Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Rheological properties of thickening products that provide the therapeutic effect on safety and efficacy of swallow in patients with post-stroke oropharyngeal dysphagia

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ARTICLE INFO

Article history:
Received 9 May 2024
Received in revised form 8 July 2024
Accepted 28 August 2024

Keywords:
Rheology
Thickening products
Shear viscosity
Extensional deformation
Texture
Maximal force
Adhesiveness
Cohesiveness
Dysphagia

ABSTRACT

Introduction: Fluid thickening improves safety of swallow in patients with oropharyngeal dysphagia due to shear, extensional and/or textural properties. We aimed to assess the effect of each of these properties of thickening products on post-stroke patients with oropharyngeal dysphagia. **Methods**: We studied 4 commercial thickening products: A, modified starch; B and C, xanthan gum, and D, a mixture of the 2 and assessed a) shear viscosity at 25 ºC and 50 and 300 s^{-1} before and after oral incubation, b) extensional deformation by the time to break up diameter, and c) maximal force, adhesiveness and cohesiveness with a texturometer. Results were correlated with videofluoroscopic studies assessing the effect of these thickening products on 267 patients with post-stroke oropharyngeal dysphagia. **Results**: 1) Oral incubation reduced shear viscosity by over 90% for thickening product A and by 19%–35% for B, C, and D. All products presented shear thinning (50%–76%) in the pharynx. 2) Safety of swallow was strongly increased in a shear viscosity-dependent manner ($P < 0.000\ 1$) and, moderately, by increasing maximal force ($P < 0.000\ 1$). Residue was increased at different shear viscosity levels ($P < 0.05$). 3) break-up diameter varied greatly between thickening products irrespective of safety/efficacy of swallow; and d) adhesiveness and cohesiveness did not affect safety or efficacy of swallow. **Conclusion**: Shear viscosity improved safety of swallow in a dose-dependent manner with all thickening products in post-stroke patients with oropharyngeal dysphagia and increased oropharyngeal residue. It was greatly affected by oral amylase in modified starch thickening products. Maximal force also moderately increased safety. In contrast, neither extensional deformation nor adhesiveness or cohesiveness presented any relationship with the therapeutic effect of thickening products in post-stroke patients with oropharyngeal dysphagia.

1. Introduction

Hydrocolloids are widely used as thickening products (TP) to manage patients with oropharyngeal dysphagia (OD) by increasing shear viscosity (ShV) of the fluid which they are mixed with[1]. TP can be divided into 3 categories according to the main thickening agent composition: modified starch (MS), xanthan gum (XG) , and mixtures (Mx)[2]. MS is composed by a number of molecules arranged in chains linked by *O*-glycosidic bonds (α-1→4) which are susceptible to be broken by salivary amylase. In addition, MS increases the viscosity of the fluid which they are mixed with by absorbing water in MS granules and swelling which confers instability over time and causes a progressive increase of viscosity. In contrast, XG forms a 3D structure when mixed with water forming β-1→4 bonds which are more protected and less affected by salivary amylase. Mx can vary the mode of action according to the quantitative composition of MS and XG[3-4].

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Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2024.9250437

ShV is a rheological parameter defined as the viscosity dependent on the shear, a behaviour which belongs to non-Newtonian fluids. When ShV is submitted to an increment in the shear rate, its value can increase (shear thickening) or decrease (shear thinning). This last behaviour is the most common for alimentary fluids and TP and acquires an important role during deglutition where shear rates vary according to bolus velocity[4-5] and therefore, the therapeutic effect of TP can be reduced.

For patients suffering from OD, 2 major shear rates values during deglutition have been established to assess the effect of TP[4]: 50 s^{-1} during the oral phase[6-7] and 300 s^{-1} in the mesopharynx[5]. There is another relevant factor in the oral phase, which needs to be considered when swallowing: the effect of oral incubation of the TP with α-salivary amylase enzyme. This oral enzyme helps digestion and formation of the bolus. However, to perform its action, bonds between TP and fluids can be broken and thus, viscosity reduced. As ShV has been closely related to the therapeutic effect of TP, the effect of oral amylase and pharyngeal shear thinning must be studied. Other parameters such as extensional viscosity also seem to have an impact on bolus flow rate when swallowing, caused by changes in elongational forces and flow directions associated with the transfer of the bolus from the oral to the pharyngeal phase[3]. Nishinari et al.[8] described the need to analyse the extensional properties of TP and their correlation with the swallowing process. It is presumed that extensional properties are linked to the bolus' maximal cohesiveness, which might affect the risk to suffer an aspiration in patients with OD if its value is low due to its internal fragmentation[3,8-10]. However, few clinical studies have determined the real impact of extensional forces on the bolus when being swallowed[8].

Nowadays, there exist several techniques to accurately and scientifically explore and assess both shear and extensional viscosity[8]. Using a rheometer or viscometer, ShV can be determined by measuring the change of velocity of a fluid when passing between 2 adjacent layers. A protocol to assess ShV of TP taking into account the main parameters affecting viscosity during oral and pharyngeal phases of swallow has been already proposed by our group for the management of patients with OD[11]. In contrast, to assess extensional viscosity, the surface tension must be determined. The formula relating apparent extensional viscosity and superficial tension was developed by McKinley and Tripathi and explained elsewhere[12]. Surface tension of the solutions can be assessed by a tensiometer and then the extensional deformation (ED) is calculated with a capillary breakup extensional rheometer (CaBER). Briefly, a small quantity of the TP is placed between 2 close-together plates. Then the equipment is adjusted to a greater distance and time and the upper plate separates from the lower plate, which remains fixed. This movement creates a TP filament, which gets thinner over time until it breaks. A laser passing through the filament calculates the decrease in diameter over time. The time to breakup diameter provides information on the extensional properties of the fluid and is directly related to ED. Differences in ShV or ED calculations depend on the deformation applied: while shear is assessed by 2 parallel layers (and the fluid passes over), the ED is caused by an uniaxial extensional flow[3,8].

Regarding textural properties such as maximum force, adhesiveness and cohesiveness, these are usually ignored for TP and tend to be characterised for solid texture modified foods[13-14]. However, these factors might have an impact on swallowing safety of patients suffering from dysphagia[3]. Maximal force is identified as the force needed to break the structure of the product. Adhesiveness has been described by Rahemm et al.[15] as the effort needed to remove food from the palate and it can be easily calculated with a texturometer[13]. It is measured by applying a compression and determining the negative area under the curve created once the probe is back to its initial position. In contrast, cohesiveness is defined as the intermolecular coherence to the fractional breakup[3,16] and has been strongly related to the maximum ED[17]. The texture profile analysis (TPA) is a textural test including double compression which is widely used for solids but less used for fluids.

By analyzing the therapeutic effect of TP and their rheological characterization, we will better understand TP behaviour when swallowed, adapt them better to the OD patient's needs and develop safer products. The main aims of this study are: 1) to assess the rheological properties ShV, ED and texture characteristics (maximal force, adhesiveness and cohesiveness) for different TP using the International System (SI) of units; 2) to determine the relationship between these rheological properties and the therapeutic effect including safety and efficacy of swallow in PSOD, and 3) to determine the relationship between rheological and textural properties.

