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Research Article

Theme: Pediatric Drug Development and Dosage Form Design
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Simulating Different Dosing Scenarios for a Child-Appropriate Valproate ER Formulation in a New Pediatric Two-Stage Dissolution Model

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Abstract. Predictive *in vitro* test methods addressing the parameters relevant to drug release in the pediatric gastrointestinal tract could be an appropriate means for reducing the number of *in vivo* studies in children. However, dissolution models addressing the particular features of pediatric gastrointestinal physiology and typical pediatric dosing scenarios have not yet been described. The objective of the present study was to combine the knowledge on common vehicle types and properties and current information on pediatric gastrointestinal physiology to design a dissolution model that enables a biorelevant simulation of the gastrointestinal conditions in young children. The novel dissolution setup consists of a miniaturized dissolution system allowing the use of small fluid volumes, physiological bicarbonate-based test media, and a proper pH control during the experiment using a pHysio-stat® device. Following design and assembly of the novel *in vitro* setup, a set of experiments screening *in vitro* drug release from a valproate-extended release formulation under typical dosing conditions in infants was performed. *In vitro* drug release profiles indicated a controlled drug release of the test product over 12 h and were in good agreement with information given in the Summary of Product Characteristics and the Patient Information Leaflet, as well as with results from an *in vivo* food effect study performed with the same product and reported in the literature. The new dissolution setup thus represents a promising *in vitro* screening tool in the development of pediatric dosage forms and may help to reduce the number of pharmacokinetic studies in children.

KEY WORDS: bicarbonate-based simulated intestinal fluid; biorelevant dissolution; dosing vehicle; infants; pediatric gastrointestinal tract.

INTRODUCTION

Today, there is a global consensus on the need of authorized, age-appropriate medicines for children of all age groups. Because of a long-lasting social and ethical paradigm that children should be protected from clinical research and since children are not a homogenous but rather inhomogeneous sub-group of various subpopulations with different biological and pharmacological characteristics, the development of safe and effective age-appropriate formulations is a real challenge. Currently, some progress in the development of pediatric formulations can be observed. Advances include a paradigm shift toward oral solid formulations and a focus on novel preparations, including flexible, dispersible, and multiparticulate oral solid dosage forms (1).

Potential pediatric patients may include neonates, toddlers, young children and adolescents, and as such will have widely varying needs. Whereas the intravenous administration of drugs will often be required in acutely ill children, whenever possible, the oral route will represent the preferred route of drug administration for long-term use (2). However, drug dosing in children poses specific problems which are often not seen to the same extent in adults. Drug absorption from the gastrointestinal (GI) tract is affected by quite a number of physiological factors, including gastric and intestinal contents and secretions, gastric emptying and intestinal passage time, bowel length and absorptive surface area, gut wall permeability, and expression of transporters. In very young children, these factors strongly differ from adult physiology and change with growth and aging. Extrapolation from adult studies is therefore hardly possible when the aim is to predict drug exposure in children (3). Besides that, the administration of oral dosage forms in children comes along

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with additional problems. Young children such as neonates, infants, and pre-school children are typically not able to swallow conventionally sized pills (4) and may resist taking forms of drugs that taste bad or have a bad mouth feeling. Swallowability and palatability of an oral dosage form are thus considered essential aspects of patient acceptance (5).

There is no general rule of how to safely and effectively administer oral medicines to pediatric patients. Current approaches to improve swallowability and/or palatability of a dosage form include the co-administration of (soft) foods and fluids; however, the scientific rational for co-administering a particular type of food or fluid is often not clear. Most of the food and fluid types that show up in the pediatric dosing recommendations of Summary of Product Characteristics (SmPCs) and the Patient Information Leaflets (PILs) represent foods and drinks that based on their taste and texture seem to be appropriate for young children, but the composition and physicochemical characteristics of such products and how these could affect oral bioavailability and stability of different active pharmaceutical ingredients (APIs) and their formulations have never been addressed in detail.

Predictive *in vitro* test methods addressing the parameters relevant to drug release in the GI tract of children could be an appropriate means for reducing the number of *in vivo* studies required for formulation screening. However, appropriate dissolution models addressing the particular features of pediatric GI physiology and typical pediatric dosing scenarios such as sprinkling the medication on soft food or fluid before administration have not yet been described.

The development of *in vitro* test methods for predicting drug release, solubility, and stability in the pediatric GI tract requires in-depth knowledge of the GI features of children of specific age groups as well as the proposed dosing conditions including the properties of the co-administered foods and fluids. As possible, *in vitro* methods should be applicable to simulate conditions in different sections of the GI tract such as the stomach and the small and the large intestine and should be applicable for screening drug release of both immediate release (IR) and extended release (ER) formulations.

