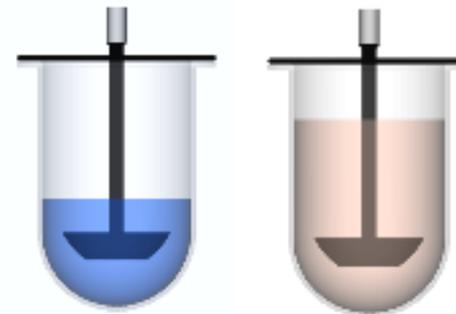
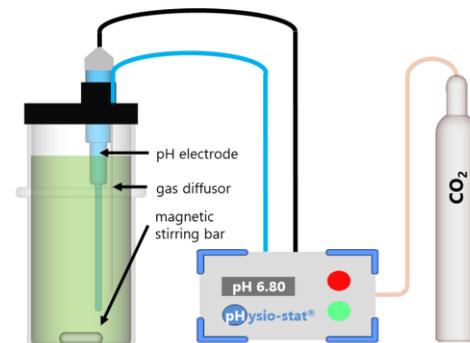




Current Landscape of Pediatric Biorelevant *In Vitro* Dissolution Testing

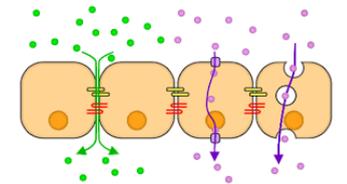
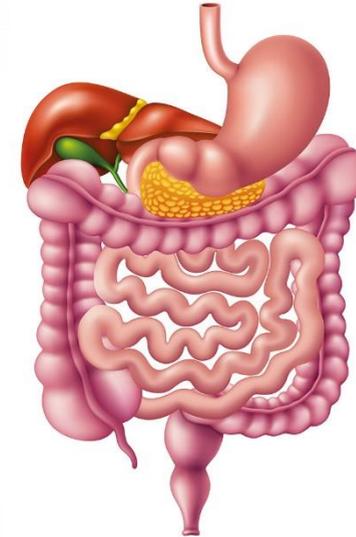
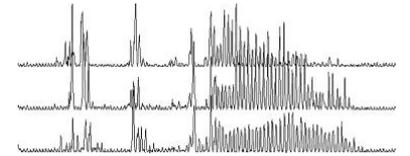
Prof. Dr. Sandra Klein
Department of Pharmacy
University of Greifswald, Germany



Oral drug delivery

Oral drug absorption – depends on ...

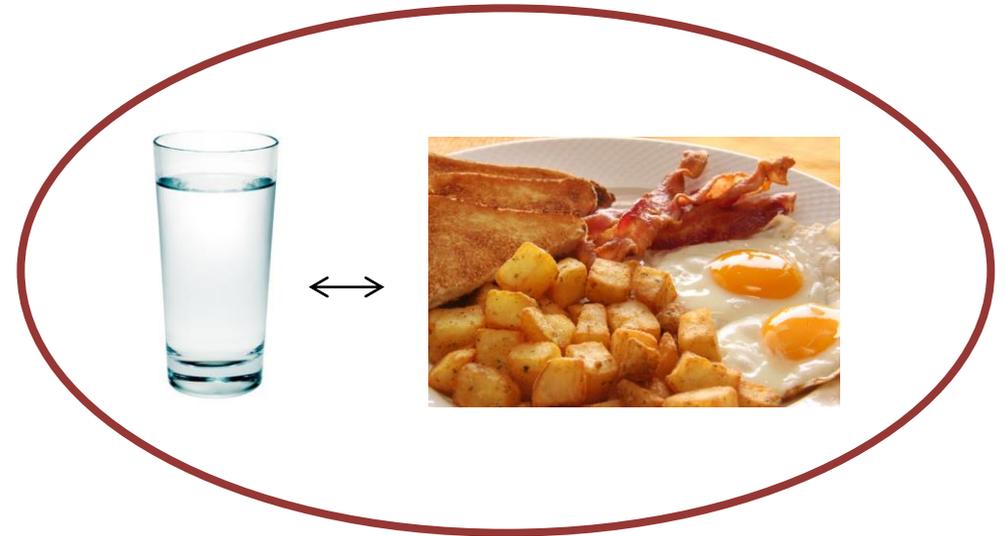
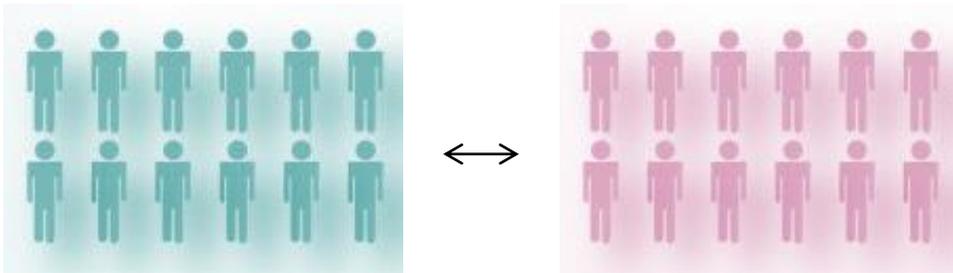
- drug release from the dosage form
 - drug solubility and stability in the GI fluids
 - drug permeability through the GI mucosa
 - GI fluid volumes and properties
 - available GI absorption surface area
 - GI passage / motility / residence times
 - dosing conditions & co-medication
- ↳ developmental aspects of the GI system
- ↳ conditions affecting the relevant GI physiology



Oral drug absorption in adults

Assessment in clinical trials

- limited number of healthy subjects
- often young adults
- standardized study protocol

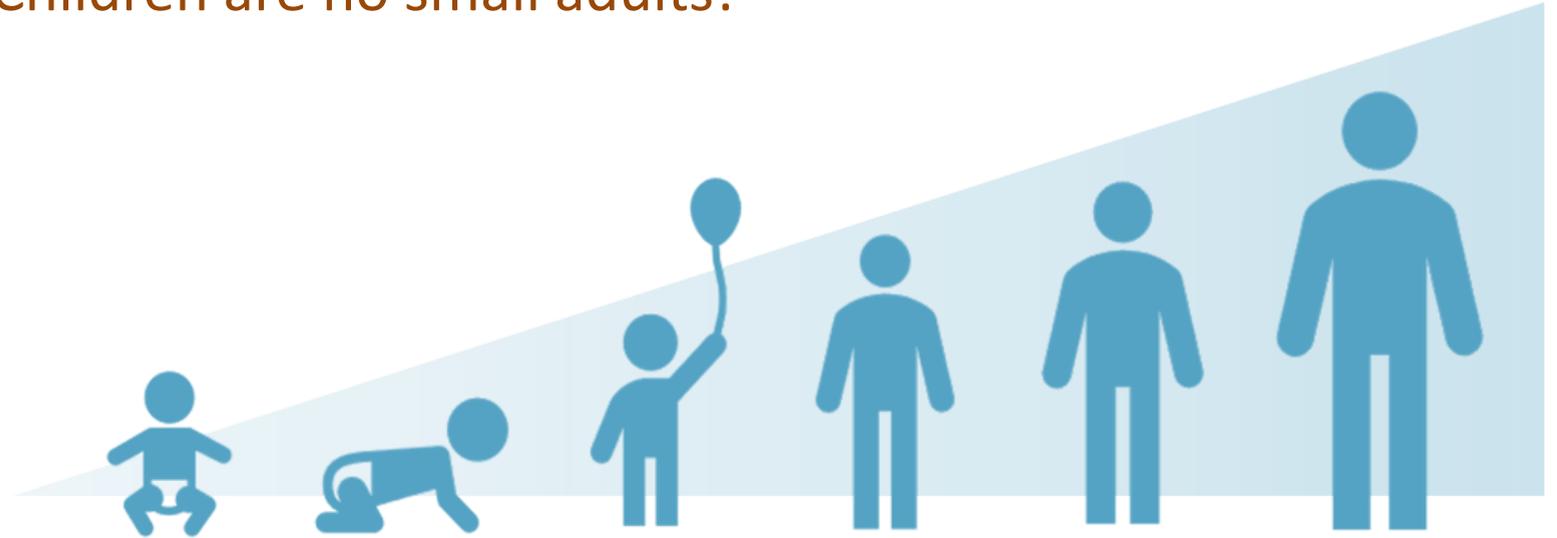


Biorelevant dissolution testing

- prediction/estimation of *in vivo* drug release and absorption
- biorelevant dissolution setups (media and apparatus) for mimicking dosing in fasted and fed states

Oral drug absorption in children

Children are no small adults!

