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Physicochemical characterisation of fluids and soft foods frequently mixed with oral drug formulations prior to administration to children

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Oral drug administration to children poses specific pharmaceutical challenges that are often not seen to the same extent in adults, and whose occurrence may also be age dependent. When an age-appropriate dosage form is not available, manipulation of adult dosage forms (e.g., splitting and crushing of tablets or opening of capsules) has been reported as a means to facilitate administration to children. To enhance swallowability and/or mask an unpleasant taste of the dosage form to be administered, crushed/split tablets or the contents of capsules are often mixed with food or drinks or suspended in a vehicle prior to administration. However, it seems that the risks and benefits of an approach whereby the dosage form is modified prior to administration in this manner are everything but clear. The aim of the present study was to gain an overview of the physicochemical properties of a number of fluids, soft foods and suspension vehicles that are commonly reported to be mixed with oral medications before administration to children to improve patient acceptability. For this purpose, physicochemical parameters of 15 different fluids, soft foods and suspension vehicles were measured. These included pH, buffer capacity, osmolality, surface tension and viscosity. Results of the study clearly show the differences in physicochemical properties of the test candidates. It is thus obvious that the type of fluid/food mixed with a drug product before administration may have a significant impact on bioavailability of the drug administered. Therefore, a risk-based assessment of such practices considering API properties, formulation features and physicochemical properties of the fluids and foods intended to be co-administered with the dosage form, in conjunction with the anatomical and physiological maturity of the gastro-intestinal tract in the intended paediatric population, should be an essential part of paediatric oral formulation development.

1. Introduction

"Better Medicines for Children" was the title of a consultation paper published in 2002, in which the European Commission presented its vision for regulatory actions on paediatric medicinal products. At that time, many of the products used in children were not specifically studied or authorised in children. Instead, doctors often used products authorised for adults, sometimes in different doses, with the associated risks of inefficacy and/or adverse reactions (European Commission 2013). The limited availability of licensed medicines for children and the lack of suitable formulations for paediatric patients resulted in Regulation 1901/2006 or the Paediatric Regulation (European Union 2006). This Regulation aims to achieve better medicines for children through several incentives including stimulation of research in areas where knowledge is scarce and making more medicines available to children (van Riet-Nales et al. 2012). Today, there is a global consensus on the need for authorised, age-appropriate medicines for children of all ages. The development of medicines for children is a real challenge due to a long-standing social and ethical paradigm that children should be protected from clinical research but also to the fact that children are not a homogenous, but rather a heterogeneous population with different biological and pharmacological characteristics and cognitive abilities. For this and many other reasons, the availability of authorised age-appropriate paediatric medicines is still limited despite numerous global initiatives focussing on the development of safe and effective medicines for children.

Before the Paediatric Regulation came into force, many pharmaceutical companies considered the adult population their key market (European Commission 2013). Thus, to-date solid oral dosage forms such as tablets and capsules are the most commonly developed dosage forms. Oral drug administration to children, however, poses specific pharmaceutical problems which are often not seen to the same extent in adults, and whose occurrence may also be age- dependent. For instance infants are typically unable to swallow conventionally-sized tablets (EMA 2013). Therefore, when an age-appropriate dosage form is not available, manipulation of adult dosage forms (such as splitting and crushing of tablets or opening of capsules) has been employed as a strategy to facilitate administration to children. As palatability is considered an essential aspect of patient acceptance (van Riet-Nales et al. 2012), crushed/split tablets, or the contents of capsules, are often mixed with food or drinks or suspended in a vehicle prior to administration with the objective of

further improving swallowability and/or to mask an unpleasant taste of the dosage form to be administered. However, it seems that the risks and benefits of the decision on how to manipulate a dosage form before dosing in many cases are everything but clear.

