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Drug delivery to the colon: Some considerations from an imaging perspective

Werner.Weitschies@uni-greifswald.de

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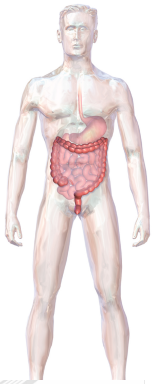
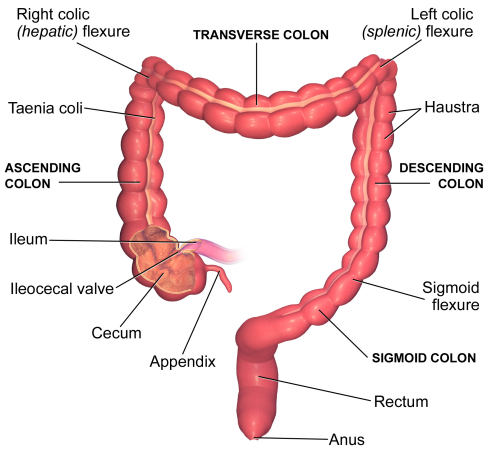
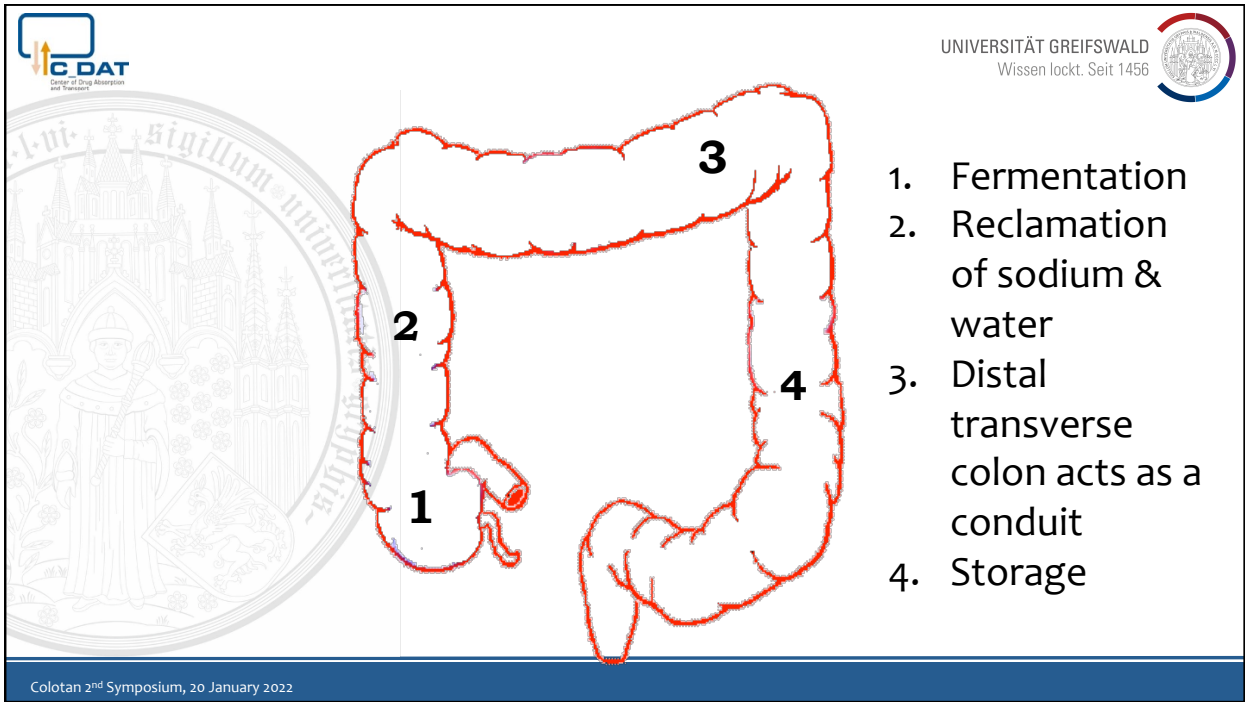
Large intestine