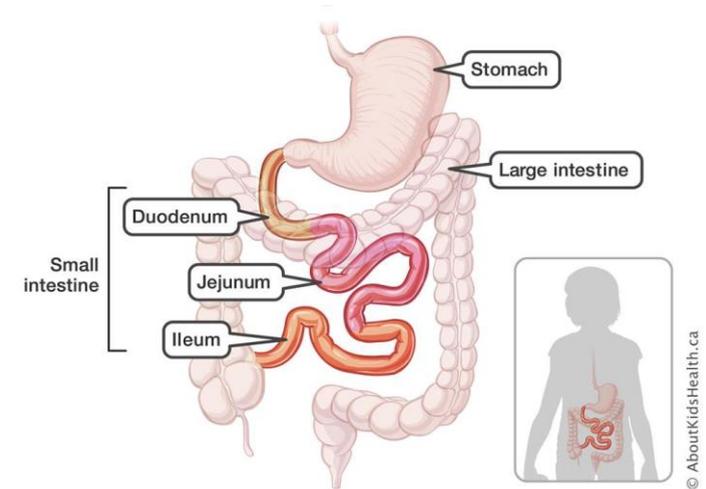


- ⇒ can we extrapolate from data obtained in adults?
- ⇒ can we predict the *in vivo* performance of pediatric medicines based on *in vitro* or *in silico* data?

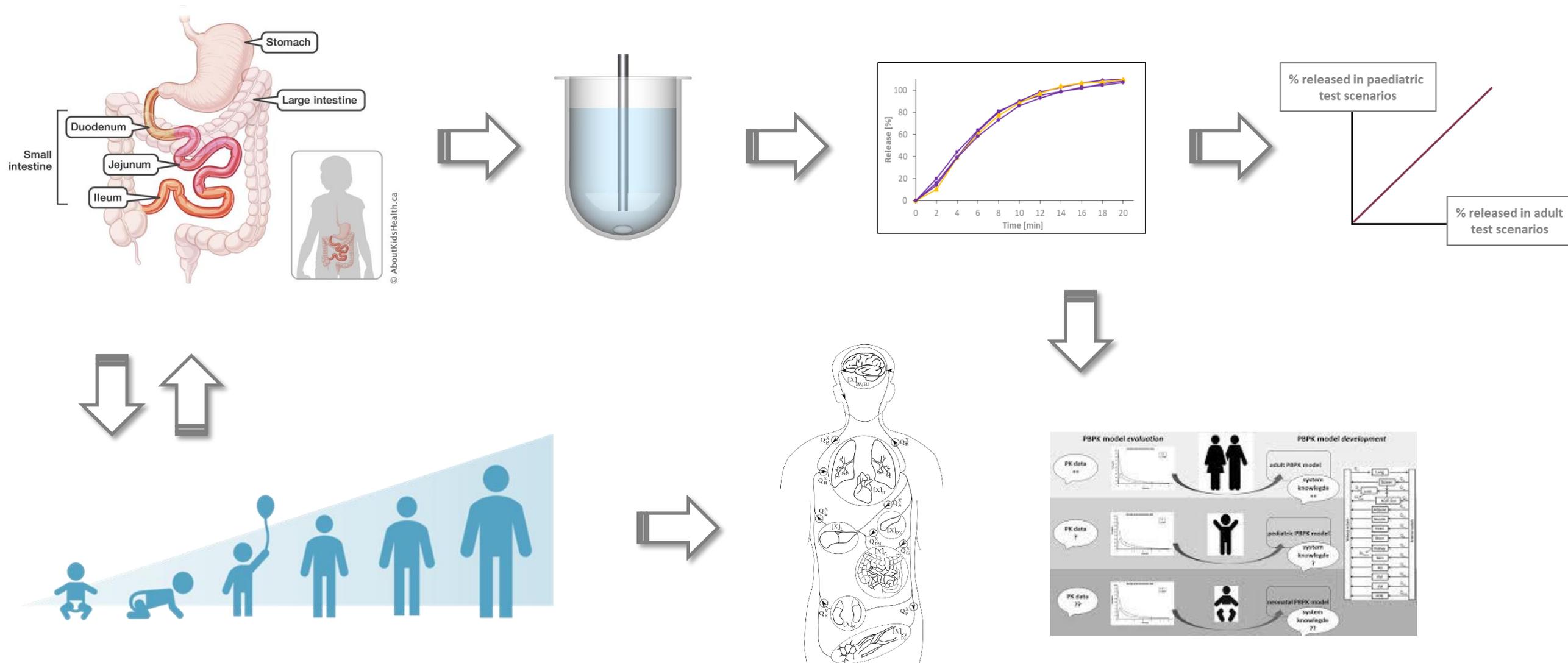
Oral drug delivery in children

How can we predict oral bioavailability in children?

- simple scaling is not sufficient
- no standardized clinical dosing protocol available
- need to establish predictive *in vitro* and *in silico* tools
- information on GI-physiology
- information on how pediatric dosage forms are administered
 - in different age groups and environments



What can be done with this information?



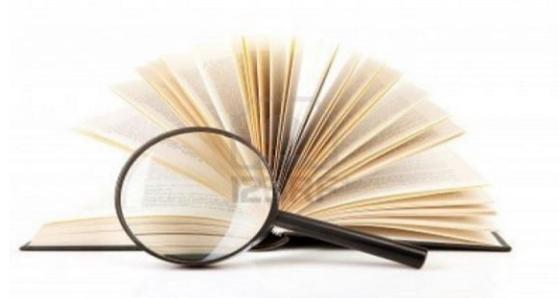
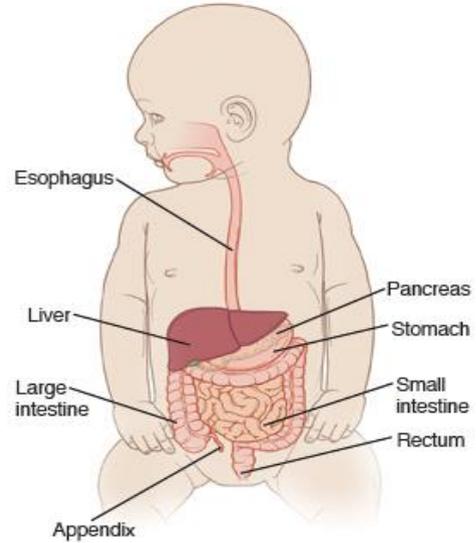
Biorelevant *in vitro* dissolution testing

Need to establish predictive methods

- children of different age groups
 - dosing in the fasted state, with a meal or a dosing vehicle
 - children in different environments
- biorelevant media
- apparatusive setup

Where to get reliable data for establishing such methods?

Our starting point ...



