to deflate the posterior air chamber (P_vacuum) and the characteristic times for actuation of the solenoid valves (t_A and t_P) (Fig. 7.3). This offers five parameters to study the effect of a suboptimal tongue coordination during swallowing (Table 7.1).
7.1.5 Doppler velocimetry

Doppler ultrasound was used to obtain quantitative information about the bolus velocity distribution during swallowing. A linear Doppler probe (Dopplex II, Huntleigh Healthcare Ltd, Cardiff, Wales, UK) was installed on the posterior part of the in vitro palate at an angle of 50° with the direction of flow (Fig. 7.10). This angle was selected based on a set of calibration measurements of the flow in a continuous recirculation rig.

The probe, commonly used for measuring vascular blood flow, emits a continuous ultrasound waveform at the frequency of 5 MHz and returns the echo of the reflected waveform. The amplitude of this signal is linearly proportional to the Doppler frequency shift ($\Delta f$) expressed by Eq. 7.1.

$$\Delta f = 2 f_0 \frac{\bar{v}}{c} \cos \varphi$$

(7.1)

Where $f_0$ is the frequency of the piezoelectric emitter (5 MHz), $\bar{v}$ the average velocity in the field of view of the probe and $\varphi$ the angle of insonation (50°). The speed of sound in the liquid media, $c$, was measured using an ultrasonic echoscope (GAMPT-scan, Merseburg, Germany).

7.1.6 Palatal pressure characterization

Three piezoresistive pressure sensors (model PX2AG2XX002BAAAX from Honeywell, Golden Valley, MN, USA) were used to monitor the pressure on the palate. The response of the transducers is ratiometric and linearly proportional to absolute pressure in the range 0 to 2 bar. The total error band of the transducers is below 2% of the Full Scale Span (FSS), defined as the algebraic difference between the output signals measured at the maximum and minimum pressure ratings. The transducers are also characterized by a response delay shorter than 2 ms. A thin polyethylene membrane is glued to the external thread of the pressure transducers to avoid fouling. Transducers were calibrated in the
7.1. Design and fabrication

range from 0 to 20 kPa. Data from the palatal pressure sensors are logged at a sampling rate of 50 Hz.

7.1.7 Mechanical tests and interfacial characterization

Mechanical and surface properties of silicone rubber were characterized and varied during the optimization of the actuator design and served as an input to the structural FE simulations. Mechanical tests made use of a Texture Analyser model TA.XT Plus equipped with a 5 kg load cell (Stable Micro Systems, Godalming, UK).

Tensile testing was performed on dog-bone shaped specimens (Fig. 7.5). The specimen geometry was obtained by scaling down by 50% the geometry of the ASTM D412 standard specimen used for elastomers and vulcanized rubber [264]. Clamps were used to constrain the samples during tensile testing.

The mechanical tests were run at a constant rate of 1 mm/s with a total displacement of 150 mm. Videos at 10 fps were recorded during the mechanical tests using a digital camera. The strain in the mid-section of the dog-bone was calculated by image analysis tracking the time evolution of two markers located 25 mm apart on the sample (gauge length). A maximum engineering strain $\epsilon$, of around 150% was measured for the specimen tested. Mechanical hysteresis was characterized following three consecutive runs.

The stress strain curves were fitted with a hyperelastic Yeoh model (Eq. 7.2).

$$
\sigma_{\text{eng}} = 2(\lambda - \lambda^{-2}) \sum_{i=1}^{3} i \ C_i \ (I_1 - 3\lambda)^{i-1}
$$

(7.2)

Where $\lambda$ is the relative elongation, defined as $\lambda = 1 + \epsilon$, with $\epsilon$ being the engineering strain, and $I_1$ the first stress invariant for uniaxial tension/compression, defined as $I_1 = \lambda^2 - 2\lambda^{-1}$.

The Young’s modulus of the samples was computed taking the limit to zero strain of a 2-parameter Mooney-Rivlin model, fitting the stress-strain curve at low deformations.
(0-10%).

\[ \sigma_{eng} = 2 \left( C_{01} + C_{10} \lambda \right) \left( 1 - \lambda^{-3} \right) \]  
(7.3)

The wettability of the silicone rubber was also characterized. To this extent rectangular moulds were prepared and the contact angle was measured for DI water using a drop shape analyser model DSA30B (KRÜSS GmbH, Hamburg, Germany). Measurements were repeated 6 times in different locations of the mould casted sample, taking the average reading between the left and the right hand side contact line. As with the tensile tests, contact angle measurements were repeated after 1 and 3 weeks to ensure stability and lack of surfactant leaching.

Figure 7.5: Characteristic shape and size of the specimen used for tensile tests. The gauge length is 25 mm.

### 7.1.8 FE simulations

Numerical simulations allowed to adjust the layout of the internal air chambers by considering the evolution of the contact line between the tongue and the palate in absence of the liquid bolus. The tongue was simulated as a hyperelastic solid, using the parameters obtained by fitting the results from tensile tests. The palate instead was considered Hookean. A Lagrangian contact pair condition was imposed between the tongue dorsum and the oral cavity. The lateral and inferior surfaces of the tongue were instead constrained to a null displacement field. The inflation of the internal cavities is imposed through a surface force distribution to the inner walls. The inflation is simulated through the parametric
variation of the internal pressure load while the simulation evolves at steady state. An optimization was performed by varying the thickness of the wall between the two air chambers and the inclination of the anterior wedge-shaped air chamber.

### 7.1.9 Bolus properties

Both Newtonian and shear thinning liquids were considered. Three aqueous solutions of a commercial Xanthan gum based thickener Resource® ThickenUp™Clear, in the following TUC, from Nestlé Health Science) were prepared following the indications given on the package. The thinnest solution was prepared adding 100 mL of deionized water to 1.2 g of TUC (1.19% w/w TUC). This corresponds to a Level 2 (or *Mildly-thick*) liquid under the IDDSI framework [36]. *Moderately-thick* (1.2 g TUC/100 mL or 2.35% w/w) and *Extremely-thick* (4.8 g TUC/100 mL or 4.59% w/w) consistencies were also considered. All the solutions were mixed with a magnetic stirrer for 1 h at ambient temperature and used within 24h after preparation.

The Newtonian boli were instead prepared by dilution of 99.8% glycerol (Sigma-Aldrich, CAS 56-81-5) in DI water. The concentration of glycerol was varied so that the solutions would be categorized under the same IDDSI level to the TUC solutions. This was assessed by measuring the volume of fluid discharged through the standard eccentric luer slip tip 10 mL syringe (BD, Franklin Lakes, NJ, USA) in a fixed amount of time (10 s).

Measurements of shear viscosity were taken in triplicates, at 22 °C, with a Paar Physica UDS 200 controlled stress rheometer (Anton Paar GmbH, Graz, Austria). The flow curves were obtained in rate range of shear rates between 0.1 to 500 reciprocal seconds using a cone and plate geometry (d=75 mm α=2°).

As a first approximation, DI water was used to mimic the salivary oral coating of the *in vitro* setup.
Table 7.2: Shear viscosity and IDDSI categorization for the liquid boli tested. Whenever relevant, brackets are used to report the standard deviation from repeats.

<table>
<thead>
<tr>
<th>Liquid bolus</th>
<th>Shear viscosity model</th>
<th>Shear viscosity at 50 s⁻¹</th>
<th>IDDSI flow test remaining volume</th>
<th>IDDSI Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>83% w/w glycerol</td>
<td>Newtonian</td>
<td>0.07 Pa.s</td>
<td>5.0 (0.2) mL</td>
<td>2</td>
</tr>
<tr>
<td>92% w/w glycerol</td>
<td>Newtonian</td>
<td>0.29 Pa.s</td>
<td>8.5 (0.2) mL</td>
<td>3</td>
</tr>
<tr>
<td>99% w/w glycerol</td>
<td>Newtonian</td>
<td>1.09 Pa.s</td>
<td>9.9 (0.1) mL</td>
<td>4</td>
</tr>
<tr>
<td>1.19% w/w TUC</td>
<td>( \eta_a = 1.82 \dot{\gamma}^{0.72} ) Pa.s</td>
<td>0.12 Pa.s</td>
<td>4.9 (0.2) mL</td>
<td>2</td>
</tr>
<tr>
<td>2.35% w/w TUC</td>
<td>( \eta_a = 4.12 \dot{\gamma}^{0.80} ) Pa.s</td>
<td>0.29 Pa.s</td>
<td>8.5 (0.1) mL</td>
<td>3</td>
</tr>
<tr>
<td>4.59% w/w TUC</td>
<td>( \eta_a = 6.15 \dot{\gamma}^{0.74} ) Pa.s</td>
<td>0.49 Pa.s</td>
<td>10.0 (0.1) mL</td>
<td>4</td>
</tr>
</tbody>
</table>

7.1.10 *In vitro* swallowing of Newtonian and shear thinning liquids

Swallowing tests were performed to assess the sensitivity of the device with respect to variations in bolus rheology.

For each liquid, the swallowing sequence was repeated five times. The first run started after a dry swallow while the further sequential runs followed (repeated swallows). Palatal pressures, Doppler waveform and high speed videos were recorded for every swallow. Measurements of discharged bolus mass were also consistently taken after every test.

