Regulatory Education for Industry (REdI) and CERSI Workshop

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

September 23-25, 2019

College Park, MD

BREAKOUT SESSION C DAY 1:

Gastrointestinal (GI) Systems Parameters (Mucus, Volume, Motility): Where are the Pitfalls and How to Overcome Them?

Moderators and scribes: Mirko Koziolek (U of Greifswald); Yang Zhao (FDA), André Dallmann (Bayer AG); Xavier Pepin (AstraZeneca);

Session Background

The facts:

- Gastrointestinal fluid volume kinetics and gastrointestinal motility are highly relevant for the *in vivo* performance of oral IR and MR drug products.
- Both parameters contribute significantly to the variability of PK profiles.
- The role of mucus in oral drug delivery remains unclear.
- All three aspects are poorly considered in biopredictive *in vitro* and *in silico* tools.

How can we overcome this?

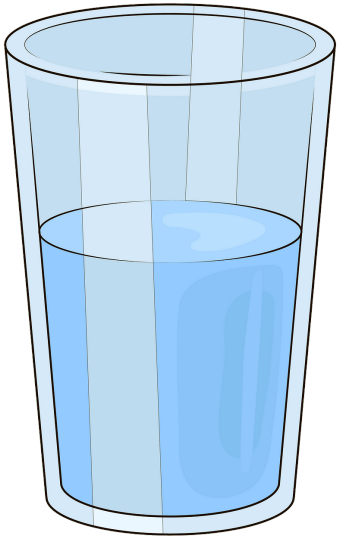
Session Outline

Proposed Questions	Moderator	Scribe
1. Motility in stomach: What are the critical components missing for gastric motility and emptying? a. What are the best practices to measure stomach emptying? b. Do we have examples where the IMMC affected in vivo performance? c. What are the challenges and gaps in knowledge?	*Mirko*	*Xavier, Yang, André*
2. How do we assess and integrate particle/dosage form segregation in the stomach in the fasted and fed state in the models? a. IR vs MR formulations b. Impact on hydrodynamics and dissolution	*Mirko*	*André, Yang, Xavier*
3. Motility in GI tract: How do we integrate mechanistically hydrodynamics in the modes- velocity profiles or hydrostatic pressures or rpm equivalent? a. How to best prepare this information for model input in support of manufacturing changes? b. What are the gaps in knowledge?	*André*	*Yang, Mirko, Xavier*
4. Intestinal fluid volume : Contribution of mucus and GI secretions to volume of fluid, fluid distribution along the SI and colon– What are the pitfalls? a. How to translate from in vitro and integrate into mechanistic modelling ?	*Xavier*	*Yang, Mirko, André*
5. Individual PK profiles can show large variations on the absorption phase (lag time and partial gastric emptying) should we co-administer markers of gastric emptying in the clinic and in PBPK tools to improve model performance (reduce noise related to stomach emptying phases)? a. What are the pitfalls? What key data are missing to accomplish this?	*Mirko*	*André, Yang, Xavier*

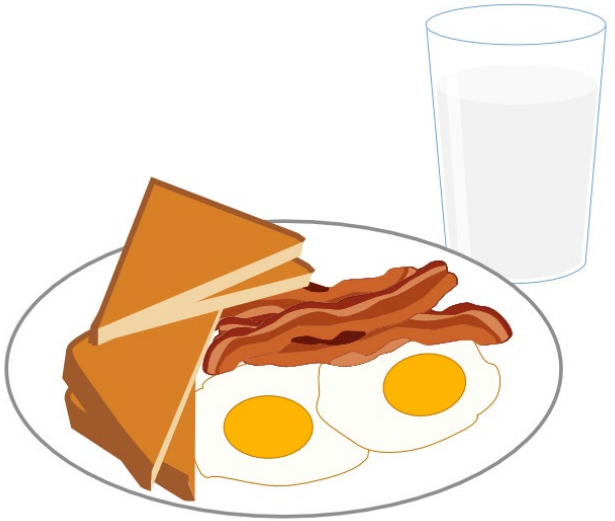
Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach

Fasted state

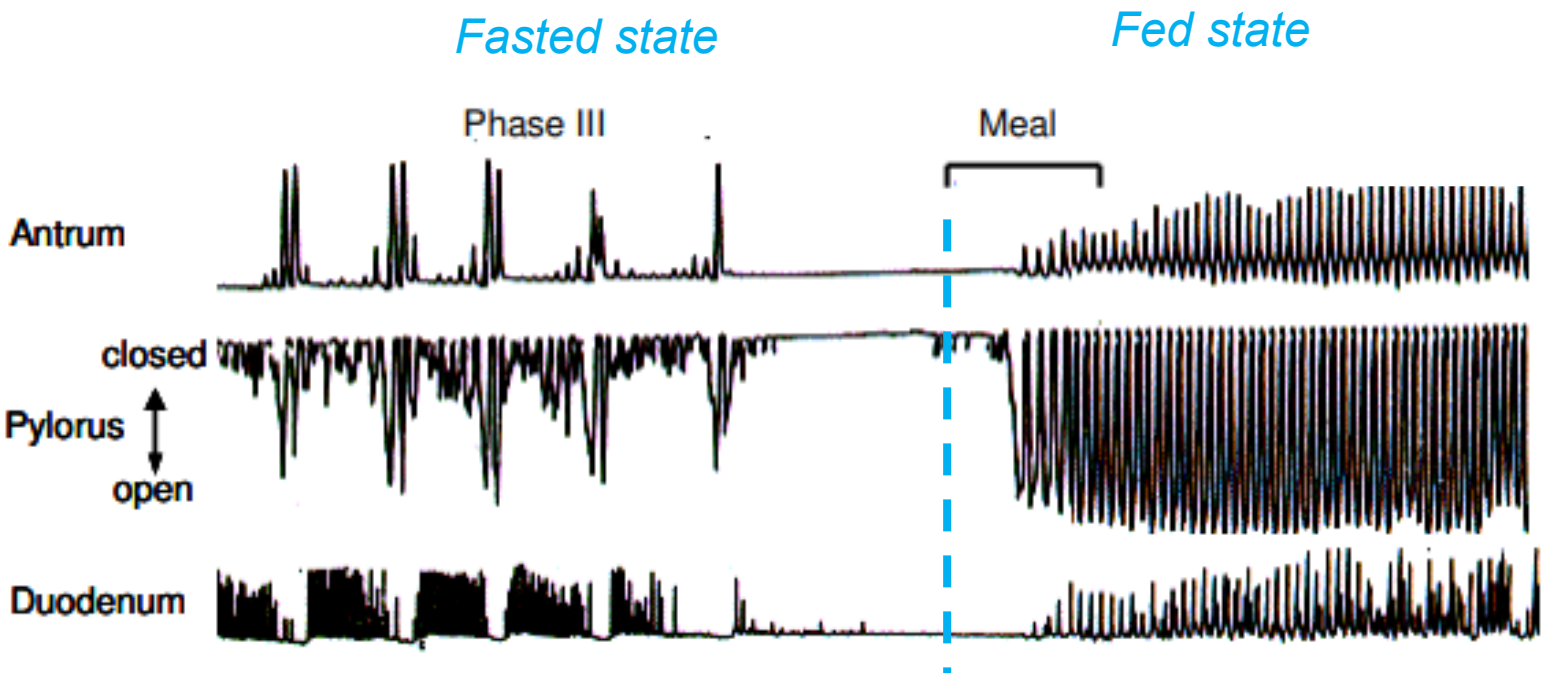


Fed state



Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach

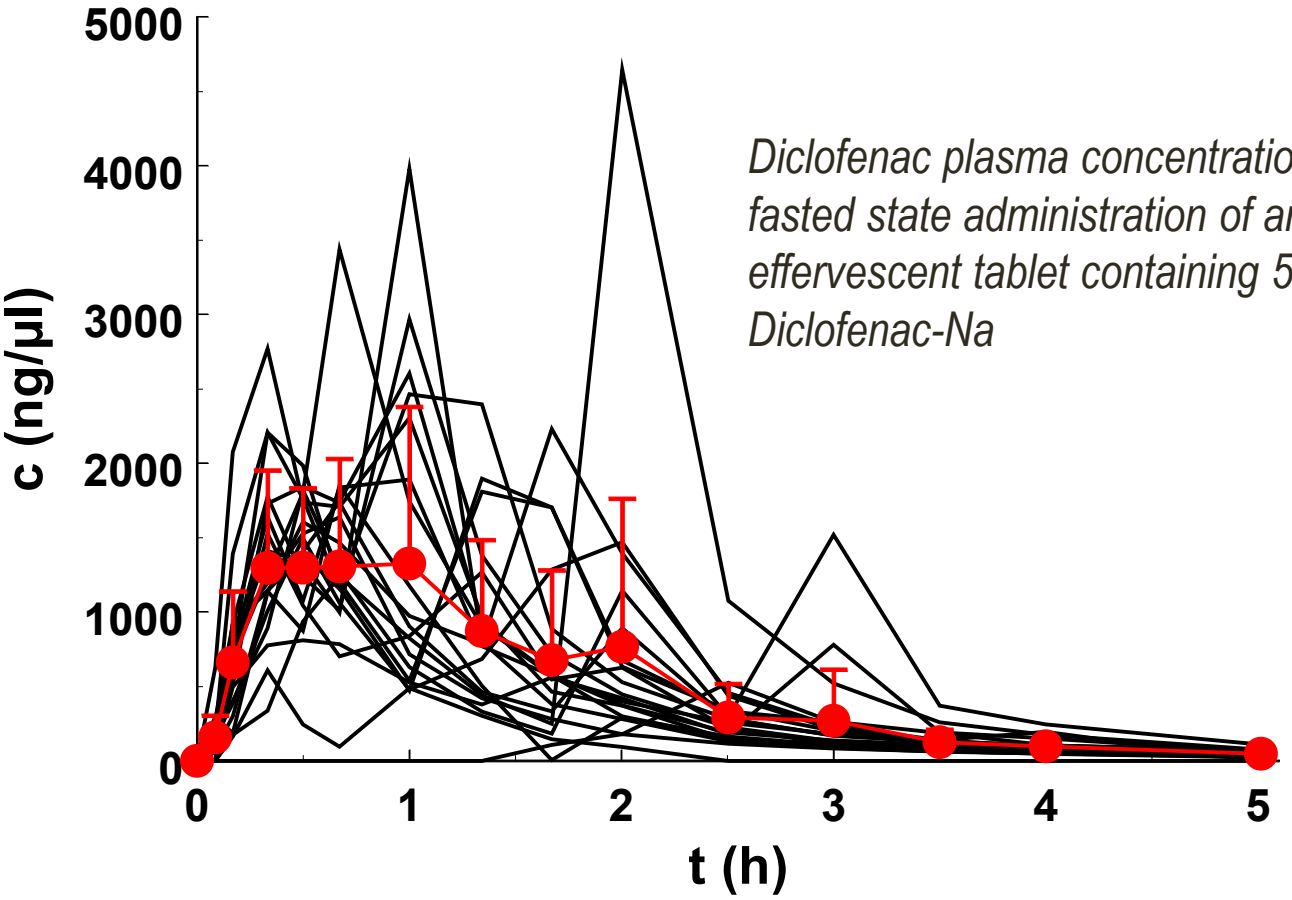


Motility patterns in the upper GI tract.