Literature Review



- acquisition of data relevant for designing *in vitro* and *in silico* models
- pediatric GI physiology & significant disease-related changes



- healthy children
- different age groups
- prandial status
- large cohorts
- non-invasive assessment

Ontogeny of GI luminal conditions – target parameters

Oral cavity

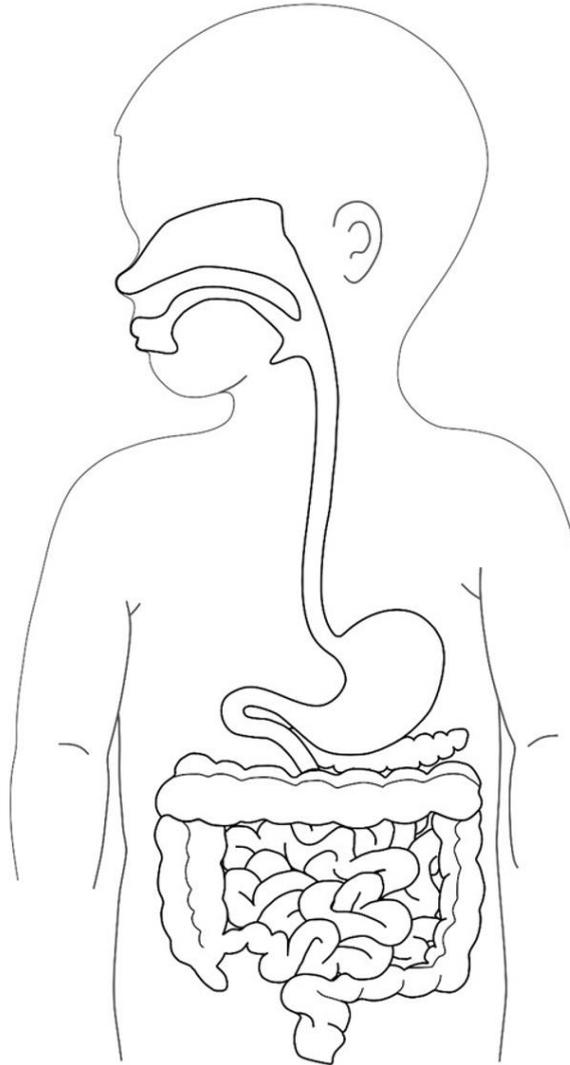
- surface area
- salivary flow rate
- salivary pH
- salivary composition
- salivary buffer capacity
- salivary osmolality

Stomach

- gastric acid secretion and pH
- gastric fluid secretion and volume
- gastric fluid composition and physicochemical properties
- gastric enzymes
- gastric motility
- gastric emptying
- pylorus characteristics

Colon

- colonic contents
- colonic motility
- colonic transit time



Swallowing

- swallowing characteristics
- oral and pharyngeal transit time
- tongue pressure

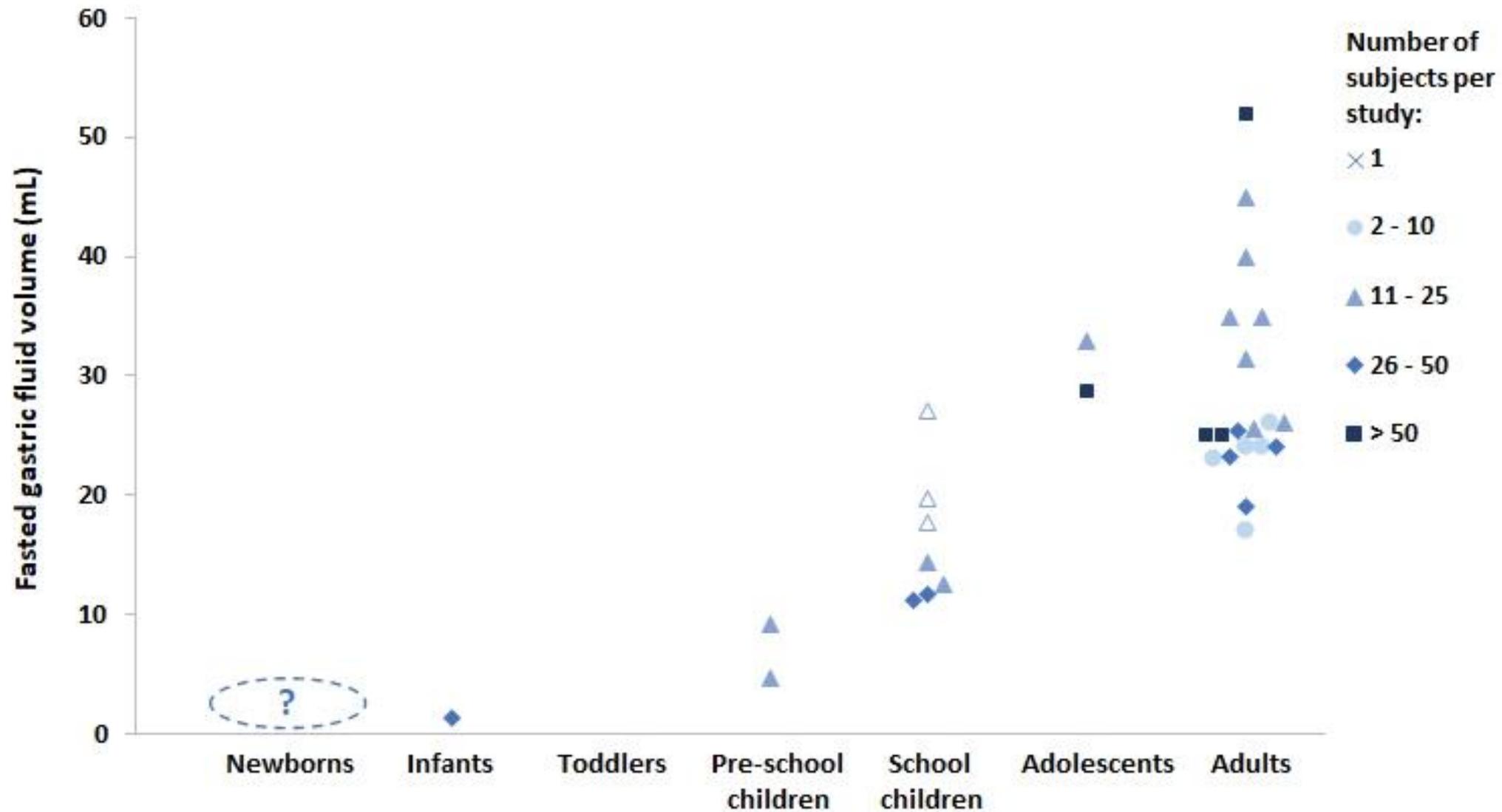
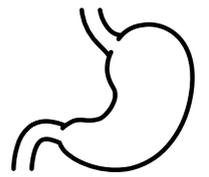
Esophagus