To approximate the effect of a salivary coating, the model was thoroughly washed from bolus residues flushing water through the bolus loading hole and performing three dry swallows to clear the excess water. This is then followed by a normal swallowing sequence (water pre-wetted swallow).

7.2 Results

7.2.1 Mechanical and interfacial properties of the soft pneumatic tongue

Mechanical tests show that the elastomer used to mould cast the tongue model has a high elongation at break and a pronounced hyperelastic behaviour. The force-displacement
curve significantly deviates from Hookean behaviour for strains above 20% (Fig. 7.7) and mechanical hysteresis was observed upon relaxing the applied load only during the first stretch-relaxation cycle (Fig. 7.6). Similar results are found in the literature (255). The material response is well captured by the Yeoh model, Eq. 7.2 (Fig. 7.7).

![Figure 7.6: Force-distance curves from repeated uni-axial stretch of mould-cased silicone rubber (Ecoflex 00-30) specimens.](image)

The addition of anionic surfactant (Span® 80) altered both the mechanical and the surface properties of the silicone rubber. At low concentrations of surfactant (0.5% w/w), the tensile response did not highlight significant differences with respect to the original elastomer. The stiffness of the samples is also strongly affected by addition of surfactant. This is well captured by the value of the Young’s moduli in the initial linear elastic response, that registered a 3-fold decrease at the highest concentration of added surfactant (Table 7.3). An explanation for the degrading mechanical properties of the elastomer lays in the plasticizing effect of the surfactant. The same surfactant was reported to lower the stiffness of PLA and polymethacrylate (265; 266).

The measurements of contact angle show a sharp decrease in the hydrophobicity of the silicone rubber even for low concentrations of surfactant (Table 7.3) leading to contact angle similar to those reported for salivary lubricated tongue (119). Increasing the con-
Figure 7.7: Stress-strain curves from uni-axial tensile tests for mould cased silicone rubber (Ecoflex 00-30) specimens with added surfactant (Span® 80). The mechanical response is well-fitted by the Yeoh model (Eq. 7.2).

Table 7.3: Young’s modulus (E) and contact angle (CA) of Eco-Flex 00-30 with added sorbitan monooleate (Span® 80).

<table>
<thead>
<tr>
<th>Span® 80 (% w/w)</th>
<th>E (kPa)</th>
<th>CA (DEG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>77.0 (8.6)</td>
<td>103.7 (4.8)</td>
</tr>
<tr>
<td>0.5</td>
<td>74.7 (3.9)</td>
<td>45.7 (6.1)</td>
</tr>
<tr>
<td>1</td>
<td>51.6 (3.6)</td>
<td>48.9 (5.5)</td>
</tr>
<tr>
<td>2</td>
<td>25.3 (1.6)</td>
<td>46.0 (6.6)</td>
</tr>
</tbody>
</table>

The concentration of Span® 80 does not lead to any significant further reduction in the contact angle. This, combined with the significant material weakening at higher concentration, led to select the 0.5% w/w concentration for the soft peristaltic actuator.

7.2.2 Numerical simulations of the inflation of the soft tongue

FE simulations were set up to optimize the shape of the air chambers inside the actuator. The tongue was modelled as an hyperelastic Yeoh solid using the fitting constants derived from the tensile tests. The bolus flow and its interaction with the actuator were not considered in the FE analysis. The simulation considered a Lagrangian contact condition with the hard palate, modelled as a rigid Hookean body. A friction condition at the
contact point was added to improve numerical stability. Null displacement was imposed
to the tongue base and its lateral surface, while a linearly increasing/decreasing pressure
was applied to the interior walls of the air chamber to simulate inflation/deflation. All
the simulations were run at steady state. The mesh was composed of tetrahedrons with
added boundary layers in proximity of the dorsum of the tongue for improved contact
detection.

Two dimensional simulations of the tongue sagittal cross section were initially run to
delineate the basic shape for the two air chambers. In these simulations the tongue
inflation was assessed by varying 1) the slope of the superior wall of the anterior air
chamber, 2) the thickness of the wall dividing the two air chambers, 3) the thickness of
the posterior wall and 4) the length of the second air chamber. Results from these tests
defined the parametric space for further geometrical optimization and highlighted key
drivers for the final prototype. A more wedged shape of the anterior air chamber leads
to a more pronounced asymmetry inflation, with the anterior part of the tongue reaching
palate contact before the dorsum. This motion, highly desirable for bolus propulsion, can
however lead to a kink in proximity of the posterior air chamber. This discontinuity can
be minimized by decreasing the thickness of the wall that separates the two air chambers
or increasing the length of the posterior air chamber. However, variations to this second
parameter affect the amount of liquid that can be held in position before triggering the
swallowing sequence.

The variation in the thickness of the wall that separates the actuators’ chambers (labelled
$s$ in Fig. 7.8) was more thoroughly studied, given the high strains that this region has to
withstand. To this extent, 3D simulations followed the 2D simulations to ascertain the
effect of varying $s$ between 0.5 and 3 mm. Wall thicknesses above 2.5 mm strongly limited
the continuity of the tongue movement. Conversely, for small values of wall thickness,
results show a noticeable increase in the maximum strains at identical inflation pressures.
However, this leads to an undesired increase in the deformation of the anterior air chamber
towards its thin back-wall, thus reducing the asymmetry required for bolus propulsion.
A 2 mm thickness was selected for the wall separating the two chambers of the actuator,
The thickness of the posterior wall of the pneumatic tongue also constitutes a relevant parameter to ensure a smooth transit of the bolus, especially when the posterior chamber gets deflated under vacuum. Numerical simulations show that increasing the wall thickness limits buckling and generates a spoon-like dip on the dorsum of the tongue, whose depth is proportional to the thickness of the posterior wall (Fig. 7.8 c). The presence of a similar dip during swallowing can lead to a dead volume for bolus transit that is not compatible with the deformation of the human tongue. Conversely, a reduction in the thickness of the posterior wall below approx. 1.5 mm leads to a complete buckling of the posterior part of the tongue that can effectively eliminate the dip when the posterior air chamber is deflated (Fig. 7.9). The collapse of the posterior wall also leaves a wider gap between the tongue and the palate, thus enabling a smoother transit of the bolus.
7.2. Results

Figure 7.9: Deformation of the posterior wall of the pneumatic tongue for negative applied pressures to the actuator. Parallel lines are drawn to visualize the curvature.

Figure 7.10: Screenshots from *in vitro* swallowing tests with an IDDSI Level 2 glycerol-water solution. The tip of the Doppler probe is visible on the left.
7.2.3 *In vitro* swallowing tests

*In vitro* oral transit

Characteristic oral transit times and intra-bolus velocity profiles were obtained from the videos and by Doppler velocimetry. The oral transit time was defined as the time required for the bolus front to exit the lower part of the *in vitro* oropharynx (Fig. 7.10).

The oral transit time increases with bolus viscosity (Table [7.4]). Comparing the results obtained for glycerol and TUC highlights similar transit times for low and intermediate bolus consistencies. The thickest glycerol and TUC solutions flow more slowly, however longer transit times were measured for the thickest glycerol solution.

The effect of pre-wetting with water is not strong and seems to point in the direction of slightly increasing oral transit times.
Figure 7.12: Examples of Doppler waveforms from *in vitro* tests with aqueous solutions of glycerol and TUC, of similar consistencies (IDDSI Level 2).

**Doppler velocimetry**

Doppler US spectra allowed to infer the magnitude of bolus velocity during swallowing. An example of these spectra is given in Fig. 7.12 for solutions of TUC and glycerol of identical IDDSI consistency. The beginning of the swallowing sequence is unequivocally identified matching the position of the signal baseline at the final deflation of both chambers (Fig. 7.12). Doppler spectra typically present two main peaks within the duration of the swallowing sequence (0-0.6 s). The first peak corresponds to the bolus front entering in the field of view of the probe. The signal then progressively decreases as the bolus transits between the posterior palate and the root of the tongue. A second, narrower, peak is observed when the posterior chamber re-inflates, clearing the remaining liquid residues. Profiles for TUC and glycerol show a similar pattern, but with lower absolute values of the signal in the latter case. Velocity readings were obtained following an off-line calibration in a continuous recirculation rig. Introducing the calibration constants for the different liquids leads to values of bolus velocity during *in vitro* swallowing that are within the range of values reported *in vivo* (<0.5 m/s) (267).

When comparing liquids of different consistency, the peak of the signal generally decreased
Table 7.4: Transit times from video recordings of the experiment at different in vitro swallowing condition. Standard deviation from three repeats in brackets.