Ehrlein *et al.*

Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach (fasted state)

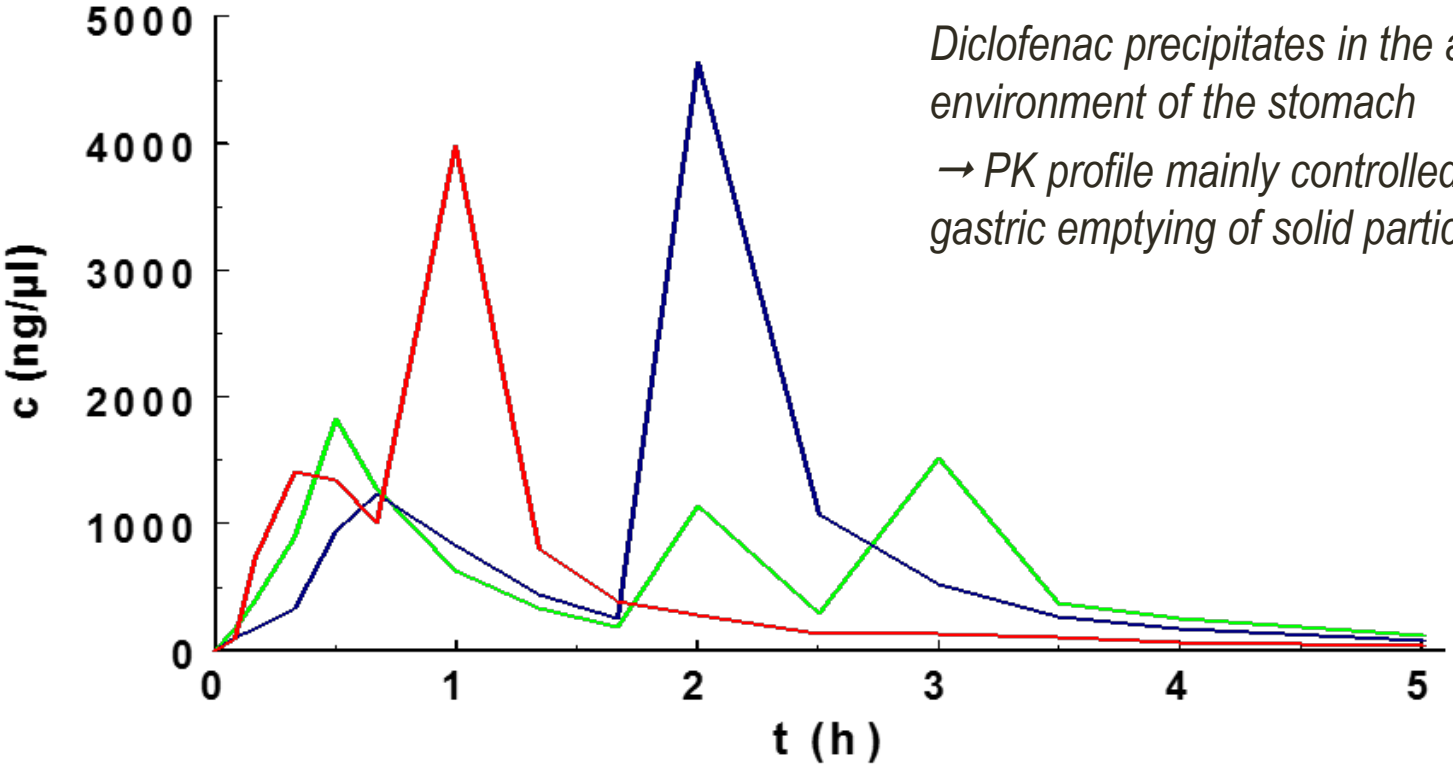


Diclofenac plasma concentrations after fasted state administration of an effervescent tablet containing 50 mg Diclofenac-Na

Terhaag et al. *Int J Clin Pharmacol Ther* (2000)

Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach (fasted state)



