Gastrointestinal imaging with MRI: providing information about conditions at the site of drug delivery

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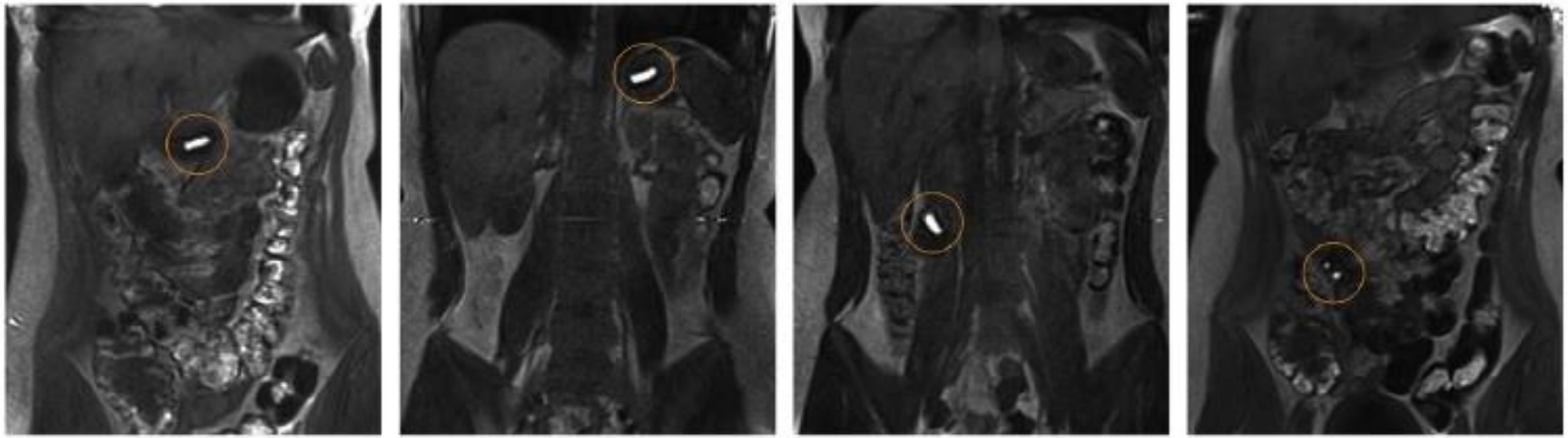
Magnetic Resonance Imaging (MRI)

Pros:

- Anatomical imaging (organs visible)
- High spatial resolution
- Safety



Magnetic Resonance Imaging (MRI)

Cons:

- Low temporal resolution (transport dynamics?)
- Restricted body position (supine)
- Duration of measurements (discomfort)
- Limited contrast: Identification of dosage forms requires labelling

Use of MRI to investigate GI conditions drug delivery systems meet

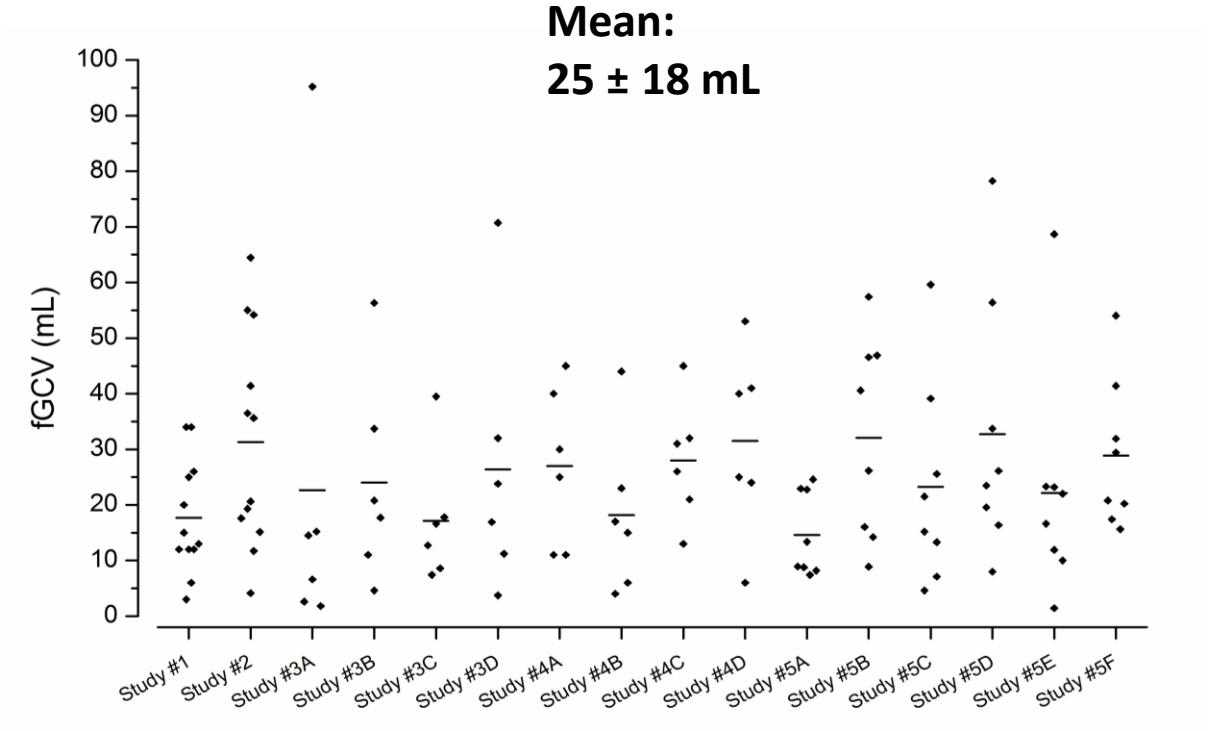
Fasting intake conditions

Standardized conditions (FDA, EMA) in Clinical Pharmacology (Phase 1 studies)

- at least 10 h (Europe 8 h) fasting (over night)
- Volunteer takes the dosage form with 1 glass of water (240 mL, 20 °C)
- further fasting for at least 4 h
- first water intake after > 1 h

Fasting intake conditions: The stomach

What is inside the stomach after overnight fasting?



Grimm et al. Eur J Pharm Biopharm. 2018

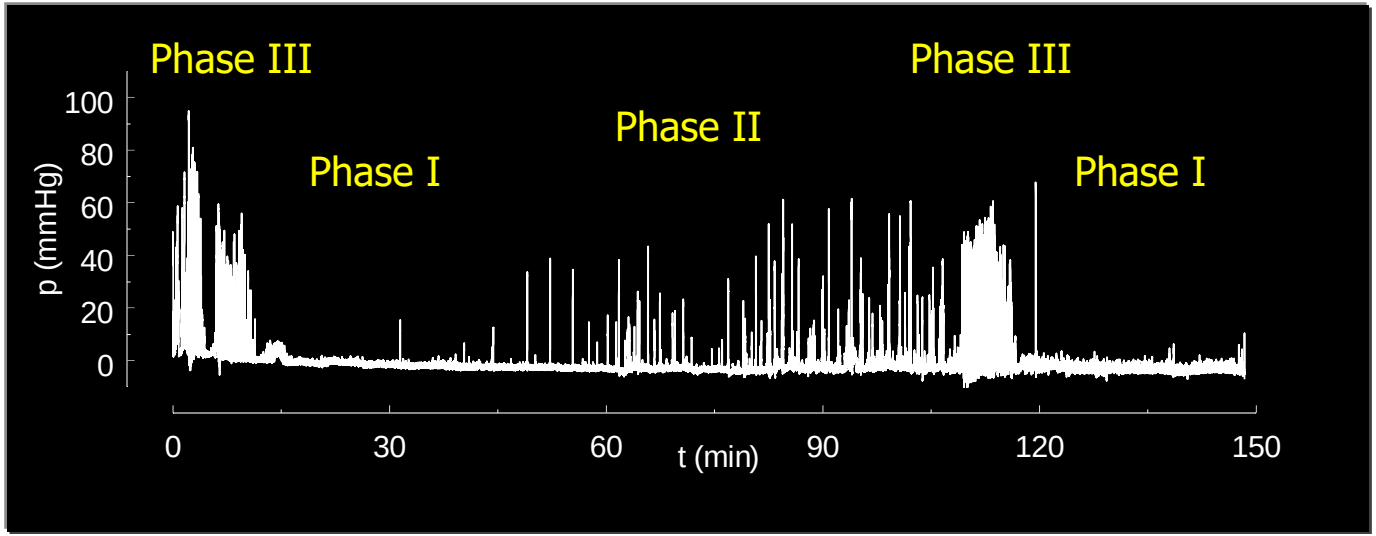
Why only a few Millilitres?