Recently, we have introduced two devices that enable an automatic pH monitoring and control of bicarbonate-based dissolution media during dissolution/drug release experiments (6,7). With these devices it is possible to realistically simulate the intestinal environment including ionic composition, pH and phyisological pH changes during a GI passage. However, to date, dissolution/drug release experiments performed with the use of these devices did only address adult physiology, i.e., the experiments were performed in a conventional sized dissolution apparatus (USP apparatus II—paddle apparatus) applying fluid volumes that do not relate to the fluid volumes available in the GI tract of young children. Proper modification of the original test setup could, however, provide the oppurtunity to realistically simulate the GI passage in children.

When screening the SmPCs and PILs of medications that are administered to children, it becomes obvious that even for the same drug product, the composition of recommended dosing vehicles can be quite different. Consequently, different dosing vehicles may affect *in vivo* dissolution/drug release of the co-administered dosage form to a different extent. Therefore, when the aim is to co-administer an oral dosage form with a dosing vehicle, it would be essential to address properties of the dosing vehicle that may affect bioavailability of the drug product.

For getting a better estimate of how different soft foods and drinks that are frequently co-administered with oral drug formulations might affect the safety and efficacy of the respective formulations in different subgroups of the pediatric population, we have recently screened the physicochemical properties of several foods and fluids that commonly show up in SmPCs and PILs (8).

The objective of the present study was to combine the knowledge on common vehicle types and properties and current information on pediatric GI physiology to design a dissolution model that enables a biorelevant simulation of the pH conditions and fluid volumes in the GI tract of young children. The model should be applicable to address different dosing conditions including fasted administration with a glass of water or together with common dosing vehicles such as different fluids and soft foods. Finally, the new model should be applied to screen drug release of a valproate ER formulation, i.e., an oral dosage form that contains a well-known and well-characterized drug, that has been used in the treatment for epilepsy in infants for quite some time and that according to the SmPC and PIL in pediatric use is allowed to be dosed with (carbonated) beverages or soft foods.

MATERIALS AND METHODS

Materials

The model product Orfiril® long 150-mg capsules (# 14005652, Desitin Arzneimittel, Hamburg, Germany) was obtained via the local hospital pharmacy. Valproic acid sodium salt reference material (# MKBS5723V) was purchased from Sigma-Aldrich (Steinheim, Germany). All other chemicals for media preparation and the acetonitrile for HPLC were of analytical or gradient grade and purchased commercially. All dosing vehicles (Table I) were purchased from a local supermarket or drugstore, respectively.

Methods

Dissolution Apparatus

Even though there is little data available on intraluminal fluid volumes in the GI tract, it is obvious that particularly in very young children GI fluid volumes are much smaller than in adults (3). When the aim is to develop bio-predictive *in vitro* test methods for oral pediatric dosage forms, it is thus not possible to apply dissolution test methods that are used to simulate GI conditions in adults. Consequently, a novel dissolution setup comprising a new dissolution device and age-appropriate fluid compositions and fluid volumes had to be developed. For the purpose of applying small fluid volumes, a dissolution vessel matching the dimensions of USP apparatus III (inner diameter = 47 ± 1.4 mm) was modified by shortening the height and mounting a glass ring on the outer surface which enables the fixation of the vessel in

Table I. Fluid and Soft Foods used as Dosing Vehicles

Fluid/soft food	Commercial product	Ingredients	Manufacturer/source	pH
Water	Humana Babywasser	Water obtained from double reverse osmosis	Humana, Herford, Germany	7.3
Apple juice	Alosa Apfelsaft klar	Apple juice, ascorbic acid (antioxidant)	Brands & Systems BSG, Hamburg, Germany	3.3
Apple sauce	Babylove Apfel pur	Pureed apples	dm-drogerie markt, Karlsruhe, Germany	4.2
Yoghurt	LC1 Pur Nestlé	Mild (milk) yoghurt, 3.5% fat, cultures of lactobacillus LC1	Lactalis Nestlé Frischprodukte Deutschland GmbH, Kehl/Rhein, Germany	3.8
Pudding (chocolate)	Sahne Pudding Vollmilch Schokolade	85% cream, sugar, modified starch, 1.9% low-fat cocoa powder, 1.1% milk chocolate (sugar, cocoa butter, milk powder from whole milk and skimmed milk, cocoa paste, soy lecithin (emulsifier), potassium nitrate, vanillin), caramelized sugar syrup, thickener (carrageenan), vanillin	Dr. August Oetker Nahrungsmittel, Bielefeld, Germany	6.8

a water bath. This novel standardized dissolution vessel allows to perform tests in a volume range of 30 to 110 mL, which is much lower than typical fluid volumes applicable in the compendial USP apparatus II device or a miniaturized modification thereof (9,10) (see Fig. 1).