<table>
<thead>
<tr>
<th>Bolus</th>
<th>IDDSI index</th>
<th>Transit time first swallow</th>
<th>Transit time repeated swallows</th>
<th>Transit time water pre-wetting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>2</td>
<td>0.26 (0.01) s</td>
<td>0.31 (0.02) s</td>
<td>0.32 (0.01) s</td>
</tr>
<tr>
<td>solutions</td>
<td>3</td>
<td>0.32 (0.02) s</td>
<td>0.30 (0.01) s</td>
<td>0.32 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.43 (0.02) s</td>
<td>0.42 (0.03) s</td>
<td>0.44 (0.01) s</td>
</tr>
<tr>
<td>TUC solutions</td>
<td>2</td>
<td>0.27 (0.01) s</td>
<td>0.31 (0.04) s</td>
<td>0.29 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.30 (0.01) s</td>
<td>0.31 (0.02) s</td>
<td>0.32 (0.01) s</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.34 (0.01) s</td>
<td>0.33 (0.03) s</td>
<td>0.34 (0.03) s</td>
</tr>
</tbody>
</table>

Table 7.5: Peak velocities from Doppler US measurements at different in vitro swallowing condition. Standard deviation from three repeats in brackets.

<table>
<thead>
<tr>
<th>Bolus</th>
<th>IDDSI index</th>
<th>Peak Doppler velocity repeated swallows</th>
<th>Peak Doppler velocity water pre-wetting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>2</td>
<td>0.154 (0.06) m/s</td>
<td>0.178 (0.05) m/s</td>
</tr>
<tr>
<td>solutions</td>
<td>3</td>
<td>0.135 (0.05) m/s</td>
<td>0.127 (0.07) m/s</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.086 (0.06) m/s</td>
<td>0.067 (0.07) m/s</td>
</tr>
<tr>
<td>TUC solutions</td>
<td>2</td>
<td>0.390 (0.06) m/s</td>
<td>0.426 (0.08) m/s</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.323 (0.10) m/s</td>
<td>0.401 (0.03) m/s</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.302 (0.08) m/s</td>
<td>0.400 (0.03) m/s</td>
</tr>
</tbody>
</table>

when increasing the bolus viscosity. This general trend is more remarked for glycerol, and is consistent with results reported in the literature [29].

Instead, the peak velocity for TUC is not strongly dependent on the consistency level. This observation is in agreement with the weak dependence of the measured bolus transit time on TUC concentration.

The effect of model pre-wetting with water on the measured Doppler signal could not be discerned from the experimental error and will be subject of future studies.

**Actuation pressures**

The pressure profiles enable to follow the swallowing sequence that starts with the deflation of the posterior air chamber, shortly followed, after \( t_A \), by the inflation of the anterior part of the soft tongue. A steep pressure increase in the anterior chamber is observed within the first 0.2 s of the swallowing sequence. This corresponds to the deformation observed in Fig. 7.10 and Fig. 7.11. The pressure gradient progressively decreases
at large strains and approaching contact with the hard palate (Fig. 7.13). The re-inflation of the posterior air chamber, triggered at the time $t_P$, results in a slight decrease in the available air pressure to the front air chamber (Fig. 7.13). This dip does however not influence the transit of the bolus, whose duration is always shorter than $t_P$, as discussed in the previous section. The actuation pressures were not a function of the bolus rheology (Fig. 7.13). This confirms that the system is consistently driven at imposed stresses.

![Figure 7.13: Absolute value of inflation pressure of the pneumatic tongue during the in vitro swallowing sequence for dry swallows and tests with a glycerol-water solution with IDDSI consistency Level 4.](image)

**Palatal pressures**

Palatal pressures were a function of the bolus rheology. The pressure distribution increases at the front of the palate after approximately 0.2 s from the deflation of the posterior chamber. This delay can be controlled by changing $t_A$. The onset of the pressure wave on the anterior palate is shortly followed by a sharper increase in the measured pressure at the median palate (Fig. B.2).
The pressure driving force in the direction of swallowing sharply decreases as the two profiles intersect. Video recordings of the experiment show that this event occurs after the bolus has left the *in vitro* oral cavity. The further increase in the measured pressures after the bolus transit is the result of the remaining film of liquid being squeezed against the palate. This condition is identified by a change in the slope of the profiles and suggests that driving pressures below the maximum are propelling the bulk of the bolus. This observation can be put in relation with the low values of intra-bolus pressures measured by Redfearn and Hanson in their quasi bi-dimensional *in vitro* model of tongue/palatal squeeze (268).

A peak in the anterior and median palatal pressure profiles is found after 0.6 s from the start of the swallowing sequence. This peak is the result of the slight pressure decrease in the anterior air chamber following the re-inflation of the posterior air chamber. This is well illustrated in Fig. 7.13.

The value of the peak pressures scales with bolus viscosity both for glycerol and TUC. Peak median palate pressures for the thinnest and thickest glycerol solutions are in the order of 12 kPa and 16 kPa respectively. The intermediate glycerol solution shows a pressure peak of about 14 kPa. These values are within the physiological range reported in the literature 1-45.3 kPa (269).

The maximum peak pressures at median palate for TUC are smaller than glycerol: values for TUC Level 4, are approximately 3 kPa lower than those of the thickest glycerol solution. Differently from glycerol, the onset of the pressure profile at the median palate is slightly delayed in the case of TUC. As a result, TUC at medium to high consistencies has a steeper increases of pressure as a function of time. Accordingly, this observation can be justified by considering the shear thinning rheology of the gum-based thickener and the interpretation of this finding can be related to the faster transit time of TUC at the same IDDSI level consistency.

This observation is consistent with the findings of Redferan and Hanson who reported a lower value of clearance pressure for highly shear thinning liquid boli (268).
Figure 7.14: Absolute pressure during *in vitro* swallowing measured at the anterior, median and posterior palate for glycerol-water (a, c and e) and TUC solutions (b, d and f) of increasing IDDSI level consistency (rows from top to bottom: Level 2, Level 3 and Level 4).
Table 7.6: Ratio of ejected bolus mass relative to the injected bolus mass as a function of the in vitro swallowing condition: first swallow, repeated swallows and % variation for water pre-wetted swallows against the first swallow. Standard deviation from three repeats in brackets.

<table>
<thead>
<tr>
<th>Bolus IDDSI index</th>
<th>Transiting bolus mass first swallow</th>
<th>Transiting bolus mass repeated swallows</th>
<th>% variation water pre-wetted vs first swallow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol solutions</td>
<td>2 75 (3) %</td>
<td>89 (6) %</td>
<td>7 (12) %</td>
</tr>
<tr>
<td></td>
<td>3 60 (3) %</td>
<td>82 (6) %</td>
<td>12 (11) %</td>
</tr>
<tr>
<td></td>
<td>4 56 (4) %</td>
<td>77 (5) %</td>
<td>5 (16) %</td>
</tr>
<tr>
<td>TUC solutions</td>
<td>2 87 (3) %</td>
<td>99 (4) %</td>
<td>-7 (11) %</td>
</tr>
<tr>
<td></td>
<td>3 75 (2) %</td>
<td>98 (4) %</td>
<td>-1 (11) %</td>
</tr>
<tr>
<td></td>
<td>4 73 (5) %</td>
<td>96 (7) %</td>
<td>-1 (16) %</td>
</tr>
</tbody>
</table>

The effect of water pre-wetting was not strong and did not result in an appreciable variation in the pressure profiles.

Bolus mass and residues

The mass of bolus ejected was measured during the experiments. This value is normalized with respect to the injected bolus mass (i.e. 10 mL per each swallow) and listed in Table 7.6 as a function of the swallow condition considered.

Thicker liquids leave more residues after the first swallow (i.e. dry mouth). In this case the transiting bolus mass decreases with increasing bolus consistency. The normalized ejected bolus mass increases with further iteration of the swallowing sequence and can overshoot 100% due to the residues in the in vitro oropharynx approaching a terminal steady state (Table 7.6). The small leakage before and after the experiments, in particular with thin Newtonian boli, does not allow to precisely back calculate the amount of residues after each swallow.

Results after the first swallow show that thick Newtonian boli are less effectively transported in the in vitro model, therefore leaving a higher amount of post-swallow residues (Table 7.6). TUC performs better than glycerol for the same IDDSI category. The transiting bolus mass noticeably decreases, when moving from TUC Level 2 to TUC Level 3. However, increasing the concentration of TUC to 4.8 g/100 mL (Level 4) does not
significantly deteriorate this score. This observation suggests that the amount of post swallow residues does not strongly depend on the consistency level for TUC.

Finally, the transiting bolus mass when the model was pre-wetted with water did not show a significant variation. Cross comparing the average values obtained for TUC and glycerol only suggests a potential benefit of water pre-wetting for the latter, for which a general increase in the ejected bolus mass, hence reduction of post-swallow residues, was measured.

### 7.2.4 Modifications to the swallowing sequence

The *in vitro* model presented in this study offers a flexibility in the timing for pneumatic actuation. Whilst a full characterization of the capabilities of the system lies outside the scope of the present research, some preliminary tests have been conducted to analyse the variability in the measured transit time, transiting bolus mass and Doppler profiles were changing the sequence of events during the inflation of the anterior air chamber. Tests were run with a delay for the inflation of the anterior air chamber $t_A$ between -0.2 and +0.2 s, with 0.1 s increments. Negative values of $t_A$ indicate that the inflation of the anterior air chamber was anticipated with respect to the deflation of the posterior air chamber. This delay is partially compensated by the induction time required for the complete inflation of the air chamber, that is in the order of 0.2 s (Fig. 7.4). *In vitro* tests for this set of experiments only considered repeated swallow conditions with the thickest solution of TUC (IDDSI Level 4). This liquid was preferred over thinner and Newtonian boli as to limit dripping and premature spillage when altering the timings for the pneumatic actuation.

