Simulating different dosing scenarios for a paediatric valproic acid ER formulation in a new paediatric multistage dissolution model

Frank Karkossa, Jana Urbaniak, Sandra Klein

Institute of Biopharmaceutics and Pharmaceutical Technology,
Department of Pharmacy, University of Greifswald, Germany

Frank.Karkossa@uni-greifswald.de

ERNST MORITZ ARNDT
UNIVERSITÄT GREIFSWALD

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Introduction

Predictive *in vitro* test methods addressing the parameters relevant to drug release in the gastrointestinal (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 paediatric GI physiology and also typical paediatric dosing scenarios such as sprinkling the medication on soft food or fluid before administration were not yet described. Recently, we have designed a dissolution model that enables addressing the pH conditions and small fluid volumes available in the gastrointestinal tract of neonates and infants allowing a biorelevant simulation of a passage through different sections of the paediatric GI tract. The aim of the present work was to apply the newly designed dissolution model for screening drug release of a paediatric valproic acid ER formulation during a simulated GI passage and in different dosing conditions in infants.

Materials and Methods

Orfiril® long 150 mg capsules (Desitin Arzneimittel GmbH, Hamburg, Germany), containing sodium valproate ER mini tablets and being used in the treatment of epilepsy in infancy were used as model formulations. Test scenarios simulating fasted administration of the mini tablets with water or apple juice or sprinkled on a teaspoon of soft food (apple sauce, yoghurt or pudding) followed by some sips of water were designed (figure 1 a). Gastric conditions were simulated by mixing a physiological volume of simulated gastric resting fluid pH 1.8, with the amount of fluid or soft food + water assumed to be co-ingested with the dosage form. After a simulated gastric residence time of 30 min, mini tablets and gastric contents were transferred into a second vessel containing simulated small intestinal fluid, i.e. a pH 6.8 bicarbonate-based simulated intestinal fluid (Carbonate-SIF). Drug release in these conditions was screened for another 12 hours which would represent residence in the small intestine and proximal colon. A modified assembly of the pHysio-grad® device (figure 1 b) was used to maintain the pH of the intestinal bicarbonate-based buffer system constant over the entire test duration. Samples were taken at predetermined time points and analysed by HPLC.

Table 1: *In vitro* test design

Gastric conditions

Dosing vehicles						Simulated gastric fluid				Simulated gastric stage		
Fluid/Soft Food	Vehicle volume	Additional fluid intake	pH	Temp.		Volume	pH	Temp.		Volume	pH	Residence time
Water	10 mL	150 mL	7.3	25 °C						170 mL	2.6	30 min
Apple juice	10 mL	150 mL	3.3	25 °C						170 mL	3.3	30 min
Yoghurt	10 mL (2 tsp)	150 mL (water)	4.2	25 °C	+	10 mL	1.8	37 °C	→	170 mL	4.2	30 min
Apple sauce	10 mL (2 tsp)	150 mL (water)	3.8	25 °C						170 mL	3.4	30 min
Pudding	10 mL (2 tsp)	150 mL (water)	6.8	25 °C						170 mL	5.9	30 min

Small and large intestinal conditions

Simulated small and large intestinal stage			
Composition	pH	Temp.	Residence times
60 mL gastric content + 50 mL Carbonate-SIF	6.8	37 °C	240 min (small intestine) + 480 min (colon)