Basal gastric inflow (gastric juice + saliva): about 2 mL / min
i.e. 120 mL / h or up to 1 L during night!

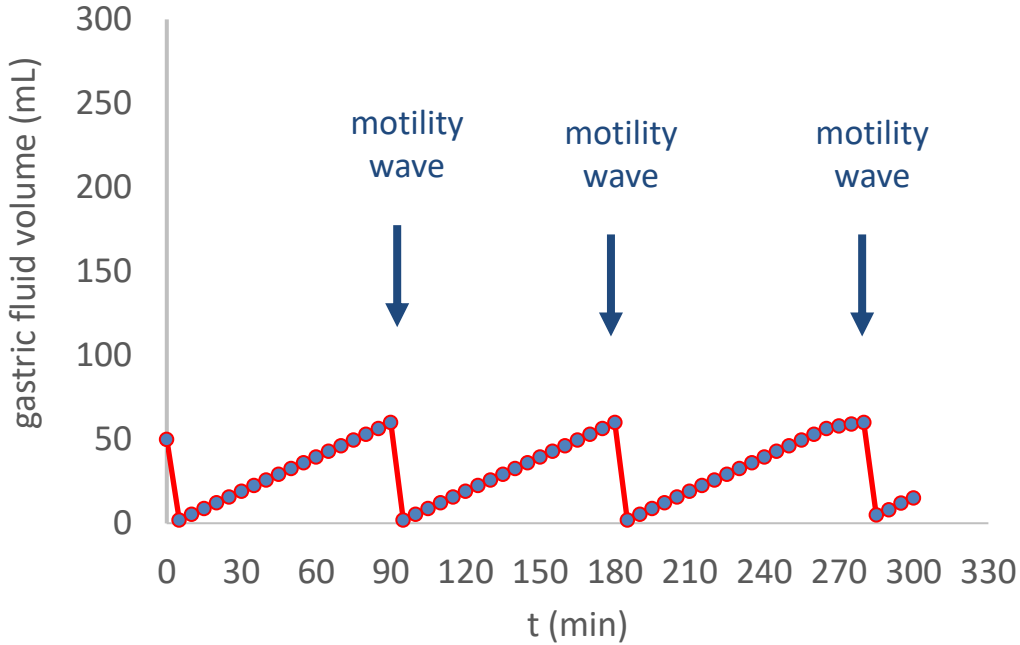
The (human) stomach ‘falls asleep’ during rest

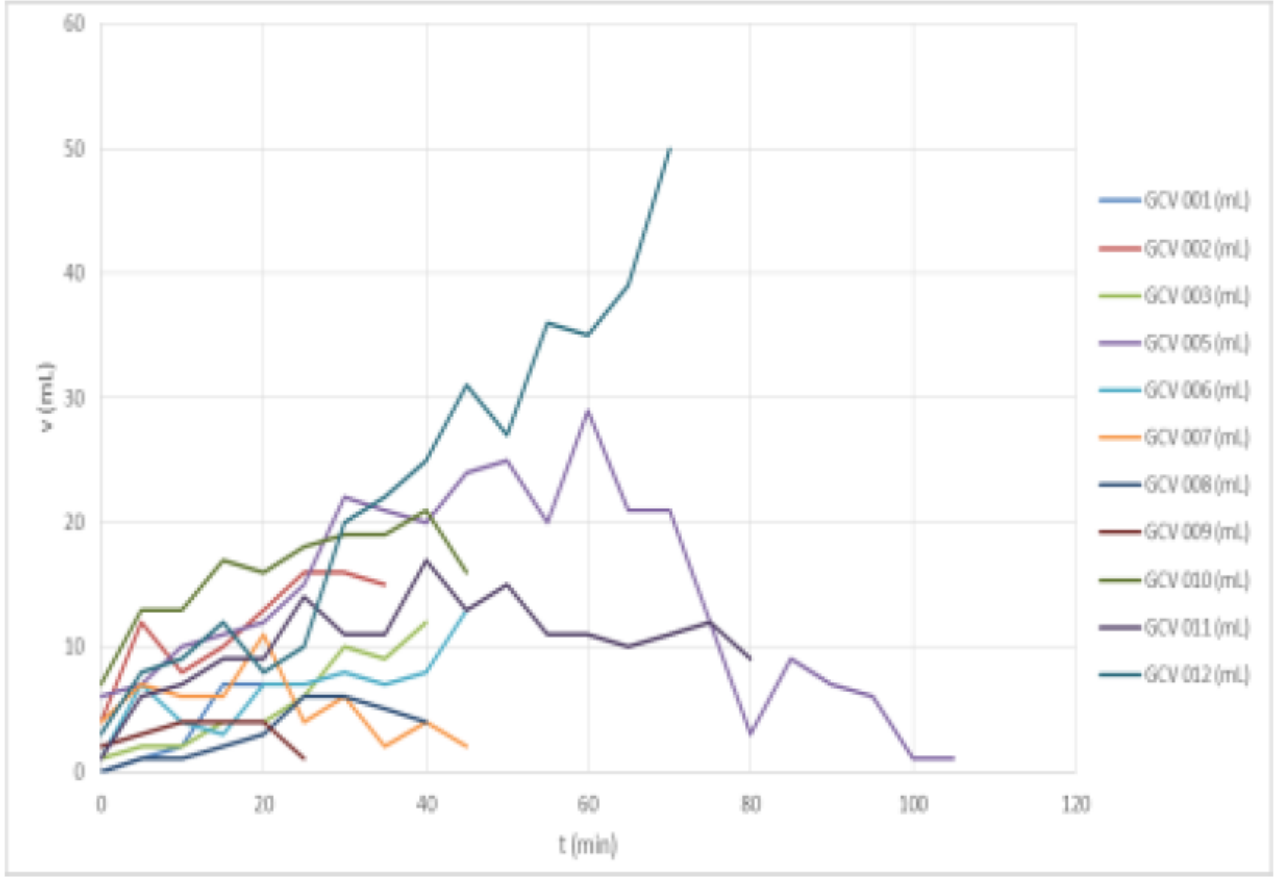
Interdigestive
Migrating Motor Complex (IMMC)

(pressure sensor placed in antrum of stomach)



Our understanding





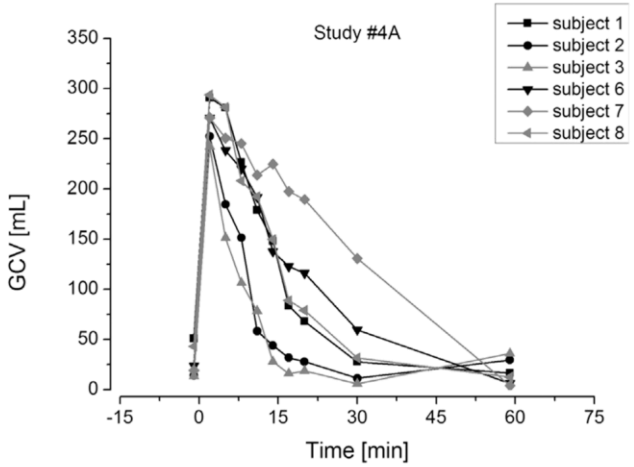
Subjects drank 240 mL of water, graph shows volume changes of GCV in fasted state after completed water emptying

