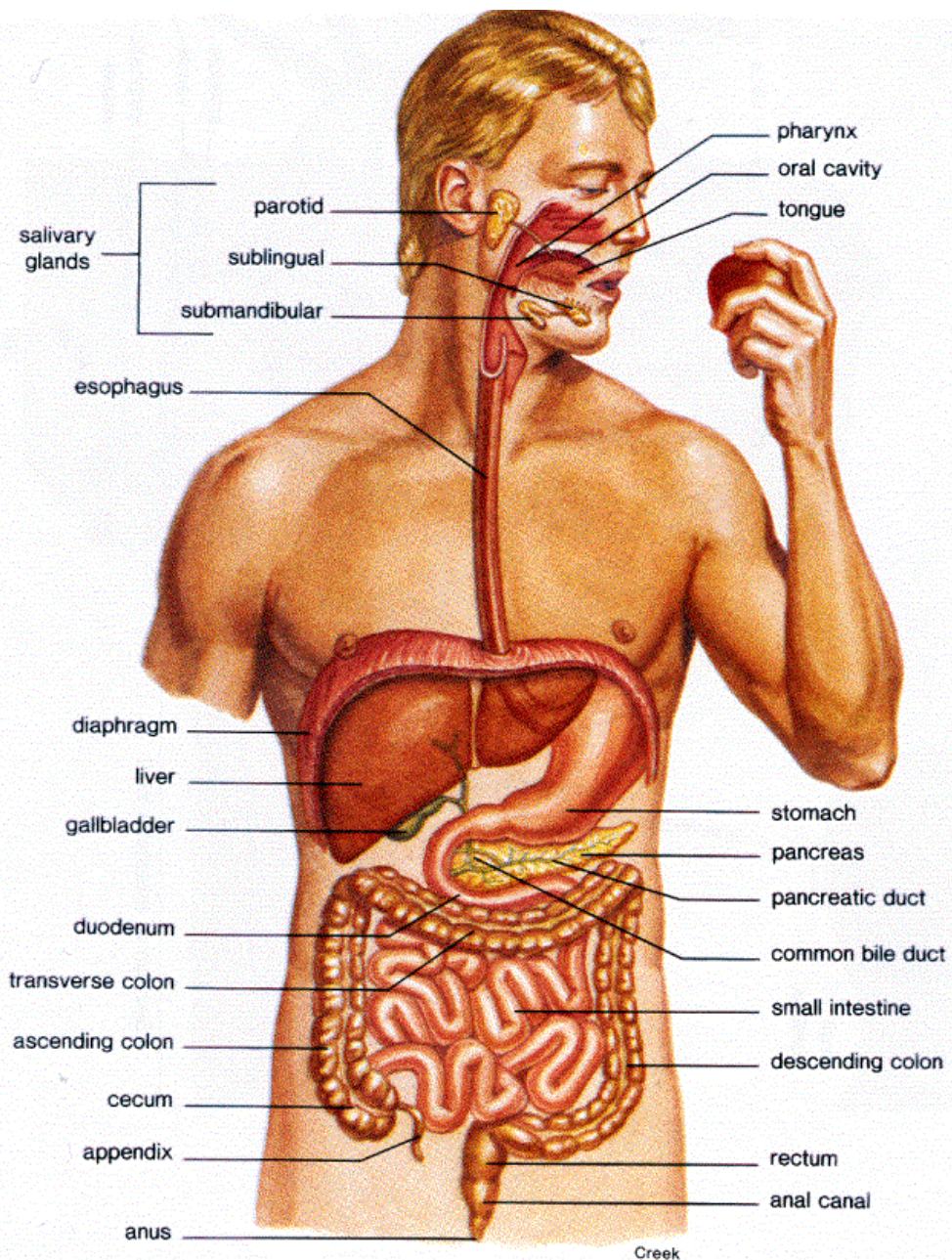# Predicting Food Effects on Drug Absorption

Anette Müllertz, PhD
Professor & Head of Center
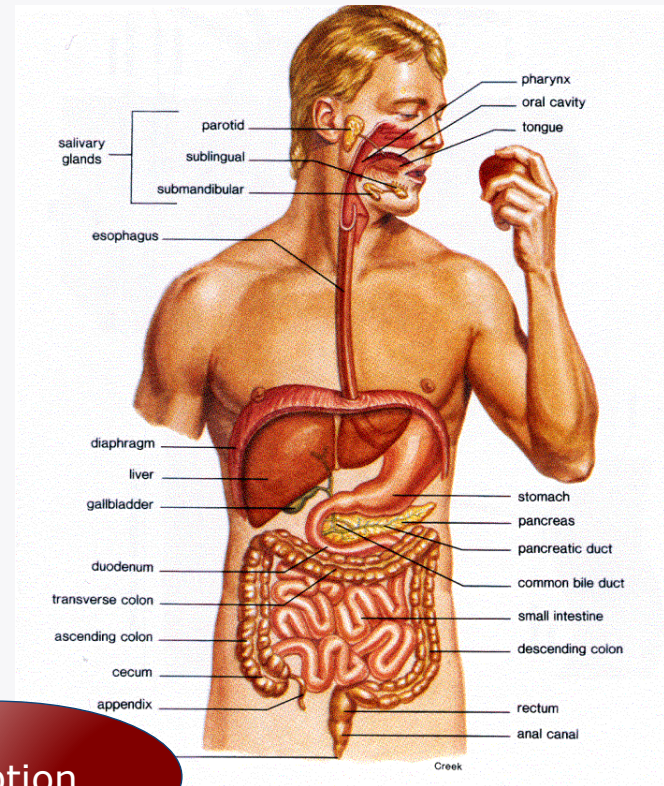
Der Mensch als Industriepalast