When a product is indicated in children and an appropriate paediatric formulation is as yet unavailable, detailed instructions on how to facilitate administration by healthcare professionals, caregivers or parents are given in the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL). Even in cases where a dosage form is considered age-appropriate, a proportion of patients may not be able to take the dosage form as intended. Consequently, the EMA guideline on paediatric pharmaceutical development (EMA/CHMP/QWP/805880/2012 Rev. 2) (EMA 2013) advocates mixing of paediatric medicines with food and drinks as 'a further means to improve the patient acceptability including the ease of swallowing of an otherwise already palatable medicinal product' provided it will not negatively impact safety and efficacy. Information that can be found in the respective sections of SmPCs and PILs is specific for each product and is very heterogeneous. Even for essentially the same product advice on how to administer the drug can range from recommendations such as "Give tablets with food or a milky drink, where possible" through "The tablets should be swallowed whole - however, for children who find them difficult to swallow, they may be crushed just before being taken and mixed with food or a milky drink (Malarone Paediatric Tablets PIL) to "Tablets may be crushed and mixed with condensed milk just prior to administration for children who may have difficulty swallowing tablets." (Malarone Tablets & Malarone Pediatric Tablets prescribing information). Overall, advice in SmPCs and PILs can be quite general, as e.g. "Granules can be given either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (for example, applesauce, ice cream, carrots and rice)" (Singulair Paediatric 4 mg Granules PIL) or can contain very specific "dos" & "don'ts" such as "In young infants, micro granules should be mixed with a small amount of apple juice and given from a spoon directly before the feed. In weaned infants, granules should be taken with acidic liquids or soft foods (e.g. mixed with apple juice or apple puree), but without chewing, directly before the meal. When giving micro granules to young or weaned infants the apple juice should not be diluted. Alternatively, the granules can be mixed with a small amount of milk and administered to the infant immediately. The granules should not be added to the baby's bottle." (Creon Micro PIL).

It also becomes clear from these case examples that there is no general rule on how to safely and effectively administer oral medicines to the paediatric population. (Soft) foods and liquids are often co-administered in paediatric patients, but the scientific rationale for co-administering a particular type of food is often not clear. Most of the food and fluid types that appear in the paediatric dosing recommendations of SmPCs and PILs represent foods and drinks that based on their taste and texture seem to be appropriate for young children. However, the physiochemical properties of such products and how these could affect oral bioavailability and stability of different active pharmaceutical ingredients (APIs) had never been addressed in a systematic study.

The purpose of the present work was to screen physicochemical properties of foods and drinks that are frequently co-administered with medicines to children to improve swallowability and palatability and thereby to start to get a better understanding of how different foods and fluids might affect safety and efficacy of drugs and dosage forms to be administered to different subgroups of the paediatric population.

2. Investigations and results

The following physicochemical properties of a number of different fluids, soft foods and suspension vehicles were assessed; pH, buffer capacity, osmolality, surface tension and viscosity. These particular physicochemical parameters were selected as they might have a significant impact the solubility and dissolution rate of a drug (all), but might also affect gastric emptying (viscosity) and therefore could have a significant impact on the pharmacokinetic profile of a drug compound (Horter and Dressman 1997).

Results are given in Table 1. In addition, the viscosity profiles depicted in Figs 1-4 represent the viscosity of those samples that, in contrast to the fluids listed in Table 1, did not exhibit Newtonian flow. Apparent viscosity profiles obtained with increasing and decreasing shear rates at two different temperatures relevant to co-administration with medicines are shown to provide information on the reversibility and time-dependency of shear-induced viscosity changes and furthermore on the impact of temperature changes on fluid/food apparent viscosity.

Even though at the first glance significant differences in the characteristics of the different fluids, soft foods and suspension vehicles are apparent, clear trends can be observed for some properties such as the pH value of juices (pH ∼3-5) and milky drinks (pH ∼6-7). However, even though the fluids screened in the present study can be clearly distinguished into juices and milky drinks based on their pH, the remaining physicochemical parameters of these beverages do not necessarily follow the same trend.

When screening the properties of the soft foods, the pH value of the samples could not be predicted based on knowledge of the main component. This can be seen when comparing the pH of vanilla pudding, which corresponds well with that of the milk-based drinks, and that of yoghurt, a product that is also made from milk, but as the result of the manufacturing process (fermentation), in which lactic acid is produced, is characterised by a slightly acidic pH. Furthermore, yoghurt has a much higher buffer capacity than all other milk-based products studied.

