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Colonic drug permeability in humans and predictive preclinical models

David Dahlgren

COLOTAN 2022

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Who am I?

- David Dahlgren, MSc Pharmacy, 2013
- PhD, Biopharmaceutics, Uppsala University, 2018
- Post Doc, GI physiology, Uppsala University, 2020
- Researcher, GI physiology & Translational Drug Discovery and Development, Uppsala University, 2021

AZ partners

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My research areas

- Cancer
  - Hepatocellular carcinoma
- GI physiology
  - Luminal, hormonal and neural regulation of intestinal fluid flux, bicarbonate secretion, motility, and permeability
- GI pathophysiology
  - Characterization and treatment of intestinal barrier dysfunction and chemotherapy-induced mucositis
- Biopharmaceutics:
  - Disposition of PROTACs – PhD position available, deadline application in 8 h
  - Permeation enhancing excipients and enabling nano formulations
  - **In vivo regional intestinal drug permeability**

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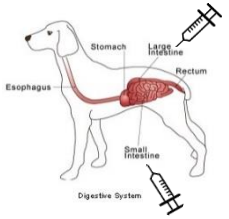
In vivo regional intestinal drug permeability

Human



Regional Intestinal Permeability in Dogs: Biopharmaceutical Aspects for Development of Oral Modified-Release Dosage Forms

David Dahlgren,[†] Carl Roos,[†] Pernilla Johansson,[‡] Anders Lundqvist,[‡] Christer Tannergren,[‡] Bertil Abrahamsson,[‡] Erik Sjögren,[†] and Hans Lennernäs[*,†]

[†]Department of Pharmacy, Uppsala University, Uppsala SE-751 23, Sweden
[‡]AstraZeneca R&D, Gothenburg SE-431 50, Sweden

REVIEW

Direct *In Vivo* Human Intestinal Permeability (P_{eff}) Determined with Different Clinical Perfusion and Intubation Methods

DAVID DAHLGREN, CARL ROOS, ERIK SJÖGREN, HANS LENNERNÄS

Human *in Vivo* Regional Intestinal Permeability: Quantitation Using Site-Specific Drug Absorption Data

Erik Sjögren,* David Dahlgren, Carl Roos, and Hans Lennernäs

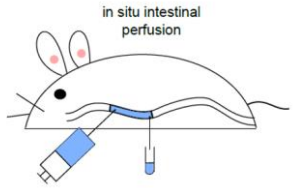
Department of Pharmacy, Biopharmaceutic Research Group, Uppsala University, SE-751 23 Uppsala, Sweden

Supporting Information

Regional Intestinal Permeability of Three Model Drugs in Human

David Dahlgren,[†] Carl Roos,[†] Anders Lundqvist,[‡] Bertil Abrahamsson,[‡] Christer Tannergren,[‡] Per M. Hellström,[§] Erik Sjögren,[†] and Hans Lennernäs[*,†]

Predictive models



pharmaceutics

MDPI

Article

Regional Intestinal Drug Permeability and Effects of Permeation Enhancers in Rat

David Dahlgren [1], Maria-Jose Cano-Cebrián [2], Tobias Olander [1], Mikael Hedeland [3,4], Markus Sjöblom [5] and Hans Lennernäs [1,*]

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Rat intestinal drug permeability: A status report and summary of repeated determinations

I.R. Dubbelboer, D. Dahlgren, E. Sjögren, H. Lennernäs*

Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden

molecular pharmaceutics

Article

pubs.acs.org/molecularpharmaceutics

Regional Intestinal Permeability in Rats: A Comparison of Methods

Carl Roos,[†] David Dahlgren,[†] Erik Sjögren,[†] Christer Tannergren,[‡] Bertil Abrahamsson,[‡] and Hans Lennernäs[*,†]

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Evaluation of drug permeability calculation based on luminal disappearance and plasma appearance in the rat single-pass intestinal perfusion model

D. Dahlgren[a], C. Roos[a], K. Peters[a], A. Lundqvist[b], C. Tannergren[b], E. Sjögren[a], M. Sjöblom[c], H. Lennernäs[a,*]

Outline

- **Background**
  - **Intestinal drug absorption**
  - **Permeability**
  - **Regional intestinal differences**
- **Human permeability data and studies**
- **Preclinical studies**
  - **Dog**
  - **Rat**
- **Permeation enhancer colon**

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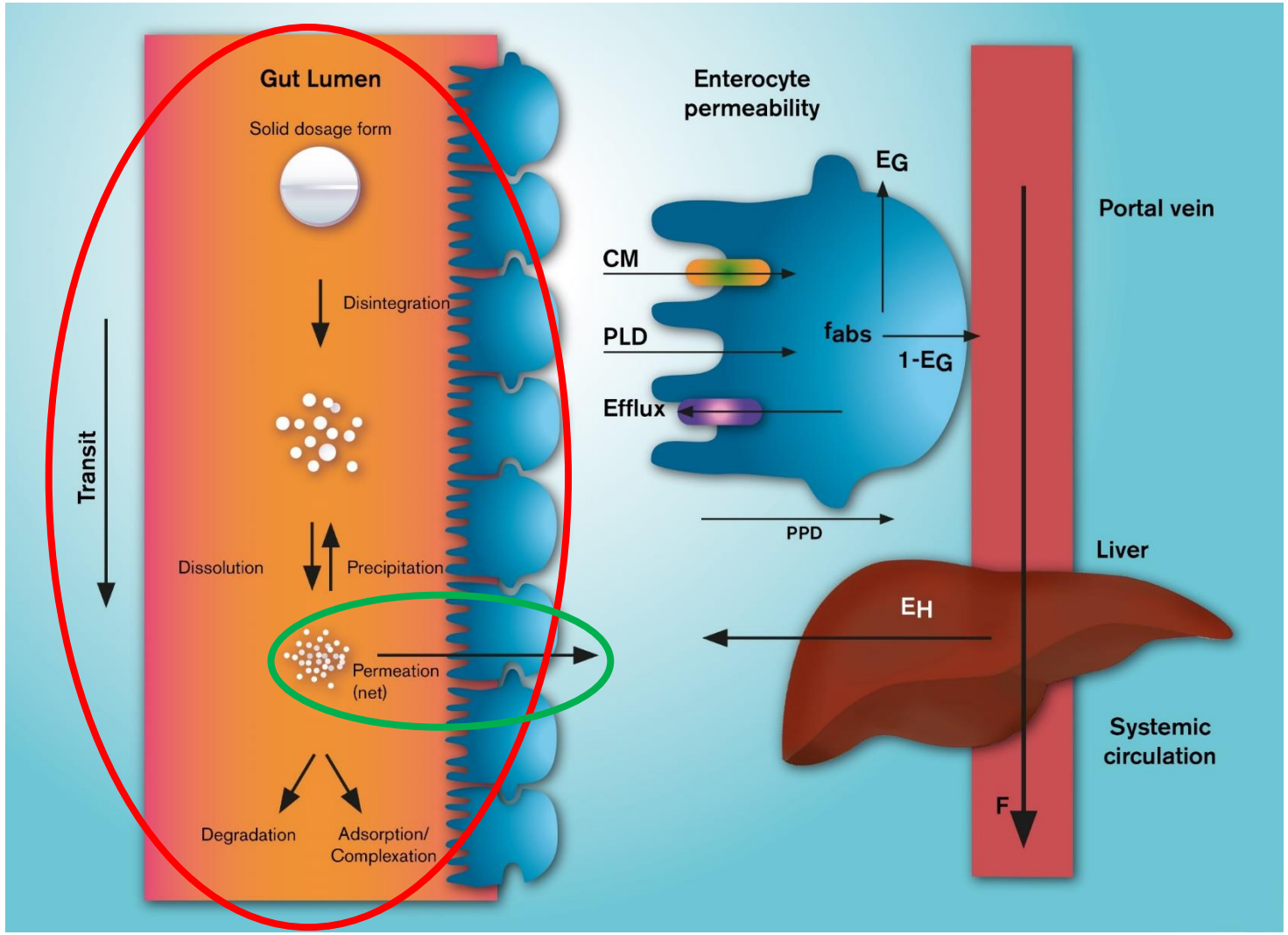
Intestinal drug absorption



- Processes determining fraction absorbed (f_{abs})
- Permeability is the net transport rate (cm/s) of a dissolved molecule across the mucosal epithelium

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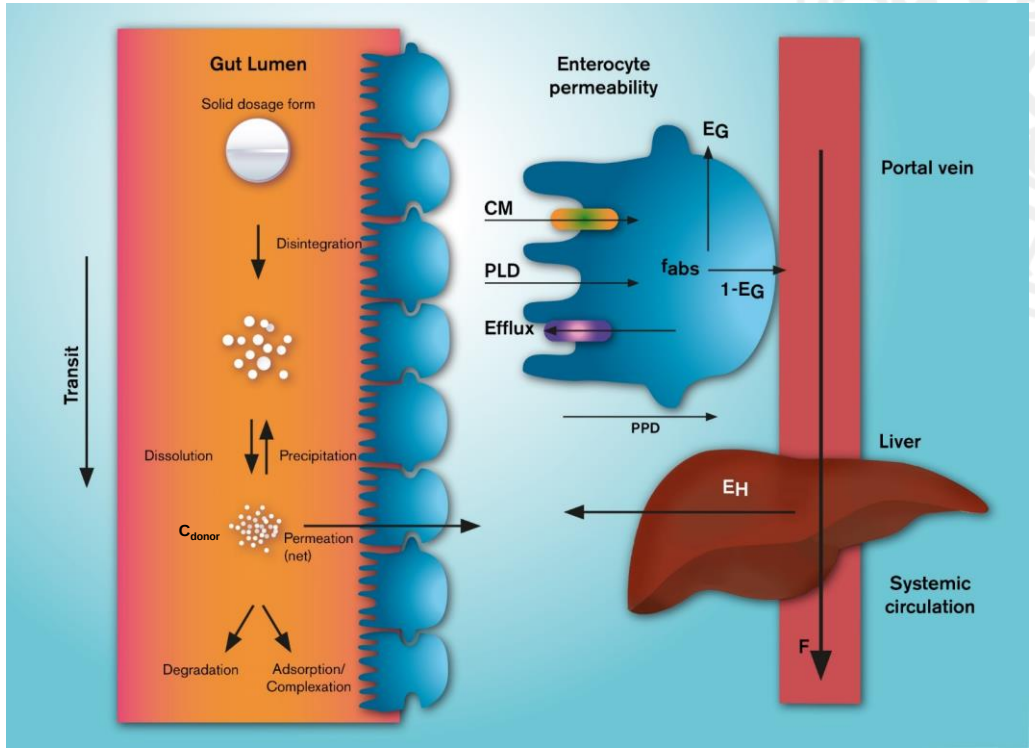
Flux and Permeability

$$J = P\,C_{donor} \Leftrightarrow P = \frac{J}{C_{donor}}$$

J = Flux (mass/time/area)
C_{donor} = Concentration (mass/volume)
P = Permeability (length/time)



Permeability (P) is the **intrinsic parameter** of a solute that **relates flux** (J), to the **concentration gradient** (C_{donor}) across a barrier (lumen-to-blood)

Permeability is different depending on conditions – pH, transporter saturation, **intestinal site**

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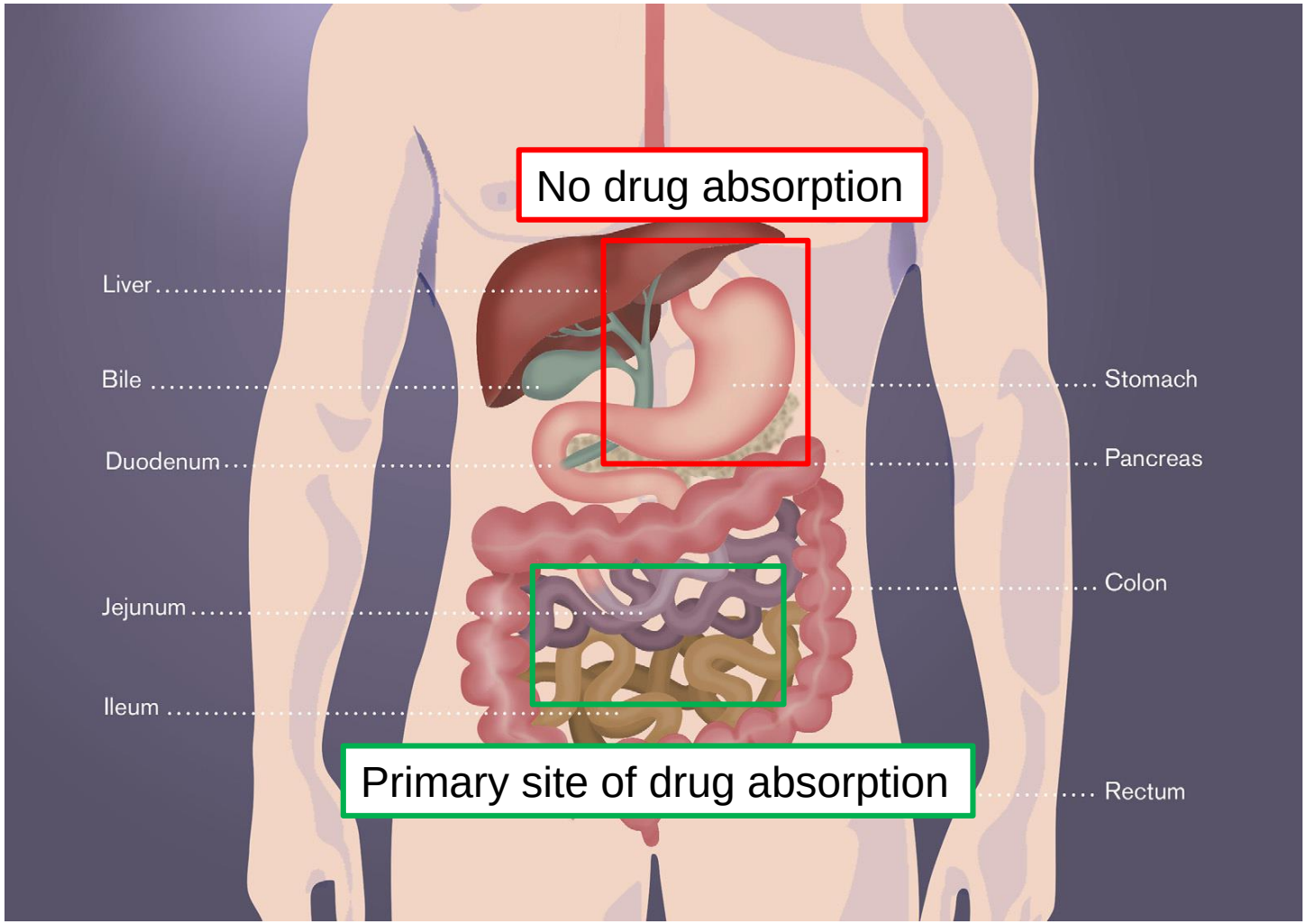
Gastrointestinal anatomy



Lengths (in vivo):

Small intestine	≈ 3 m
Colon	≈ 1.5 m

Transit:

Small intestine	≈ 3-4 h
Colon	≈ 8-36 h

But colon can be important!

