An *in vitro* experiment to simulate how easy tablets are to swallow

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Abstract

The compliance of patients to solid oral dosage forms is heavily conditioned by the perceived ease of swallowing, especially in geriatric and pediatric populations. This study proposes a method, based on an *in vitro* model of the human oropharyngeal cavity, to quantitatively study the oral phase of human swallowing in presence of single or multiple tablets. The dynamics of swallowing was investigated varying the size and shape of model tablets and adjusting the applied force to the mechanical setup to simulate tongue pressure variations among individuals. The evolution of the velocity of the bolus, the oral transit time, and the relative position of the solid oral dosage form within the liquid bolus were measured quantitatively from high speed camera recordings. Whenever the solid dosage forms were big enough to interact with the walls of the *in vitro* oral cavity, a strong effect of the volume of the medication in respect of its swallowing velocity was observed, with elongated tablets flowing faster than spherical tablets. Conversely, 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. The oral phase of swallowing multiple tablets was also considered in the study by comparing different sizes while maintaining a constant total mass. The predictive power of different theories was also evaluated against the experimental results, providing a mechanistic interpretation of the dynamics of the *in vitro* oral phase of swallowing. 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.

Keywords: Bolus, Swallowing, Capsules, Tablets, Solid oral dosage forms, Oral cavity, Palate.

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1. Introduction

Deglutition is a fast and complex process, involving bolus transport from the oral cavity to the esophagus without compromising the functionality of the airway. From the clinical perspective, swallowing is usually divided into an oral phase, a pharyngeal phase and an esophageal phase that are subsequent but non-independent from one another (Leonard and Katherine, 2008). The swallowing reflex is first triggered by the motion of the tongue and is then accomplished by involuntary nerve impulses that provide protection of the airway. The bolus is safely guided through the glossopalatal junction (GPJ) to the upper esophageal sphincter (UES), where progressive peristaltic contractions lead it through the esophagus to the lower esophageal sphincter (LES). The overall process, starting from the first preparatory phase, in which the food bolus is chewed and wetted with saliva, until the latter esophageal phase, involves the motion of more than 40 pairs of intrinsic and extrinsic muscles (Groher, 2016). Swallowing is therefore a precisely timed process and the typical transit times for a liquid bolus to pass through the pharynx is of the order of 2 seconds, while it takes less than 6 seconds to reach the stomach (Brotherman et al., 2004). While reviewing the mechanisms controlling swallowing, the roles of the tongue and the laryngeal musculature, in ensuring the correct pressure driving force to allow for a safe swallow, have been highlighted (Groher, 2016). In particular, the importance of lingual coordination in the preparatory and oral phase of deglutition cannot be underestimated: the high mobility of the tongue, ensured by its set of extrinsic and intrinsic muscles, gives it several degrees of freedom to shape, hold and ultimately propel the bolus into the oropharynx.

Lack of tongue coordination can therefore lead to an alteration of the normal swallowing sequence that can compromise part of the time sequence of mechanisms held in place to protect the trachea from food and liquid penetration. Patients affected by swallowing disorders have to strictly control their eating habits, for instance by properly adjusting the texture of the food and drinks consumed. The correct oral drug therapy for these patients, for which comorbidities are common, has to deal with the low acceptance for classical solid oral dosage forms that could become trapped in the larynx folds, leading to a potential risk of choking and triggering local inflammations, esophagitis, and ulceration (FDA, 2013). Similar challenges in the oral administration route of solid formulations are interestingly found also in different age subsets, such as adolescents and pediatric populations for which the swallowing threshold has to be considered by both the practitioner and the caregiver (Liu et al., 2014; Stegemann et al., 2012; Mistry and Batchelor, 2017).

Although oral formulations 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 (FDA, 1997; Slavkova and Breitzkreutz, 2015), by virtue of the longer stability of the active pharmaceutical ingredient (API) and the higher standardization of the tableting process. 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 (Salmon et al., 2013; Stubbs et al., 2008; Fields et al., 2015; Manrique et al., 2014; Radhakrishnan, 2016).

