In Vitro Tools to Risk Assess the Likelihood of a Food/Vehicle Effect in Pediatric Populations

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M-CERSI, EuPFI, IQ • Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products
Hyattsville, MD • USA • June 8-9 • 2016

Oral bioavailability

Drug solubility & dissolution rate in the upper GI tract

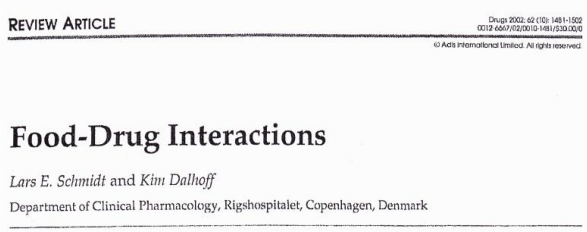
- physicochemical properties of the drug
- formulation properties
- physiological conditions in the upper GI tract at the time of dosing

↳ subject to food effects

⇒ benefit of increased bioavailability

⇒ risk of

  - reduced efficacy
  - increased toxicity



REVIEW ARTICLE

Food-Drug Interactions

Lars E. Schmidt and *Kim Dalhoff*

Department of Clinical Pharmacology, Rigshospitalet, Copenhagen, Denmark

DRUG DISPOSITION

Effects of Food on Clinical Pharmacokinetics

Brahma N. Singh

Department of Pharmacy and Administrative Sciences, College of Pharmacy and Allied Health Professions, St John's University, Jamaica, New York, USA

Food effects in pediatric patients?

Dosing scenarios

- medication is administered after a meal (e.g. breakfast)
- unpleasant taste / difficulties in swallowing:

  ⇒ powder, tablet bits, sprinkles are admixed with soft food or fluids before administration

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Food effects in pediatric patients?

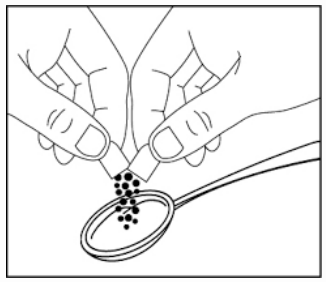
Co-administration with a meal or modification of the dosage form…

- can affect physical / chemical stability of the drug / formulation

Case example: Enteric coated pellets

"In vitro stability, potency, and dissolution of duloxetine enteric-coated pellets after exposure to apple sauce, apple juice, and chocolate pudding"

- exposure of the pellets to the different foods
  - → potency and impurities
  - → dissolution



- enteric coating of duloxetine pellets was not negatively affected by mixing with apple sauce or apple juice
- exposing the pellets to chocolate pudding damaged the coating

Apple juice (25 °C): pH 3,5
Apple sauce (25 °C): pH 3,7
Vanilla pudding (25 °C): pH 6,5

K.A. Wells et al., Clinical Therapeutics 2008, 30 (7): **1300-1308**

Food effects in pediatric patients?

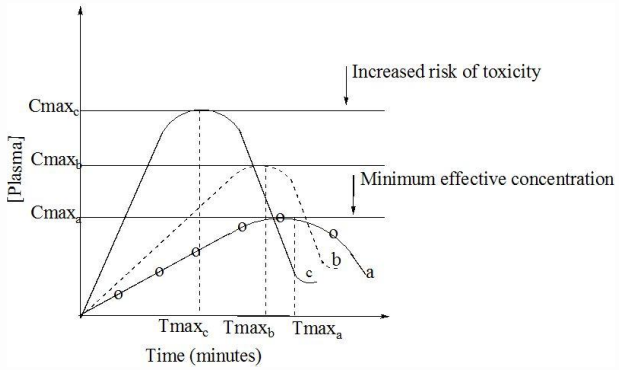
Co-administration with a meal or modification of the dosage form…

- can affect physical / chemical stability of the drug

  ⇒ stability studies

- can alter the clinical performance of a drug by changing its bioavailability

  ⇒ how can we predict that?



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Biorelevant *in vitro* dissolution methods

Biorelevant dissolution media

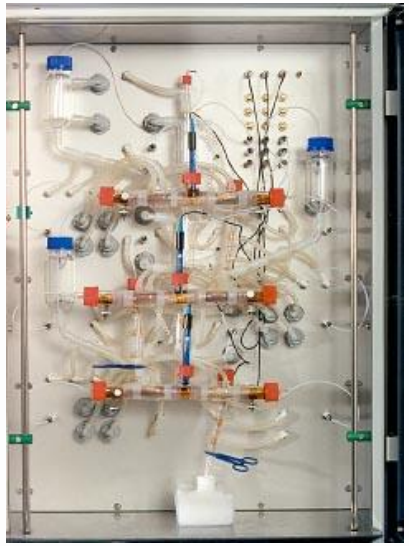
- address composition and properties of intraluminal fluids after fasted and fed dosing

Further parameters of importance

- gastric emptying time, small intestinal transit time
- GI motility and pressures

Advanced dissolution models

- dynamic gastric model, stress test device, …
- multicompartmental models , e.g. USP 3/4, transfer model, gastroduodenal model, TIM-1 …



Biorelevant *in vitro* dissolution methods

- physiologically based *in vitro* dissolution models can be helpful in establishing an IVIVC in many cases, however …

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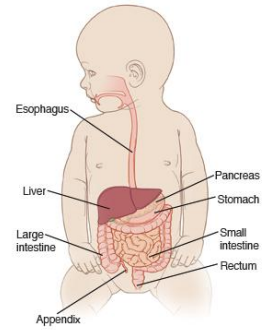
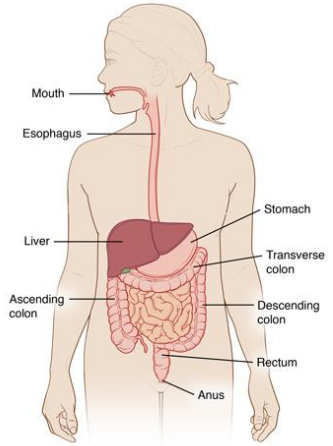
Biorelevant *in vitro* methods for children

What is required for the test design?





- key parameters for *in vivo* drug release
  - physiological parameters
    → fluid volume & composition in the GI sections
    → residence times / GI passage
  - dosing conditions /manipulation
    → co-administered food/fluid volumes & properties
    → clinical/real dosing conditions?

- application of adult models will not work
- an universal pediatric approach is unlikely

⇒ there is need for appropriate test designs!