Aus Kahn, DAS LEBEN DES MENSCHEN/Franckh'sche Verlagshandlung, Stuttgart

The Gastro-Intestinal Tract

mouth

saliva
amylase

stomach

HCl
pepsin
Gastric lipase

duodenum

pancreas
enzymes

bile

jejunum

absorption

Ileum

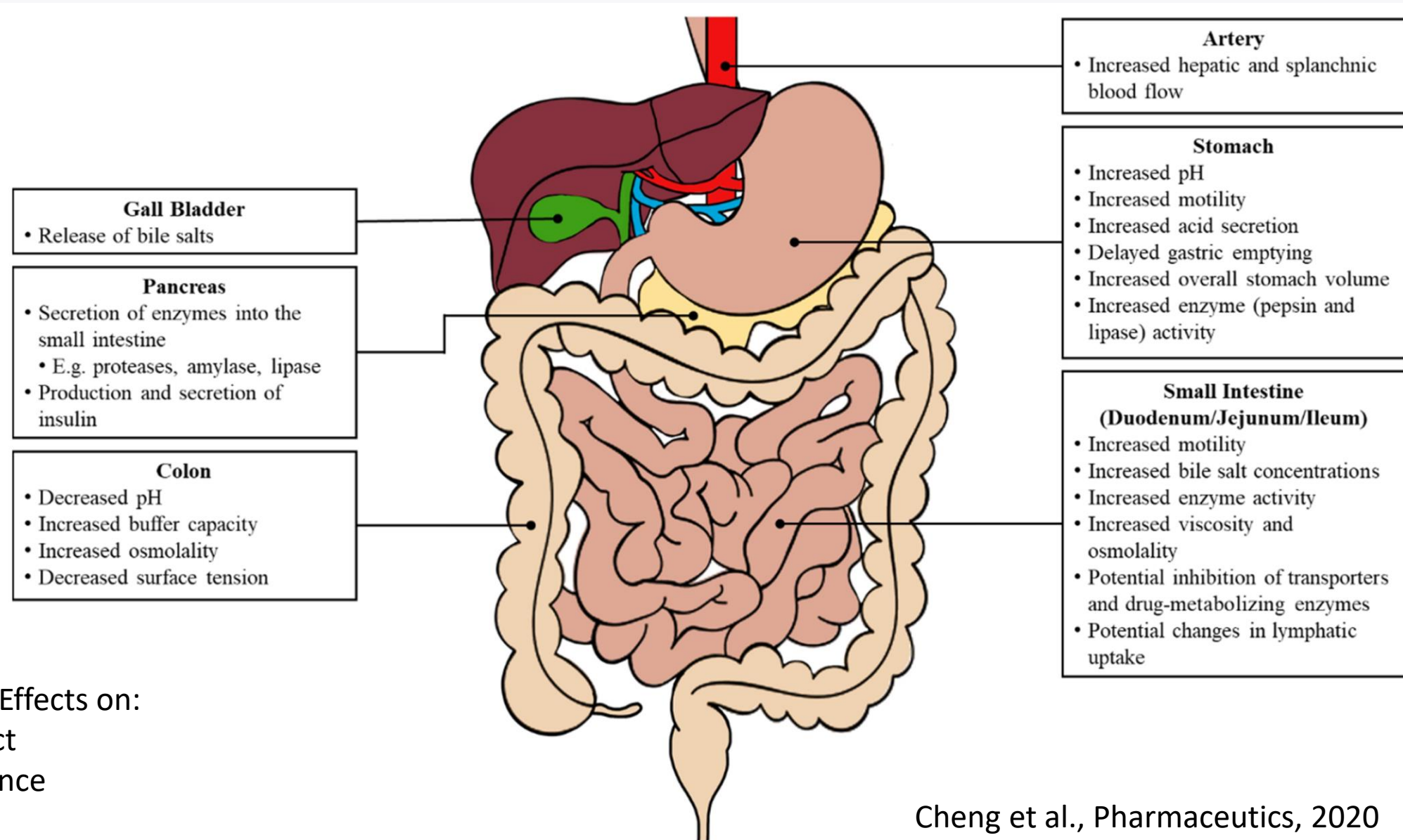microbiota

colon
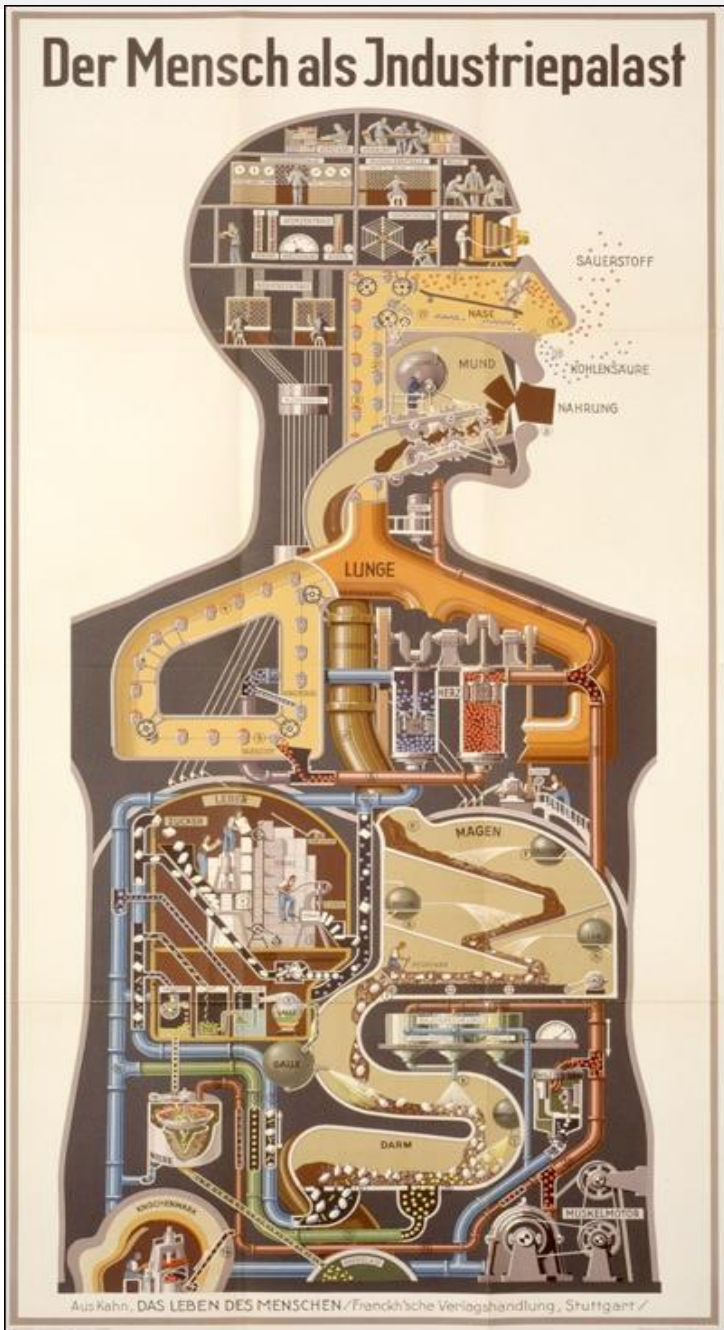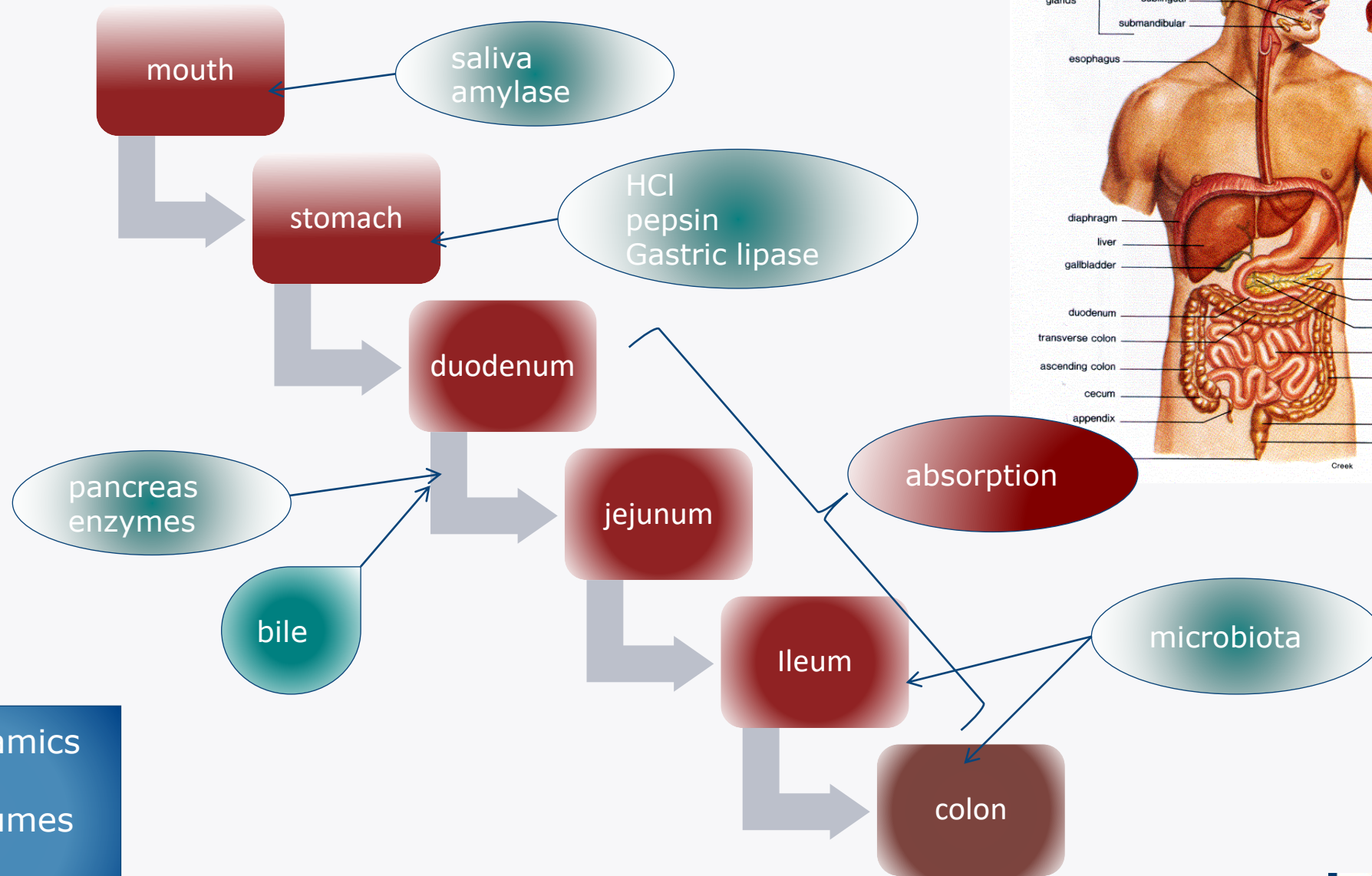
Hydrodynamics

Liquid volumes

Transit times
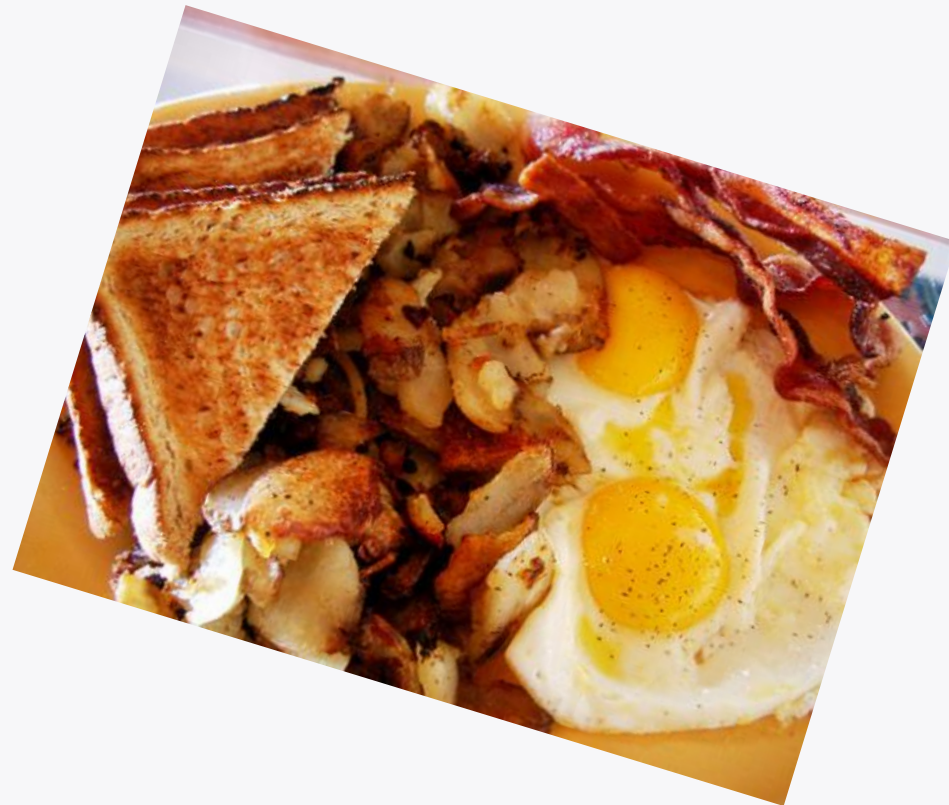
Food Effects....

Food effects on drug absorption

Gall Bladder
- Release of bile salts

Pancreas
- Secretion of enzymes into the small intestine
  - E.g. proteases, amylase, lipase
- Production and secretion of insulin

Colon
- Decreased pH
- Increased buffer capacity
- Increased osmolality
- Decreased surface tension

Artery
- Increased hepatic and splanchnic blood flow

Stomach
- Increased pH
- Increased motility
- Increased acid secretion
- Delayed gastric emptying
- Increased overall stomach volume
- Increased enzyme (pepsin and lipase) activity

Small Intestine (Duodenum/Jejunum/Ileum)
- Increased motility
- Increased bile salt concentrations
- Increased enzyme activity
- Increased viscosity and osmolality
- Potential inhibition of transporters and drug-metabolizing enzymes
- Potential changes in lymphatic uptake

Different Food Effects on:
- Drug product
- Drug substance

Cheng et al., Pharmaceutics, 2020

Clinical study – food effect of a poorly soluble drug, Danazol

SULFASALAZINE

AZOREDUCTASES

5-ASA

SULFAPYRIDINE

paracetamol

danazol

Sunesen et al., 2005

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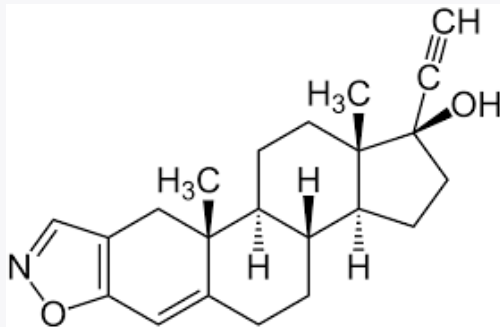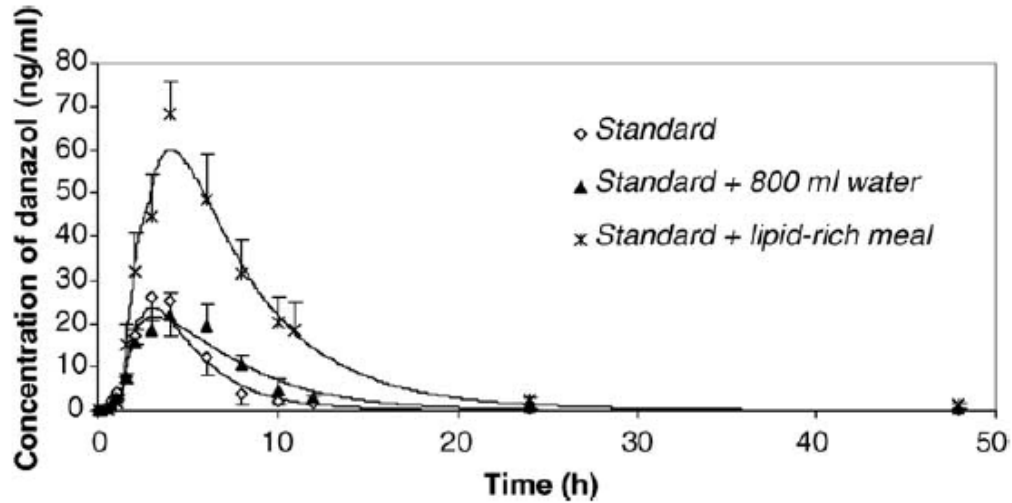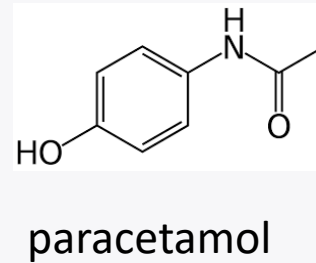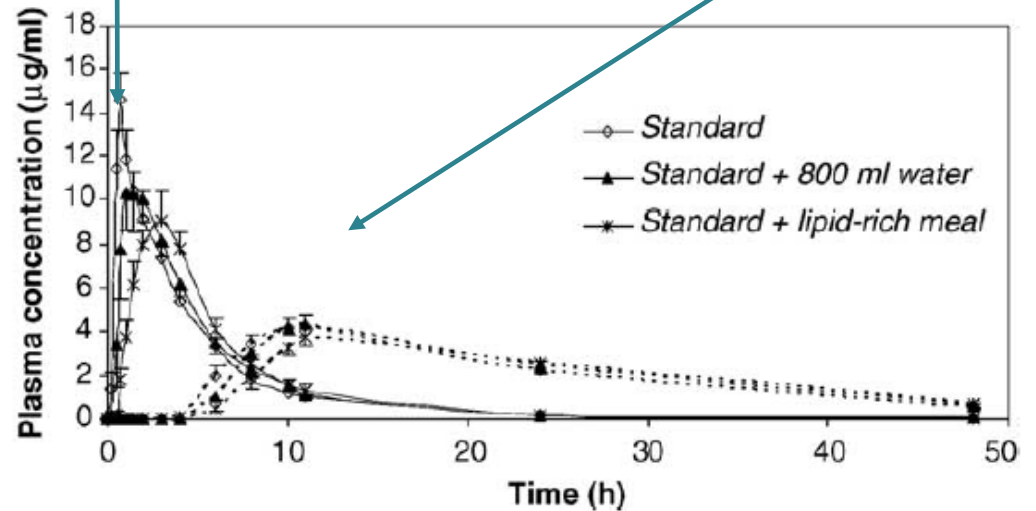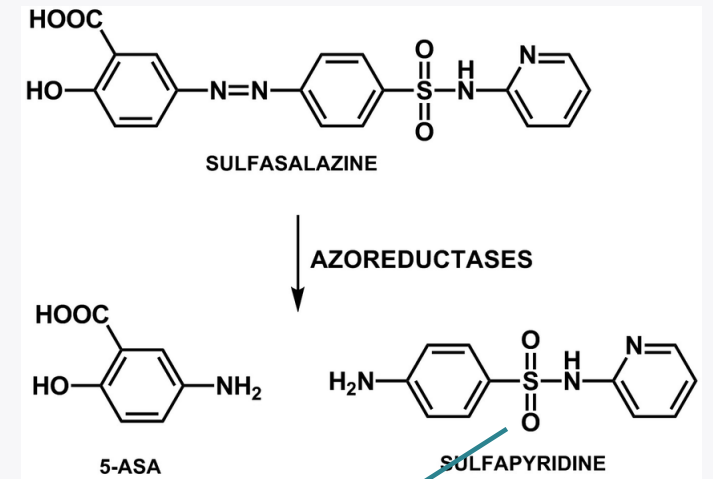
Pharmacokinetics and Transit Parameters
Danazol BA in healthy volunteers

