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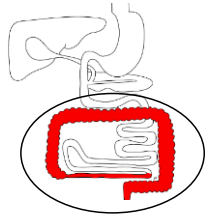
In vivo and in vitro assessment of colonic drug disposition

1

Colonic drug disposition



- Formulation approach
- Low solubility/permeability

- Local activity
- Absorption

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OUTLINE

- In vitro tools: overview
- Celecoxib and Sulindac
  - Colonic permeation (in vitro)
  - Colonic accumulation (in vitro/ex vivo)
  - Metabolism (in situ)
  - Systemic versus gut driven tissue accumulation (in vivo)
  - Characterization of colonic content

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In vitro tools

- Stability (enzymes - faecal contents – colonic contents)
- Uptake
- Permeability

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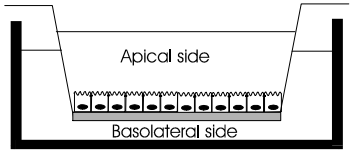
Caco-2



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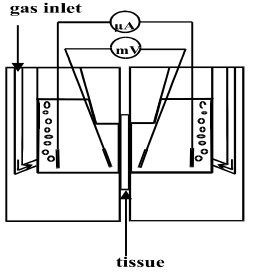
Ussing chamber



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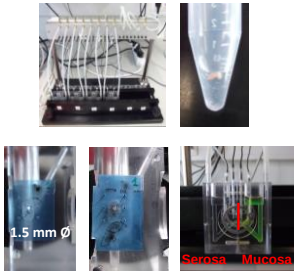
Colonic permeability: Ussing chambers



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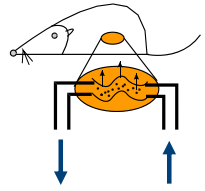
Rat in situ perfusion (colon versus small intestine)



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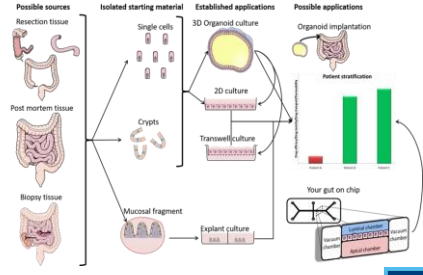
2D and 3D organoids



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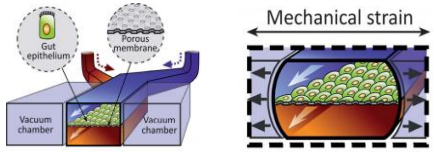
Organ-on-a-chip



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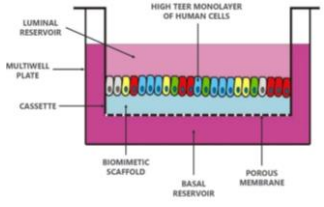
RepliGut®



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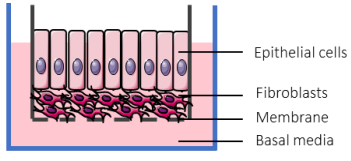
EpiIntestinal



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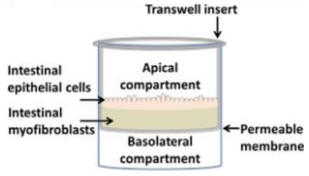
Bilayered architecture



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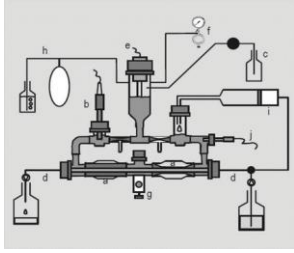
in vitro model of the colon (TIM-2)



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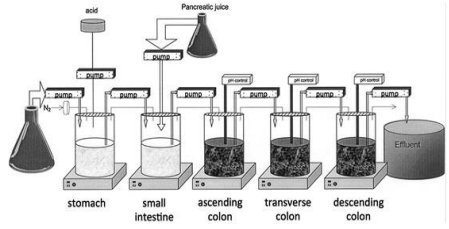
SHIME® (Simulator of Human Intestinal Microbial Ecosystem)