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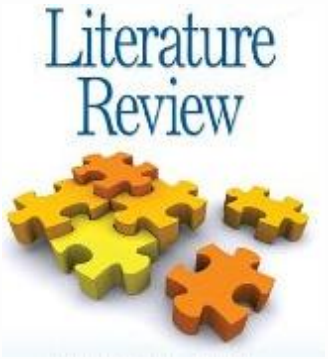
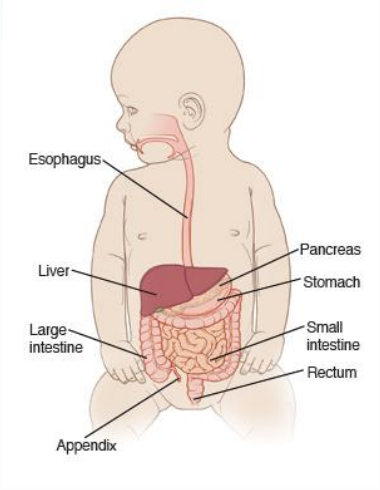
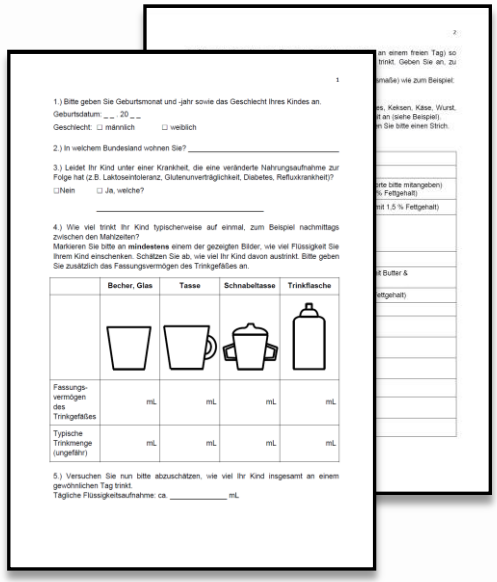
A possible starting point ….







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Pediatric vs. adult GI physiology

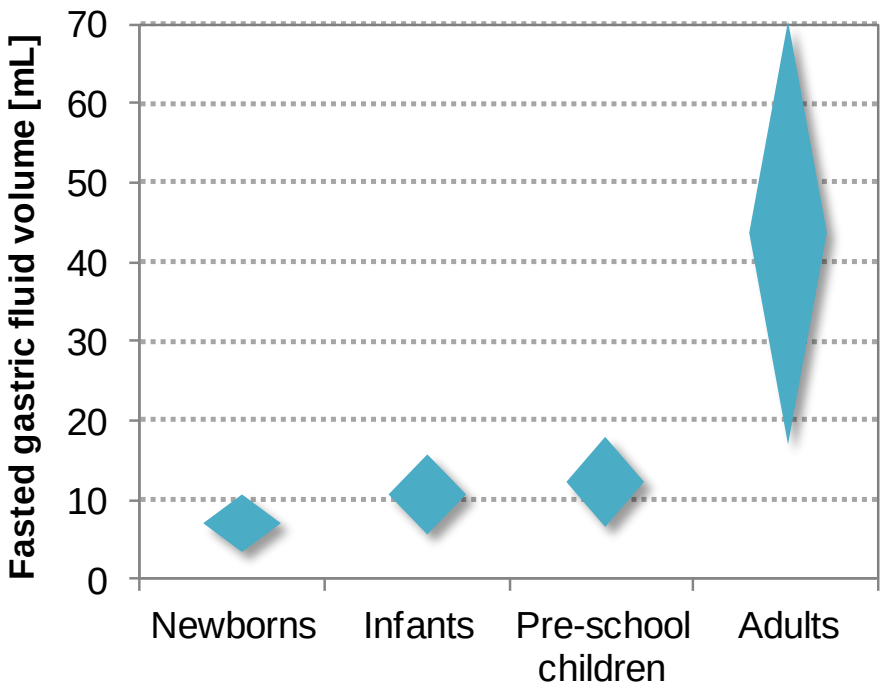
⇒ the biggest differences are found in preterms and neonates

- gastric pH
- gastric emptying
- gastric acid secretion
- stomach capacity
- small intestinal pH
- small intestinal transit time
- production of digestive enzymes
- pancreatic secretion
- bile secretion