The thick shear thinning liquid bolus was successfully transported and ejected from the oral cavity for all the values of $t_A$ here examined. Premature spillage was not observed even when the inflation of the anterior chamber was delayed to up to 0.2 s. This result confirms the benefit of thick and shear thinning products for an improved bolus control on the tongue prior to swallowing.
Figure 7.15: Oral transit times from video recordings of the experiment for different time delays of bolus propulsion ($t_A$). The thickest TUC solution (IDDSI Level 4) was used as a model liquid bolus.

The oral transit times were found to be strongly dependent upon $t_A$. The shortest transit time (0.27 s) was measured for a zero time delay. Conversely, longer transit times were instead measured either for a delayed or an anticipated front chamber inflation.

While a faster dynamics is expected as $t_A$ is reduced, it is less obvious that the oral transit time increases less than linearly with the imposed time delay. The transit time only slightly increases from 0.37 to 0.41 s when the delay was doubled from 0.1 to 0.2 s (Fig. 7.15). Notably, these values roughly correspond to a 50% increase in transit time with respect to the zero delay case (0.27 s) (Fig. 7.15).

When the inflation was anticipated, experiments yet showed an increase in the duration of oral transit. This observation can be justified by considering the progressive reduction in the pumping efficiency for negative actuation delays, caused by the the loss of asymmetry in the deformation of the soft tongue. Differently from the transit times, the transiting bolus mass does not highlight a strong dependency on the actuation delay.

The Doppler profiles provide a semi-quantitative indication of the efficiency of the bolus transport. A positive shift in the onset of the Doppler signal is observed for a delayed
Figure 7.16: Doppler velocity profiles from in vitro swallowing experiments for different time delays of bolus propulsion (t_A). The thickest TUC solution (IDDSI Level 4) was used as a model liquid bolus.

In these cases the spectra show the characteristic second peak following the re-inflation of the posterior air chamber, that clears the remaining bolus residues from the posterior palate. However, the amplitude of this second peak is significantly smaller when the delay was set to 0 s, which suggests that a lower amount of liquid residues are left on the posterior palate for this swallowing pattern (Fig. 7.16). A similar observation can also be drawn for t_A=-0.1 s with the difference that lower peak velocities and an overall wider time-distribution were attained in the latter case (Fig. 7.16).

Further anticipating the inflation of the anterior air chamber (t_A=-0.2 s) gives a swallowing sequence with a wider and more irregular temporal duration of the Doppler spectra (Fig. 7.16). The velocity distribution also features the characteristic second peak, thus indicating the presence of post-swallow residues (Fig. 7.16).
7.3 Conclusions

This last chapter of the thesis proposes a novel approach to study the oral phase of swallowing based on the use of a realistic three dimensional geometry in combination with a soft-pneumatic actuator to simulate the functionality of the tongue. The soft pneumatic model allows to replicate the dynamics of swallowing for a wide range of bolus consistencies while overcoming some of the significant limitations that affected past in vitro studies of swallowing (Chapter 3). Preliminary tests showed that the model is able to reproduce physiological conditions, in good agreement with the literature. A remarkable effect of bolus rheology on the oral transit time and on the peak palatal pressures was observed. In this regard, the flow of thick Newtonian liquids was slower than shear thinning liquids of comparable IDDSI consistency level. The flow of thin Newtonian boli could also be quantified. Pre-wetting the model with water showed no significant differences in the measured transit times and bolus velocity. This motivates further research to consider more realistic models of lubricating liquids to mimic the role of the salivary pellicle. This soft robotic tongue offers unique capabilities to study in more depth the effect of the lubricating properties of saliva and other complex fluid, while maintaining all other factors constant. The degrees of freedom of this soft actuator lend themselves to provide insight into the role of poor tongue coordination on swallowing disorders and on the mitigating role of bolus rheology.
Chapter 8

Conclusions

8.1 Key results

The approach and the results presented in this thesis contribute to further understanding the biomechanics of swallowing and its implication in the design of food and pharmaceutical products that are easy to swallow.

8.1.1 Reviewing the in vitro and in silico models of swallowing based on motor control

A comprehensive review of the state of the art on the approaches to model swallowing was compiled. This review work, extended to more than 30 previous studies, led to the introduction of a novel categorization of the models with respect to the motor control strategy. The approach of imposing forces (stresses) was compared against that of imposing displacements (strains) and to models mixing the two (stresses and strains). This categorization is instrumental to compare the results of different in vitro and in silico studies. These different strategies also highlight the need to further target clinical trials to further understand the physiology of the motor control during swallowing.
The review also outlined other critical aspects that have often been overlooked: the importance of modelling the fluid-structure interaction was put in relation to the bolus flow in the pharynx, and, in particular, around the epiglottis. Attention was also drawn to the limited number of models considering the effect of salivary lubrication, which some authors suggest is a key factor in the formation of post swallow residues.

8.1.2 Behaviour of viscoelastic liquids during swallowing

The role of liquid viscoelasticity in the oral phase of swallowing was studied, elucidating the dominant contribution of steady shear rheology during the oral transit of thickened liquid boli. *In vitro* experiments, considering gum-based food thickeners and model viscoelastic liquids, showed that the latter form more cohesive boli, and thus help to reduce uncontrolled fragmentation (i.e. splashing) in the transition between the oral cavity and the pharynx. The bolus shape during *in vitro* swallowing was analysed using non-dimensional quantities commonly used in the description of viscoelastic flows. In the range of conditions considered, experiments demonstrated that the oral swallowing dynamics was not affected by elasticity. However, thin elastic liquids show a more compact bolus shape during and after the transition to the *in vitro* pharynx, limiting also amount of post-swallow residues with respect to weakly elastic gum-based thickeners currently used in dysphagia management. Tests also show that, when the shear viscosity was sufficiently high to affect the regime of bolus transit *in vitro*, the effect of elasticity caused die swelling during the bolus ejection from the *in vitro* oral cavity. This results in a slow-moving bolus, followed by an increased amount of post swallow-residues: an undesirable combination. These positive results constitute a strong support for a clinical evaluation of viscoelastic liquids for dysphagia management.
8.1.3 Design of tablets and multiparticulate formulations for improved swallow-ability

The physical attributes of tablets and capsules can be adapted for ease of oral bolus transport by designing smaller and more elongated shapes. This conclusion is aligned to the results obtained by a few clinical studies and is in agreement with the guidelines from the FDA \(^{(208)}\). This study brings further quantitative insight on the mechanism governing these effects.

*In vitro* tests were performed in presence of suspended particles to elucidate effect of particle size and shape on the oral swallowing dynamics. Model spherical particles of increasing diameters from 4.8 to 10 mm were considered in the study. Results show that an increase in the tablet diameter leads to a longer duration of the *in vitro* swallowing. The swallowing dynamics was predicted with the introduction of a scaling factor proportional to the fourth power of the ratio of the tablet and the bolus cross-sectional diameters. The same scaling factor was originally proposed by Ellis and Charles in the study of hydraulic transport of capsules \(^{(270)}\) \(^{(271)}\).

The tablet size also conditioned the relative motion within the liquid bolus. The position of the tablet remained unchanged throughout the oral trajectory for intermediate tablet diameters (6.35 and 8 mm). Conversely, a relative backward motion was observed for smaller tablets. This observation was justified in light of theoretical studies considering the peristaltic transport of suspended solids.

The impact of tablet shape, at constant tablet volume, was assessed for ellipsoidal tablets of increasing aspect ratios. In line with the expectations, shapes with a smaller cross section in the direction of the flow led to shorter transit times. Moreover, the model was sensitive enough to provide an indication of the optimal combination of tablet size and shapes that minimize the impact on swallowing dynamics. Above a critical diameter of approx. 8 mm the tablets transport was significantly delayed. Below a diameter of approx. 6 mm, tablets did not influence the *in vitro* bolus dynamics, but their migration
towards the bolus tail could bring the solid oral dosage forms in contact with the tongue. This significant conclusion should be confirmed clinically, once pertinent video fluoroscopy studies became available.

8.1.4 Shear thinning vehicles ease administration of multiparticulates

Requirements for increased dosage flexibility in geriatric and paediatric patients have stimulated interest towards novel formulations, including mini-tablets and multiparticulate systems. These formulations require to understand the combined effect of particle size and suspending vehicle rheology on the attributes of perceived ease of swallow, palatability and the amount of post-swallow oral residues. Results from sensory tests are however often confused by the simultaneous perceptions of different attributes. Moreover, the intra-subject variability can mask the real underlying effect of different product attributes. To assess quantitatively these effects and compare the in vitro model against sensory data, a collaboration with the UCL School of Pharmacy was established.