Size and shape are deemed the most important reasons that limit acceptability of solid oral dosage forms (FDA, 2013; Schiele et al., 2015). Aspiration and choking during the oropharyngeal phase of deglutition become increasingly common with increasing the size of solid oral dosage forms (Kelly et al., 2010). 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 (Brotherman et al., 2004). It has also been shown that size is a major player in determining the esophageal transit time, smaller tablets flowing faster (Brotherman et al., 2004; Yamamoto et al., 2014; Liu et al., 2014). 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 (Ren et al., 1996). 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 behavioral performance of swallowing tablets 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 (Yamamoto et al., 2014). 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 (Hey et al., 1982). 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 (Stegemann et al., 2012).

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 (Hey et al., 1982; Schiele et al., 2015; Liu et al., 2014) and capsules are generally preferred to and tablets (Overgaard et al., 2001). 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 (Wilson et al., 2000). Behavioral tests seem however to suggest the preference of panelists 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 (Liu et al., 2014). 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 (Channer and Virjee,

1986) 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 (Kasashi *et al.*, 2011). In general, several reports have
95 proved tablet coating improves the acceptability in patients (Liu *et al.*, 2014). 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 (Hey *et al.*, 1982). The type of film coating can also greatly affect the tendency for solid oral formulations to adhere to the esophageal
100 epithelium as reported in several *in vitro* studies (Wilson *et al.*, 2000; Liu *et al.*, 2014). 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 flavored
105 gels containing glycerol to be applied to the back of the mouth prior to taking the medication (Diamond and Lavalley, 2010).

Finally, 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
110 pediatric and adolescent patients' body weight or age (Lopez *et al.*, 2015). Oral liquid formulations indeed constitute the most widely used oral forms in pediatrics (Liu *et al.*, 2014). Preliminary clinical studies showed a non-significant difference in acceptability in newborns between a 15% glucose syrup and a single mini-tablet of $d=2$ mm (Klingmann *et al.*, 2015). In the report however
115 the volume and rheology of the suspending liquid vehicles was not discussed in relaxation to that of the syrup. Another clinical research showed that small tablets ($d=3$ mm) can be easily swallowed by children from 2 to 6 years of age (Thomson *et al.*, 2009). A study involving 124 children aged 6 to 11 years, also demonstrated a high acceptability towards ingestion of a flat round tablet of $d=7$
120 mm, especially upon training (Meltzer *et al.*, 2006). Swallowing performance of multiple tablets in children has been subject of few studies, as reviewed by Mistry & Batchelor (Mistry and Batchelor, 2017). 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 (Mistry and Batchelor, 2017; Kluk *et al.*, 2015). Improvement
125 in children compliance when taking mini-tablets was achieved dispersing the tablets into flavored liquids jelly, as proposed by Jagani *et al.* (Jagani *et al.*, 2016) and Kluk *et al.* (Kluk *et al.*, 2015). However the same study, although confirming the high palability of mini-tablets, showed lower acceptability and a higher occurrence of chewing when the number of mini-tablets ($d=3$ mm) was
130 increased (Kluk *et al.*, 2015). Hayakawa *et al.* showed that the ease of swallowing of multiple tablets as a unit dose decreases with their number, 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 (Hayakawa *et al.*, 2016).

Based on all these premises, this study aims at presenting a novel method to
135 quantitatively assess the role of the physical properties of tablets, such as their size, shape and number, on the oral dynamics of swallowing. In order to lay the basis for a mechanistic understanding of these phenomena, the study considered

an *in vitro* model of the oral cavity which had been previously validated against
in vivo measurement while evaluating the effect of bolus rheology (Hayoun et al.,
 140 2015; Mowlavi et al., 2016).

2. Materials and methods

2.1. 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*
 145 *vitro* oral transit time and bolus velocity. The effect of size for different solid
 oral dosage forms was studied using calibrated polypropylene spheres (The Pre-
 cision 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 re-
 150 moved, 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 revolu-
 tion with volumes comparable to either a 8 mm or a 10 mm sphere (Table 1).
 To this extent, elongated particles were designed and 3D printed by UV curing
 155 (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 1). Density was measured by gas pycnometry (Accu-
 Pyc pycnometer 1330, Micrometrics Instrument Corp., Norcross, GA, USA) for
 160 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 (Kasashi et al., 2011). Similarly, the
 specific density of different liquid vehicles was tested *in vitro* without showing
 165 any significant variation in the bolus velocity (Mowlavi et al., 2016).