The three soft foods and tomato juice showed non-Newtonian flow behaviour. Thus, their viscosity was measured with a rotational viscometer. All tested samples displayed reversible pseudoplastic behavior. Whereas the viscosity of tomato juice changes only slightly as a function of the applied shear rate (see Fig. 1), the soft foods are characterised by much higher apparent viscosities, well defined yield values (when plotting shear stress [Pa] versus shear rate [s^{-1}] (data not shown)) as well as significant shear-thinning behaviour (see Figs. 2-4). None of the soft foods studied showed thixotropic or dilatant flow characteristics apart from tomato juice, which displayed some time-dependent flow behavior at 25 °C as indicated by the displacement of the up-curve from the down-curve (Fig. 1).

The highest apparent viscosity was observed for vanilla pudding. This is not surprising as amongst other ingredients pudding contains milk and macromolecules (starch) and thus represents a complex system with a substantial microstructure "inner structure" that results in an extraordinary flow behaviour and a significant increase in viscosity when compared with that of milk itself. Compared to those of apple sauce and yoghurt, the rheological characteristics of pudding are most sensitive to temperature, as can be seen when comparing the viscosity profiles obtained at 25 °C and 37 °C (Figs. 2-4).

At first sight, the physicochemical properties of the two ORA®-Sweet suspension vehicles are somewhat surprising. For an aqueous-based sugar (ORA®-Sweet) or sodium-saccharin/xanthan-based (ORA®-Sweet SF) syrup one would not necessarily expect an acidic pH as determined in the present series of tests. However, both vehicles are "sweet citrus-berry

Table 1: Mean values (± *S.D.*) of the different physicochemical parameters of fluids, suspension vehicles and soft foods frequently mixed with oral dosage forms administered to children to improve patient acceptability (n = 6 per measurement)

		Fluids										Suspension vehicles		Soft foods		
Parameter	Temp.	Water	Apple juice	Grape juice	Orange juice	Tomato juice	Whole milk	Chocolate milk	Vanilla milk	Condensed milk	Formula milk	ORA®-Sweet	ORA®-Sweet SF	Apple sauce	Vanilla pudding	Yoghurt
pH-value	25 °C	7,31 *(0,01)*	3,47 *(0,03)*	3,45 *(0,02)*	3,87 *(0,04)*	4,30 *(0,01)*	6,72 *(0,02)*	6,55 *(0,03)*	6,42 *(0,01)*	6,11 *(0,02)*	6,59 *(0,02)*	4,22 *(0,01)*	4,30 *(0,01)*	3,71 *(0,02)*	6,55 *(0,02)*	4,27 *(0,02)*
	37 °C	7,89 *(0,01)*	3,49 *(0,01)*	3,43 *(0,02)*	3,85 *(0,02)*	4,27 *(0,00)*	6,63 *(0,01)*	6,51 *(0,01)*	6,36 *(0,00)*	6,05 *(0,02)*	6,57 *(0,02)*	4,24 *(0,01)*	4,29 *(0,01)*	3,70 *(0,01)*	6,47 *(0,02)*	4,26 *(0,01)*
Buffer capacity [mEq/pH/L]	25 °C	0,11 *(0,00)*	33,4 *(1,7)*	49,7 *(0,7)*	48,4 *(2,1)*	52,6 *(1,0)*	14,4 *(0,2)*	20,3 *(0,5)*	21,5 *(0,4)*	39,3 *(1,4)*	5,6 *(0,1)*	5,2 *(0,1)*	14,6 *(0,4)*	26,23 *(1,9)*	19,7 *(0,7)*	93,8 *(4,1)*
	37 °C	0,06 *(0,0)*	33,9 *(0,3)*	50,1 *(0,7)*	49,1 *(1,1)*	53,9 *(0,2)*	13,9 *(0,2)*	22,1 *(0,2)*	22,0 *(0,3)*	42,4 *(1,5)*	5,8 *(0,1)*	5,5 *(0,1)*	14,3 *(0,3)*	25,8 *(0,4)*	20,7 *(0,7)*	91,5 *(0,3)*
Osmolality [mOsmol/kg]		4 *(1)*	677 *(5)*	1073 *(2)*	558 *(8)*	519 *(8)*	285 *(3)*	508 *(2)*	545 *(3)*	579 *(2)*	289 *(3)*	3046 *(3)*	1886 *(6)*	1052 *(5)*	596 *(5)*	484 *(6)*
Surface tension [mN/m]	25 °C	70,2 *(0,36)*	64,17 *(0,32)*	63,40 *(0,13)*	42,63 *(2,10)*	42,12 *(0,25)*	54,20 *(0,40)*	46,61 *(0,80)*	43,39 *(0,10)*	47,57 *(0,15)*	43,61 *(0,26)*	63,69 *(0,58)*	59,26 *(0,08)*	45,00† *(0,33)*	43,09† *(0,08)*	45,23† *(0,21)*
	37 °C	68,74 *(0,46)*	62,51 *(0,45)*	63,38 *(0,22)*	49,10 *(1,10)*	39,42 *(0,22)*	49,80 *(0,60)*	45,23 *(0,61)*	43,31 *(0,15)*	46,03 *(0,30)*	43,24 *(0,07)*	63,19 *(0,08)*	58,83 *(0,09)*	42,27† *(0,22)*	41,68† *(0,13)*	43,82† *(0,16)*
Viscosity [mPa*s]	25 °C	0,91 *(0,00)*	1,26 *(0,00)*	1,53 *(0,00)*	1,45* *(0,00)*	‡	1,90 *(0,04)*	2,68 *(0,02)*	6,47 *(0,10)*	10,42 *(0,04)*	6,59 *(0,02)*	67,39 *(0,19)*	26,56 *(0,27)*	‡	‡	‡
	37 °C	0,72 *(0,00)*	0,96 *(0,00)*	1,14 *(0,00)*	1,29* *(0,01)*	‡	1,50 *(0,04)*	1,92 *(0,01)*	3,10 *(0,04)*	7,10 *(0,01)*	6,57 *(0,02)*	33,82 *(0,27)*	19,71 *(0,06)*	‡	‡	‡