|	Standard + 200 ml water	Standard + 800 ml water	Standard + lipid-rich meal
C_{max} (ng/ml)	25±17	23±15	60±24[ab]
T_{max} (h)	3.1 (2.3-4.0)	3.8 (2.5-5.2)[a]	4.0 (2.9-5.7)[a]
Absolute bioavailability (%)	11±5.2	17±3.4[a]	44±12[ab]

Standard: Administration of danazol in the fasted state with 200 ml water.
[a] Significantly different from *Standard* (p<0.05).
[b] Significantly different from *Standard + 800 ml water* (p<0.05).
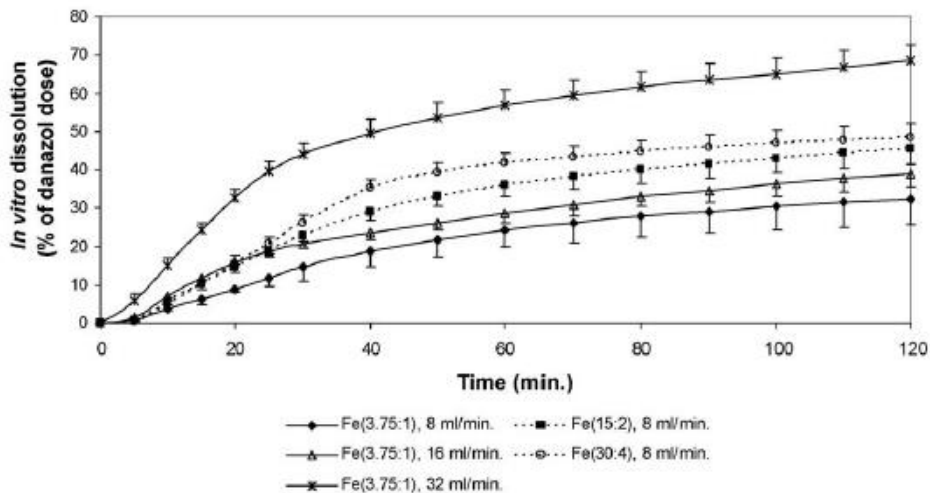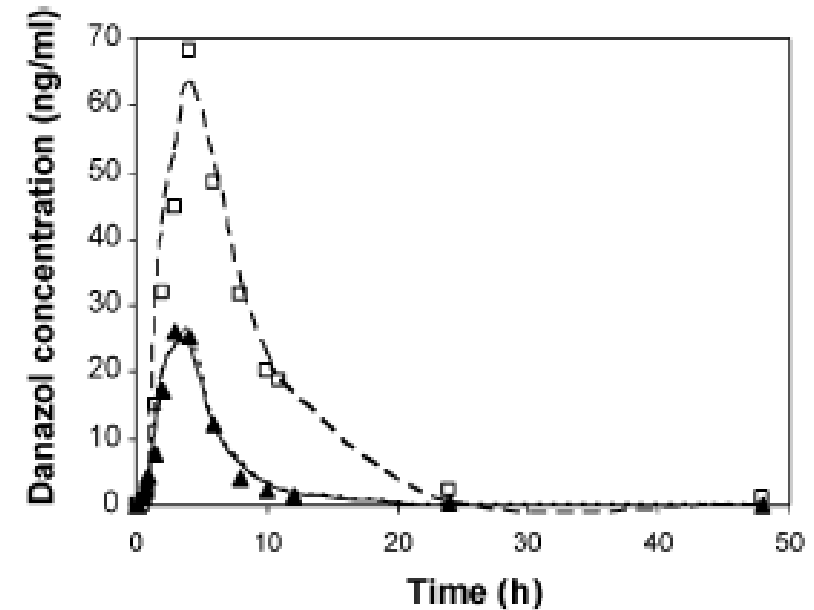
Sunesen et al., 2005

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Clinical study – food effect of a poorly soluble drug, Danazol

Mean deconvolution profiles of danazol
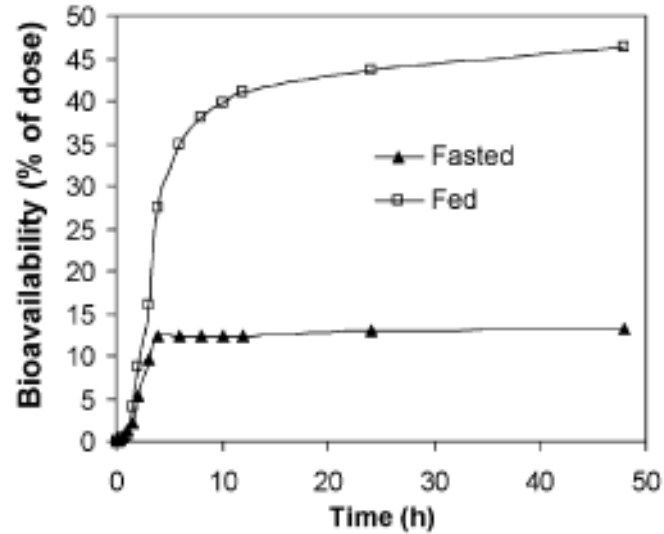
PDx-IVIVCTM (GloboMax® LLC, UK)

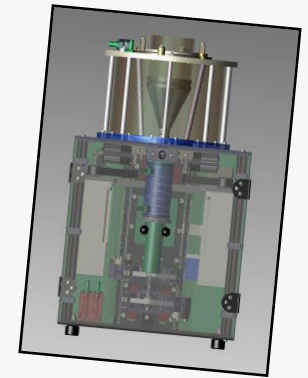$$x_{vivo}(t) = a1 + a2x_{vitro}(-b1 + b2t)$$

Sunesen et al., 2005

Predicting dosage form – and drug – behavior
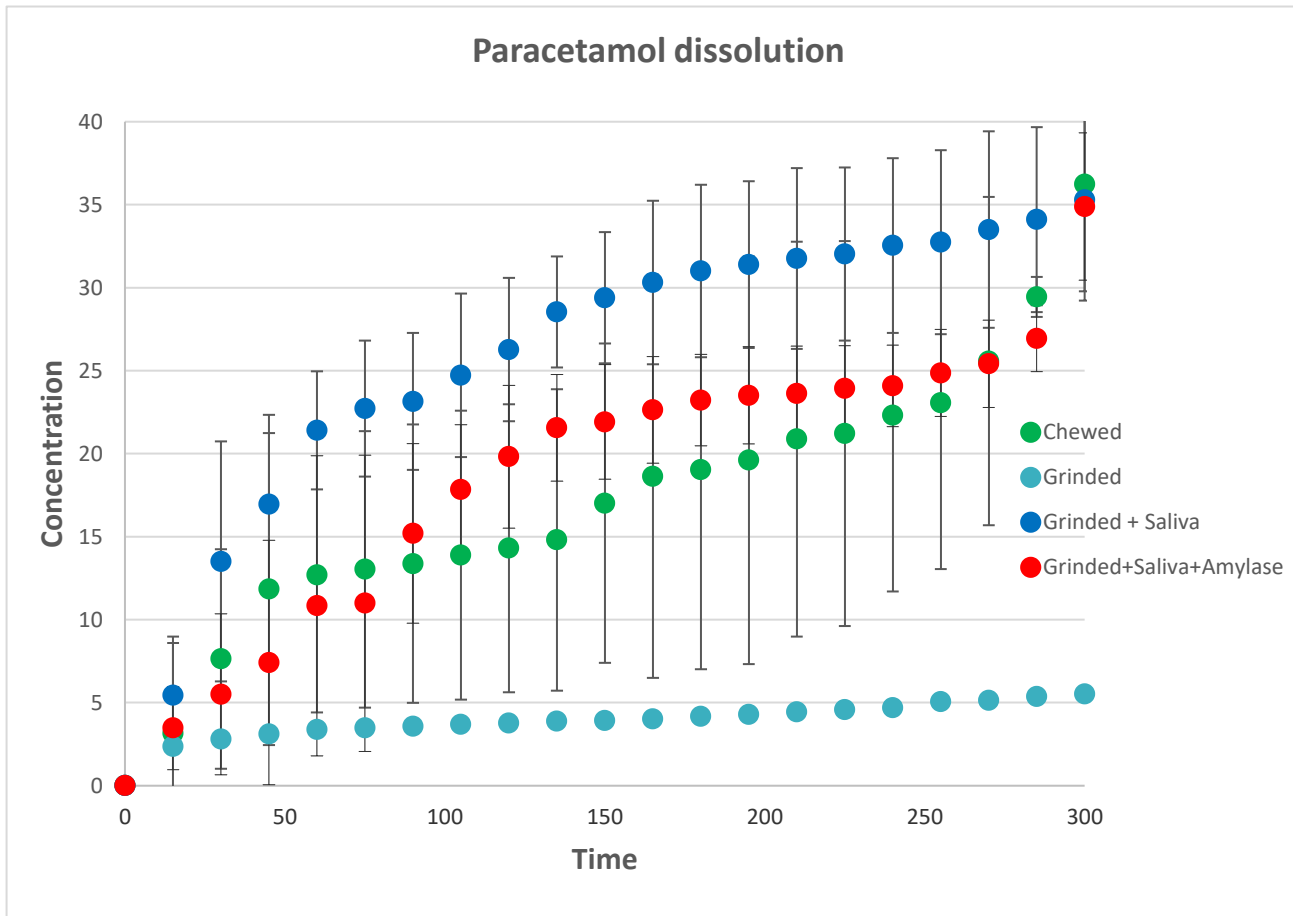-   in the gastro—intestinal tract