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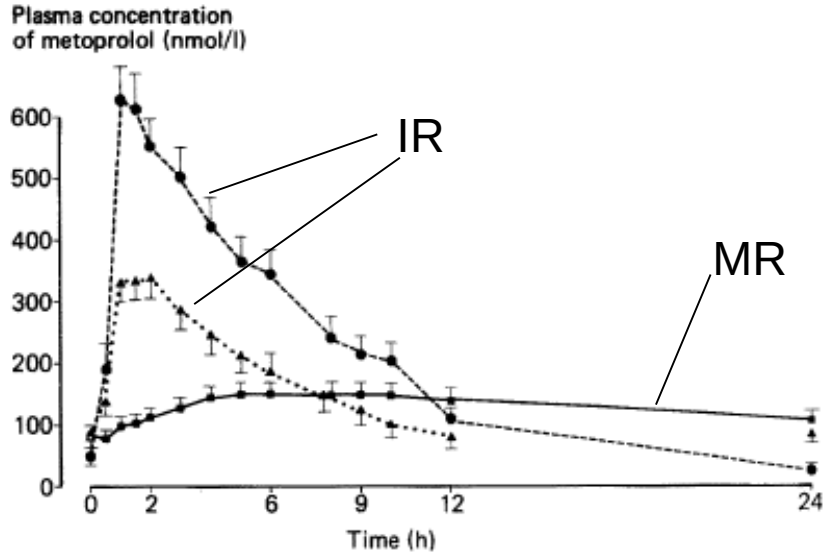
Why is colon interesting?

Drugs incompletely absorbed in the small intestine – low solubility and/or permeability

Drugs intended to be released in the colon - modified-release (MR) dosage forms



Why MR?

- ✓ Once daily treatment
- ✓ Better compliance
- ✓ Consistent 24 h effect
- ✓ Fewer side effects

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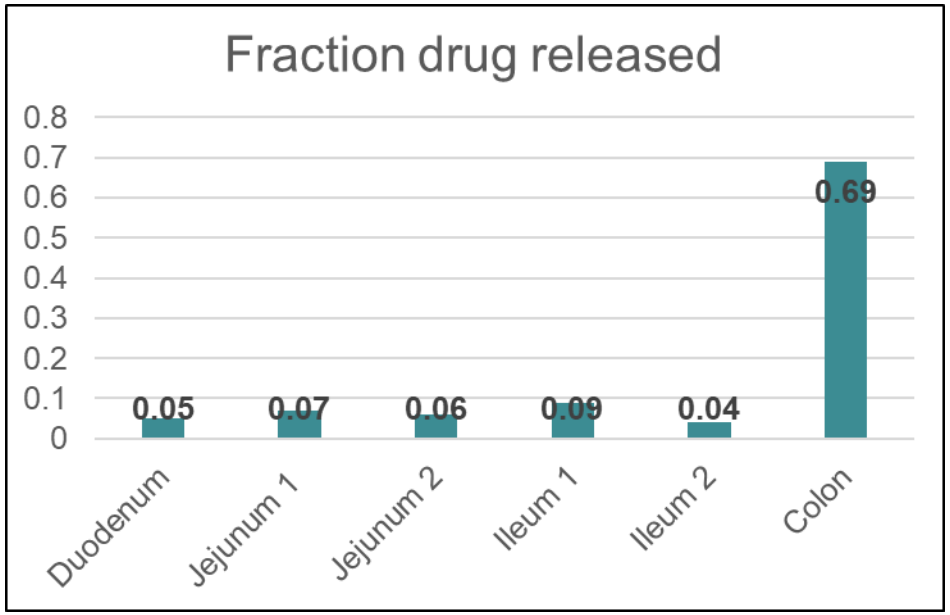
Modified-release dosage forms

Drug release > SI transit (≈3h)



Idealized example showing that 69% of a drug is released in the colon if the drug release is 10% per hour)

Development of MR formulations often (65%) fail because of low colonic absorption[1]

We need to be able to predict human colonic permeability!

Connor, A., King, G., & Jones, K. (2007). Evaluation of human regional bioavailability to assess whether modified release development is feasible. Proc AAPS, 9(S2), 724

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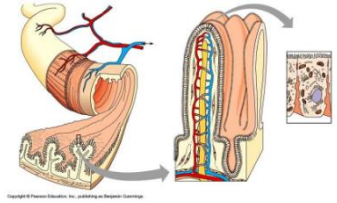
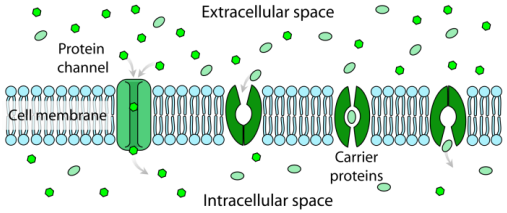
Why regional differences in permeability?

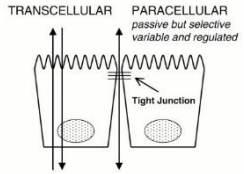
Intestinal surface area



Transport protein abundance

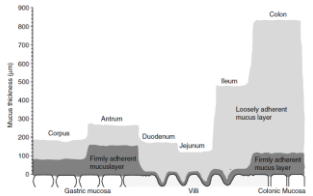


Paracellular space

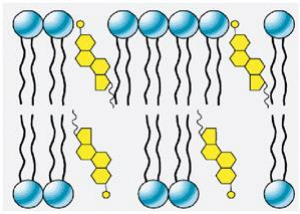


Luminal pH

Mucus layer, and aqueous boundary layer, thickness



Lipoidal cell membrane properties



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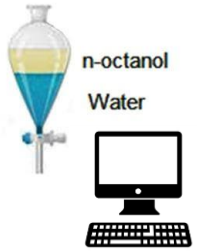
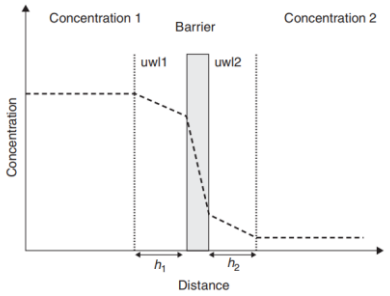
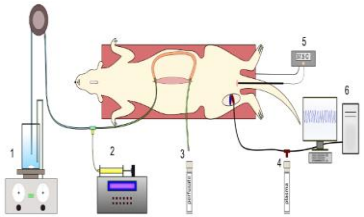
Preclinical permeability models



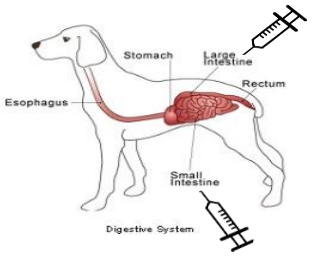
Phys-Chem
QSAR
Computational



Diffusion chamber
(Caco-2, Ussing)



In situ
(SPIP, closed loop)



In vivo
(dog, pig)

Lower complexity → Higher complexity

Prediction of human permeability (and f_{abs})

Not validated with regard to regional differences in human permeability

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Human regional permeability

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Summary of all human SPIP data - review

REVIEW

Direct *In Vivo* Human Intestinal Permeability (P_{eff}) Determined with Different Clinical Perfusion and Intubation Methods

DAVID DAHLGREN, CARL ROOS, ERIK SJÖGREN, HANS LENNERNÄS

Department of Pharmacy, Uppsala University, Uppsala, Sweden

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ABSTRACT: Regional *in vivo* human intestinal effective permeability (P_{eff}) is calculated by measuring the disappearance rate of substances during intestinal perfusion. P_{eff} is the most relevant parameter in the prediction of rate and extent of drug absorption from all parts of the intestine. Today, human intestinal perfusions are not performed on a routine basis in drug development. Therefore, it would be beneficial to increase the accuracy of the *in vitro* and *in silico* tools used to evaluate the intestinal P_{eff} of novel drugs. This review compiles historical P_{eff} data from 273 individual measurements of 80 substances from 61 studies performed in all parts of the human intestinal tract. These substances include: drugs, monosaccharaides, amino acids, dipeptides, vitamins, steroids, bile acids, ions, fatty acids, and water. The review also discusses the determination and prediction of P_{eff} using *in vitro* and *in silico* methods such as quantitative structure–activity relationship, Caco-2, Ussing chamber, animal intestinal perfusion, and physiologically based pharmacokinetic (PBPK) modeling. Finally, we briefly outline how to acquire accurate human intestinal P_{eff} data by deconvolution of plasma concentration–time profiles following regional intestinal bolus dosing. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: absorption; bioavailability; biopharmaceutics classification system; human intestinal permeability; intestinal perfusion; intestinal transporters; oral drug delivery; pharmacokinetics; physiologically based pharmacokinetic modeling

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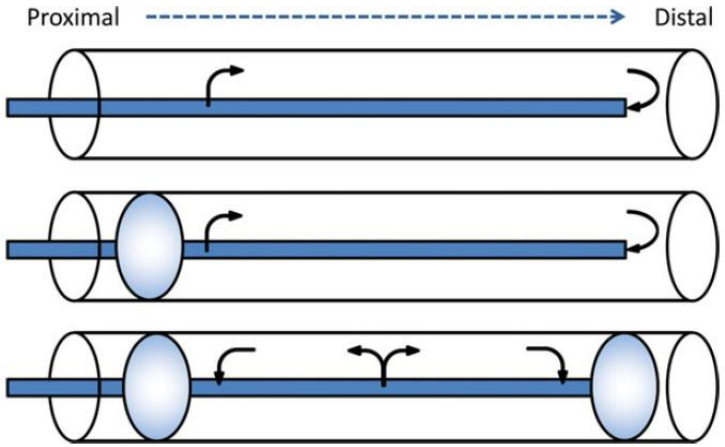
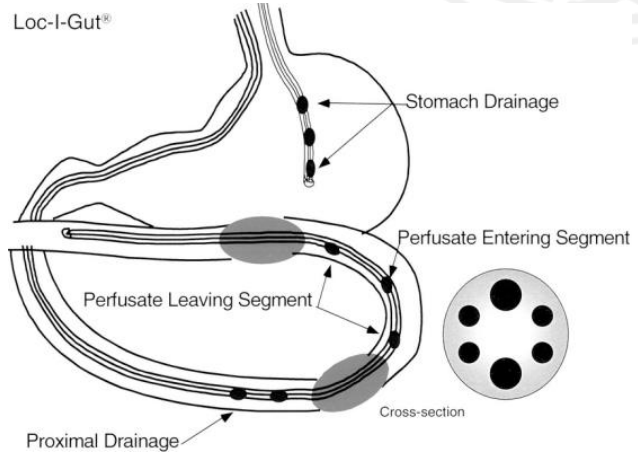
Summary of all human SPIP data - review

Single-pass intestinal perfusion (SPIP) model

Multi-lumen tubes





Direct determination of intestinal effective permeability (P_{eff}) based on *luminal drug disappearance*

$$P_{\mathrm{eff}} = Q_{\mathrm{in}} \times \frac{(C_{\mathrm{in}} - C_{\mathrm{out}})}{(C_{\mathrm{out}} * Area)}$$

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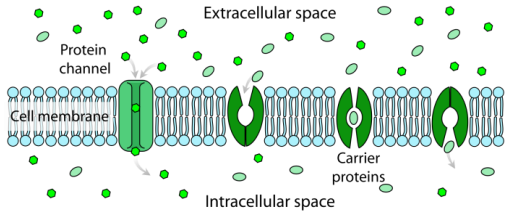
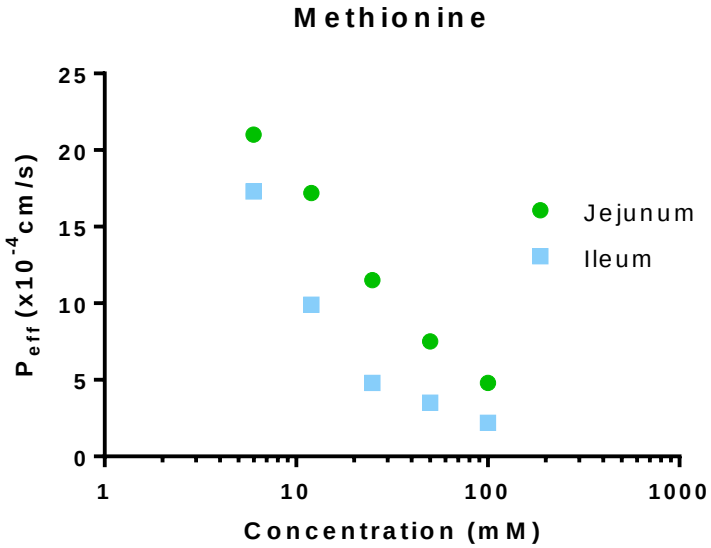
Summary of all human SPIP data - review

273 P_{eff} calculations

- Vitamins
- Dipeptides
- Amino acids
- Fatty acids
- Sugars
- Steroids
- Ions
- Water
- Drugs (jejunum)
- Drugs (jejunum vs. ileum)
- Drugs (Colon)