Pretreatment: at least 10h overnight fast, intake of 240 mL water

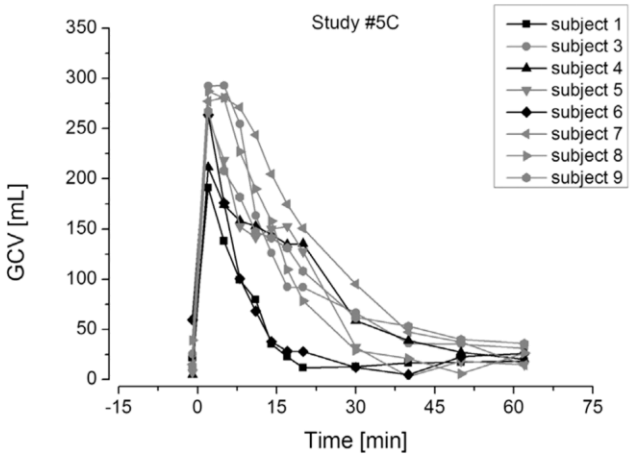
Fasting intake conditions: The stomach

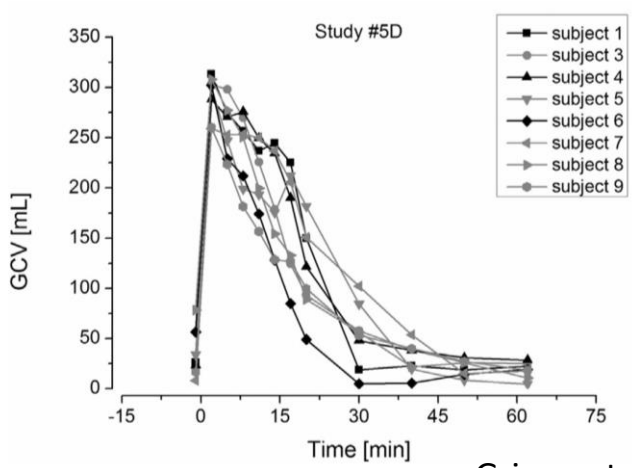
What happens with 240 mL of water (20 °C) taken on an empty stomach?

Gastric content volumes (GCV) after drinking 240 mL water



85 ± 13% of initially available gastric volume are emptied after 30 min.