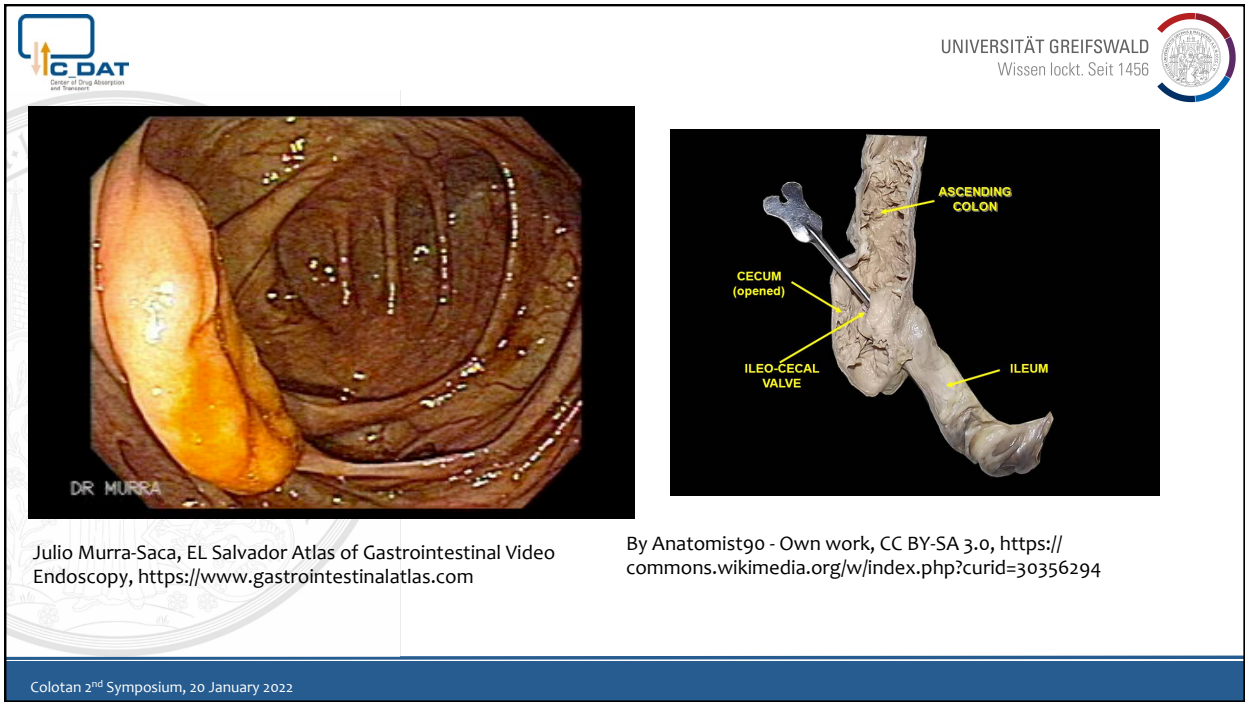




Length: 110 -165 cm

Source: Wikipedia





Julio Murra-Saca, EL Salvador Atlas of Gastrointestinal Video Endoscopy, https://www.gastrointestinalatlas.com

By Anatomist90 - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=30356294

Anatomical variability

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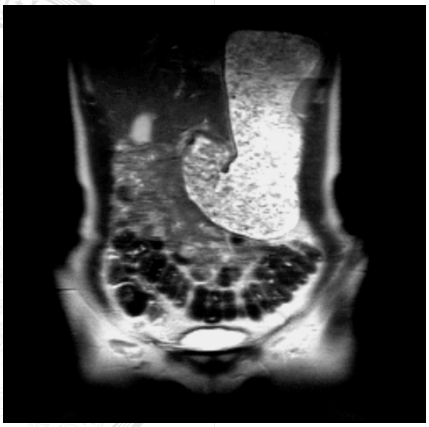
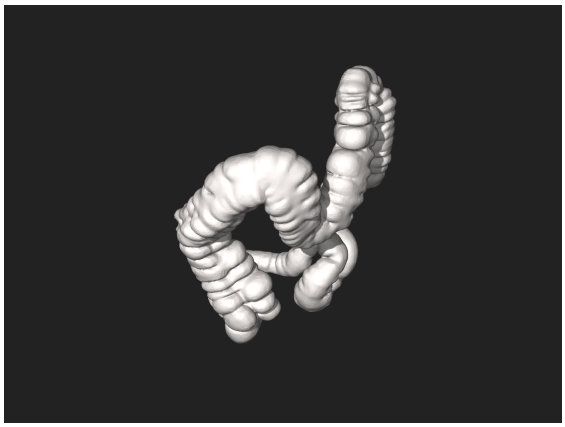