Amino acids are absorbed with transporter proteins





Regional and concentration dependent P_{eff}

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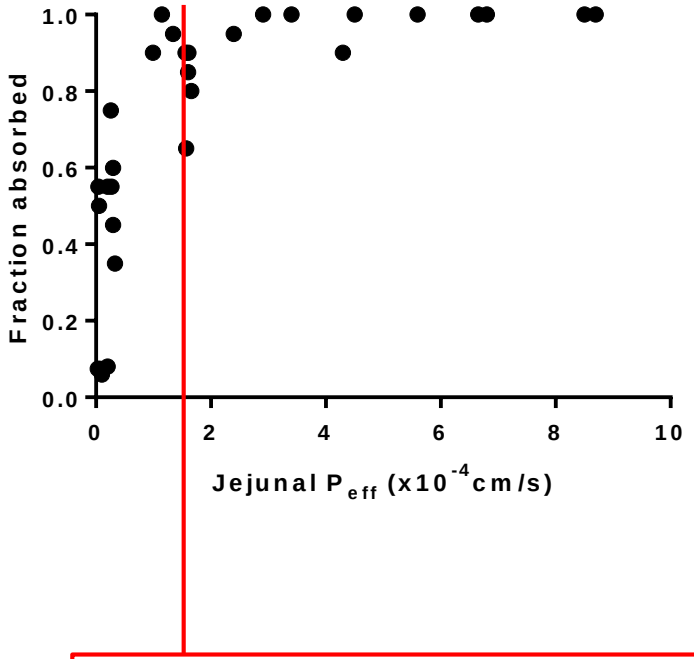
Summary of all human SPIP data - review

273 P_{eff} calculations

- Vitamins
- Dipeptides
- Amino acids
- Fatty acids
- Sugars
- Steroids
- Ions
- Water
- **Drugs (jejunum)**
- Drugs (jejunum vs. ileum)
- Drugs (Colon)



Cut-off at a jejunal P_{eff} of
≈ **1.5** x 10^{-4} cm/s → f_{abs} > 90%

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Summary of all human SPIP data - review

273 P_{eff} calculations

- Vitamins
- Dipeptides
- Amino acids
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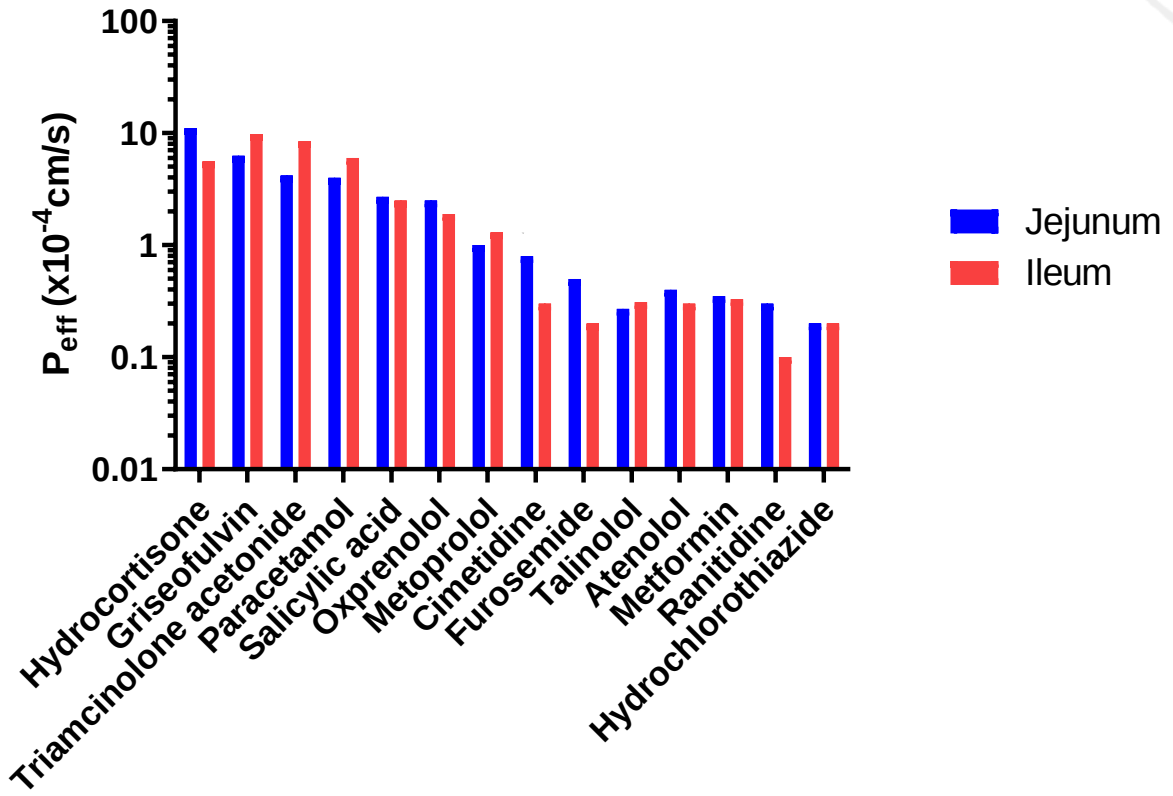
- Sugars
- Steroids
- Ions
- Water
- Drugs (jejunum)
- **Drugs (jejunum vs. ileum)**
- Drugs (Colon)



Small differences in drug P_{eff} between jejunum and ileum

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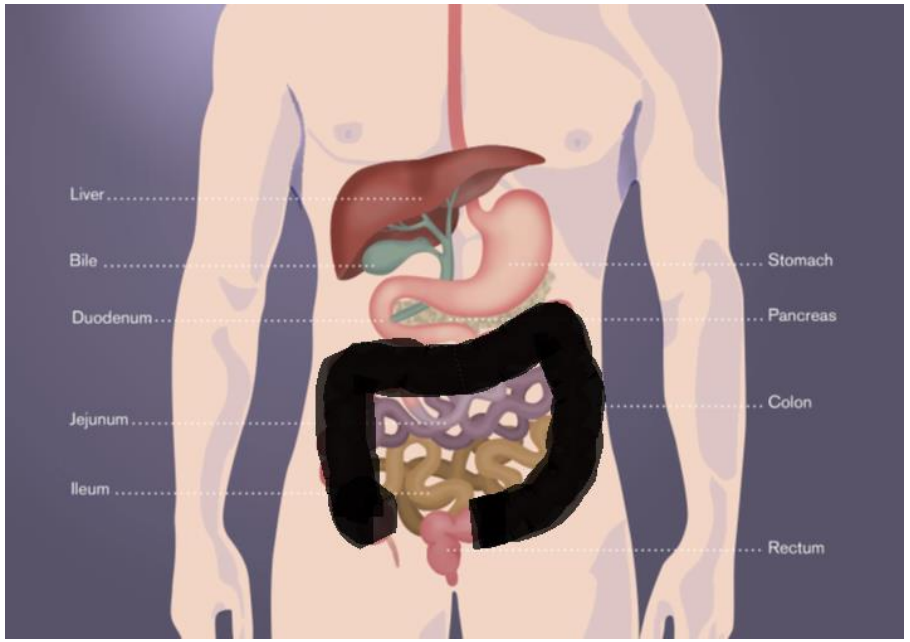
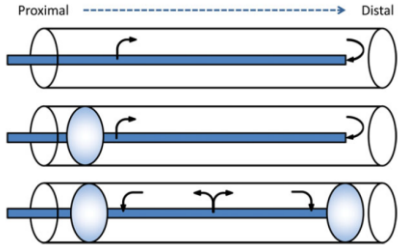
Summary of all human SPIP data - review

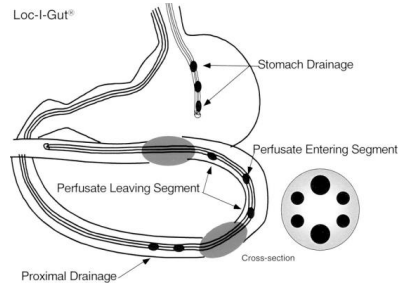
273 P_{eff} calculations

- Vitamins
- Dipeptides
- Amino acids
- Fatty acids
- Sugars
- Steroids
- Ions
- Water
- Drugs (jejunum)
- Drugs (jejunum vs. ileum)
- **Drugs (Colon)**

No colonic drug P_{eff} data!
“black-box”







Alternative methods are needed determine human colonic P_{eff}

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New method for determining human in vivo P_{eff}

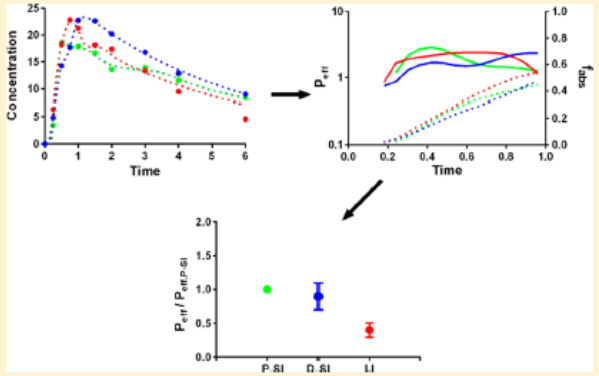
Human *in Vivo* Regional Intestinal Permeability: Quantitation Using Site-Specific Drug Absorption Data

Erik Sjögren,* David Dahlgren, Carl Roos, and Hans Lennernäs

Department of Pharmacy, Biopharmaceutic Research Group, Uppsala University, SE-751 23 Uppsala, Sweden

Supporting Information

ABSTRACT: Application of information on regional intestinal permeability has been identified as a key aspect of successful pharmaceutical product development. This study presents the results and evaluation of an approach for the indirect estimation of site-specific *in vivo* intestinal effective permeability (P_{eff}) in humans. Plasma concentration−time profiles from 15 clinical studies that administered drug solutions to specific intestinal regions were collected and analyzed. The intestinal absorption rate for each drug was acquired by deconvolution, using historical intravenous data as reference, and used with the intestinal surface area and the dose remaining in the lumen to estimate the P_{eff}. Forty-three new P_{eff} values were estimated (15 from the proximal small intestine, 11 from the distal small intestine, and 17 from the large intestine) for 14 active pharmaceutical ingredients representing a wide range of biopharmaceutical properties. A good correlation (r^2 = 0.96, slope = 1.24, intercept = 0.030) was established between these indirect jejunal P_{eff} estimates and jejunal P_{eff} measurements determined directly using the single-pass perfusion double balloon technique. On average, P_{eff} estimates from the distal small intestine and large intestine were 90% and 40%, respectively, of those from the proximal small intestine. These results support the use of the evaluated deconvolution method for indirectly estimating regional intestinal P_{eff} in humans. This study presents the first comprehensive data set of estimated human regional intestinal permeability values for a range of drugs. These biopharmaceutical data can be used to improve the accuracy of gastrointestinal absorption predictions used in drug development decision-making.



KEYWORDS: *human in vivo intestinal permeability, colon, site-specific permeability, regional permeability*

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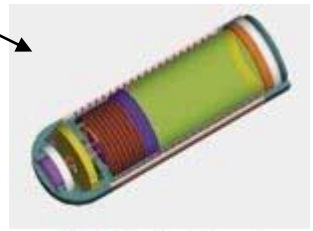
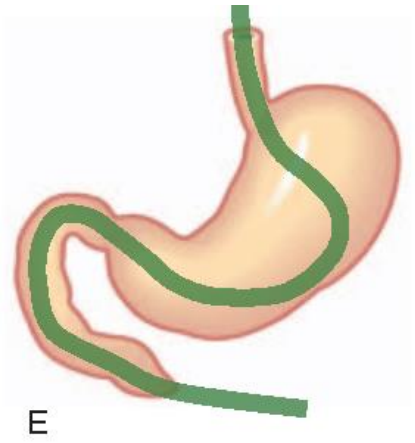
Deconvolution-P_{eff} model

Indirect method to determine P_{eff} based on *drug plasma appearance* (concentration-time data) following regional intestinal **dose dumping** of drug solutions

Bioperm capsule



Remote-controlled capsules



"Thin" intestinal tubes

E

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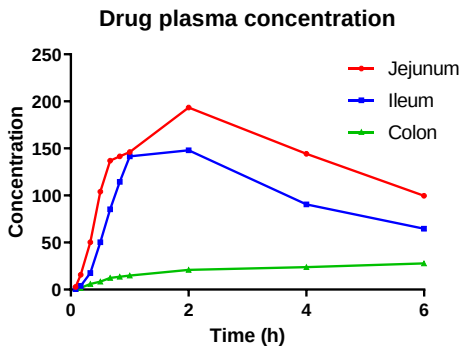
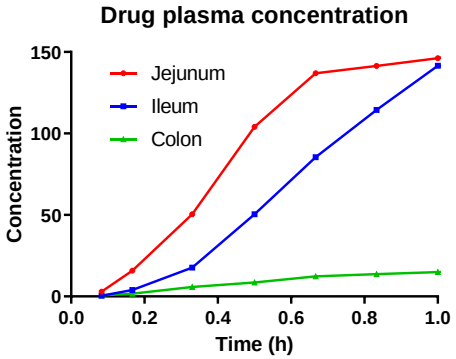
Deconvolution-P_{eff} model

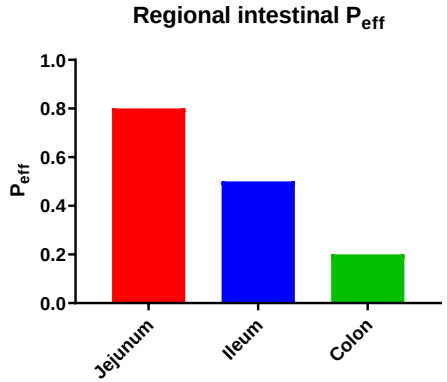
Indirect method to determine P_{eff} based on *drug plasma appearance* (**concentration-time data**) following regional intestinal dose dumping of **drug solutions**



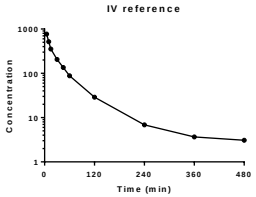
60 min



Deconvolution



- iv reference
- corrected for EG/EH



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Deconvolution-P_{eff} model

ALL published plasma data from regional intestinal dose dumpings were used to calculate permeability

API	Jejunum	Ileum	Colon
	P_{eff} (10^{-4} cm s^{-1})		
Bevirimat	5.9	3.7	0.21
Budesonide	1.9	3.4	0.59
Cyclosporin	2.2 2.6	0.84	0.0001
Fenofibric acid	8.6	2.3	0.48
Fexofenadine	0.27	0.062	0.025
Ipsapirone	0.31		0.33 0.42
Lisdexamfetamine	3.1	3.3	0.11
Lumiracoxib	3.7	7.2	2.5
Metoprolol	1.5	2.0	1.6
Nifedipine	4.4		1.2 2.0
Ranitidine (tube)	0.39		0.071
Ranitidine (capsule)	0.21	0.11	0.060
Rivastigmine	16	12	10
Sumatriptan	1.7		0.27
Theophylline		0.92	0.74

43 new drug P_{eff} values:

15 from the jejunum

11 from the ileum

17 from the colon - for the first time!