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
 170 that of the spherical beads ($\rho_S=850 \pm 50 \text{ kg m}^{-3}$). The volume of a d=8 mm
 sphere is comparable to a size 3 capsule and the volume of a d=10 mm sphere is
 almost double. A much bigger size 00 capsule was also considered as a limiting
 case, given that it is the maximum capsule size recommended by the Food and
 Drug Administration (FDA, 2013).

175 To assess the dynamics of the bolus in presence of multiple tablets, exper-
 iments 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 mm spherical tablet.

180 Glycerol (Sigma-Aldrich, CAS Number 56-81-5) was primarily used as liq-
 uid carrier, although a number of tests were also carried out using orange juice

Table 1: Geometry of the solid oral dosage forms used in the *in vitro* experiments to model swallowing of a single solid oral dosage form.

	Tablet shape	Characteristic size (d or L x H)	Tablet to bolus cross section	Volume	Weight
Effect of tablet size	Sphere	d=4.8 mm	15 %	0.06 mL	50 mg
	Sphere	d=6.4 mm	28 %	0.13 mL	120 mg
	Sphere	d=8 mm	44 %	0.27 mL	240 mg
	Sphere	d=10 mm	68 %	0.52 mL	460 mg
Effect of tablet shape: volume of 0.27 mL	Oblate spheroid	12.7 x 3.2 mm AR=0.25	28 %	0.27 mL	310 mg
	Prolate spheroid	10.5 x 6.9 mm AR=1.5	33 %	0.27 mL	310 mg
	Prolate spheroid	14.7 x 5.9 mm AR=2.5	24 %	0.27 mL	310 mg
	Prolate spheroid	18.4 x 5.3 mm AR=3.5	19 %	0.27 mL	310 mg
	Capsule size 3	15.5 x 5.8 mm AR=2.80	22 %	0.27 mL	280 mg
Effect of tablet shape: volume of 0.52 mL	Oblate spheroid	15.8 x 3.9 mm AR=0.25	42 %	0.52 mL	610 mg
	Prolate spheroid	13.1 x 8.7 mm AR=1.5	52 %	0.52 mL	610 mg
	Prolate spheroid	18.4 x 7.4 mm AR=2.5	37 %	0.52 mL	610 mg
	Prolate spheroid	23.1 x 6.6 mm AR=3.5	30 %	0.52 mL	610 mg
Effect of tablet shape	Capsule size 00	32.5 x 8.5 mm AR=2.80	49 %	0.95 mL	900 mg

Figure 1: From left to right different shapes of solid oral dosage forms considered: a) sphere b) oblate spheroid of AR=0.25, 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 the direction of swallowing.

from concentrate (Tesco Stores Ltd., Welwyn Garden City, Hertfordshire, UK). 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 (Hayoun et al., 2015) and comparable to *in vivo* values reported in literature (Alsanei, 2015; Kluk et al., 2015). All the experiments were performed at $22 \pm 1^\circ\text{C}$ and, at this temperature, the rheology of the two liquid vehicles was characterized in compliance with ISO standard 3219 with a controlled stress-controlled rheometer (Model UDS 200, Paar Physica, Germany). Both the glycerol solution and the orange juice exhibited a Newtonian behavior over the range of shear rates considered ($1 - 500 \text{ s}^{-1}$) and their viscosity was $\mu=1.05 \pm 0.05 \text{ Pa s}$ and $\mu=0.03 \pm 0.01 \text{ Pa s}$ respectively.