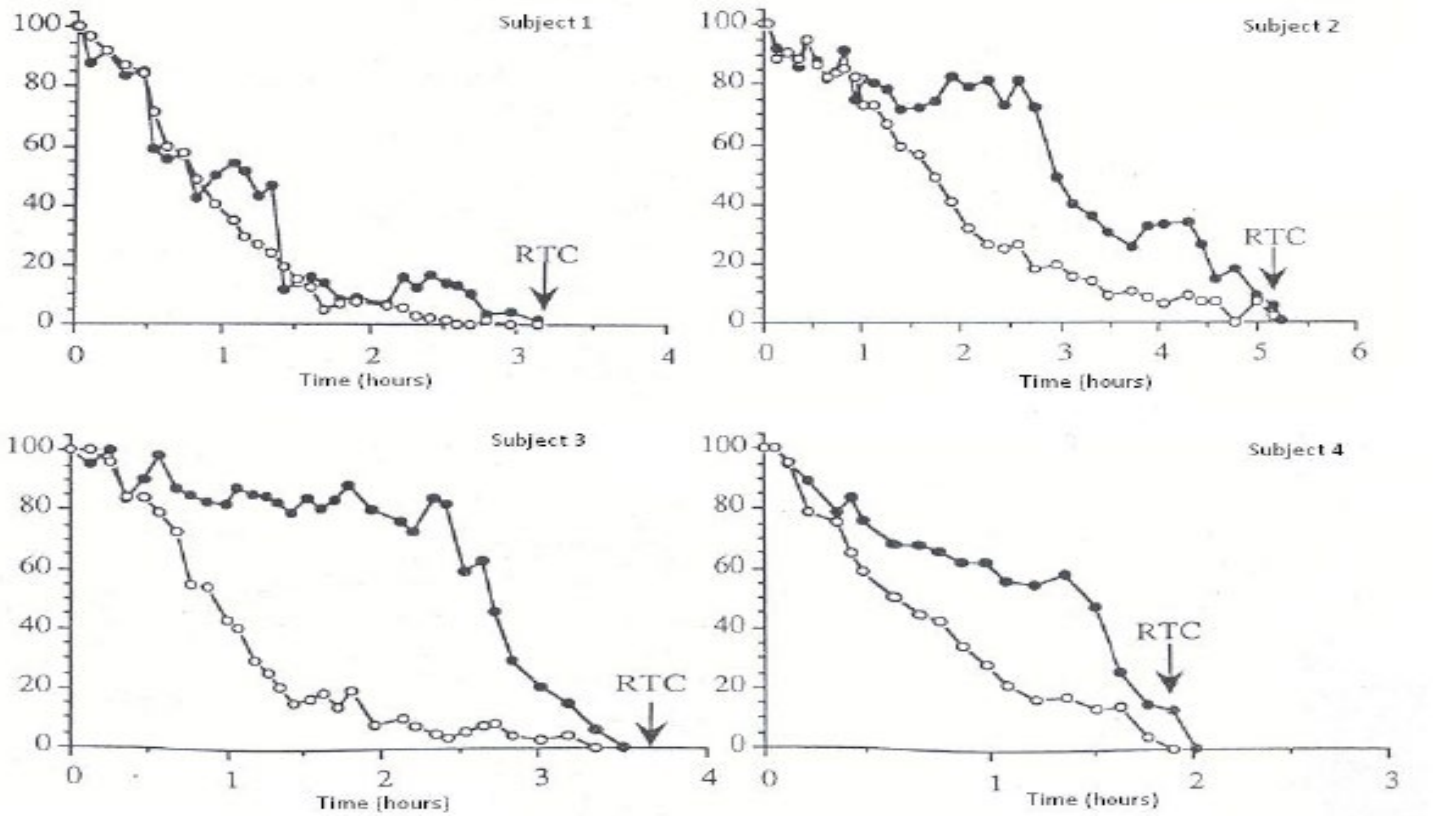
Diclofenac precipitates in the acidic environment of the stomach

→ PK profile mainly controlled by the gastric emptying of solid particles (MMC?)

Terhaag et al. *Int J Clin Pharmacol Ther* (2000)

Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach (fed state)

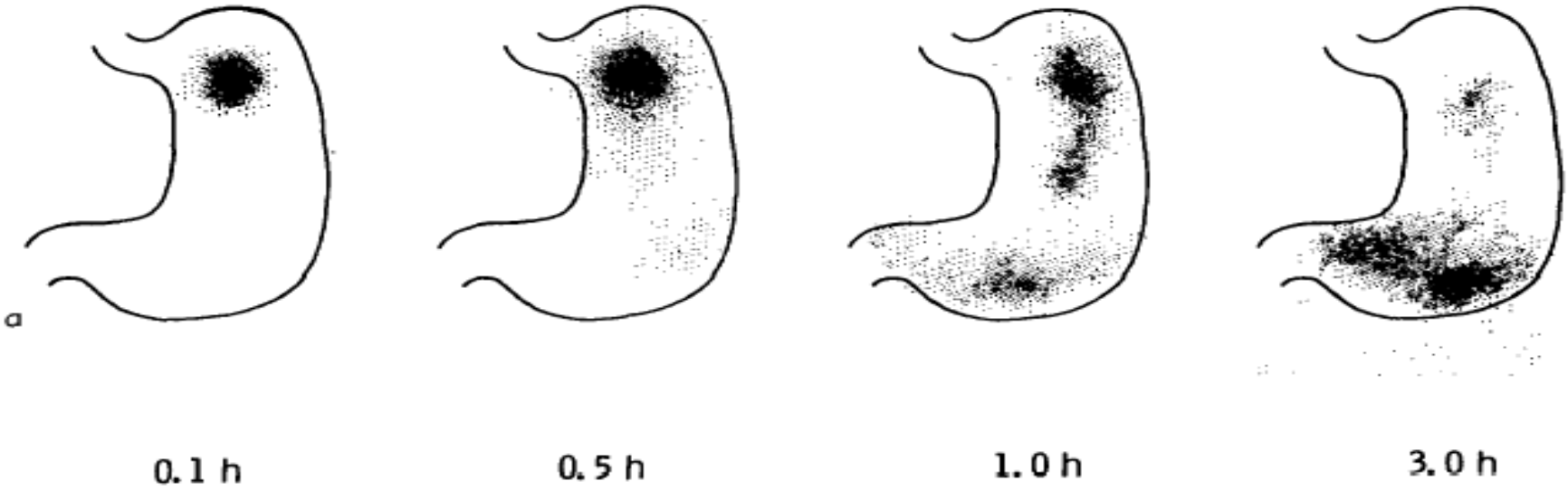


Gastric emptying of food (light meal,○), pellets (0.8-1.1 mm, ●) and a radiotelemetric capsule (RTC)

Coupe et al. *Int J Pharm* (1993)

Key Points from BO Session C, Day 1, Question 1 & 2

Motility in stomach (fed state)



Gastric emptying of anion exchange resin pellets (0.7-1.3 mm) dosed in form of a capsule after a meal

O'Reilly et al. *Int J Pharm* (1987)

Key Points from BO Session C, Day 1, Question 1

Motility in stomach: What are the critical components missing for gastric motility and emptying?

a. What are the best practices to measure stomach emptying?
b. Do we have examples where the IMMC affected in vivo performance?
c. What are the challenges and gaps in knowledge?