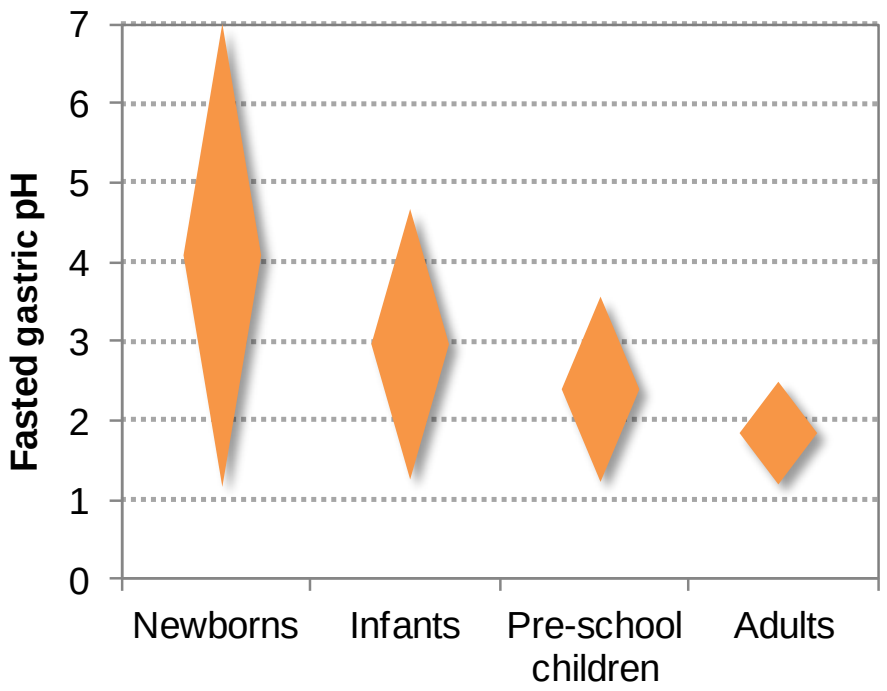
Fasted gastric fluid volumes and pH

Typical trends in healthy patients

Gastric fluid volume



Fasted gastric pH



E. Kersten, S. Klein, AAPS Annual Meeting, San Antonio, USA, 2013 (Poster)

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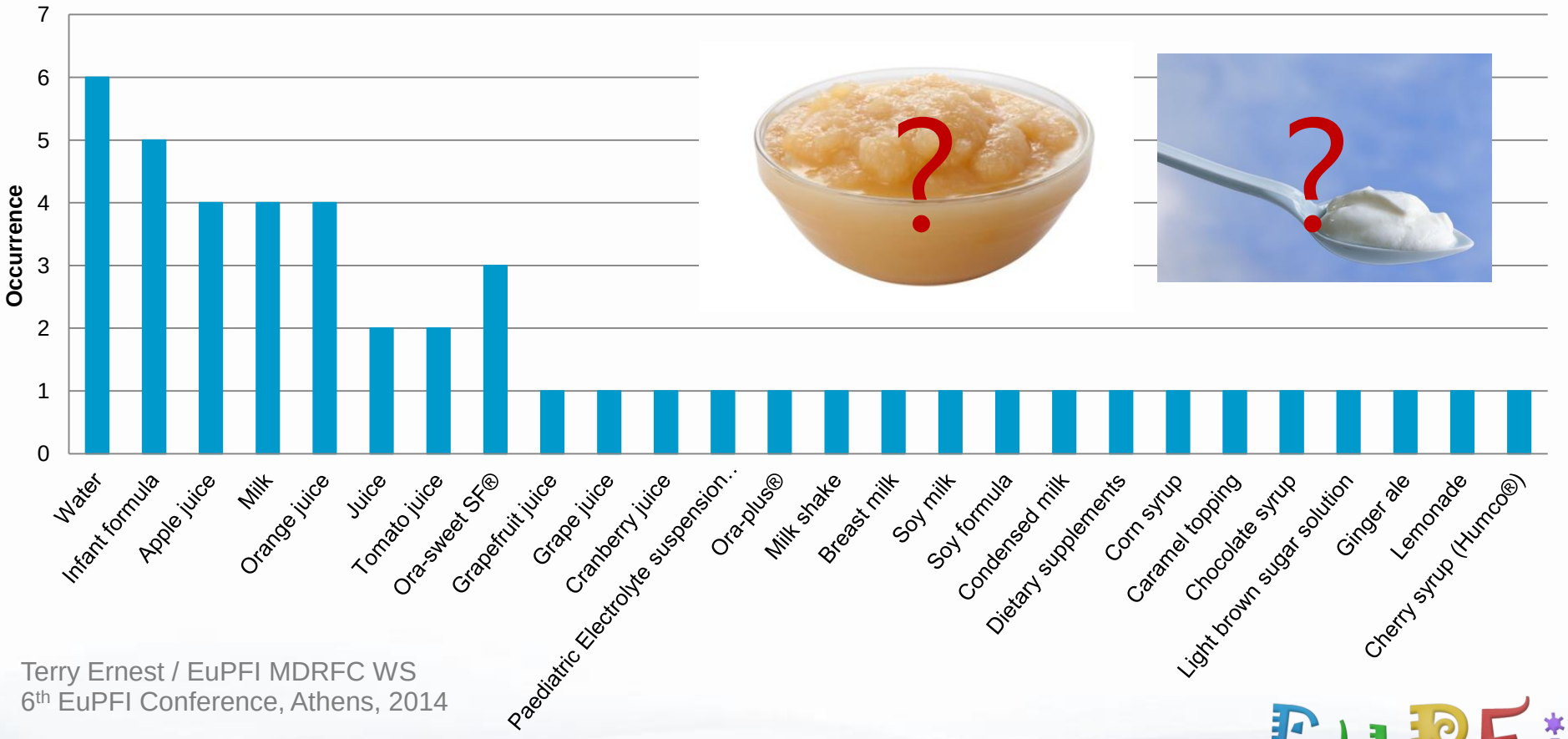
Current practices of manipulating medicines

Occurrences of different types soft foods/ drinks appearing on administration instructions for pediatric medicines (SmPCs and PILs)



Terry Ernest / EuPFI MDRFC WS
6th EuPFI Conference, Athens, 2014

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Typical breakfasts ingested by infants (1yr)

Preparation & physicochemical characterization

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Food / fluid properties

Can affect …

- drug / formulation stability
- drug solubility
- dissolution rate / drug release rate

Might affect …

- gastric emptying

Most relevant physicochemical characteristics

- pH
- buffer capacity
- osmolality
- surface tension
- viscosity

Type of food? Portion size / volume?

Relevant physicochemical characteristics

Parameter	Temp.	Fluids										Suspension vehicles		Soft foods		
		Water	Apple juice	Grape juice	Orange juice	Tomato juice	Whole milk	Chocolate milk	Vanilla milk	Conden-sed milk	Formula milk	ORA®-Sweet	ORA®-Sweet SF	Apple sauce	Vanilla pudding	Yoghurt
pH-value	25°C	7,31	3,47	3,45	3,87	4,30	6,72	6,55	6,42	6,11	6,59	4,22	4,30	3,71	6,55	4,27
		(0,01)	*(0,03)*	*(0,02)*	*(0,04)*	*(0,01)*	*(0,02)*	*(0,03)*	*(0,01)*	*(0,02)*	*(0,02)*	*(0,01)*	*(0,01)*	*(0,02)*	*(0,02)*	*(0,02)*
	37°C	7,89	3,49	3,43	3,85	4,27	6,63	6,51	6,36	6,05	6,57	4,24	4,29	3,70	6,47	4,26
		(0,01)	*(0,01)*	*(0,02)*	*(0,02)*	*(0,00)*	*(0,01)*	*(0,01)*	*(0,00)*	*(0,02)*	*(0,02)*	*(0,01)*	*(0,01)*	*(0,01)*	*(0,02)*	*(0,01)*
Buffer capacity [mEq/pH/L]	25°C	0,11	33,4	49,7	48,4	52,6	14,4	20,3	21,5	39,3	5,6	5,2	14,6	26,23	19,7	93,8
		(0,00)	*(1,7)*	*(0,7)*	*(2,1)*	*(1,0)*	*(0,2)*	*(0,5)*	*(0,4)*	*(1,4)*	*(0,1)*	*(0,1)*	*(0,4)*	*(1,9)*	*(0,7)*	*(4,1)*
	37°C	0,06	33,9	50,1	49,1	53,9	13,9	22,1	22,0	42,4	5,8	5,5	14,3	25,8	20,7	91,5
		(0,0)	*(0,3)*	*(0,7)*	*(1,1)*	*(0,2)*	*(0,2)*	*(0,2)*	*(0,3)*	*(1,5)*	*(0,1)*	*(0,1)*	*(0,3)*	*(0,4)*	*(0,7)*	*(0,3)*
Osmolality [mOsmol/kg]		4	677	1073	558	519	285	508	545	579	289	3046	1886	1052	596	484
		(1)	*(5)*	*(2)*	*(8)*	*(8)*	*(3)*	*(2)*	*(3)*	*(2)*	*(3)*	*(3)*	*(6)*	*(5)*	*(5)*	*(6)*
Surface tension [mN/m]	25°C	70,2	64,17	63,40	42,63	42,12	54,20	46,61	43,39	47,57	43,61	63,69	59,26	45,00†	43,09†	45,23†
		(0,36)	*(0,32)*	*(0,13)*	*(2,10)*	*(0,25)*	*(0,40)*	*(0,80)*	*(0,10)*	*(0,15)*	*(0,26)*	*(0,58)*	*(0,08)*	*(0,33)*	*(0,08)*	*(0,21)*
	37°C	68,74	62,51	63,38	49,10	39,42	49,80	45,23	43,31	46,03	43,24	63,19	58,83	42,27†	41,68†	43,82†
		(0,46)	*(0,45)*	*(0,22)*	*(1,10)*	*(0,22)*	*(0,60)*	*(0,61)*	*(0,15)*	*(0,30)*	*(0,07)*	*(0,08)*	*(0,09)*	*(0,22)*	*(0,13)*	*(0,16)*
Viscosity [mPa*s]	25°C	0,91	1,26	1,53	1,45*	‡	1,90	2,68	6,47	10,42	6,59	67,39	26,56	‡	‡	‡
		(0,00)	*(0,00)*	*(0,00)*	*(0,00)*		*(0,04)*	*(0,02)*	*(0,10)*	*(0,04)*	*(0,02)*	*(0,19)*	*(0,27)*			
	37°C	0,72	0,96	1,14	1,29*	‡	1,50	1,92	3,10	7,10	6,57	33,82	19,71	‡	‡	‡
		(0,00)	*(0,00)*	*(0,00)*	*(0,01)*		*(0,04)*	*(0,01)*	*(0,04)*	*(0,01)*	*(0,02)*	*(0,27)*	*(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 5.2.4* for more details