2. Material and methods

2.1 Study design

This was an observational, single-centre study including 1) *in vitro* and *ex vivo* characterization of ShV, extensional deformation, maximal force, adhesiveness and cohesiveness of 4 different commercially available TP in the Spanish market; and 2) analysis of the therapeutic effect reported by previous controlled trials that used videofluoroscopy to assess the therapeutic effect of these TP on safety and efficacy of swallow in patients with PSOD.

2.1.1 Clinical trials

Results from three CT assessing the therapeutic effect of different viscosity levels of TP with VFS were selected to review the therapeutic effect of TP[18-20]. All CT were conducted in our healthcare centre by our research group using similar methodologies and experimental design to avoid any bias in the assessment of the therapeutic effect of TP. Only the results of patients with PSOD from these studies were included in the present one to analyse the effect of TP on this phenotype of patients and avoid any potential effect from the different pathophysiologies (studies approved by the ethics committee from Consorci Sanitari del Maresme under codes 17/11, 57/15 and 41/15).

2.1.2 TP

A total of 4 commercially available TP previously assessed in CT on patients with PSOD were selected: Resource Thicken Up (A; Nestle S.A., Barcelona, Spain), Resource Thicken Up Clear (B; Nestle S.A., Barcelona, Spain); Nutilis Clear (C; Nutricia N.V., Zoetermeer, The Netherlands), and Fresubin Thickener Clear

(D; Fresenius Kabi GmbH, Bad Homburg, Deutschland). Qualitative TP composition is shown in Table 1. TP were divided in 3 categories according to their main component (MS, XG, and Mx). Dose (grams and solvent) for each viscosity level used for the VFS performed in the CT are presented in Table 1. TP were prepared following the instructions on the label of each brand. Product B solutions were prepared 3-h prior to the analysis as indicated.

2.2 Patients

Poststroke patient data included in the three previous CT were obtained to assess the therapeutic effect of TP. During admission, all the patients were clinica lly diagnosed with OD with the V-VST as previously described in our articles[21]. Following discharge, they were examined with VFS during the follow up at the beginning of the chronic phase, as also previously described by our team[22]. Only the results of patients with chronic PSOD from these studies were included in the present one to analyze the effect of TP on this phenotype of patients. Demographics and stroke characteristics of the population selected for each CT are detailed in Table 2. Number of participants included, gender, Barthel index, time from stroke and type of stroke (ischemic and hemorrhagic) were recorded. The main inclusion criteria for the participants in the study were patients in the chronic post-stroke phase, no alteration in consciousness, positive diagnosis of OD by VFS and written informed consent.

The impact of oral salivary amylase on ShV was determined in a separate group of 3 healthy young volunteers with no associated comorbidities.

2.3 Rheological characterisation

2.3.1 Shear viscosity

To assess ShV the Haake Viscotester®550 (Thermo Fisher Scientific, Haake Viscotester®550, Germany) was used. Briefly, the bolus to be measured (10 mL) is placed in the sensor system's gap. The bolus exerts a resistance to the rotational movement produced by the rotor and results are analysed by the Software RheoWin (Job Manager® and Data Manager®). A total of 2 sensory systems were used depending on the viscosity of the bolus tested: for low viscosities (50 to 300 mPa·s), MV1 (gap: 0.96 mm) was selected, while for high viscosities (> 300 mPa·s), SV1 was used (gap: 1.45 mm). Temperature was controlled at 25 ºC by the Thermo Scientific system which consists of 50% water, 50% deionized water and anti-algae.

The impact of oral salivary amylase on ShV was determined in a group of 3 healthy young volunteers. Viscosity was assessed after an oral incubation of 30 s in a shear rate range from 0 to 1 000 s^{-1}.

Table 1
TP group, composition, and target viscosity levels selected from the clinical trials.

TP	Qualitative composition (Classification)	CT Viscosity levels	Grams	Solvent (mL)	Bolus volume (mL)
A	Modified starch (MS)	Thin liquid	0	100 mL (1:1, *V/V*) Mineral water:Gastrografin	5
		Nectar	3.5		5
		Pudding	8		5
B	Maltodextrine Xanthan gum (XG)	Thin liquid	0	100 mL (1:1, *V/V*) Mineral water:Gastrografin	5
		Nectar	2.4		5
		Extreme spoon thick	5.4		5
C	Maltodextrine Xanthan gum Guar gum (XG)	Thin liquid	0	50 mL (1:1, *V/V*) Mineral water:Omnipaque	10
		250 mPa·s	0.85		10
		800 mPa·s	2.31		10
		2 000 mPa·s	5.61		10
D	Modified starch Xanthan gum Maltodextrine (Mx)	Thin liquid	0	50 mL (1:1, *V/V*) Mineral water:Omnipaque	5
		100 mPa·s	0.7		5
		1 000 mPa·s	2.3		5
		2 000 mPa·s	4.2		5

Note: Doses are shown as the grams and solvent used to prepare each videofluoroscopy viscosity level and the volume of each bolus.

Table 2
Population obtained from each CT assessing the therapeutic effect of TP.

TP		A	B	C	D	Total
Number participants		46	76	114	31	267
Gender (% men)		65	57	54.4	89	66.40
Age (mean ± SD)		75.63 ± 8.40	74.83 ± 10.86	76.70 ± 8.9	79.42 ± 1.36	76.65 ± 2.00
Time from stroke (months)		7.45 ± 8.97	27.32 ± 72.04	431.7 ± 1031.9	–	16.39 ± 10.08
Barthel index		83.26 ± 22.64	72.92 ± 26.32	–	74.83 ± 5.31	77.34 ± 5.15
Type of stroke (%)	Ischemic	42.35	34.20	78.1	–	51.55
	Hemorrhagic	5.88	43.42	11.4	–	20.23
	Unknown	5.88	22.37	10.5	–	12.92

Note: – represents not reported.

Reduction of viscosity in the oral cavity caused by the effect of α-salivary amylase was calculated as shown in Eq.1.

$$\text{Reduction of viscosity (\%)} = \frac{\text{Viscosity at 50 s}^{-1} - \text{Viscosity at 50 s}^{-1}\text{ after oral incubation}}{\text{Viscosity at 50 s}^{-1}} \times 100 \quad (1)$$

To assess the effect of shear rate, viscosity at 50 and 300 s^{-1} at 25 ºC were interpolated from the regression line obtained from the shear rate range from 1 to 1 000 s^{-1}. Viscosity flow curves were fitted to the Ostwald-de Waele model or Power Law (Eq. 2) and the index flow (n) and consistency (K) were obtained for each viscosity level to assess the viscosity (η) behaviour of the TP at the shear rate studied (γ). The index flow describes the relationship between viscosity and shear rate and divides fluid behaviour into pseudoplastic (< 1; shear thinning) or dilatant (> 1; shear thickening). The consistency factor indicates the fluid viscosity at the specific shear rate of 1.

$$\text{Lg } \eta = (n-1) \text{ lg } \gamma' + K \quad (2)$$

Viscosity flow curves are represented by a Cartesian coordinate system where the dependent variable is the shear rate range represented in s^{-1} and the independent variable shows the relative viscosity in mPa.