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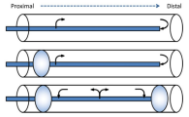
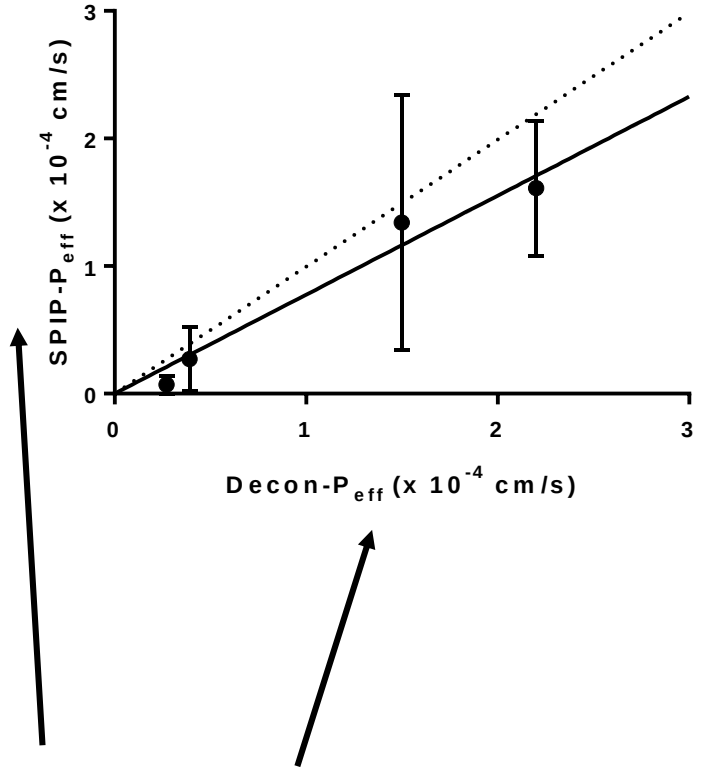
Deconvolution-P_{eff} model – validation in human



API	Decon P_{eff} (10^{-4} cm s^{-1})	SPIP P_{eff} (10^{-4} cm s^{-1})
Cyclosporin	2.2	1.61 ± 0.53
Fexofenadine	0.27	0.07 ± 0.07
Metoprolol	1.5	1.34 ± 1.0
Ranitidine	0.30	0.27 ± 0.25



Good agreement between jejunal P_{eff} values from the **SPIP** and **Decon** methods

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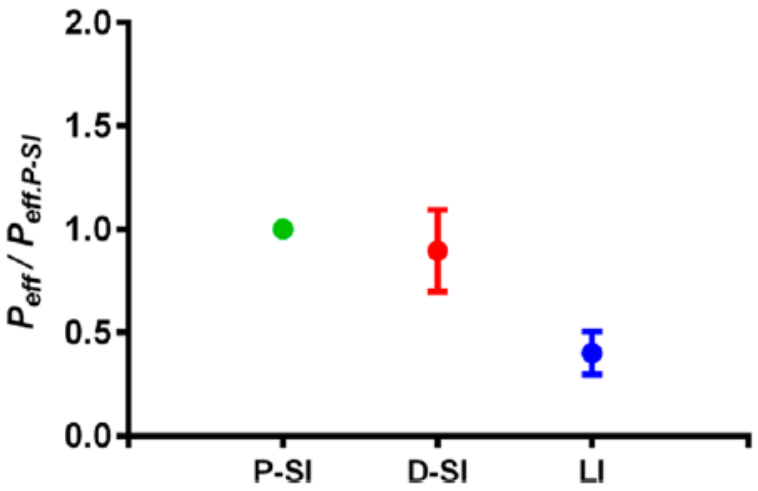
Deconvolution-P_{eff} model



General trend lower **relative** colonic P_{eff}

Absolute P_{eff} values less reliable:

- Different subjects/studies (iv and intestinal)
- No individual data
- Regional uncertainty

Plasma data from controlled conditions missing

↓

Reliable, **absolute** individual P_{eff} values that can be used to validate preclinical models

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Clinical P_{eff} study

Regional Intestinal Permeability of Three Model Drugs in Human

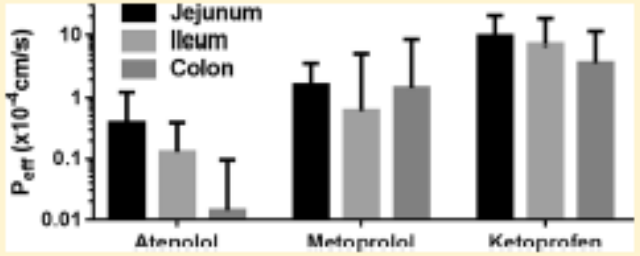
David Dahlgren,[†] Carl Roos,[†] Anders Lundqvist,[‡] Bertil Abrahamsson,[‡] Christer Tannergren,[‡] Per M. Hellström,[§] Erik Sjögren,[†] and Hans Lennernäs*[,†]

[†]Department of Pharmacy, Uppsala University, Uppsala SE-751 23, Sweden

[‡]AstraZeneca R&D, Gothenburg, Sweden

[§]Department of Medical Sciences, Uppsala University, Uppsala SE-751 05, Sweden

ABSTRACT: Currently there are only a limited number of determinations of human P_{eff} in the distal small intestine and none in the large intestine. This has hindered the validation of preclinical models with regard to absorption in the distal parts of the intestinal tract, which can be substantial for BCS class II−IV drugs, and drugs formulated into modified-release (MR) dosage forms. To meet this demand, three model drugs (atenolol, metoprolol, and ketoprofen) were dosed in solution intravenously, and into the jejunum, ileum, and colon of 14 healthy volunteers. The P_{eff} of each model drug was then calculated using a validated deconvolution method. The median P_{eff} of atenolol in the jejunum, ileum, and colon was 0.45, 0.15, and 0.013 × 10^{-4} cm/s, respectively. The corresponding values for metoprolol were 1.72, 0.72, and 1.30 × 10^{-4} cm/s, and for ketoprofen 8.85, 6.53, and 3.37 × 10^{-4} cm/s, respectively. This is the first study where the human P_{eff} of model drugs has been determined in all parts of the human intestinal tract in the same subjects. The jejunal values were similar to directly determined values using intestinal single-pass perfusion, indicating that the deconvolution method is a valid approach for determining regional P_{eff}. The values from this study will be highly useful in the validation of preclinical regional absorption models and in silico tools.



KEYWORDS: *intestinal permeability, regional intestinal drug absorption, effective permeability, pharmacokinetics*

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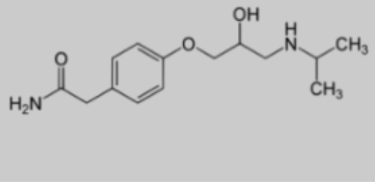
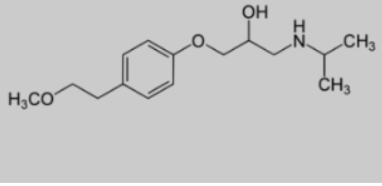
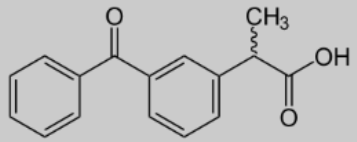
Clinical P_{eff} study

Low **Permeability** High

Atenolol	Metoprolol	Ketoprofen
		

Three model drugs were administered as a cocktail solution

Four administrations (**iv, jejunum, ileum, colon**) to 14 volunteers:

Deconvolution during **30-min** (60 min in previous study)

Intestinal site verified with tube length, and x-ray

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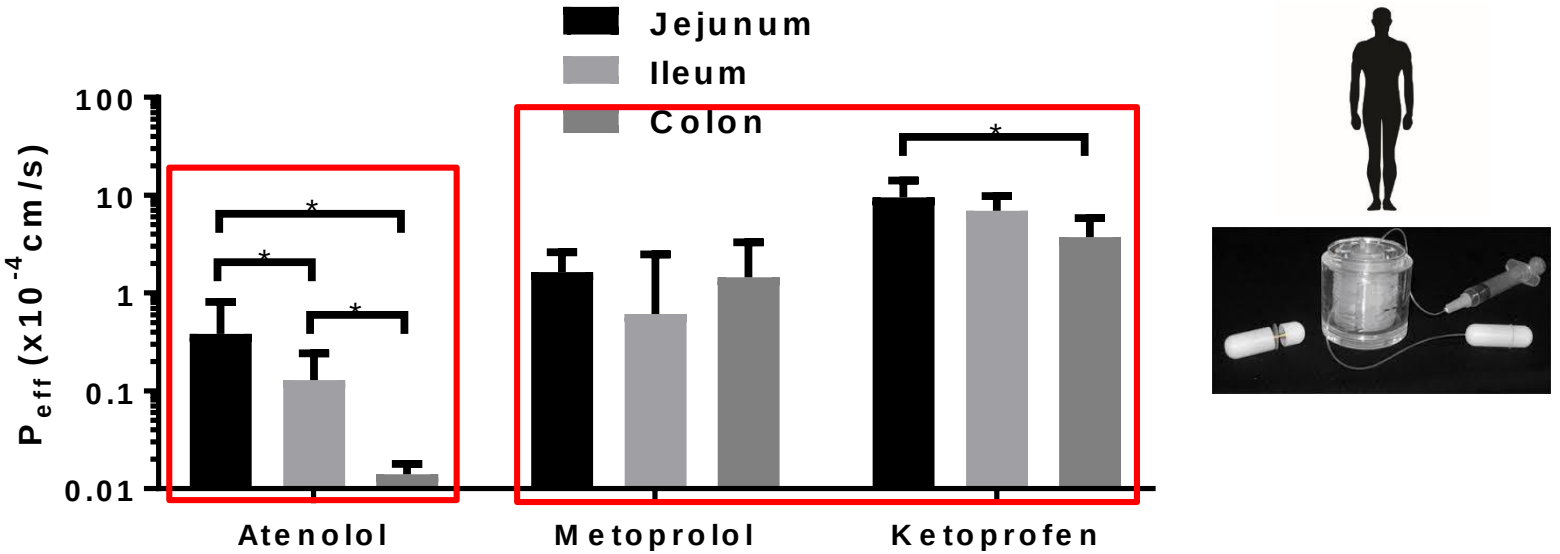
Clinical P_{eff} study



The P_{eff} was high (>1 x 10^{-4} cm/s) in all regions for the medium-to-high permeability drugs, metoprolol and ketoprofen

The P_{eff} was substantially lower in the colon for the low permeability drug, atenolol

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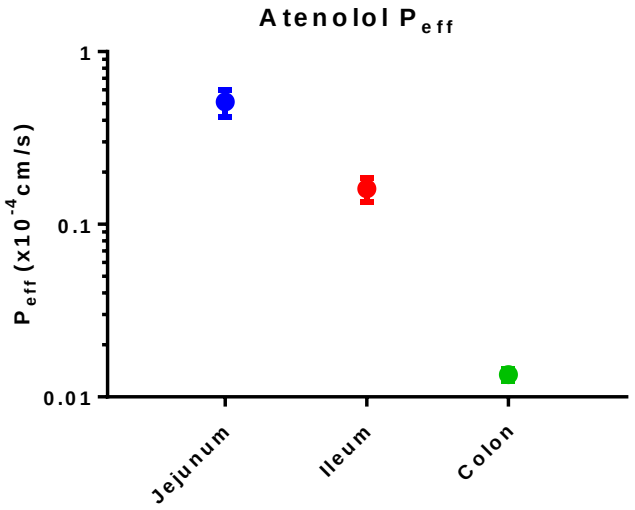
Clinical P_{eff} study

Surface area compared to a tube (folds/villi):

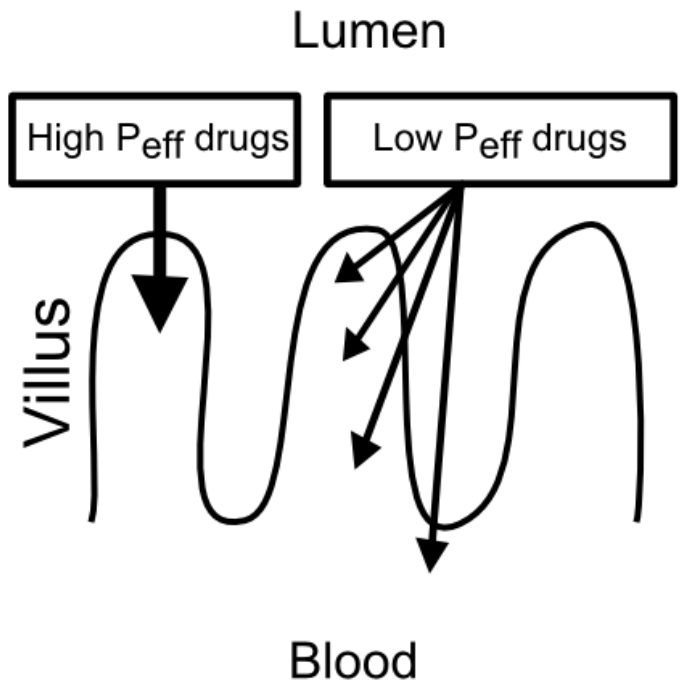
- Jejunum **19** fold
- Ileum **10** fold
- Colon **1** fold