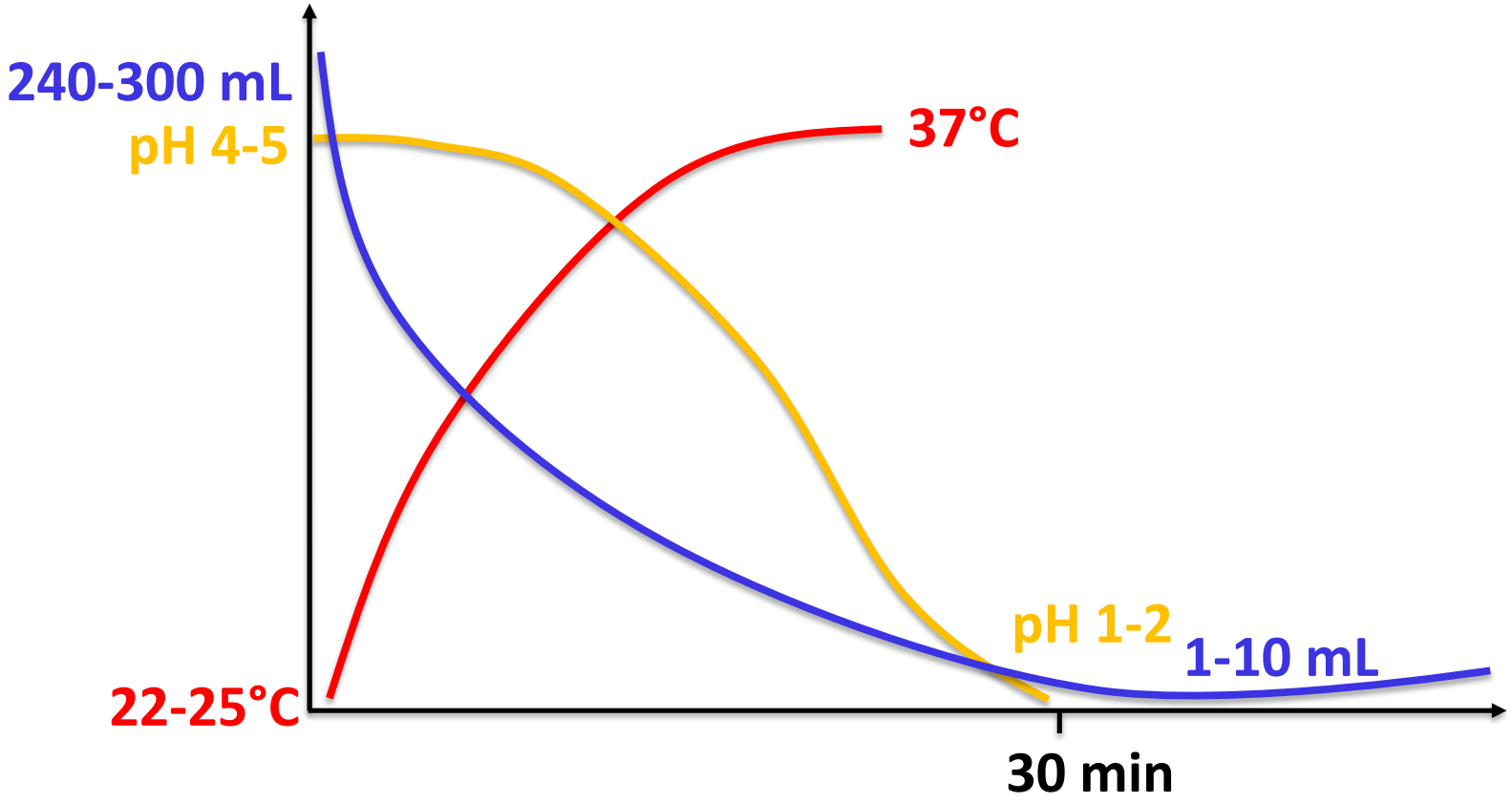
Grimm et al. Eur J Pharm Biopharm. 2018

Gastric content volumes (GCV) after drinking 240 mL water

Interindividual and intraindividual variability are comparable

Grimm et al. Eur J Pharm Biopharm. 2018

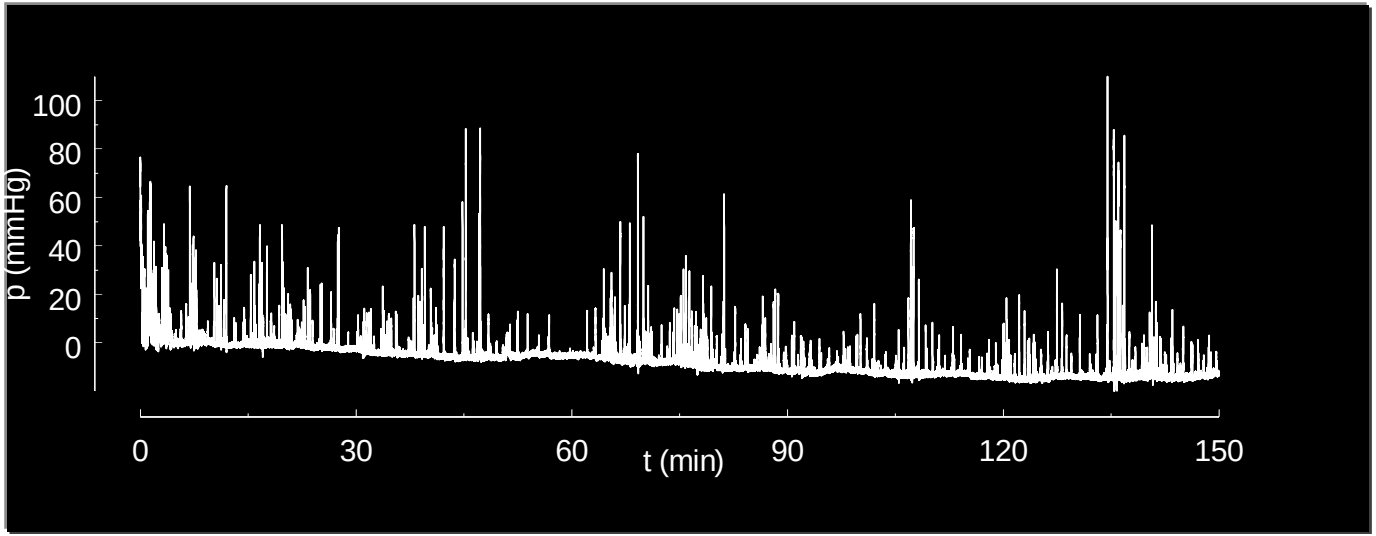
Fasting intake conditions: The stomach



‘Awakening’ of the stomach is triggered by food intake

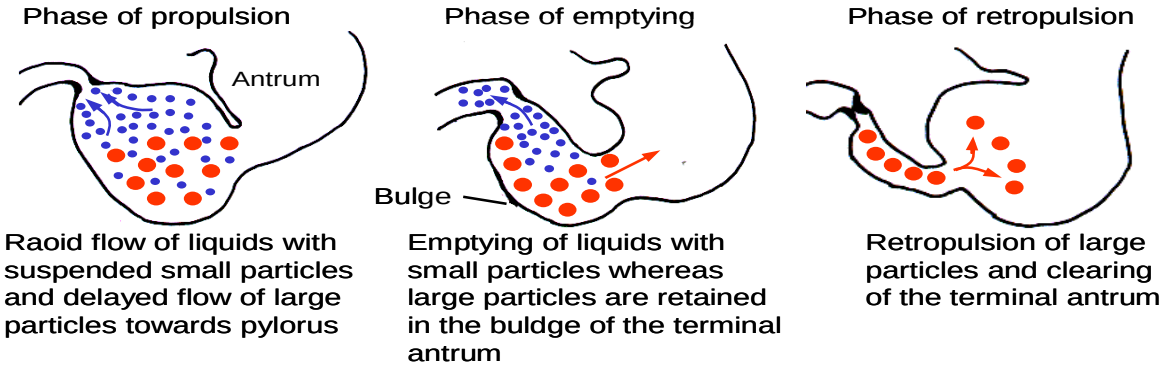
Migrating Motor Complex (MMC)

(pressure sensor placed in antrum of stomach)

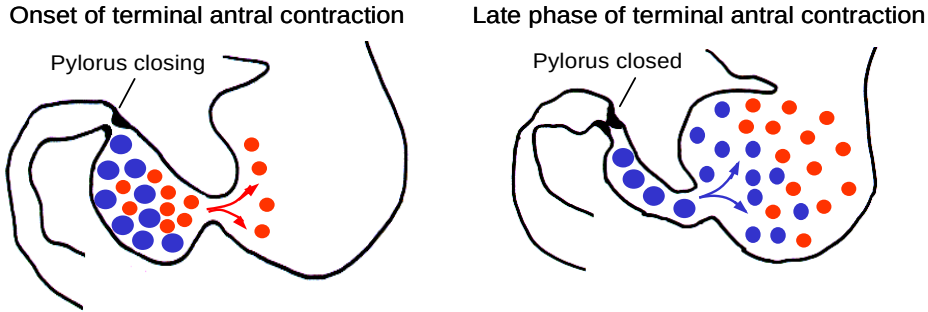


Gastric emptying of solid meals

Gastric sieving:

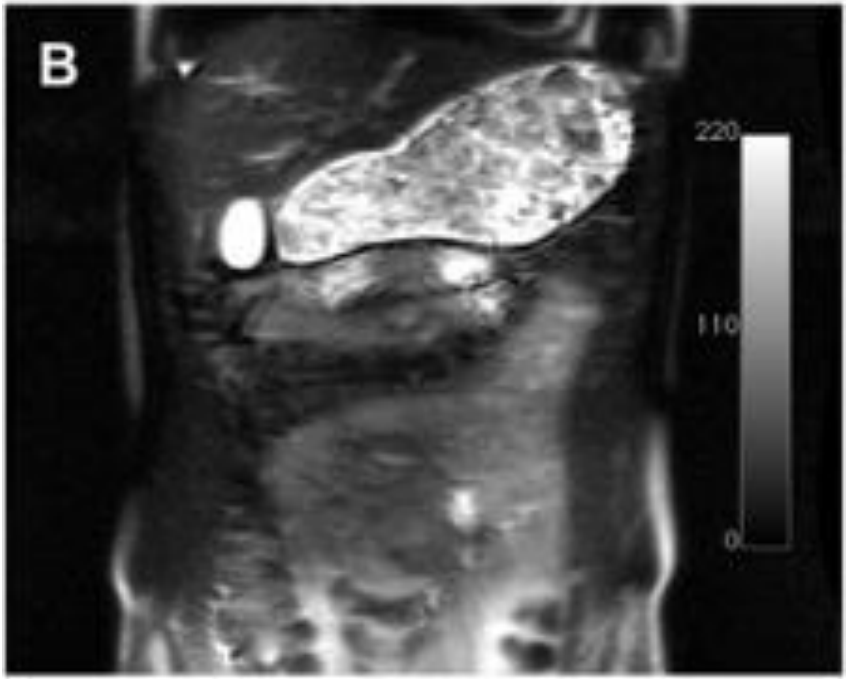


Gastric grinding:



Fed intake conditions: The stomach

What is inside the stomach after the „FDA breakfast“?



Fed intake conditions

Study design (in compliance with guidelines of FDA and EMA)

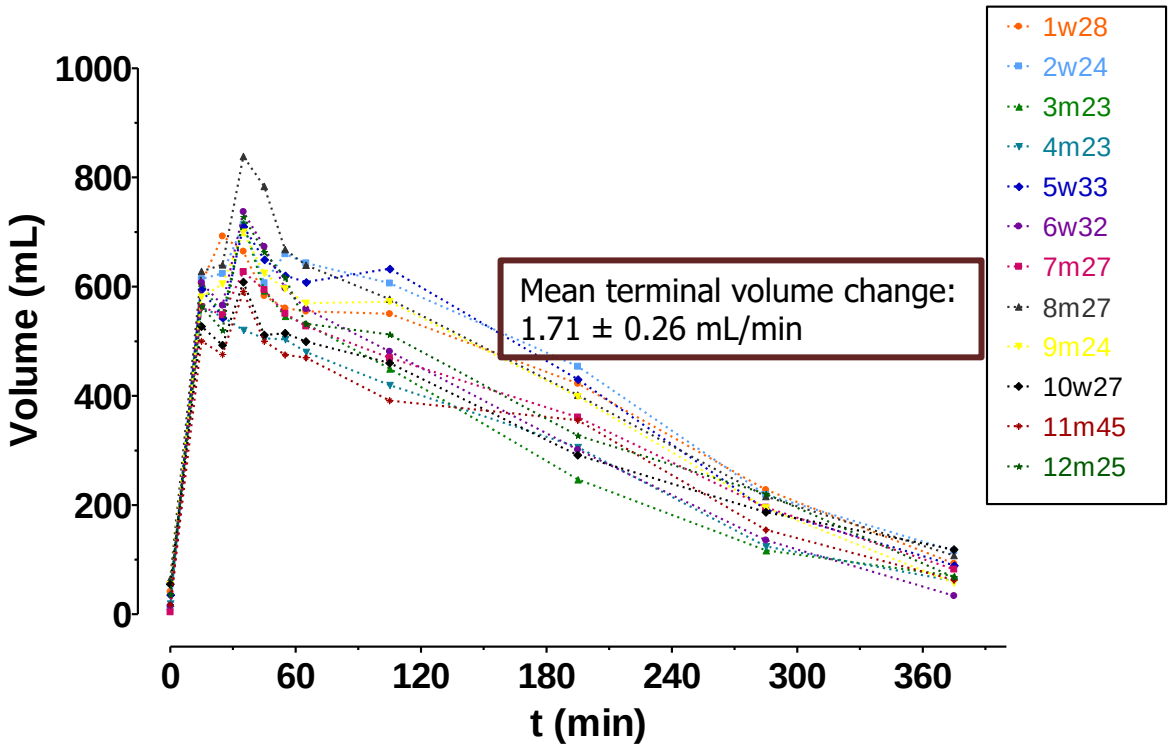
- 12 volunteers (7 male, 5 female, 23-45 y)
- 10 h fasting over night
- Breakfast in the morning
  - “FDA” breakfast
  - 964 kcal (> 50 % fat)
  - 535-540 g
  - 480-500 mL

