Paediatric Solid Oral Dosage Forms for Combination Products: Improving In Vitro Swallowability of Minitablets Using Binary Mixtures with Pellets

Alejandro Avila-Sierra, Anaïs Lavoisier, Timpe Carsten, Peter Kuehl, Leonie Wagner, Carole Tournier, Marco Ramaioli

▶ **To cite this version:**

Alejandro Avila-Sierra, Anaïs Lavoisier, Timpe Carsten, Peter Kuehl, Leonie Wagner, et al.. Paediatric Solid Oral Dosage Forms for Combination Products: Improving In Vitro Swallowability of Minitablets Using Binary Mixtures with Pellets. 2023. hal-03938323

HAL Id: hal-03938323
https://hal.science/hal-03938323

Preprint submitted on 17 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Paediatric Solid Oral Dosage Forms for Combination Products: Improving *In Vitro* Swallowability of Minitablets Using Binary Mixtures with Pellets

Avila-Sierra, Alejandro,[1*] Lavoisier, Anais,[1] Timpe, Carsten,[2] Kuehl, Peter,[2] Wagner, Leonie,[2] Tournier, Carole,[3,4] Ramaioli, Marco[1]

[1] Université Paris-Saclay, INRAE, AgroParisTech, UMR SayFood, 91120 Palaiseau, France

[2] F. Hoffmann-La Roche AG, Konzern-Hauptsitz Grenzacherstrasse 124, Basel, Switzerland

[3] Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAE, Institut Agro, Université de Bourgogne Franche-Comté, 21000 Dijon, France

[4] INRAE, PROBE research infrastructure, ChemoSens facility, 21000 Dijon, France

Corresponding author: Alejandro Avila-Sierra (alejandro.avila-sierra@inrae.fr)

Abstract

There is a growing interest in determining and improving the acceptability of solid oral dosage forms (SODF) in paediatric populations. Combination products can be an interesting solution to combine two active pharmaceutical ingredients. This study shows that binary mixture of paediatric SODF could enhance formulation swallowability and palatability.

Using the Paediatric Soft Robotic Tongue (PSRT) – an *in vitro* device inspired by the anatomy and physiology of 2-year-old children – we investigated the oral phase of swallowing of multi-particulate formulations, i.e., pellets (350 and 700 µm particles), minitablets (MTs, 1.8 mm), and their binary mixtures (BM), by measuring the oral swallowing time, the fraction of particles swallowed, and the post-swallow residues. The

effects of the feeding method, bolus volume, type of carrier, particle size, and particle volume fraction on pellets swallowability were also systematically studied.

The flowing ability of the carriers was affected by the addition of pellets: shear viscosity generally increased, yet little effect was observed on their shear thinning behaviour. Xanthan gum-based solutions achieved excellent swallowing levels for pellets (≥ 75 %), especially at high concentrations, i.e., 0.5 and 1%, favouring pellets transport without affecting post-swallow residues. Particle swallowability does not appear to be influenced by pellet size but increasing particle volume fraction (v.f.) above 10% reduced the percentage of particles swallowed. At v.f. 0.4, pellets were easier to swallow (+ 13.1%) than MTs, being the administration method used strongly dependent of the characteristics of the multi-particulate formulation under study. To enhance MT swallowability, a novel approach involving MT-pellets binary mixtures was explored, whereby the maximum solid packing fraction of the formulation was increased. Mixing MTs with only 24% of pellets improved particle swallowability, achieving swallowing levels similar to those of pellets alone. Therefore, a combination of SODF, i.e., MTs and pellets, improved particle swallowability, opening the door to new ways of modulating product palatability, particularly attractive for combination products.

Keywords

Soft robotics; swallowing; pellets; minitablet; binary mixture; flexible solid oral dosage form; combination products

Acronyms

SODF: solid oral dosage form

PSRT: Paediatric Soft Robotic Tongue

MT: Minitablet

BM: Binary mixture

v.f.: Volume fraction

IDDSI: International Dysphagia Diet Standardisation Initiative

FDC: Fixed-dose combination

API: active pharmaceutical ingredient

1. Introduction

Difficulty with swallowing solid pharmaceutical formulations is a barrier that must be overcome across a broad range of ages, including young children (VandenBerg et al., 2022). Developing drugs for paediatric use is a complex and tedious process but essential as children need age-appropriate dosage forms of high quality, ethically researched, and appropriately authorised (Mistry et al., 2017; Ternik et al., 2018; Wollmer et al., 2022). According to the European Medicines Agency (EMA), acceptability assessment must be part of the Paediatric Pharmaceutical Development Program of new formulations and described in the Paediatric Investigation Plan (PIP) (Committee for Medical Products for Human Use and Paediatric Committee, 2013).

The use of liquid oral pharmaceutical formulations has been traditionally preferred for paediatric use, yet major limitations have been reported (e.g., stability issues, regular use of excipients that may be harmful to children, and high storage and transportation costs) (Orubu et al., 2018). The provision of flexible solid oral dosage forms (SODF) as an alternative has been proposed (WHO, 2012; Wollmer et al., 2022), which allow for a flexible dosing regime and the use of safe excipients that ensure both high acceptability and adequate bioavailability.

When it comes to multi-particle oral dosage forms, size and shape, taste and aftertaste, dose volume, and ease of administration are generally considered critical drivers of acceptability (Kozarewicz, 2014). Children under 6 years old should not take tablets and capsules due to swallowing difficulties and choking risks (EMA 2006; Yeung and Wong, 2005) but minitablets (≤ 4 mm in diameter) are currently considered suitable for children between 2 and 5 years old (Mistry et al., 2017). A number of clinical studies using placebos have demonstrated that young children (aged between 6 months and 5 years old) are able to swallow multiple minitablets simultaneously (Klingmann, 2017; Klingmann et al., 2018; Kluk et al., 2015) and tend to prefer this format over alternative formulations like powders, suspensions, or syrups (Klingmann et al. 2013, 2015, 2017; Musiime et al. 2014; Riet-Nales et al. 2013; Spomer et al. 2012; Thomson et al. 2009). On the other hand, pellets or beads (< 1.5 mm) could be also suitable for the administration of medicines to adults and children (4-year-old and above) (Lopez et al., 2018a), being these sprinkle forms also preferred over traditional formulations like syrup (Cloyd et al., 1992; Motte et al., 2005; Verrotti et al., 2012). Recently, Miyazaki et al. (2022) has investigated and compared the acceptability and swallowability of minitablets (2 mm), pellets (mean diameter 263 ± 108 µm) and liquid formulations (syrup) among sixty-five Japanese children distributed in different age groups (2 ≤ 4, 4 ≤ 7, and 7 ≤ 9 years old). They showed better acceptability and swallowability of pellets and liquid formulations than of minitablets. An important practical limitation of minitablets and pellets, especially of the latter, is that large volumes would be often required, affecting palatability. Lopez et al. (2018a) reported a negative grittiness perception by 60% of children and 51% of adults using pellets of sizes ranging between 200-1000 µm at a volume fraction of ~ 0.12 in spring water.

Several *in vitro* models to study swallowability have been proposed in the literature as summarised by (Marconati et al., 2019). Some were used in the past to further our

understanding of the effect on the oral phase of swallowing of the size and shape of SODF and of the carrier rheology (Marconati et al., 2018a; 2018b). More recently, a novel *in vitro* model inspired specifically by the anatomy and physiology of 2-year-old children – the Paediatric Soft Robotic Tongue (PSRT) – has been proposed (Lavoisier et al., 2022). This soft robotic device has been used to demonstrate that a particle volume fraction up to 0.2 did not significantly deteriorate *in vitro* swallowability of minitablets (2.5 mm), however, both the way minitablets were administered in the carrier and the type of carrier did. Semi-solid foods with a shear viscosity of at least ~ 150 mPa.s at a shear rate of 50 s^{-1} and intermediate yield stresses (2-5 Pa) may facilitate drug transport (minitablets 2.5 mm) without affecting either bolus velocity or post swallow residues (Lavoisier et al., 2022). However, the rheological properties of the carriers may be affected by the addition of multi-particulates, altering both carrier consistency and shear thinning behaviour (Mueller et al., 2010), and therefore changing the dynamics of swallowing (Marconati et al., 2018b).

Pharmaceutical forms containing a single active pharmaceutical ingredient (API) are easier to manufacture since physicochemical interactions between APIs can be avoided. However, fixed-dose combination (FDC) - a combination of drugs, with at least two APIs, in a single dose form – is especially attractive for enhancing compliance in poly-medicated patients (Fernández-García et al., 2020); it is well known and widely used in antimicrobial and antiretroviral therapies. A recent review covering in detail a range of commercialised FDCs and their associated manufacture challenges can be found in Fernández-García et al. (2020). FDCs have several advantages over monotherapy, including the modification of pharmacokinetic and pharmacodynamic profiles of the drug (Schlosser, 2019; Moriarty et al., 2019), as well as the reduction of manufacturing (e.g., fewer excipients), packaging, and distribution costs (Sadia et al., 2018).

The behaviour of granular systems is strongly linked to the packing fraction (Pillitteri et al., 2020), being it conditioned by the mechanical and geometrical properties of the particles (Wiącek, 2016). Mixing particles of differing size and volume fraction is a common way to increase the maximum packing density of a granular system. For instance, in binary mixtures formed by small and large particles, small particles may fit into the voids left by the large ones, allowing rearrangements, altering flowing and jamming behaviours without changing its volume (Wiącek, 2016; Ikeda et al., 2012; Haxton et al., 2011; Song et al., 2008). We hypothesised that this fundamental knowledge can be applied to improving multi-particulate pharmaceutical formulations and that the combination of different SODF sizes may enhance the maximum packing fraction and reduce the suspension viscosity, thus facilitating the swallowing process (see hypothesis illustration in **Figure 1**). This could in turn reduce other unpleasant sensations associated to palatability (e.g., grittiness) that large volumes of small formulations like pellets may cause. Additionally, this approach could favour the formulation of combination products, where SODF coating would avoid interactions, allowing the API dosage to be adjusted accordingly.

Using the Paediatric Soft Robotic Tongue (PSRT) model developed by Lavoisier et al. (2022), this study investigates the oral phase of swallowing of solid multi-particulate oral formulations (i.e., pellets, minitablets, and their binary mixture) by monitoring swallowing time, number of particles swallowed, and the amount of post-swallow residues. The effects of the feeding method, bolus volume, type of SODF carrier, particle size, and particle volume fraction on pellets swallowability were also systematically studied.