-   Using the Dynamic Gastric Model – and its Duodenal Module

Agenda

- Chewing

- Physiology of the human stomach

- The Dynamic Gastric Model (DGM)

- Duodenal Module

- Cases

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Effect of chewing – acetaminophen release

Paracetamol dissolution

Legend:
- Chewed
- Grinded
- Grinded + Saliva
- Grinded+Saliva+Amylase
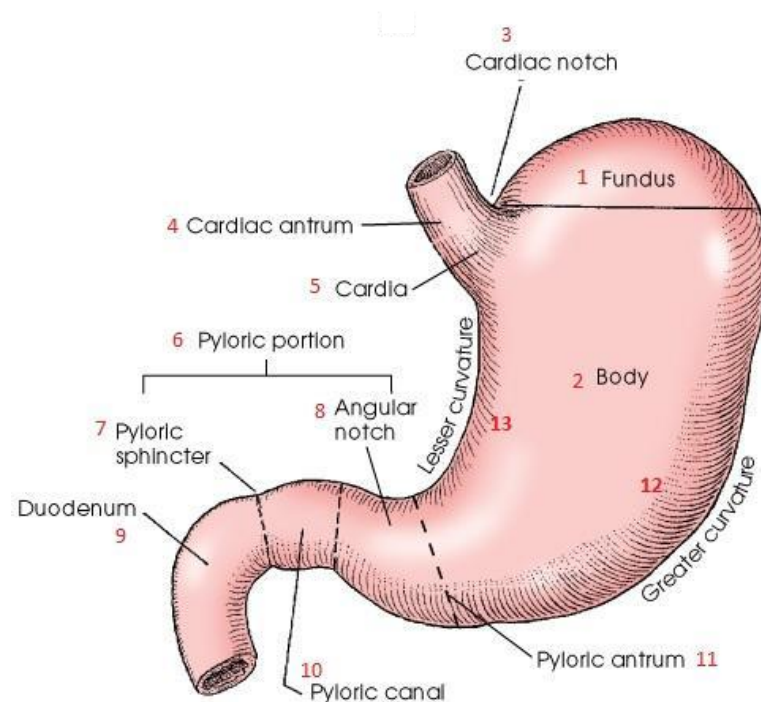
Only grinding lead to reduced release

Grinding & artificial saliva – Increase release

Grinding & artificial saliva & amylase
– same release as chewing

Stomach physiology and function

The stomach can be divided into:

- 3 anatomic regions: Fundus, body, and antrum
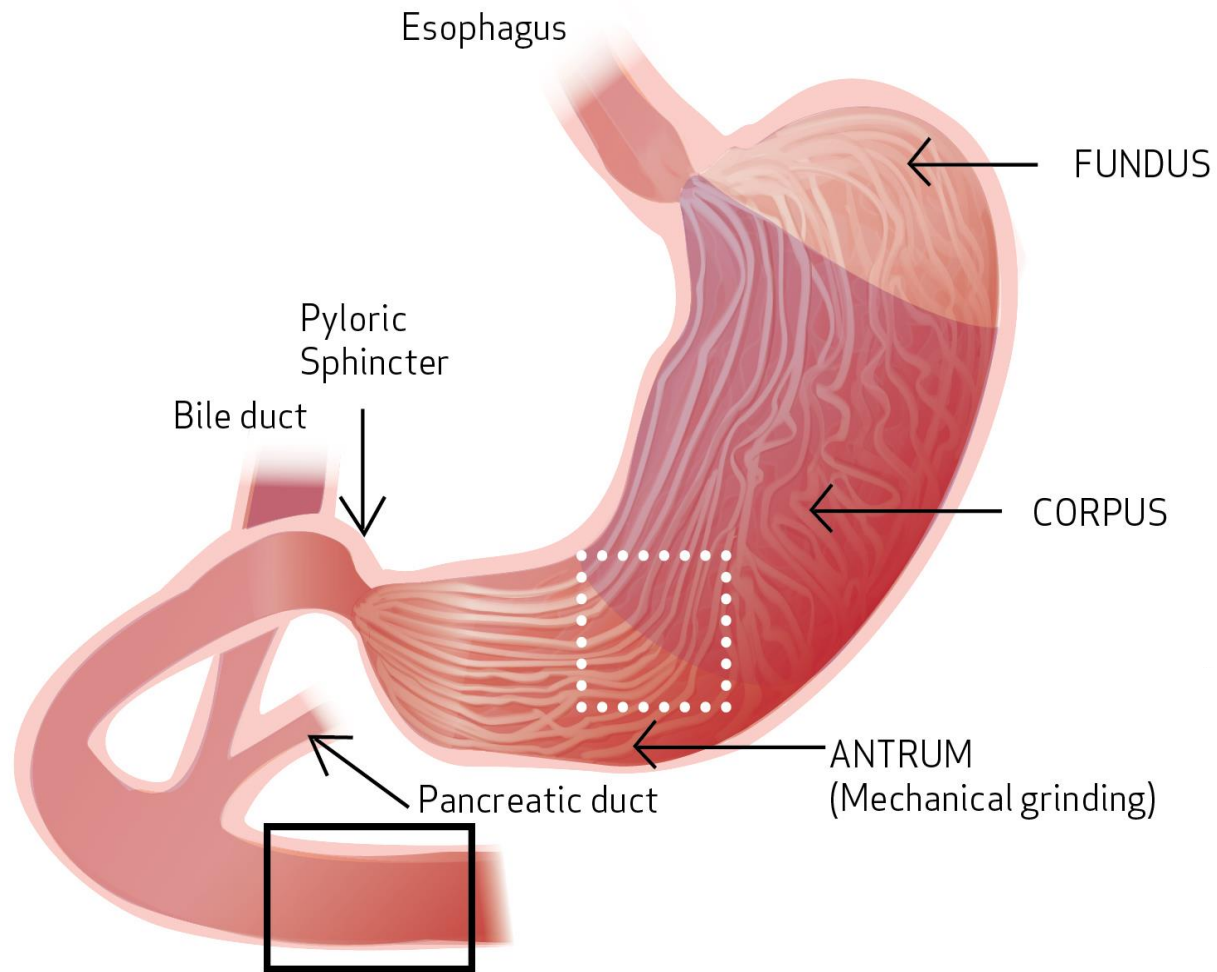- 2 functional regions: "Storage" (fundus+body) & "Mixing" (antrum)

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Function

- Reservoir for ingested food
- Initial food digestion (pepsin and lipase)
- Eliminates bacteria (acid HCl)
- Physical mixing and homogenization of stomach content ("particle" size reduction)
- Controlled release of content to intestine

The Stomach

Esophagus

FUNDUS

Pyloric Sphincter

Bile duct

CORPUS

ANTRUM
(Mechanical grinding)

Pancreatic duct

Gastric secretions:
Pepsin
Gastric Lipase
HCl
Mucins

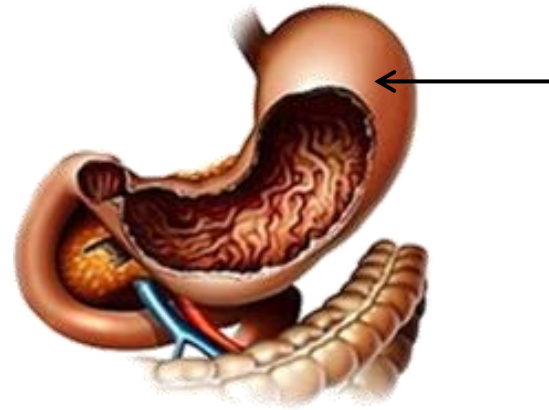**Gastric content**
Fasted state:
pH: 1.6 - 3
Vol: 25-75 ml

Fed state:
pH: Food dependent
Vol: Food intake dependent

Leaky container – releasing digested food to the duodenum in a well controlled manner

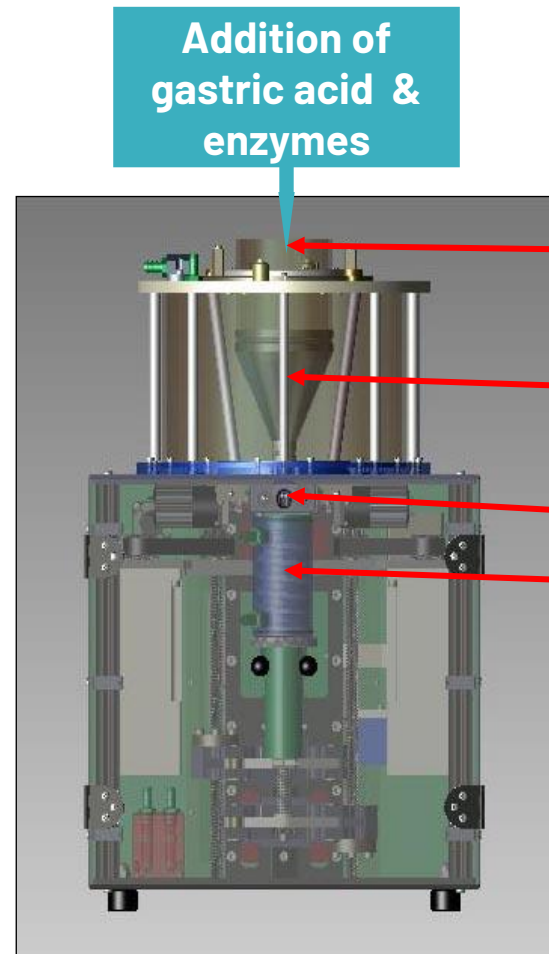Berthelsen et al, 2016

Gastric mixing and pH profile

Fundus mixing

- Low stirring
- Heterogeneous
- Strongly dependent on meal-type
- Potential for long residency
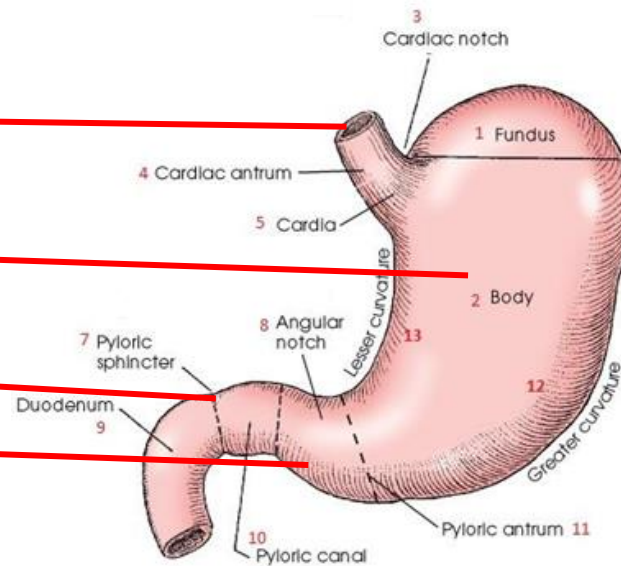- Addition of acid from the gastric glands