- 30 min after start of breakfast (15 min after end of breakfast) intake of 240 mL water whilst in the MRI via a tube

Koziolek et al. Mol Pharm. 2014

Fed intake conditions: The stomach

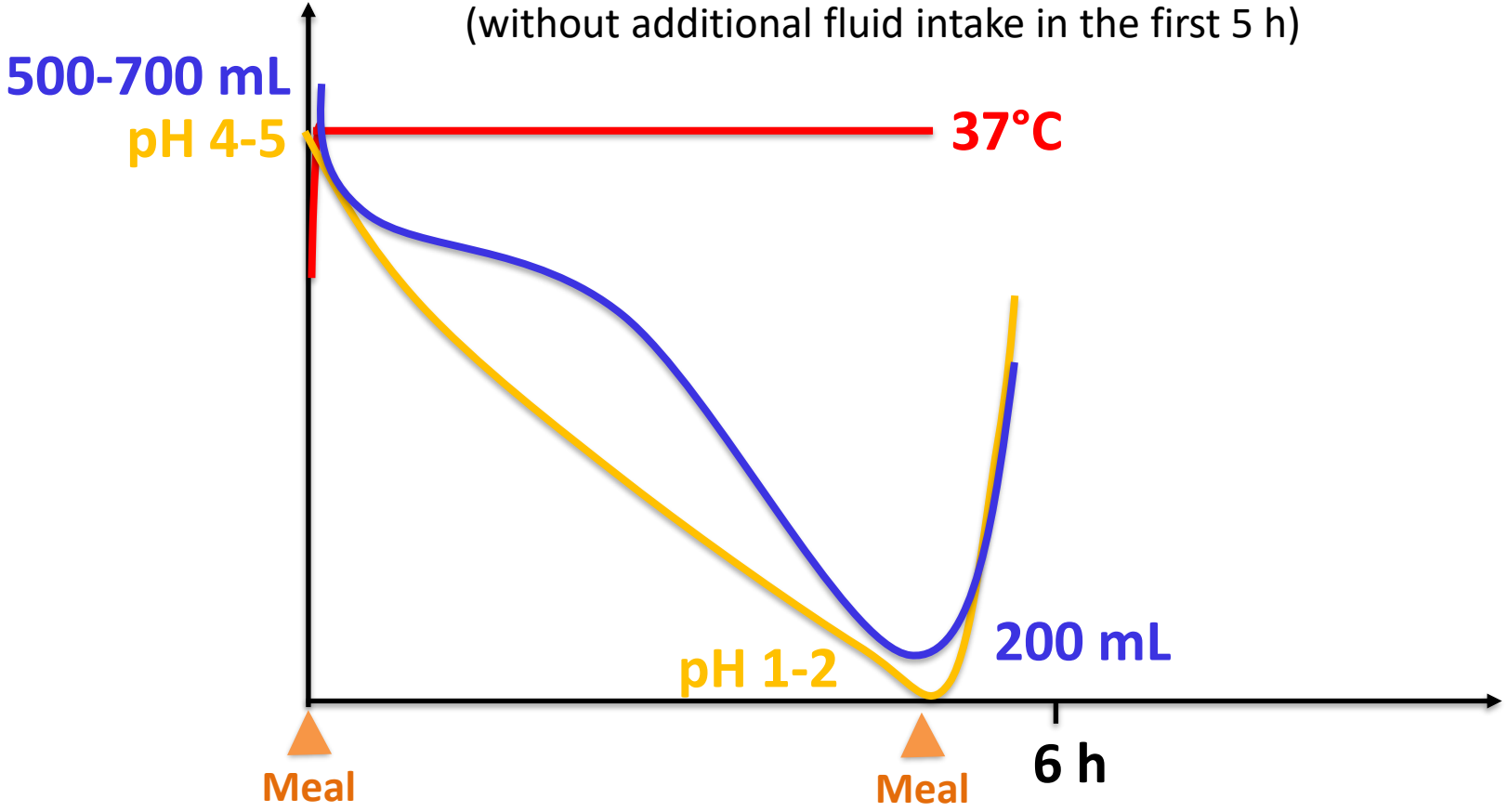
Gastric content volumes



Koziolek et al. Mol Pharm. 2014

Fed state intake conditions: The stomach in bioavailability/bioequivalence studies

(without additional fluid intake in the first 5 h)



Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2002
BP

A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 hour before or 2 hours after a meal)

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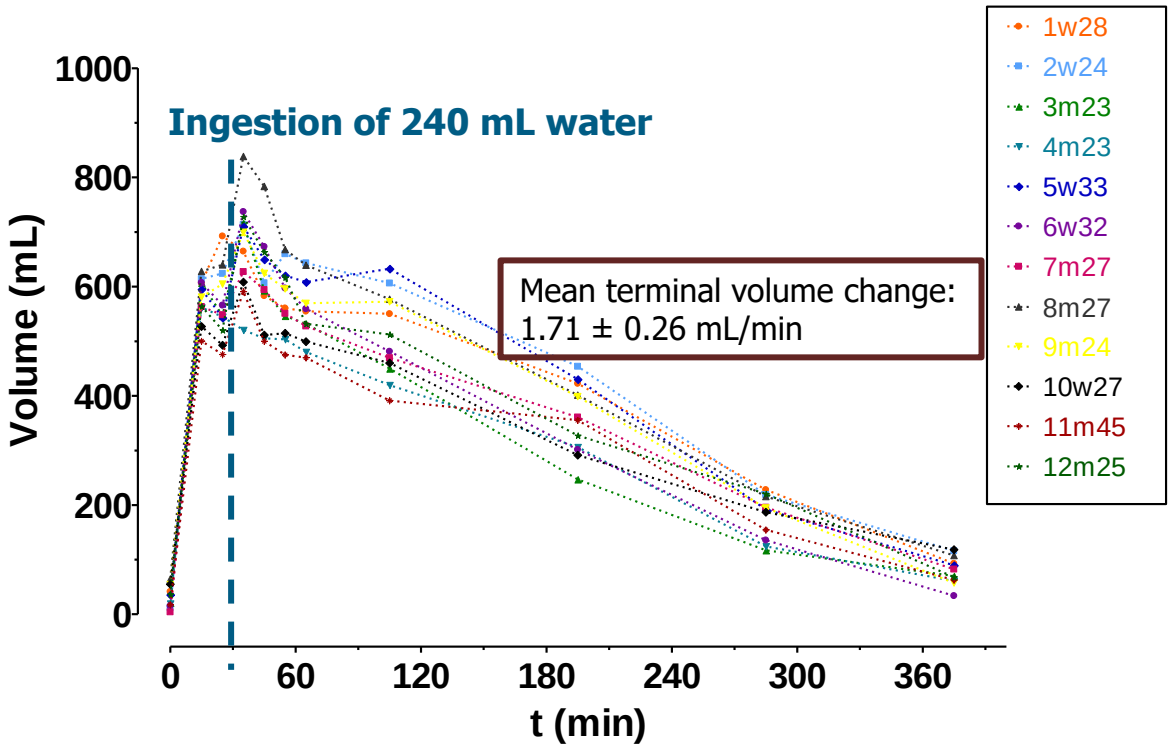
wrong