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

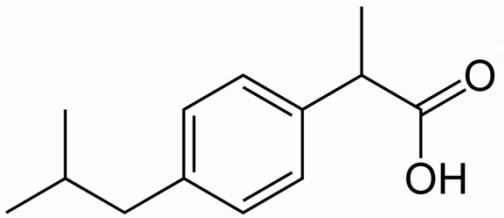
* to ensure complete pulp removal, orange juice was filtered through a 12 µm cellulose nitrate filter (Schleicher & Schuell, Dassel, Germany) using a vacuum filtration device before measuring viscosity

E. Kersten, A. Barry, S. Klein, DiePharmazie, 2016; 71 (3): 122-127(6)

Case example

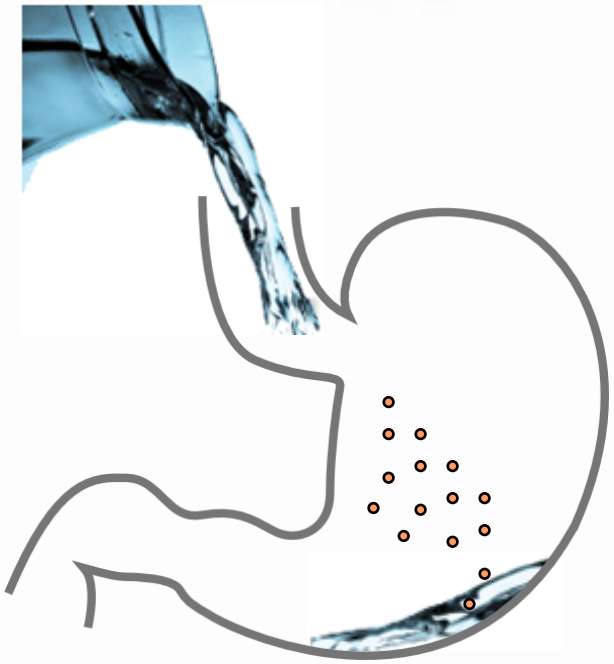
Ibuprofen

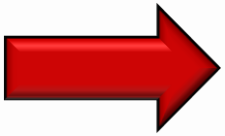
- used in children of all age groups
- adults: BCS class 2 → pediatric BCS class?
- food-effect?

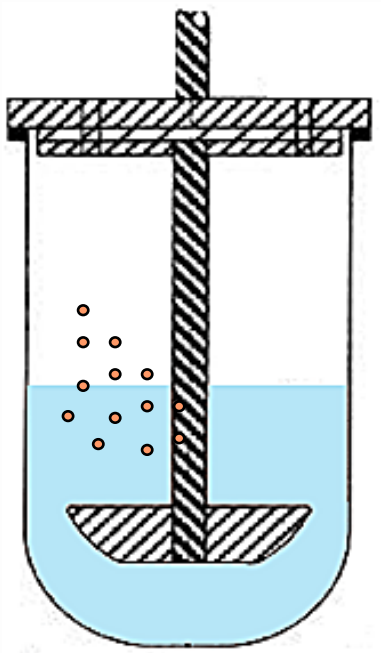


How can the drinking volumes, fluid and food properties affect *in vivo* dissolution in neonates and infants?

Test design – gastric dissolution







Resting gastric fluid pH

1.8; 2.5; 3.5; 4.0; 5.0; 7.0

Mini Paddle

200 mL, 75 rpm

Predictive test methods for newborns

Simulating drug release in the fasted stomach of a 3 kg newborn

		Furosemide	Ibuprofen
	Dosing recommendation	2 mg/kg	20 mg/kg
	Test dose	6 mg	60 mg
Scenario 1	Fluid volume available for dissolution	5 mL residual gastric fluid + 25 mL co-ingested fluid	
	Dose:gastric volume ratio	6 mg/30 mL	60 mg/30 mL
	Upscaled dose:volume ratio	40 mg/200 mL	66.7 mg/200 mL