Surface area of the digestive tract – revisited

HERBERT F HELANDER & LARS FÄNDRIKS



Crypt-villus transport



Differences in regional intestinal surface area important for low P_{eff} compounds! (but not for high P_{eff})

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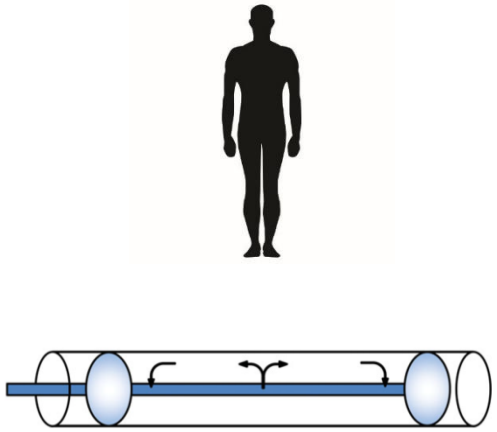
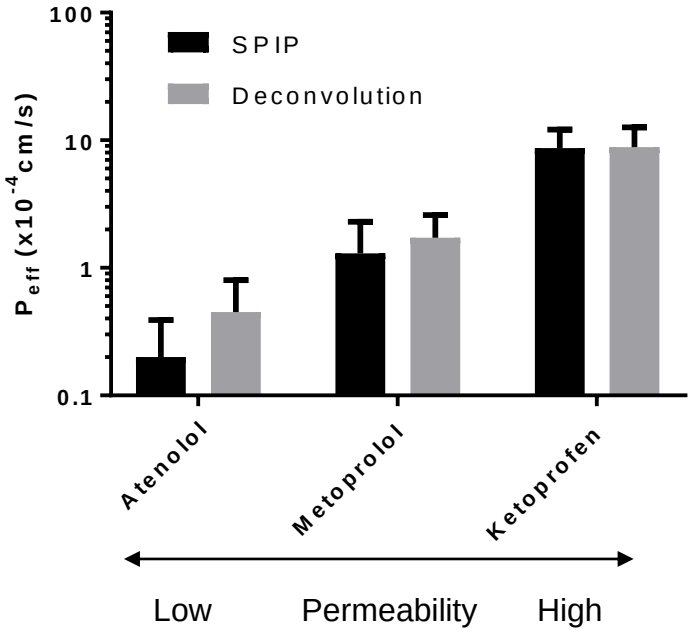
Clinical P_{eff} study

SPIP





Deconvolution

Good agreement between jejunal P_{eff} values

Further supports the use of the Decon-P_{eff} model

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Deconvolution-P_{eff} model – validation in rat

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Research paper

Evaluation of drug permeability calculation based on luminal disappearance and plasma appearance in the rat single-pass intestinal perfusion model

D. Dahlgren[a], C. Roos[a], K. Peters[a], A. Lundqvist[b], C. Tannergren[b], E. Sjögren[a], M. Sjöblom[c], H. Lennernäs[a,*]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] AstraZeneca R&D, Gothenburg, Sweden
[c] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
Intestinal perfusion
Intestinal permeability
Intestinal physiology
Intestinal fluid transport

ABSTRACT

The rat single-pass intestinal perfusion (SPIP) model is commonly used to investigate gastrointestinal physiology and membrane drug transport. The SPIP model can be used with the intestinal segment inside or outside the abdomen. The rats can also be treated with parecoxib, a selective cycloxygenase-2 inhibitor that has been shown to affect some intestinal functions following abdominal surgery, such as motility, epithelial permeability, fluid flux and ion transport. However, the impact of extra-abdominal placement of the intestinal segment in combination with parecoxib on intestinal drug transport has not been investigated. There is also uncertainty how well intestinal permeability determinations based on luminal drug disappearance and plasma appearance correlate in the rat SPIP model. The main objective of this rat *in vivo* study was to investigate the effect of intra- vs. extra-abdominal SPIP, with and without, pretreatment with parecoxib. The effect was evaluated by determining the difference in blood-to-lumen ^{51}Cr-EDTA clearance, lumen-to-blood permeability of a cassette-dose of four model compounds (atenolol, enalaprilat, ketoprofen, and metoprolol), and water flux. The second objective was to compare the jejunal permeability values of the model drugs when determined based on luminal disappearance or plasma appearance. The study showed that the placement of the perfused jejunal segment, or the treatment with parecoxib, had minimal effects on membrane permeability and water flux. It was also shown that intestinal permeability of low permeability compounds should be determined on the basis of data from plasma appearance rather than luminal disappearance. If permeability is calculated on the basis of luminal disappearance, it should preferably include negative values to increase the accuracy in the determinations.

Comparison between P_{eff} calculated based on plasma appearance (Decon) and luminal disappearance in the rat SPIP model

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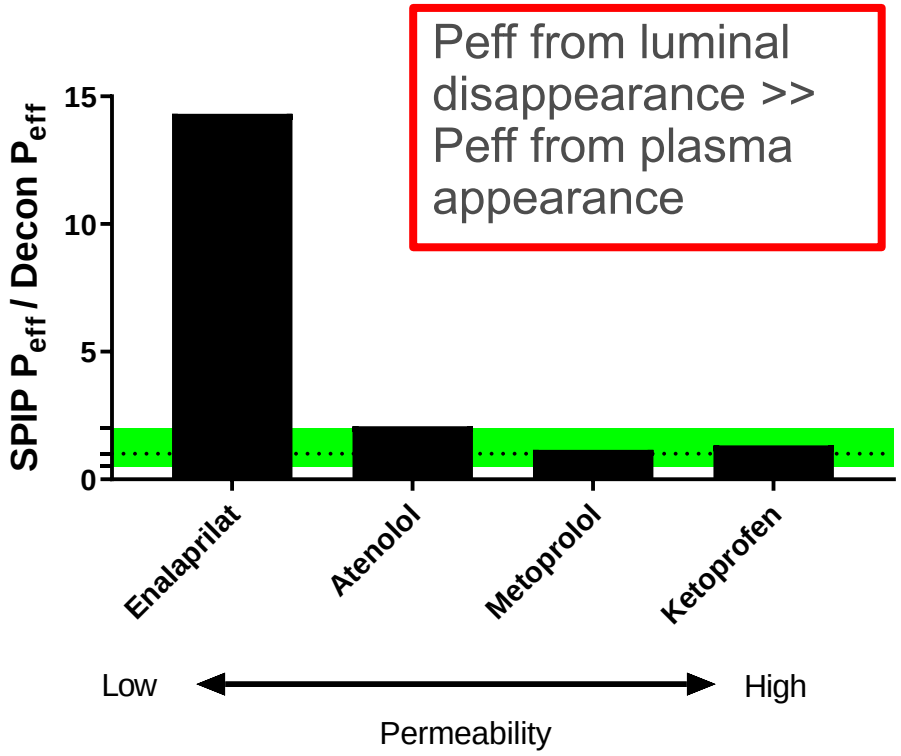
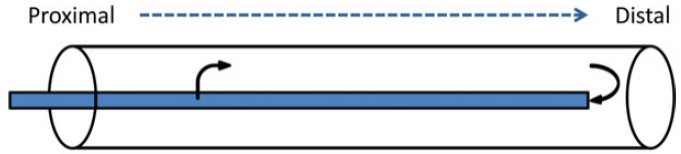
Deconvolution-P_{eff} model – validation in rat



Low permeability means little luminal disappearance

Cin
= 100 mM



Cout
= 99 mM

Small difference in Cin and Cout = difficult to determine Peff with high accuracy = Peff is overestimated

Decon-P_{eff} (plasma appearance) model superior for low-P_{eff} drugs

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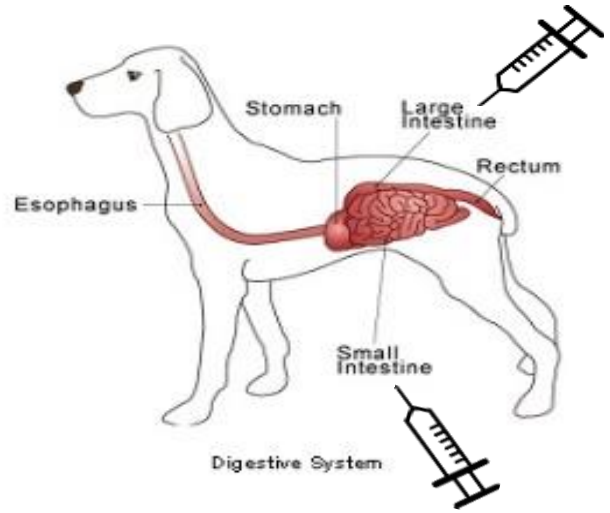
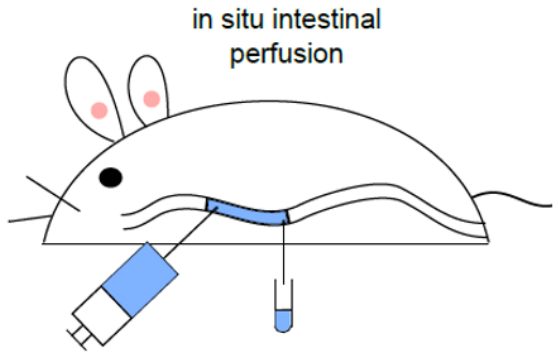
Regional permeability in predictive preclinical models





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Dog regional permeability

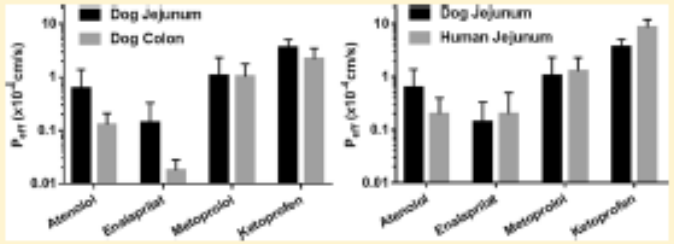
Regional Intestinal Permeability in Dogs: Biopharmaceutical Aspects for Development of Oral Modified-Release Dosage Forms

David Dahlgren,[†] Carl Roos,[†] Pernilla Johansson,[‡] Anders Lundqvist,[‡] Christer Tannergren,[‡] Bertil Abrahamsson,[‡] Erik Sjögren,[†] and Hans Lennernäs*[,†]

[†]Department of Pharmacy, Uppsala University, Uppsala SE-751 23, Sweden

[‡]AstraZeneca R&D, Gothenburg SE-431 50, Sweden

ABSTRACT: The development of oral modified-release (MR) dosage forms requires an active pharmaceutical ingredient (API) with a sufficiently high absorption rate in both the small and large intestine. Dogs are commonly used in preclinical evaluation of regional intestinal absorption and in the development of novel MR dosage forms. This study determined regional intestinal effective permeability (P_{eff}) in dogs with the aim to improve regional P_{eff} prediction in humans. Four model drugs, atenolol, enalaprilat, metoprolol, and ketoprofen, were intravenously and regionally dosed twice as a solution into the proximal small intestine (P-SI) and large intestine (LI) of three dogs with intestinal stomas. Based on plasma data from two separate study occasions for each dog, regional P_{eff} values were calculated using a validated intestinal deconvolution method. The determined mean P_{eff} values were 0.62, 0.14, 1.06, and 3.66×10^{-4} cm/s in the P-SI, and 0.13, 0.02, 1.03, and 2.20×10^{-4} cm/s in the LI, for atenolol, enalaprilat, metoprolol, and ketoprofen, respectively. The determined P-SI P_{eff} values in dog were highly correlated ($R^2 = 0.98$) to the historically directly determined human jejunal P_{eff} after a single-pass perfusion. The determined dog P-SI P_{eff} values were also successfully implemented in GI-Sim to predict the risk for overestimation of LI absorption of low permeability drugs. We conclude that the dog intestinal stoma model is a useful preclinical tool for determination of regional intestinal permeability. Still, further studies are recommended to evaluate additional APIs, sources of variability, and formulation types, for more accurate determination of the dog model in the drug development process.