- esophageal motility
- esophageal transit time

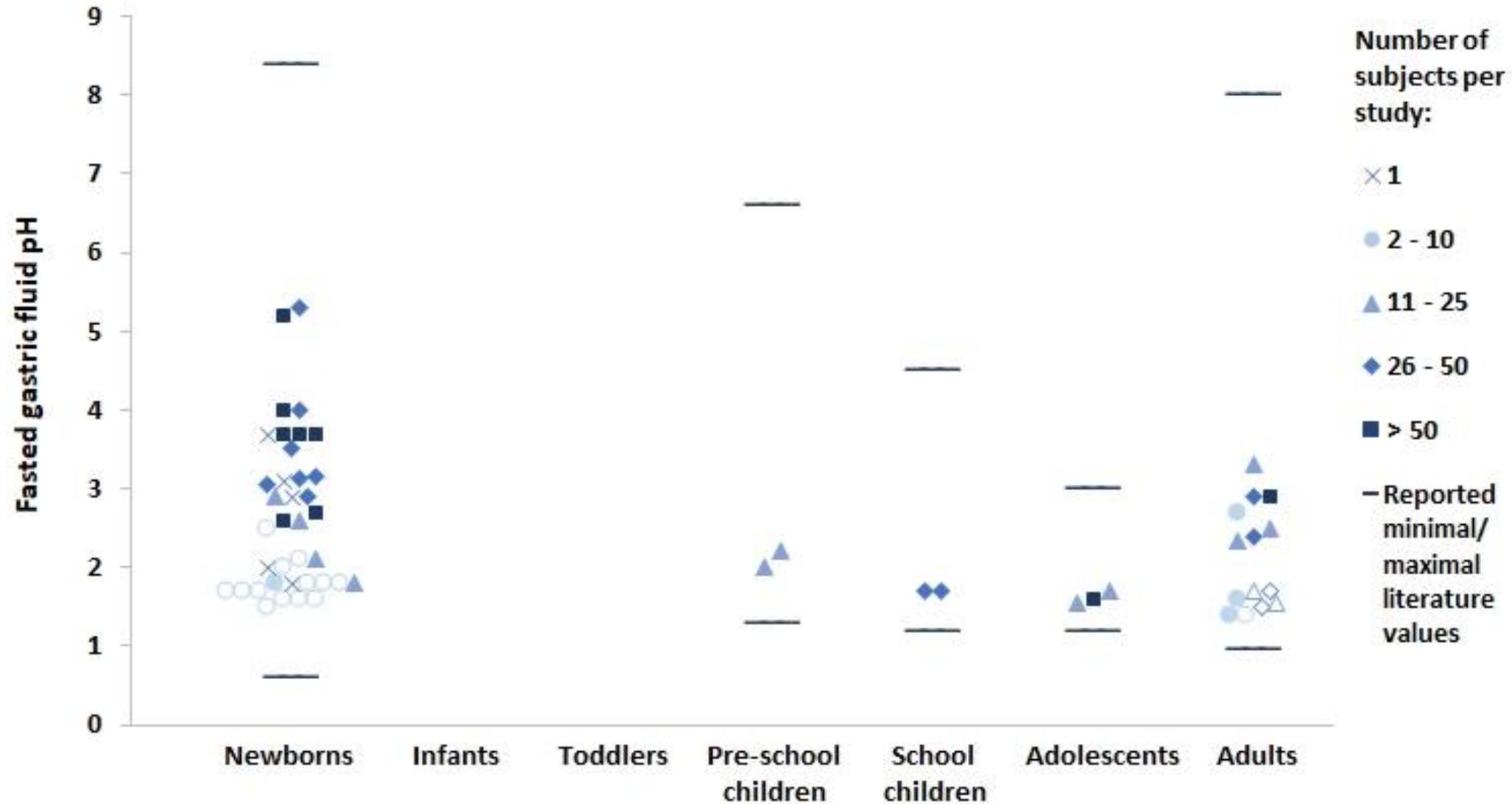
Small intestine

- duodenal contents
- duodenal bile salts
- pancreatic enzymes
- small intestinal motility
- small intestinal transit

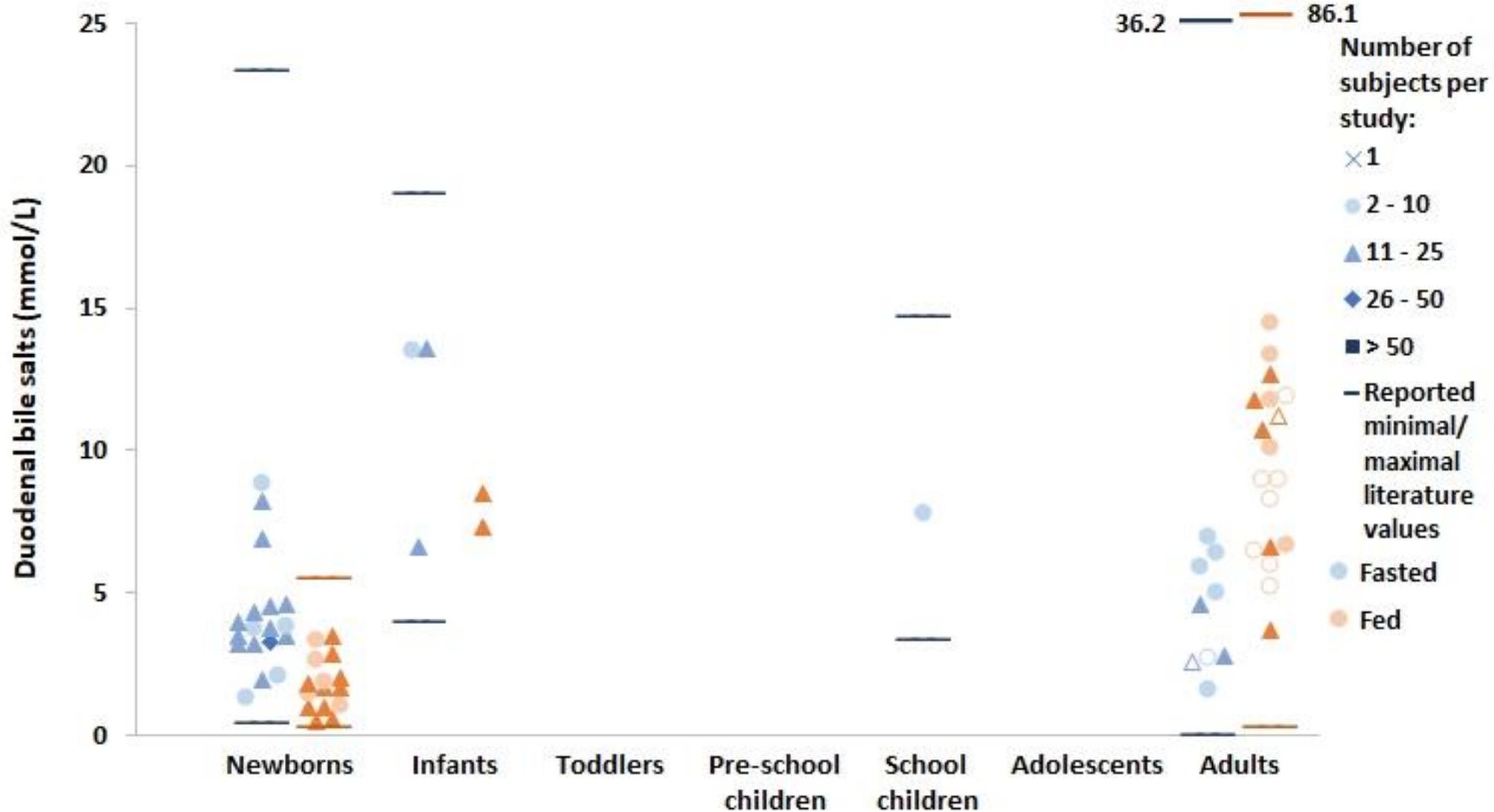
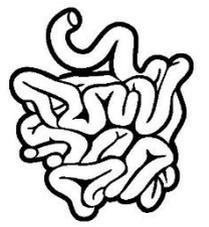
Gastric fluid volume