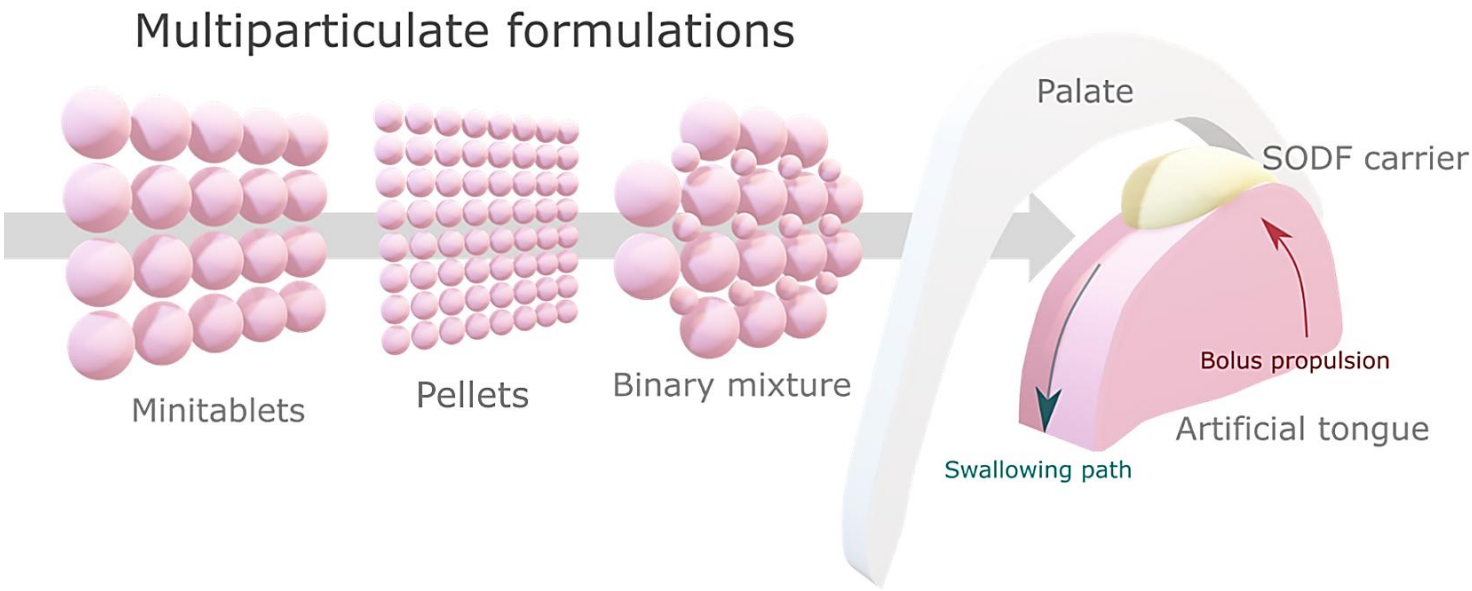

Figure 1. Hypothesis illustration. Multi-particulate pharmaceutical formulations: minitablets, pellets, and their high packing density binary mixture. On the right, the *in vitro* oral phase of swallowing of a representative carrier is illustrated.

2. Materials & Methods

2.1 Carriers

Two semi-solid food carriers, apple puree ("Pomme nature", 100 g, Andros France SNC, Biars-sur-Cère, France) and stirred yoghurt ("Velouté yaourt nature brassé", 125 g, Danone SA, Paris, France) were considered. Each carrier was diluted with artificial saliva (Brodkorb et al., 2019; Minekus et al., 2014) at a dilution ratio (carrier: artificial saliva) of 5:1 to mimic saliva incorporation during bolus formation in the mouth before swallowing (Lavoisier et al., 2022). Xanthan gum solutions in mineral water (Vittel) at three different concentrations (0.25, 0.5, and 1 % w/v; 43708, xanthan from Xanthomonas campestris, Sigma-Aldrich, St. Louis, MO, USA) were used as carriers of reference; Xanthan gum is commonly used as thickeners for dysphagia (swallowing disorders) management.

2.2 Solid oral multiparticulate formulations

Placebo formulations, i.e., minitablets (1.8, 2.3, 2.5, and 3 mm in diameter) and pellets (Cellets®; 350 and 700 µm in diameter) were provided by Roche Pharma (Basel, CH) (**Figure 2a**). All formulations were coated with an ethylcellulose-based coating (Surelease® E-7-7050, Colorcon, Darford, Kent, UK) to avoid swelling and solubilisation during testing.

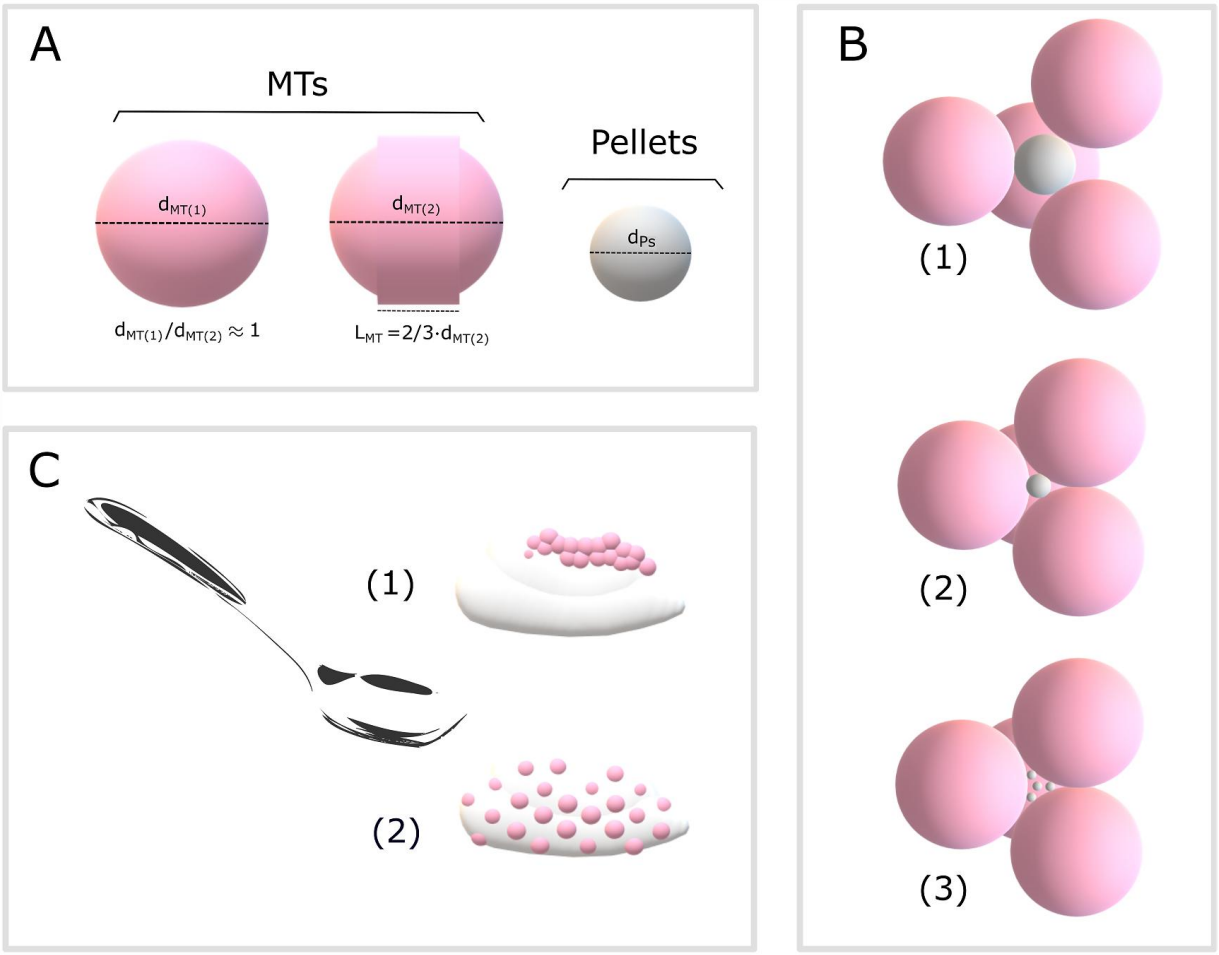

Figure 2. Schematic representation of the paediatric solid oral formulations tested: (A) shape and proportions of minitablets (MTs), frontal (left) and lateral (right) view, and pellets, L_{MT}, d_{MT}, and d_{Ps} refer respectively to the length and diameter of the cylindrical part of MTs, and to the diameter of pellets; (B) sketch of binary mixtures for different size ratios (α) (increasing α from sketch (1) to (3)) in a scenario where MTs dominate and pellets fill the voids formed between MTs; (C) feeding methods used: (1) pellets were spread on top of, or (2) fully mixed with the carrier. Images are not in scale.

2.3 Packing fraction of binary mixtures

Krieger and Dougherty (Krieger & Dougherty, 1959) proposed a semi-empirical correlation for effective viscosity of solid-liquid suspensions:

$$\frac{\eta}{\eta_o} = \left(1 - \frac{\varphi}{\varphi_m}\right)^{-[\eta]\cdot\varphi_m} \qquad \textbf{Eq. (1)}$$

Where η is dynamic viscosity of the suspension, η_o is the dynamic viscosity of the fluid phase of the suspension, φ the fraction in volume of the disperse solid phase of the suspension, φ_m

the maximum packing fraction of particles in the disperse solid phase, and [η] the intrinsic viscosity, which depends on both the specific viscosity (ratio between the viscosity of the suspension and the dispersion liquid) and the volume fraction of solids.

The behaviour of granular systems, e.g., pharmaceutical formulations, is strongly linked to the packing fraction φ, being defined as the ratio between the true volume V and the apparent volume V_a of a granular assembly (Pillitteri et al., 2020). Voids left by the grains allow rearrangements in the structure, triggering the φ both flowing and jamming behaviours (Ikeda et al., 2012; Haxton et al., 2011; Song et al., 2008). In granular materials, binary mixtures are systems made of particles with two different sizes. For the case of spherical particles, one can define the size ratio (α) as a control parameter:

$$\alpha = \frac{R_{MT}}{} \qquad \textbf{Eq. (2)}$$

Where R_{MT} and R_{Cs} are the radii of large and small particles, respectively. We considered that both MTs and pellets are fully spherical particles, thus simplifying MT geometry. Large size ratios are known to reach higher packing fraction values than monodisperse systems (Pillitteri et al., 2020). When the size ratio is large enough, small particles naturally percolate due to gravity. When the size ratio is higher than $\alpha_p = (3 + 2\sqrt{3} \approx 6.46)$ (Soddy, 1936), gravity systematically leads to percolation of small particles through an ordered porous medium made by large ones. The minimum pore size between three kissing large particles (**Figure 2b**) can be defined as:

$$\text{Minimum pore size} = \frac{R_{MT}}{} \qquad \textbf{Eq. (3)}$$

Any small particle with a radius $R_{Cs} < R_{MT}/\alpha_p$ can then percolate.

The model used for calculating the maximum packing fraction of our binary mixtures formed by MTs and pellets is described by (Pillitteri et al., 2020), which considers granular

segregation (further information of the model and its implementation are shown in **SI**). The main parameters of the model are the volume fraction (*f*) of small particles, i.e., pellets, and the particle size ratio (α) defined in **Eq. 2**. The volume fraction of small particles is then defined as:

$$f = \frac{V_{Cs}}{\quad} \qquad \textbf{Eq. (4)}$$

Where V_{MT} and V_{Cs} are respectively the true volumes of minitablets and pellets.