from: Schiller et al., *Aliment Pharmacol Ther*. 2005. 22:971-979



By © Nevit Dilmen, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=68613543

Anatomical variability

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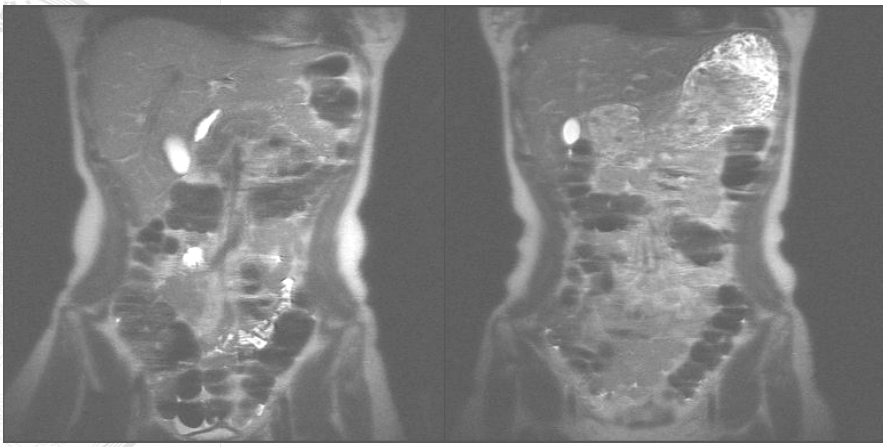

Schiller et al., Aliment Pharmacol Ther. 2005;22:971-979

Colon arrival transit times: Common perception

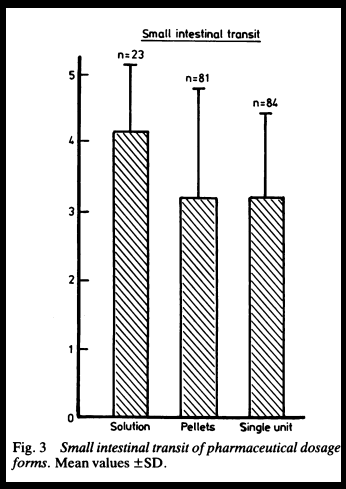

Fig. 3 *Small intestinal transit of pharmaceutical dosage forms*. Mean values ±SD.

Gut, 1986, **27**, 886–892

Alimentary tract and pancreas

Transit of pharmaceutical dosage forms through the small intestine

S S DAVIS, J G HARDY, AND J W FARA

Colon arrival

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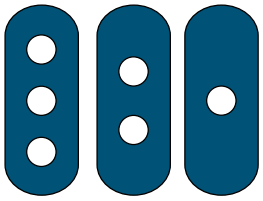
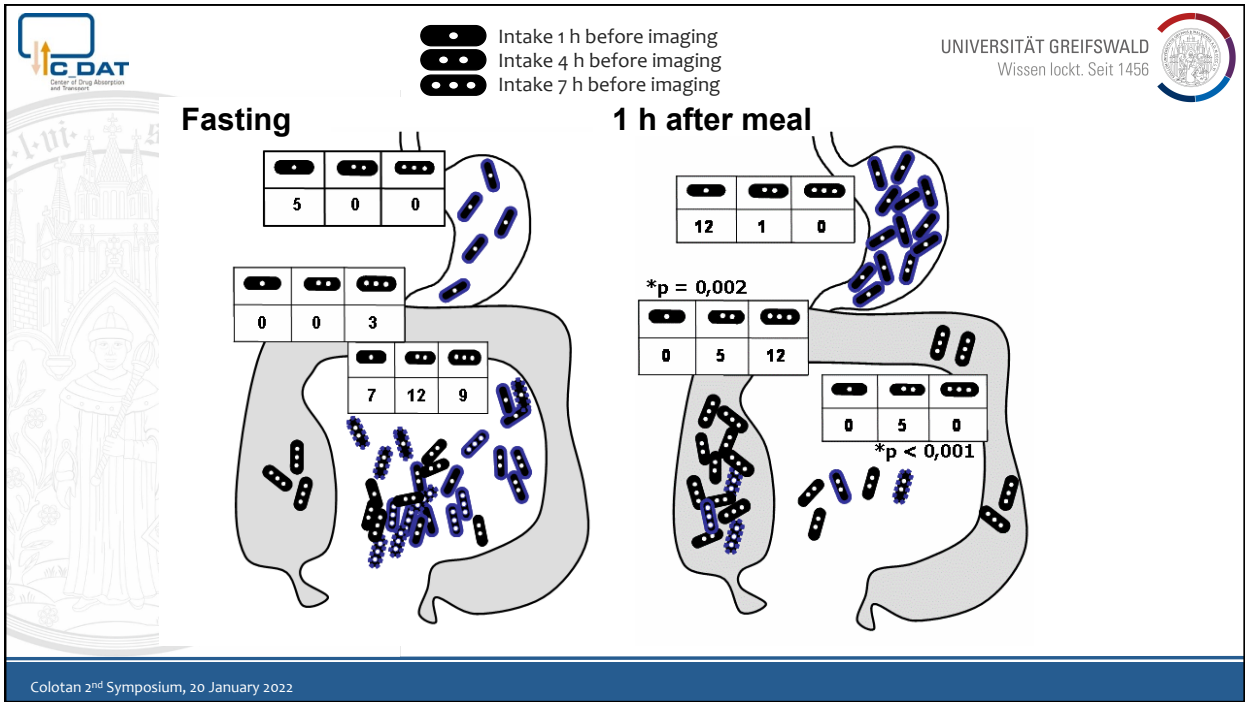
„Dosage form“:

- Solid triglyceride (melting point > 37 °C; glycerol tripalmitate)
- Identification by 1, 2 or 3 incorporated hydrogel pellets (diameter 2 mm)
- Intake conditions:
  - 7 h (three dots) before imaging
  - 4 h (two dots) before imaging
  - 1 h (one dot) before imaging



Schiller et al. *Aliment Pharmacol Ther*. 2005. 22:971-979



Pharmaceutical Research, Vol. 26, No. 2, February 2009 (© 2008)
DOI: 10.1007/s11095-008-9749-2

Research Paper

Meal-Induced Acceleration of Tablet Transit Through the Human Small Intestine

Hala M. Fadda,[1] Emma L. McConnell,[1] Michael D. Short,[2] and Abdul W. Basit[1,3]

Table IV. Gastrointestinal Transit Times of Tablets Administered with the Pre-Feed Regimen in Which the Tablets had Emptied from the Stomach Before Food Arrived at 45 min

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
1	40	72	112
2	12	122	134
4	31	134	165
6	37	91	128
7	28	120	148
10	15	148	163
Median	19	100	130
Interquartile range	14–34	84–124	122–152

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Colon arrival is a function of meal timing!

Situation in Clinical Pharmacology (Phase 1 studies)

- at least 10 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

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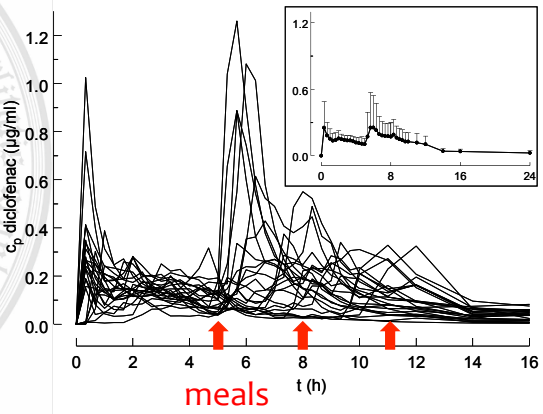
Plasma profiles (24 subjects) after administration of diclofenac ER tablets ("Voltaren retard") under fasting conditions.



Garbacz et al. Eur J Pharm Biopharm. 2008

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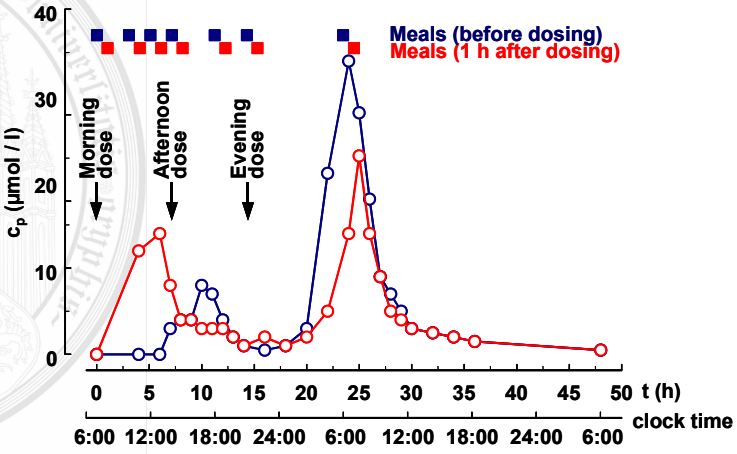
5-ASA plasma concentrations (median, n = 12) after 3 times dosing of 3 each time 3 enteric coated tablets (Claversal, total dose: 4,5 g)