Gastric fluid pH

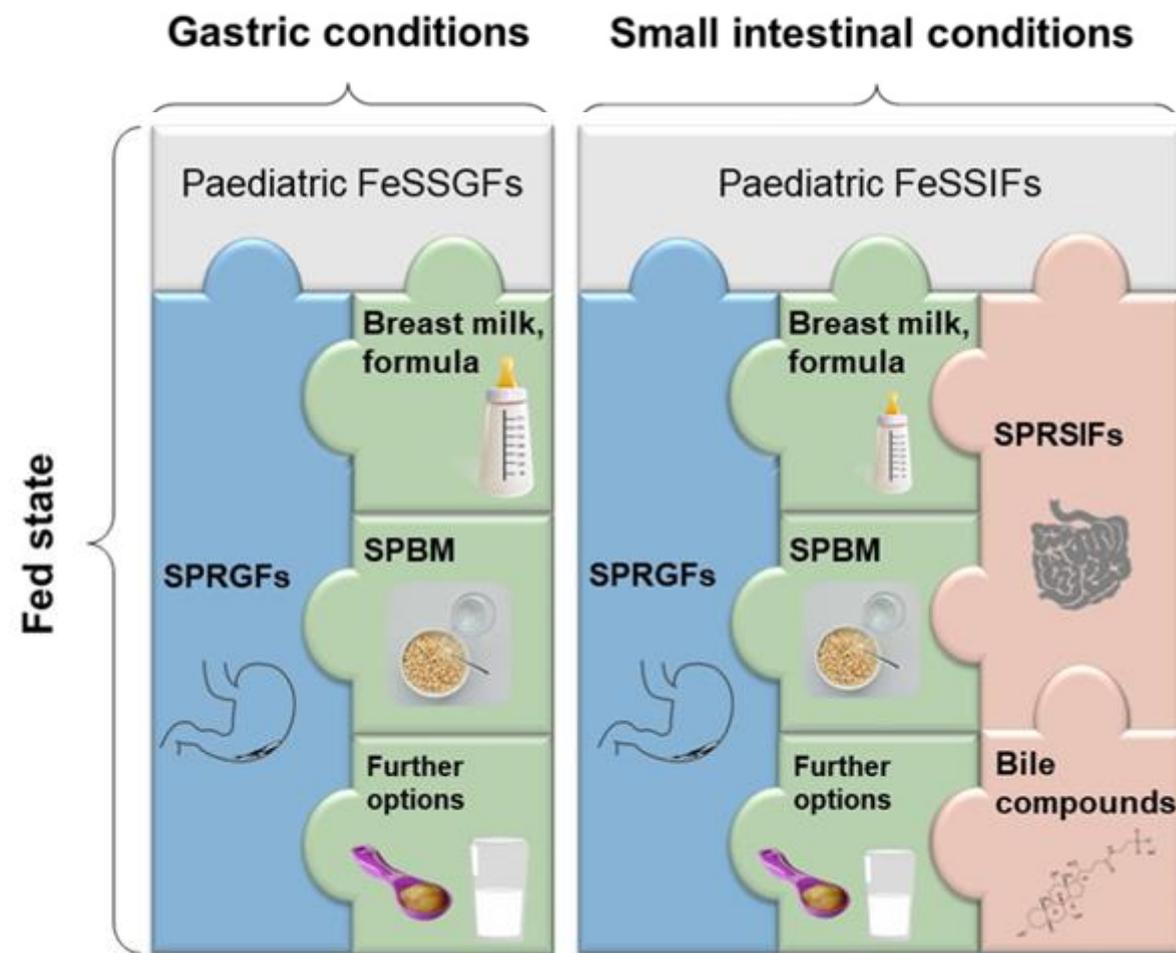
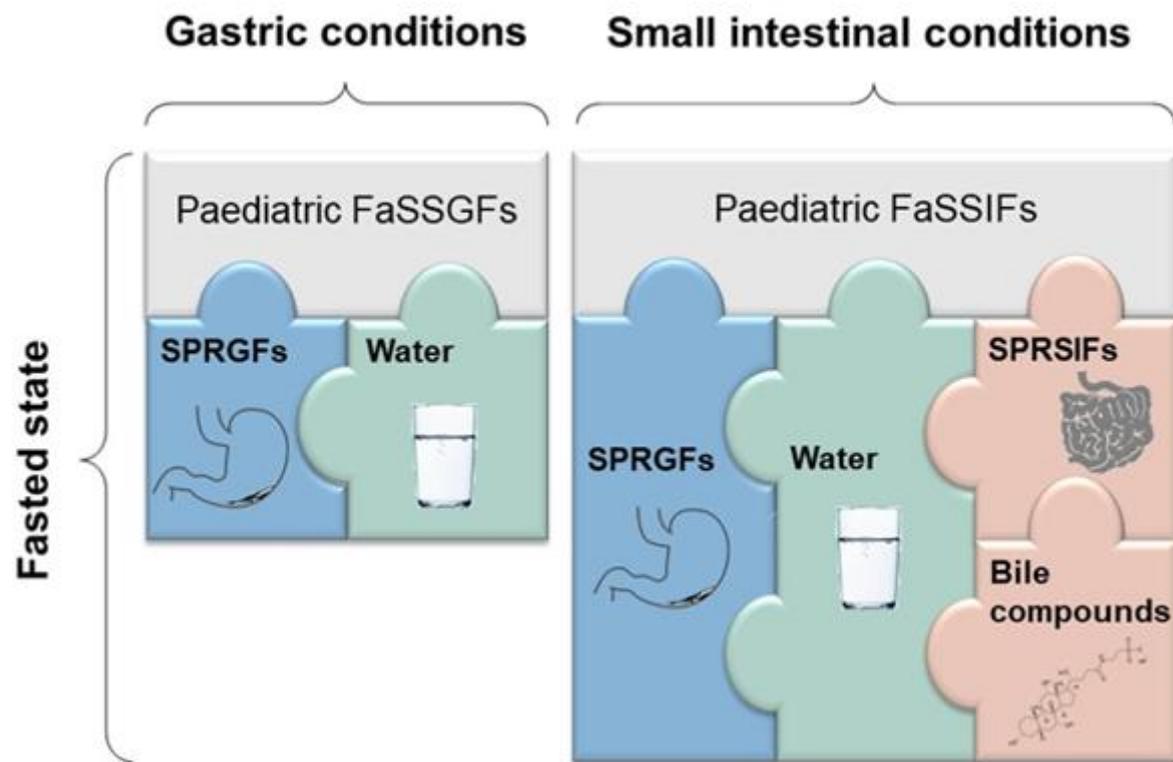


Duodenal bile salt concentration



Biorelevant *in vitro* dissolution media - toolbox

- children of different age groups
- fasted and fed-state dosing conditions



Identification of target parameters – fasted state

Simulated Pediatric Resting Gastric Fluids (SPRGFs)

Physicochemical properties	Neonates	Infants/toddlers	Pre-school children	School children	Adolescents
pH	1.8				
buffer capacity (mEq/pH/L)	10				
osmolality (mOsmol/kg)	120	120	150	150	200
bile salts (μM)	30	10	20	40	60

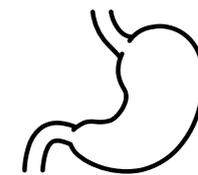


Simulated Pediatric Resting Small Intestinal Fluids (SPRSIFs)

Physicochemical properties	Neonates	Infants/toddlers	Pre-school children	School children	Adolescents
pH	6.0				
buffer capacity (mEq/pH/L)	4				
osmolality (mOsmol/kg)	250				
bile salts (μM)	4000	7500			



Biorelevant media design – fasted state



Simulated Pediatric Resting Gastric Fluids (SPRGFs)