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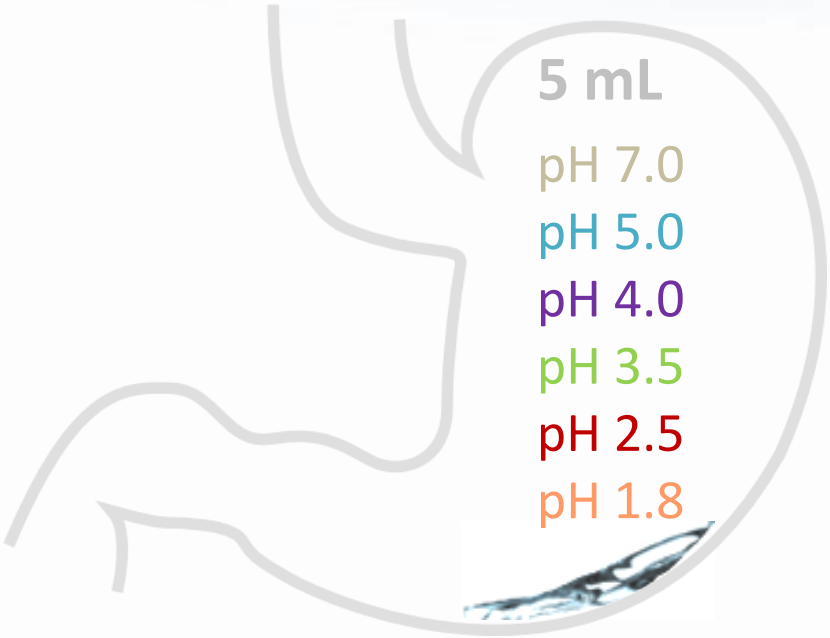
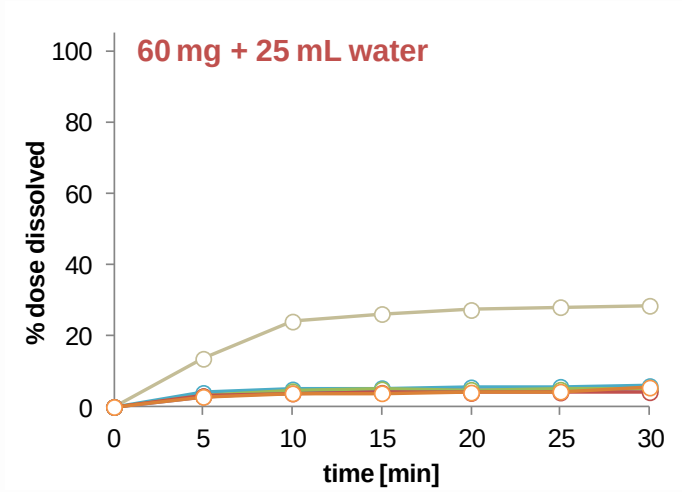
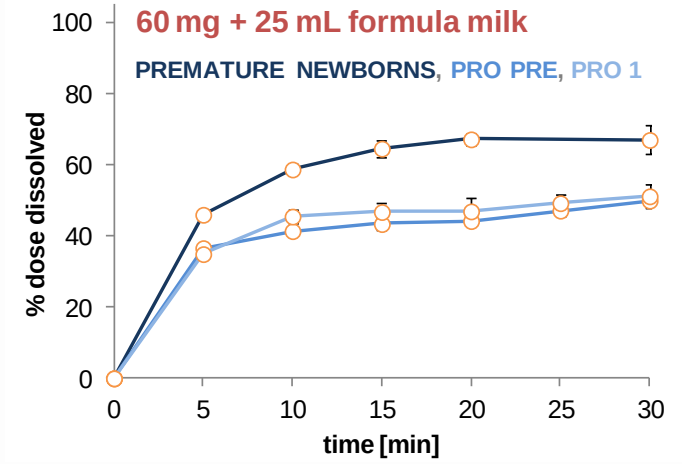
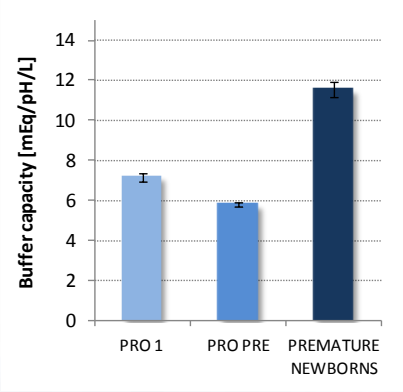
Ibuprofen – newborns









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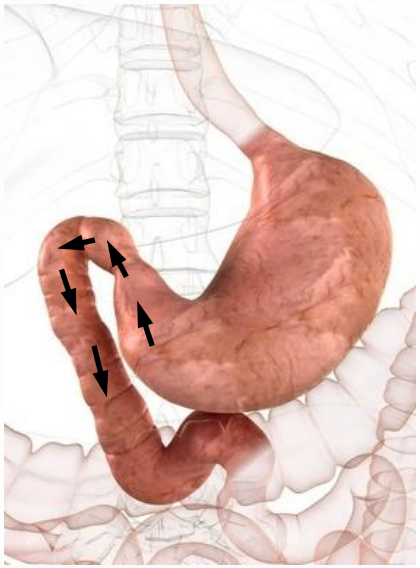
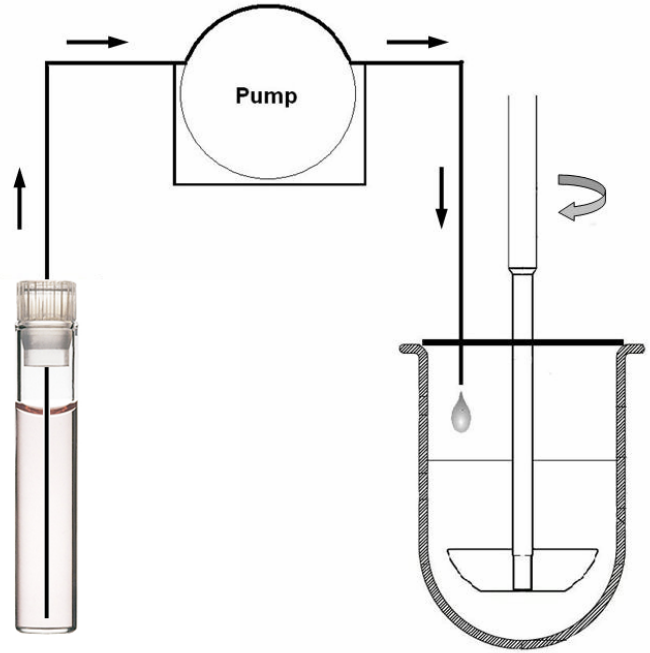
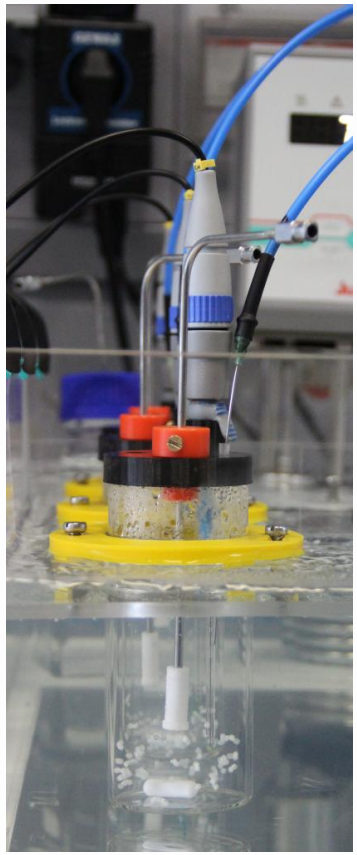
Ibuprofen – newborns