2.4 Feeding conditions

The volume of food typically swallowed by 2-year-old children is 5 mL (Jones & Work, 1961; Vaiman et al., 2004). The different feeding conditions used in this study are presented in **Table 1**. Two different scenarios were considered (**Figure 2c**) for SODF administration: (i) SODF were spread on the top of the carrier, or (ii) fully mixed with the carrier. The different SODF fractions and bolus mass used in this work are presented in **Table 2**. For all cases, an initial swallow with the carrier under study was performed to lubricate the *in vitro* oral cavity.

Table 1. Feeding conditions used in the present study.

Type of feeding	Experimental details
Method 1: Carrier + SODF + Carrier	2.5 mL of the carrier was fed first, then the SODF were spread on top of another 2.5 mL of the carrier, fed from the bottom part and then swallowed. SODF were not covered by the carrier. A syringe was used for carrier administration into the oral cavity.
Method 2: SDOF mixed with carrier	SODF were mixed completely with the carrier. Bolus administration into the oral cavity was performed directly from the top holes. Bolus and carrier volume according to the detailed in **Table 2**.

Table 2. SODF fractions, sizes, and bolus masses used in the present study.

SODF volume fraction	Pellets size (μm)	SODF mass (gr)	Total bolus volume (mL)
0.10	350	0.65	5.00
0.20	350/700	1.30	5.00
0.30	350	1.95	5.00
0.40	350	2.60	5.00
0.15	350	1.15	5.89
0.20	350	1.62	6.25
0.40	350	4.34	8.34

2.5 Rheological measurements

The rheological properties of the carriers described in **section 2.1** and of their mixtures with pellets (particle volume fraction of 0.2) were assessed with a Modular Compact Rheometer 301 (Anton Paar GmbH, Graz, Austria), using concentric cylinder geometry (CC27) of 1 mm gap. The mixtures were prepared just before testing. The shear viscosity of the carriers and mixtures was evaluated by steady shear tests in a range of shear rates between 5 and 500 reciprocal seconds, at room temperature (20°C). The yield stress of the carriers was estimated through steady stress tests by increasing the shear stress from 0.01 to 30 Pa. Concerning the mixtures with pellets, in order to avoid pellets swelling due to the relative long time required for the steady stress test (~20 minutes), the yield stress (τ_o) of the mixtures with pellets was estimated from flow curves using the Herschel-Bulkley equation (**Eq. 5**).

$$\tau = \tau_o + \mathrm{k} \cdot \gamma^n \qquad \textbf{Eq. (5)}$$

Where τ and γ are the shear stress (Pa) and the shear rate (s^{-1}), respectively. K is the consistency index (Pa s), and n is the flow behaviour index (dimensionless). The yield stress of the carriers was also estimated using the HB model for comparison.

2.6 IDDSI flow test

The International Dysphagia Diet Standardisation Initiative (IDDSI) flow test was performed at room temperature to evaluate the IDDSI level of each liquid carrier (IDDSI, 2019). A standard Luer Slip Tip syringe was filled up to the 10 mL with the sample of interest. Then, the liquid is allowed to flow for 10 seconds. Based on the remaining volume left in the syringe, liquid samples are categorised in four levels of increasing thickness consistency: Level 0 (< 1 mL left); Level 1 (1–4 mL); Level 2 (4–8 mL); Level 3 (> 8 mL); Level 4 (10 mL).

2.7 Sedimentation condition of pellets

The sedimentation condition of pellets in the carrier was estimated using the Stokes' law for a single sphere motion and sedimentation in a yield stress Herschel-Bulkley fluid (Coussot, 2012) described as:

$$F_{Dmin} = \alpha R^2 \tau_c \qquad \textbf{Eq. (6)}$$

With $\alpha = 14\pi$. The symbols R and τ_c are the pellet radii and the yield stress of the carrier, respectively. No sedimentation occurs if $d_{pellet} < d_{critic}$, being d_{critic} defined by:

$$d_{critic} = \frac{21\tau_c}{g(\rho_c - \rho)} \qquad \textbf{Eq. (7)}$$

Where g is the acceleration due to gravity (9.81 $m.s^{-2}$) at the Earth's surface, ρ_c and ρ the density of the particle, i.e., pellet, and of the carrier respectively. Particle density was determined by weighing the volume occupied by the formulation of interest.

2.8 *In vitro* swallowing with the Paediatric Soft Robotic Tongue (PSRT)

A novel Paediatric Soft Robotic Tongue (PSRT) (see Lavoisier et al., 2022 for full description) inspired on the oral anatomy and physiology of 2-year-old children was used to investigate the swallowability of multi-particulate paediatric oral formulations. The top of the oral cavity was pierced with 4 holes to locate pressure transducers for recording the dynamic evolution of palatal pressure during *in vitro* swallowing. The first and second holes were used as feeding holes for feeding method 1 and 2 respectively (**Table 1**). The feeding holes were sealed by rubber plug before triggering the swallow. The maximal pressure applied against the palate was fixed at 8 kPa for mimicking the swallowing of 2-year-old children (Lavoisier et al., 2022). The target inflation pressures for the anterior and posterior chambers of the tongue were therefore adjusted (set at 20-25 kPa and 12-15 kPa, respectively). There was no delay between the deflation of the posterior chamber and the inflation of the anterior chamber. At least three repeatitions were performed per swallowing test (**Tables 1** and **2**).

2.8.1 Variables measured

A high-speed camera (acA2040-120um, Basler, Germany) was used to record the bolus transit at 150 frames per seconds. The time required for the bolus front to exit the oral cavity is called time bolus front out (t_{FO}).

The number of particles successfully swallowed during the *in vitro* swallowing test was also monitored. The bolus propelled out of the PSRT was collected in a pre-weighed aluminium container for being later placed in an oven at 105°C overnight to determine dry matter content. The number of SODF swallowed was calculated from the known dry matter content of the carrier.

The water fraction of the carrier of interest ($X^{Carrier}$) is calculated as:

$$X^{Carrier} = m_W{}^{Carrier} / m^{Carrier} \qquad \textbf{Eq. (8)}$$

Where $m_W{}^{Carrier}$ and $m^{Carrier}$ are the water mass in the carrier and the total mass of carrier, respectively. Then, quantifying the mass of water lost during drying ($m_{W,\,Out}{}^{Carrier}$), the mass of the carrier swallowed can be calculated as:

$$m_{Out}{}^{Carrier} \quad m_{W.\,Out}{}^{Carrier} \qquad \textbf{Eq. (9)}$$

The mass of SODF swallowed is:

$$m_{Out}{}^{Cellets} = m_{Out}{}^{Total} \qquad \textbf{Eq. (10)}$$

Where $m_{In/Out}{}^{Total}$ is the mass of bolus fed (in) or swallowed (out), $m_{In/Out}{}^{Carrier}$ is the mass of carrier fed (in) or swallowed (out), and $m_{In/Out}{}^{SODF}$, the mass of SODF introduced (in) or swallowed (out).

The amount of carrier residues left in the oral cavity was calculated as:

$$m_{residues} = m_{sample\ fed} - m_{sample\ swallowed} \qquad \textbf{Eq. (11)}$$

$$m_{carrier\ residues} = m_{total\ residues} - m_{SODF\ left\ in\ the\ cavity} \qquad \textbf{Eq. (12)}$$

The mass of SODF left in the oral cavity after swallowing can be estimated as:

$$m_{Res}{}^{SODF} = m_{In}{}^{SODF} \qquad \textbf{Eq. (13)}$$

2.9 Statistical analyses

One-way analysis of variance (ANOVA) (Gelman, 2005) was applied to identify statistical differences between the means of two or more groups. The statistical analysis was completed using Fisher's least significant difference test (LSD) (Salkind, 2010) for pairwise comparisons of a target group of data.

3. Results & Discussion

3.1 Rheological properties of the carriers

As highlighted in the introduction, acceptability of multi-particulate medicines potentially depends on the rheology of the suspending liquid carrier (Lopez et al., 2016). In the following sections, the rheological properties of the carriers and their mixtures with pellets have been carefully investigated as they may compromise critical quality attributes such as suspendability, palatability (i.e., appearance, taste, and mouthfeel) and swallowability.

3.1.1 IDDSI flow test

Of the five carriers selected (**section 2.1**), xanthan gum-based solutions (XG) were used as a reference. The consistency of each carrier was first qualitatively evaluated according to the International Dysphagia Diet Standardisation Initiative (IDDSI) framework (IDDSI, 2019), being the carriers classified as: XG 0.25%, Level 1; XG 0.5% and yoghurt diluted with simulated salivary fluid (SSF), Level 2; and XG 1% and apple puree diluted with SSF, Level 3. The volume left in the syringe for the five the carrier used is reported in **Table 3**. The five carriers tested, therefore, show a wide variety of liquid thicknesses, ranging from slightly thick (L1) to moderately thick (L3).

3.1.2 Shear viscosity of both carriers and their mixtures with pellets

The flow curves obtained in steady shear (**section 2.5**) at 20°C are presented in **Figure 3**. In general, all carriers showed shear thinning behaviour across the range of shear rates studied ($\dot{\gamma}$ 5-500 s^{-1}), decreasing the apparent viscosity as $\dot{\gamma}$ increased. At low $\dot{\gamma}$ (< 50 s^{-1}), apple puree diluted with artificial saliva (AP) and XG 1 % showed similar rheological behaviour, same as happened for both diluted yoghurt (Y) and XG 0.5 %, whilst XG 0.25 % clearly showed the lowest shear viscosity of the five carriers tested. As $\dot{\gamma}$ increased (> 50 s^{-1}), the shear thinning behaviour of the food carriers, i.e., AP and Y, was less marked than those of XG carriers, implying significant viscosity differences compared to the liquids of reference at high $\dot{\gamma}$.

The inclusion of multiparticles is expected to produce an increase in both consistency and shear thinning behaviour (Mueller et al., 2010; Marconati et al., 2018b). When pellets were added to the carrier and fully mixed, some rheological differences were observed as a function of $\dot{\gamma}$: AP+pellets shows a higher shear viscosity than XG 1% across the full $\dot{\gamma}$ range studied, whilst Y+pellets is less shear thinning, when compared to Y alone. Despite Y+pellets and XG0.5%+pellets having similar viscosities at low $\dot{\gamma}$, the viscosity of Y+pellets changed considerably depending on the $\dot{\gamma}$ applied: between 40-50 s^{-1}, it shows a similar viscosity to XG1%+pellets, while at higher $\dot{\gamma}$ (300-500 s^{-1}) it behaves more like AP+pellets.