Shear rate effect was calculated by the variations in apparent viscosity between the value at 50 s^{-1} and at 300 s^{-1} (Eq. 3).

$$\text{Shear rate (\%)} = \frac{\text{Viscosity at 50 s}^{-1} - \text{Viscosity at 300 s}^{-1}}{\text{Viscosity at 50 s}^{-1}} \times 100 \quad (3)$$

2.3.2 Extensional deformation

Extensional properties of each TP were assessed with a capillary breakup extensional rheometer (HAAKE CaBER, Thermo Fisher Scientific, Waltham, Massachusetts, USA). Briefly, a small quantity of sample (< 0.2 mL) is placed between two circular plates. The upper plate is separated from the under plate forming a fluid filament. When the stretching finishes, the fluid at the mid-point of the filament is submitted to extensional strain rate according to the extensional fluid properties. A laser monitors the filament diameter and the time at which the filament breaks (filament diameter = 0). The time to break up diameter (BUD) was assessed for each viscosity level for all the TP selected. The parameters selected to carry out the ED analysis are shown in Table 3. Each dose of TP was produced in triplicate.

Table 3
Parameters selected for the ED analysis.

Parameter	Value
Temperature (ºC)	25
Initial diameter (mm)	6
Initial height (mm)	1.50
Final height (mm)	12.15

2.3.3 Textural characterization

A TPA was performed for each dose of TP to assess the maximal force, adhesiveness and cohesiveness at each viscosity level. TPA corresponds to two extrusion forces performed by a Texturometer TA.XTplus (Stable Micro Systems, Haslemere, UK). Each sample was tested in triplicate, giving a plot of force *vs*. time (Texture Expert for Windows version. 1.05 software, Stable Micro Systems, Haslemere, UK). Maximal force was determined by the 1st peak force obtained. Adhesiveness was extracted from the mean assessed by the negative value of the area under the curve (–AUC). Cohesiveness was calculated by area 2/area 1. Table 4 presents the texturometer settings for the TPA of each solution. Calibration of the texturometer was performed with 2 kg. A quantity of 30 g of each TP solution was used to perform the analysis.

Table 4
Probe and texturometer settings.

Mode	TPA
Sample volume	30 g
Option	Return to start
Pre-test speed	1 mm/s
Test speed	1 mm/s
Post-test speed	5 mm/s
Distance	5 mm
Trigger type	Auto 5 g
Tare mode	Auto
Data acquisition rate	200 pps

2.4 Assessment with VFS of the therapeutic effect of TP on patients with PSOD

Therapeutic effect was determined by the revision of the 3 CTs mentioned with the TPs described in Table 1. CTs were performed with VFS, the gold standard for analysing swallowing function. Prevalence of safe swallows was determined by the Penetration Aspiration Scale and efficacy of swallow was determined by the prevalence of oral and pharyngeal residue. Time to laryngeal vestibule closure (LVC) was selected as the critical oral swallowing response (OSR) event to detect the risk of aspirations. Kinematics of swallowing was analysed with the bolus velocity (m/s) at each viscosity level selected. The methods to assess the main VFS signs of impaired safety and efficacy of swallow and the metrics of timing and bolus kinematics during the swallow response in post-stroke patients with OD have been previously described by our group[21-23].

2.5 Statistical analysis

Data on the safety of swallowing were handled as binary by dividing the patients in 2 categories: patients who could swallow safely (penetration aspiration scale (PAS) 1–2) *vs*. patients who could not (PAS 3–8). The efficacy of swallowing was also handled as binary data (presence or absence). Dose-responses curves were performed with the prevalence of PAS 1–2 and residue (oral or pharyngeal) *vs*. each viscosity level presented in logarithm.

Statistical tests were conducted with a significance level of 5%. All confidence intervals are presented two-sided with a confidence level of 95%. A resultant probability value of $P < 0.05$ was judged as statistically significant. Qualitative data has been used to describe the decrease in viscosity through salivary amylase or shear rate and is presented in percentages as absolute frequencies. Continuous data is presented as mean ± standard deviation (SD).

The correlation between the prevalence of safe or efficacy of swallows with ShV, extensional deformation, maximal force, adhesiveness and cohesiveness and the correlation between rheological parameters compared with each other were determined with the Spearman correlation coefficient. To establish the type of relationship, a linear and a dose-response test was applied between variables.

2.6 Ethics approval

All procedures performed in this study involving participants were conducted according to the Declaration of Helsinki. The study was approved by the ethics committee of Consorci Sanitari del Maresme under code 12/19.

3. Results

3.1 Rheological characterisation

3.1.1 Shear viscosity

Viscosity for solutions prepared with thin liquid at 50 s^{-1} were: (2.20 ± 0.06) and (1.66 ± 0.10) mPa·s for solutions with Gastrografin and Omnipaque, respectively. TP A presented a viscosity at 50 s^{-1} of (116 ± 6.21) mPa·s for the descriptor "nectar" viscosity and incremented until (3 375.06 ± 302.03) mPa·s for the descriptor "pudding" viscosity levels. In contrast, viscosity levels for XG TPs (B and C) ranged between (229.25 ± 8.28) and (2 264.73 ± 80.83) mPa·s. TP D (Mx) presented a viscosity of (281.90 ± 28.41) mPa·s for the lowest viscosity level and (3 256.80 ± 148.33) mPa·s for the highest. Results on ShV levels and descriptors assessed in the clinical trials are presented in Table 5.

Oral incubation of TP in healthy volunteers caused a reduction of viscosity at 50 s^{-1} above 90% for TP A. For xanthan-gum-based TP (TP B and C) maximum effect was a reduction of 19% and for TP D the effect ranged between 19%–35% (Table S1). Shear thinning

Table 5
Rheological characterisation of ShV.

TP	Viscosity descriptors	Viscosity at 50 s^{-1} (mPa·s)	Viscosity post oral incubation 50 s^{-1}	Viscosity at 300 s^{-1} (mPa·s)
A	Nectar	116.33 ± 6.21	7.59 ± 1.14	57.95 ± 13.60
	Spoon thick	3 375.06 ± 302.03	3.96 ± 3.50	1 268.41 ± 57.17
B	Nectar	294.33 ± 18.00	254.67 ± 63.65	92.00 ± 1.93
	Extreme spoon thick	1 259.38 ± 4.01	1 015.21 ± 63.55	313.92 ± 5.63
C	250 mPa·s	229.25 ± 8.28	197.13 ± 26.14	55.66 ± 1.54
	800 mPa·s	848.35 ± 59.90	749.36 ± 75.91	204.11 ± 12.98
	2 000 mPa·s	2 264.73 ± 80.83	2 391.46 ± 83.43	582.17 ± 20.25
D	250 mPa·s	281.90 ± 28.41	192.98 ± 31.78	79.35 ± 7.73
	1 000 mPa·s	1 449.87 ± 56.00	1 181.40 ± 35.48	346.60 ± 16.26
	2 000 mPa·s	3 256.80 ± 148.33	2 102.75 ± 122.01	801.21 ± 28.23

Note: Viscosity at 50 s-1 prior and after oral incubation and 300 s^{-1} are presented for each TP.