Meal Liver

Spinal cord 36 min 48 min 72 min Dilution
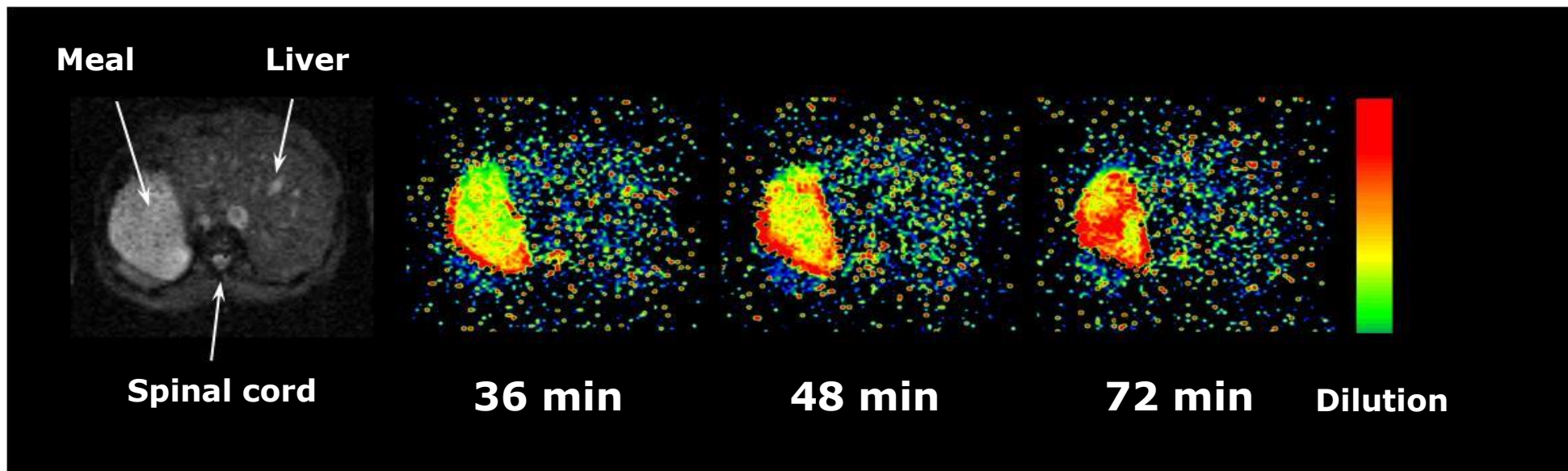
Marciani *et al.* Am. J. Physiology 280, G1227, 2001

Dynamic Gastric Model (DGM)

Addition of gastric acid & enzymes

Dynamic Gastric Model

Body/fundus

- Light contractions
- In-homogenous environment

**Antrum**

- Contractions 10x/min
- High shear (300 mbar)
- Homogenization

Emptying

- Controlled release of content

3 Cardiac notch
4 Cardiac antrum
5 Cardia
1 Fundus
2 Body
7 Pyloric sphincter
8 Angular notch
13
12
Lesser curvature
Greater curvature
Duodenum
9
10 Pyloric canal
Pyloric antrum 11

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Dynamic Gastric Model (DGM) and Duodenal Module predict drug and dosage form behavior in the gastro-intestinal tract
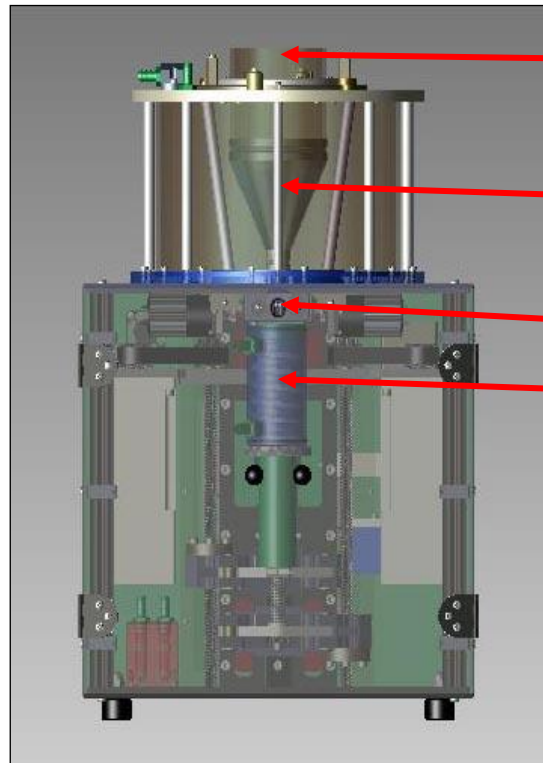

Dynamic Gastric Model
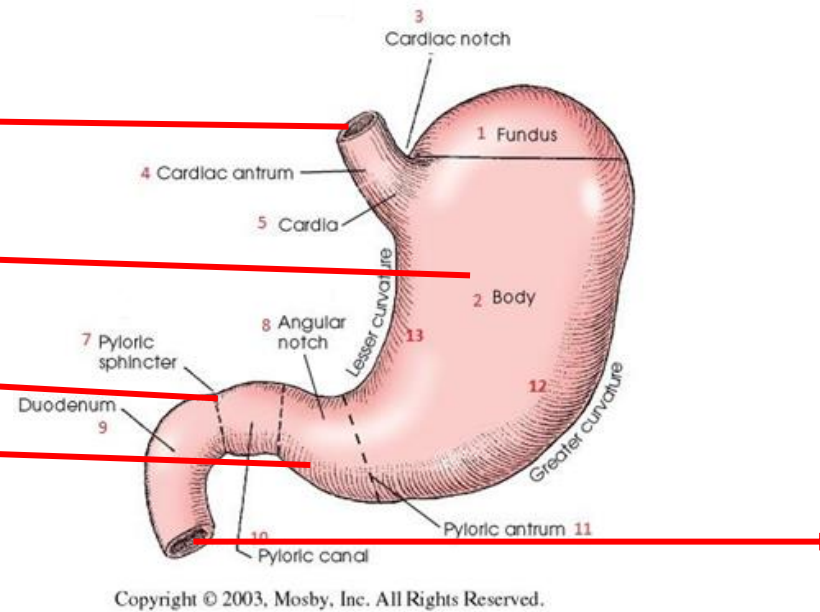
Duodenal Module

Flexible Duodenal Module – Coupled with DGM or stand-alone

- DGM samples incubated with simulated intestinal fluid
- Simulating digestion
- 37 °C, pH 6.5 (pH stat)
- Dosage form behavior
- Dissolution/precipitation of API

Simulated intestinal fluid:
- Bile extract (porcine)
- Lecithin
- Pancreatin
  - (trypsin, amylase and **lipase**, ribonuclease, and **proteases**)

Porcine pancreatin

NaOH

pH stat

Temperature-controlled reaction vessel

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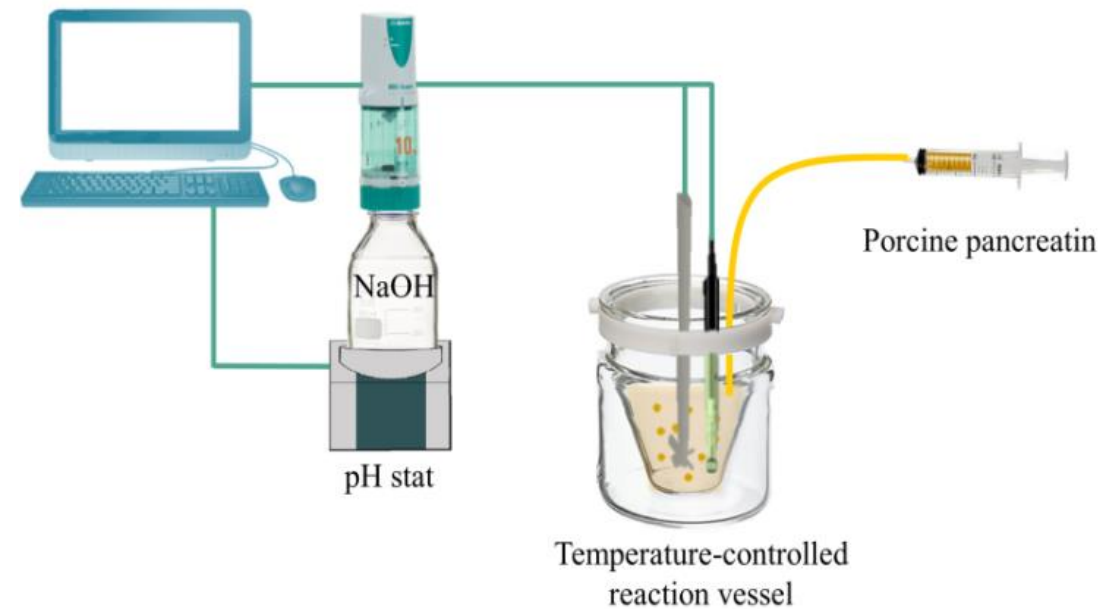
DGM: Fasted and Fed state conditions
Clinical protocols

Fasted state set-up

- Gastric acid priming solution

- 240 mL tap water
  + dosage form

- Dynamic addition of acid and enzyme
  solutions

Run time - approx. 30 minutes

Fed state set-up

- Gastric acid priming solution

- + chewed meal

- Dynamic addition of acid and enzyme
  solutions

- At 30 min: 240 ml tap water + dosage form

Run time – approx. 4 hours

For both set-ups:
- Acid solution is added as a **function of measured pH**
- Enzyme solution added as a **function of volume** of meal chyme present in the DGM

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"FDA Breakfast"

"...approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively."