Before starting an experiment, the miniaturized vessels are filled with media and fixed in a water bath equipped with a Julabo ED thermostat (Julabo Labortechnik GmbH, Seelbach, Germany) for proper temperature control. Proper agitation of the media is ensured by equipping each vessel with a cylindrical-shaped magnetic stir bar (length = 21 mm, diameter = 6 mm) and placing the water bath with the vessels on a six-field magnetic stirrer (Variomag Telesystem 6, Thermo Scientific, Waltham MA, USA). Media evaporation is prevented by a custom-made vessel cover, incorporating ports for a sample probe, a pH electrode, and a gas diffusor. A schematic overview and an image of the novel setup equipped with sample probes and electrodes are shown in Fig. 2.

Following design and assembly of the novel apparatus, a set of experiments screening *in vitro* drug release from a valproate ER formulation under typical dosing conditions in infants was performed.

Drug Release Experiments

Orfiril® long 150-mg capsules containing sodium valproate ER mini tablets and being used in the treatment of epilepsy in infancy (11) were used as model formulation. Since they are easy to swallow and enable precise dose measurement, mini tablets with a diameter of 1–3 mm are considered as a child-appropriate dosage form for oral medication (12). Several mini tablet formulations can be dispersed in liquids or be sprinkled on food (1) which can further increase palatability and, consequently, compliance. Therefore, besides liquids, multiparticulate and orodispersible mini tablets belong to the formulations of choice in oral drug administration to (very) young children (13,14). Based on these aspects and since the intention of our study was to develop an *in vitro* model that allows to simulate conditions in different sections of the pediatric GI tract, a pediatric ER mini tablet formulation was regarded as an appropriate model product for the present study.

Test scenarios simulating fasted administration of the mini tablets in infants with water alone or with different dosing vehicles were designed. All experiments were performed in triplicate ($n = 3$) and a passage through the stomach (30 min),

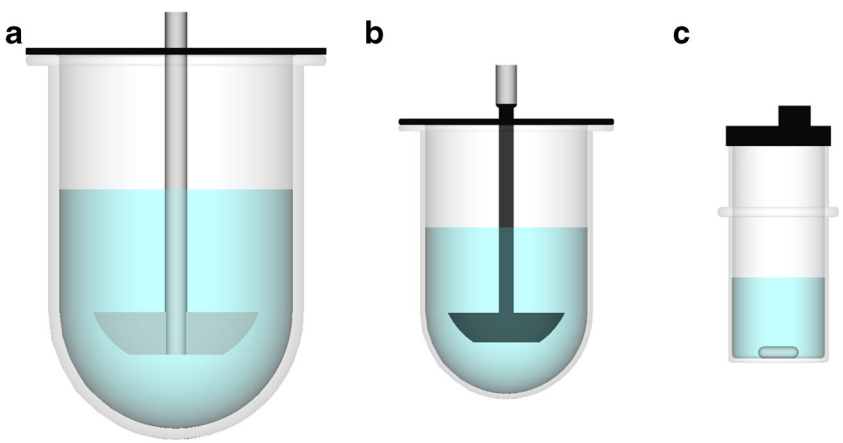

Fig. 1. Schematic comparison of a USP apparatus II (**a**), a miniaturized USP II apparatus (7,8) (**b**), and a vessel of the novel apparatus (**c**)