KEYWORDS: *dog intestinal permeability, regional intestinal drug absorption, bioavailability, effective permeability, pharmacokinetics, intestinal perfusion, pharmaceutical development*

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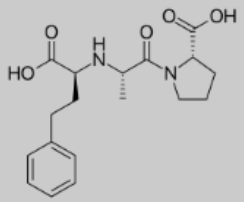
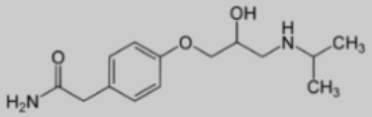
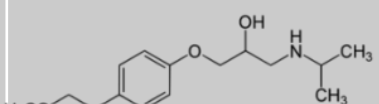
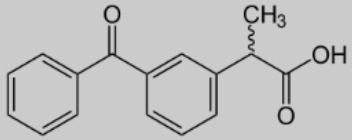
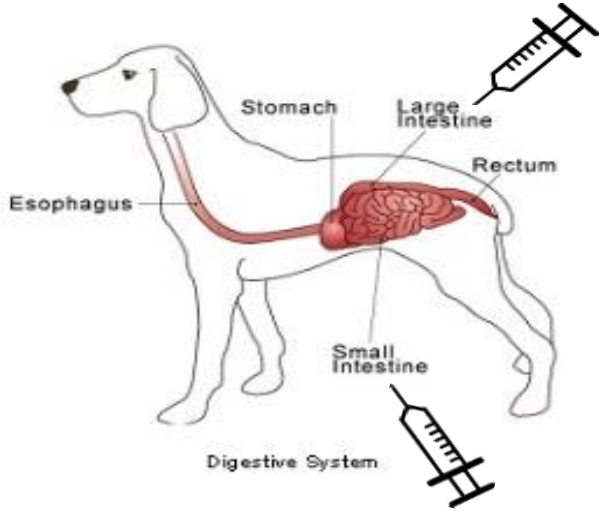
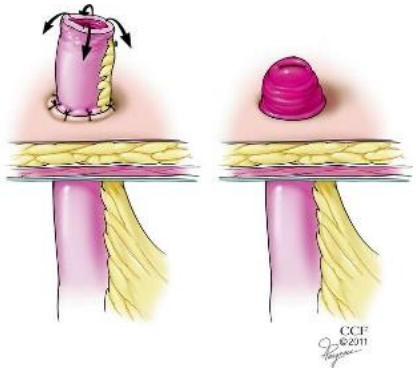
Dog regional permeability

Low **Permeability** High

Enalaprilat	Atenolol	Metoprolol	Ketoprofen
			

Four model drugs were administered as a cocktail solution





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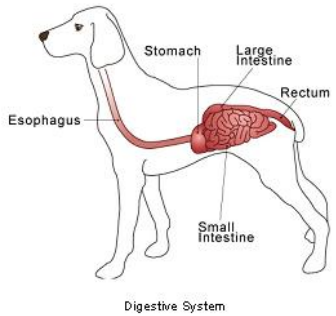
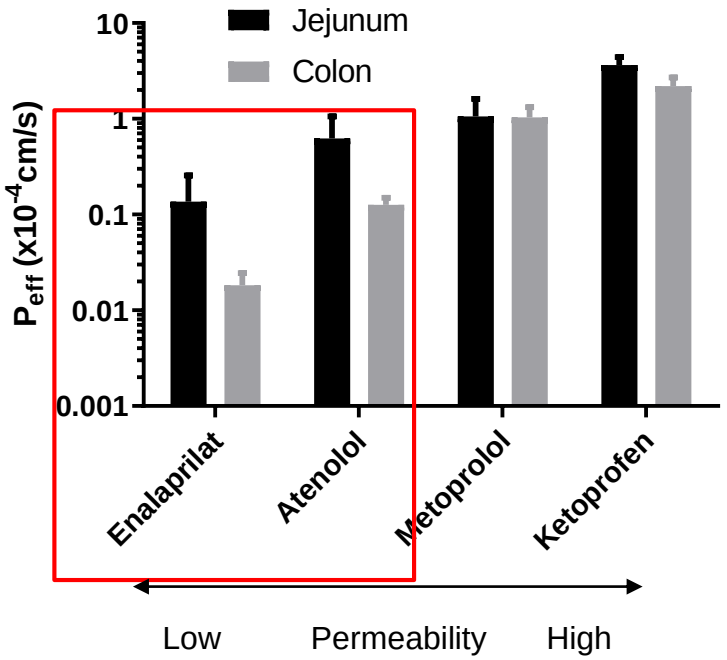
Dog regional permeability



Jejunum vs. colon



Lower colonic permeability for the low permeability compounds, as for humans

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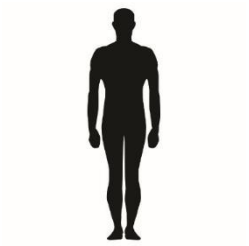
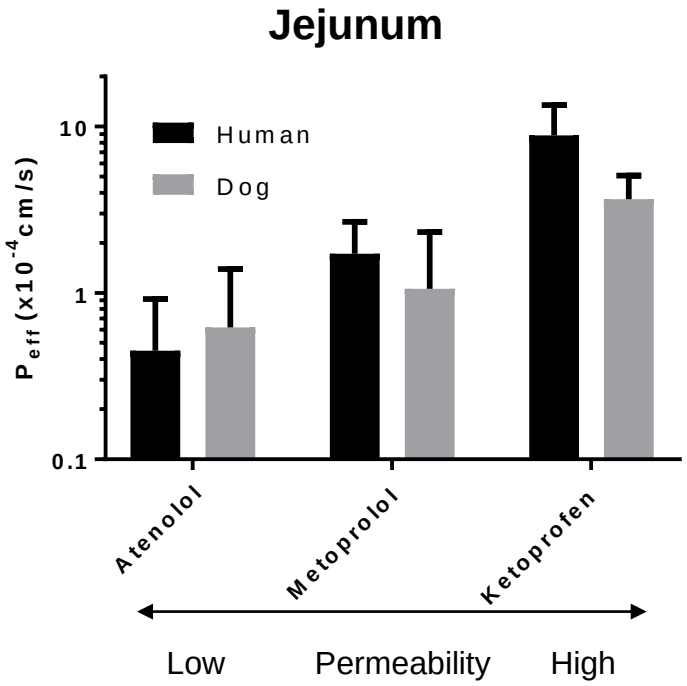
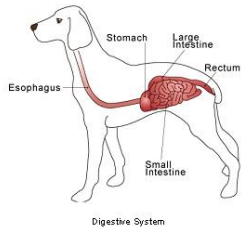
Dog regional permeability







Good agreement between human and dog jejunal P_{eff} values

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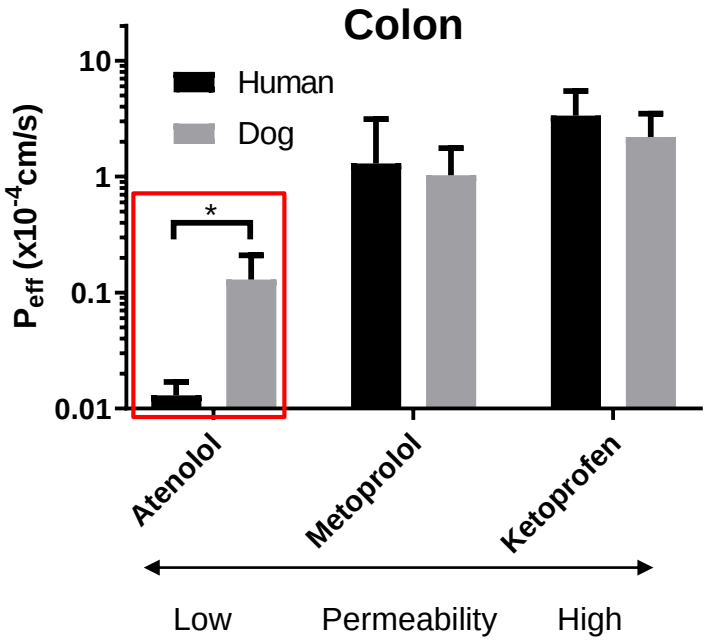
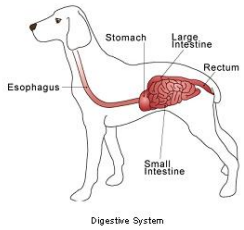
Dog regional permeability





The dog colon was substantially more permeable (10-fold) to atenolol

The dog may overestimate human colonic absorption of low permeability drugs, still useful!

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Rat regional permeability

molecular pharmaceutics

Article

pubs.acs.org/molecularpharmaceutics

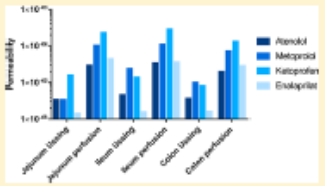
Regional Intestinal Permeability in Rats: A Comparison of Methods

Carl Roos,[†] David Dahlgren,[†] Erik Sjögren,[†] Christer Tannergren,[‡] Bertil Abrahamsson,[‡] and Hans Lennernäs*[,†]

[†]Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden

[‡]Pharmaceutical Technology and Development, AstraZeneca R&D, 431 83 Gothenburg, Sweden

ABSTRACT: Currently, the screening of new drug candidates for intestinal permeation is typically based on *in vitro* models which give no information regarding regional differences along the gut. When evaluation of intestinal permeability by region is undertaken, two preclinical rat models are commonly used, the Ussing chamber method and single-pass intestinal perfusion (SPIP). To investigate the robustness of *in vivo* predictions of human intestinal permeability, a set of four model compounds was systematically investigated in both these models, using tissue specimens and segments from the jejunum, ileum, and colon of rats from the same genetic strain. The influence of luminal pH was also determined at two pH levels. Ketoprofen had high and enalaprilat had low effective (P_{eff}) and apparent (P_{app}) permeability in all three regions and at both pH levels. Metoprolol had high P_{eff} in all regions and at both pHs and high P_{app} at both pHs and in all regions except the jejunum, where P_{app} was low. Atenolol had low P_{eff} in all regions and at both pHs, but had high P_{app} at pH 6.5 and low P_{app} at pH 7.4. There were good correlations between these rat *in situ* P_{eff} (SPIP) and human *in vivo* P_{eff} determined previously for the same compounds by both intestinal perfusion of the jejunum and regional intestinal dosing. The results of this study indicate that both investigated models are suitable for determining the regional permeability of the intestine; however, the SPIP model seems to be the more robust and accurate regional permeability model.



KEYWORDS: *intestinal permeability, Ussing chamber method, single-pass intestinal perfusion, jejunum, ileum, colon, rat*

Rat Ussing and rat SPIP *disappearance*

pharmaceutics

MDPI

Article

Regional Intestinal Drug Permeability and Effects of Permeation Enhancers in Rat

David Dahlgren [1], Maria-Jose Cano-Cebrián [2], Tobias Olander [1], Mikael Hedeland [3,4], Markus Sjöblom [5] and Hans Lennernäs [1,*]

1 Department of Pharmacy, Division of Biopharmaceutics, Uppsala University, 752 36 Uppsala, Sweden; david.dahlgren@farmaci.uu.se (D.D.); olander92@hotmail.com (T.O.)
2 Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia, 46010 València, Spain; Maria.Jose.Cano@uv.es
3 Department of Medicinal Chemistry, Analytical Pharmaceutical Chemistry, Uppsala University, 752 36 Uppsala, Sweden; mikael.hedeland@ilk.uu.se
4 Department of Chemistry, Environment and Feed Hygiene, National Veterinary Institute (SVA), 751 89 Uppsala, Sweden
5 Department of Neuroscience, Division of Physiology, Uppsala University, 752 36 Uppsala, Sweden; Markus.Sjoblom@neuro.uu.se
* Correspondence: hans.lennernas@farmaci.uu.se

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check for updates

Rat SPIP *appearance (Decon)*

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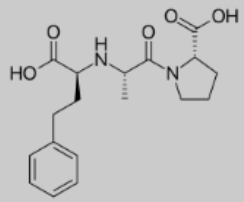
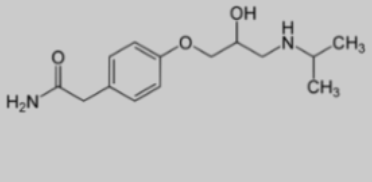
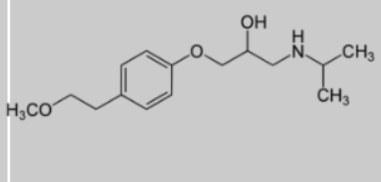
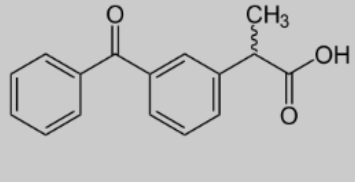
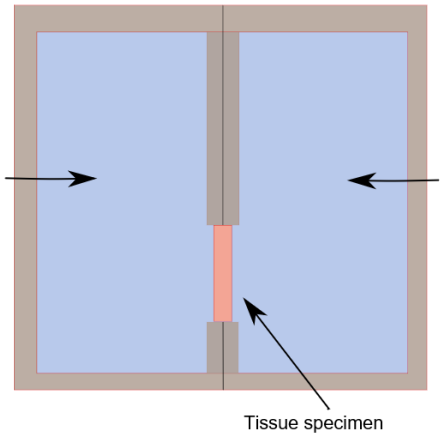
Rat regional permeability

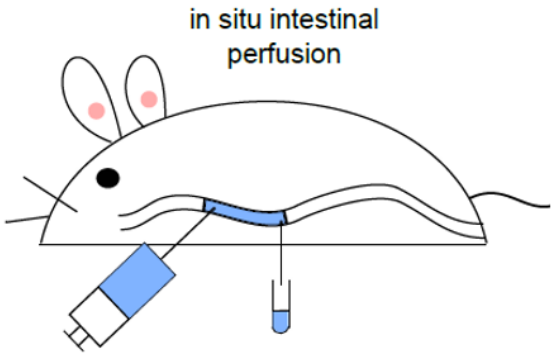
Low **Permeability** High

Enalaprilat	Atenolol	Metoprolol	Ketoprofen
			

Four model drugs as a cocktail solution

Rat Ussing





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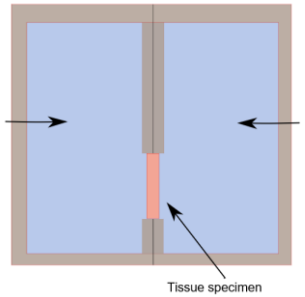
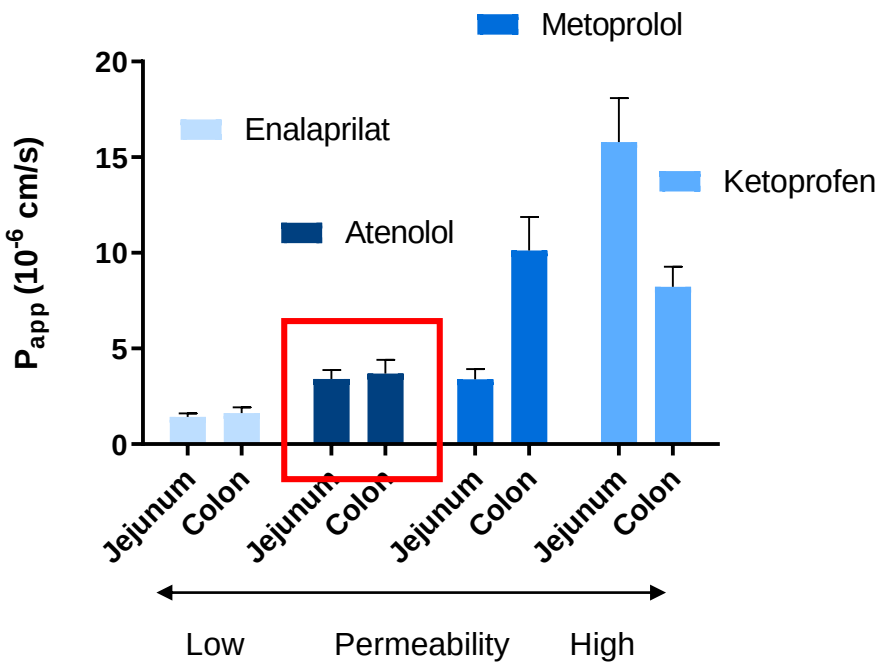
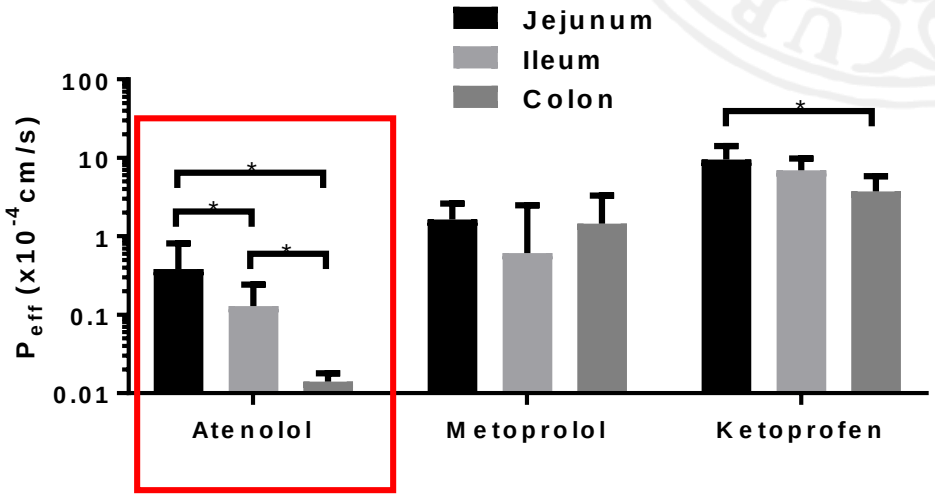
Rat regional permeability - Ussing