Combining gastric and small intestinal compartment

- use of physiologically relevant test volumes
- transfer of gastric contents into the small intestine







S Klein *et al*. AAPS PharmSciTech13 (4) (2012):1230-5

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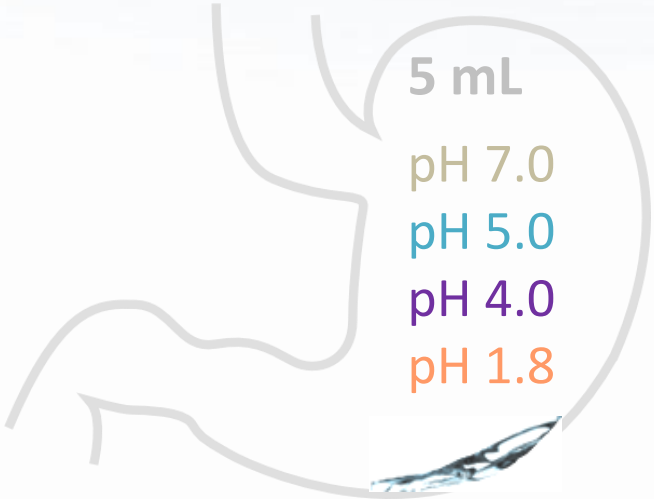
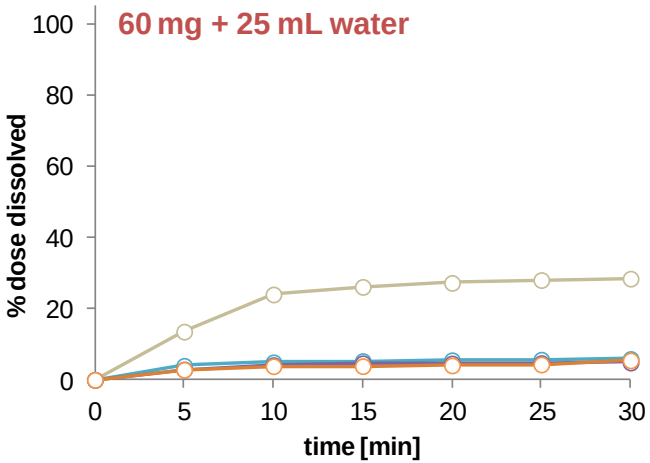
Ibuprofen – newborns





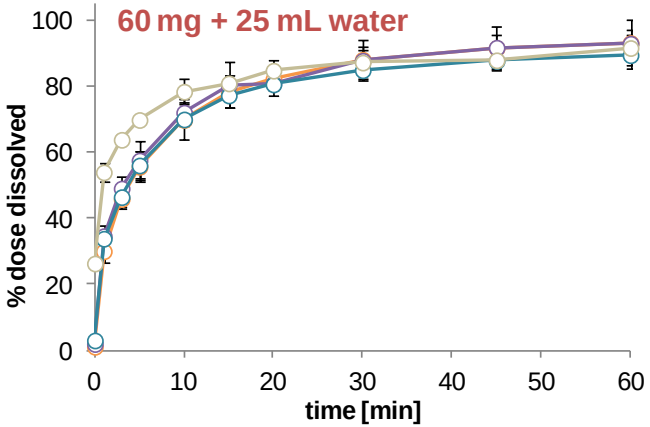
100 mL

pH 7.0 → pH 6.8

pH 5.0 → pH 6.8

pH 4.0 → pH 6.8

pH 1.8 → pH 6.8



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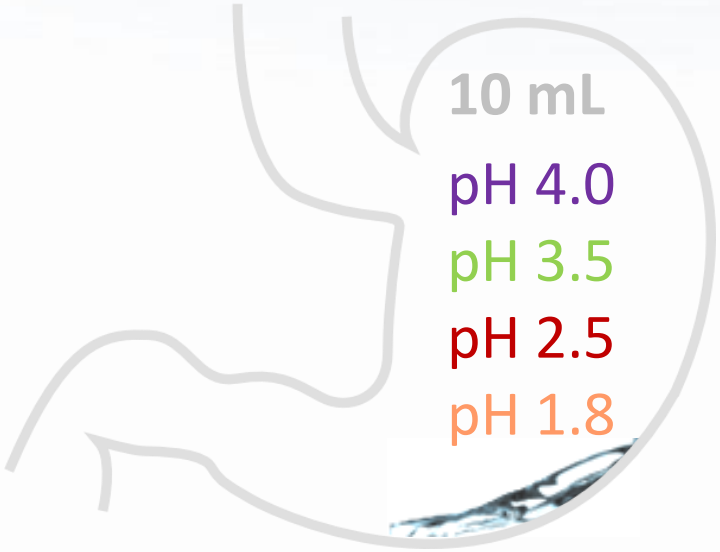
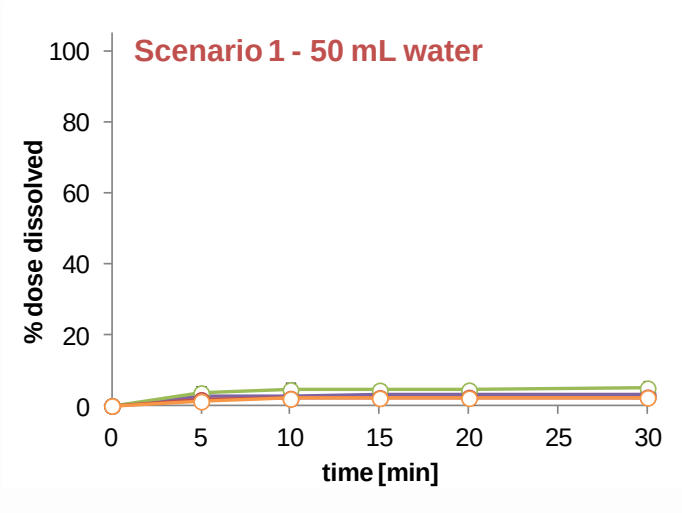
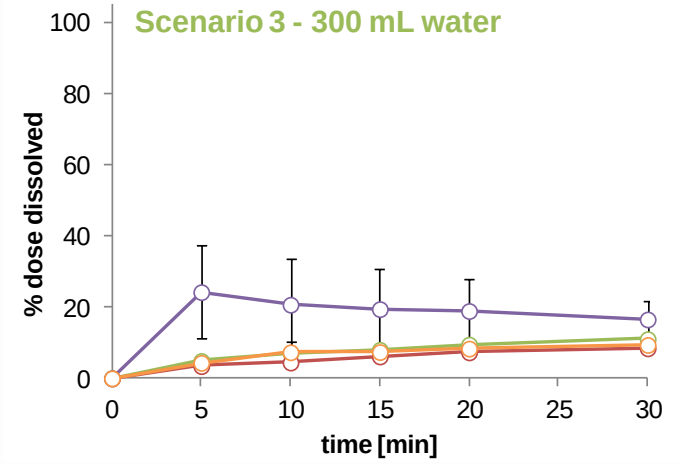
Ibuprofen – infants