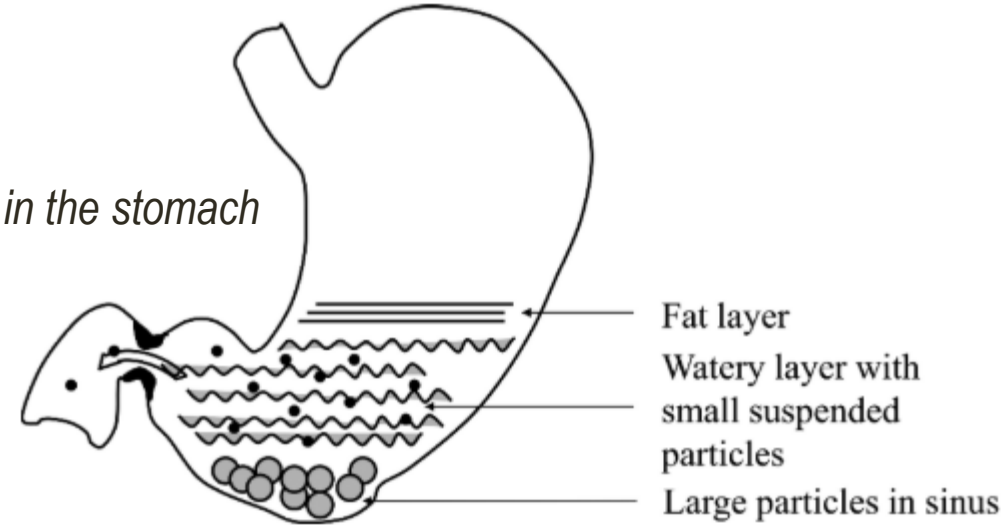
Key Points from BO Session C, Day 1, Question 2

How do we assess integrate **particle/dosage form segregation** in the stomach in the fasted and fed state in the models?

a. IR vs MR formulations

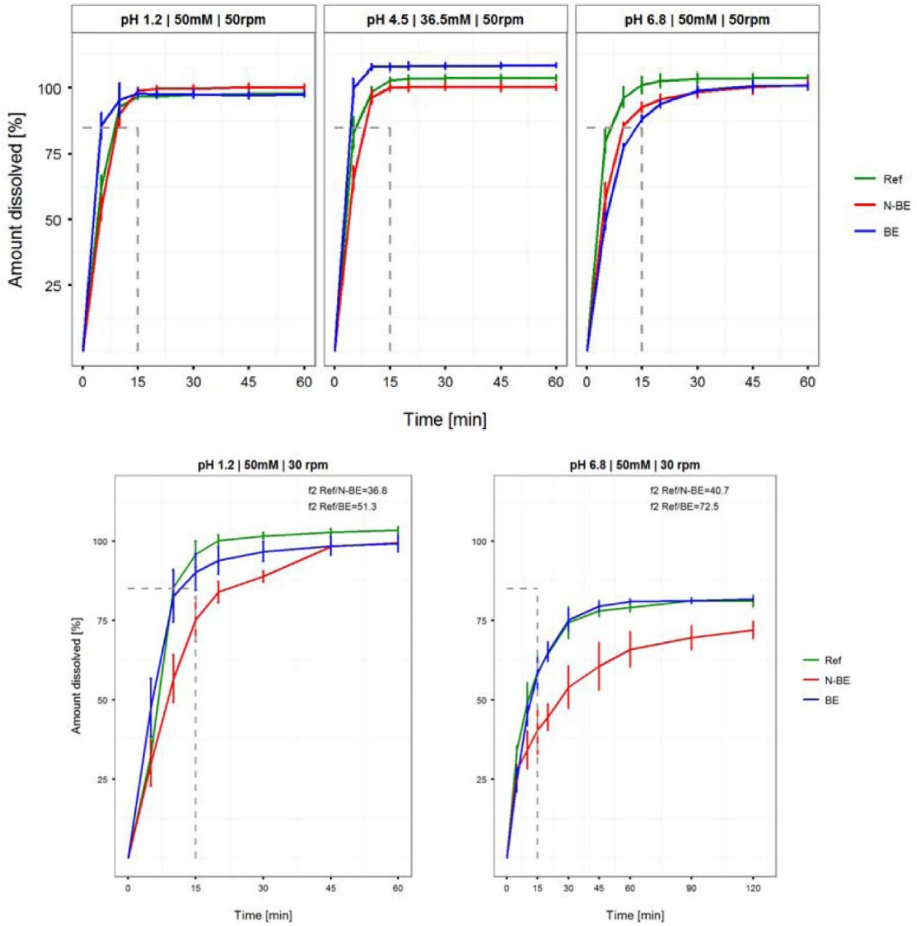
b. Impact on hydrodynamics and dissolution