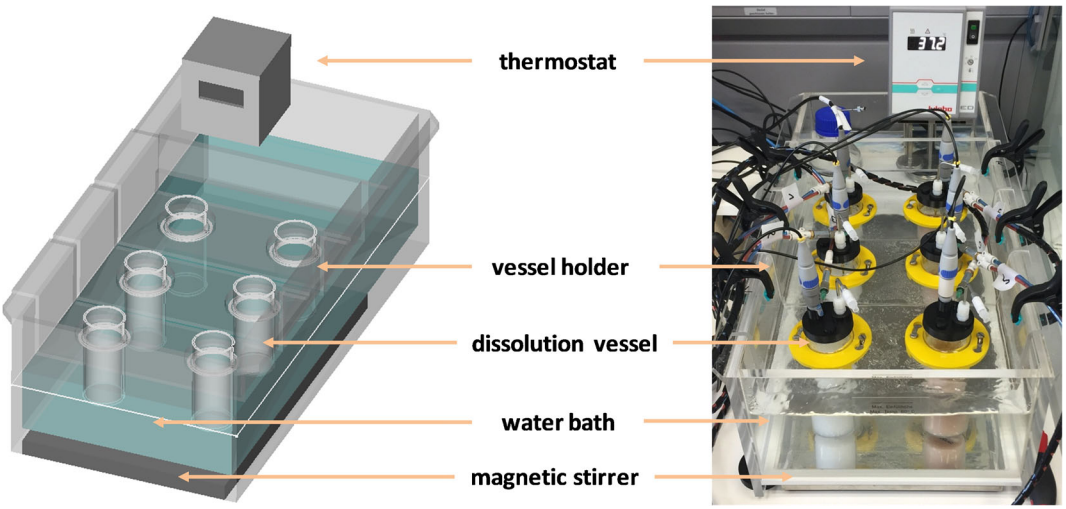

Fig. 2. Schematic overview and image of the novel dissolution device

the small intestine (240 min), and proximal tomid colon (480 min) was simulated. All experiments in the novel dissolution apparatus were performed at a stirring speed of 550 rpm. Samples of 3 mL were taken via a sample probe equipped with a 10-µm poroplast cannula filter (Erweka, Heusenstamm, Germany) at 30, 60, 120, 180, 240, 300, 360, 420, 480, 600, and 720 min into a 3-mL glass syringe (Fortuna Optima, Poulten & Graf, Wertheim, Germany). Each sample was then filtered through a 0.45-µm cellulose acetate syringe filter (Puradisc 30 FP 30/0.45 CA-S, Whatman/GE Healthcare Life Sciences, Buckinghamshire, UK) and following appropriate dilution analyzed by HPLC/UV. *Screening the Impact of Gastric pH on Drug Release.* The focus of the first set of experiments was to screen the impact of the reported infant fasted gastric pH range (15–18) on drug release. For this purpose, the administration of the content (=ER mini tablets) of two Orfiril® long 150-mg capsules together with a small amount of water to infants was simulated as follows: Gastric conditions were simulated by mixing 10 mL of simulated gastric residual fluid (16,17) in the pH range of 1.8–4.0 with 50 mL of water assumed to be co-ingested with the dosage form. The pH of residual gastric fluid was either simulated with a modified version of simulated gastric fluid *sine pepsin* (SGF*sp*) pH 1.8 or a 2-mM sodium acetate buffer solution pH 4.0. The content of two capsules was added into each of the novel miniaturized vessels containing the pre-warmed (37°C) mixture of water and simulated residual gastric fluid and the experiment was started immediately. After a simulated gastric residence time of 30 min, samples were taken and assayed for the amount of valproate released under gastric conditions. Subsequently, the entire content of each vessel was transferred into a second vessel containing 50 mL of a simulated small intestinal fluid, i.e., a pH 6.8 bicarbonate-based simulated intestinal fluid (Carbonate-SIF, CarbSIF), containing 120 mM sodium chloride, 5 mM potassium chloride, and 15 mM sodium bicarbonate, resulting in a total small intestinal volume of 110 mL. Drug release in these conditions was screened for 12 h representing an average residence time in the small intestine and proximal to the mid colon.

Screening the Impact of Co-administration of Different Vehicles on Drug Release. Since SmPC and PIL of Orfiril® long 150-mg permit the administration of the capsule content together with a (carbonated) beverage drink or with soft food (11), the objective of the second set of experiments was to screen the impact of co-administering such dosing vehicles on drug release. For this purpose, test scenarios simulating fasted administration of the formulation with water or apple juice or sprinkled on soft food (apple sauce, yoghurt, or pudding) followed by some additional water intake were developed. In accordance with the dosing recommendation for children in the age range of 2 to 6 years, the content of two capsules of the Orfiril® long 150-mg formulation, i.e., 300 mg valproate in total, was tested in all cases. Gastric conditions in infants were simulated as follows: A physiological volume (10 mL) of pre-warmed (37°C) simulated residual gastric fluid, SGF*sp* pH 1.8, was added to each vessel. Then, the content (=ER mini tablets) of two Orfiril® long 150-mg capsules was mixed with the dosing vehicle. In detail, the content of each of the two capsules was sprinkled separately on a single teaspoon (tsp) containing 5 mL of the corresponding liquid or semi-solid vehicle. Immediately after mixing, the mixture was added to the vessel. Finally, additional 150-mL fluid assumed to be co-ingested with the dosage form was added to each vessel, before the experiment was started. When using apple juice as liquid vehicle, the additional fluid was also apple juice, since it seems to be likely that the child would want to continue with the same fluid type. In all other cases, the additional fluid was water. In contrast to the simulated residual gastric fluid, which was pre-warmed to 37°C, both dosing vehicles and additional fluid were pre-warmed to 25°C to address typical dosing conditions, i.e., dosing at room temperature. A detailed overview of the gastric test design is given in Fig. 3.

Since the total gastric fluid volume in these experiments was higher than that in the first set of experiments (170 *versus* 60 mL), the first part of the release experiments, i.e., the simulation of gastric residence, was performed in the mini paddle apparatus (DT 626 HH, Erweka, Heusenstamm, Germany) (9,10) with a paddle speed of 75 rpm. After a simulated gastric residence time of 30 min, a sample was