In vitro and sensory tests were carried out separately, considering oral administration of multiparticulates of different particle size suspended in water and in thickened solutions to verify whether smaller multiparticulates and thickened liquids led to an improved palatability and smoother transport. Overall, this hypothesis was confirmed. The study showed how palatability and after-swallow feel of micro-particulates can be noticeably improved by reducing the suspended particle size and using thicker suspending vehicles. The in vitro model showed a significant discrimination-ability and was able to find differences among formulations also in cases when in vivo results were confounded by other factors. The study however also outlined the limitations of the original experimental apparatus. The lack of compliance and the absence of active force modulation during swallowing led to mechanical jamming and irregular flow when working with thin liquid vehicles and coarse suspended particles. These limitations are deemed not representative of the in vivo physiology. This observation, combined with the need for considering soft tissues,
lubricated contacts and more realistic geometries, led to the design of a novel in vitro model of the oral phase of swallowing based on a soft pneumatic actuator, inspired by the human tongue.

8.1.5 A novel soft robotic model to study swallowing

The development of this novel soft robotic tongue constitutes an important methodological advance in the context of in vitro models of swallowing. The novel actuator design has been developed to be closer to human anatomy than previous in vitro models. The surface wettability has been enhanced by adding an anionic surfactant. This allows to obtain a well-distributed water coating to approximate a lubricated swallowing condition. The design of the tongue-inspired actuator introduces additional, physiologically sound, degrees of freedom: the actuation mechanism allows us to vary both the timing of inflation of the pneumatic chambers and the inflation pressure (i.e. tongue force), which gives significant flexibility to explore different swallowing conditions. The experimental setup can characterise the bolus dynamics by recording its instantaneous position, measuring the bolus velocity and the palatal pressures during swallowing.

Preliminary results confirmed the robustness of the model while testing a broad range of bolus consistencies. The model gave physiological values of peak palatal pressures and transit times. Results showed increasing peak palate pressures with the bolus viscosity. The increase was however weaker when considering highly shear thinning model boli, compared to Newtonian fluids.

Water lubrication of the hydrophilic palate soft tongue did not did not lead to any noticeable change in the kinematics and dynamics of swallowing. Although, some differences were found in the amount of post-swallow residues, further tests are needed to elucidate the role of oral lubrication. In particular considering lubricants that can more closely represent the complex rheology of saliva. Tribological measurements are also needed to complement the study.
8.2 Limitations and future work

While investigating the role of the extensional properties of liquids, a correlation was found between the bolus elongation and the elasticity number $E$. The value of this non-dimensional quantity was however insufficient to identify a clear threshold for the occurrence of bolus shortening upon leaving the $in vitro$ oral cavity. A theory capable of describing the bolus dynamics at the transition between oral and pharyngeal cavities should be developed to predict bolus swelling. Numerical particle-based methods, such as SPH and MPS could represent a useful tool to simulate this transient phenomena, provided a set of experimental results allowing an accurate validation are also available.

A more comprehensive understanding of the internal flow of the bolus during swallowing would also be valuable in consideration to the transport of tablets and multiparticulates. Preliminary tests with tracers already revealed the existence of an internal recirculation within the bolus. This observation, consistent with the theory of peristaltic flow, should be quantitatively described as a function of bolus rheology. To this extent, Particle Image Velocimetry (PIV) could lead to a better characterisation of the internal bolus fluid dynamics before attempting numerical simulations. Visual tracking of suspended neutrally buoyant particles, could be performed, using a camera rotating with the bolus and a lens with a narrow depth of field to avoid disturbances from particles in different planes.

The potentialities of the novel soft pneumatic actuator inspired by the tongue should be further exploited by characterising more systematically the impact of operational parameters on the swallowing response. The quality of the kinematic and dynamic data from $in vitro$ tests could be further enhanced using more accurate pressure transducers and using ultrasound imaging to observe bolus transit. Moreover, further validation against clinical data is necessary. Finite element simulations were able to actively support the development of the soft robotic tongue, but a more robust optimisation approach should be developed to bridge the gap between the $in vitro$ and $in vivo$ tongue kinematics during swallowing. Advanced techniques for mesh refinement and mesh design are also needed,
to reduce the numerical instability of the FE simulations at large strains. On the longer term, the implementation of fully coupled fluid-structure simulations would allow for a more direct understanding of the in vitro results, both in terms of palatal pressure and intra-bolus velocity profiles. Further to healthy swallowing, the soft robotic system lends itself to simulate swallowing disorders, but a significant research effort is still needed to develop realistic control sequences inspired directly by clinical observations (e.g. videofluoroscopy).

Finally, adapting in vitro models to study the swallowing dynamics in paediatric populations constitutes also an important next step to support the development of easy-to-swallow formulations. Tests with the peristaltic simulator have been conducted assessing the sensitivity of the device with respect to reductions in the width of the plastic membrane, to simulate the smaller cross section of the oral cavity in infants. Results confirmed the weak effect of this parameter, as correctly predicted by the mechanistic theory. However, a more comprehensive investigation is required to account for the different curvature of the palate. This aspect could be considered in the future, redesigning the in vitro model.

8.3 List of contributions

8.3.1 Poster presentations

- UK Particle Technology Forum (Guildford, UK, 2016);
- Powders and Grains (Montpellier, France, 2017);
- Complex Motion in Fluids (Cambridge, UK, 2017);
- UK Swallowing Research Group (London, UK, 2018);
- Food Oral Processing (Nottingham, UK, 2018).
8.3.2 Oral presentation

- Food Oral Processing (Nottingham, 2018).

8.4 Publications

8.4.1 Conference proceedings


8.4.2 Journal articles


8.5 Co-supervision of MEng and MSc students


- Marconati, M., Pani, S., Burbidge, A., Engmann, J., Ramaioli, M. A soft peristaltic actuator inspired by the human tongue to study the biomechanics of swallowing. In preparation, based on the results presented in Chapter 7 of this thesis.


Appendix A

Theoretical model of the *in vitro* peristaltic simulator

This appendix details the theoretical model used in the prediction of the dynamics of the *in vitro* swallowing simulator used throughout Chapter 4 to 6. To account for the presence of suspended particles the viscous dissipation is modified introducing an additional drag coefficient, derived from the annular flow theory. In case of multiple, well dispersed suspended solids, the bolus viscosity is approximated with the Krieger-Dougherty equation.

A.1 Rotational dynamics

The experimental setup described in Chapter 4, reported for convenience in Fig. A.1, replicates the peristaltic motion of the tongue during the oral phase of swallowing.

The theory of sinusoidal peristaltic flows has been developed in the literature and the effect of peristaltic wave shape and liquid rheology have already been investigated. Although effective in modelling the simpler geometries of the esophagus and ureter, the extension of the peristaltic flow assumption to the oral cavity during swallowing finds several difficulties due to the more articulated lingual gestures.
A.1. Rotational dynamics

An alternative and simpler simple model was nonetheless successfully used to evaluate the inertial and viscous contributions for the \textit{in vitro} tests \cite{8}. This mechanistic theory, here synthetically revised, describes the rotational dynamics from the Lagrangian equation of motion, approximating the work done by the viscous bolus is with a Poiseuille drag flow.

In the mechanical model used to simulate the oral phase of swallowing the total kinetic energy $K$ is made up by: 1) the roto-translational motion of the bolus (of mass $m_B$, linear velocity $v_B$, and inertia $I_B$), 2) the hanging weight (mass $m$ and linear velocity $v_m$), and 3) the rotation of the central assembly, of inertia $I$ at angular velocity $\dot{\theta}$ (Eq. \ref{A.1}). Linear velocities can be put in relation to the angular velocity of the pulley $\dot{\theta}$, knowing the radial distances from the centre of rotation $r_A$ (see Fig.\ref{fig:A.1}).

\begin{equation}
K = \frac{1}{2} (m_B v_B^2 + I_B \dot{\theta}^2) + \frac{1}{2} m v_m^2 + \frac{1}{2} I \dot{\theta}^2 \tag{A.1}
\end{equation}

The overall potential energy of the system $U$ is calculated from the displacement of the hanging mass and the vertical position of the bolus centre of mass (Eq. \ref{A.2}).

\begin{equation}
U = m g \theta r_p + m_B g r_A \sin(\theta) \tag{A.2}
\end{equation}

Negative work on the system is done by the viscous dissipation $F_d$, tangential to the roller trajectory, and function of the angular velocity $\dot{\theta}$, the rheology of the liquid carrier $\eta$ and the geometry of the bolus. The equation of motion of the mechanical system,
Appendix A. Theoretical model of the in vitro peristaltic simulator characterized by the single degree of freedom of angular rotation $\theta$, is obtained from the Lagrange equations of dynamics, where $Q$ is the generalized force (Eq. [A.4]).

$$\frac{d}{dt} \left( \frac{d}{d\theta} (K - U) \right) - \frac{d}{d\theta} (K - U) = Q$$  \hspace{1cm} (A.3)

$$Q = F_d \cdot \frac{\partial x}{\partial \theta}$$  \hspace{1cm} (A.4)

Substituting the expression for $K$ and $U$ gives, an explicit relation that can be used to obtain the roller angular acceleration $\ddot{\theta}$ knowing the geometrical and inertial properties.

$$\ddot{\theta} = -F_d r_A + m g r_p + m g r_A \cos(\theta) \frac{I + I_B + m_B r^2_A + m r^2_p}{I} \hspace{1cm} (A.5)$$

Asymptotic analysis of Eq. [A.5] predicts two different regimes of motion: at low angular velocities the contribution of viscous dissipation through Eq. [A.7] becomes negligible and the dynamics of swallowing is driven by the external applied force and the inertia of the system, hence giving rise to constant angular acceleration. Conversely, when the magnitude of the viscous force becomes of the same order of magnitude of the moment of the driving force $(m g r_p)$ the numerator in Eq. [A.5] vanishes and the motion of the bolus approaches constant values of angular velocity that justify the definition of $F_d$. The inertia of the central rotating assembly was determined once for all with empty runs of the device. Its value, being two orders of magnitude higher than that of the bolus led Hayoun et al. to consider it through a constant multiplication factor $\delta > 1$ to $I$ in Eq. [A.5].