Viscosities at $\dot{\gamma}$ = 50 s^{-1} have been found to correlate with the initial thickness perception and are commonly used as a reference value for comparison between samples (Stokes et al., 2013; Chen & Engelen, 2012; Chen, 2009). Shear viscosity data at $\dot{\gamma} = 50$ s^{-1} and 20°C for both the carriers and their mixtures with pellets are listed in **Table 3**. Formulations were also classified according to the Japanese consistency scale as a function of shear viscosity for thickened drinks (Cichero et al., 2013) using a blue-based colour scale of differing intensities. The most marked differences are found for AP and XG 0.25%, showing the highest and the lowest shear viscosities, respectively. AP is the only carrier which could be classified as over extremely thick at room temperature (587 ± 14 mPa.s), followed closely by XG 1% as extremely thick (460 ± 59 mPa.s). On the other hand, Y and XG 0.5% showed medium viscosity data (254 ± 11 mPa.s and 167 ± 1 mPa.s, respectively) and could be classified as moderately thick liquids, whilst XG 0.25%, the carrier with the lowest shear viscosity at room temperature, could be considered as mildly thick. The addition of pellets increased shear viscosity of the formulation, and subsequently, the consistency level. Two carriers+pellets remained in the same consistency scale compared to the properties of the carrier alone, i.e., XG 0.25% and AP, being categorised as mildly and over extremely thick liquids, respectively. On the other hand, XG0.5%+pellets and XG1%+pellets increased a level of consistency,

whilst Y+pellets increased two consistency levels from moderately to over extremely thick (same consistency level that AP and XG 1%). The most drastic increase in viscosity at $\dot{\gamma} = 50$ s^{-1} was observed for both AP+pellets (+741 mPa.s) and Y+pellets (+481 mPa.s).

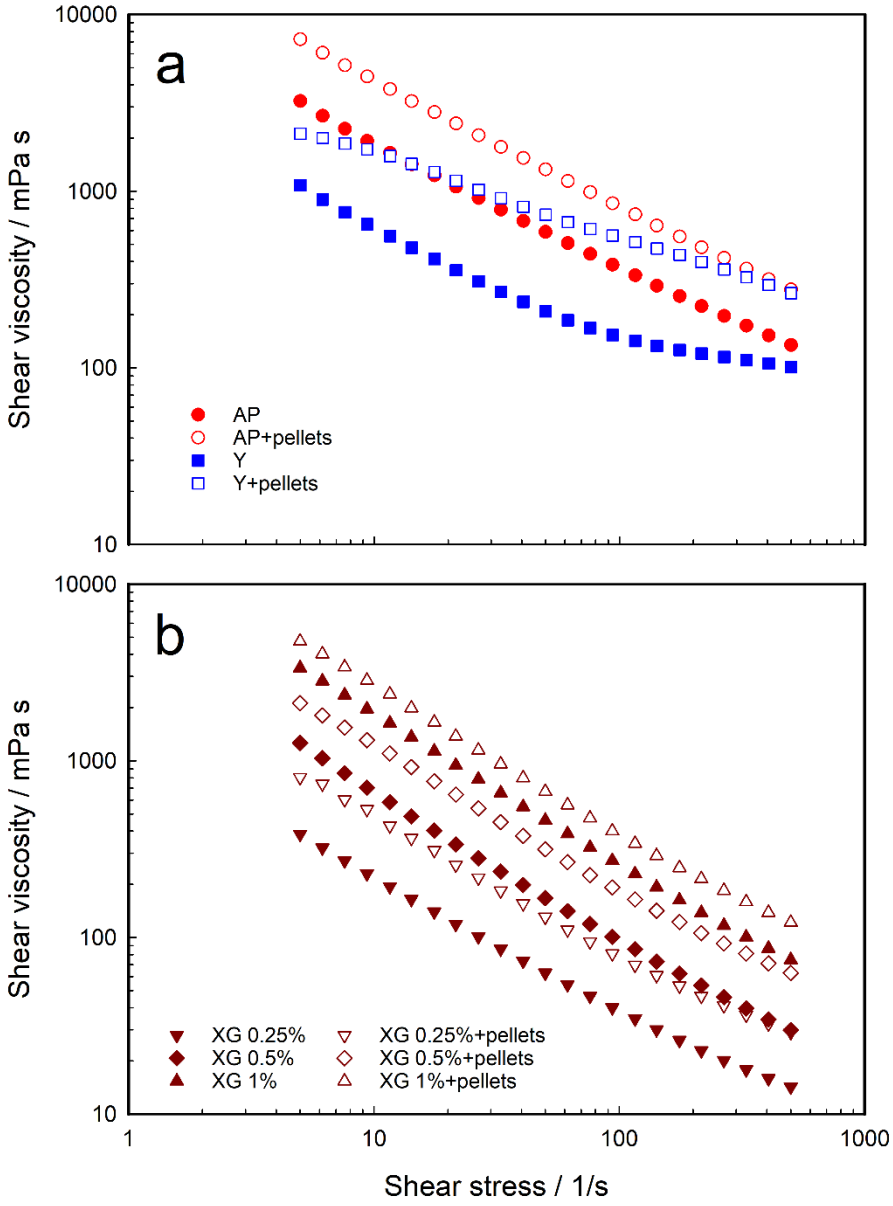

Figure 3. Shear viscosity data of the carriers tested along their mixtures with pellets (350 µm in diameter at a particle volume fraction of 0.2) as a function of shear rate: (a) semi-solid food carriers, apple puree and yoghurt, and (b) the xanthan gum solutions at three different concentrations (0.25, 0.5, and 1 % w/v). The experiments were carried out at 20°C. The geometry used was a concentric cylinder geometry (CC27) of 1 mm gap for all samples. Average data of at least two repeats.

	IDDSI level / mL left	Shear viscosity ($50s^{-1}$) / mPa s		Japanese consistency scale
		Carriers (20°C)	Carriers + pellets (20°C)	
AP + SSF	L3 / 9.8	587 ± 14	1328 ± 100	Less mildly thick
Y + SSF	L2 / 7.6	254 ± 11	735 ± 28	Mildly thick
XG 0.25%	L1 / 3.2	63 ± 0	131 ± 4	Moderately
XG 0.5%	L2 / 7.0	167 ± 1	316 ± 11	Extremely
XG 1%	L3 / 9.8	460 ± 59	670 ± 22	Over extremely

Table 3. IDDSI level and volume left in the syringe for the five the carrier used. Shear viscosity data (**Figure 3**) of carriers and their mixtures with pellets at a shear rate of 50 s^{-1} and 20°C. Average data of at least two repeats. Consistency scale according to the scale reported in (Cichero et al., 2013) for thickened drinks in Japan.

3.1.3 Yield stress of carriers and their mixtures with pellets

Yield stress is representative of the level of the internal structure of carriers which must be overcome before flowing can occur (Zargaraan et al., 2013). It provides valuable information about the effort needed to swallow a bolus (Malouh et al., 2020) and the ability for suspending particles, limiting sedimentation. As detailed in **section 2.5**, yield stress data of carriers was determined by the steady stress test, whilst the yield stress of the mixtures with pellets was estimated from the flow curves using the Herschel-Bulkley (HB) equation (**Eq. 5**) to avoid particle swelling and solubilisation. Yield stress values are listed in **Table 4**.

The highest and lowest yield stresses were measured for XG 1% (12.2 ± 0.9 Pa) and XG 0.25 % (0.9 ± 0.2 Pa), respectively. The rest of carriers tested showed intermediate yield stresses of 4.5 Pa, 4.1 Pa and 2.4 Pa for AP, XG 0.5%, and Y (**Table 4**). When pellets were added, the yield stress increased drastically for most cases, except for yoghurt, for which it seems to decrease in the presence of the particles, being now the formulation with the lowest yield stress. This fact is likely related to a signature of a shear-dependent microstructure due

to the nonlinear behaviour of the interstitial fluid, which makes these materials containing particles different from suspensions in Newtonian media (Ovarlez et al., 2015). Further information of the fitting model can be found in the **SI, section 2**.

3.1.4 Sedimentation of pellets

The sedimentation of pellets in the carriers of interest was estimated according to the theory of a single sphere motion in a yield stress Herschel-Bulkley fluid (**section 2.7**), where no sedimentation occurs if $d_{pellet} < d_{critic}$. The d_{crit} is shown in **Table 4** as a function of the type of carrier used.

In general, the size of the pellets (i.e., 350 or 700 µm) used is much lower that the critical diameter estimated for sedimentation. Therefore, pellets should remain suspended in the carrier during swallowing experiments. This estimation agrees with previous works (Lopez et al., 2018b), reporting that XG hydrogels at 0.25% w/v (η = 70 mPa.s at $\dot{\gamma}$ = 50 s^{-1}) would be sufficient to maintain pellets (< 1000 µm in diameter) in suspension for at least 10–15 min.

	Yield stress / Pa		**ρ / kg.m^{-3}**	**d_{critic} / m**
	Carriers	Carriers + pellets		
Apple puree	4.5 ± 0.1 | 8.7 ± 0.3*	14.3 ± 0.6*	1080	4.39E-2
Yoghurt	1.7 ± 0.3 | 6.6 ± 0.2*	1.2 ± 1.0*	1010	1.25E-2
XG 0.25%	0.9 ± 0.2 | 1.5 ± 0.0*	3.9 ± 0.1*	985	6.12E-3
XG 0.5%	4.1 ± 0.1 | 5.3 ± 0.0*	9.9 ± 0.3*	993	2.86E-2
XG 1%	12.2 ± 0.9 | 13.7 ± 0.4*	21.6 ± 0.6*	1034	9.81E-2

* Values estimated by the HB model.

Table 4. Yield stress of both the carriers and of their mixtures with pellets of 350 µm in diameter at a volume fraction of 0.2 and 20°C. For the carriers, yield stress was determined using both the steady stress method and estimated by the HB model (**section 2.5**). For their mixtures with pellets, yield stress was estimated using the HB model. CC27 geometry was

used for characterisation. Average data of at least two repeats. Density of the carrier at 20°C and sedimentation diameter calculated according to the detailed in **section 2.7** are also shown.

3.2 *In vitro* swallowing of size-reduced multiparticle solid oral formulations

3.2.1 Effect of the administration method on pellets swallowability

The effect of the administration method on *in vitro* swallowing of pellets (350 µm in diameter) has been investigated using XG 1% (5 mL) and a particle volume fraction (v.f.) of 0.15 (**Table 2**). Two different scenarios were considered (**Figure 2c**):

(i) pellets were placed on top of the carrier

(ii) pellets were distributed in the carrier matrix before feeding.

In the first case, pellets were placed at the top part of the carrier-air interface without apparent distribution through the carrier, reducing the percentage of pellets swallowed to only ~10% (**Figure 4**). In real conditions, this could also lead to an unpleasant sensation due to the large number of particles of small size in contact with the palate. In contrast, the 2nd administration method led to a uniform distribution of pellets on the carrier matrix, without apparent segregation of the particles once they were introduced into the in vitro oral cavity, favouring the swallowability of the pharmaceutical formulations (ca. 80% of pellets swallowed; **Figure 4**). In terms of bolus velocity and residues, no significant differences were found between the two feeding approaches.