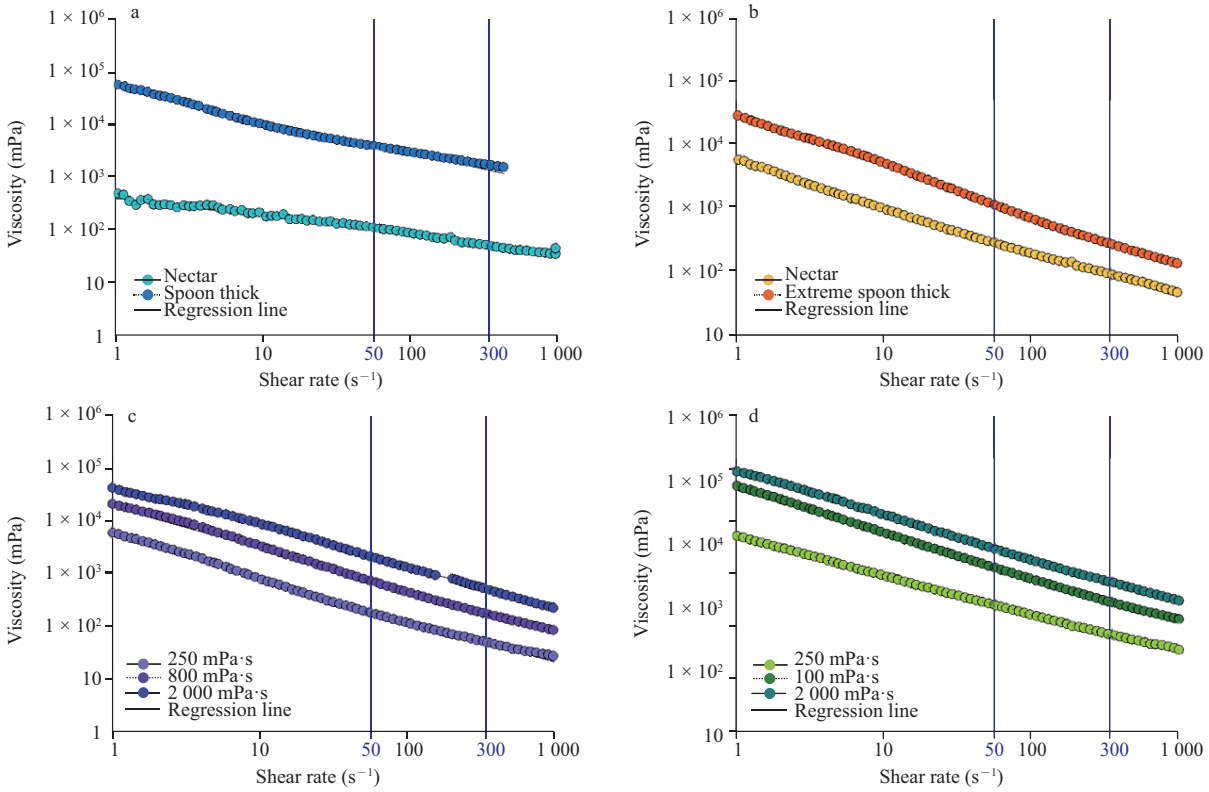

Fig. 1 Viscosity flow curves for each TP. (a) TP A; (b) TP B; (c) TP C; (d) TP D. Note strong reduction caused by salivary amylase in product A (modified starch-based TP).

effect ranged between 50%–62% for TP A and between 69%–76% for products with XG (TP B, C and D) (Fig. S1).

Flow index confirmed the shear-thinning non-Newtonian fluid behaviour of all the TP selected for the study (Table 6, Fig. 1). Highest values were obtained for product A (0.66–0.38). Flow index for products B, C and D ranged between 0.18 and 0.29 confirming a Non-Newtonian behaviour. Consistency index ranged between 2.60 and 4.90 Pa·s^n according to the ShV achieved (Table 6).

Table 6
Flow index and consistency index of each TP viscosity level assessed.

	Viscosity at 50 s^{-1}		
TP	Viscosity descriptors	Flow index (*n*)	Consistency index (K; Pa·s^n)
A	Nectar	0.66	2.60
	Spoon thick	0.38	4.70
B	Nectar	0.29	3.72
	Extreme spoon thick	0.22	4.42
C	250 mPa·s	0.20	3.70
	800 mPa·s	0.22	4.26
	2 000 mPa·s	0.24	4.64
D	250 mPa·s	0.27	3.70
	1 000 mPa·s	0.18	4.58
	2 000 mPa·s	0.20	4.90

3.1.2 *Extensional deformation*

For thin liquids, break up time was (79.67 ± 14.44) and (60.07 ± 44.92) ms for solutions with Gastrografin or Omnipaque in water, respectively. For product A, time to BUD (mean ± SD) was extremely low ranging between 0.04 and 0.02 ms for nectar and spoon thick viscosity, respectively. In contrast, for products B, C, and D, BUD was increased by the increment of ShV. Time to BUD is presented in Table 7 for each TP dose and the graphical representation is shown in Fig. 2.

Table 7
Time to break up diameter for each TP at each viscosity level.

TP	CT viscosity descriptors	Time to break up diameter (ms; mean ± SD)
A	Nectar	40.34 ± 41.65
	Spoon thick	24.00 ± 5.45
B	Nectar	250.57 ± 63.16
	Extreme spoon thick	3 040.99 ± 2 392.68
C	250 mPa·s	237.41 ± 103.93
	800 mPa·s	756.56 ± 328.54
	2 000 mPa·s	6 506.00 ± 4 563.31 (+ not broken)
D	250 mPa·s	68.36 ± 13.01
	1 000 mPa·s	599.50 ± 156.75
	2 000 mPa·s	21 743.67 ± 2 990.92