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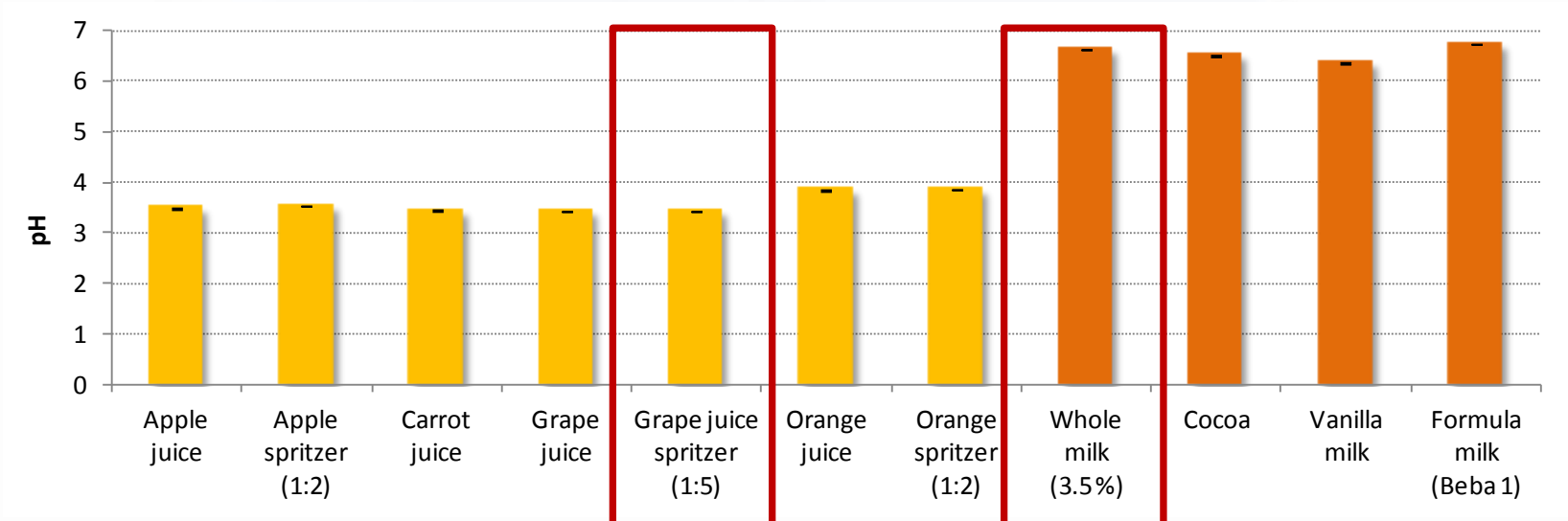
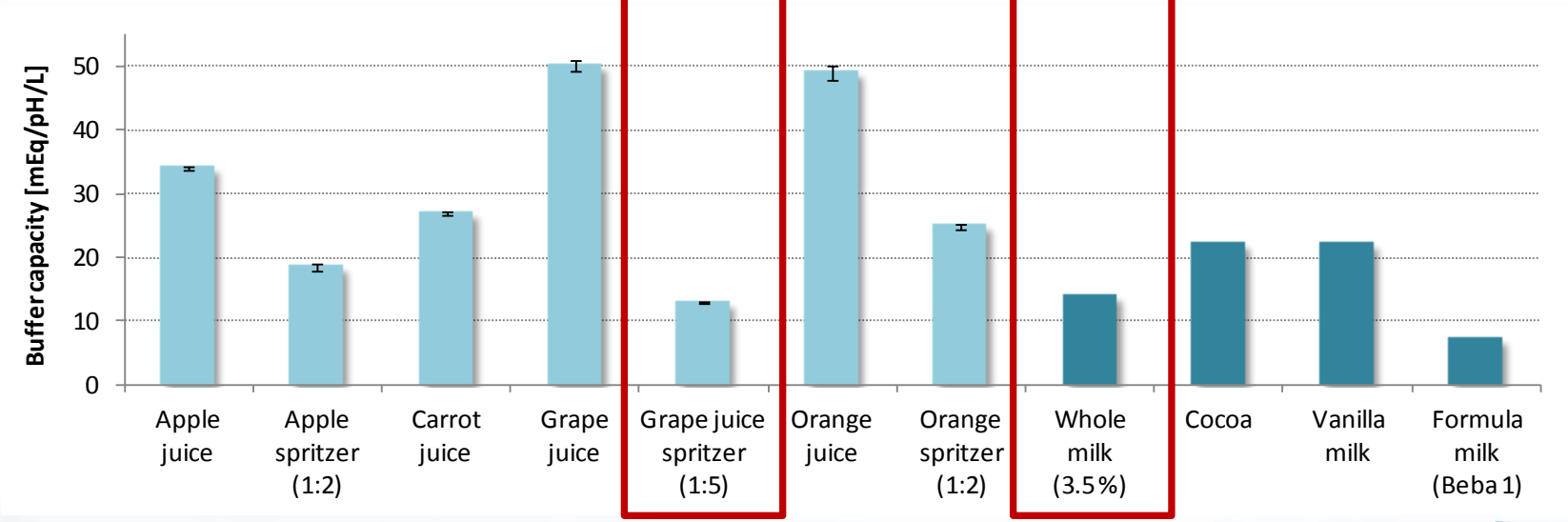
Properties of co-administered fluid