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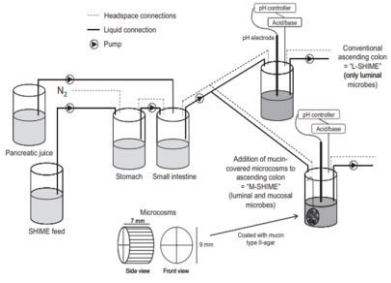
M-SHIME



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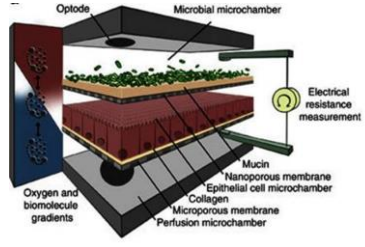
HuMiX: the human–microbial crosstalk model



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pharmaceutics
MDPI
Review

Drug Disposition in the Lower Gastrointestinal Tract: Targeting and Monitoring

Glenn Lemmens [1,†], Arno Van Camp [1,†], Stephanie Kourula [2,†], Tim Vanuytsel [3] and Patrick Augustijns [1,*]

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- In vitro tools: overview
- Celecoxib and Sulindac
  - Colonic permeation (in vitro)
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  - Metabolism (in situ)
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  - Characterization of colonic content

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Colonic diseases – Epidemiologic data

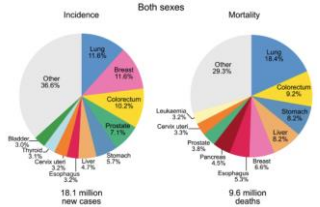

Table II. *Risk reduction - adenomas.*

Trial (reference)	Drug	Duration	Risk reduction
Baron *et al.* (40)	Aspirin 81 mg/d, OR 325 mg/ d	1 year	0.96
Benamouzig *et al.* (41)	Aspirin 160 mg/d, OR 300 mg/d	1 year	0.61
PreSAP (45)	Celecoxib, 400 mg/d	3 years	0.64
APC (44)	Celecoxib, 400 mg/d, OR 800 mg/d	3 years	0.67 (0.43 for higher dose celecoxib)
APPROVe (43)	Rofecoxib 25 mg/d	3 years	0.76

APPROVe, Adenomatous polyp prevention on vioxx; APC, antrochoanal polyp; PreSAP, prevention of sporadic adenomatous polyps.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. Cancer J. Clin. 68, 394–424.

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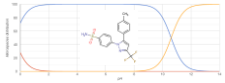
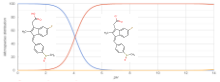
Physico Chemical Properties

Celecoxib



Mw: 381.37 pKa: 10.60
LogP: 4.01 BCS II

Sulindac



Mw: 356,41 pKa: 4.09
LogP: 2.93 BCS II/I

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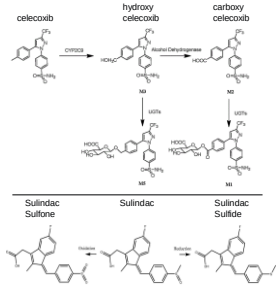
Metabolism



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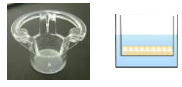
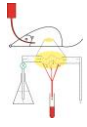
Translational intestinal models



Caco-2


Ussing chambers




In situ perfusion

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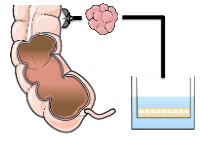
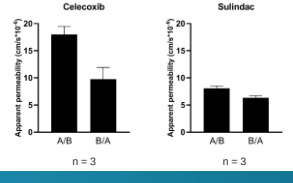
Permeation





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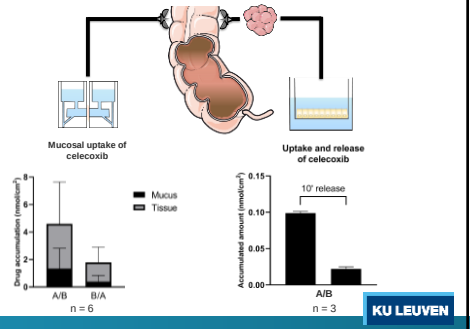
Mucosal accumulation