De Mey & Meineke, *Br. J. Clin. Pharmacol.*, 1992

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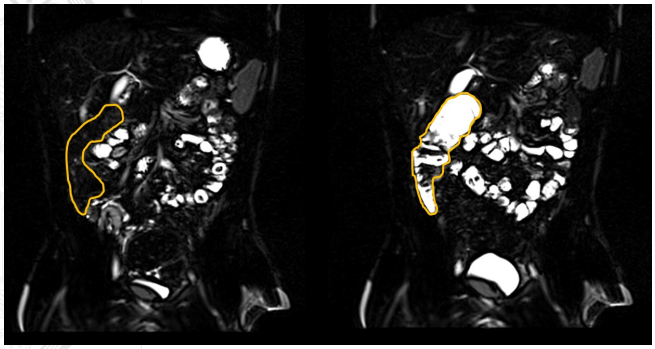
Gastro-ileocecal reflex

Impact of stomach on deeper compartments of GI tract

- Gastric filling influences the filling of the colon
- Gastro-ileal reflex triggered by gastric wall distension and caloric stimulus



T2w MRI of gastrointestinal fluids 20 min and 40 min after intake of 240 mL fructose solution

Grimm et al., Mol. Pharm., 2018

Gastro-ileocecal reflex

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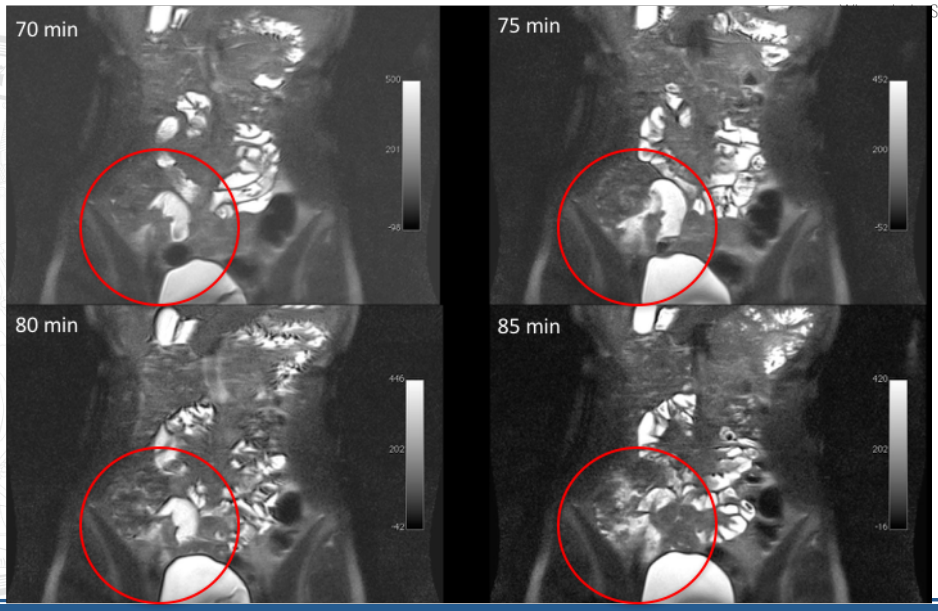

Colon transit

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Colon transit

Colon Transit: Transit times

OCT: 3.9 ± 0.7 h
CTT: 35.6 ± 9.0 h
WGT: 39.5 ± 8.6 h

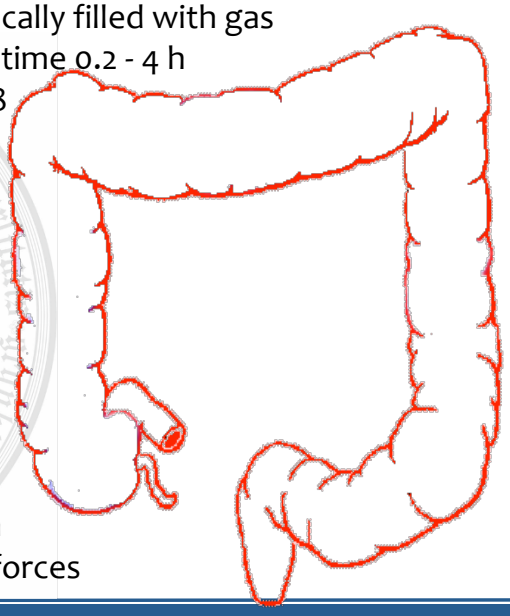
(determined from fecal excretion)