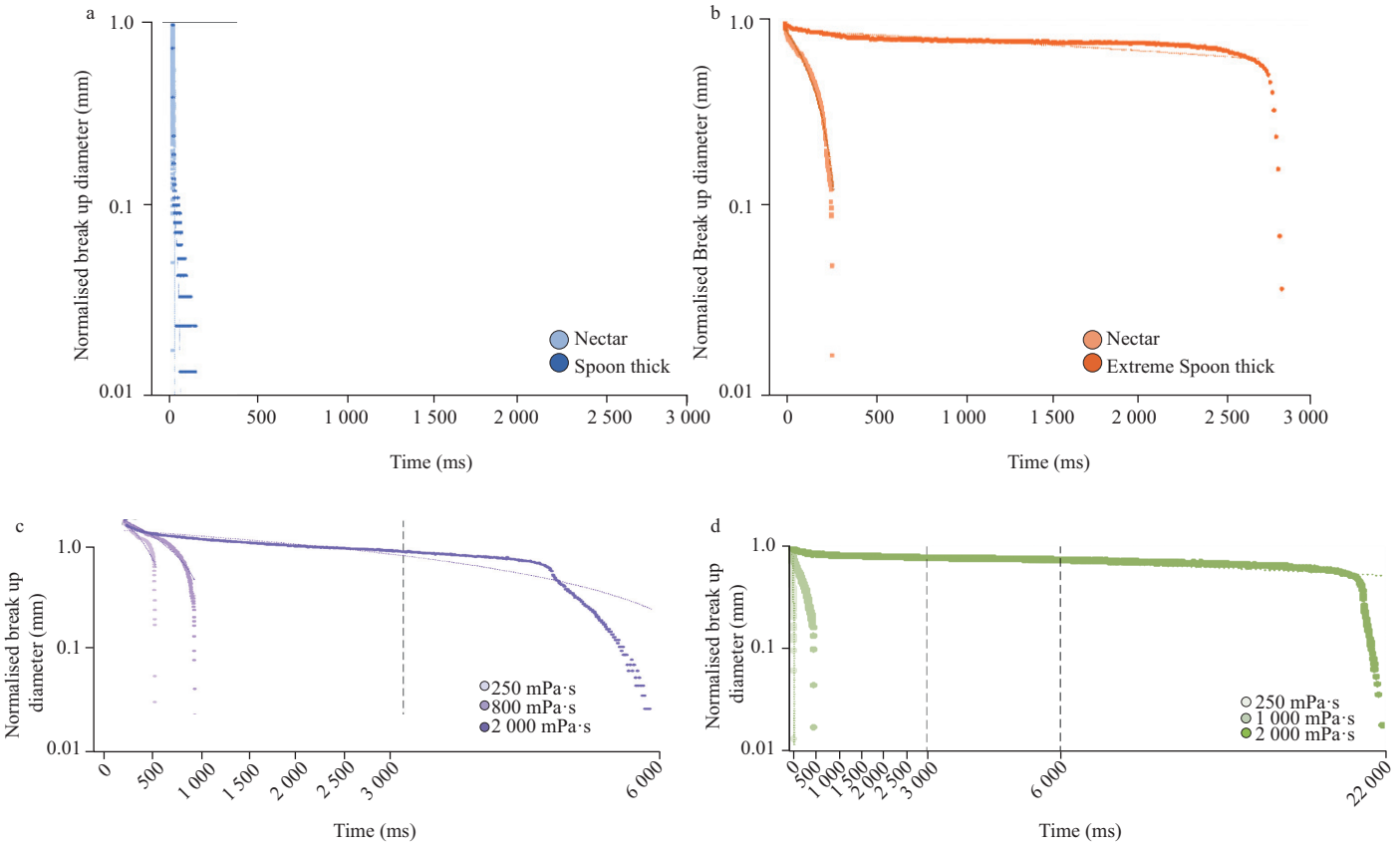

Fig. 2 Normalized break up diameter *vs.* time for all the viscosity levels of each TP assessed. (a) TP A; (b) TP B; (c) TP C; (d) TP D.

Time required to BUD was extremely low for all ShV values assessed except for the highest viscosity levels for TP B, C and D. Lowest time to BUD was observed for TP A (MS) which presented the highest ShV value (3 400 mPa·s). For each TP, the increment of viscosity produced an increment in the time to BUD but no consistent relationship was observed between ShV and ED (Fig. S1).

3.2 Textural characterisation

For thin liquids with X-ray contrast, Gastrografin and Omnipaque, respectively, texture parameters were: (0.18 ± 0.00) and (0.18 ± 0.01) N for hardness, (1.15 ± 0.01) and (1.11 ± 0.01) N·s for adhesiveness and 1.19 ± 0.03 and 1.16 ± 0.02 for cohesiveness. Maximal force was increased by increasing the ShV level for all the TP assessed: 0.45–1.01 N (A), 0.19–0.52 N (B), 0.26–1.03 (C), 0.27–0.80 (D). Significant differences in maximal force ($P < 0.05$) appeared for product C (250 *vs*. 2 000 mPa·s) and product D (200 *vs*. 2 000 mPa·s). Adhesiveness was also increased by increasing the ShV level: 0.56–1.95 (A), 0–0.53 (B), 0.05–1.04 (C), 0.003–1.12 (D). Product C and D presented significant differences in adhesiveness ($P < 0.05$) when comparing the lowest (250 and 200 mPa·s) *vs*. the highest thickened viscosity level (2 000 mPa·s). In contrast, cohesiveness increased for TP A with the increment of ShV but decreased for TP B, C and D. Significant difference in cohesiveness ($P < 0.05$) was only observed for product D between 200 and 2 000 mPa·s. Table 8 and Fig. 3 show the textural results of all the TP at each viscosity level assessed.

3.3 Therapeutic effect in PSOD

3.3.1 Safety of swallow

Safety of swallow for thin liquid ranged between 36% and 53%, with 4.65%–17.50% presenting aspiration into the airway. Prevalence of safe swallows for thic kened viscosities went from 62% to 97%. For low viscosities (nectar and 250 mPa·s) the highest percentage was seen for product B, achieving 79% of safe swallows at the first thickened level. For higher viscosities, including spoon thick (A), extreme spoon thick (B), 800, 1 000, and 2 000 mPa·s levels, safe swallows ranged between 90%–97%. Prevalence of safe swallows for the different doses of the TPs are presented in Table 9.

All TP showed a strong ShV-dependent effect on prevalence of patients with safe swallow. A significant strong correlation was obtained between ShV and safety of swallow ($P < 0.000\ 1$, $R^2 = 0.923$; Fig. 4) in a dose-response manner ($P < 0.000\ 1$, $R^2 = 0.96$).

Table 8
Maximum force, cohesiveness and adhesiveness for each viscosity level assessed for all the TP selected.

TP	Viscosity level	Maximum force (N)	Adhesiveness (N·s)	Cohesiveness
A	Nectar	0.45 ± 0.10	0.56 ± 0.03	0.80 ± 0.02
	Pudding	1.01 ± 0.03	1.95 ± 0.17	0.93 ± 0.02
B	Nectar	0.19 ± 0.002	0.00	1.09 ± 0.05
	Extreme spoon thick	0.52 ± 0.01	0.53 ± 0.01	0.74 ± 0.03
C	250 mPa·s	0.26 ± 0.008	0.05 ± 0.005	0.82 ± 0.021
	800 mPa·s	0.50 ± 0.02	0.42 ± 0.001	0.74 ± 0.01
	2 000 mPa·s	1.03 ± 0.02	1.04 ± 0.05	0.71 ± 0.04
D	250 mPa·s	0.27 ± 0.004	0.003 ± 0.005	0.95 ± 0.06
	1 000 mPa·s	0.47 ± 0.03	0.47 ± 0.04	0.81 ± 0.02
	2 000 mPa·s	0.80 ± 0.02	1.12 ± 0.04	0.78 ± 0.009

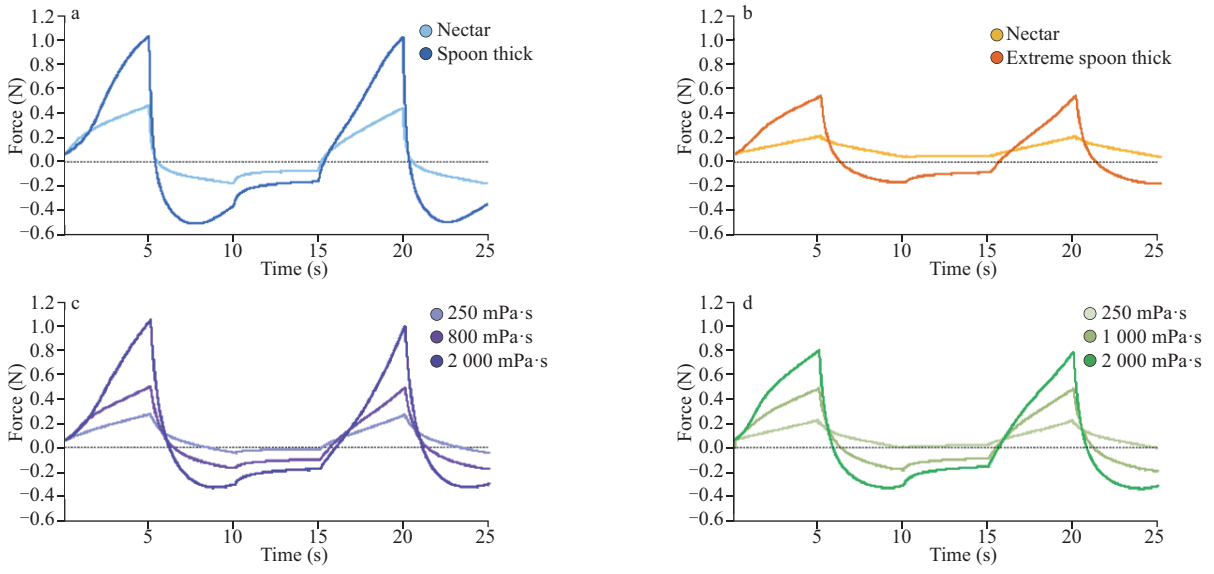

Fig. 3 TPA curves for all the viscosity levels of each TP assessed. (a) TP A; (b) TP B; (c) TP C; (d) TP D.