† mean of n = 18 calculated from measuring surface tension a set of 3 dilutions at concentrations above the critical micelle concentration (CMC) – *see 4.2.4* for more details.

‡ measured with the rotational viscometer (see Figures 1-4 for viscosity profiles).

* to ensure complete pulp removal, orange juice was filtered through a 12 µm cellulose nitrate filter (Schleicher & Schuell, Dassel, Germany) using a vacuum filtration device before measuring viscosity.

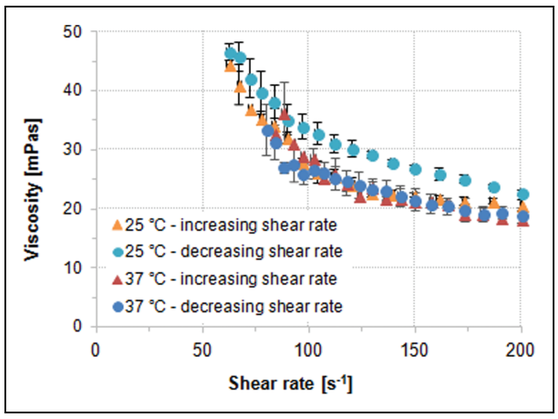

Fig. 1: Viscosity of tomato juice obtained at 25 °C and 37 °C and different shear rates in the increasing and decreasing shear rate mode, respectively, mean of n = 6 ± S.D.

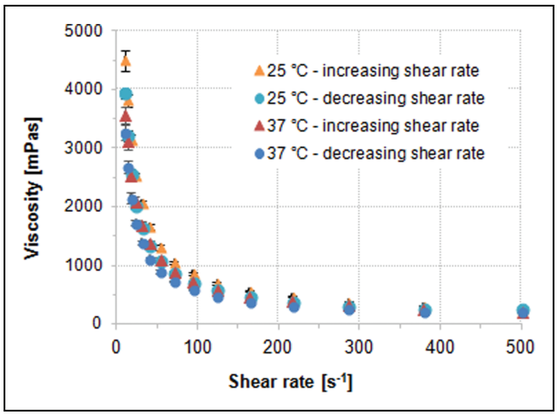

Fig. 2: Viscosity of apple sauce obtained at 25 °C and 37 °C and different shear rates in the increasing and decreasing shear rate mode, respectively, mean of n = 6 ± S.D.