Kolbow et al. J Clin Pharmacol. 2015

Transverse colon:
- periodically filled with gas
- transit time 0.2 - 4 h
- pH 5 - 8

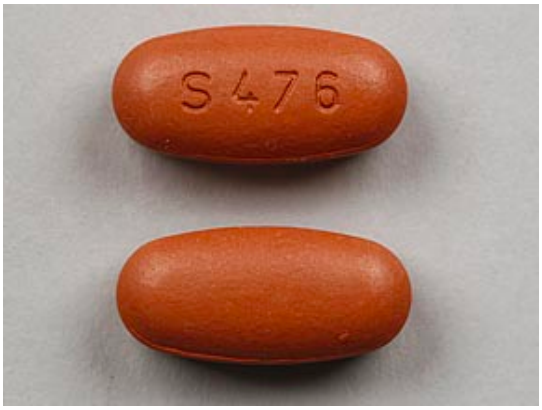
Ascending colon:
- periodically filled with fluid
- transit time 3 - 5 h
- pH 5 - 8

Ileocecal region:
- pH 6.4 - 8
- often stagnation
- high propulsive forces

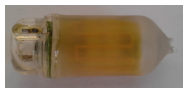


Descending colon & sigmoid colon:
- predominantely feces
- transit time 5-72 h

Wilson Int. J. Pharm. 2010



SmartPill



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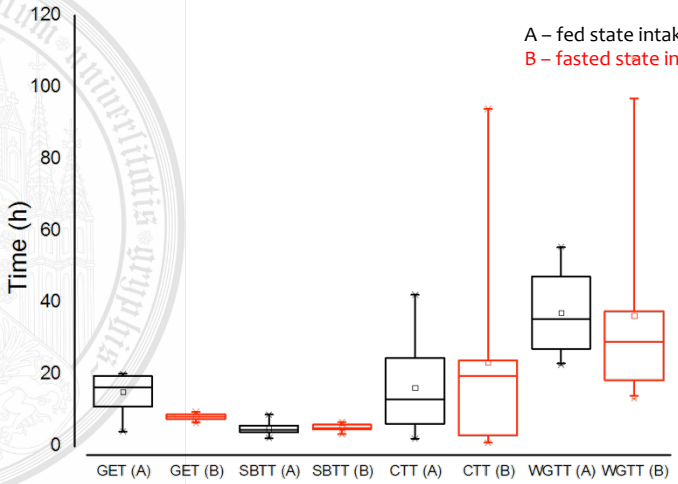

A – fed state intake 8.30 am (n=19)
B – fasted state intake 8.30 am (n=9)

GET .. Gastric emptying time
SBTT .. Small intestinal transit time
CTT .. Colon transit time

box: 50%; whisker: 5-95%; square: mean, asterisks: max/min

Koziolek et al., JCR, 2015, Schneider et al. 2016

Meal intake and colon transport (mass movement)

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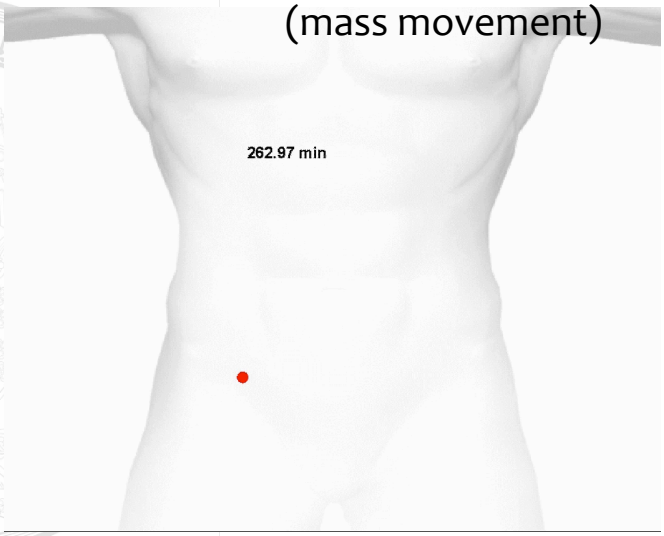