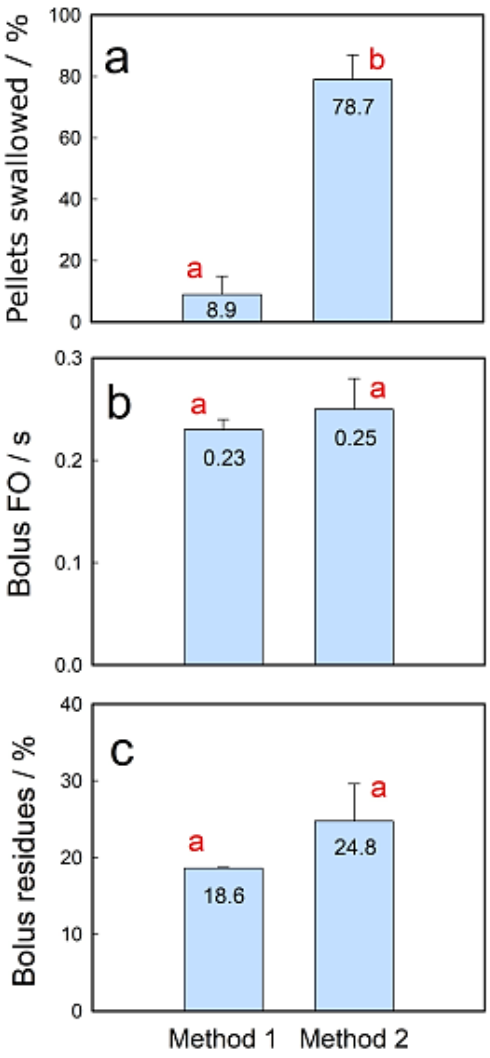

Figure 4. Effect of the feeding method on *in vitro* swallowing. Method 1: pellets were spread on top of the carrier; Method 2: pellets were fully mixed with the carrier of interest. The swallowing variables studied were: (a) the percentage of pellets swallowed, (b) the time of bolus front out, and (c) the percentage of bolus residues. The carrier used was XG 1% (volume 5 mL), pellets of 350 µm in diameter, and a particle volume fraction of 0.15. Average data of at least three repeats. Red letters indicate significant differences ($p < 0.05$) between data groups.

Multi-particulates dispersed in polymeric hydrogels tend to be easier to swallow for adults than multi-particulates dispersed in water, reducing the feeling of particles left in the mouth after swallowing (Marconati et al., 2019; Kluk & Sznitowska, 2014). A previous *in vitro* work has shown that, in order to favour the swallowing process, minitablets (2.5 mm) should be placed on top of a spoon full of carrier rather than mixed with the carrier in its container (Lavoisier et al., 2022). According to these results, the administration method used

will strongly depend on the characteristics of the multi-particulate formulation under study (i.e., mini-tablets vs pellets).

The feeding method considered for further testing using pellets is: pellets and carrier mixed before feeding, keeping a total volume of the bolus constant at 5 mL. This agrees with a real scenario where pellets are poured into a commercial food product (i.e., yoghurt) and mixed homogenously before administration, taking then a certain amount of product with a teaspoon. A practical limitation of this scenario would be that the child should eat all the food to receive the right amount of drug.

3.2.2 Effect of the type of semi-solid carrier on pellets swallowability

The effect of the type of semi-solid food carrier on the *in vitro* swallowability of pellets was investigated using 350 µm pellets at v.f. = 0.2. Results are shown in **Figure 5**. In general, all the swallowing parameters evaluated (time of bolus front out, percentage of pellets swallowed, and percentage of both bolus and carrier residues) were affected by the type of carrier used. Regarding the percentage of pellets swallowed (**Figure 5a**), less particles were successfully swallowed with yoghurt and apple puree under the tested conditions, whilst xanthan gum-based solutions reached excellent success rates (≥ 75 %), especially at high concentrations, i.e., 0.5 and 1%. The addition of particles to the carrier increased its shear viscosity (cf. **section 3.1.2**), a fact that at first instance could favour the swallowing of pellets when using carriers of low viscosity and low yield stress. However, when the shear viscosity of formulations was above 300 mPa.s at high $\dot{\gamma}$ (i.e., 330 s^{-1}) pellets swallowability decreased (**Figure 6**). This scenario seems to agree with previous *in vivo* studies where, in terms of the vehicle used, adult participants preferred samples with low and middle-range consistencies (XG 0.25-0.5%) over the extremely thick ones such as XG 1% (despite the good swallowing behaviour of this formulation), as those carriers achieved a good balance by "concealing the presence of particles in the mouth" but not being too thick, which had a detrimental impact on

mouthfeel (Lopez et al., 2018b); they used a pellets volume fraction of ca. 0.06, a lower particle fraction than the one considered in this work. On the other hand, when pellets were added to the carriers in the current study, the formulation complexity of food products seems to lead to more complex interactions than the carriers of reference; for instance, the viscosity of diluted yoghurt and pellets, in particular, would be highly affected by the shear applied during swallowing (**section 3.1.2**).

Regarding the other swallowing variables investigated, bolus velocity seems to be related to both carrier rheology (cf. **Figure 4**) and the position of the bolus before triggering the swallow (see **SI**, **section 3**). Bolus containing carriers with low shear viscosity and low yield stress (i.e., XG 0.25%, 0.5% and diluted yoghurt) were distributed along the artificial tongue and showed shorter swallowing times, compared to bolus containing AP and XG 1% (products with high shear viscosity and high yield stress), that were positioned closer to the artificial tongue's tip (see **SI**, **section 3**). The three XG solutions tend to reach lower levels of post-swallow residues after swallowing than food-based carriers (**Figure 5c**), but data variability led to no marked differences.

Even if XG solutions appeared to be better transporters than the other carriers, we assumed that children would prefer to consume food products rather than thickened liquids as reported for adults and older people with swallowing difficulties (Lopez et al., 2016; O'Leary et al., 2010). Therefore, diluted yoghurt was selected for further testing against apple puree as it showed (i) a faster bolus front out and (ii) a slightly higher percentage of pellets swallowed (+ 3.4%)., and (iii) could also get a better acceptability by children (e.g., masking power) for administration of the pharmaceutical formulations (Morel et al., 2021).

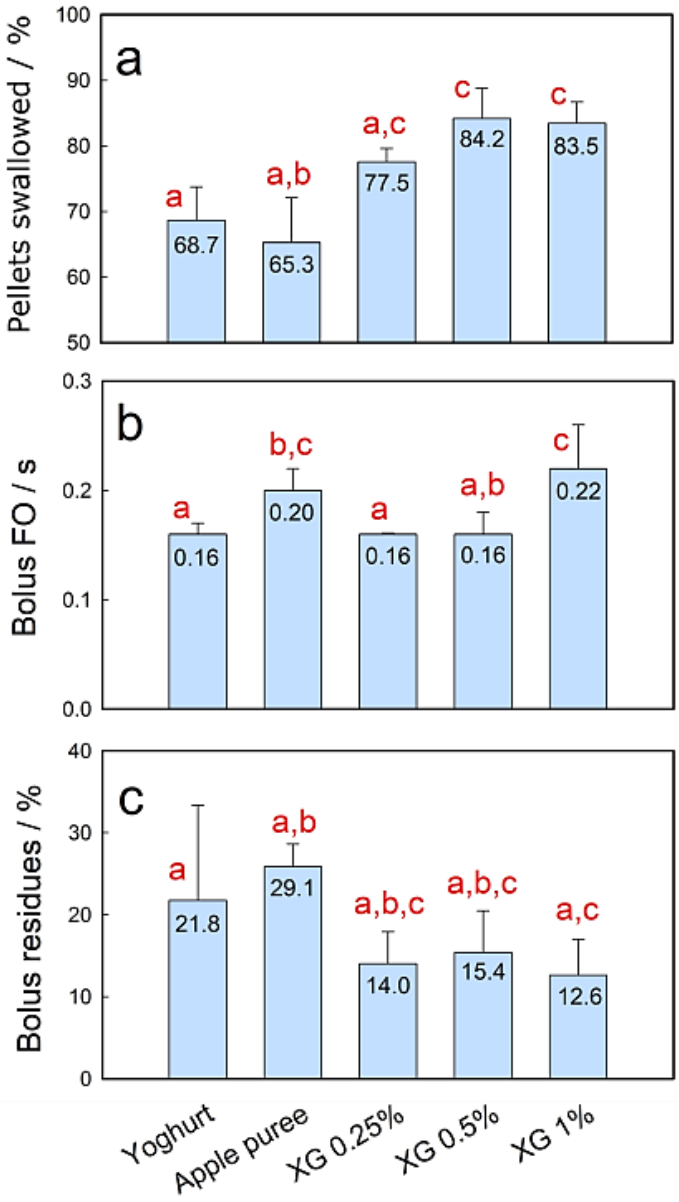

Figure 5. Effect of the type of carrier used on the *in vitro* swallowability of pellets of 350 µm in diameter: (a) percentage of pellets swallowed, (b) time of bolus front out (s), and (c) percentage of post-swallow residues. The carrier tested were diluted apple puree, diluted yoghurt, XG 0.25%, XG 0.5%, and XG 1%. Average data of at least three repeats. Red letters indicate significant differences ($p < 0.05$) between data groups.

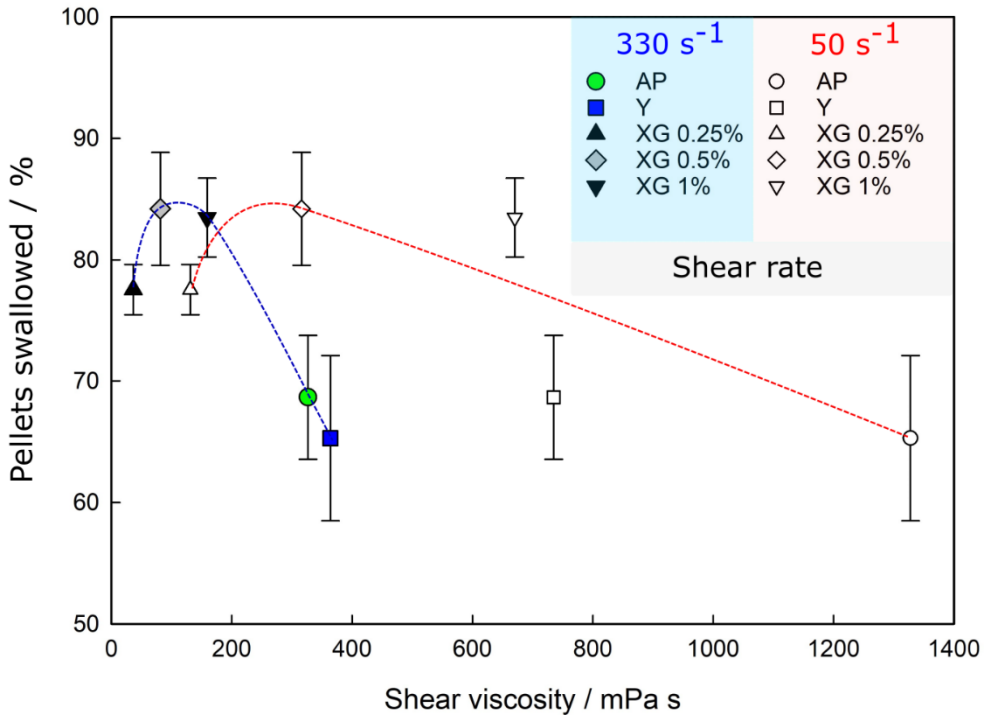

Figure 6. Percentage of pellets (350 µm) swallowed as a function of the shear viscosity values of the carrier-pellets formulations tested at two different shear rate, 50 s^{-1} (red) and 330 s^{-1} (blue). Average data of at least two repetitions. Lines are a guide to the eye.