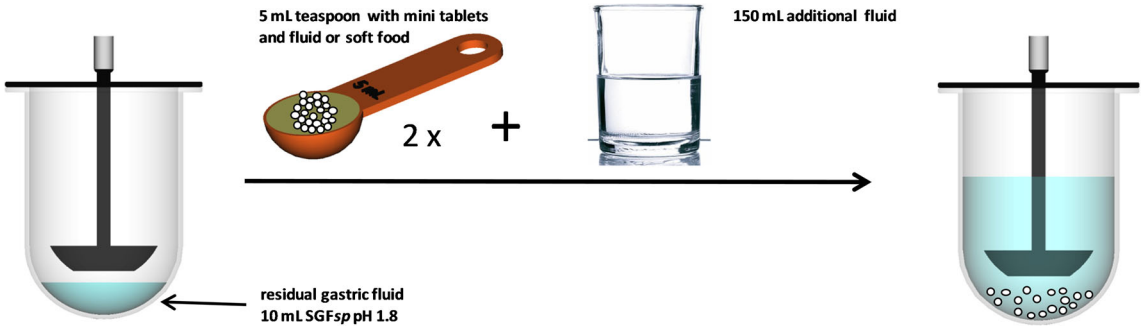

Fig. 3. Dosing scenario and gastric setup used to simulate co-administration of liquid and semi-solid dosing vehicles

withdrawn, before mini tablets and 60 mL of the gastric contents were transferred into a vessel of the novel dissolution device containing 50 mL CarbSIF pH 6.8 at 37°C. This resulted in a total small intestinal volume of 110 mL. Like in the first set of experiments, drug release in these conditions was screened for 12 h representing residence time in the small intestine and proximal colon.

pH Measurement and pH Control Over the Entire Test Duration

A modified assembly of the pHysio-stat® device (6) was used to control the pH of the CarbSIF over the duration of the simulated passage through small intestine and proximal colon. The assembled components of this device are schematically shown in Fig. 4. In contrast to the original pHysio-stat® setup (6) which had been designed for drug release experiments simulating adult GI physiology, in the present set of experiments, media pH was measured by a small pH electrode (InLab micro pH electrode, MettlerToledo, Schwerzenbach, Switzerland) and the original gas diffusor also was replaced by a 0.8 × 120-mm stainless steel cannula (Sterican, B.Braun Melsungen AG, Melsungen, Germany) which was connected to the carbon dioxide supply for purging carbon dioxide into the medium when a pH adjustment was required. Upon mixing gastric content with CarbSIF, the pH of the resulting simulated intestinal content was less than pH 6.8 and thus initially raised by manually passing inert gas (nitrogen) into the mixture until the target pH value of 6.8 was reached. Throughout the rest of the experiment, an online pH measurement was applied and carbon dioxide was purged into the medium when required.

Analytical Quantification

All samples were analyzed using a Waters HPLC system consisting of a 1525 binary pump, an 2707 autosampler, and a 2998 photodiode array (PDA) detector (Milford, MA, USA). Data acquisition and processing were performed with the Waters Breeze™ 2 software.

The samples from the first set of experiments and the co-administration experiments with water, apple sauce, and apple juice were quantified using a reverse-phase LiChrospher® 100 RP-18 (4 × 125 mm, 5 μm) column protected by a LiChrospher® 100 RP-18 (4 × 4 mm, 5 μm) guard (pre-) column. The mobile phase consisted of a 50-mM phosphate buffer pH 6.8 and

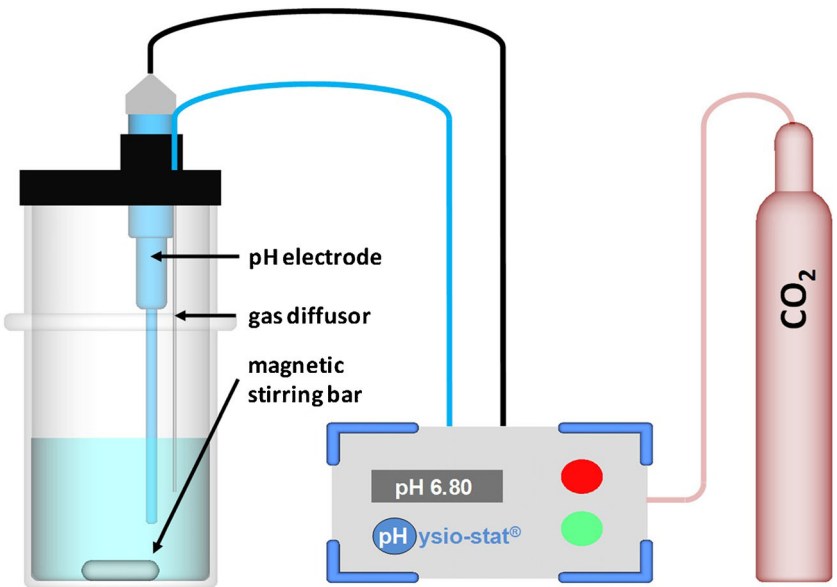

Fig. 4. Modified (miniaturized) pHysio-stat® assembly for the small intestinal setup

acetonitrile (80:20, *v*:*v*), the flow rate was set at 1 mL/min and the column temperature was 50°C. The injection volume was 100 µL and valproic acid was detected at a wavelength of 200 nm. The method had been validated before application. Calibration curves were linear in the range of 0.007 to 0.7 mg/mL ($r^2 >$ 0.999), precision and accuracy of standard/control samples that had been prepared and analyzed in the same way as the samples were all within 5% of the nominal concentration.