Rat Ussing







The rat Ussing model was **not** predictive of regional human P_{eff} values

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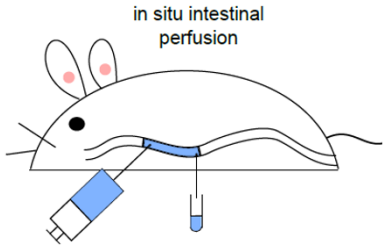
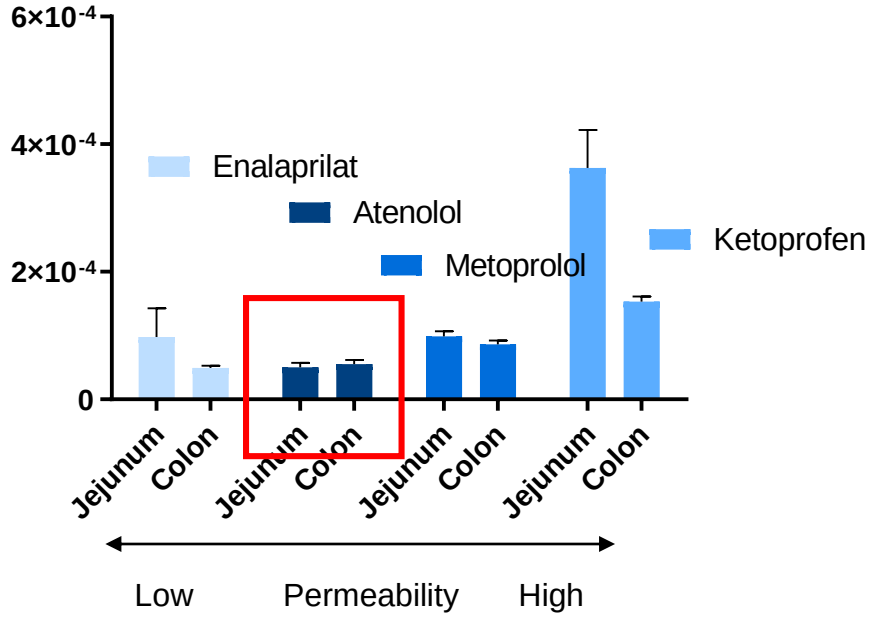
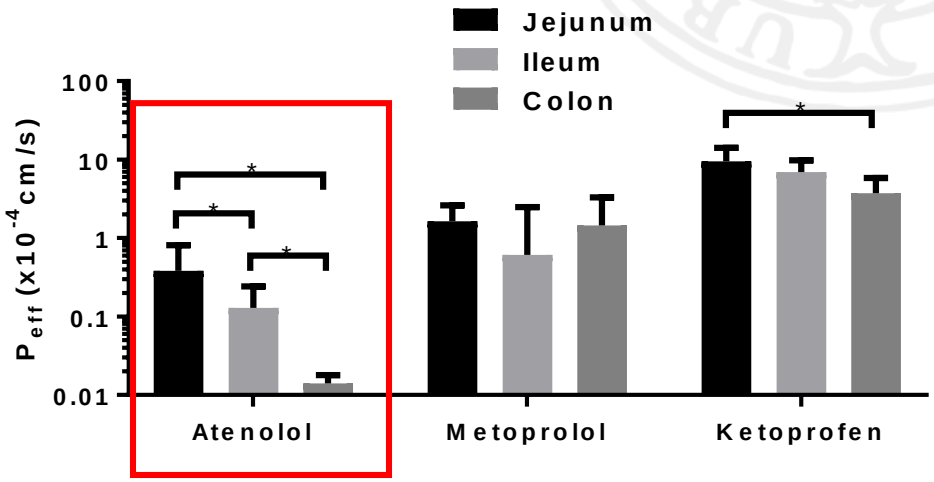
Rat regional permeability – SPIP dissapearance







The rat SPIP *disappearance* was **not** predictive of regional human P_{eff} values

Is this because the *disappearance* method cant determine the P_{eff} of low-P_{eff} drugs?

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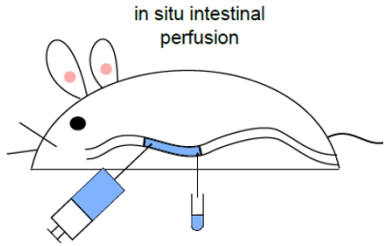
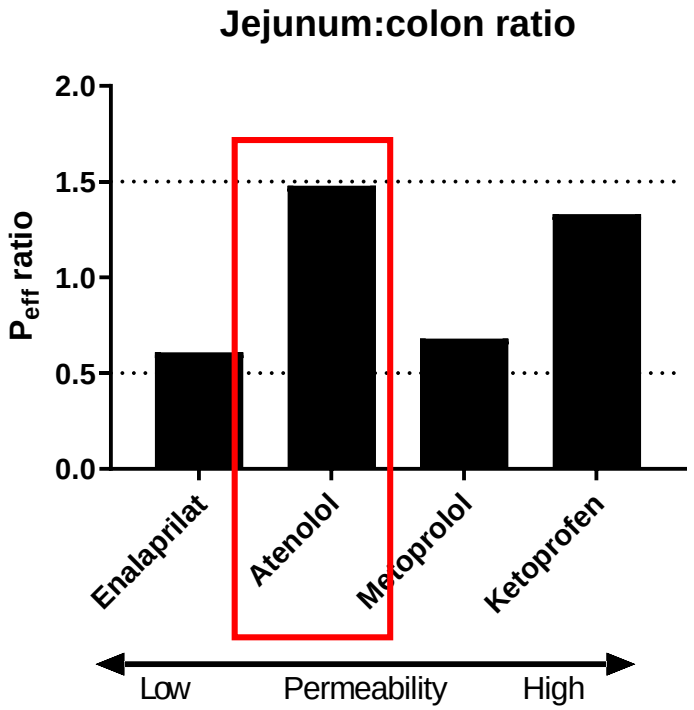
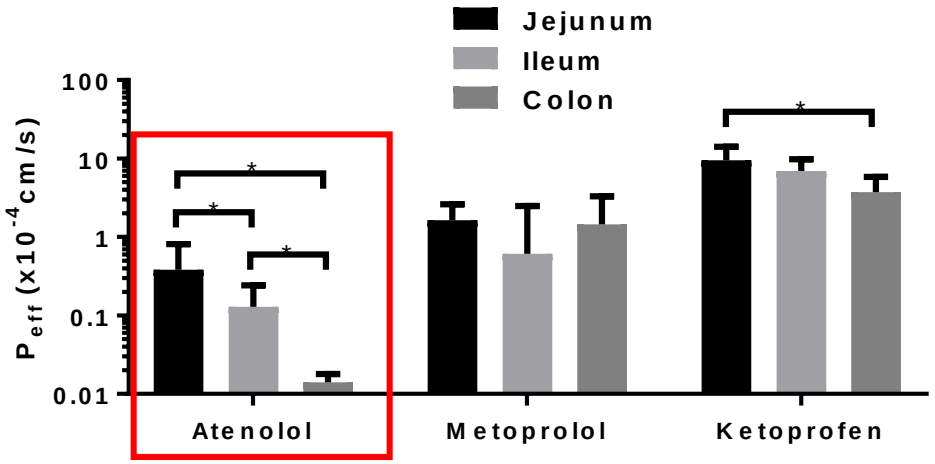
Rat regional permeability – Decon-Peff appearance



The rat colon is *not suitable* for predicting human colonic P_{eff}





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All reported rat intestinal permeability data data

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Rat intestinal drug permeability: A status report and summary of repeated determinations

I.R. Dubbelboer, D. Dahlgren, E. Sjögren, H. Lennernäs*

Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden

ABSTRACT

Intestinal permeability is a key biopharmaceutical variable in pharmaceutical research and development, and regulatory assessment. In situ rat models are often used to predict the corresponding human intestinal permeability data. The rat single-pass intestinal perfusion (SPIP) and intestinal closed loop (ICL) models are commonly applied. The primary objective of this study was to collect, summarize, and evaluate all the available intestinal permeability data for drugs that have been obtained using these two in-situ rat models. The permeability data were also investigated for variability between the experimental designs. The literature survey found 635 permeability determinations for 90 drugs. The studies were performed on the jejunum (n = 284), whole small intestine (n = 111), colon (n = 108), ileum (n = 101), and duodenum (n = 30). All the SPIP (n = 484) and ICL (n = 147) permeability values were summarized in an easily accessible database. There was wide variability in the intestinal permeability to each drug between studies, which was unrelated to the permeability class of the drug. There was no relationship between rat intestinal permeability and luminal pH, luminal drug concentration, rat strain, experimental method, or intestinal region. There was, however, a correlation between permeability values determined in the same laboratory. This report showed that the SPIP and ICL methods are important in situ models for understanding and predicting intestinal drug absorption. However, conclusions based on permeability values sourced from different laboratories may not be reliable. Because each permeability study is unique and because between- and even within-laboratory variability can be substantial, data from individual studies should preferably be interpreted separately.

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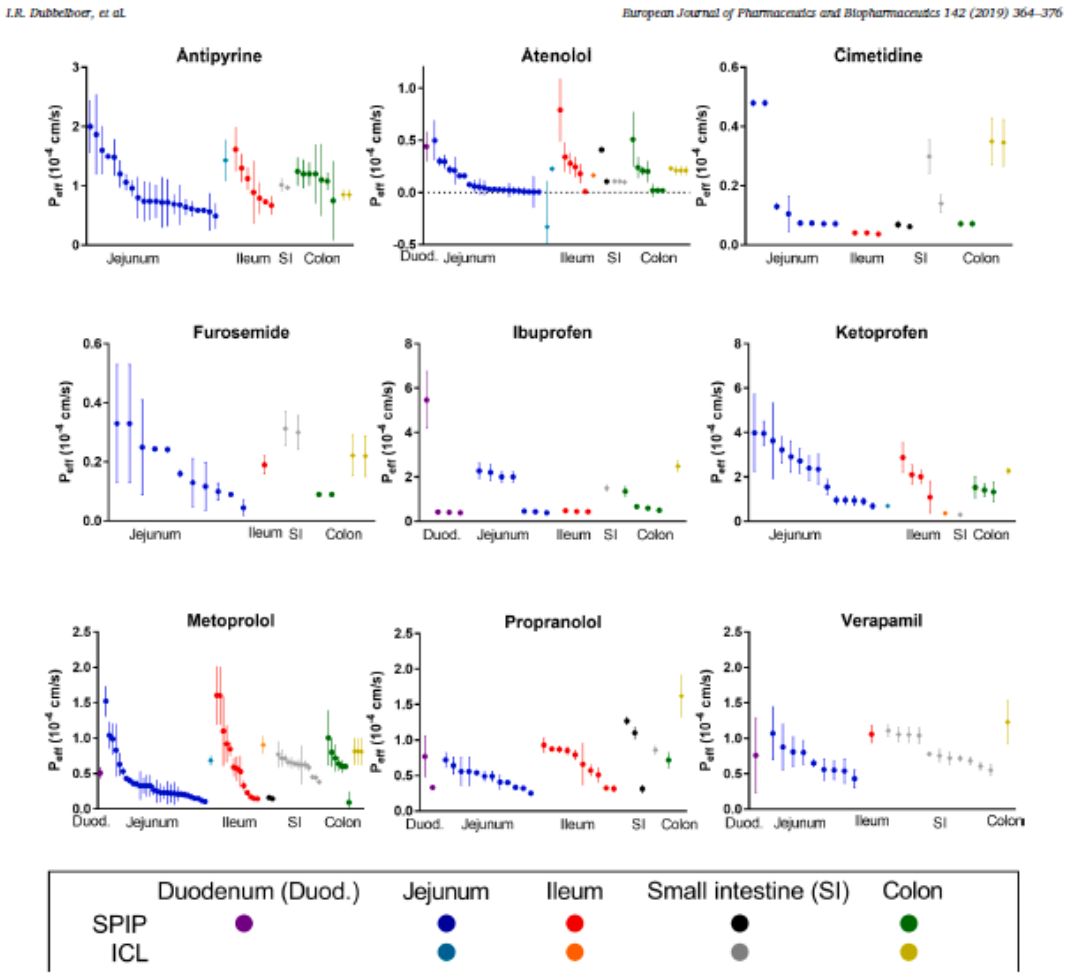
All reported rat intestinal permeability data data