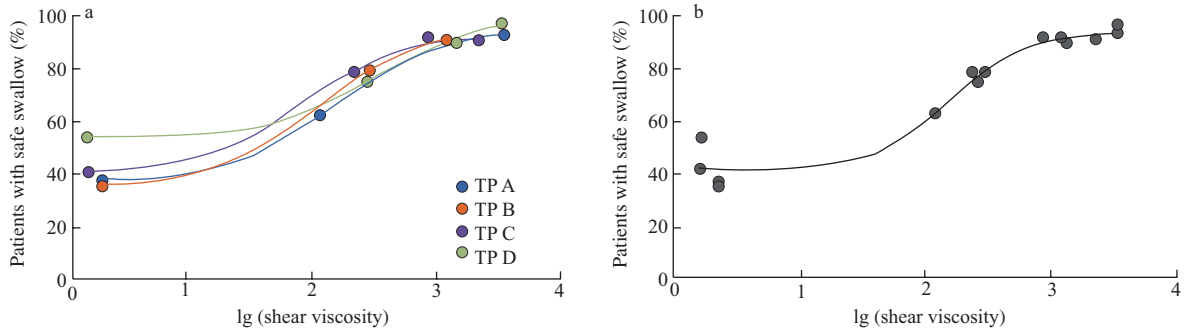

Fig. 4 Log viscosity-response effect for safety of swallow at the different viscosity levels assessed for each TP. (a) Dose-response curve for all viscosities assessed; (b) Curves for each TP.

Table 9
Percentage of patients with safe swallows for each viscosity level and for thickener.

TP	Viscosity descriptors	Safe swallows (% patients)	Penetrations (% patients)	Aspirations (% patients)
A	Thin liquid	37.21	58.14	4.65
	Nectar	62.22	37.78	0.00
	Spoon thick	93.33	6.67	0.00
B	Thin liquid	35.82	56.72	7.46
	Nectar	79.22	15.58	5.19
	Extreme spoon thick	90.91	7.79	1.30
C	Thin liquid	41.20	41.20	17.50
	250 mPa·s	78.10	9.60	12.30
	800 mPa·s	92.10	2.60	5.3
	2 000 mPa·s	91.20	6.10	2.70
D	Thin liquid	53.33	30.00	16.67
	250 mPa·s	75.00	14.29	10.71
	1 000 mPa·s	90.00	10.00	0.00
	2 000 mPa·s	96.77	3.23	0.00

Increasing ShV reduced the prevalence of aspirations and penetrations (Table 9). In contrast, ED (time to BUD) did not present any correlation with safety of swallow ($P = 0.123$, $R^2 = 0.527$), and widely divergent ED values ((756.56 ± 328.54) ms *vs.* (21 743.67 ± 2 990.92) ms) provided similar safety levels (92% and 96%, respectively).

Regarding textural properties, maximal force significantly correlated with safety of swallow ($P < 0.000\ 1$, $R^2 = 0.879$) in a positively moderate significant manner ($P < 0.000\ 1$, $R^2 = 0.505$) but adhesiveness ($P = 0.06$, $R^2 = –0.134$) and cohesiveness ($P = 0.114$, $R^2 = –0.447$) did not (Fig. 5).

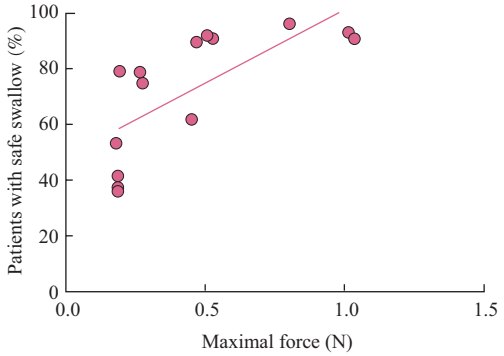

Fig. 5 Linear regression for safety of swallow (% patients with safe swallow) and maximal force.

3.3.2 *Efficacy of swallow*

Oral residue was unaffected for product A and B when increasing viscosity. In contrast, for products C and D, oral residue was increased significantly between 36% and 54% ($P < 0.05$ *vs.* thin liquid). Pharyngeal residue was increased significantly for TP A at spoon thick viscosity ($P < 0.05$ *vs.* thin liquid) but no significant increment was observed when increasing viscosity for TP B, C and D (Table 10). However, no dose-dependent relationship was observed between ShV and oral or pharyngeal residue (Fig. 6) for any TP. Neither BUD nor textural properties (hardness, adhesiveness and cohesiveness) presented any relationship with oral or pharyngeal residue.

3.4 *Relationship between rheological and textural variables*

Shear viscosity was strongly, positively, linearly and significantly correlated with maximal force ($P < 0.000\ 1$, $R^2 = 0.85$) and weakly, inversely correlated with cohesiveness ($P = 0.044$, $R^2 = 0.29$). Linear regressions of both parameters are presented in Fig. 7. No other relationship was found for the other rheological or textural parameters assessed ($P > 0.05$, $R^2 < 0.40$).

Table 10
Percentage of patients with pharyngeal residue for each viscosity level and for each thickener.

TP	Viscosity descriptors	Oral residue (% patients)	Pharyngeal residue (% patients)
A	Thin liquid	20.93	23.26
	Nectar	17.39	32.61
	Spoon thick	15.22	45.65
B	Thin liquid	7.46	7.46
	Nectar	10.39	7.79
	Extreme spoon thick	11.69	9.09
C	Thin liquid	38.6	41.2
	250 mPa·s	58.8	41.2
	800 mPa·s	51.8	44.7
	2 000 mPa·s	54.4	37.7
D	Thin liquid	19.36	30.00
	250 mPa·s	35.71	46.43
	1 000 mPa·s	41.94	56.67
	2 000 mPa·s	38.71	38.71