Layering in the stomach



Key Points from BO Session C, Day 1, Question 3

Discriminatory power of the BCS-biowaiver in vitro methodology



Colón-Useche et al. *Molecular Pharmaceutics* (2015)

At 50 rpm, all three zolpidem formulations showed similar dissolution profiles in vitro suggesting bioequivalence

However, in vivo PK profiles were not conclusive, but showed a 14% mean difference in C_{max} precluding bioequivalence

Dissolution at 30 rpm was found to be discriminatory and the nonbioequivalent formulation exhibited a slower disintegration rate at this rotation speed

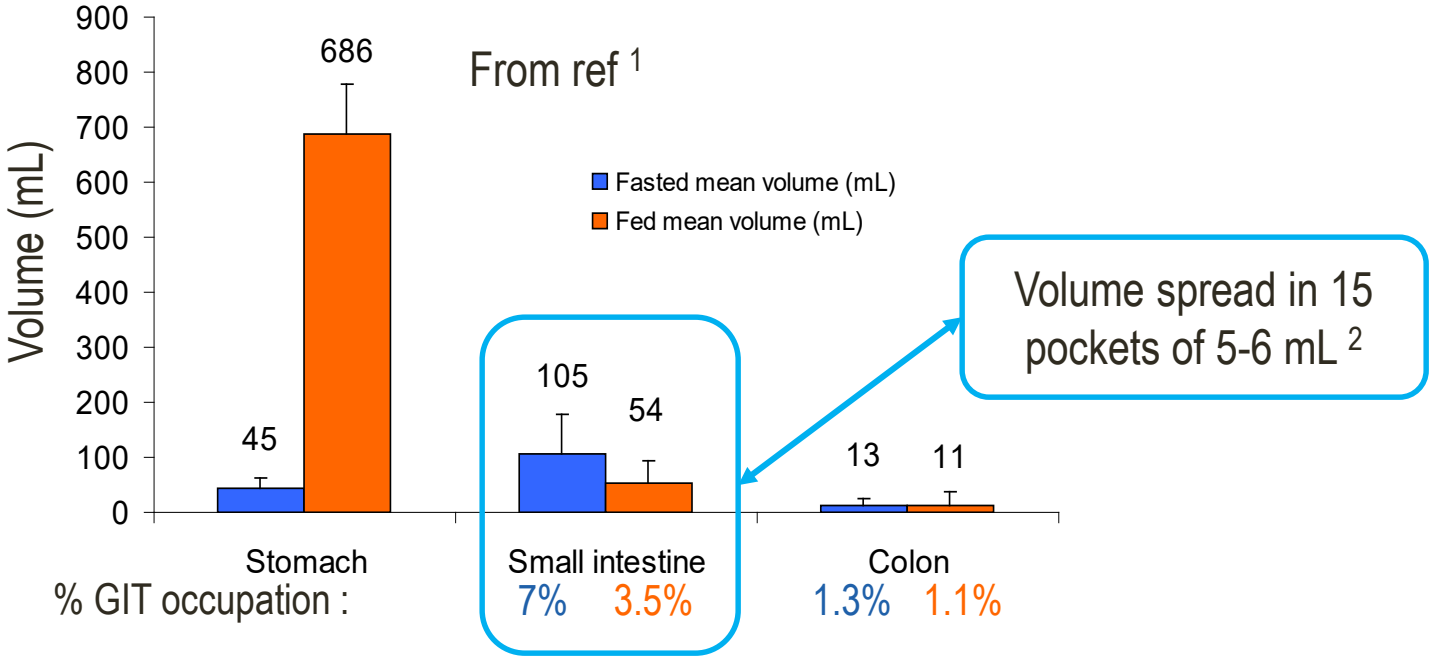
Key Points from BO Session C, Day 1, Question 3

Motility in GI tract: How do we integrate mechanistically hydrodynamics in the modes- velocity profiles or hydrostatic pressures or rpm equivalent?

a. How to best prepare this information for model input in support of manufacturing changes?
b. What are knowledge gaps?

Key Points from BO Session C, Day 1, Question 4

Intestinal fluid volume: Contribution of mucus and GI secretions to volume of fluid, fluid distribution along the SI and colon – What are the pitfalls?

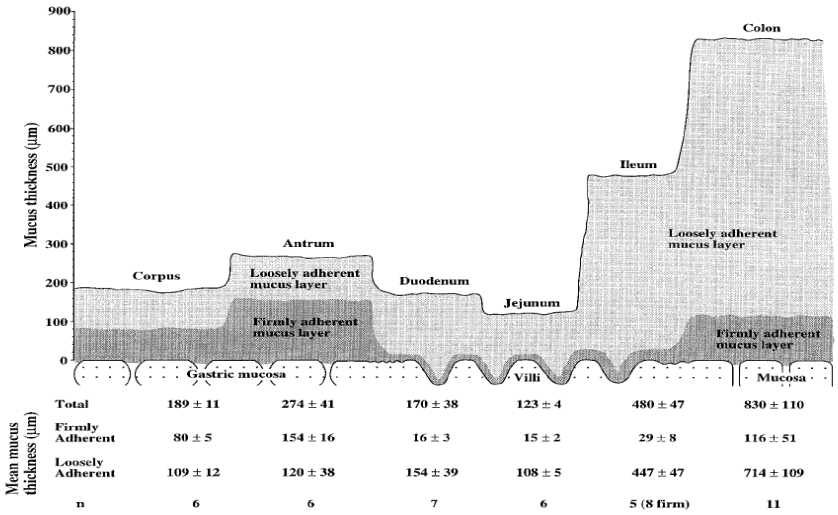


After stomach ?