Physicochemical properties	Neonates (nn)	Infants/toddlers (it)	Pre-school children (psc)	School children (sc)	Adolescents (ad)
Sodium taurocholate	30 μ M	10 μ M	20 μ M	40 μ M	60 μ M
Lecithin	7.5 μ M	2.5 μ M	5 μ M	10 μ M	15 μ M
NaCl	46.5 mM	46.5 mM	65.0 mM	65.0 mM	90.3 mM
HCl conc.	<i>qs ad 1.8</i>	<i>qs ad 1.8</i>	<i>qs ad 1.8</i>	<i>qs ad 1.8</i>	<i>qs ad 1.8</i>
Deionized water	<i>ad 1 L</i>	<i>ad 1 L</i>	<i>ad 1 L</i>	<i>ad 1 L</i>	<i>ad 1 L</i>
pH	1.81 \pm 0.01	1.80 \pm 0.02	1.78 \pm 0.01	1.78 \pm 0.03	1.80 \pm 0.01
Osmolality (mOsmol/kg)	125 \pm 2	123 \pm 6	162 \pm 6	160 \pm 6	207 \pm 3
Buffer capacity (mEq/pH/L)	19.09 \pm 0.44	18.49 \pm 0.37	19.06 \pm 0.68	19.69 \pm 0.79	17.54 \pm 1.65
Surface tension (mN/m)	45.75 \pm 7.58	57.46 \pm 5.49	42.34 \pm 3.45	45.88 \pm 3.34	41.74 \pm 3.02

Biorelevant media design – fasted state



Simulated Pediatric Resting Small Intestinal Fluids (SPRSIFs)

Physicochemical properties	Neonates (nn)	All other age groups (it-ad)
Sodium taurocholate	4 mM	7.5 mM
Lecithin	0.3 mM	0.5 mM
Maleic acid	11.6 mM	11.9 mM
NaCl	112.6 mM	112.4 mM
NaOH	<i>qs ad</i> pH 6.0	<i>qs ad</i> pH 6.0
Deionized water	<i>ad</i> 1 L	<i>ad</i> 1 L
pH	6.00 ± 0.04	6.04 ± 0.01
Osmolality (mOsmol/kg)	246 ± 2	244 ± 2
Buffer capacity (mEq/pH/L)	4.23 ± 0.03	4.53 ± 0.12
Surface tension (mN/m)	45.48 ± 0.93	45.85 ± 1.05

Development of simulated pediatric breakfast media (SPBM)

Objective

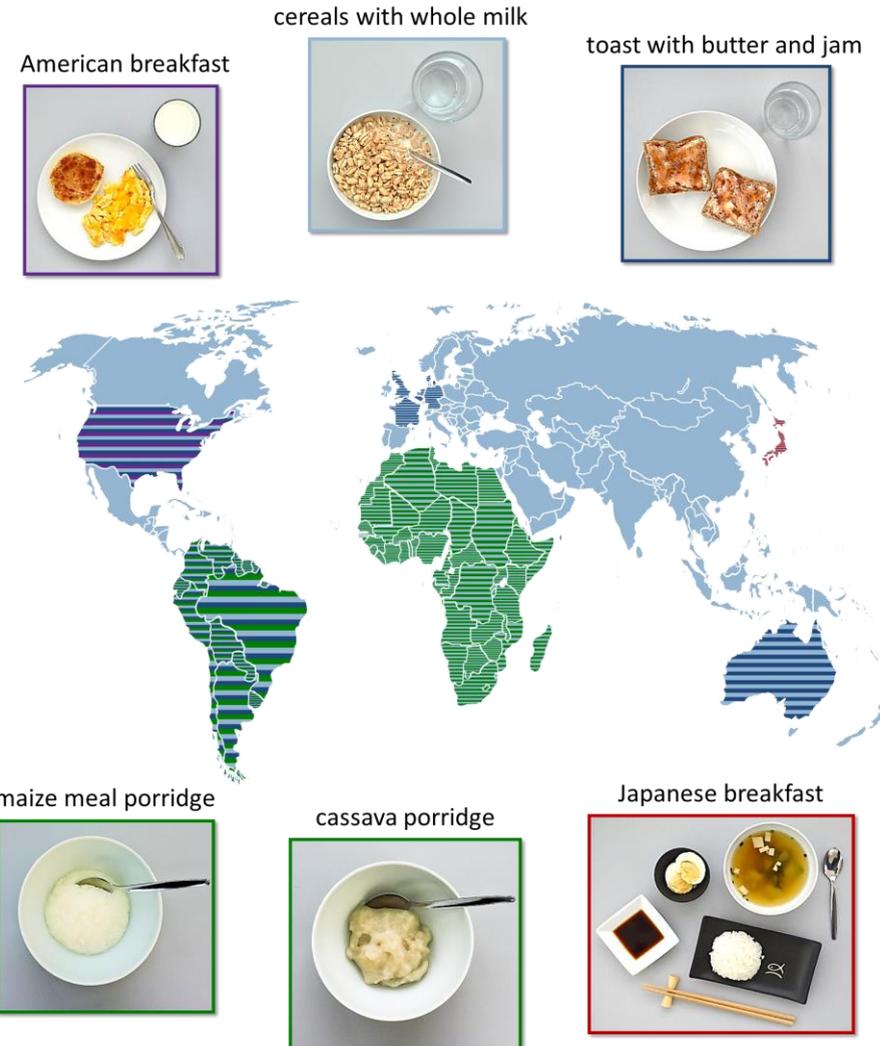
- to enable simulation of upper GI conditions after drug administration with typical children's breakfasts in different geographical regions of the world



Development of simulated pediatric breakfast media (SPBM)

Media development

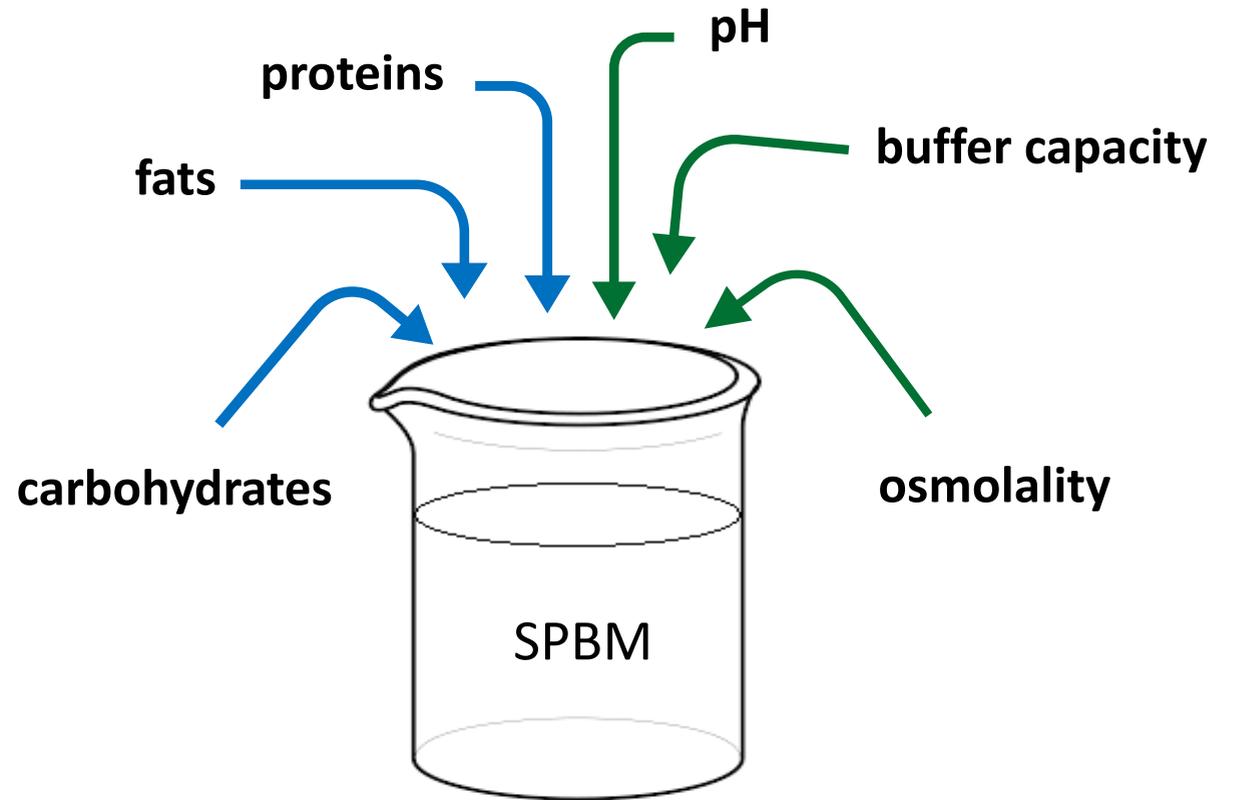
- a) Literature screen to **identify typical breakfasts**
- b) Breakfast preparation and homogenization
- c) Determination of the physicochemical properties, i.e., **pH, buffer capacity, osmolality and surface tension**
- d) Documentation of **fat:protein:carbohydrate ratios and caloric content**