Similarly, a constant $F_{\text{min}}$ was used to correct for the friction of the roller, as a minimum external applied weight of approx. 0.4 N was needed for the roller to start moving. In light of these observations, the final form of Eq. [A.5] was approximated with the following
A.2 Viscous dissipation

The viscous force $F_d$ that appears in Eq. (A.6) was assumed linearly proportional to the bolus velocity, obtained multiplying its angular velocity $\dot{\theta}$ by the radial distance of the roller from the centre of rotation $r_A = 47$ mm (8). A similar linear dependency holds at relatively low swallowing velocities, as comprehensively investigated by Mowlavi et al. (8). A simple model for $F_d$ based on a Poiseuille flow assumption was used to predict the experimental bolus velocity profiles. Under this hypothesis, the bolus was idealized as cylindrical element of fluid of uniform cross section and length $L_B$ moving with an average velocity equal to the roller velocity (theta). This is consistent to the experimental observation that the length of the bolus is approximately constant during the flow. The resulting viscous force was computed, considering the liquid viscosity $\eta$, via Eq. (A.7). The constant $\beta = 3.23$ was fitted on the experimental results to account for the system friction and is independent of the applied load and the fluid considered.

$$F_d = \beta 8\pi \eta L_B \dot{\theta} r_A$$  \hspace{1cm} (A.7)

The theory above was then extended considering the additional drag due to the particle interaction with the mean flow. Bungay and Brenner investigated the case of close fitting particles in tubes (272), while Wang and Skalak (273) studied the additional resistance in the case of a train of equally spaced spheres. The extension to the flow of spheroidal and cylindrical particles was presented by Chen and Skalak (274) and, comprehensively revisited by Pozrikidis and Davis (275). Semi empirical correlations developed over a wide range of flow regimes in cylindrical tubes have also been proposed, in particular in the
study of the pipeline flow of elongated capsules (271). Following the latter approach, a simple mathematical model considered the annular flow in the gap between the flowing solid (of cross sectional radius $R_i$) and the pipe radius $R_e = R_B$. In this geometry, the boundary conditions impose that the inner cylindrical solid (i.e. the solid oral dosage form) moves longitudinally with velocity equal to that of the roller $\theta r_A$, while a no-slip condition was applied to the external shell (i.e. the plastic membrane in which the bolus was contained).

A.3 Annular flow in infinitely long shells

The theory of annular flow in laminar regime is developed in consideration of the results proposed by Charles (271). The basic hypothesis are reported together with a step by step derivation of the analytical expression for pressure drop.

A.3.1 Assumptions

The derivation of the theoretical model used to describe the velocity distribution in an annulus assumes

- Laminar regime
- Steady state
- Axial symmetry
- Newtonian liquid
- Isothermal system
- Horizontal straight pipe
A.3.2 Derivation

The Navier-Stokes set of differential equations, combined with the continuity equation reduces to:

\[
0 = -\frac{\partial P}{\partial z} + \eta \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{dv_z}{dr} \right) \right) \tag{A.8}
\]

that can be integrated twice obtaining

\[
v_z = v_z(r) = \frac{1}{4\eta} \frac{\partial P}{\partial z} r^2 + c_1 \ln r + c_2 \tag{A.9}
\]

The boundary conditions for the problem here considered (Fig. A.2) are expressed as:

\[
\begin{align*}
v_z(R_i) &= v_i \\
v_z(R_e) &= 0
\end{align*} \tag{A.10}
\]

Upon substitution in A.9:

\[
\begin{align*}
v_i &= \frac{1}{4\eta} \frac{\partial P}{\partial z} R_i^2 + c_1 \ln R_i + c_2 \\
0 &= \frac{1}{4\eta} \frac{\partial P}{\partial z} R_e^2 + c_1 \ln R_e + c_2
\end{align*} \tag{A.11}
\]

Solving for \(c_1\) and \(c_2\) leads to:

\[
\begin{align*}
c_1 &= \left( v_i - \frac{1}{4\eta} \frac{\partial P}{\partial z} (R_i^2 - R_e^2) \right) \frac{1}{\ln(R_i/R_e)} \\
c_2 &= \left( -\frac{1}{4\eta} \frac{\partial P}{\partial z} R_e^2 - c_1 \ln R_e \right)
\end{align*} \tag{A.12}
\]
The analytical expression for the velocity can therefore be rearranged in the form:

$$v_z(r) = \frac{1}{4\eta} \frac{\partial P}{\partial z} \left( r^2 - R_e^2 + \frac{(R_i^2 - R_e^2)}{\ln(R_i/R_e)} \ln(R_e/r) \right) + \frac{v_i}{\ln(R_i/R_e)} \ln(r/R_e)$$  \hspace{1cm} (A.13)

That can be integrated to find the volumetric flow rate in the annulus:

$$Q_A = \int_A v_z(r) \, dA$$  \hspace{1cm} (A.14)

Hence,

$$Q_A = \int_{R_i}^{R_e} 2\pi r v_z(r) \, dr$$  \hspace{1cm} (A.15)

$$Q_A = 2\pi \int_{R_i}^{R_e} \left( \frac{1}{4\eta} \frac{\partial P}{\partial z} r^3 + c_1 r \ln r + r c_2 \right) \, dr$$  \hspace{1cm} (A.16)

Which, upon integration, becomes:

$$Q_A = 2\pi \frac{1}{4\eta} \frac{\partial P}{\partial z} \frac{R_e^4 - R_i^4}{4} + 2\pi c_1 \left( \frac{R_e^2 \ln R_e - R_i^2 \ln R_i}{2} - \frac{R_e^2 - R_i^2}{4} \right) + 2\pi c_2 \frac{R_e^2 - R_i^2}{2}$$  \hspace{1cm} (A.17)
After the introduction of $c_1$ and $c_2$, and further factorization of the common terms:

$$Q_A = \frac{\pi}{8\eta} \frac{\partial P}{\partial z} \left[ \frac{(R_e^2 - R_i^2)^2}{\ln (R_e/R_i)} - (R_i^4 - R_i^4) \right] + \pi v_i \left[ \frac{R_i^2 - R_e^2}{2\ln (R_i/R_e)} - R_i^2 \right]$$ (A.18)

The total volumetric flow rate in the overall pipe section ($\pi R_e^2$) must also account for the flow rate of the inner cylinder (i.e. the solid particle of radius $R_i$) moving at velocity $v_i$.

$$Q_{Tot} = Q_A + Q_{particle}$$

$$Q_{particle} = v_i \pi R_i^2$$ (A.19)

$$Q_{Tot} = \bar{v}\pi R_e^2$$

The average velocity in the overall pipe cross section $\bar{v}$ is generally different from the velocity of the particle $v_i$.

$$Q_{Tot} = \frac{\pi}{8\eta} \frac{\partial P}{\partial z} \left[ \frac{(R_e^2 - R_i^2)^2}{\ln (R_e/R_i)} - (R_i^4 - R_i^4) \right] + \pi v_i \left[ \frac{R_i^2 - R_e^2}{2\ln (R_i/R_e)} - R_i^2 \right] + v_i \pi R_i^2$$ (A.20)

$$\bar{v}\pi R_e^2 = \frac{\pi}{8\eta} \frac{\partial P}{\partial z} \left[ \frac{(R_e^2 - R_i^2)^2}{\ln (R_e/R_i)} - (R_i^4 - R_i^4) \right] + \pi v_i \left[ \frac{R_i^2 - R_e^2}{2\ln (R_i/R_e)} \right]$$ (A.21)

$$0 = \frac{1}{8\eta} \frac{\partial P}{\partial z} \left[ \frac{(R_e^2 - R_i^2)^2}{\ln (R_e/R_i)} - (R_i^4 - R_i^4) \right] + v_i \left[ \frac{R_i^2 - R_e^2}{2\ln (R_i/R_e)} \right] - \bar{v}R_e^2$$ (A.22)

Rearranging the above equation to find the pressure drop leads to:

$$\frac{\partial P}{\partial z} = \frac{8\eta \left\{ \bar{v}R_e^2 - v_i \left[ \frac{R_i^2 - R_e^2}{2\ln (R_i/R_e)} \right] \right\}}{\frac{(R_e^2 - R_i^2)^2}{\ln (R_e/R_i)} - (R_i^4 - R_i^4)}$$ (A.23)
Appendix A. Theoretical model of the in vitro peristaltic simulator