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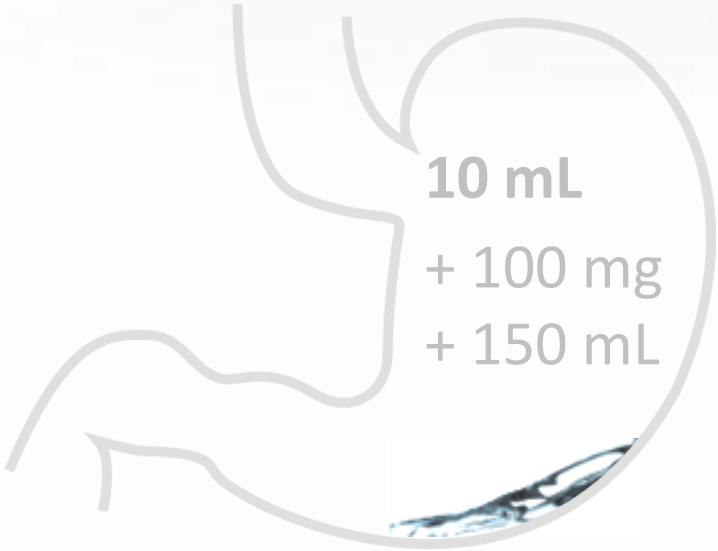
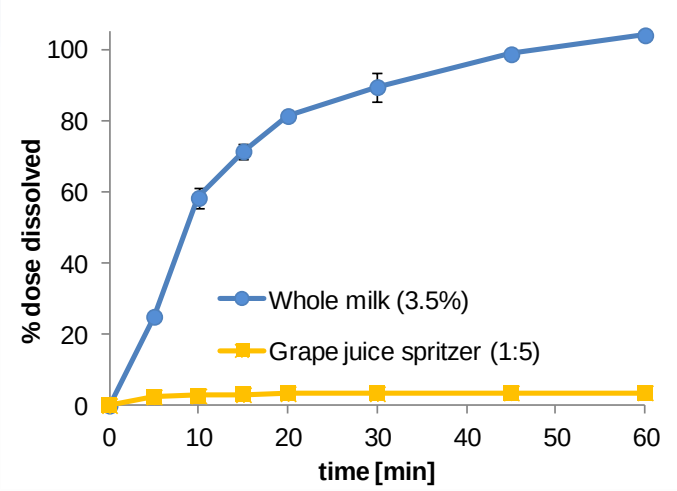
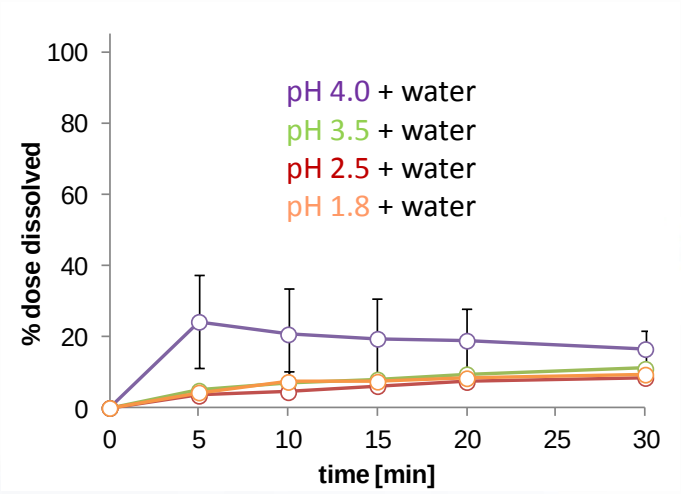
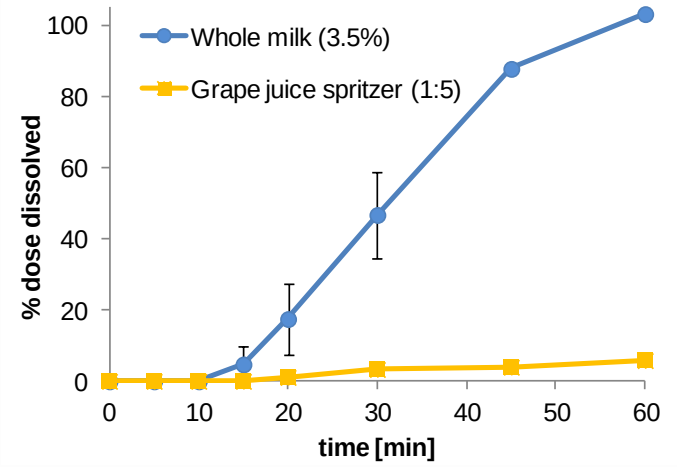
Ibuprofen – infants









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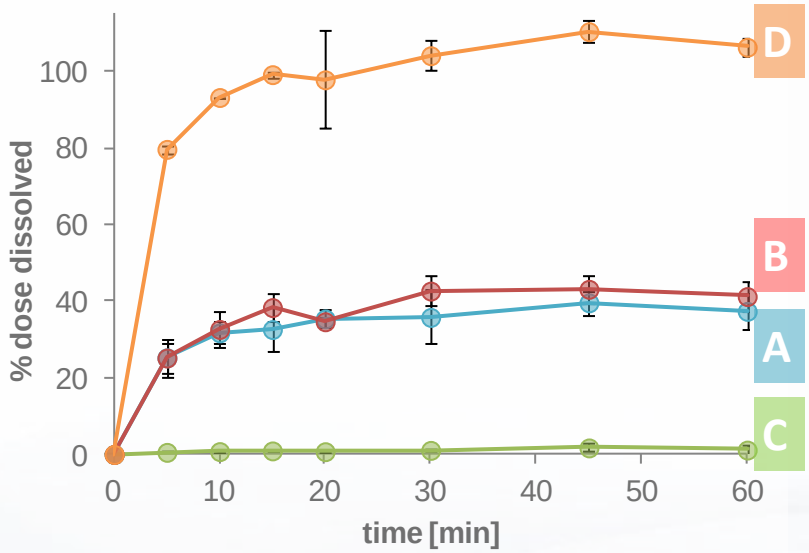
Ibuprofen – infants

Simulating postprandial gastric conditions in infants – ibuprofen (1 year)



- design & application of individual, but reproducible postprandial gastric media
  - carbohydrates
  - proteins
  - fat
  - pH
  - volume

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Predicting food effects in children …

- a safe dosing recommendation requires fundamental background information on drug/formulation, food/fluid properties, co-administered food/fluid portions and GI physiology
- with this information, it should be possible to design appropriate *in vitro* tools to risk assess the likelihood of a food/vehicle effect in pediatric populations

Current status

\+ we have a lot of experience for adults

– both *in vitro* and *in vivo* test methods cannot simply be downscaled from adult designs

Predicting food effects in children …

Where are the needs?

- new *in vitro* methods with pediatric relevance including apparatus, test settings and media
- appropriate *in vivo* screening methods to compare with

↳ a lot of gaps to fill on GI features of the pediatric population

↳ this is only possible with international collaboration and sufficient support

- modern and biopredictive pediatric in *vitro tools* will hopefully help to reduce the number of clinical studies required for releasing safe pediatric drug products to the market

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Biopharmaceutics Workstream

AAF - Modification of Dosage Forms Required for Children Workstream

Thank you

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