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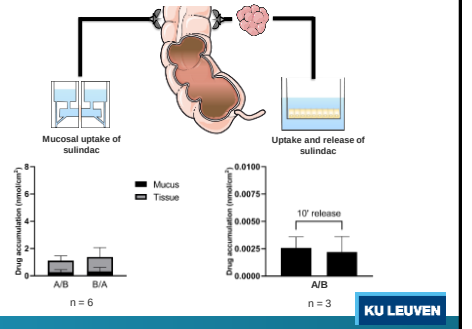
Mucosal accumulation



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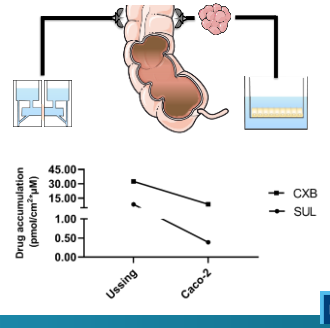
Mucosal accumulation



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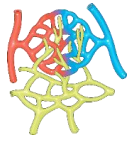
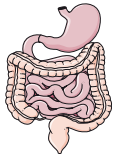
Colonic disposition

Systemic driven accumulation



Gut driven accumulation?



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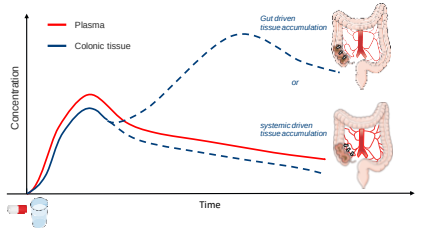
Colonic disposition – set up



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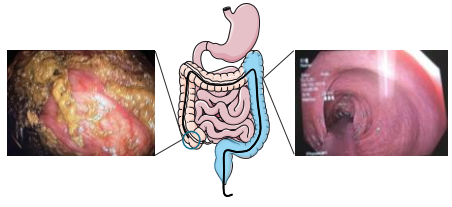
Optimizing colonic cleansing (Presentation Tim Vanuytsel)



- 250 mL enema
- Suction channel of colonoscope for caecal content

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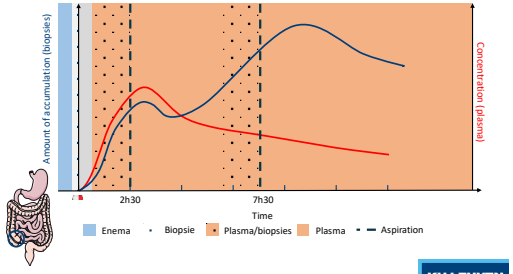
Colonic disposition – set up



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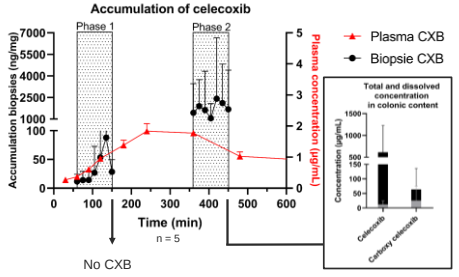
Systemic versus gut driven accumulation



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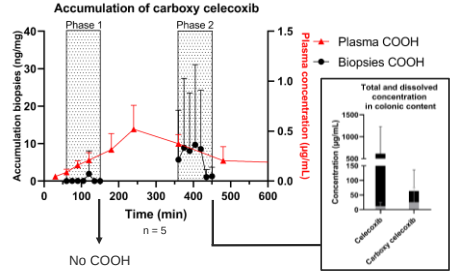
Systemic versus gut driven accumulation



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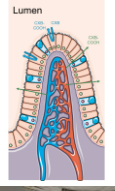
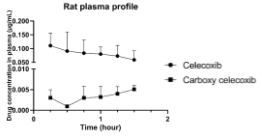
Excretion of Carboxy celecoxib

1) Local biotransformation: **no biotransformation to carboxy celecoxib**

2) Extensive secretion towards the gut from the systemic circulation: **below the LOD**