1: Schiller et al. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment. Pharmacol. Ther 2005, 22, 971-979

Key Points from BO Session C, Day 1, Question 4

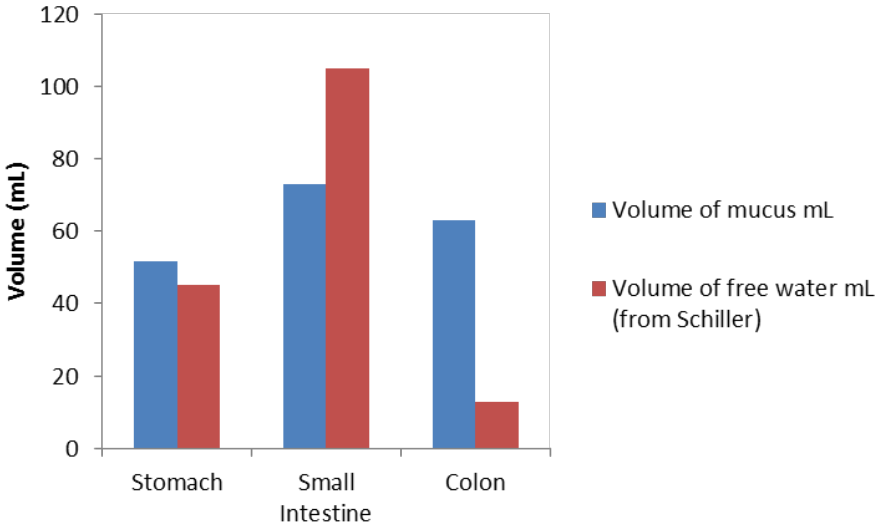
Contribution of mucus



Mean mucus thickness (μm)							
Total	189 ± 11	274 ± 41	170 ± 38	123 ± 4	480 ± 47	830 ± 110
Firmly Adherent	80 ± 5	154 ± 16	16 ± 3	15 ± 2	29 ± 8	116 ± 51
Loosely Adherent	109 ± 12	120 ± 38	154 ± 39	108 ± 5	447 ± 47	714 ± 109
n	6	6	7	6	5 (8 firm)	11

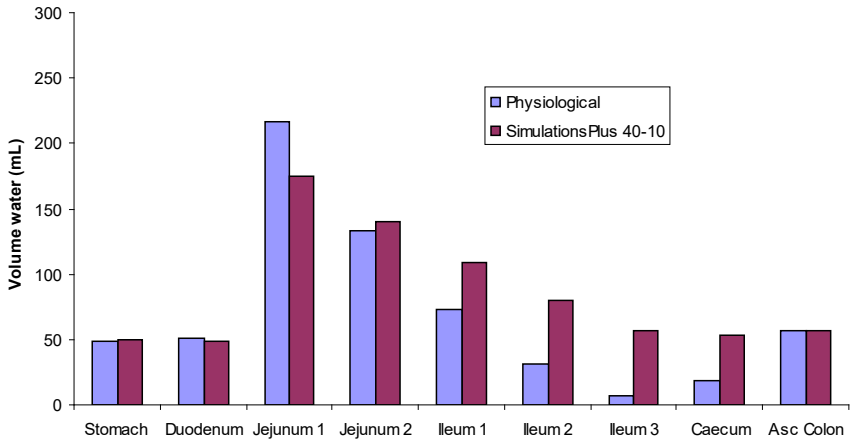
Atuma, C., et al. (2001). "The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo." American journal of physiology. Gastrointestinal and liver physiology 280(5): G922-929.

Mucus doubles the volume seen by MRI. Main contribution in the colon



Mucus accessible to solutes, micelles and nanoparticles <200nm but not to >micron size solid dosage forms

Key Points from BO Session C, Day 1, Question 4



Volume is dynamic (stomach) and intestine with secretions-reabsorption
Volume is spread in pockets

Intestine is a "washing machine" with 9 liters secreted/ingested and absorbed each day !

Volume "seen" by a product during transit is larger than basal measured volumes

This water is not apparent (since reabsorbed) but could contribute to product "clearance"
Nernst-Brunner equation controlling dissolution is not adapted to handle secretions (bulk, well stirred)

Add a clearance term ?
Notion of bulk ? Spread of particles ?

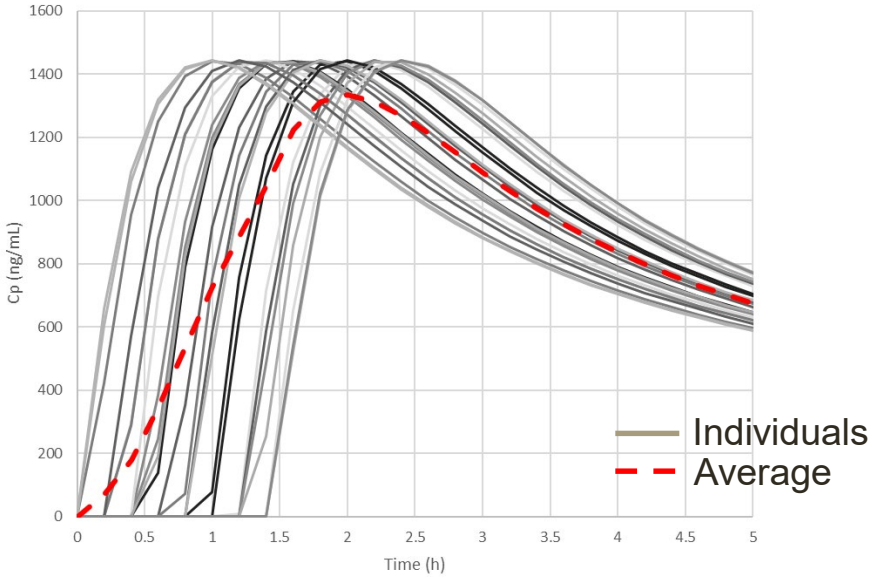
$$\frac{dm_{solid}}{dt} = -\left(\frac{D \times A(t)}{h(t)}\right) \times \left(S - C_{bulk}(t)\right)$$