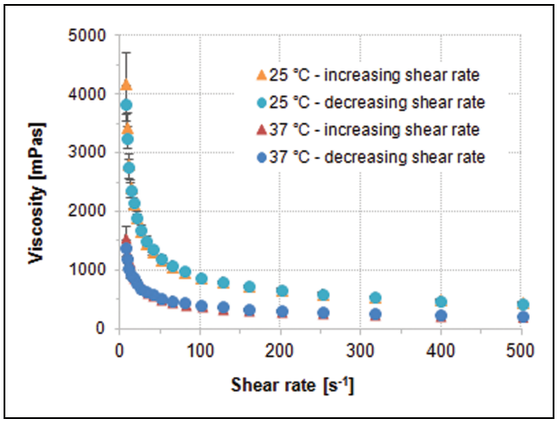

Fig. 3: Viscosity of vanilla pudding obtained at 25 °C and 37 °C and different shear rates in the increasing and decreasing shear rate mode, respectively, mean of n = 6 ± S.D.

flavoured" and, after a closer look at their excipient lists, contain a citrate buffer which is the major determinant for the pH. Another point to mention is that the two suspension vehicles do not only differ in their sugar content, but also show significant differences in buffer capacity, osmolality and viscosity. Compared to other fluids and foods studied, particularly ORA®

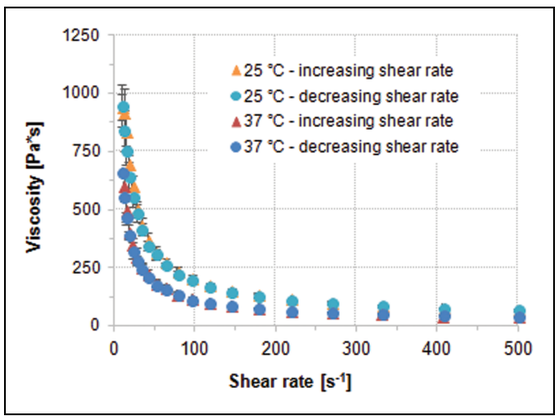

Fig. 4: Viscosity of yoghurt obtained at 25 °C and 37 °C and different shear rates in the increasing and decreasing shear rate mode, respectively, mean of n = 6 ± S.D.

Sweet with its low buffer capacity and very high osmolality represents a vehicle with some rather "extreme" properties.

3. Discussion

The aim of the present study was to gain an overview of the physicochemical properties of a number of fluids, soft foods and suspension vehicles that are commonly mixed with oral medications before administration to children to improve patient acceptability.

To date a general approach to mixing paediatric medicines with food or drinks has not been proposed, nor has an universal administration vehicle been reported, and as such, the selection of foods and drinks to be co-administered with a drug product is often based on empirical data rather than having a solid scientific basis. As a result, and perhaps also as a consequence of when the product was approved, SmPCs and PILs contain either very general recommendations like "before administration sprinkle on a spoonful of soft food" or precisely defined "dos" and "don'ts" such as "mix with acidic food and do not mix with milk prior to administration", the latter typically resulting from studies where these particular fluid and food types were used with the test treatment in a clinical study. For a risk assessment in the development of new paediatric dosage forms such information from SmPCs and PILs might not be of much help. Therefore, the present dataset is proposed as a starting point to support an evaluation of the suitability of these fluids and soft foods as candidates for co-administration with oral medications in paediatric drug therapy.

When considered together with the characteristics of the API (chemical structure & stability, solubility, pKa and logP) to be administered and formulation parameters relevant to drug release, the dataset provided in Table 1 should be helpful in estimating potential food effects such as drug degradation or precipitation, dissolution of enteric/protective coatings, enhanced/decreased wetting or solubilisation, enhanced or hindered disintegration, dissolution or diffusion etc. and rate of gastric emptying, all of which may affect bioavailability of the API. Such interactions (e.g., precipitation, dissolution of enteric coatings) have been reported in the literature on mixing drug products with food prior to oral administration (Jann et al. 1986; Notterman et al. 1986; Fleisher et al. 1990; Wells and Losin 2008; Manrique et al. 2014). As such, it is proposed that a risk-based assessment is performed early in development in which the properties of the API, dosage form and developmental status of the intended paediatric population are collectively considered

both to enable rational selection of foodstuffs and fluid types as potential candidates for mixing with the drug product prior to administration and to aid definition of an appropriate level of evaluation to verify that the proposed modification does not alter safety or efficacy.