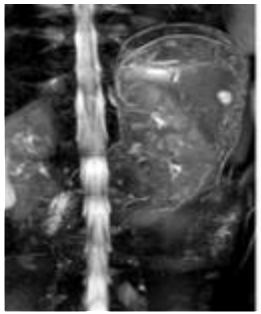
Fed intake conditions: The stomach

Gastric content volumes



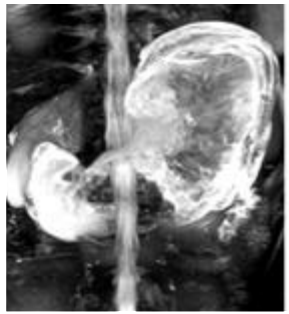
Koziolek et al. Mol Pharm. 2014

Fed intake conditions: The stomach



0 s

36 s



72 s

162 s

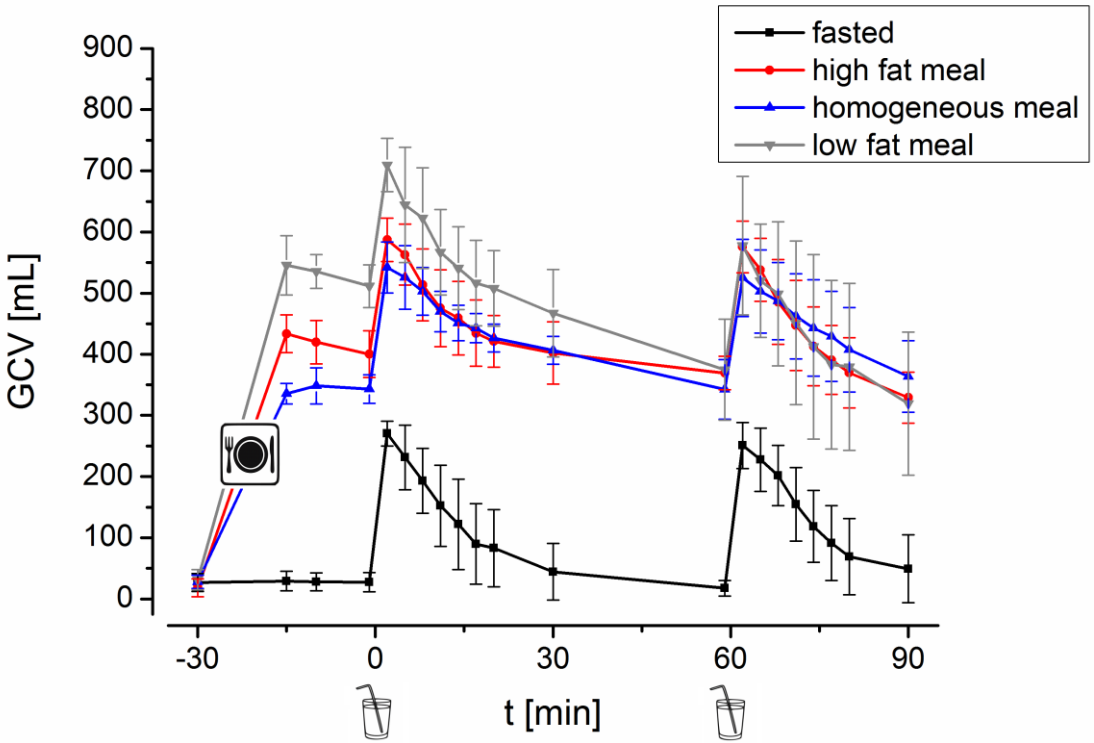
234 s

Maximum intensity projections of the stomach after ingestion of 240 mL of water (0 s indicates the starting point of drinking).

- Rapid emptying of water: Magenstrasse

Koziolek et al. Mol Pharm. 2014

Rapid emptying of water: Magenstrasse (‘stomach road’)



High fat meal (FDA breakfast)
460 kcal (63% from fat)

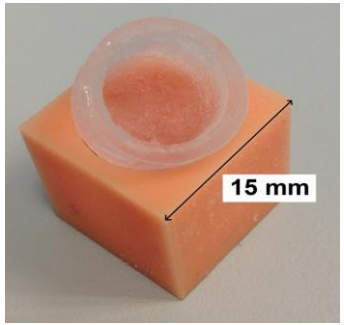
Homogeneous meal (chocolate mousse)
491 kcal (59 % from fat)

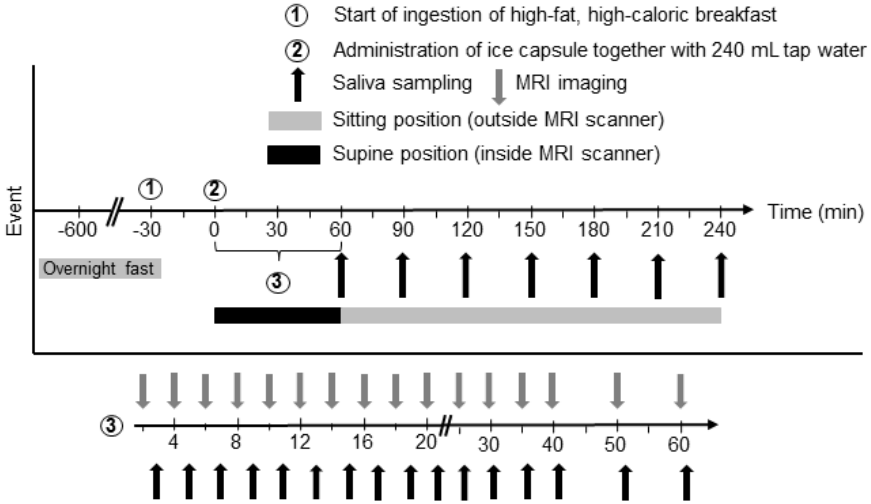
Low fat meal (typical breakfast)
466 kcal (13 % from fat)

Grimm et al. Mol Pharm. 2017

Rapid emptying of water: Validation using caffeine in “ice capsule”

Caffeine solution (0.5 ml, 35 mg caffeine) frozen in “ice capsule” (extremely fast melting after ingestion).

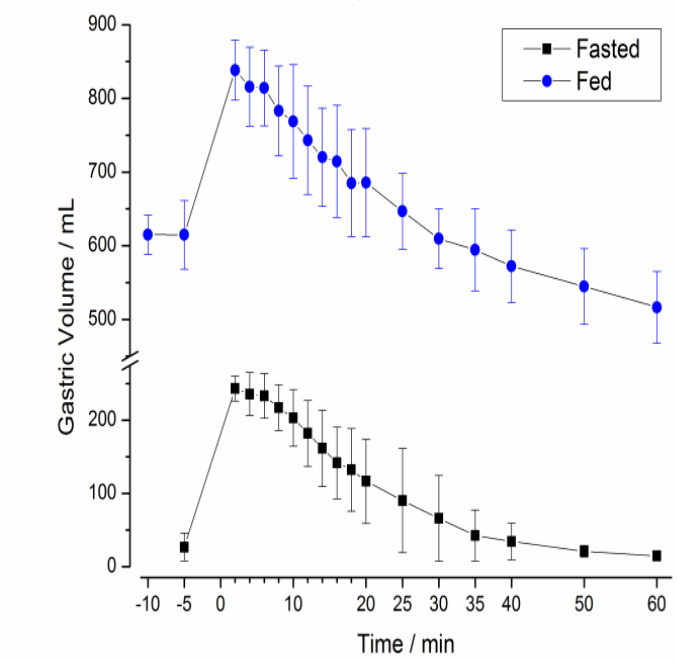




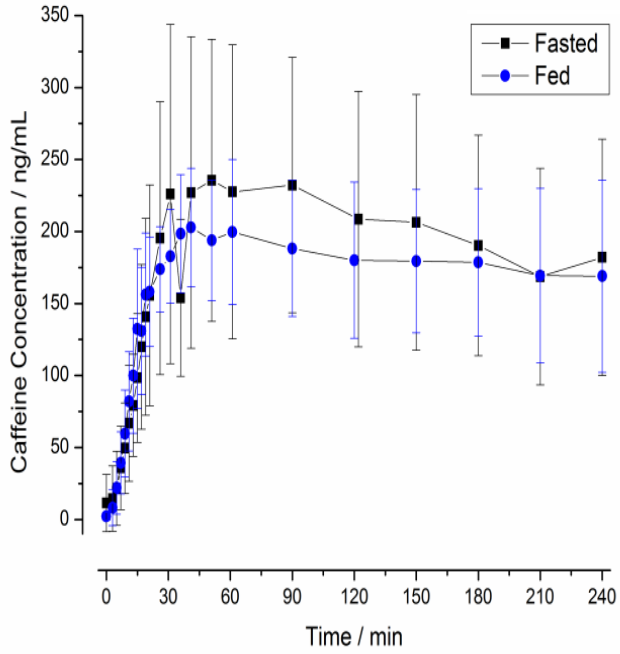
Sager et al. Eur J Pharm Biopharm. 2018

Comparison: Fasted - Fed

Gastric volumes (MRI)