Cited from: "Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies", FDA 2002.
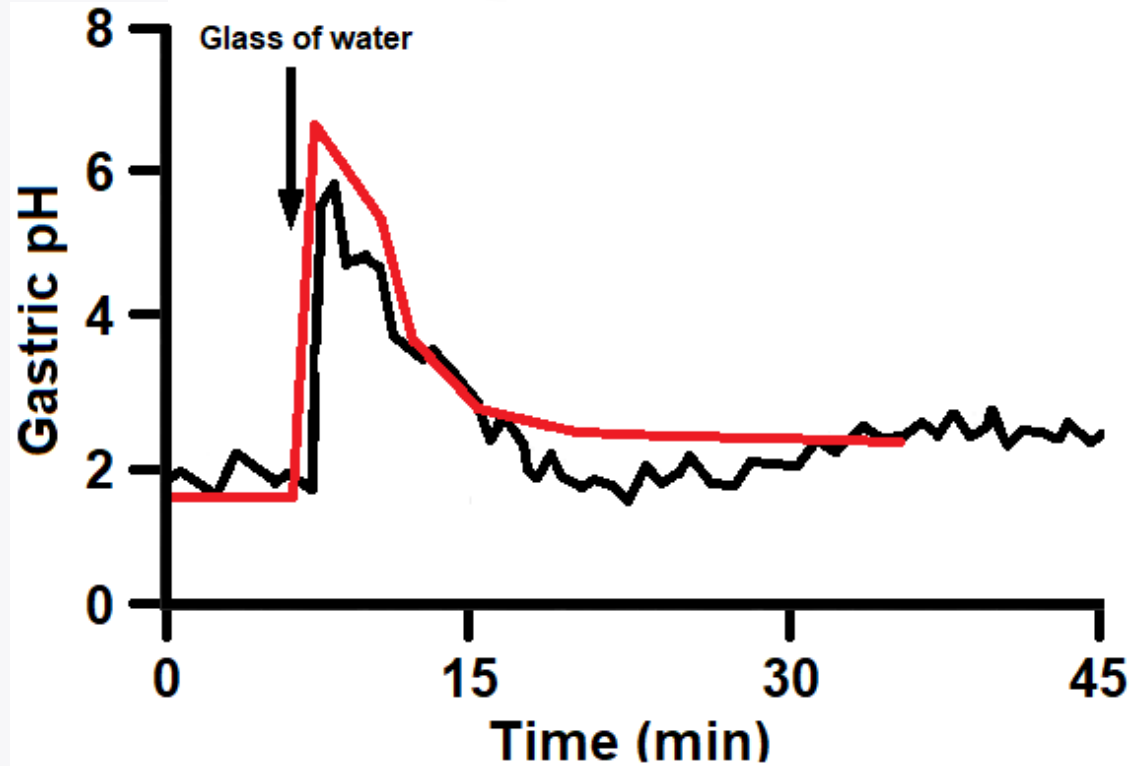
Example of meal composition
- 2 slices of toast
- 20 g butter
- 2 eggs
- 4 bacon strips
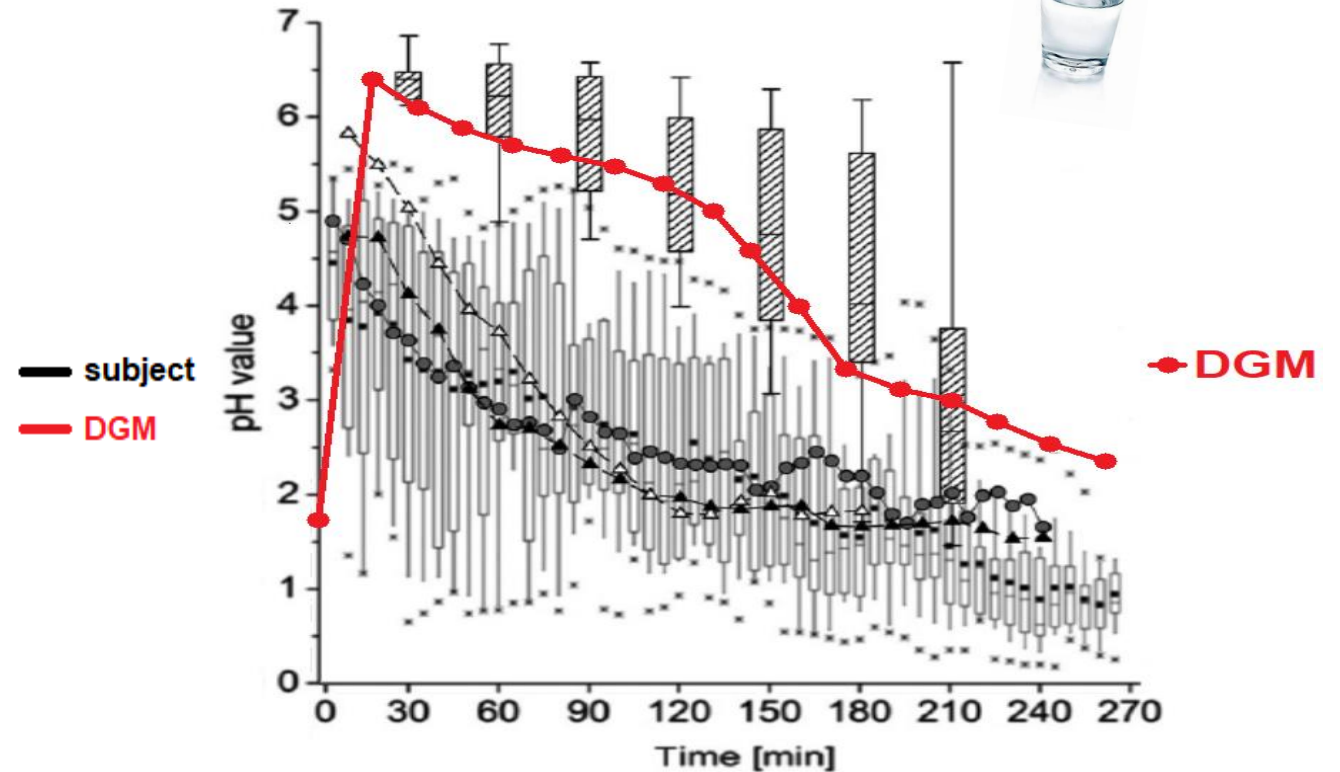- fried potatoes (4 hash browns)
- 1 glass of whole milk

bionEr

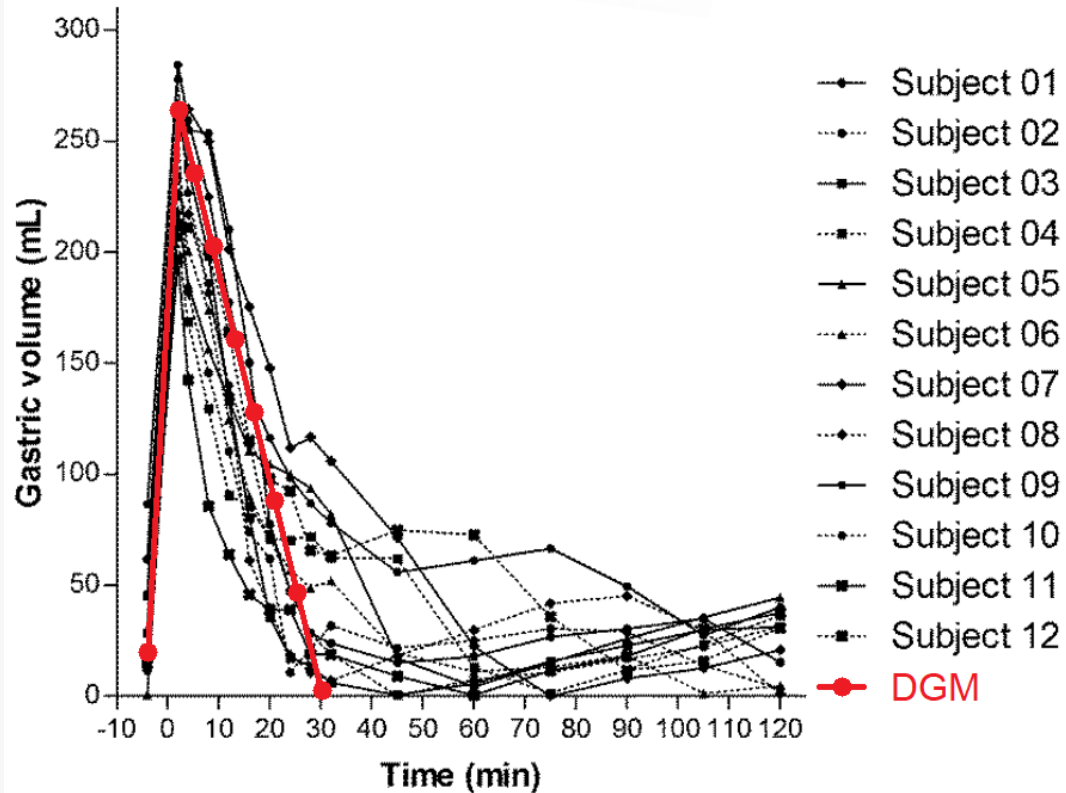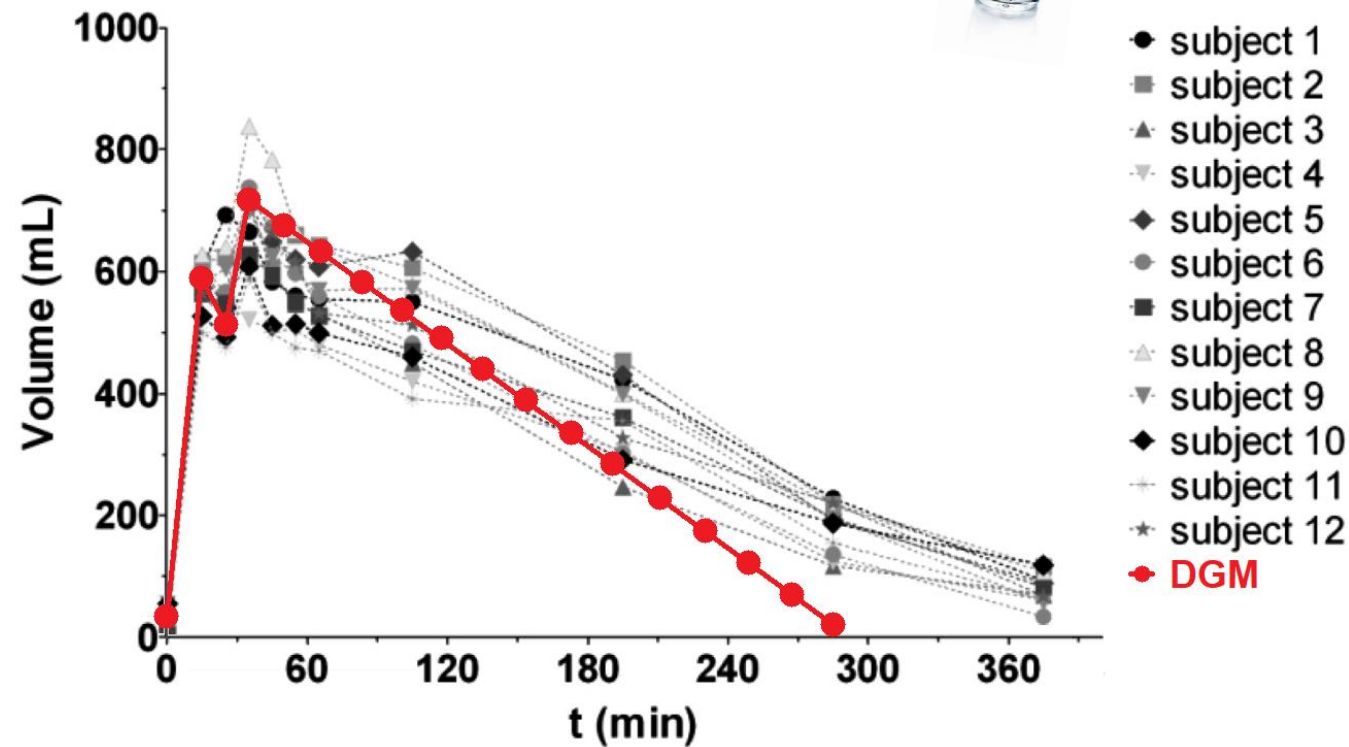# DGM pH profile – Fasted/Fed State

Fasted State

Fed State
"FDA breakfast"

Karamanolis et al., Dig Dis Sci 2008

Pentafragka et al., JPP 2019

Gastric Emptying – DGM vs Humans

Fasted State
240 ml water

Fed State
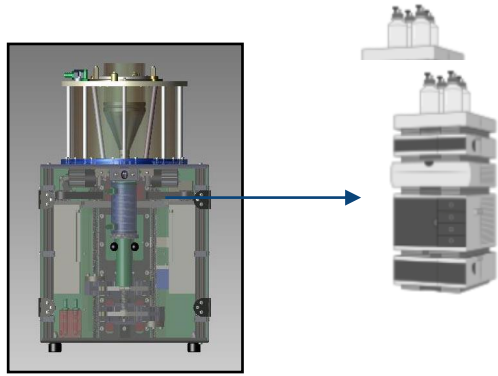"FDA breakfast"