Which can be rewritten in the form of macroscopic pressure difference $\Delta P$ over the pipe length $L$

$$
\Delta P = 8\eta L \left\{ \bar{v} R_e^2 - v_i \left[ \frac{R_i^2 - R_e^2}{2 \ln(R_i/R_e)} \right] \right\}
\left[ \frac{(R_e^2 - R_i^2)^2}{(R_i^2 R_e^2)} - (R_e^4 - R_i^4) \right]
$$

(A.24)

The drag force is expressed by:

$$
F = \pi R_e^2 \Delta P
$$

(A.25)

When instead considering a Hagen-Poiseuille flow (absence of solid particles) the theory simplifies to:

$$
\frac{\partial P}{\partial z}_{H-P} = \frac{8\eta \bar{v}}{R_e^2}
$$

(A.26)

And the viscous dissipation becomes:

$$
F_{H-P} = \pi R_e^2 \Delta P = 8\pi \eta L \bar{v}
$$

(A.27)

The effect of considering a cylindrical occlusion moving at velocity $v_i$ in a pipe, results in an increase in the measured drag force that can be expressed by the ratio

$$
\frac{F_A}{F_{H-P}} = \frac{8\eta L \left\{ \bar{v} R_e^2 - v_i \left[ \frac{R_i^2 - R_e^2}{2 \ln(R_i/R_e)} \right] \right\}}{8\pi \eta L \bar{v}} = \frac{1}{\bar{v}} \left\{ \bar{v} R_e^2 - v_i \left[ \frac{R_i^2 - R_e^2}{2 \ln(R_i/R_e)} \right] \right\}
\left[ \frac{(R_e^2 - R_i^2)^2}{(R_i^2 R_e^2)} - (R_e^4 - R_i^4) \right]
$$

(A.28)

That becomes a sole function of the pipe geometry when the velocity of the solid particle
A.3. Annular flow in infinitely long shells

is assumed equal to the mean velocity in the tube cross section \( v_i = \bar{v} \).

\[
\frac{F_A}{F_{H-P}} = \frac{\left\{ R_e^2 - \left[ \frac{R_i^2 - R_e^2}{2 \ln(R_i/R_e)} \right] \right\}}{\frac{(R_e^2 - R_i^2)^2}{\ln(R_e/R_i)} - (R_e^4 - R_i^4)} \tag{A.29}
\]

It is easy to see that the limit of the above ratio tends towards 1 for vanishing shell (i.e. particles) radii.

A.3.3 Empirical correlations

Several authors published experimental results dealing with velocity characterization, flow instability and forces required to effectively transport solid object in pipes \([276, 277, 271, 270]\). Charles proposed a simple model to correlate the experimental findings in the case of elongated capsules, considering the same type of geometry illustrated in Fig. A.2 \([271]\) obtaining a simplified expression for the axial velocity \( v_z(r) \) for \( R_i < r < R_e \).

\[
v_z(r) = \frac{\Delta P}{4\eta L} (R_e^2 - r^2) \tag{A.30}
\]

The velocity of the inner cylinder is given by

\[
v_i = \frac{\Delta P}{4\eta L} (R_e^2 - R_i^2) \tag{A.31}
\]

The volumetric flow rate in the annulus is given by the integral of \( 2\pi v_z(r) \) between \( R_i \) and \( R_e \).

\[
Q_A = \frac{\Delta P}{8\eta L} \pi (R_e^2 - R_i^2)^2 \tag{A.32}
\]
Appendix A. Theoretical model of the in vitro peristaltic simulator

Which, considering the expression of the inner cylinder velocity, can be rearranged as:

\[ Q_A = \frac{\pi}{2} v_i (R_e^2 - R_i^2) \]  (A.33)

The average velocity in the overall pipe section can be computed through the following:

\[ \bar{v} = \frac{Q_A + Q_{\text{particle}}}{\pi R_e^2} \]  (A.34)

And, upon substitution with the analytical expressions found for \( Q_A \) and \( Q_{\text{particle}} \),

\[ \bar{v} = \frac{\pi}{2} v_i \left( \frac{R_e^2 - R_i^2}{\pi R_e^2} \right) + \frac{\pi R_i^2 v_i}{\pi R_e^2} = \frac{1}{2} \left( \frac{R_e^2 + R_i^2}{R_e^2} \right) v_i = \frac{1}{2} \left( 1 + R_i^2 / R_e^2 \right) v_i \]  (A.35)

Being \( R_i / R_e \) necessarily > 0, the particle velocity always exceeds the mean velocity of the whole section of the pipe. Moreover, the average velocity in the annulus is considered to be different from that of the particle and given by:

\[ \bar{v}_A = 2v_i \frac{\pi R_e^2}{\pi \left( R_e^2 - R_i^2 \right)} \]  (A.36)

so that, the value of \( \bar{v}_A \) can be expressed in terms of average velocity on the entire pipe cross section \( \bar{v} \) by the following

\[ \bar{v}_A = \frac{\bar{v}}{\left( 1 + R_i^2 / R_e^2 \right) \left( 1 - R_i^2 / R_e^2 \right)} = \frac{\bar{v}}{\left( 1 - R_i^4 / R_e^4 \right)} \]  (A.37)

Thereby the pressure drop can be related to that of a Hagen-Poiseuille flow replacing \( \bar{v} \) (the mean velocity in the pipe cross section) with \( \bar{v}_A \) (mean velocity in the annular
Adapting the theory on experimental results in laminar flow conditions, Ellis found that the pressure drop experienced in transporting an infinitely long cylindrical neutrally buoyant object without axial offset, can be related to the pressure drop in a Poiseuille flow, with identical mean velocity, corrected by a factor dependent upon the ratio of radii $k = R_i/R_e$ of the suspended solid and the pipe (270). On this basis, the same correction was applied to relate the viscous dissipation of the bolus flow in presence of solid oral dosage forms to that of a Poiseuille flow.

$$F_d = (1 - k^4)^{-1/2} 8\pi \eta L \bar{v} \quad (A.39)$$

In which $L$ is assumed equal to the bolus length $L_B$, $k$ is the ratio of the suspended solid and the bolus cross sectional radii and the average velocity $\bar{v}$ equals the bolus velocity $\dot{\theta} r_A$. Eq. [A.39] is consistent with the theory presented by Hayoun et al. when the cross sectional size of the tablet vanishes.

## A.4 Monodispersed suspensions

The flow behaviour in presence of multiple suspended particles, discussed in Chapter 5 and Chapter 6, was modelled introducing a correction coefficient to the viscosity of the liquid carrier ($\eta_0$). In the case of diluted suspensions of non-interacting spherical particles, the corrective factor is a function of the volume fraction of the suspended phase ($\phi$). The functional relationship is quantitatively detailed by the Einstein equation (Eq. [A.40]).

$$\eta = \eta_0 (1 + 2.5\phi) \quad (A.40)$$
Eq. [A.40] neglects the hydrodynamic interactions between a particle and its neighbours and typically holds for well-dispersed systems when $\phi < 0.01 \{278, 279\}$.

At higher suspended particle concentrations the pair- and the multi-particle interactions induce a significant additional energy dissipation that results in a more than linear increase in the suspension viscosity with $\phi$.

Several empirical and phenomenological relations have been proposed over the years to model the viscosity of dispersed systems \{278, 279\}.

For the purpose of this study the flow of multiple suspended solids of volume fraction $\phi$ was modelled following the Krieger-Dougherty model for spherical particles (Eq. [A.41]).

$$\eta = \eta_0 \left(1 - \frac{\phi}{\phi_m}\right)^{-2.5 \phi_m} \quad (A.41)$$

This equation describes the experimental viscosity increase as a function of $\frac{\phi}{\phi_m}$, where $\phi_m$ is the maximum packing fraction, here considered that of a random close packing of spherical particles ($\phi_m=0.64$) \{278\}.

The model correctly predicts the viscosity of colloidal suspensions at high concentrations, but oversimplifies the hydrodynamic interactions between the suspended particles when their size is comparable to that of the system geometry and for non-laminar flows. In this regard, Eq. [A.41] represents the limiting case of the \textit{in vitro} experiment for small and well-dispersed solids, suspended in thick vehicles.
Appendix B

In vitro tests for flow constrictions

The applications of in vitro methods in the study of the swallowing function of paediatric populations needs to account for the different size of the oropharynx. This Appendix reports the results of a final year MEng research project that considered variations in the width of the in vitro oral cavity of the peristaltic model experiment presented in Chapter 4, and theoretically described in Appendix A.

B.1 Methods

The study considered both Newtonian and shear thinning boli. Glycerol solutions with viscosities of approximately 0.03 and 1.05 Pa.s respectively were considered as model Newtonian boli. Aqueous solutions of PEO were used as model viscoelastic and shear thinning boli. The geometry of the in vitro oral cavity was adapted by reducing the width of the plastic membrane that contains the bolus. The standard membrane width of 23 mm, used throughout Chapters 3 to 6, and previously validated against in vivo data in adults [8], was reduced to 19 and 15 mm to simulate a smaller oral cavity. The volume of bolus $V_B$ was varied accordingly to maintain unaltered the bolus length. The standard membrane (23 mm wide) was filled with 6 mL of liquid, consistently with the tests presented in Chapter 4 and Chapter 5. The volumes for the 19 mm and 15 mm
Appendix B. *In vitro tests for flow constrictions*

Figure B.1: The bolus volume was scaled to maintain the same bolus length when the width of the membrane was reduced from 23 mm (c) to 19 mm (b) and 15 mm (a).

membranes were scaled accordingly.