3.2.3 Effect of the size of pellets on *in vitro* swallowing

Previous *in vivo* studies in adults showed that swallowing of pellets using XG solutions (0.25-1%) was more difficult when increasing particle size (from 200 to 700 µm) (Lopez et al., 2018a, 2018b; Marconati et al., 2018b). Here, the effect of the pellet size on *in vitro* swallowing was investigated using diluted yoghurt as a carrier at v.f. = 0.2. Results are presented in **Figure 7(a-c)**.

In general, no significant differences were found between the two sizes of pellets considered, 350 and 700 µm. However, the marked rheological change of the diluted yoghurt in presence of pellets (**section 3.1**) could be masking the effect of the pellet size on the swallowing parameters examined. Despite the size of the pellets seems not to affect the swallowing parameters studied, it is important to bear in mind that particle size affects oral grittiness (Kimura et al., 2015; Mishra et al., 2009; Engelen et al., 2005; Imai et al., 1995), where small

multi-particulates are considered less gritty and more pleasant than large ones (Lopez et al., 2016; 2018a), and the feeling of residual particles in the mouth (Marconati et al., 2018b).

3.2.4 Effect of the particle volume fraction on pellets swallowability

As discussed in the introduction, large volumes of multi-particulates are often required in practice, and it is still unclear the number of particles that could be administered maintaining acceptability. In this section, the effect of the particle volume fraction (v.f. = 0.1-0.4) on *in vitro* pellets swallowability was investigated using diluted yoghurt as carrier, keeping a total bolus volume of 5 mL. Results are presented in **Figure 7(d-f)**.

All swallowing parameters studied were affected by the percentage of pellets added to the carrier. Overall, an v.f. increase resulted in a marked decrease of both the percentage of pellets swallowed and the bolus velocity (**Figure 7d** and **7e**, respectively). At v.f. 0.1 and 0.2, there were not significant differences between bolus FO. However, the time for the oral phase of swallowing doubled as v.f. increased from 0.1 to 0.4. The percentage of pellets successfully swallowed decreased linearly by 1/3 as v.f. increased from 0.1 to 0.4, resulting in a swallowing success rate around 50 % at v.f. 0.4. On the other hand, post-swallow residues seem to increase as the volume fraction increased (**Figure 7f**), however, differences were not statistically significant.

3.2.5 Effect of the bolus volume on pellets swallowability

The effect of bolus volume (i.e., 5 mL, 6.25 mL, and 8.34 mL; **Table 2**) at two different v.f., 0.2 and 0.4 (**Figure 7(d-i)**) on pellets swallowability was investigated using pellets of 350 µm in diameter and diluted yoghurt (5 mL) as carrier. Both carrier and pellets were mixed before feeding into the *in vitro* oral cavity (**section 2.4**). According to these results, no significant differences between swallowing variables were found. Therefore, the volume of

the bolus in the oral cavity (or the filling level) under the range of conditions tested did not affect the swallowability of pellets.

3.2.6 *In vitro* swallowing comparison between pellets and minitablets

The effects of the feeding method, type of carrier, particle size, and particle volume fraction on minitablets swallowability have been reported in previous work (Lavoisier et al., 2022). In this section, the effect of the type of SODF used, i.e., MTs 1.8 mm or pellets 350 µm in diameter, on *in vitro* swallowing was investigated at v.f. = 0.4, using diluted yoghurt as a carrier. The total volume of the bolus was kept constant at 5 mL. Both the carrier and the SODF of interest were fully mixed before feeding (**section 2.4**). Results are shown in **Figure 7(j-l)**. In terms of the percentage of particles successfully swallowed, pellets led to better outcomes than MTs (+ 13.1%; **Figure 7j**). However, no differences were found between MTs and pellets for the other swallowing variables studied (bolus FO and post-swallow residues) under the conditions tested.

3.2.7 *In vitro* swallowing of a novel binary mixture formed by minitablets and pellets

Combining MTs and pellets might enhance their swallowability by increasing the maximum packing fraction of the solid phase which may help particle flow during swallowing. The size ratio and the minimum pore size (size of the voids formed by MTs), in air, of the possible binary mixtures (BM) formed by both MTs and pellets were calculated as detailed in **section 2.3** and results are shown in **Table 5**. The most favourable packing conditions would be at the highest size ratio, which corresponds to the mixture formed by MT of 3 mm and pellets of 350 µm. However, avoiding pellets flow throughout the voids formed by the MTs (i.e., particle segregation) is desired to favour packing. Therefore, the minimum pore size was also taken into consideration. According to **Table 5**, the optimum binary mixture should be the one formed by MTs of 1.8 mm and pellets of 350 µm in diameter. This

SODF combination was then selected for further testing. Using the theoretical model implemented in the **SI** (**section 1**) proposed by (Pillitteri et al., 2020), the maximum packing fraction (η_{max}) of the binary mixtures formed by the MT (1.8 mm) and pellets (350 µm) occurs at a value of *f* 0.24, being *f* the fraction of pellets. Therefore, 24 % of pellets should be added to the binary formulation to favour flowing of the particles during swallowing.

Keeping a total bolus volume of 5 mL, the *in vitro* swallowability of the binary mixture was tested using diluted yoghurt as carrier at a v.f. of 0.4. Swallowing results are shown in **Figure 7(j-l)**. The binary mixture improved particle swallowability compared to MTs (ca. +17%) but did not outperform pellets significantly (+3.6%). On the other hand, no significant differences were found in terms of bolus velocity and post-swallow residues. However, the post-swallow residues seem to be slightly greater for MTs than for both BM and pellets (**Figures 7k** and **7l**), decreasing the percentage of residues as the proportion of pellets increases.

Therefore, our initial hypothesis was confirmed, as by adding 24% pellets to a binary granular formulation in which minitablets were the dominant granular system, swallowability was improved, reaching swallowing levels to those reported by small particles like pellets.

3.3 Limitations and perspectives for future studies

One limitation of this study concerns the oral salivary lubrication, not considered here. Regarding the SODF tested, MTs were considered fully spherical for calculations. Moreover, among the several possible binary mixtures, only the mixture at the maximum solid packing fraction has been tested. Therefore, future research could be conducted considering these aspects, exploring the impact that a more realistic lubrication may have on the swallowing process of a wider variety of SODF mixtures.

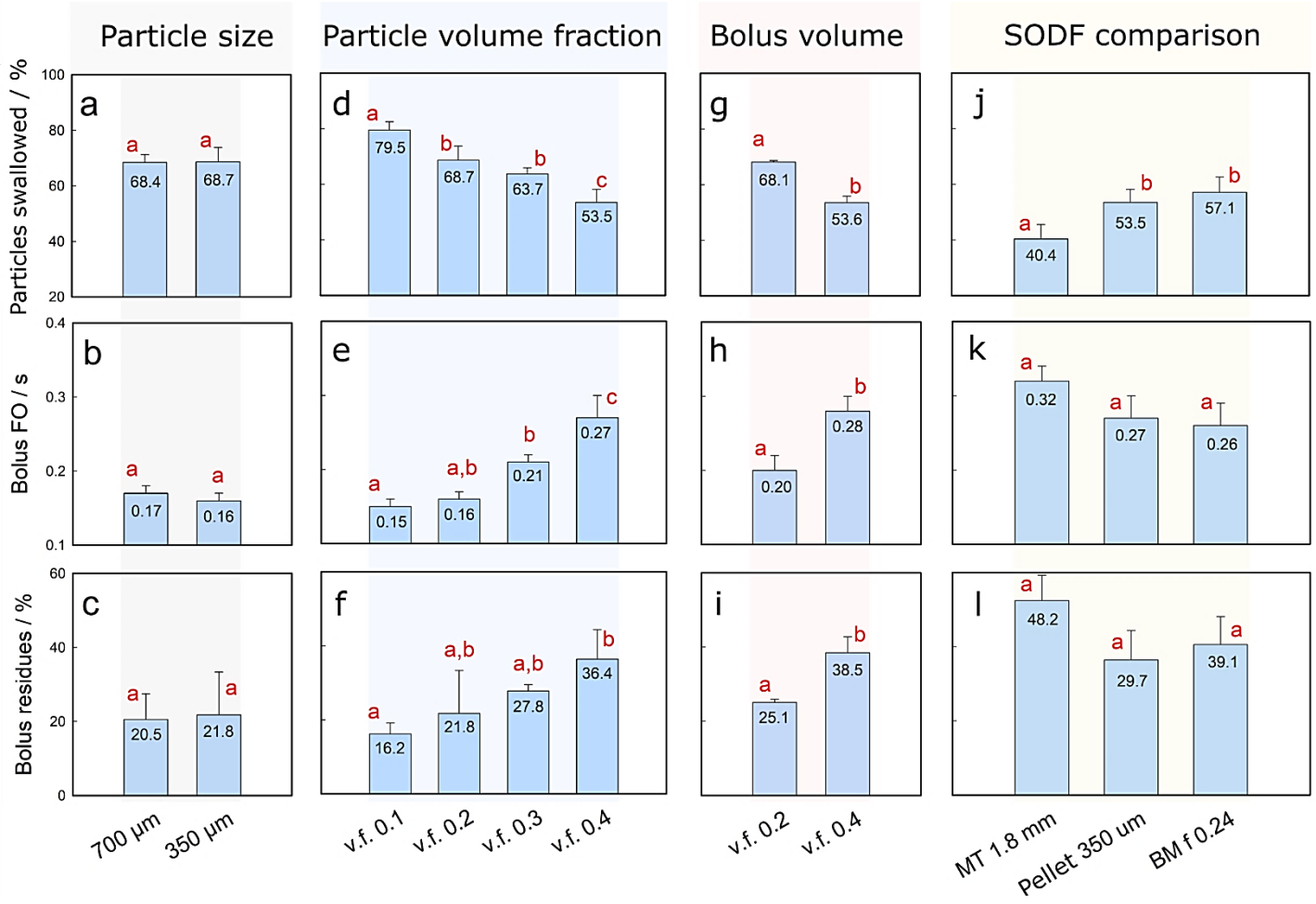

Figure 7. Effect of size (a-c), particle volume fraction (d-f) and bolus volume (g-i) of pellets, and of the type of SODF used (j-l) on the *in vitro* swallowing of SODF. The swallowing variables investigated are: (a, d, g, j) the percentage of the particles swallowed, (b, e, h, k) the time of bolus front out (s), and (c, f, i, l) the percentage of bolus post-swallow residues. Average data of at least three repeats. Red letters indicate significant differences ($p < 0.05$) between data groups. Abbreviations are: (v.f.) particle volume fraction, (MT) minitablet, and (BM) binary mixture formed by MTs and pellets as the detailed in **section 2.3**, where *f* defines the fraction of pellets.