3) Biliary excretion: **0.83 ± 0.44 % of the intravenous dose was recovered in bile**
   - 1.08% CXB
   - 10.43% CXB-OH
   - 87.62% CXB-COOH





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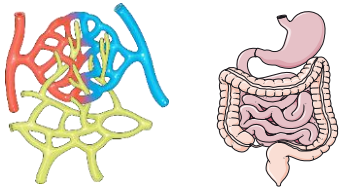
Systemic versus gut driven accumulation

Concentrations of celecoxib required in most cell culture experiments to induce apoptosis: 10 –100 µM*



*Grösch, S., Maier, T.J., Schiffmann, S., Geisslinger, G., 2006. Cyclooxygenase-2 (COX-2)-independent Anticarcinogenic Effects of Selective COX-2 Inhibitors. JNCI J. Natl. Cancer Inst. 98, 736–747. https://doi.org/10.1093/jnci/djj208

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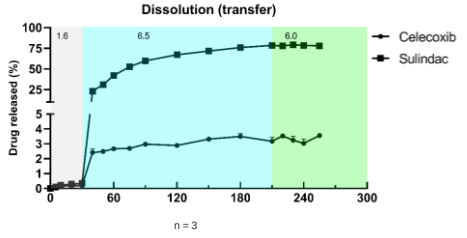
Colonic disposition



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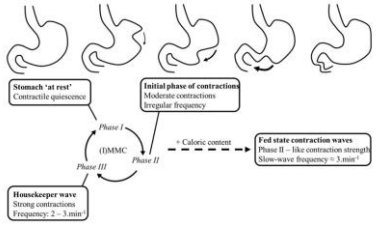
Systemic versus gut driven accumulation



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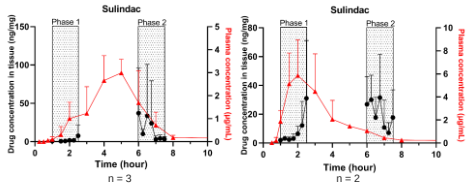
Systemic versus gut driven accumulation

Group 1
Slow transfer to intestine

Group 2
Fast transfer to intestine



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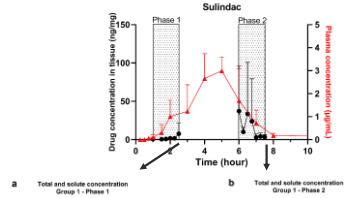
Systemic versus gut driven accumulation

Group 1 - Slow transfer to intestine



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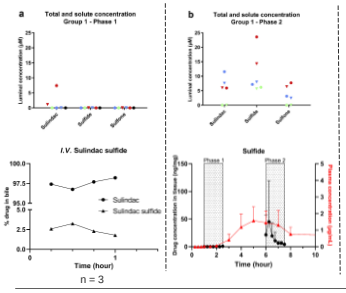
Metabolization

2.5 h after intake ⟶ 7.5 h after intake ⟶ Faeces



19% of dose*

- 1% SUL
- 99% IDE/ONE

Bacterial Metabolization

*Duggan, D.E., Hare, L.E., Ditzler, C.A., Lei, B.W., Kwan, K.C., 1977. The disposition of sulindac. Clin. Pharmacol. Ther. 21, 326–335. https://doi.org/10.1002/cpt1977213326

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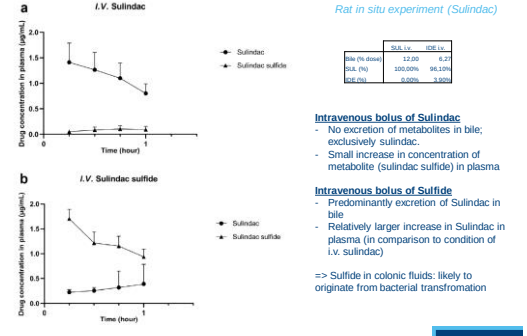

Rat in situ experiment (Sulindac)

	SUL i.v.	IDE i.v.
Bile (% dose)	12.00	6.27
SUL (%)	100.00%	96.10%
IDE (%)	0.00%	3.90%