Consequently, 4 mL of liquid was used for 19 mm tube and 2.5 mL of fluid was used for the 15 mm tube (Fig. B.1).

The viscous dissipation from the Poiseuille-derived model was adapted to the smaller cross section of the membrane. The theory for Newtonian boli does not predict any dynamic effect following variations in the bolus cross section beside the slight variation the variation in the rotational inertia caused by the different mass of the bolus. This effect however is negligible, compared to the rotational inertia of the system.

Conversely, the drag force for shear thinning liquids scales with the radius of the *in vitro* oral cavity to the power $1 - n$ where $n$ is the flow behaviour index for PL liquids ($n < 1$). Consequently highly shear thinning boli are expected to flow faster when the size of the *in vitro* oral cavity is reduced.

### B.2 Key results and Conclusions

Experimental velocity profiles were not significantly affected by the variation in bolus width for thick Newtonian liquids. Thick PEO solutions at low driving forces show instead a dynamics that is slightly more influenced by the width of the *in vitro* oral cavity. A
smaller bolus cross section led to a faster transit. In all cases, increasing the driving force and/or decreasing the bolus thickness led to a weaker effect of the membrane width, in agreement with the theory. These results confirm the validity of the theoretical approach presented in Appendix A and confirm the assumption that the viscous dissipation is distributed within the bolus and the contraction flow in proximity of the roller does not play a major contribution to the swallowing dynamics.

Figure B.2: Roller angular velocities for a 1.05 Pa.s Newtonian bolus (a) and a 4% w/w aqueous solution of PEO ($M_W 10^6$ g/mol) (b). Experiments were run at two load configurations (2 and 4 N) for different values of membrane width (15, 19 and 23 mm).
Appendix C

Doppler velocimetry

The direct supervision of two MSc research projects allowed to test the feasibility of using Doppler ultrasounds (US) as a complementary technique to obtain quantitative information about bolus velocity during swallowing. Doppler measurements, taken adapting the geometry of the peristaltic simulator presented in Chapter 4, were compared against velocities measured by image analysis. Tests highlighted a good quantitative agreement between the two methods.

C.1 Background

Ultrasound imaging is a non-ionising, inexpensive, and portable diagnostic tool used regularly in the health service. Devices used for medical imaging commonly employ frequencies in the range from 2 to 40 MHz \((280\, 59)\). Transducers for ultrasonic equipment are made of multiple piezoelectric crystals. Piezoelectric materials, such as lead zirconate titanate (PZT), can reversibly convert electrical potential energy (voltage) into mechanical deformation, hence mechanical waves upon application of oscillating electrical signals.

The acoustic properties of materials and biological tissues affect the speed of propagation and the energy loss of the travelling sound waves. Echoes are generated whenever an acoustic wave hits the interface between two media of different acoustic impedance,
z, defined as the product of density and speed of sound. Reflected and backscattered ultrasound waves provide a direct information of the thickness of the penetrated layers. Curvilinear probes, composed of multiple arrays of piezoelectric transducers, allow to reconstruct the morphology of wider areas. Moving interfaces generate echoes whose frequencies are shifted with respect to the sound wave of the piezoelectric emitter. Doppler velocimetry is commonly used in healthcare, a typical example is represented by the measurement of blood flow to diagnose partially occluded arteries.

C.2 Methods

The in vitro peristaltic model presented in Chapter 4 and Chapter 5 was adapted to fit two non-directional vascular Doppler probes (Dopplex II, Huntleigh Healthcare Ltd, Cardiff, Wales, UK) Fig. C.1. Both probes were inclined $50^\circ$ with respect to the local tangent to the bolus trajectory. The Doppler signal was calibrated against known values of flow rate in a continuous recirculation rig. Linear calibration lines were obtained within the range of velocities relevant for the deglutition process (0-1 m/s). Figure C.1: Schematics of the in vitro setup with highlighted the position of the two Doppler probes used to measure the bolus velocity during swallowing. The probes are both inclined $50^\circ$ towards the local tangent.
The *in vitro* tests followed the same protocol described in Chapter 4. The experiments aimed at comparing the bolus velocity and transit times obtained via Doppler velocimetry with those from image analysis. Tests considered Newtonian (glycerol) and shear thinning (TUC) liquids of different levels of consistencies. The effect of bolus volume and driving forces was also investigated.

### C.3 Key results and Conclusions

Results allow to appreciate the sensitivity of Doppler velocimetry with respect to variations in the parameters of the *in vitro* model. Lower average values of Doppler signal were measured for thicker boli and when the experiment was driven at low applied forces. Conversely, the calculated width of the calculated velocity distribution narrows significantly when the system is driven, in the inertial regime, the velocity profiles became significantly narrower showing higher average values the calculated bolus velocity.

![Figure C.2: Examples of Doppler waveforms recorded during *in vitro* swallowing tests with a \( \eta = 0.03 \) Pa.s Newtonian bolus under an applied load of 4 N. Snapshots from the simultaneous video recordings show a good match with the characteristic features of the US spectra.](image)

The Doppler US spectra showed a peak within the duration of the swallowing sequence. The time delay between the peaks was comparable to the time taken for the roller to cross the field of view of the two probes. This suggests that the peak velocity measured
Table C.1: comparison between the peak velocities measured by Doppler US with those obtained through image analysis at the instant the roller transits in front of probe A or probe B.

<table>
<thead>
<tr>
<th>Viscosity</th>
<th>Load</th>
<th>Method</th>
<th>Measured velocity Position A</th>
<th>Measured velocity Position B</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 % w/w glycerol-water solution</td>
<td>2 N</td>
<td>US</td>
<td>0.36 m/s</td>
<td>0.41 m/s</td>
</tr>
<tr>
<td></td>
<td>4 N</td>
<td>Video</td>
<td>0.37 m/s</td>
<td>0.48 m/s</td>
</tr>
<tr>
<td></td>
<td>2 N</td>
<td>US</td>
<td>0.38 m/s</td>
<td>0.47 m/s</td>
</tr>
<tr>
<td></td>
<td>4 N</td>
<td>Video</td>
<td>0.56 m/s</td>
<td>0.67 m/s</td>
</tr>
<tr>
<td>99 % w/w glycerol-water solution</td>
<td>2 N</td>
<td>US</td>
<td>0.28 m/s</td>
<td>0.37 m/s</td>
</tr>
<tr>
<td></td>
<td>4 N</td>
<td>Video</td>
<td>0.24 m/s</td>
<td>0.3 m/s</td>
</tr>
<tr>
<td></td>
<td>2 N</td>
<td>US</td>
<td>0.28 m/s</td>
<td>0.38 m/s</td>
</tr>
<tr>
<td></td>
<td>4 N</td>
<td>Video</td>
<td>0.43 m/s</td>
<td>0.54 m/s</td>
</tr>
</tbody>
</table>

by the Doppler US is relatable to the roller velocity. This theory is well supported by cross comparing the position of the maxima with the corresponding snapshots of the experiments taken at the same time, as illustrated in Fig. C.2.

The absolute value of the bolus velocity measured by US was always found to be lower than the roller velocity measured by image analysis (Table C.1). This offset suggests that the overall flow pattern in the in vitro model significantly differs from the calibration conditions. Further work is thereby needed to better understand the internal velocity distribution in the bolus during swallowing.
Bibliography


[16] V. Mathieu, C. de Loubens, C. Thomas, M. Panouillé, A. Magnin, and I. Sou-
chon, “An experimental model to investigate the biomechanical determinants of
pharyngeal mucosa coating during swallowing,” *Journal of Biomechanics*, vol. 72,
pp. 144–151, apr 2018.

Reconstruction,” *IEEE/ASME Transactions on Mechatronics*, vol. 22, pp. 2102–
2110, oct 2017.

[18] A. Ho, R. Affoo, N. Rogus-Pulia, M. Nicosia, Y. Inamoto, E. Saitoh, S. Green,
and S. Fels, “Inferring the effects of saliva on liquid bolus flow using computer

ing as a clinically-inspired bolus rheometry technique,” *Measurement Science and


Cichero, K. Coutts, R. O. Dantas, J. Duivestein, L. Giosa, B. Hanson, P. Lam,
C. Lecko, C. Leigh, A. Nagy, A. M. Namasivayam, W. V. Nascimento, I. Odendaal,
C. H. Smith, and H. Wang, “The Influence of Food Texture and Liquid Consistency
Modification on Swallowing Physiology and Function: A Systematic Review,” *Dys-

[23] A. S. Burbidge, J. A. Y. Cichero, J. Engmann, and C. M. Steele, “‘A Day in the
Life of the Fluid Bolus ‘: An Introduction to Fluid Mechanics of the Oropharyngeal
Phase of Swallowing with Particular Focus on Dysphagia,” *Appl. Rheol*, vol. 26,
no. 64525, pp. 1–10, 2016.


[265] R. Gruetzmann and W. K., “Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from eudragit rs films by differential scanning