2.2. The *in vitro* swallowing model

The experimental setup used to study the oral phase of swallowing simplified the *in vivo* flow pattern considering a bi-dimensional projection in the sagittal plane. A thin, flat and freely deformable membrane, obtained by sealing together two polyethylene (PE) sheets, was stuck to the rigid surface mimicking the human palate, and used to constrain and hold the bolus. The propulsion of the bolus was instead generated by a roller, sealing anteriorly the membrane filled with the liquid and the solid oral dosage forms. The thin membrane and the roller provided together the two lingual functions of bolus containment and propulsion. The rigid roller was supported by a pivoting arm, attached to a revolving shaft driven through a set of hanging weights, as schematically depicted in Fig. 2. Upon triggering of the experiment, the roller moves, following the curved path, squeezing the liquid bolus through the PE membrane. A theoretical model, derived in Appendix A, was used to describe the dynamics of the *in vitro* setup and relate the velocity of the bolus tail to the rheology of the liquid carrier and the size and number of solid oral dosage forms. 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 *in vivo* data from the literature (Hayoun et al., 2015). Results from the same *in vitro* model were successfully validated against *in vivo* ultrasound measurements with thickened fluids (Mowlavi et al., 2016) and the swallowing simulator matched well the *in vivo* bolus dynamics when applying a force of 2 N.

2.3. Methods

The different solid oral dosage forms listed in Table 1 were first incorporated into the suspending liquid carrier and subsequently the bolus was pushed manually into the membrane through its anterior opening (Fig. 2). The initial position of the tablets in the bolus is essentially dictated by buoyancy as the

Figure 2: Schematics of the *in vitro* setup.

225 density of the model tablets 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
 230 (Fig. 1).

The roller movement was triggered by releasing a pin and lateral images
 were recorded using a fast camera (model ac1920-155 um, Basler, Germany) at
 150 frames per second. The dynamics of the bolus was measured from the video
 recordings: image processing tools were used to extract the instantaneous posi-
 tion of the roller (corresponding to the bolus tail), of the bolus center of mass,
 of the tablet center of mass, and to measure the bolus area. The instantaneous
 velocity of the roller was calculated from the time dependent roller positions by
 numerical differentiation. Results were compared to the theoretical predictions
 obtained considering the system dynamics and the drag force defined in Eq. A.8
 and A.9. Finally, 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 bo-
 lus tail and of the tablet, as schematically illustrated in Fig. 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.

$$\Delta\theta = \theta_{tablet} - \theta_{roller} \quad (1)$$

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.

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.

3.1. *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. 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 2.

From the snapshots in Fig. 3 and the data listed in Table 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 2 well compares with the typical values of oral transit times reported in literature when considering swallow of homogeneous thickened fluids. When considering administration of solid oral dosage forms, only a few references are found in literature: Kasashi *et al.* provide slightly longer oral transit times (1.14-2.23 s), based on videofluoroscopy assessment of capsule swallowing (Kasashi et al., 2011), while EMG recordings from Yamamoto *et al.* show a one-fold increase in the swallowing duration when taking a large d=9 mm biconvex tablet compared to the water control (Yamamoto et al., 2014), but a less significant 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.* (Hayoun et al., 2015).

The results obtained with different solid oral dosage forms shapes and sizes were compared to the theoretical predictions obtained considering the system

Figure 3: Screenshots of *in vitro* experiments using a 2 N load, a 1.05 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 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 1.05 Pa s Newtonian liquid carrier. Theoretical curves are obtained using Eq. A.8.

270 dynamics and the drag force defined in Eq. A.8 and illustrated in the charts with thin lines.

Variations in the driving load applied to the mechanical device strongly conditioned the bolus dynamics, as discussed by Hayoun *et al.* (Hayoun et al., 2015). The combined effect of applied force and size for spherical solid oral dosage forms is illustrated in Fig. 4 and Fig. 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. 4). By contrast, experiments at higher applied loads only showed the inertial regime.

280 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. 4 and 5.

290 Conversely, tests with significantly bigger model tablet 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. 4. Conversely, at the highest load (4 N), no significant effect of the tablet diameter was observed, although the *in vitro*

Figure 5: Roller velocity profiles for model spherical tablets of $d=6.4$, 8 and 10 mm at 2.7 and 4 N load and a 1.05 Pa s Newtonian liquid carrier. Theoretical curves are obtained using Eq. A.8.

Table 2: Characteristic oral transit times measured with the mechanical model when swallowing a single spherical tablets in a 1.05 Pa s liquid carrier (glycerol).