Development of simulated pediatric breakfast media (SPBM)

Media development

- a) Literature screen to **identify typical breakfasts**
- b) Breakfast preparation and homogenization
- c) Determination of the physicochemical properties, i.e. **pH, buffer capacity, osmolality** and **surface tension**
- d) Documentation of **fat:protein:carbohydrate ratios** and **caloric content**
- e) Preparation of standardized media - SPBM



1. Adaption of the breakfast composition
2. Adaption of the physicochemical properties

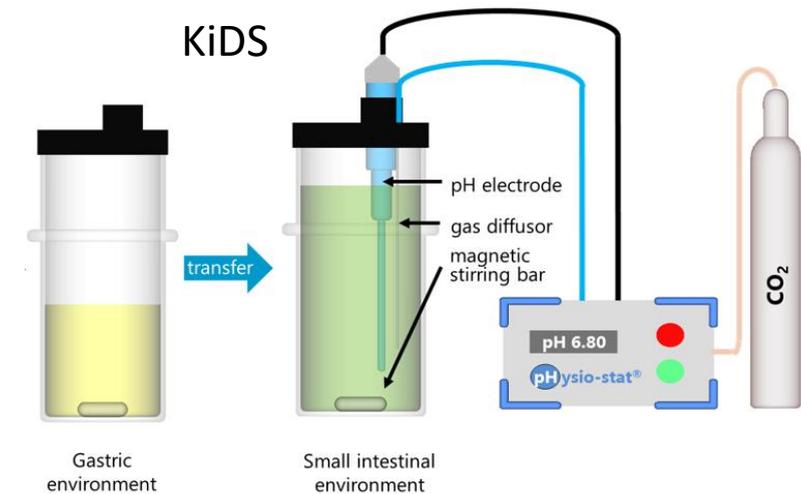
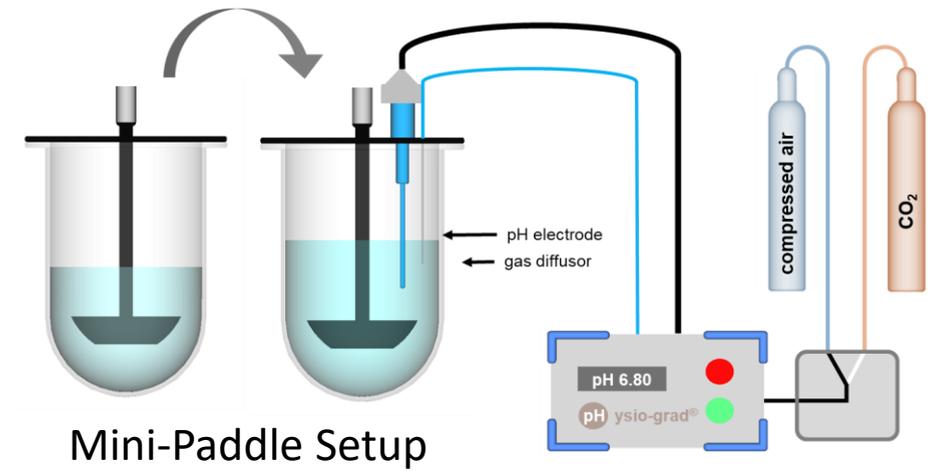
Simulation of pediatric *in vivo* conditions in the upper GI tract

In vitro test design



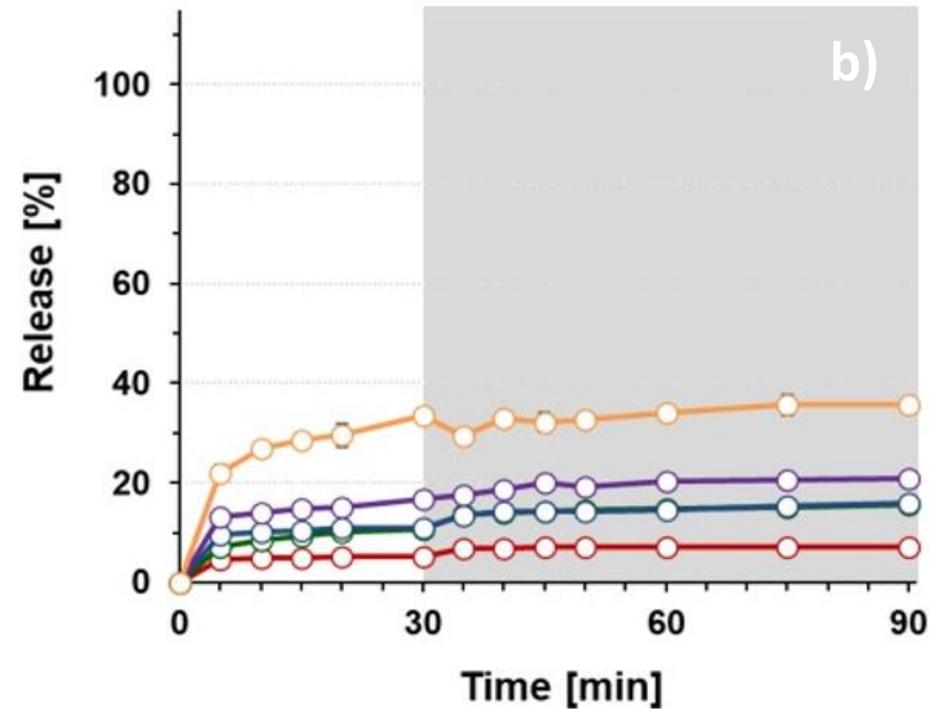
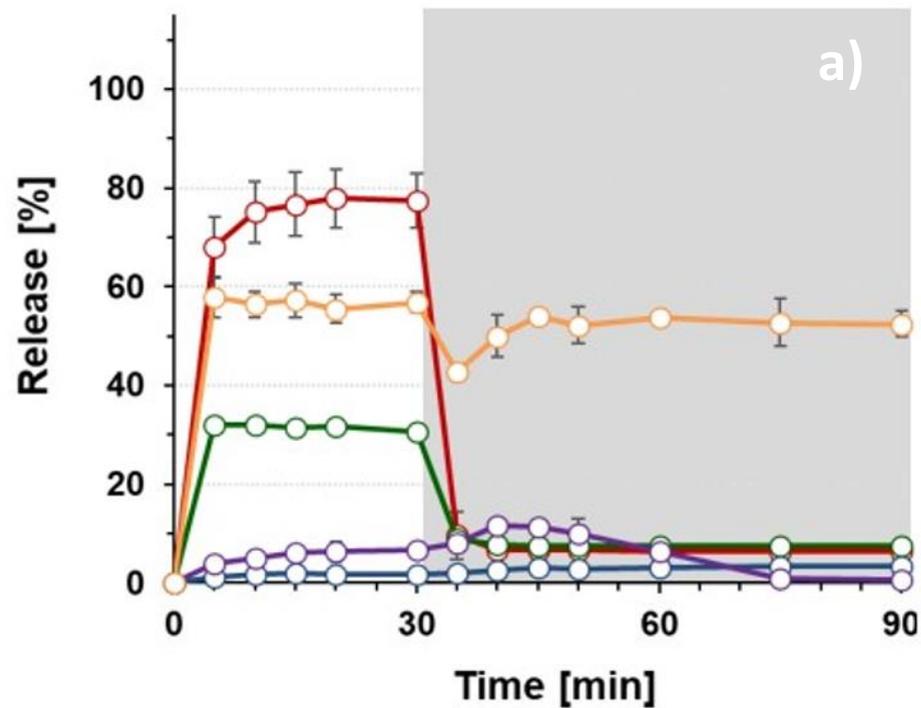
Simulation of pediatric *in vivo* conditions in the upper GI tract