Intravenous bolus of Sulindac
- No excretion of metabolites in bile; exclusively sulindac.
- Small increase in concentration of metabolite (sulindac sulfide) in plasma

Intravenous bolus of Sulfide
- Predominantly excretion of Sulindac in bile
- Relatively larger increase in Sulindac in plasma (in comparison to condition of i.v. sulindac)

=> Sulfide in colonic fluids: likely to originate from bacterial transfromation

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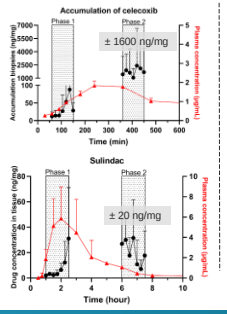
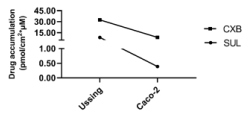
Systemic versus gut driven accumulation

In vivo



In vitro/ex vivo



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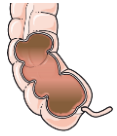
Characterization of colonic content



Study	Caecum/right colon pH
Watson, 1972[2]	5.5–7.5
Bown, 1974[3]	6.0
Evans, 1988[4]	6.4
Fallingborg, 1989[5]	5.7
Raimundo, 1992[7]	6.7
Fallingborg, 1998[9]	5.8
Sasaki, 1997[9]	6.8
Press, 1998[10]	6.1
Ewe, 1999[11]	6.2

➡ pH: 6.44 ± 0.59

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Fallingborg, J., 1999. Intraluminal pH of the human gastrointestinal tract. Dan. Med. Bull. 46, 183–196

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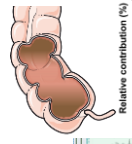
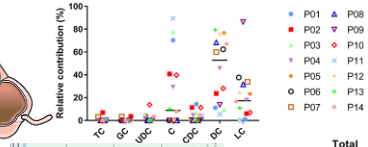
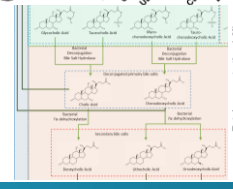
Characterization of colonic content

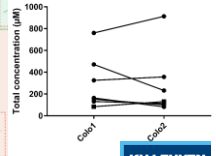
Bile salts colonic content







Total



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OUTLINE

- In vitro tools: overview
- Celecoxib and Sulindac
  - Colonic permeation (in vitro)
  - Colonic accumulation (in vitro/ex vivo)
  - Metabolism (in situ)
  - Systemic versus gut driven tissue accumulation (in vivo)
  - Characterization of colonic content

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Future perspectives

Intestinal disposition of:

- Budesonide (BCS II)
  Budesonide Ferring/ Budenofalk/ Entocort/PPI
- Mesalazine (BCS III)
  Claversal/ Pentasa/ Mezavant
- Naproxen

- Organoids (functionality transporters and enzymes)
- Use of in situ perfusion (rodents)
- Characterisation of colonic contents (similar collection conditions)

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Glenn Lemmens [a,d], Joachim Brouwers [a,d], Jan Snoeys [b], Patrick Augustijns [a,*], Tim Vanuytsel [c]

[a] Drug Delivery and Disposition, KU Leuven, Gasthuisberg O&N II, Herestraat 49 – Box 921, 3000 Leuven, Belgium
[b] Drug Metabolism and Pharmacokinetics, Janssen Biotă Turnhoutseweg 30, 2340 Beerse, Belgium
[c] Translational Research Center for Gastrointestinal Disorders, TARGID, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

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Glenn Lemmens[a,1], Joachim Brouwers[a,1], Jan Snoeys[b], Patrick Augustijns[a,*], Tim Vanuytsel[c]

[a] Drug Delivery and Disposition, KU Leuven, Gasthuisberg O&N II, Herestraat 49 – box 921, 3000, Leuven, Belgium
[b] Drug Metabolism and Pharmacokinetics, Janssen Biotă, Turnhoutseweg 30, 2340, Beerse, Belgium
[c] Translational Research Center for Gastrointestinal Disorders, TARGID, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

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