Applied force	Tablet diameter	Average bolus FO (SD n=3)	Average bolus TO (SD n=3)
2 N	4.8 mm	0.58 (0.03) s	0.73 (0.02) s
	6.4 mm	0.61 (0.04) s	0.78 (0.04) s
	8 mm	0.64 (0.03) s	0.82 (0.02) s
	10 mm	0.97 (0.17) s	1.27 (0.18) s
2.7 N	4.8 mm	0.45 (0.02) s	0.58 (0.01) s
	6.4 mm	0.46 (0.02) s	0.59 (0.01) s
	8 mm	0.47 (0.01) s	0.60 (0.01) s
	10 mm	0.53 (0.03) s	0.66 (0.03) s
4 N	4.8 mm	0.34 (0.02) s	0.43 (0.03) s
	6.4 mm	0.34 (0.02) s	0.43 (0.02) s
	8 mm	0.33 (0.02) s	0.43 (0.01) s
	10 mm	0.38 (0.01) s	0.48 (0.02) s

transit time of the biggest sphere was still slightly slower than the others (Fig. 5).

295 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 the other beads.
The theory used to describe the viscous dissipation (Eq. A.8) captured well the
transition between inertial to viscous regimes in absence of significant solid-solid
interaction between the tablet and the sidewalls (i.e. smaller solids). Conversely,
300 a noticeable under-prediction of drag force was observed for the largest sphere
at the lowest driving force where the friction between tablet and PE tube,
although mitigated by the lubricating effect of glycerol, played a significant role
in the swallowing dynamics (Fig. 4). This both outlines the limits of the simple
theoretical model assumed by the study and the relevance of using *in vitro*
305 experiments to evaluate the effect of different shapes of solid oral dosage forms.

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.* that commented on the different
flow rate between liquid and solid portions of the swallowed bolus. The angular
310 distance between the position of the roller and the position of the center 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 from the roller velocity profiles
315 of Fig. 4 and Fig. 6. Nonetheless the typical average profiles of $\Delta\theta$ reported,
as a function of the tablet size and applied load, in Fig. 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
320 order to limit the occurrence of liquid leaking before triggering the experiment.
At low applied force, Fig. 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
325 toward the tail of the bolus. This result somehow confirms that small objects
are less efficiently transported by peristalsis, as indicated in previous works in
that field (Fauci, 1992; Hung and Brown, 1976). 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
330 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, whilst no noticeable variations in relative position in
335 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 very large solids might limit the active volume of liquid available to wash
them out during the pharyngeal and esophageal phase of swallowing and also

340 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
 345 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 (Yamamoto et al., 2014).

The effect of shape was considered comparing results of spherical, oblate
 350 (flattened) and prolate (elongated) solid oral dosage forms (Fig. 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.8.

355 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 geometry was found to affect more significantly the dynamics of larger solid oral dosage forms (Fig. 6). The set of data
 360 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. 6). As the cross section of the tablet fell below 40% of that of the bolus, the effect of shape for spheroids became less
 365 and less important (Fig. 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. 6b). This consideration allows to highlight the
 370 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
 375 tablet shape became therefore marginal. This observation is in good agreement with the clustering of the velocity profiles observed in Fig. 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
 380 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.8 does not account for the length of the solid oral dosage form in the direction of swallowing, but only considers its cross sectional
 385 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 (Overgaard et al., 2001). 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 pediatric formulations, such as paracetamol suspensions (Batchelor et al., 2015). Thickened liquids and jelly have also been used to aid tablet and mini-tablet swallowing in geriatric and pediatric patients (Kluk et al., 2015; Mistry and Batchelor, 2017). 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 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 (Mowlavi et al., 2016). 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. 7, remarkably differ from those of Fig. 6b. The low viscous dissipation calculated in case of the concentrated juice predicts 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 3 with the velocity profiles Fig. 7 shows comparable transit times for the most elongated (AR 3.5) and the flat-test (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 identifying the cause for a similar behavior 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 TO times, as reported in Table 3.

Table 3: Characteristic oral transit times at 2 N load for different aspect ratios of spheroidal tablets of equivalent volume to a d=10 mm sphere in glycerol and concentrated orange juice.