Table 5. Size ratio and minimum pore size (size of the voids formed by minitablet), in air, for the possible minitablets-pellets combinations. The optimum binary mixture selected for further testing is marked in bold. The pore sizes leading to percolation of the binary mixtures are highlighted in grey.

MT / mm	Pellet / µm	α	Pore size / µm
1.8	700	2.6	278.6
2.3	700	3.3	356.0
2.5	700	3.6	387.0
3.0	700	4.3	464.4
1.8	**350**	**5.1**	**278.6**
2.3	350	6.6	356.0
2.5	350	7.1	387.0
3.0	350	8.6	464.4

4. Conclusions

The Paediatric Soft Robotic Tongue (PSRT) – an *in vitro* device inspired by the anatomy and physiology of 2-year-old children – was used to investigate the oral phase of swallowing of multiparticle solid oral dosage forms (SODFs), i.e., pellets (350 and 700 µm particles), minitablets (MTs, 1.8 mm), and their binary mixtures (BM). Swallowing time, fraction of particles swallowed, and the amount of post-swallow residues were measured. A systematic study was also conducted to determine how the feeding method, bolus volume, type of carrier, particle size, and particle volume fraction affect pellets swallowability.

The ability of the carriers to flow was significantly affected by the addition of pellets: shear viscosity generally increased, yet little effect was observed on their shear thinning behaviour. Xanthan gum-based solutions achieved excellent success rates (≥ 75 %), especially at high concentrations, i.e., 0.5 and 1%, favouring pellets transport without affecting post-swallow residues. Despite the size of the pellets (350 and 700 µm) not having a significant impact on particle swallowability, the volume fraction (v.f.) of particles used above 10% did; the number of particles swallowed decreased as the volume fraction increased. At v.f. 0.4, pellets were easier to swallow (+ 13.1%) than MTs, while the administration method used strongly depended on the characteristics of the multi-particulate formulation under study. To increase MT swallowability, a novel approach involving MT-pellets binary mixtures was explored, which increased the maximum solid packing fraction of the formulation. Our results confirm that by adding 24% pellets to MTs, SODF swallowability was improved, reaching swallowing levels similar to pellets. Such flexible formulations are therefore easier to swallow *in vitro* and should be explored for combination products.

Acknowledgements

This study was funded by F. Hoffmann-La Roche AG

References

Brodkorb, A., Egger, L., Alminger, M., Alvito, P., Assunção, R., Ballance, S., Bohn, T., Bourlieu-Lacanal, C., Boutrou, R., Carrière, F., Clemente, A., Corredig, M., Dupont, D., Dufour, C., Edwards, C., Golding, M., Karakaya, S., Kirkhus, B., Le Feunteun, S., Lesmes, U., Macierzanka, A., Mackie, A.R., Martins, C., Marze, S., McClements, D.J., Ménard, O., Minekus, M., Portmann, D., Santos, C.N., Souchon, I., Singh, P., Vegarud, G.E., Martin, Wickham, S.J., Weitschies, W., Recio, I., 2019. INFOGEST Static in Vitro Simulation of Gastrointestinal Food Digestion. Nat. Prot. 14(4):991–1014. https://doi.org/10.1038/s41596-018-0119-1

Chen, J., 2009. Food oral processing — A review. Food Hydrocoll. 23, 1-25. https://doi.org/10.1016/j.foodhyd.2007.11.013

Chen, J., Engelen, L., 2012. Food Oral Processing: Fundamentals of Eating and Sensory Perception Hoboken: Wiley Blackwell.

Cichero, J.A.Y., Steele, C., Duivestein, J., Clavé, P., Chen, J., Kayashita, J., Dantas, R., Lecko, C., Speyer, R., Lam, P., Murray, J., 2013. The Need for International Terminology and Definitions for Texture-Modified Foods and Thickened Liquids Used in Dysphagia Management: Foundations of a Global Initiative. Curr. Phys. Med. Rehabil. Rep. 1(4), 280–291. https://doi.org/10.1007/s40141-013-0024-z

Cloyd, J.C., Kriel, R.L., Jones-Saete, C.M., Ong, B.Y., Jancik, J.T., Remmel, R.P., 1992. Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference. J. Pediatr. 120, 634–638. https://doi.org/10.1016/S0022-3476(05)82496-5

Committee for Medical Products for Human Use, and Paediatric Committee, 2013. Guideline on Pharmaceutical Development of Medicines for Paediatric Use. European Medicines Agency.

Coussot, P., 2012. Rhéophysique, la matière dans tous ses états. EDP Sciences 338, 978-2-7598-0759-8. ⟨hal-00952045⟩

EMA 2006. EMEA/CHMP/PEG/194810/2005

Engelen, L., Van der Bilt, A., Schipper, M., Bosman, F., 2005. Oral size perception of particles: effect of size, type, viscosity and method. J. Texture Stud. 36, 373–386. https://doi.org/10.1111/j.1745-4603.2005.00022.x

Fernández-García, R., Prada, M., Bolás-Fernández, F., Ballesteros, M.P., Serrano, D.R., 2020. Oral Fixed-Dose Combination Pharmaceutical Products: Industrial Manufacturing Versus Personalized 3D Printing. Pharm Res. 37: 132. https://doi.org/10.1007/s11095-020-02847-3

Gelman, A., 2005. Analysis of variance — why it is more important than ever. Ann. Stat. 33, 1–53. https://doi.org/10.1214/009053604000001048

Haxton, T.K., Schmiedeberg, M., Liu, A.J., 2011. Universal jamming phase diagram in the hard-sphere limit. Phys Rev E Stat Nonlin Soft Matter Phys 83:031503. https://doi.org/10.1103/PhysRevE.83.031503

IDDSI. (2019). Complete IDDSI Framework detailed definitions 2.0.

Ikeda, A., Berthier, L., Sollich, P., 2012. Unified study of glass and jamming rheology in soft particle systems. Phys. Rev. Lett. 109, 018301. https://doi.org/10.1103/PhysRevLett.109.018301

Imai, E., Hatae, K., Shimada, A., 1995. Oral Perception of Grittiness: Effect of Particle Size and Concentration of the Dispersed Particles and the Dispersion Medium. J. Texture Stud. 26(5):561–76. https://doi.org/10.1111/j.1745-4603.1995.tb00804.x

Jones, D.V., Work, E.C., 1961. Volume of a Swallow. Am. J. Dis. Children 102(3):427–427. https://doi.org/10.1001/archpedi.1961.02080010429023

Kimura, S., Uchida, S., Kanada, K., Namiki, N., 2015. Effect of granule properties on rough mouth feel and palatability of orally disintegrating tablets. Int. J. Pharm. 484, 156–162. https://doi.org/10.1016/j.ijpharm.2015.02.023

Klingmann, V., Spomer, N., Lerch, C., Stoltenberg, I., Frömke, C., Bosse, H.M., Breitkreutz, J., Meissner, T., 2013. Favorable Acceptance of Mini-Tablets Compared with Syrup: A Randomized Controlled Trial in Infants and Preschool Children. J. Pediatrics 163(6):1728-1732.e1. https://doi.org/10.1016/j.jpeds.2013.07.014

Klingmann, V., Seitz, A., Meissner, T., Breitkreutz, J., Moeltner, A., Bosse, H.M., 2015. Acceptability of Uncoated Mini-Tablets in Neonates—A Randomized Controlled Trial. J. Pediatrics 167(4):893-896.e2. https://doi.org/10.1016/j.jpeds.2015.07.010

Klingmann, V., 2017. Acceptability of Mini-Tablets in Young Children: Results from Three Prospective Cross-over Studies. AAPS PharmSciTech. 18, 2. https://doi.org/10.1208/s12249-016-0639-3

Klingmann, V., Linderskamp, H., Meissner, T., Mayatepek, E., Moeltner, A., Breitkreutz, J., Bosse, H.M., 2018. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. J. Pediatrics 201:202-207.e1. https://doi.org/10.1016/j.jpeds.2018.05.031

Kluk, A., Sznitowska, M., 2014. Application Properties of Oral Gels as Media for Administration of Minitablets and Pellets to Paediatric Patients. Int. J. Pharmaceutics 460(1–2):228–33. https://doi.org/10.1016/j.ijpharm.2013.10.052

Kluk, A., Sznitowska, M., Brandt, A., Sznurkowska, K., Plata-Nazar, K., Mysliwiec, M., Kaminska, B., Kotlowska, H., 2015. Can Preschool-Aged Children Swallow Several Minitablets at a Time? Results from a Clinical Pilot Study. Int. J. Pharmaceutics 485(1):1–6. https://doi.org/10.1016/j.ijpharm.2015.02.068

Kozarewicz, P., 2014. Regulatory Perspectives on Acceptability Testing of Dosage Forms in Children. Int. J. Pharmaceutics 469(2):245–48. https://doi.org/10.1016/j.ijpharm.2014.03.057

Krieger, I.M., Dougherty, T.J., 1959. A Mechanism for Non- Newtonian Flow in Suspensions of Rigid Spheres. Trans. Soc. Rheol. 3, 137-152. https://doi.org/10.1122/1.548848

Lavoisier, A., Avila-Sierra, A., Timpe, C., Kuehl, P., Wagner, L., Tournier, C., Ramaioli, M., 2022. A novel soft robotic pediatric in vitro swallowing device to gain insights into the swallowability of mini-tablets. Int. J. Pharm. 629 (2022) 122369. https://doi.org/10.1016/j.ijpharm.2022.122369

Lopez, F.L., Bowles, A., Orlu Gul, M., Clapham, D., Ernest, T.B., Tuleu, C., 2016. Effect of Formulation Variables on Oral Grittiness and Preferences of Multiparticulate Formulations in Adult Volunteers. European J. Pharmaceutical Sci. 92:156–62. https://doi.org/10.1016/j.ejps.2016.07.006

Lopez, F.L., Mistry, P., Batchelor, H.K., Bennett, J., Coupe, A., Ernest, T.B., Orlu, M., Tuleu, C., 2018a. Acceptability of placebo multiparticulate formulations in children and adults. Scientific reports 8, 9210. https://doi.org/10.1038/s41598-018-27446-6