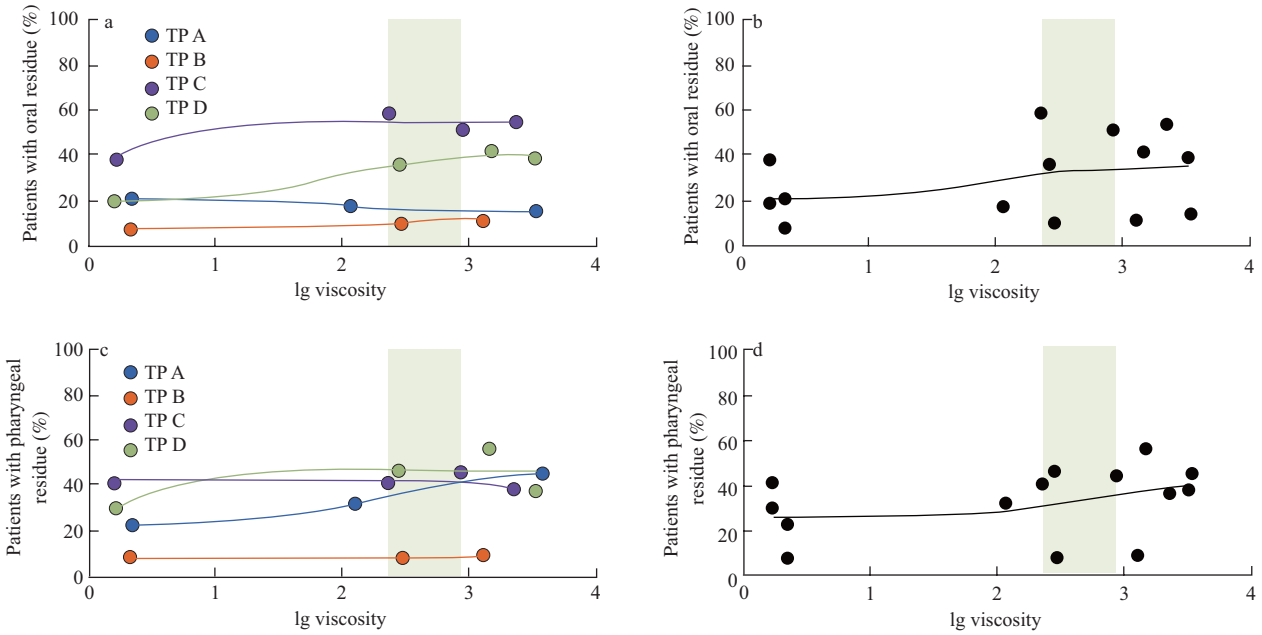

Fig. 6 Lg viscosity-response effect for efficacy of swallow at the different viscosity levels assessed for each TP. (a) Dose-response curves for oral residue for each TP. (b) Dose-response curves for oral residue for all viscosities assessed. (c) Dose-response curves for pharyngeal residue for each TP. (d) Dose-response curves for pharyngeal residue for all viscosities assessed. Green bars depict the therapeutic range in XG-based TP.

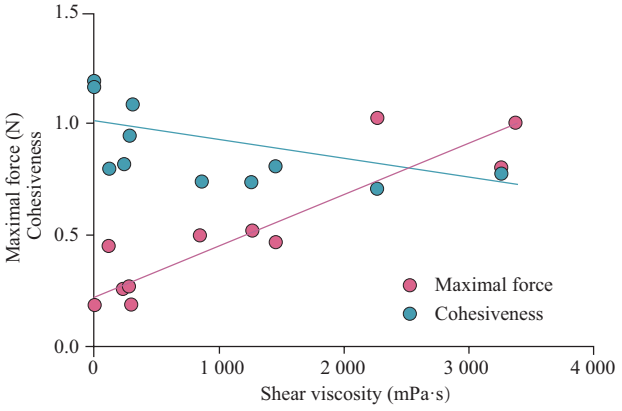

Fig. 7 Linear regression for maximal force and cohesiveness *vs*. ShV.

3.5 Effect of TP on oropharyngeal swallow response and bolus kinematics

The effect of all TP on time to LVC was analysed for each ShV level (Table 11). LVC was delayed for all the PSOD populations analysed with values above 160 ms[21]. No significant differences for thin liquid or the thickened levels assessed were observed between products A, B and D. In contrast, a significant reduction in time to LVC was observed when comparing thin liquid *vs.* all the thickened levels assessed ($P < 0.001$) for product C.

Bolus velocity presented no significant differences between the viscosity levels assessed except for product C which showed significant reduction for 800 and 2 000 mPa·s levels when compared to thin liquid ($P < 0.001$). In comparison, with healthy volunteers (0.31[24]–0.33 m/s[25]), mean bolus velocity was reduced for all TP at every viscosity level assessed.

Table 11
Time to LVC and bolus velocity in the pharynx for each level of viscosity for each thickener presented as the mean with its standard deviation.

TP	Viscosity descriptors	LVC (ms)	Bolus velocity (m/s)
A	Thin liquid	413 ± 132.30	0.26 ± 0.099
	Nectar	416.52 ± 130.25	0.227 ± 0.089
	Spoon thick	400 ± 166.96	0.235 ± 0.093
B	Thin liquid	365.6 ± 139.5	0.275 ± 0.1
	Nectar	347.9 ± 107.3	0.257 ± 0.099
	Extreme spoon thick	371.9 ± 185.5	0.247 ± 0.107
C	Thin liquid	382.5 ± 139.1	0.313 8 ± 0.126 5
	250 mPa·s	330.1 ± 143.4	0.293 ± 0.106 7
	800 mPa·s	303.3 ± 94.7*	0.261 3 ± 0.078 4
	2 000 mPa·s	300.4 ± 107.8*	0.272 9 ± 0.101
D	Thin liquid	392 ± 150.91	0.242 ± 0.069
	250 mPa·s	390.67 ± 120.08	0.244 ± 0.081
	1000 mPa·s	338.06 ± 102.16	0.240 ± 0.099
	2 000 mPa·s	335.48 ± 128.86	0.213 ± 0.075

Note: *$P < 0.001$ *vs*. thin liquid.

4. Discussion

The main conclusion arising from this study is that the therapeutic effect of TP on the safety of swallow is very strong and is mainly caused by ShV in a dose-dependent manner in patients with post-stroke OD. Maximal force also moderately increased safety. In contrast, neither extensional deformation, cohesiveness nor adhesiveness played any role on safety of swallow in these patients. Oral and pharyngeal residue was moderately increased at high viscosity values for some of the TP assessed without a dose-dependent effect, and unaffected by the other rheological or textural properties.

Fluid thickening is a well-established management strategy for OD[1]. Several clinical trials developed by our group confirmed the strong therapeutic effect of TP on safety of swallow in various OD phenotypes: post-stroke, older, neurodegenerative diseases, but found much lower therapeutic effect in head and neck cancer patients[18-20,24,26-27]. As far as we know, this is the very first study to demonstrate that ShV is the main rheological property linked to the therapeutic effect of TP on safety of swallow in a significant and dose-response manner. Another relevant factor arising from the results of this study is the correlation we found between maximal force and swallow safety. This is further supported by the strong correlation we found between ShV and maximal force. However, the correlation obtained by the analysis of maximal force and safety of swallow did not result in a proper dose-response curve but in a moderately positive linear correlation. Another relevant result from this study showed there was no relationship between ED nor adhesiveness or cohesiveness with the prevalence of safety of swallow with the TPs we used in this study. None of these parameters (extensional viscosity, maximal force, adhesiveness and cohesiveness) presented a significant relationship with the prevalence of safe swallows. In addition, we observed that TP with similar ShV but different extensional deformation, cohesiveness and adhesiveness presented similar therapeutic effects, further suggesting that ShV is the main rheological property causing the therapeutic effect of TP on safety of swallow. This is in contrast with studies that suggested a major role for extensional viscosity on safety of swallow[3,28]. However, other studies assessing extensional parameters of TPs indicate the need to do a more exhaustive analysis on swallowing safety and its relationship with ED by developing clinical trials with patients[3,28-29], as we did in this study.