Liquid vehicle	Tablet AR	Average bolus FO (SD n=3)	Average bolus TO (SD n=3)
Glycerol	0.25	0.67 (0.09) s	0.92 (0.05) s
	1.5	0.69 (0.06) s	0.95 (0.10) s
	3.5	0.65 (0.04) s	0.87 (0.04) s
Orange juice	0.25	0.31 (0.03) s	0.43 (0.02) s
	1.5	0.39 (0.09) s	1.59 (0.35) s
	3.5	0.31 (0.02) s	0.42 (0.02) s

Figure 6: Effect of tablet shape using a 2 N load in a 1.05 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.8.

Figure 7: Effect of the carrier liquid vehicle viscosity at 2 N load when considering *in vitro* swallowing of oblate (flattened) and prolate (elongated) spheroidal tablets of different aspect ratio (AR 0.25, 1.5 and 3.5). Theoretical curves are obtained using Eq. A.8 for a tablet diameter of 10 mm.

Figure 8: Angular distance between the bolus tail and the center of mass of spherical solid oral dosage forms using a 1.05 Pa s Newtonian liquid carrier at respectively a) 2 N, and b) 2.7 N applied force.

3.2. *In vitro* swallowing of multiple tablets

430 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
 435 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 considering the effect of pushing the volume fraction to $\phi=0.15$ v/V (920-960 mg/6 mL).

Figure 9: Effect of the particle size and applied force on the evolution of the angular velocity with time, at constant solid volume fraction ($\phi=0.08$ v/V) and using a 1.05 Pa s Netwonian liquid carrier. Theoretical angular velocity profiles obtained from Eq. A.9.

Average velocity profiles at $\phi=0.08$ v/V, obtained from three repetitions for the different diameters and applied forces, are plotted in Fig. 9. The correspond-
 440 ing characteristic transit times reported in Table 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
 445 ϕ 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. 9).

Increasing the suspended particle volume fraction to $\phi=0.15$ v/V affected
 450 more significantly the flow of smaller tablets and accentuated the viscous dissipation leading to a lower steady state velocity and a faster onset of the steady

Table 4: Characteristic oral transit times when swallowing a fixed dose of spherical tablets of different diameters in a 1.05 Pa s Newtonian liquid carrier.

Applied load	Tablet diameter	Number of tablets	Average bolus FO (SD n=3)	Average bolus TO (SD n=3)
2 N	4.8 mm	9	0.69 (0.04) s	0.91 (0.04) s
	6.4 mm	4	0.76 (0.07) s	1.01 (0.08) s
	8 mm	2	0.75 (0.08) s	0.99 (0.09) s
	10 mm	1	0.97 (0.17) s	1.27 (0.18) s
2.7 N	4.8 mm	9	0.48 (0.02) s	0.68 (0.03) s
	6.4 mm	4	0.54 (0.04) s	0.73 (0.06) s
	8 mm	2	0.50 (0.02) s	0.68 (0.03) s
	10 mm	1	0.53 (0.03) s	0.66 (0.03) s
4 N	4.8 mm	9	0.35 (0.01) s	0.47 (0.02) s
	6.4 mm	4	0.36 (0.02) s	0.47 (0.03) s
	8 mm	2	0.45 (0.02) s	0.65 (0.03) s
	10 mm	1	0.38 (0.01) s	0.48 (0.02) s

state. 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 vivo* when swallowing multiple tablets, indicating the need for effortful swallows (Yamamoto et al., 2014).

Figure 10: Screenshots from the *in vitro* experiment using a 2 N load and multiple spherical tablets ($d=4.8$ mm, $\phi=0.08$ v/V) in a 1.05 Pa s Newtonian liquid carrier. Tablets moving towards the bolus tail are circled.

The increase in apparent liquid carrier viscosity predicted through the Krieger-Dougherty model (Eq. A.9) led to a slower theoretical dynamics, as can be appreciated comparing the results presented in Fig. 9 with those of Fig. 4 and Fig. 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.

465 Image analysis revealed that when the size of the solid oral dosage was reduced, these moved towards the tail of the bolus. This effect is qualitatively illustrated in Fig. 10 where clustering of suspended solids in proximity of the roller can be observed. The buildup of solids close to the roller resulted in a concentration gradient that limits the applicability of Eq. A.9, justifying the gap
470 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
475 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
480 amount of mini-tablets, as already demonstrated by Kluk *et al.* (Kluk et al., 2015). 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 not able to swallow 10 mini-tablets with a single sip of water (Hayakawa et al., 2016). The result led the authors to conclude that
485 there is an optimal number of tablets above which the perceived attribute of ease of swallow with respect to conventional tablets deteriorates (Hayakawa et al., 2016). 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.