Nevertheless, as mentioned previously, the present dataset is only intended to be a starting point. In the present work physicochemical properties of fluids and soft foods frequently mentioned in SmPCs and PILs were studied at 25 °C (temperature of ICH climatic zones I & III (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2003) and a potential temperature of the food when mixed with oral formulations) and 37 °C (body temperature and temperature that the food and dosage form will equilibrate to after ingestion). However, as a result of cultural differences in flavour preferences, accessibility of foods around the globe and also due to the fact that in some cases, caregivers might not strictly follow the advice given in SmPCs and PILs, it is likely that alternate fluids/food stuffs might be used to achieve adequate patient acceptability. Therefore, to improve the understanding of risks that could accompany co-administration of paediatric medicines with different fluid- and food types, future work will focus on the characterisation of a range of additional child- and age-appropriate fluids and soft food products that are known to be frequently used to increase acceptability of medicines for children in different countries of the world.

The dataset presented in this manuscript demonstrates significant differences in the physicochemical properties of fluids, soft foods and suspension vehicles that are commonly used to manipulate oral dosage forms before administration to children. Even without relating the different fluid/food types to a particular type of API/dosage form to be administered to a specific patient-subgroup, it is obvious that the type of fluid/food selected for this purpose may range from having no effect to exhibiting significant effects on stability, dissolution/drug release and even the gastric environment and gastric emptying rate, particularly in very young patients where gastric fluid volume and capacity are very small.

Because of the aforementioned reasons, a scientific discussion considering API properties, formulation features, physicochemical properties of the fluids and foods intended to be co-administered to improve patient acceptability and the anatomical and physiological maturity of the gastro-intestinal tract in the intended paediatric population should be an essential part of paediatric oral formulation development. It goes without saying that the present dataset is still small. Future work will thus be dedicated to complementing the present dataset with properties of a range of other fluids and foods that have been reported to be mixed with oral paediatric formulations to improve acceptability. The EMA guideline on paediatric pharmaceutical development acknowledges that food and drinks are usually not standardised products but equally that the whole range of variability cannot be verified. In this context some understanding of variability of properties of different brands of apparently similar fluid and food products could be interesting information to consider within the risk-based assessment proposed previously. Finally, the temperature of fluids and soft foods co-administered with oral paediatric formulation will also require attention.

4. Experimental

4.1. Products studied

In total 15 different fluids, soft foods and suspension vehicles were tested. Since the study was performed in Germany, products available on the German market were used as study materials.

4.2. Physicochemical characterization of the different fluids and soft foods

Physicochemical characterisation of all fluids, suspension vehicles and soft foods included the following parameters: pH value and buffer capacity, osmolality, surface tension and viscosity. With the exception of osmolality, parameters were recorded at two temperatures, i.e. 25 °C and 37 °C

Table 2: Fluids, soft foods and suspension vehicles studied

Fluids	**Commercial product studied**
Water (non carbonated)	Humana Babywasser (Humana GmbH, Herford Germany)
Apple juice	Albi Apfelsaft klar (Albi GmbH, Berghülen, Germany)
Grape juice (red)	Vitafit Premium Traubensaft (Lidl, Neckarsulm, Germany)
Orange juice (without pulp)	Amecke Sanfte Säfte, Orangensaft ohne Fruchtfleisch (Amecke Fruchtsaft GmbH, Menden, Germany)
Tomato juice	Rewe Beste Wahl Tomatensaft (Rewe Markt GmbH, Köln, Germany)
Whole milk (3,5 % fat)	Haltbare Vollmilch, homogenisiert, 3,5 % Fett (Mark Brandenburg, Elsterwerda, Germany)
Chocolate milk*	Nestlé Nesquik (Nestlé Deutschland AG, Frankfurt/Main, Germany) and whole milk
Vanilla milk	Milbona Milchdrink Vanille (Gropper, Bissingen, Germany)
Condensed milk (10 % fat)	Bärenmarke - Die Ergiebige 10 (Bärenmarke Vertriebsgesellschaft mbH, Polling, Germany)
Formula milk**	Beba Pro Anfangsmilch Pre (Nestlé Nutrition GmbH, Frankfurt/Main, Germany)
Suspension vehicles	**Commercial product studied**
ORA-Sweet®	ORA-Sweet® (Perrigo® Company plc, Dublin Ireland)
ORA-Sweet® sugar-free	ORA-Sweet® SF (Perrigo® Company plc, Dublin Ireland)
Soft foods	**Commercial product studied**
Apple sauce	Oberlausitzer Apfelmus (Lausitzer Früchteverarbeitung GmbH, Sohland, Germany)
Vanilla pudding	Genuss Dessert, Vla mit Sahne Bourbon Vanille (De Zuivelhoeve Produktie BV, Twekkelo, Netherlands)
Yoghurt (3,5 % fat)	Weihenstephan Frischer Joghurt mild, 3,5 % Fett (Molkerei Weihenstephan GmbH & Co. KG, Weihenstephan, Germany)