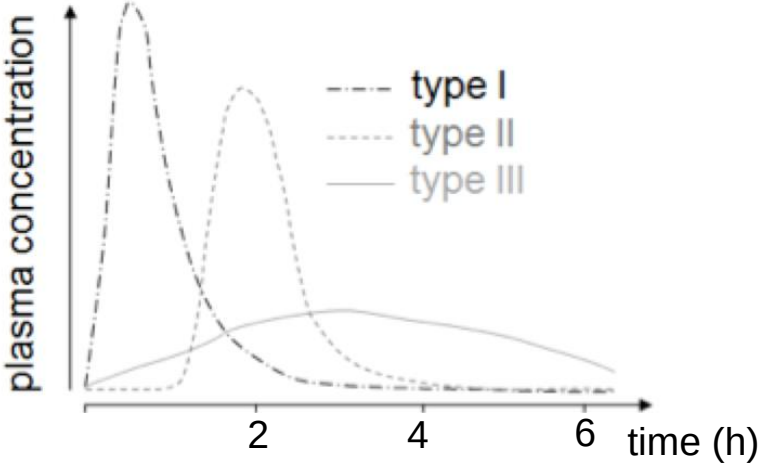


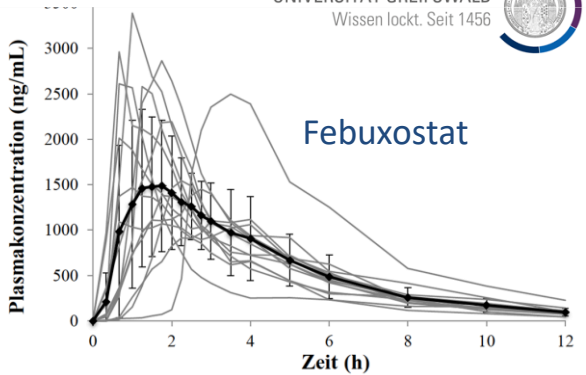
Caffeine concentrations in saliva

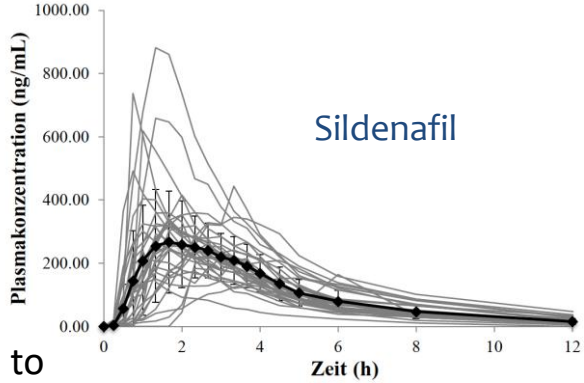


Sager et al. Eur J Pharm Biopharm. 2018

Rapid emptying of water: Magenstrasse (‘stomach road’)







- **Type I**: Rapid intragastric disintegration/dissolution, evacuation of suspended/dissolved API with co-swallowed water via “Magenstrasse”
- **Type II**: Slow intragastric disintegration/dissolution, local enrichment due to poor gastric mixing (fundus region), evacuation (“wash out”) of suspended/dissolved API with later swallowed water via “Magenstrasse”
- **Type III**: Material mixed with gastric contents, evacuation with gastric chyme

Schick et al. Mol Pharm. 2019, Koziolek et al. ADDR, 2016

Development of a rapidly dissolving tablet that delivers caffeine straight to the stomach in order to label the co-swallowed water

(Sager et al., 2018)*

Limitations:

- 15 mm size – inconvenient to swallow
- Storage and transportation are challenging
- Melts quickly at room temperature and in the oral cavity

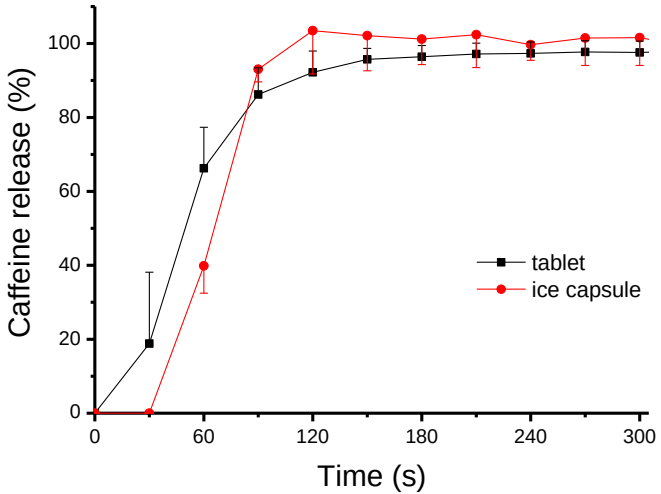
Solution:

- Development of a compression-coated tablet as an alternative vehicle

Tzakri et al. In preparation

In vitro dissolution and *in vivo* performance

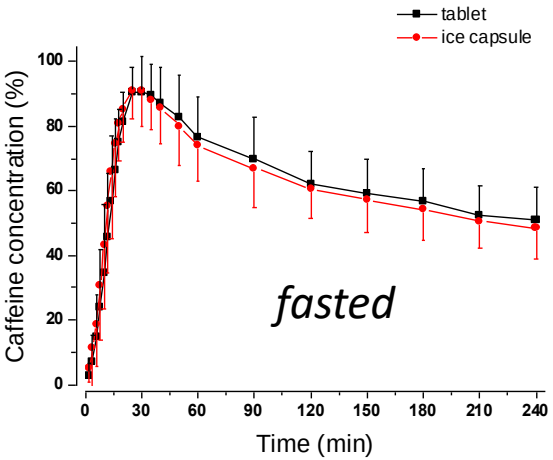
Paddle: 300 ml $SGF_{sp,}$ pH 1.2; 25 °C; 25 rpm