490 With respect to tablet size, *in vivo* data from literature does not currently allow to complement the *in vitro* observations as comparable videofluoroscopy swallowing studies aiming at describing the dynamics of tablet swallowing are scarce. In one of these studies Kasashi *et al.* compared the effect of size for two different gelatin capsules (size 1 and size 4) and density ($\rho_S=690-1370\text{kg m}^{-3}$)
495 together with the patients' head position during swallowing (Kasashi et al., 2011). 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
500 preferences in patients (Kasashi et al., 2011). Numerous other sensory and hedonic reports have shown how the attribute of ease of swallowing for single tablets consistently increases, decreasing the size of the solid oral dosage forms (Liu et al., 2014). This observation is confirmed by the present experimental study that shows the negligible impact of small tablets on the oral swallowing
505 dynamics (Fig. 4 and Fig. 5).

Sensory trials with mini-tablets ($d<4$ mm) showed a higher acceptability in children and newborns than other conventional types of oral delivery medications (i.e. syrup) (Liu et al., 2014; Klingmann et al., 2015; Mistry and Batchelor, 2017). This conclusion should however be put in relation to the viscosity of the

510 different liquid vehicles used for tablet administration as it highly conditions
the palatability and grittiness perception (Liu et al., 2014; Lopez et al., 2016).
Therefore, examination of oral transit of similar solid oral dosage forms against
liquid oral medicines would greatly benefit from a solid *in vitro* testing base.

515 An interesting future direction is to extend the *in vitro* experiment to con-
sider also the pharyngeal and esophageal phases of swallowing which would
enable to assess more holistically the impact of tablet formulation on all stages.

Finally, modeling the complex physics of salivary lubrication and wall inter-
action although outside the aim of the present study could constitute an impor-
tant development in view of a more comprehensive description of wall friction
520 and adhesion with the oral mucosa, following notable examples of *in vitro* works
dealing with tablet adhesion to the esophagus (Cook and Khutoryanskiy, 2015).

4. Conclusions

This study investigated the effect of the presence of a single or multiple solid
oral dosage forms in a peristaltic flow relevant for the oral phase of swallowing, to
525 improve the understanding of the mechanical phenomena governing swallowing
of tablets and capsules. The effect of tablet size, shape, volume fraction, and
applied force were studied in a controlled and consistent way in an *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
530 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.

535 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*
540 *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 dif-
ferent aspect ratios but identical volumes to those of two calibrated spherical
545 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 ap-
preciable for the largest tablets and under low roller applied force, but it is
accentuated with low viscosity liquid carriers. In the case of single tablets, the
simple theoretical model proposed gives reasonably good predictions for small
550 particles, but fails to capture the complex phenomena occurring when consid-
ering 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. Given the pharmaceutical interest for new solid oral formulations, targeting the special needs of infants and elderly, the *in vitro* approach presented in this study could help screening novel formulations and help designing more targeted *in vivo* studies, before running *in vivo* investigations.

Appendix A. Derivation of the theory

The flow in the esophagus has previously been modeled considering a peristaltic flow in a duct (Brasseur, 1987; Li et al., 1990). In this type of geometry the progressive contraction and relaxation of the sphincters provides the pressure driving force for bolus transport. In the literature, the effect of peristaltic wave shape, type of pumped fluid and presence of single or multiple suspended solids have been investigated showing an increase in particle velocity and displacement with particle diameter (Fauci, 1992; Hung and Brown, 1976). Although effective in modeling 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 simple model was nonetheless developed to evaluate the effect of viscosity during the *in vitro* swallowing of liquids without any suspended solid (Mowlavi et al., 2016). This mechanistic theory here synthetically considers the dynamics of the roller and of the bolus, driven by the external applied load and slowed down by the inertia and by the viscous dissipation in the bolus.