Key Points from BO Session C, Day 1, Question 5

Error made in using average vs individual

Simulation of n=24 subjects, variable lag [0-1.5h]

Dose	100	mg
k_a	1	h-1
Tlag	variable [0-1.5]	h
$V = V_1$	20	L
V_2	40	L
k_{12}	1	h-1
k_{21}	0.5	h-1
k_e	0.5	h-1



Errors made using average profile

	Prediction error using average profile (%)
ka	-24
$V = V_1$	80
V_2	-18
k_{12}	-72
k_{21}	-39
k_e	-40
V_{SS}	15
C_{max}	-8
AUC	0

Key Points from BO Session C, Day 1, Question 5

Individual PK profiles can show large variations on the absorption phase (lag time and partial gastric emptying).

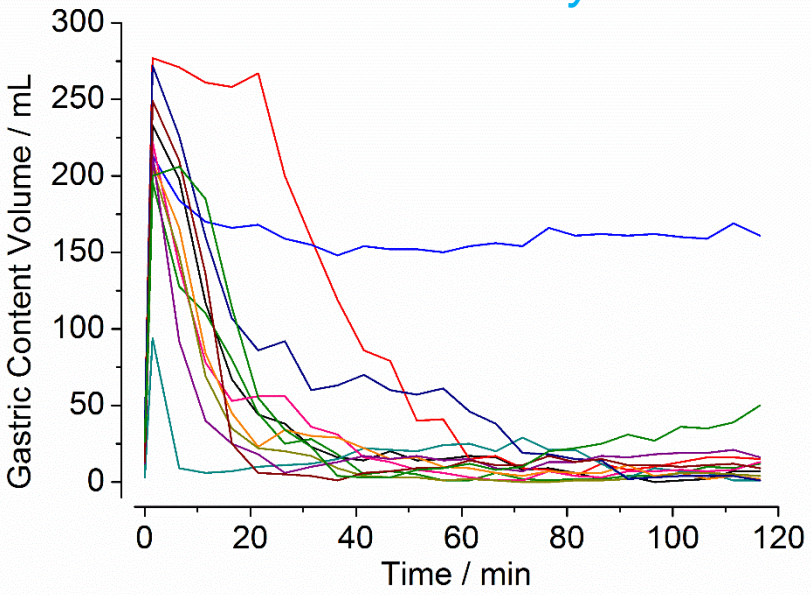
Methods for assessing gastric emptying:

- scintigraphy
- MRI
- telemetric capsules
- breath test
- paracetamol absorption technique
- salivary tracer technique

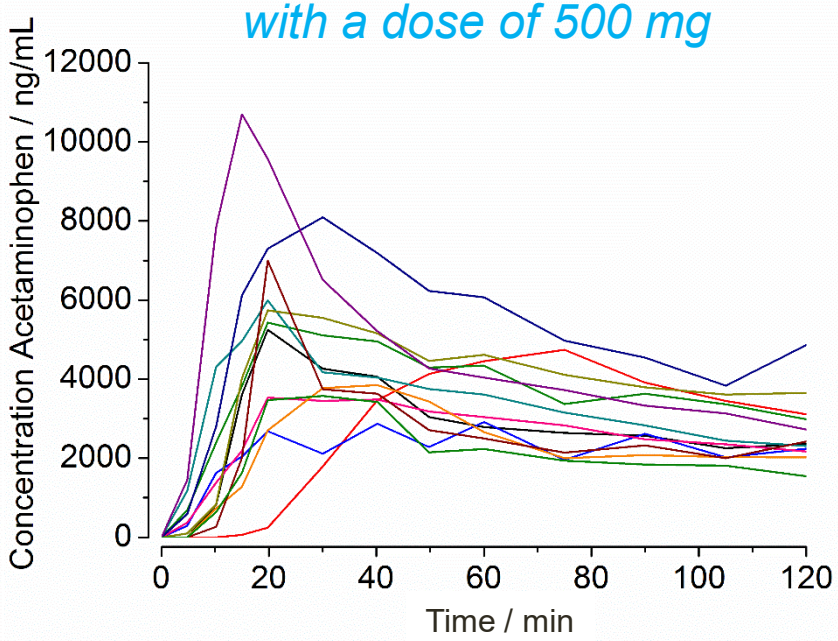
Key Points from BO Session C, Day 1, Question 5

Individual PK profiles can show large variations on the absorption phase (lag time and partial gastric emptying).

Gastric fluid volumes after 240 mL of a non-caloric fluid determined by MRI



Plasma concentrations of paracetamol after 240 mL of an aqueous solution with a dose of 500 mg



Paulick et al. *unpublished*

Key Points from BO Session C, Day 1, Question 5

Individual PK profiles can show large variations on the absorption phase (lag time and partial gastric emptying). Should we co-administer markers of gastric emptying in the clinic and in PBPK tools to improve model performance (reduce noise related to stomach emptying phases)?

a. What are the pitfalls?
b. What key data are missing to accomplish this?

Overall Conclusions