Lopez, F.L., Ernest, T.B., Orlu, M., Tuleu, C., 2018b. The Effect of Administration Media on Palatability and Ease of Swallowing of Multiparticulate Formulations. Int. J. Pharmaceutics 551(1–2):67–75. https://doi.org/10.1016/j.ijpharm.2018.08.021

Malouh, M.A., Cichero, J.A.Y., Manrique, Y.J., Crino, L., Lau, E.T.L., Nissen, L.M., Steadman, K.J., 2020. Are Medication Swallowing Lubricants Suitable for Use in Dysphagia? Consistency, Viscosity, Texture, and Application of the International Dysphagia Diet Standardization Initiative (IDDSI) Framework. Pharmaceutics 12(10):924. https://doi.org/10.3390/pharmaceutics12100924

Marconati, M., Raut, S., Burbidge, A., Engmann, J., Ramaioli, M., 2018a. An in vitro experiment to simulate how easy tablets are to swallow. Int. J. Pharmaceutics 535(1-2), 27-37. https://doi.org/10.1016/j.ijpharm.2017.10.028

Marconati, M., Lopez, F., Tuleu, C., Orlu, M., Ramaioli, M., 2018b. In Vitro and Sensory Tests to Design Easy-to-Swallow Multi-Particulate Formulations. European J. Pharmaceutical Sci. 132:157–62. https://doi.org/10.1016/j.ejps.2019.02.026

Marconati, M., Engmann, J., Burbidge, A.S., Mathieu, V., Souchon, I., Ramaioli, M., 2019. A Review of the Approaches to Predict the Ease of Swallowing and Post-Swallow Residues. Trends Food Sci. Tech. 86:281–97. https://doi.org/10.1016/j.tifs.2019.02.045

Minekus, M., Alminger, M., Alvito, P., Ballance, S., Bohn, T., Bourlieu, C., Carrière, F., Boutrou, R., Corredig, M., Dupont, D., Dufour, C., Egger, L., Golding, M., Karakaya, S., Kirkhus, B., Le Feunteun, S., Lesmes, U., Macierzanka, A., Mackie, A., Marze, S., McClements, D.J., Ménard, O., Recio, I., Santos, C.N., Singh, R.P., Vegarud, G.E., Wickham, M.S.J., Weitschies, W., Brodkorb, A., 2014. A Standardised Static in Vitro Digestion Method Suitable for Food – an International Consensus. Food Funct. 5(6):1113–24. https://doi.org/10.1039/C3FO60702J

Mishra, B., Sharma, G., Shukla, D., 2009. Investigation of Organoleptic Characteristics in the Development of Soft Chews of Calcium Carbonate as Mineral Supplement. Yakugaku Zasshi, 129, 1537-1544. https://doi.org/10.1248/yakushi.129.1537

Mistry, P., Batchelor, H., 2017. Evidence of Acceptability of Oral Paediatric Medicines: A Review. J. Pharmacy Pharmaco. 69(4):361–76. https://doi.org/10.1111/jphp.12610

Morel, S., Aranyos, A., Lechat, H., Ayouni, F., Bonnefille, M., 2021. Selecting the food matrix with the highest masking power for delivering Recommendations for children intake. Formulating Better Medicines for Children, EuPFi – European Paediatric Formulation Initiative.

Moriarty, F., Bennett, K., Fahey, T., 2019. Fixed-dose combination antihypertensives and risk of medication errors. Heart. 105: 204–209. http://dx.doi.org/10.1136/heartjnl-2018-313492

Motte, J., Pedespan, J.M., Sevestre, M., Chiron, C., 2005. Acceptability and tolerance of sodium valproate, a new sustained-action granule formulation, in monotherapy for epileptic children from 3 years old. Arch. Pediatr. 12, 1533–1539. https://doi.org/10.1016/j.arcped.2005.07.009.

Mueller, S., Llewellin, E.W., Mader, H.M., 2010. The Rheology of Suspensions of Solid Particles. Proceed. Royal Soc. A: Math., Phys. and Eng. Sci. 466(2116):1201–28. https://doi.org/10.1098/rspa.2009.0445

Musiime, V., Fillekes, Q., Kekitiinwa, A., Kendall, L., Keishanyu, R., Namuddu, R., Young, N., Opilo, W., Lallemant, M.A., Walker, S., Burger, D., Gibb, D.M., 2014. The Pharmacokinetics and Acceptability of Lopinavir/Ritonavir Minitab Sprinkles, Tablets, and Syrups in African HIV-Infected Children. JAIDS J. Acq. Immune Def. Syndromes 66(2):148–54. https://doi.org/10.1097/QAI.0000000000000135

Miyazaki, K., Hida, N., Kamiya, T., Yamazaki, T., Murayama, N., Kuroiwa, M., Kurata, N., Ishikawa, Y., Yamashita, S., Nakamura, H., Nakamura, A., Harada, T., 2022. Comparative acceptability of mini-tablets, fine granules, and liquid formulations in young children: An exploratory randomized crossover study. J. Drug Delivery Sci. Tech. 70, 103154. https://doi.org/10.1016/j.jddst.2022.103154

O'Leary, M., Hanson, B., Smith, C., 2010. Viscosity and Non-Newtonian Features of Thickened Fluids Used for Dysphagia Therapy. J. Food Sci. 75, E330-8. https://doi.org/10.1111/j.1750-3841.2010.01673.x

Orubu, S., Okwelogu, C., Opanug, O., Tuleua, C., 2018. A survey of caregivers of Nigerian children less than 6 years of age to determine the experience and perception of acceptability of oral solid dosage forms. Int. J. Pharmaceutics 536, 582–589. https://doi.org/10.1016/j.ijpharm.2017.10.047

Ovarlez, G., Mahaut, F., Deboeuf, S., Lenoir, N., Hormozi, S., Château, X., 2015. Flows of suspensions of particles in yield stress fluids. J. Rheology 59 (6): 1449. https://hal.archives-ouvertes.fr/hal-01223726

Pillitteri, S., Opsomer, E., Lumaya, G., Vandewalle, N., 2020. How size ratio and segregation affect the packing of binary granular mixtures. Soft Matt. 16, 9094. https://doi.org/10.1039/D0SM00939C

Riet-Nales, D.A., de Neef, B.J., Schobben, A.F., Ferreira, J.A., Egberts, T.G.C., Rademaker, C.M.A., 2013. Acceptability of Different Oral Formulations in Infants and Preschool Children. Arch. Disease Childhood 98(9):725–31. https://doi.org/10.1136/archdischild-2012-303303

Sadia, M., Isreb, A., Abbadi, I., Isreb, M., Aziz, D., Selo, A., Timmins, P., Alhnan, M.A., 2018. From 'fixed dose combinations' to 'a dynamic dose combiner': 3D printed bi-layer antihypertensive tablets. Eur. J. Pharm. Sci. 123: 484–94. https://doi.org/10.1016/j.ejps.2018.07.045

Salkind, N.J., 2010. Encyclopedia of Research Design, volume 1.

Schlosser, R., 2019. Fixed-dose and fixed-ratio combination therapies in type 2 diabetes. Can. J. Diabetes 43: 440–444. https://doi.org/10.1016/j.jcjd.2019.05.005

Soddy, F. 1936. The Kiss Precise. Nature 137, 1021. https://doi.org/10.1038/1371021a0

Song, C., Wang, P., Makse, H.A., 2008. A phase diagram for jammed matter. Nature 453, 629–632. https://doi.org/10.1038/nature06981

Spomer, N., Klingmann, V., Stoltenberg, I., Lerch, C., Meissner, T., Breitkreutz, J., 2012. Acceptance of Uncoated Mini-Tablets in Young Children: Results from a Prospective Exploratory Cross-over Study. Arch. Disease Childhood 97(3):283–86. https://doi.org/10.1136/archdischild-2011-300958

Stokes, J.R., Boehm, M., Baier, S.K., 2013. Oral processing, texture and mouthfeel: From rheology to tribology and beyond. Current Op. Colloid Interface Sci. 18, 349-359. https://doi.org/10.1016/j.cocis.2013.04.010

Ternik, R., Liu, F., Bartlett, J.A., Khong, Y.M., Tan, D.C.T., Dixit, T., Wang, S., Galella, E.A., Gao, Z., Klein, A., 2018. Assessment of Swallowability and Palatability of Oral Dosage Forms in Children: Report from an M-CERSI Pediatric Formulation Workshop. Int. J. Pharmaceutics 536(2):570–81. https://doi.org/10.1016/j.ijpharm.2017.08.088

Thomson, S.A., Tuleu, C., Wong, I.C.K., Keady, S., Pitt, K.C., Sutcliffe, A.G., 2009. Minitablets: New Modality to Deliver Medicines to Preschool-Aged Children. Pediatrics 123(2):e235–38. https://doi.org/10.1542/peds.2008-2059

Vaiman, M., Segal, S., Eviatar, E., 2004. Surface Electromyographic Studies of Swallowing in Normal Children, Age 4–12 Years. Int. J. Pediatric Otorhinolaryngology 68(1):65–73. https://doi.org/10.1016/j.ijporl.2003.09.014

VandenBerg, C.J., Adams, A., Bockrath, R., Kim, S.H., Rodriguez, G., Fawcett, A.J., Jhaveri, R., 2022. Interventions to Improve Pediatric Ability to Swallow Solid Oral Medications: A Systematic Review. Pediatrics, 149:557.

Verrotti, A., Nanni, G., Agostinelli, S., Alleva, E.T., Aloisi, P., Franzoni, E., Spalice, A., Chiarelli, F., Coppola, G., 2012. Effects of the abrupt switch from solution to modified-release granule formulation of valproate. Acta Neurol. Scand. 125, 14–18. https://doi.org/10.1111/j.1600-0404.2011.01568.x

WHO, 2012. Technical Report Series 970, Annex 5.

Wiącek, J., 2016. Geometrical parameters of binary granular mixtures with size ratio and volume fraction: experiments and DEM simulations. Granular Matter 18, 42. https://doi.org/10.1007/s10035-016-0642-0

Wollmer, E., Ungell , A.L., Nicolas, J.M., Klein, S., 2022. Review of paediatric gastrointestinal physiology relevant to the absorption of orally administered medicines. Adv. Drug Deliv. Rev. 181:114084. https://doi.org/10.1016/j.addr.2021.114084

Yeung, V.W., Wong, I.C.K., 2005. When do children convert from liquid antiretroviral to solid formulations?. Pharm World Sci. 27, 399–402. https://doi.org/10.1007/s11096-005-7911-z.

Zargaraan, A., Rastmanesh, R., Fadavi, G., Zayeri, F., Mohammadifar. M.A., 2013. Rheological Aspects of Dysphagia-Oriented Food Products: A Mini Review. Food Sci. Human Wellness 2(3):173–78. https://doi.org/10.1016/j.fshw.2013.11.002