Pellet (1mm)

Start of video sequence: 20 min after lunch

Real time

Anschütz et al., Int. J. Clin. Pharmacol., 2009

Drug absorption from colon

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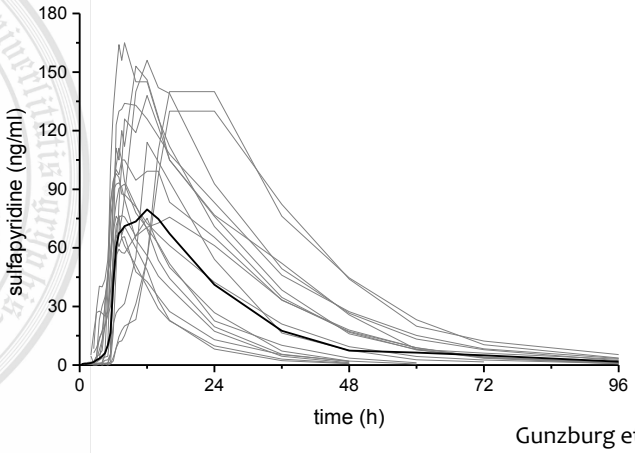
Absorption of sulfapyridine
(after bacterial cleavage of sulfasalazine)



Gunzburg et al., J. Clin. Pharmacol., 2014

Drug absorption from colon

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Some drugs are well absorbed from ascending colon/caecum

For example:

- Dclofenac
- Prednisolone
- Ibuprofen
- Metoprolol
- Nifedipine
- Rivastigmin
- Theophyllin

Drug absorption from colon

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Absorption from transverse colon?

Absorption from descending colon?

Colon imaging: Hurdles

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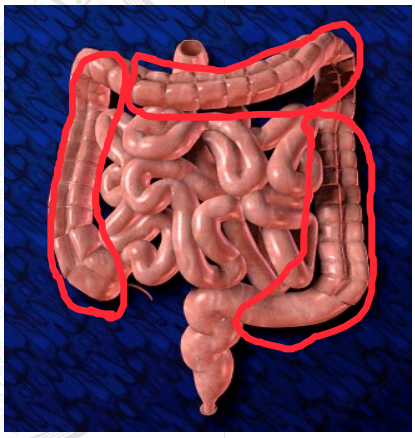

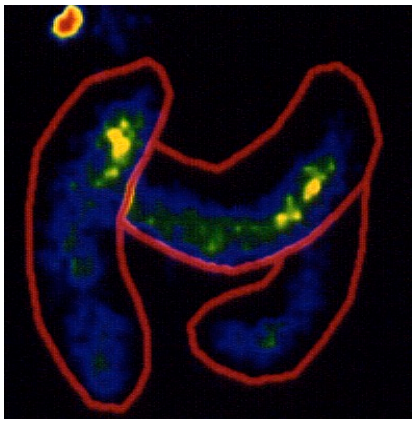

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Going down the intestines: Problems are arising

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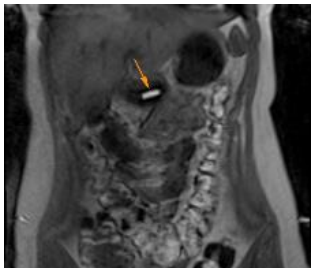
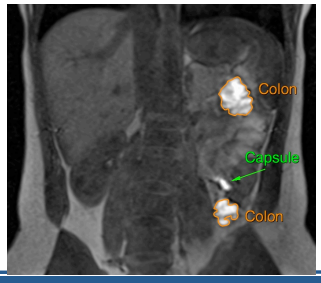
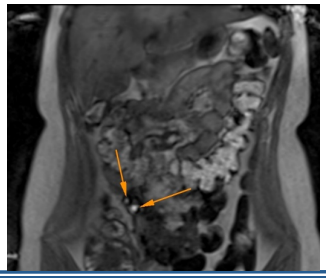
- Colonic tracking is mostly impossible with T1-markers as fecal signal intensity is typically higher than signal derived from contrasting agent







Improvement of labelling technique for colon imaging

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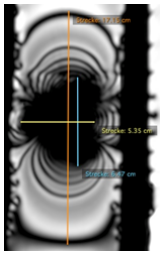
→ Switch to black iron oxide (food additive E172)