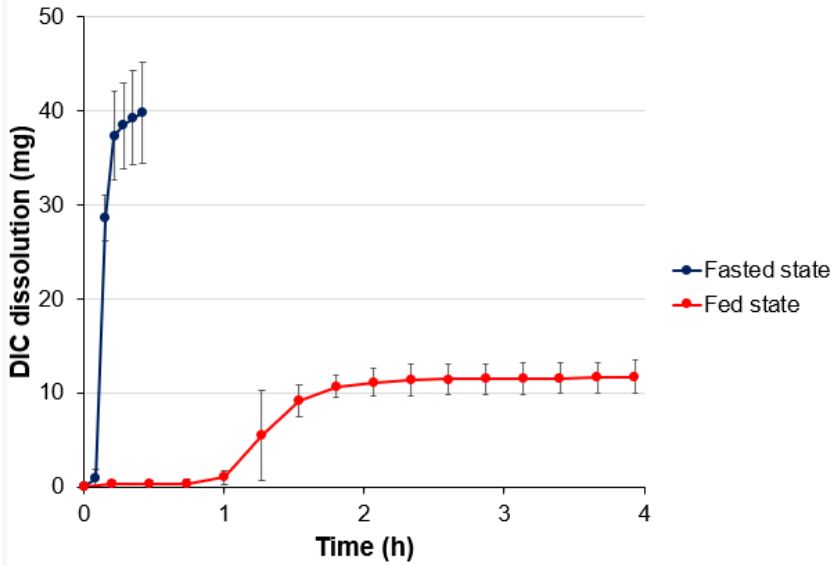*Mudie et al., Mol Pharm 2014*

Koziolek et al., Mol Pharm 2014

Food effects on drug absorption

Predicting food effect of Diclofenac potassium 50 mg (Cataflam®)
Negative food effect

Gastric dissolution
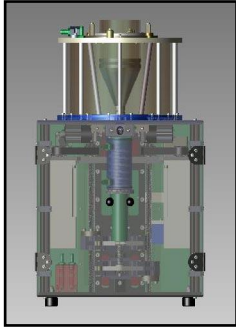
DIC dissolution (mg) vs Time (h)

- Fasted state
- Fed state

Duodenal dissolution

DIC dissolution (mg) vs Time (h)

- Fasted state
- Fed state

bionEer
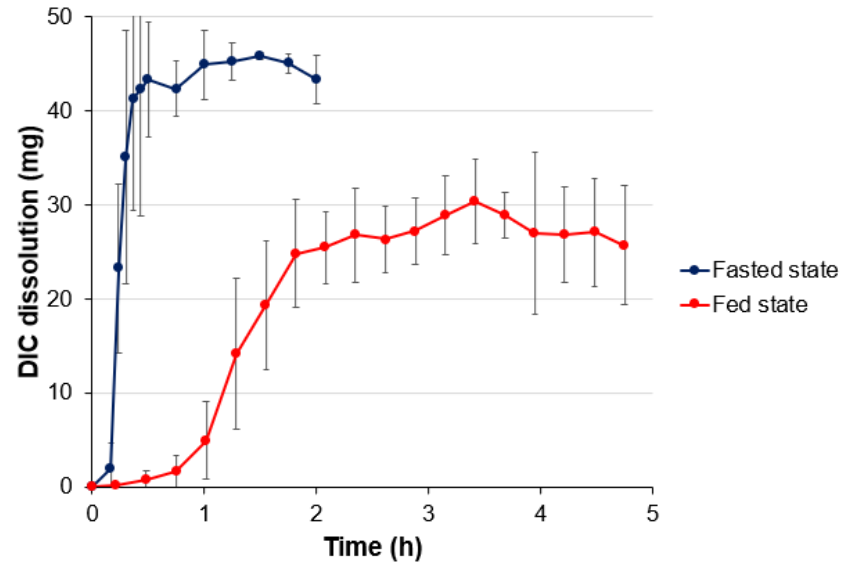
Predicting food effect of guaifenecin (Mucinex®) modified release tablets

Duodenal dissolution convolution
- Volume of distribution (Vd): 300 L
- Plasma half-life (t1/2): 60 min
- Oral bioavailability: 100%

Albrecht et al. Multidis Resp Med, 12(1), 1–11 (2017)

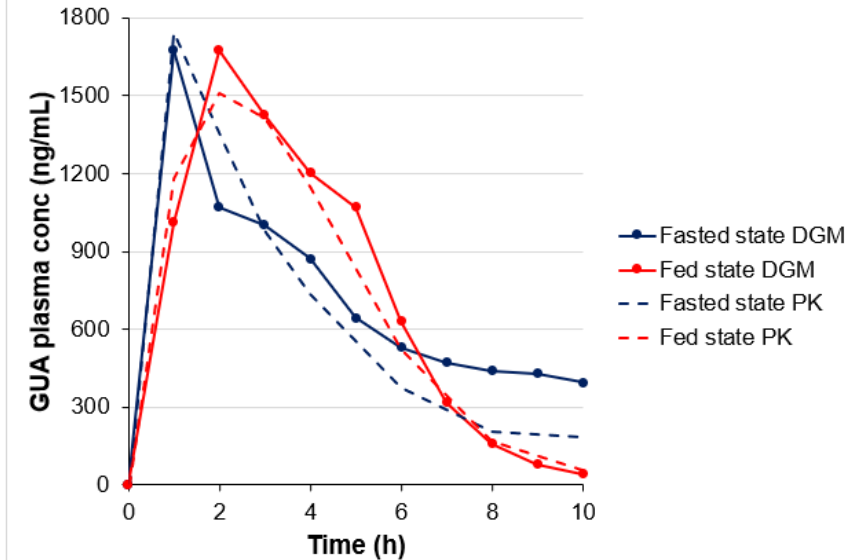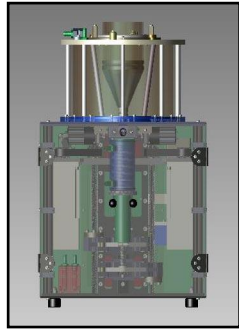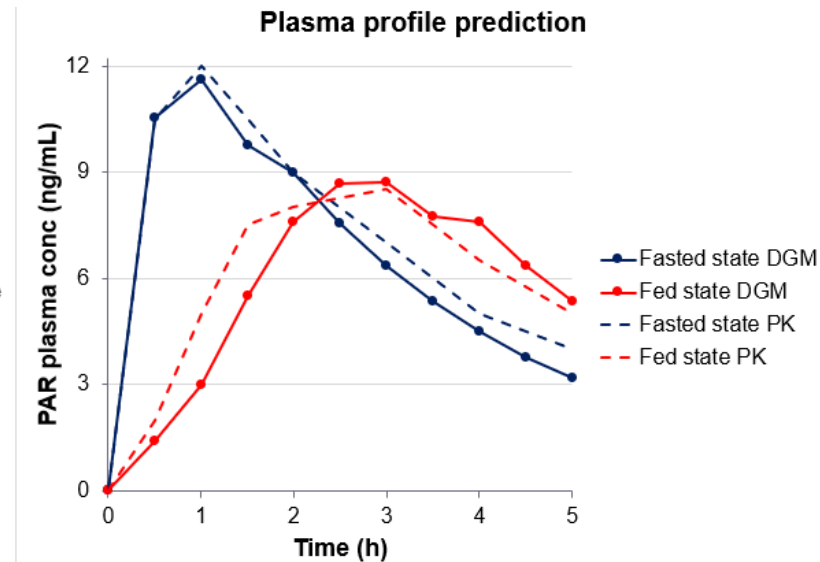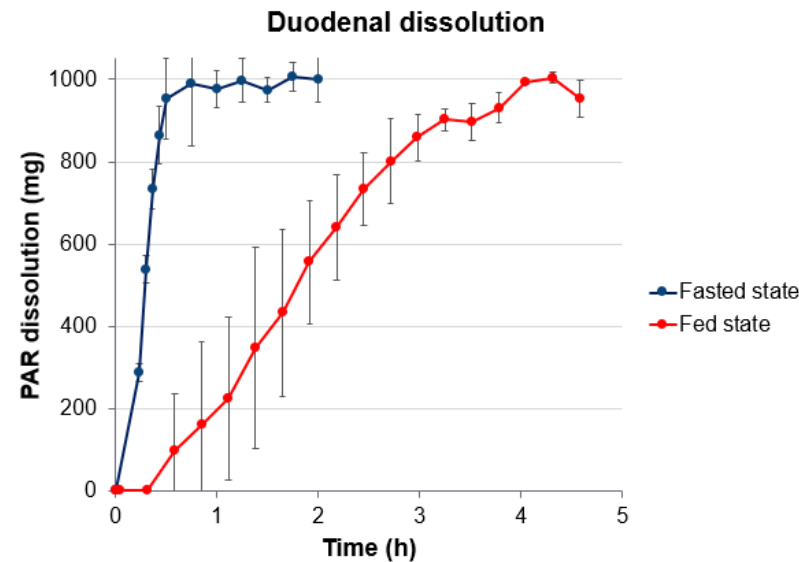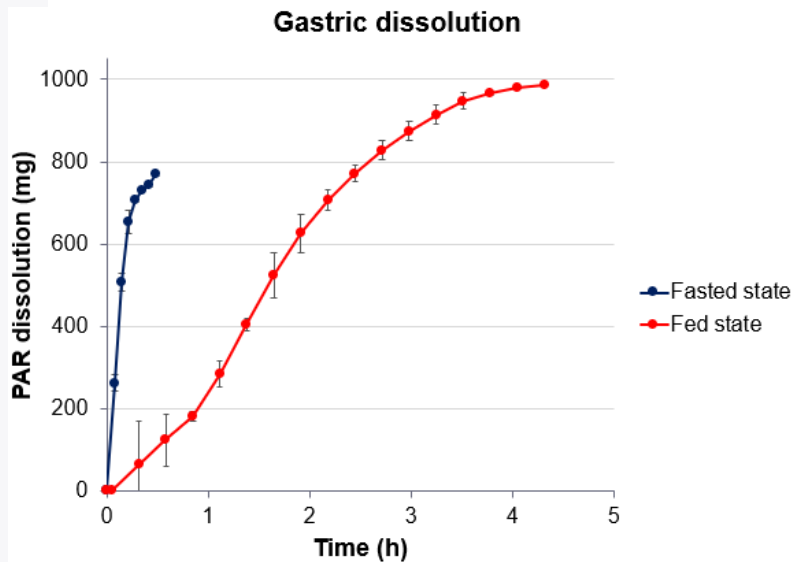*Vilson et al., Clin Pharm Drug Dev, 2013*

Predicting food effect of paracetamol/acetaminofen (500 mg tablets)

Duodenal dissolution convolution
- Weight: 70 kg
- Volume of distribution (Vd): 0.9 L/kg
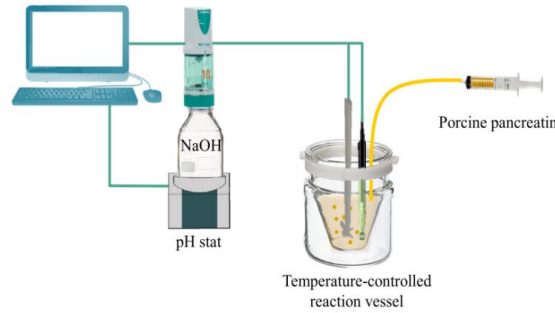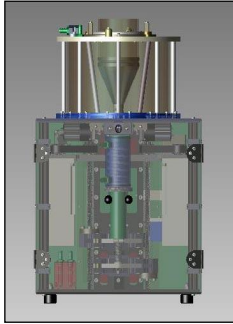- Plasma half-life ($t_{1/2}$): 60 min
- Oral bioavailability: 100%