As a result of their more complex composition, samples from co-administration experiments with pudding and yoghurt required both a special sample preparation before injection and different chromatographic conditions. For the analysis of these samples, an end-capped reverse-phase LiChrospher® 100 RP-18e (4.6 × 250 mm, 5 µm) column connected to a LiChrospher® 100 RP-18 (4 × 4 mm, 5 µm) guard column was used. The mobile phase was a mixture of acetonitrile and a 0.32% (m/V) potassium dihydrogen phosphate solution adjusted to pH 2.5 with orthophosphoric acid (40:60, *v*:*v*). The flow rate was set at 1.5 mL/min, the column temperature was 35°C, the injection volume 100 µL, and the detection wavelength 210 nm.

As indicated, samples from the drug release experiments with pudding and yoghurt could not be injected as such, but before injection were prepared according to the following protocol: Upon sampling, 2 mL of each sample was centrifuged at 13,000 rpm for 30 min (Heraeus Biofuge pico, Kendro Laboratory Products, Osterode, Germany). Following centrifugation 800 µL of the aqueous phase were withdrawn, mixed with 200 µL of a 50% (*v*:*v*) aqueous solution of trifluoroacetic acid and vortexed for 30 s at 3000 rpm (IKA Vortex 4 digital, Staufen, Germany). After additional 30 min centrifugation at 13,000 rpm, 600 µL of the supernatant was removed and mixed with 400 µL acetonitrile. The resulting mixture was vortexed for 30 s at 3000 rpm and again centrifuged at 13,000 rpm for 30 min. Finally, the supernatant of the centrifugate was filtered through a 0.45-µm PVDF syringe filter (Puradisc 13, PVDF, Whatman/GE Healthcare Life Sciences, Buckinghamshire, UK) directly into a HPLC vial and analyzed as described above.

RESULTS AND DISCUSSION

Impact of Gastric pH on Drug Release

The focus of the first set of experiments was to screen the impact of typical pH conditions in the fasted stomach of infants (15–18) on drug release. Figure 5 displays the results obtained in the dissolution experiments with the content of two Orfiril® long 150-mg capsules in the fasted infant test scenario. As can be clearly seen, simulated gastric pH had no impact on overall drug release and even in the little fluid volume available in simulated intraluminal conditions of the small intestine and the proximal colon, a robust drug release could be observed. During the short-simulated fasted gastric residence time of 30 min, almost no drug was released. Drug release under simulated intestinal conditions was controlled. About 50–60% of the dose was released during simulated small intestinal residence time and drug release was complete at the end of the simulated passage through the small intestine and proximal/mid colon, i.e., after 12 h. Since preliminary experiments (data not shown here) had indicated that variations in intestinal pH within the pH range of pH 5–7 had no impact on drug release, in the present infant test scenario, we had worked with a physiologically relevant small intestinal buffer system, but kept the intestinal pH at 6.8 over the entire residence time in the small intestine and proximal/mid colon. However, since drug release from other pediatric formulations, such as, e.g., enteric-coated formulations, can be significantly affected by GI pH conditions (19), future experiments will focus on simulating the varying small intestinal pH conditions in more detail.

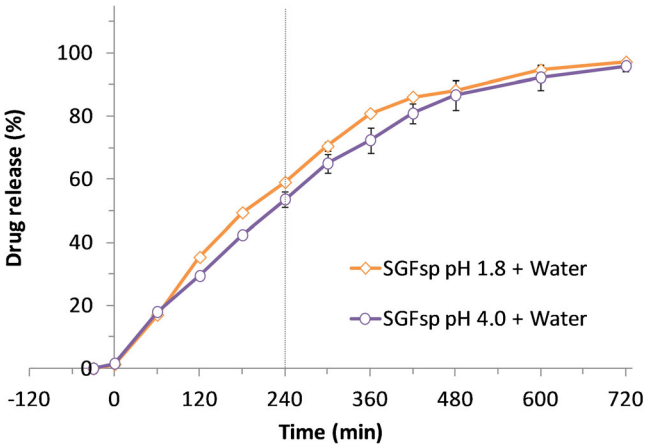

Fig. 5. Drug release from Orfiril® long ER mini tablets (2 × 150 mg) during a simulated a passage through an infant's stomach (*left* from *y* axis), small intestine (0–240 min), and proximal colon (240–720 min) when simulating different gastric pH conditions in infants and co-administration with a small amount (50 mL) of water (mean of $n = 3 \pm$ S.D.)