- Disadvantage:
  Drug delivery system is no longer not visible, only the artifact ("black hole")



Identifcation and quantification of colonic contents

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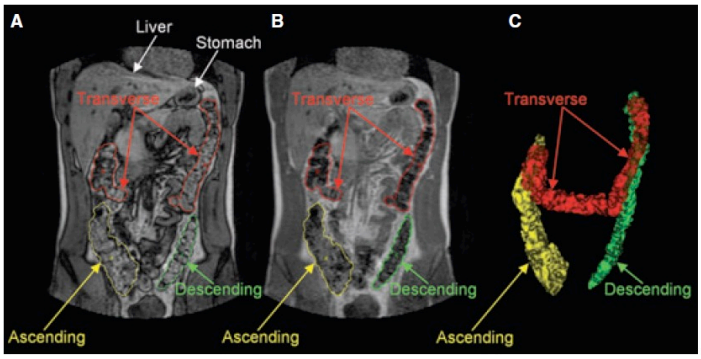
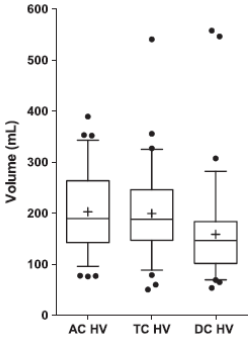


Manual quantification method for colonic volumes including gas!



Pritchard et al. (2014) Neurogastroenterol Motil

Identifcation and quantification of colonic contents

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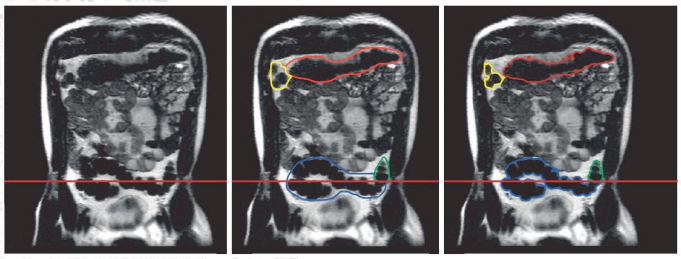
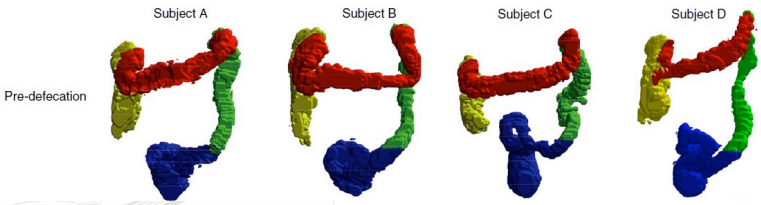


Semiautomatic quantification method for colonic volumes including colonic walls and gas!



Nilsson et al. (2015) Neurogastroenterol Motil

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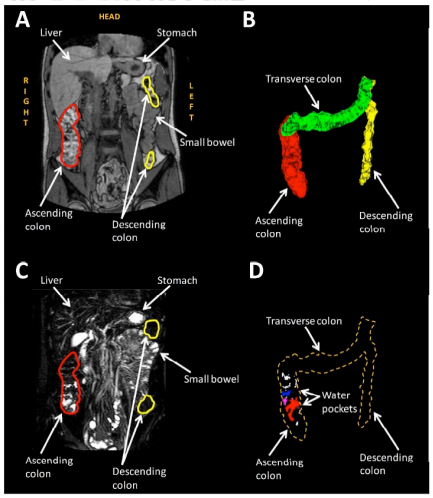
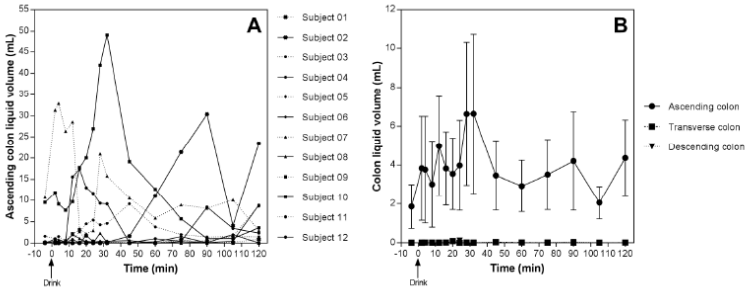
Identifcation and quantification of colonic contents





Murray et al. (2017) Molecular Pharmaceutics