Gastric dissolution

— Fasted state
— Fed state

Duodenal dissolution

— Fasted state
— Fed state

Plasma profile prediction

— Fasted state DGM
— Fed state DGM
--- Fasted state PK
--- Fed state PK

Clinical data: Rostami-Hodjegan et al., Drug Dev Ind Pharm, 2002

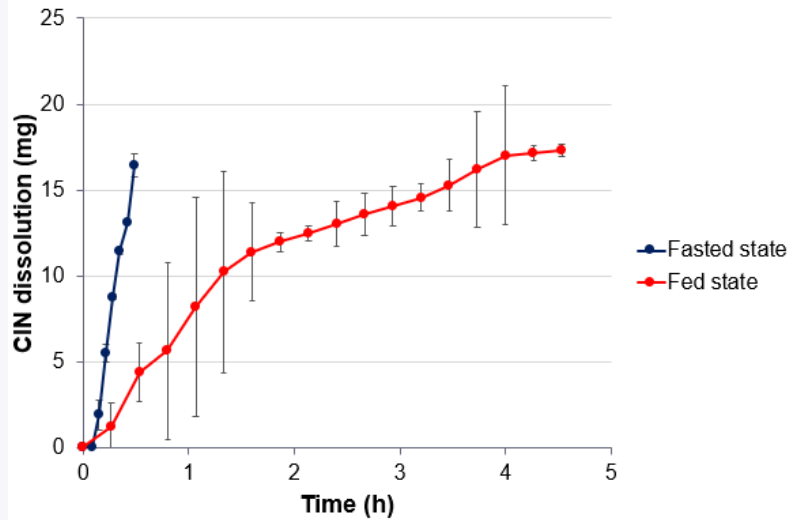bionEer

Predicting food effect of Stugeron®
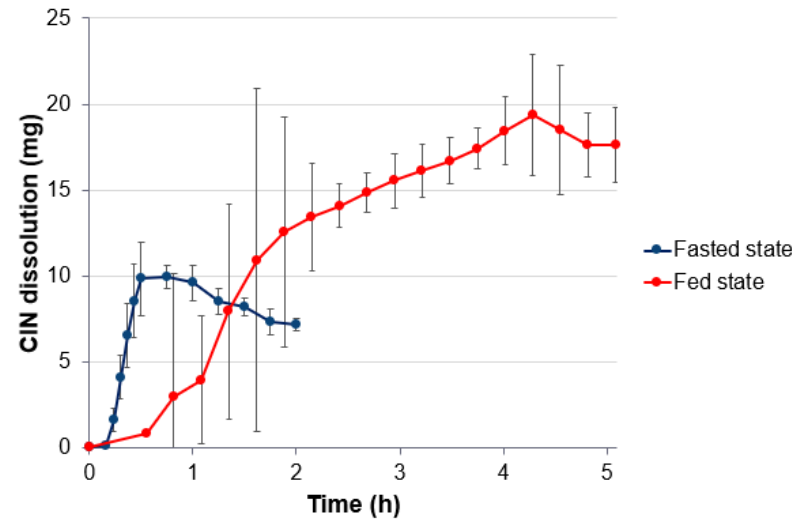
25 mg cinnarizine

Duodenal dissolution convolution
- Volume of distribution (Vd): 300 L
- Plasma half-life ($t_{1/2}$): 240 min
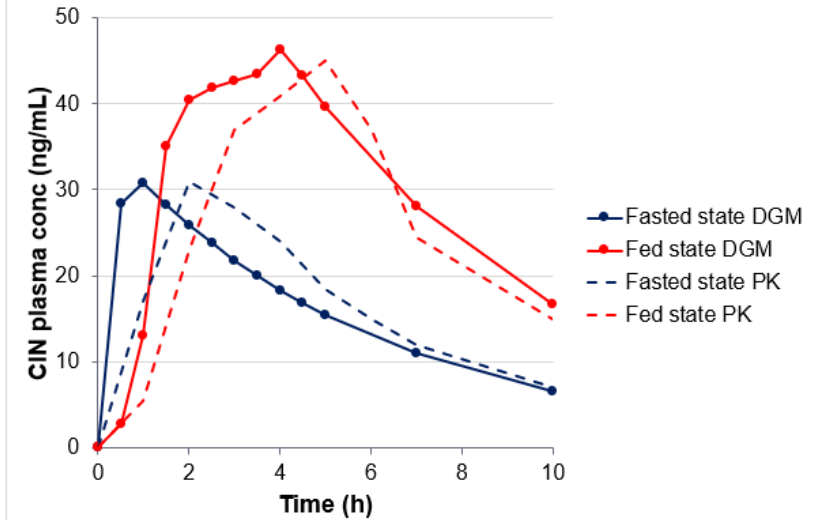- Oral bioavailability: 100%

Gastric dissolution

- Fasted state
- Fed state

Duodenal dissolution

- Fasted state
- Fed state

Plasma profile

- Fasted state DGM
- Fed state DGM
- Fasted state PK
- Fed state PK

Berlin *et al.,* Eur J Pharm Biopharm, 2014

bion

Survival of probiotic microorganisms embedded in chocolate

Aim:
To investigate the **viability of probiotic bacteria** in two types of chocolate during passage of the upper gastro-intestinal tract in the **fasted state**
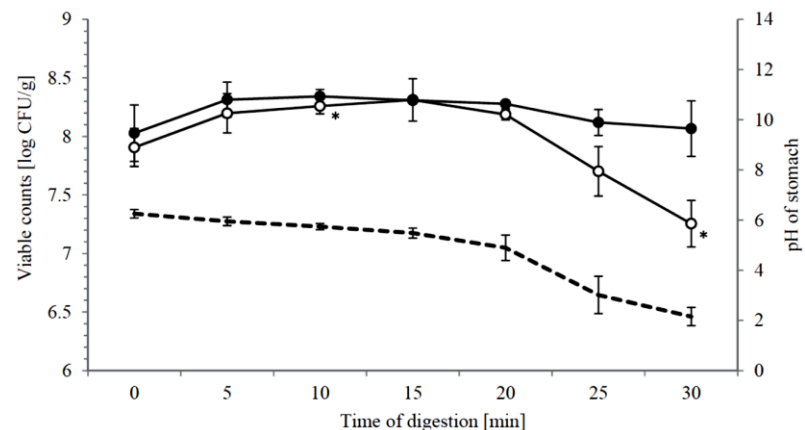Chocolate pieces mixed with saliva prior to DGM experiment

Open circles: Lactobacillus acidophilus NCFM®
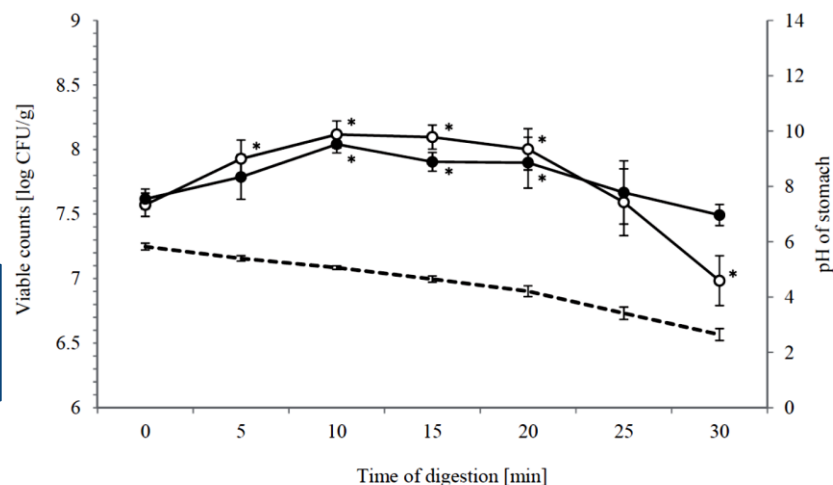Closed circles: Bifidobacterium lactis HN019
Stipulated line: pH

Viability of B. lactis slightly higher than Lb. acidophilus
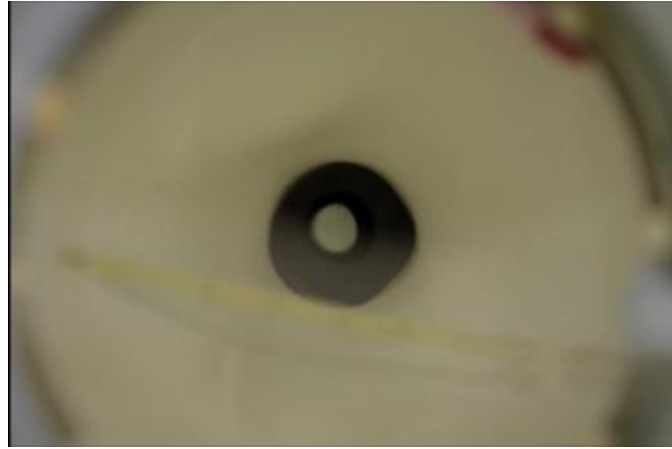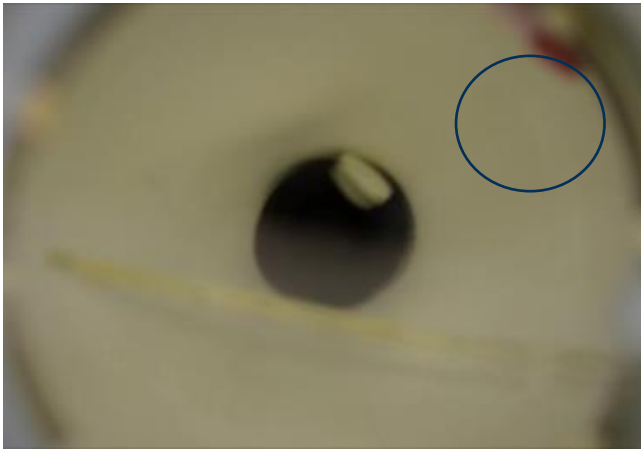Milk chocolate is the most protective carrier

MILK CHOCOLATE, 57 %

DARK CHOCOLATE, 72 %

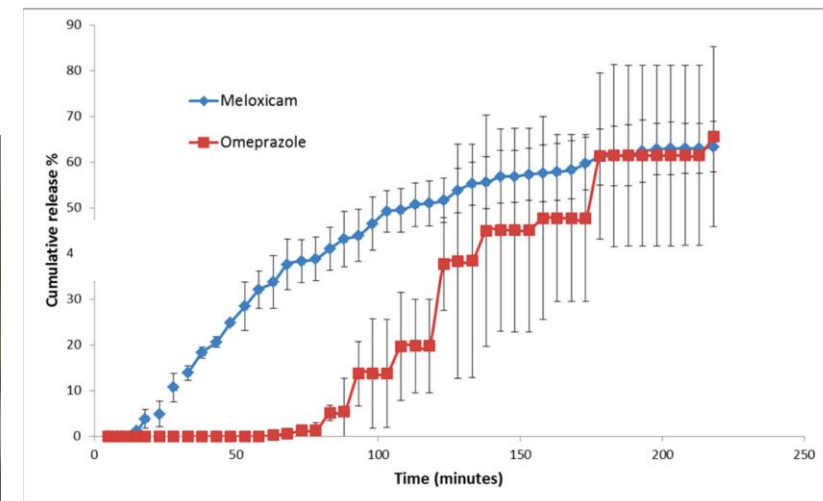Klindt-Toldam et al., LWT Food Sci Tech, 2016

DGM studies for fixed dose combinations

Snapshots of the formulation addition to the DGM

The capsule floated on the surface.
The tablet sank immediately inside the antrum.

DGM + Duodenal Module Flexibility

- Digestion of an entire meal (e.g. "FDA breakfast" – but in reality any meal)

- Emptying rate customized according to the nature of the ingested meal (calories)

- Sampling in the fundus – if desired

- pH profile change (simulating PPI (higher pH))
  - Online pH measurement – in fundus

- Flexible enzyme addition (activity and kind) – both DGM and Duodenal Module

- Simulating special populations (e.g. Pediatrics) & animals (e.g. dogs)

- Optional incubation of ejected samples in the Duodenal Model

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Thank you for your attention
Questions?

anette.mullertz@sund.ku.dk