Impact of Co-administration of Different Vehicles on Drug Release

Besides pH a number of other factors can affect drug release and stability in the GI tract. For a dosage form that is allowed to be administered with a variety of dosing vehicles, the properties of the different vehicles can thus be critical for drug/formulation stability, drug solubility, and dissolution or drug release rate, respectively. Therefore, after the successful design of a setup allowing the simulation of fluid volumes and fluid composition in the GI tract of young children, this new setup was combined with the simulation of different dosing scenarios.

Figure 6a, b displays the *in vitro* release profiles obtained when simulating co-administration of a 300-mg dose Orfiril® long ER mini tablets (content of two 150-mg capsules) with liquid dosing vehicles, such as plain water (=typical fasted dosing conditions) and apple juice or soft foods including apple sauce, yoghurt, or pudding. As observed in the first set of experiments, drug release was controlled with almost no drug being released under gastric conditions, half of the dose being released during the simulated small intestinal residence time and complete release at the end of the experiment. *In vitro* release profiles from experiments simulating co-administration with water and apple juice (Fig. 6a) were almost superimposable, indicating that fluid pH and composition had no impact on drug release. Hence, the co-administration with different types of aqueous-based beverages is not expected to alter the bioavailability of Orfiril®

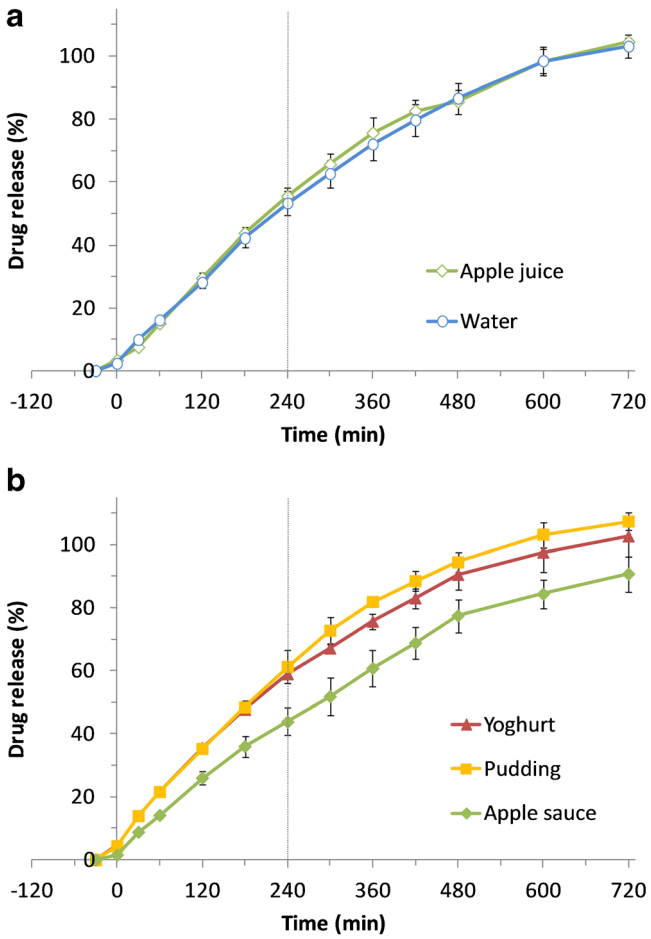

Fig. 6. Drug release from Orfiril® long ER mini tablets (2 × 150 mg) during a simulated passage through an infant's stomach (*left* from *y* axis), small intestine (0–240 min) and proximal colon (240–720 min) after co-administration with fluids (**a**) and soft foods (**b**) (mean of $n = 3 \pm$ S.D.)

long. Thus, results from the *in vitro* study also confirm the appropriateness of the pediatric dosing recommendation given in the SmPC and PIL of the product (11), where co-administration with water and different (carbonated) beverages is permitted. *In vitro* release profiles from experiments simulating co-administration with different soft foods such as apple sauce, yoghurt, or pudding (Fig. 6b) were similar to those obtained in water and apple juice, suggesting that co-administration of soft food will not affect bioavailability of the ER formulation. Drug release in the scenario simulating co-administration with apple sauce was somewhat slower than in the scenario simulating co-administration with yoghurt or pudding. However, the resulting release profile does not represent a real food effect, which would be represented by dose dumping or extremely slow to no release. Overall, observations made in the present *in vitro* study are in good agreement with results from a food effect study performed by Retzow *et al.* (20). In the cited study, the influence of concomitant food intake on the pharmacokinetics of 300 mg sodium valproate (Orfiril® long) was studied in 16 healthy male volunteers. When comparing plasma profiles obtained from administration with water after a 12-h overnight fast or immediately after a standardized high-caloric, high-fat breakfast, the maximum valproate plasma concentration (Cmax) and the area under the plasma concentration curve (AUC) in the fed state were bioequivalent with those in the fasted state. This indicated that food intake did not modify either the bioavailability or the slow release profile of the valproate ER mini tablets. Based on the results from the cited study, a vehicle effect on Orfiril® long bioavailability, is rather unlikely, since (a) the pediatric dosage form consists of ER mini tablets that contain a drug (sodium valproate) that is freely soluble in water and other aqueous fluids (21) and that is formulated with excipients, i.e., ethyl cellulose and ammonio methacrylate copolymer, allowing controlled, but also pH-independent drug release through pores in the tablet coating (11) and (b) the amount of vehicle co-administered with a pediatric dose of the product is much smaller than a typical (pediatric) meal. Results of the present *in vitro* study confirm these considerations and also the results reported by Retzow *et al.* (20).