* Chocolate milk was prepared by dissolving 3 spoons (12 g) of Nesquik instant powder in 150 mL whole milk

** Formula milk was prepared by suspending 12,9 g (3 measuring spoons) powder in 90 mL demineralised water, resulting in 100 mL formula milk.

(Klein et al. 2004). All experiments were run replicated (n = 6) and results expressed as mean (± S.D.). Measurements were performed as follows:

4.2.1. pH

The pH value was measured with a calibrated pH-meter (Five Easy Plus, Metter Toledo GmbH, Gießen, Germany).

4.2.2. Buffer capacity

The buffer capacity was quantified by potentiometric titration with 0.1 N or 0.01 N hydrochloric acid, respectively.

4.2.3. Osmolality

Osmolality was measured via the freezing point depression method by semi-micro osmometry (K-7400, Knauer, Berlin, Germany). Apple sauce, pudding and yoghurt required dilution prior to the measurement. Thus, for these soft foods a set of appropriate dilutions was prepared with demineralised water. These dilutions were then first mixed for 1 min using a Vortex mixer (VWR Reagenzglasschuettler, VWR International GmbH, Darmstadt, Germany) and subsequently centrifuged for 15 min at 4000 rpm (Eppendorf Centrifuge 5702 R, Eppendorf AG, Hamburg, Germany). After centrifugation, the aqueous phase of the diluted foods was used to measure the osmolality. A linear relationship between food concentration and osmolality was observed ($R^2 \geq 0.995$) for the entire set of dilutions. Thus, it was possible to extrapolate to the osmolality of the undiluted soft foods.

4.2.4. Surface tension

The surface tension was determined with a ring tensiometer (K11, Krüss GmbH, Hamburg, Germany). As experienced in the osmolality measurements, the surface tension of pudding and yoghurt could not be directly assessed. Therefore, again a set of dilutions was prepared according to the description given in section *4.2.3*. In detail, surface tension was measured for a set of aqueous dilutions containing 66,67 % (w/w), 50 % (w/w) and 25 % (w/w) of the respective soft food. Both at 25°C and 37°C no significant change in surface activity could be observed when comparing surface tension of the different dilutions. This indicates that the surfactant concentrations were above the critical micelle concentration (CMC). The surface tension of the undiluted soft foods was thus calculated as the mean (n = 18 ± S.D.) of all single data points obtained from the respective set of dilutions.

4.2.5. Viscosity

Due to the very different consistencies of the various samples, it was necessary to use two methods for the investigation of viscosity. The viscosity of all Newtonian fluids was determined with different types of Ubbelohde viscometers (type 0c, K = 0.002692 mm^2/s^2 DIN 51562, SI Analytics, Mainz, Germany; type I, K = 0.01008 mm^2/s^2 and type II, K = 0.09939 mm^2/s^2 both from LaborTherm, Jena, Germany). Expectedly, some of the fluids and the soft foods did not exhibit Newtonian flow characteristics. Therefore the rheological profiles of these samples, namely tomato juice, apple sauce, vanilla pudding and yoghurt were obtained by measuring shear stress over a range of shear rates. All experiments were performed with a rotational viscometer (proRheo R180 with cup size 2, proRheo GmbH, Althengstett, Germany) operating according to the Searle principle (cup and bob). In the case of tomato juice, share rate was gradually increased from 0 to 200 s^{-1} over a duration of 5 min. After keeping the shear rate constant for 2 min, shear rate was gradually decreased for another 5 min. In the case of apple sauce, vanilla pudding and yoghurt, the parameters were changed to increasing/decreasing the shear rate from 0 (500) to 500 (0) s^{-1} over 3 min for both up and down ramps and the holding time was 1 min. Finally viscosity was calculated for each single data point recorded and plotted versus the corresponding shear rate.

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