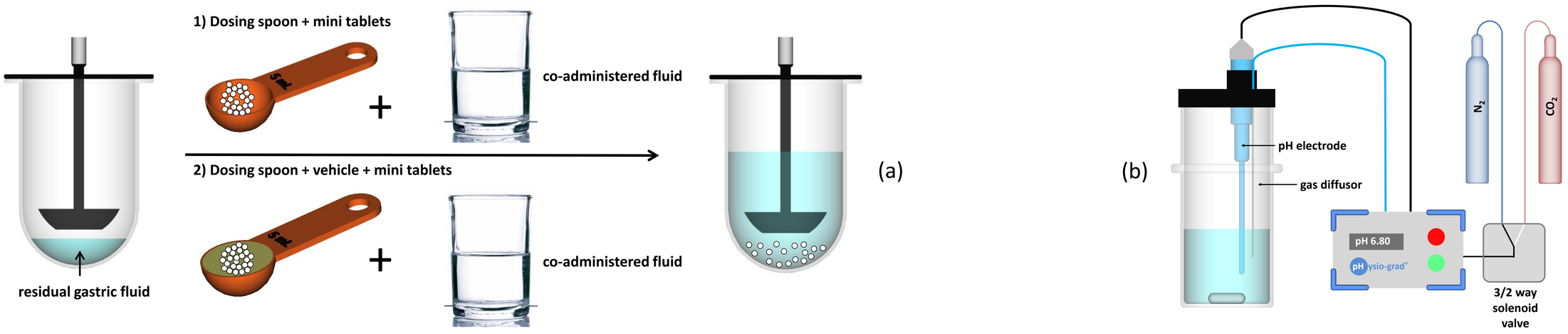

Figure 1: Dosing scenarios and gastric setup (a) and modified pHysio-grad® assembly for the small intestinal setup (b).

Results

Figure 1 displays the estimated valproic acid/valproate release in the infant GI tract when co-administering the content of two Orfiril® long 150 mg capsules with fluids, i.e. water and apple juice or soft foods, i.e. yoghurt, pudding or apple sauce.

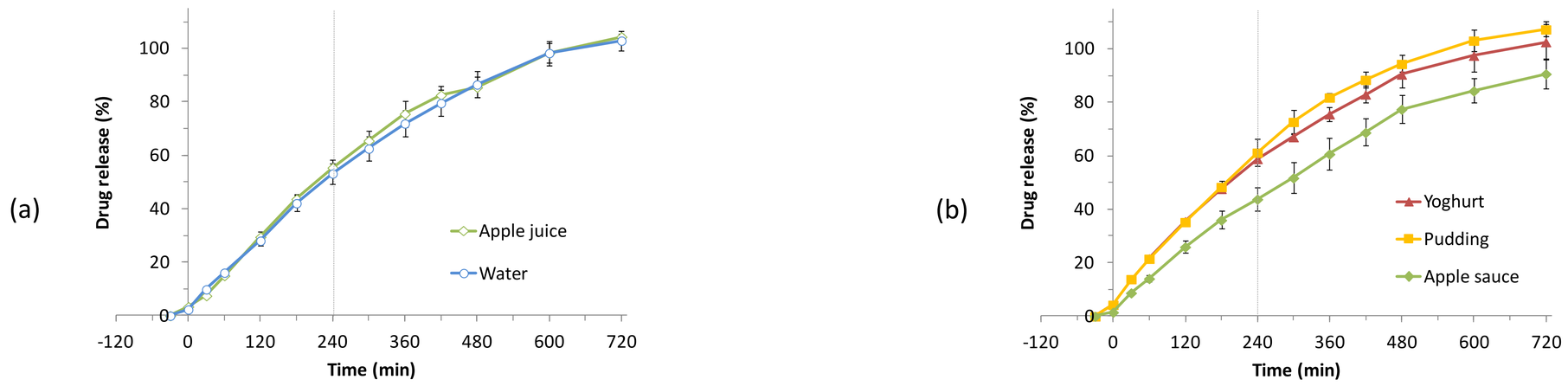

Figure 2: Drug release from Orfiril® long minitablets (2 x 150 mg) during a simulated a passage through infant stomach (left from y-axis), small intestine (0-240 min) and proximal colon (240-720 min) after co-administration with fluids (a) and soft foods (b) (mean of n=3 ± S.D.).

As we could also prove in a neonatal setup (data not shown here) simulated gastric pH had no significant impact on overall drug release and even in the little fluid available in simulated intraluminal conditions of the small intestine and the proximal colon, a robust drug release could be observed. Moreover, results obtained when simulating different dosing scenarios suggest that *in vivo* drug release and bioavailability of Orfiril® long will not be affected by the composition of the co-administered fluids and soft foods studied. This is in good agreement with the information given in the SmPc and PIL.

Conclusion

The new paediatric multistage dissolution model has proven as a very useful tool for estimating *in vivo* drug release from ER formulations administered to children. In future studies the present model will be further fine-tuned and also be adapted to other paediatric age groups.

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