CONCLUSION

A new two-stage dissolution model enabling a biorelevant simulation of the pH conditions, fluid volumes, and major fluid properties in the GI tract of young children was developed. The model was successfully applied to screen drug release of Orfiril® long, a valproate ER formulation used in the treatment of epilepsy in infants. With the new small-scale dissolution setup, it was possible to simulate different GI pH conditions as well as to address different pediatric dosing scenarios, in particular co-administration of the Orfiril® long ER mini tablets with different dosing vehicles. *In vitro* drug release profiles were in good agreement with information given in the Orfiril® long SmPC and PIL. The new dissolution setup therefore represents a promising *in vitro* screening tool in the development of pediatric dosage forms and may help to reduce the number of pharmacokinetic studies in children. Future activities will include the fine tuning of the *in vitro* model as well its adaption to other pediatric age groups. Moreover, the model will be applied to a set of model drugs and formulations where a food effect can be expected to evaluate if it is able to display known food effects from *in vivo* studies.

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REFERENCES

1. Ivanovska V, Rademaker CMA, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361–72.
2. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol. 2005;59(6):674–6.
3. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Adv Drug Deliv Rev. 2014;73:102–26.
4. Guideline on pharmaceutical development of medicines for paediatric use. In: (CHMP) CfMPfHU, (PDCO) PC, London: European Medicines Agency; 2013.
5. van Riet-Nales DA, Wang S, Saint-Raymond A, Robert JL. The EMA quality guideline on the pharmaceutical development of medicines for paediatric use. Int J Pharm. 2012;435(2):132–4.
6. Garbacz G, Kolodziej B, Koziolek M, Weitschies W, Klein S. An automated system for monitoring and regulating the pH of bicarbonate buffers. AAPS PharmSciTech. 2013;14(2):517–22.
7. Garbacz G, Kolodziej B, Koziolek M, Weitschies W, Klein S. A dynamic system for the simulation of fasting luminal pH-gradients using hydrogen carbonate buffers for dissolution testing of ionisable compounds. Eur J Pharm Sci. 2014;51:224–31.
8. Kersten E, Barry A, Klein S. Physicochemical characterisation of fluids and soft foods frequently mixed with oral drug formulations prior to administration to children. Pharmazie. 2016;71(3):122–7.
9. Klein S. The mini paddle apparatus—a useful tool in the early developmental stage? Experiences with immediate release dosage forms. Dissolut Technol. 2006;13(4):6–11.
10. Klein S, Shah VP. A standardized mini paddle apparatus as an alternative to the standard paddle. AAPS PharmSciTech. 2008;9(4):1179–84.
11. Orfiril® long Fachinformation (summary of product characteristics). Rote Liste Service GmbH; 2015.
12. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12(11):1727–40.
13. Klingmann V, Spomer N, Lerch C, Stoltenberg I, Fromke C, Bosse HM, *et al*. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. J Pediatr. 2013;163(6):1728–32.
14. Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, Bosse HM. Acceptability of uncoated mini-tablets in neonates—a randomized controlled trial. J Pediatr. 2015;167(4):893–6.
15. Nagita A, Amemoto K, Yoden A, Aoki S, Sakaguchi M, Ashida K, *et al*. Diurnal variation in intragastric pH in children with and without peptic ulcers. Pediatr Res. 1996;40(4):528–32.
16. Miller BR, Tharp JA, Issacs WB. Gastric residual volume in infants and children following a 3-hour fast. J Clin Anesth. 1990;2(5):301–5.
17. Cook-Sather SD, Harris KA, Chiavacci R, Gallagher PR, Schreiner MS. A liberalized fasting guideline for formula-fed infants does not increase average gastric fluid volume before elective surgery. Anesth Analg. 2003;96(4):965–9.
18. Litman RS, Wu CL, Quinlivan JK. Gastric volume and pH in infants fed clear liquids and breast milk prior to surgery. Anesth Analg. 1994;79(3):482–5.
19. Wells KA, Losin WG. In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to applesauce, apple juice, and chocolate pudding. Clin Ther. 2008;30(7):1300–8.
20. Retzow A, Vens-Cappell B, Wangemann M. Influence of food on the pharmacokinetics of a new multiple unit sustained release sodium valproate formulation. Arzneimittelforschung. 1997;47(12):1347–50.
21. Sweetman SC. Martindale—the complete drug reference. 33rd ed. London: Pharmaceutical Press; 2002.