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. A.1). Linear velocities can be put in relation to the angular velocity of the pulley θ , knowing the radial distances from the center of rotation r_A and r_P (see Fig.2).

$$K = \frac{1}{2}(m_B v_B^2 + I_B \dot{\theta}^2) + \frac{1}{2}M v_M^2 + \frac{1}{2}I \dot{\theta}^2 \quad (\text{A.1})$$

The overall potential energy of the system U is calculated from the displacement of the hanging mass and the vertical position of the bolus center of mass (Eq. A.2).

$$U = M g \theta r_P + m_B g r_A \sin(\theta) \quad (\text{A.2})$$

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 μ and the geometry of the bolus. The equation of motion of the mechanical system, characterized by the single degree of freedom of angular rotation θ , is obtained from the Lagrange equations of dynamics, where Q is the generalized force (Eq. A.4).

$$\frac{d}{dt} \left(\frac{d}{d\dot{\theta}} (K - U) \right) - \frac{d}{d\theta} (K - U) = Q \quad (\text{A.3})$$

$$Q = \mathbf{F}_d \cdot \frac{\partial \mathbf{x}}{\partial \theta} \quad (\text{A.4})$$

Substituting for K and U and after further rearrangement, an explicit relation to obtain the roller angular acceleration $\ddot{\theta}$ from geometrical and inertial properties is finally obtained.

$$\ddot{\theta} = \frac{-F_d r_A + M g r_P + m g r_A \cos(\theta)}{I + I_B + m_B r_A^2 + M r_P^2} \quad (\text{A.5})$$

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 bolus swallowing is driven by the applied force and the inertia of the system, hence a constant angular acceleration is predicted. 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 of 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 $\gamma > 1$ to I in Eq. A.5. Similarly a constant F_{min} was used to correct for the friction of the roller, as a minimum applied weight to the drive pulley of approx. 0.4 N was needed for the roller to start moving. In light of these latter observations the final form of Eq. A.5 was approximated by the following (Eq. A.6).

$$\ddot{\theta} = \frac{-F_d r_A + (M g - F_{min}) r_P + m_B g r_A \cos(\theta)}{\gamma I + I_B + m_B r_A^2 + M r_P^2} \quad (\text{A.6})$$

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 center of rotation $r_A=47$ mm (Mowlavi et al., 2016). A similar linear dependency holds at relatively low swallowing velocities, as comprehensively investigated by Mowlavi *et al.* (Mowlavi et al., 2016). 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 moving with an average velocity equal to the roller velocity ($\dot{\theta} r_A$). 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 μ , 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.

$$F_d = \beta 8\pi \mu L \dot{\theta} r_A \quad (\text{A.7})$$

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 (Bungay and Brenner, 1973), while Wang and Skalak (Wang and Skalak, 1969) 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 (Chen and Skalak, 1970) and more recently comprehensively described by Pozrikidis and Davis (Pozrikidis and Davis, 2013). 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 (Charles, 1963). Following the latter approach, a simple mathematical model considered the annular flow in the gap between the flowing solid (of cross sectional radius $R_i = d/2$) and the pipe radius R_e . 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 $\dot{\theta} r_A$, while a no-slip condition was applied to the external shell (i.e. the plastic membrane in which the bolus was contained).

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 of the ratio of radii $k = R_i/R_e$ of the suspended solid and the pipe (Ellis, 1964). 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.

$$F_d = (1 - k^4)^{-1} \beta 8\pi \mu L \dot{\theta} r_A \quad (\text{A.8})$$

Eq. A.8 is consistent with the theory presented by Hayoun *et al.* when the cross sectional size of the tablet vanishes.

Finally, the flow of multiple suspended solids of volume fraction ϕ was modeled considering a correction term to the viscosity of the liquid carrier (μ) obtained from the Krieger-Dougherty model for spherical particles (Eq. A.9).

$$F_d = \beta 8\pi \mu \left(1 - \frac{\phi}{\phi_m}\right)^{-2.5 \phi_m} L \dot{\theta} r_A \quad (\text{A.9})$$

The solid volume fraction ϕ_m was considered that of a random close packing of particles ($\phi_m=0.64$) (Hiemenz and Rajgopalan, 1997).

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