In vitro test design



Simulation of pediatric *in vivo* conditions in the upper GI tract

Itraconazole (a) and darunavir (b) dissolution in biorelevant fasted and fed-state gastric- (0-30 min) and small intestinal (30-90 min) conditions



- glass of water
- cassava porridge
- toast breakfast
- American breakfast
- Ensure[®] Plus

Where are we now?

- all published data obtained with biorelevant pediatric *in vitro* approaches indicate the importance of addressing pediatric GI physiology and dosing conditions
- we are still on the learning curve
- for designing appropriate test methods for pediatric patients we need to know more about
 - GI physiology
 - typical dosing conditions
 - diseases impacting oral drug absorption
 - impact of co-medication
 - ...
- we need relevant *in vivo* data!
- we need to combine expertise!



Where are we now?

Recent data

**molecular
pharmaceutics** Article

Cite This: *Mol. Pharmaceutics* 2019, 16, 3896–3903 pubs.acs.org/molecularpharmaceutics

Magnetic Resonance Imaging Quantification of Gastrointestinal Liquid Volumes and Distribution in the Gastrointestinal Tract of Children

Eleni Papadatou-Soulou,[†] Julie Mason,[†] Caron Parsons,[‡] Adam Oates,[§] Manigandan Thyagarajan,[§] and Hannah Katharine Batchelor^{*,†} 

Valuable information, but caveat:

- typically, no prospective study design
- data from children with different diseases

 European Journal of Pharmaceutics and Biopharmaceutics 

Volume 158, January 2021, Pages 156-165

Characterisation of fasted state gastric and intestinal fluids collected from children

Gopal Pawar ^a, Eleni Papadatou-Soulou ^a, Julie Mason ^a, Rafeeq Muhammed ^b, Alison Watson ^b, Catherine Cotter ^b, Mohamed Abdallah ^{c, d}, Stuart Harrad ^c, Claire Mackie ^e, Tina Arien ^e, Sabine Inghelbrecht ^e, Hannah Batchelor ^{a, f}  

 European Journal of Pharmaceutical Sciences 

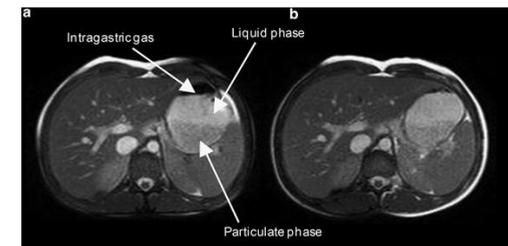
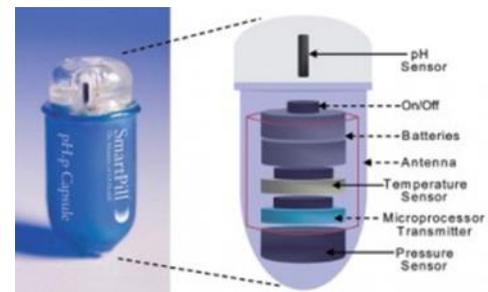
Volume 123, 15 October 2018, Pages 301-311

Gastric fluid composition in a paediatric population: Age-dependent changes relevant for gastrointestinal drug disposition

Jens Van Den Abeele ^a, Maissa Rayyan ^b, Ilse Hoffman ^c, Els Van de Vijver ^d, Wei Zhu ^e, Patrick Augustijns ^a  

Where are we now?

- how can we obtain relevant data as by-products of routine investigations?
- is there a way to standardize such examinations?
- is there a way to make assessment tools child size?
- could we sort data in dependence of critical illnesses in child age?



How shall we proceed?

We need to combine forces ...

to be
discussed
!!!



Acknowledgements



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Department of Neonatology
and Pediatric Intensive Care



ERNST MORITZ ARNDT
UNIVERSITÄT GREIFSWALD



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Seit 1456





Thank you!

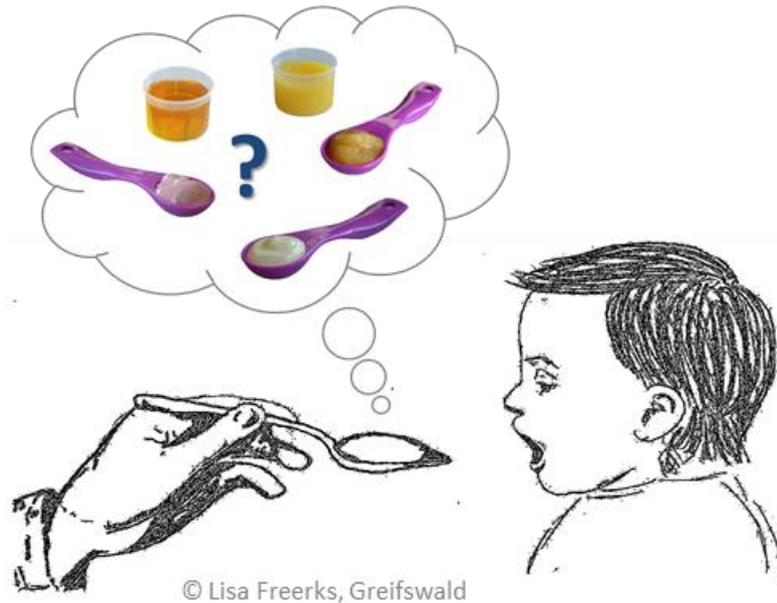
Prof. Dr. Sandra Klein
Institute of Pharmacy
Center of Drug Absorption and Transport
University of Greifswald

Sandra.Klein@uni-greifswald.de



Please help us to fill further gaps ...

... by filling in and/or forwarding our online questionnaire



For parents, caregivers and health-care professionals:
3-minute survey on drug administration in children.



The survey is available in different languages - simply choose your language in the first step!

To mask an unpleasant taste or improve swallowability, oral pediatric medicines are often administered together with liquids or soft foods.

With the aim of better understanding this mode of administration and integrating this aspect into the development of future pediatric medicines, the research group of Prof. Dr. Sandra Klein at the University of Greifswald, Germany, is compiling information on how pediatric medicines are administered in different countries around the world.

For this, **we need your help** and would be very grateful if you could **tell us how you administer oral medicines to children** by answering a few questions.

Thank you for your time and support of our efforts and activities to improve the safety and effectiveness of pediatric medicines!



soscisurvey.de/medication_children/