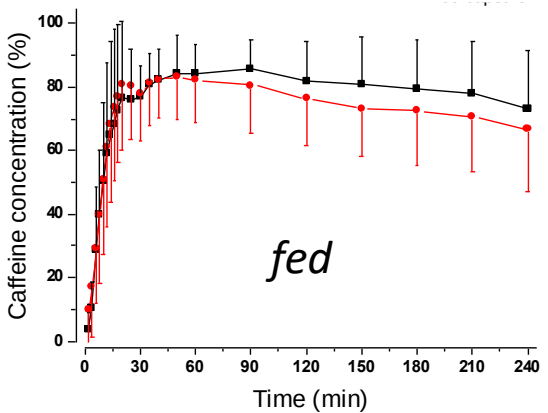


n = 3, mean ± SD

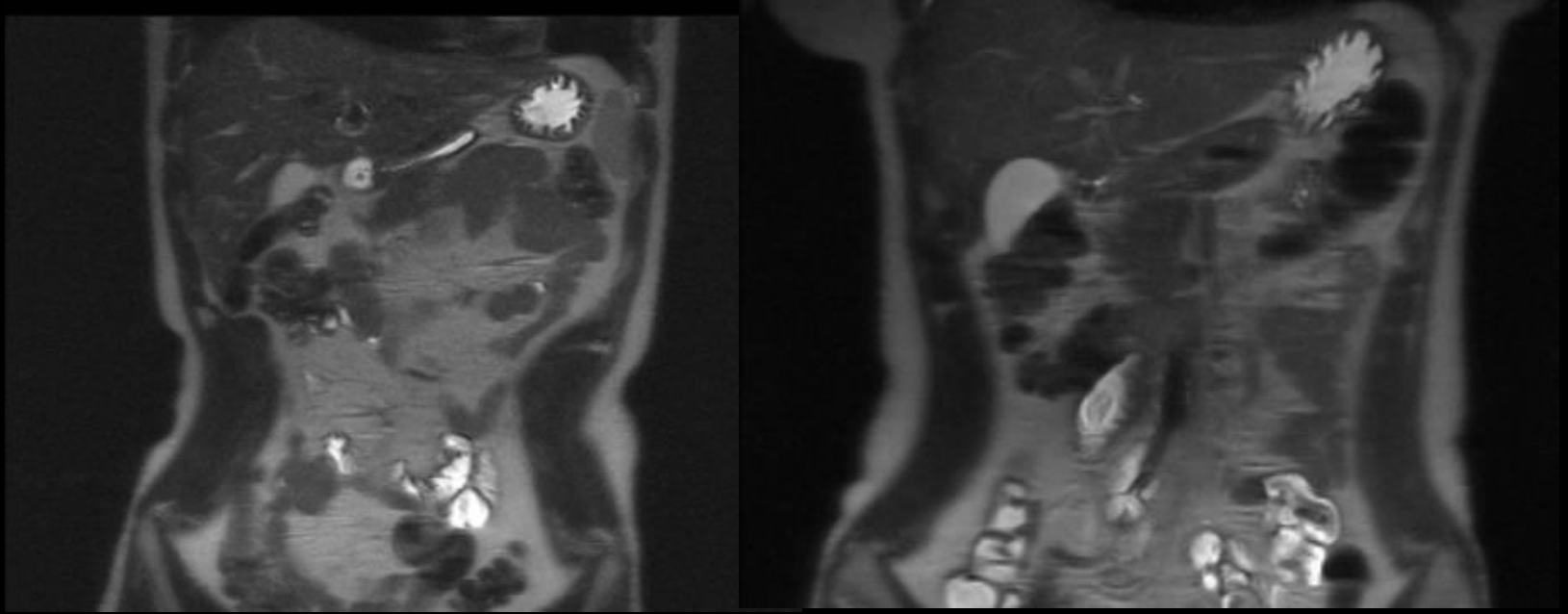
Tzakri et al. In preparation

In vivo: 12 healthy volunteers





The intestines: Fed or Fasting? What is the difference?



Fasted state

Intestinal fluid volumes

minimum	45 mL
maximum	320 mL
median	83 mL
mean	105 mL
SD	72 mL

Schiller et al. Aliment Pharmacol Ther. 2005

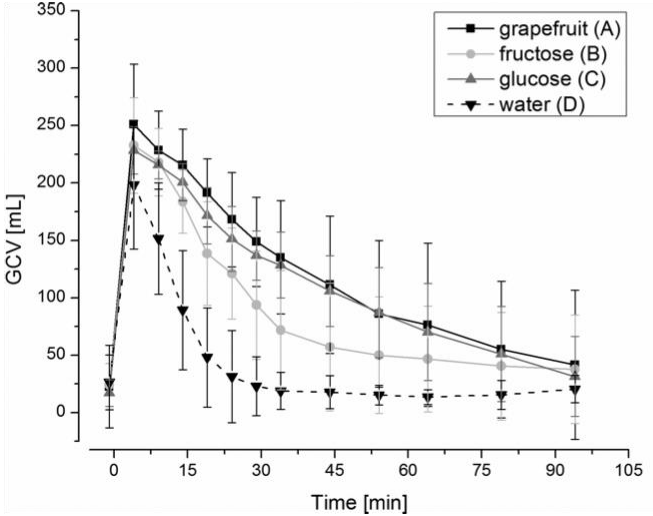
Fed intake conditions: The intestines

Influence of different carbohydrates on gastric emptying rates and small intestinal water content

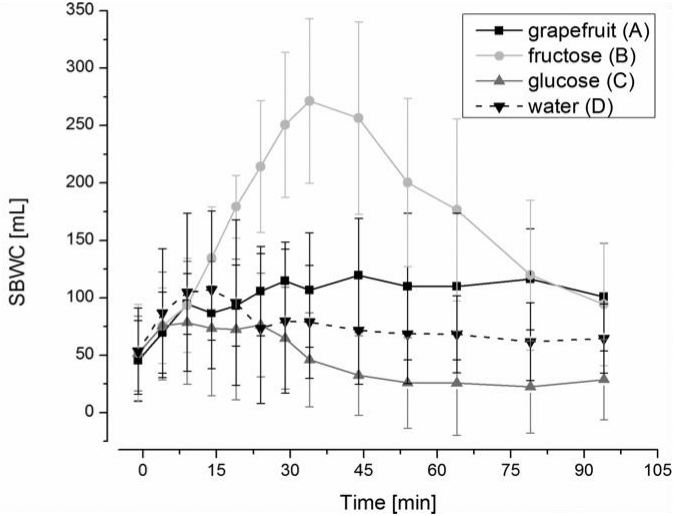
	mOsmol/kg	pH	kcal/100 mL
Grapefruit juice	554	3.3	103
Fructose solution	641	7.8	102
Glucose solution	644	7.8	102
Still water	5	7.8	0

Fed intake conditions: The intestines

Stomach

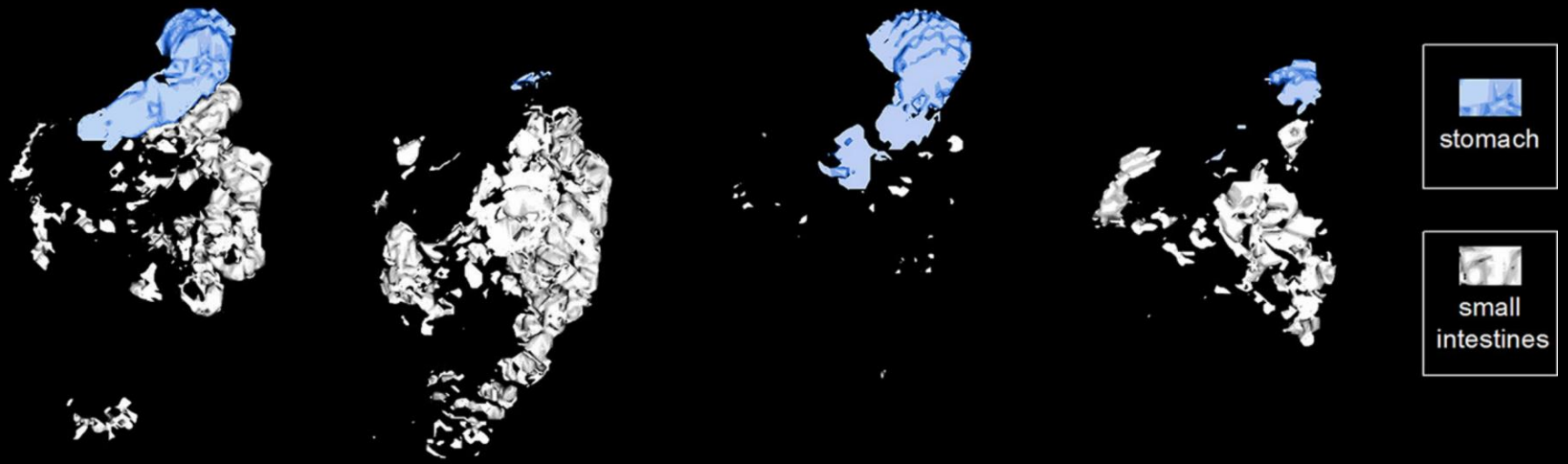


Small intestine



Fed intake conditions: The intestines

3D reconstructions from MRI data of gastrointestinal fluid distribution after different drinks



64 min after intake of 240 mL grapefruit juice

64 min after intake of 240 mL fructose solution

64 min after intake of 240 mL glucose solution

64 min after intake of 240 mL still water

Grimm et al. Mol Pharm. 2018

Conclusion

- MR Imaging provides fascinating insights into the conditions to which dosage forms are exposed to in the GI tract

- We need much more data to understand the interaction between GI physiology and drug delivery

Thank You

The “Gastronauts“

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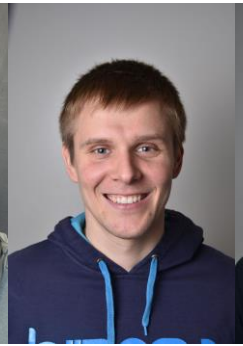
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