Our results on the effect of several ShV levels assessed in this study when using product D, B and C clearly show that we can provide a safe swallow to more than 90% patients with poststroke OD by using only 2 therapeutic ShV frames: 1) more than the 70% of them, those with mild dysphagia, can be safely treated with TP at viscosity values ranging 200–300 mPa·s, and 2) only 20%–25% of them, those with the more severe dysphagia, need to be managed with TP at viscosities between 800–1 000 mPa·s to achieve a safe swallow with thickened fluids. The therapeutic effect we found for product A is lesser than that of the other TP as 64% of patients needed the lowest frame of viscosity values and up to 38% highest viscosity frame. In one of our very first studies on TP, we found enhancing bolus viscosity to 274.40 mPa·s caused less improvement in the safety of swallowing with MS than XG or mixted TP[24]. The reduced therapeutic effect of MS compared with similar viscosity levels achieved with XG or mixed TP could be attributed to the reduction in ShV caused by salivary amylase on MS during oral processing. Therefore, our first conclusion is that the therapeutic effect of TP on the safety of swallow in patients with poststroke OD is very strong if they are used at the appropriate ShV level. We have also found that ShV values above 1 000 mPa·s did not produce any further improvement on the safety of swallow when using xantham gum or mixed TP. Taken together, these results further question the recommendations provided by many manufacturers for a too wide and too high range of viscosities (above 1 300 mPa·s and even 6 200 mPa·s)

that we found in a previous study in 8 out of 10 commercially available TP[4]. Our strategy of selecting these 2 frames of 200–300 and 800–1 000 mPa·s also perfectly aligns with use of the Volume-Viscosity Swallow test (V-VST) to prescribe the optimal viscosity level to provide safe hydration to our patients with dysphagia[30]. Our results further indicate that TP are very powerful tools to contribute to safe hydration for patients with poststroke OD[31].

The mechanism of action of xantham gum TP on safety of swallow in poststroke OD was very well studied in one of our clinical trials[19] and we found that the mode of action of TP varies in each frame of the therapeutic range depending on the level of ShV achieved: 1) at very low ShV (150 mPa·s), the therapeutic effect produced by TP is merely compensatory and depends on the intrinsic rheological properties of the TP without any significant effect on timing of swallow response nor bolus kinematics; 2) at the lowest optimal therapeutic frame (250 mPa·s), the therapeutic effect produced by TP is also associated with a significant reduction in time to LVC; and 3) at the highest optimal therapeutic level (800 mPa·s) the therapeutic effect is significantly associated with reduction in LVC and delayed UESO and reduced bolus velocity as an additional mechanism causing its therapeutic effect on safety of swallow[19,27]. This sequential ShV-dependent mechanism of action observed in the products C and D of this study is also in line with the results of previous studies which analyzed more heterogeneous populations[18,27,32] and even with other studies using different viscosity descriptors[33]. There is a strong relationship between delayed time to LVC and impaired swallow safety in patients with poststroke OD[18]. We have also observed a similar improvement in time to LVC in studies on patients with poststroke OD using oropharyngeal sensorial stimulation with pharmacological (TRP agonists) or electrical stimulation[34-35]. Therefore, we suggest the improvement of swallow response caused by increasing ShV or maximal force could be mediated through stimulation of the specialized sensory terminals perceiving mechanical, thermal or chemical stimuli in the oropharyngeal mucosa, the main candidates being mechanoreceptors involved in the effect of ShV and maximal force on LVC[36].

Regarding efficacy of swallow, oral residue was increased with the increment in ShV. However, no dose-response nor lineal relationship was observed for any of the rheological or textural parameters assessed. In contrast, pharyngeal residue was unaffected by increasing viscosity with B, C, and D products, a relevant advantage of these new compounds. On the contrary, increasing ShV with A (MS-based TP) did increase pharyngeal residue in a significant manner. Overall, increasing ShV increases oral residue for all TP independently of the specific ShV level, while pharyngeal residue is increased when increasing ShV with A but not with B, C, or D TP. This effect could be caused by the gums' mechanism of action which forms stronger bonds with water (hydrogen bonds) than MS does. In contrast, TP A mechanism of action consists in its starch granules absorbing water and swelling. Its ED is also lower than the other TP, increasing the breakage of the bolus. We previously described that patients with oropharyngeal residue showed impaired tongue propulsion leading to reduced bolus velocity and kinetic energy[37]. As ShV refers to the resistance of a fluid to flow when subjected to a shear force, that is, when layers of fluid slide over each other, fluids with a high ShV require greater force to achieve the same level of deformation or flow than fluids with a lower viscosity. Therefore, increasing both ShV and maximal force will contribute to pharyngeal residue in patients with poststroke OD as maximal force measures the peak resistive force during the first compression cycle of the TPA.

The main limitation of the study is the failure to determine extensional viscosity. However, the approximation to it by the analysis of the ED helps explain the role of this property in the use of TP. Future directions of TP are to avoid the commercialization of random qualitative viscosity levels and determine the optimal ShV levels to be prescribed (according to evidence obtained in clinical trials) as the main parameter causing the safety therapeutic effect of those products. In addition, there is a need to improve the composition of TPs, starting with avoiding the use of MS to reduce the effect of salivary amylase and increase palatability. In addition, in order to increase the effect of TP, we should move the development of new products into combining the effect produced by ShV with the stimulation of TRP agonists[38]. This new combination might reduce the viscosity levels selected to improve safety of swallow by adding another strong stimuli to improve the biomechanics of the swallow response.

In summary, this study highlights that ShV emerges as the parameter most significantly related to the safety of swallow in patients with poststroke OD. However, it is revealed that maximal force influences both parameters, showing a linear relationship to each. Furthermore, it has been determined that oral residue is more affected by the composition of the product (MS or XG), while pharyngeal residue increases with ShV but without following a specific incremental relationship. These findings highlight the importance of considering the objective measurement of ShV to improve the management of patients with OD and of establishing a common therapeutic protocol and optimal viscosity values to treat poststroke OD with TP.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Mireia Bolivar-Prados reports writing assistance was provided by Fundació Salut Consorci Sanitari del Maresme. Mireia Bolivar-Prados reports travel was provided by Biomedical Research Network Center of Hepatic and Digestive Diseases. Pere Clave reports equipment, drugs, or supplies and travel were provided by Carlos III Health Institute. Pere Clave reports financial support and equipment, drugs, or supplies were provided by Government of Catalunya. This work was supported by Fundació Salut del Consorci Sanitari del Maresme; Centro de Investigación en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III with grant number (EHD16PI02); Strategic Action on Oropharyngeal Dysphagia, Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III with grant number (PI18/00241 and PI22/01101); this research was also supported by the Territorial Competitiveness Specialization Project (PECT) of Mataró-Maresme (PRE/161/2019) financed by the Government of Catalunya- Generalitat de Catalunya within

the framework of the European Regional Developments Funds of Catalonia Operational Programme 2014–2020.

We would like to thank the Dysphagia Team from the Hospital de Mataró for the collaboration and availability in this study, especially to Noemí Tomsen for her support and Laura Chércoles and Jane Lewis for their English revision. We also like to thank Carlos Bengoechea, who allowed us to carry out a rheology training at the University of Seville and helped us in the interpretation of all the parameters.

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