- Regional intestinal differences
- SPIP vs. closed loop
- Different strains
- Intra and inter lab variability
- Active vs. passive transport
- Concentration dependence

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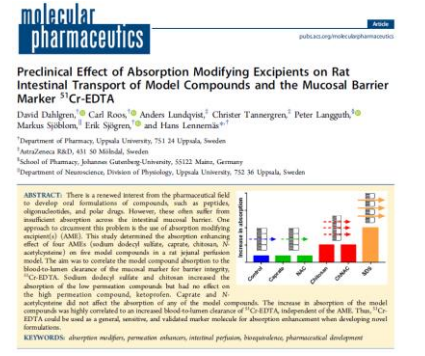
Permeation enhancer in the colon

Permeation enhancers in the colon


molecular pharmaceutics

Article

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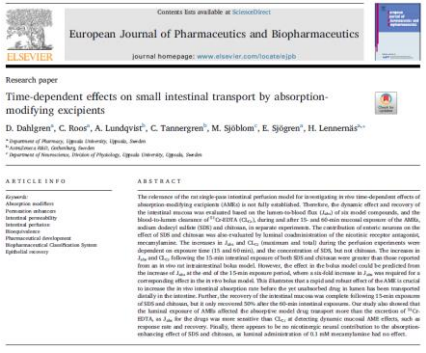
Preclinical Effect of Absorption Modifying Excipients on Rat Intestinal Transport of Model Compounds and the Mucosal Barrier Marker ^{51}Cr-EDTA

David Dahlgren,[†] Carl Roos,[†] Anders Lundqvist,[‡] Christer Tannergren,[‡] Peter Langguth,[§] Markus Sjöblom,[†] Erik Sjögren,[†] and Hans Lennernäs[*,†]

[†]Department of Pharmacy, Uppsala University, 751 24 Uppsala, Sweden
[‡]AstraZeneca R&D, 431 50 Mölndal, Sweden
[§]School of Pharmacy, Johannes Gutenberg-University, 55122 Mainz, Germany
[∥]Department of Neuroscience, Division of Physiology, Uppsala University, 752 36 Uppsala, Sweden

ABSTRACT: There is a renewed interest from the pharmaceutical field to develop oral formulations of compounds, such as peptides, oligonucleotides, and polar drugs. However, these often suffer from insufficient absorption across the intestinal mucosal barrier. One approach to circumvent this problem is the use of absorption modifying excipient(s) (AME). This study determined the absorption enhancing effect of four AMEs (sodium dodecyl sulfate, caprate, chitosan, *N*-acetylcysteine) on five model compounds in a rat jejunal perfusion model. The aim was to correlate the model compound absorption to the blood-to-lumen clearance of the mucosal marker for barrier integrity, ^{51}Cr-EDTA. Sodium dodecyl sulfate and chitosan increased the absorption of the low permeation compounds but had no effect on the high permeation compound, ketoprofen. Caprate and *N*-acetylcysteine did not affect the absorption of any of the model compounds. The increase in absorption of the model compounds was highly correlated to an increased blood-to-lumen clearance of ^{51}Cr-EDTA, independent of the AME. Thus, ^{51}Cr-EDTA could be used as a general, sensitive, and validated marker molecule for absorption enhancement when developing novel formulations.

KEYWORDS: *absorption modifiers, permeation enhancers, intestinal perfusion, bioequivalence, pharmaceutical development*


Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Time-dependent effects on small intestinal transport by absorption-modifying excipients

D. Dahlgren[a], C. Roos[a], A. Lundqvist[b], C. Tannergren[b], M. Sjöblom[a], E. Sjögren[a], H. Lennernäs[a,*]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] AstraZeneca R&D, Gothenburg, Sweden
[c] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
Absorption modifiers
Permeation enhancers
Intestinal permeability
Intestinal perfusion
Bioequivalence
Pharmaceutical development
Biopharmaceutical Classification System
Epithelial recovery

ABSTRACT

The relevance of the rat single-pass intestinal perfusion model for investigating in vivo time-dependent effects of absorption-modifying excipients (AMEs) is not fully established. Therefore, the dynamic effect and recovery of the intestinal mucosa was evaluated based on the lumen-to-blood flux (J_{wb}) of six model compounds, and the blood-to-lumen clearance of ^{51}Cr-EDTA (CL_{bl}), during and after 15- and 60-min mucosal exposure of the AMEs, sodium dodecyl sulfate (SDS) and chitosan, in separate experiments. The contribution of enteric neurons on the effect of SDS and chitosan was also evaluated by luminal coadministration of the nicotinic receptor antagonist, mecamylamine. The increases in J_{wb} and CL_{bl} (maximum and total) during the perfusion experiments were dependent on exposure time (15 and 60 min), and the concentration of SDS, but not chitosan. The increases in J_{wb} and CL_{bl} following the 15-min intestinal exposure of both SDS and chitosan were greater than those reported from an in vivo rat intraintestinal bolus model. However, the effect in the bolus model could be predicted from the increase of J_{wb} at the end of the 15-min exposure period, where a six-fold increase in J_{wb} was required for a corresponding effect in the in vivo bolus model. This illustrates that a rapid and robust effect of the AME is crucial to increase the in vivo intestinal absorption rate before the yet unabsorbed drug in lumen has been transported distally in the intestine. Further, the recovery of the intestinal mucosa was complete following 15-min exposures of SDS and chitosan, but it only recovered 50% after the 60-min intestinal exposures. Our study also showed that the luminal exposure of AMEs affected the absorptive model drug transport more than the excretion of ^{51}Cr-EDTA, as J_{wb} for the drugs was more sensitive than CL_{bl} at detecting dynamic mucosal AME effects, such as response rate and recovery. Finally, there appears to be no nicotinergic neural contribution to the absorption-enhancing effect of SDS and chitosan, as luminal administration of 0.1 mM mecamylamine had no effect.


Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The effects of three absorption-modifying critical excipients on the *in vivo* intestinal absorption of six model compounds in rats and dogs

D. Dahlgren[a], C. Roos[b], P. Johansson[b], C. Tannergren[b], A. Lundqvist[b], P. Langguth[c], M. Sjöblom[d], E. Sjögren[a], H. Lennernäs[a,e]

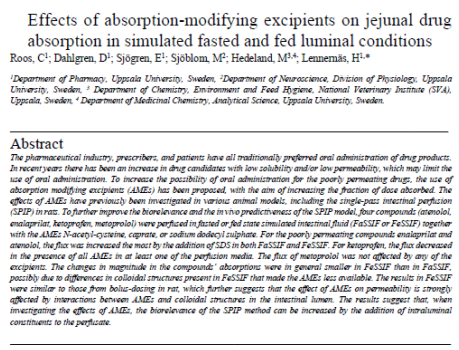
[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] AstraZeneca R&D, Gothenburg, Sweden
[c] School of Pharmacy, Johannes Gutenberg-University, Mainz, Germany
[d] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
Absorption modifiers
Permeation enhancers
Intraintestinal administration
Bioequivalence
Pharmaceutical development

ABSTRACT

Pharmaceutical excipients that may affect gastrointestinal (GI) drug absorption are called critical pharmaceutical excipients, or absorption-modifying excipients (AMEs) if they act by altering the integrity of the intestinal epithelial cell membrane. Some of these excipients increase intestinal permeability, and subsequently the absorption and bioavailability of the drug. This could have implications for both the assessment of bioequivalence and the efficacy of the absorption-enhancing drug delivery system. The absorption-enhancing effects of AMEs with different mechanisms (chitosan, sodium caprate, sodium dodecyl sulfate (SDS)) have previously been evaluated in the rat single-pass intestinal perfusion (SPIP) model. However, it remains unclear whether these SPIP data are predictive in a more in vivo like model. The same excipients were in this study evaluated in rat and dog intraintestinal bolus models. SDS and chitosan did exert an absorption-enhancing effect in both bolus models, but the effect was substantially lower than those observed in the rat SPIP model. This illustrates the complexity of the AME effects, and indicates that additional GI physiological factors need to be considered in their evaluation. We therefore recommend that AME evaluations obtained in transit-independent, preclinical permeability models (e.g. Ussing, SPIP) should be verified in animal models better able to predict in vivo relevant GI effects, at multiple excipient concentrations.


Effects of absorption-modifying excipients on jejunal drug absorption in simulated fasted and fed luminal conditions

Roos, C[1]; Dahlgren, D[1]; Sjögren, E[1]; Sjöblom, M[2]; Hedeland, M[3,4]; Lennernäs, H[1,*]

[1]*Department of Pharmacy, Uppsala University, Sweden.* [2]*Department of Neuroscience, Division of Physiology, Uppsala University, Sweden.* [3] *Department of Chemistry, Environment and Feed Hygiene, National Veterinary Institute (SVA), Uppsala, Sweden.* [4] *Department of Medicinal Chemistry, Analytical Science, Uppsala University, Sweden.*

Abstract

The pharmaceutical industry, prescribers, and patients have all traditionally preferred oral administration of drug products. In recent years there has been an increase in drug candidates with low solubility and/or low permeability, which may limit the use of oral administration. To increase the possibility of oral administration for the poorly permeating drugs, the use of absorption modifying excipients (AMEs) has been proposed, with the aim of increasing the fraction of dose absorbed. The effects of AMEs have previously been investigated in various animal models, including the single-pass intestinal perfusion (SPIP) in rats. To further improve the biorelevance and the in vivo predictiveness of the SPIP model, four compounds (atenolol, enalaprilat, ketoprofen, metoprolol) were perfused in fasted or fed state simulated intestinal fluid (FaSSIF or FeSSIF) together with the AMEs N-acetyl-cysteine, caprate, or sodium dodecyl sulphate. For the poorly permeating compounds enalaprilat and atenolol, the flux was increased the most by the addition of SDS in both FaSSIF and FeSSIF. For ketoprofen, the flux decreased in the presence of all AMEs in at least one of the perfusion media. The flux of metoprolol was not affected by any of the excipients. The changes in magnitude in the compounds' absorptions were in general smaller in FeSSIF than in FaSSIF, possibly due to differences in colloidal structures present in FeSSIF that made the AMEs less available. The results in FeSSIF were similar to those from bolus-dosing in rat, which further suggests that the effect of AMEs on permeability is strongly affected by interactions between AMEs and colloidal structures in the intestinal lumen. The results suggest that, when investigating the effects of AMEs, the biorelevance of the SPIP method can be increased by the addition of intraluminal constituents to the perfusate.


Acta Pharmaceutica Sinica B

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ORIGINAL ARTICLE

Effect of paracellular permeation enhancers on intestinal permeability of two peptide drugs, enalaprilat and hexarelin, in rats

David Dahlgren [a], Tobias Olander [a], Markus Sjöblom [b], Mikael Hedeland [c, d], Hans Lennernäs [a, *]

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International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effect of absorption-modifying excipients, hypotonicity, and enteric neural activity in an *in vivo* model for small intestinal transport

D. Dahlgren[a], C. Roos[b], A. Lundqvist[b], C. Tannergren[b], M. Sjöblom[c], E. Sjögren[a], H. Lennernäs[a,*]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] AstraZeneca R&D, Gothenburg, Sweden
[c] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
Absorption-modifying excipients
Biopharmaceutical classification system
Permeation enhancers
Intestinal perfusion
Intestinal permeability
Intestinal physiology
In vivo predictions

ABSTRACT

The small intestine mucosal barrier is physiologically regulated by the luminal conditions, where intestinal factors, such as diet and luminal tonicity, can affect mucosal permeability. The intestinal barrier may also be affected by absorption-modifying excipients (AME) in oral drug delivery systems. Currently, there is a gap in the understanding of how AMEs interact with the physiological regulation of intestinal electrolyte transport and fluid flux, and epithelial permeability. Therefore, the objective of this single-pass perfusion study in rat was to investigate the effect of three AMEs on the intestinal mucosal permeability at different luminal tonicities (100, 170, and 290 mOsm). The effect was also evaluated following luminal administration of a nicotinic receptor antagonist, mecamylamine, and after intravenous administration of a COX-2 inhibitor, parecoxib, both of which affect the enteric neural activity involved in physiological regulation of intestinal functions. The effect was evaluated by changes in intestinal lumen-to-blood transport of six model compounds, and blood-to-lumen clearance of ^{51}Cr-EDTA (a mucosal barrier marker). Luminal hypotonicity alone increased the intestinal epithelial transport of ^{51}Cr-EDTA. This effect was potentiated by two AMEs (SDS and caprate) and by parecoxib, while it was reduced by mecamylamine. Consequently, the impact of enteric neural activity and luminal conditions may affect nonclinical determinations of intestinal permeability. *In vivo* predictions based on animal intestinal perfusion models can be improved by considering these effects. The *in vivo* relevance can be increased by treating rats with a COX-2 inhibitor prior to surgery. This decreases the risk of surgery-induced ileus, which may affect the physiological regulation of mucosal permeability.


Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

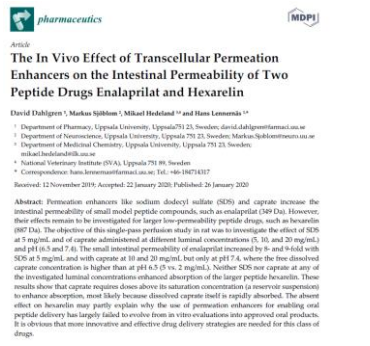
Intestinal absorption-modifying excipients: A current update on preclinical *in vivo* evaluations

D. Dahlgren[a], M. Sjöblom[b], H. Lennernäs[a,c]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] Department of Neuroscience, Division of Physiology, Uppsala University, Uppsala, Sweden

ABSTRACT

Pharmaceutical excipients in drug products are defined as pharmacologically inactive and are integral constituents of all types of oral dosage forms. However, some excipients may increase drug absorption by interacting with the mucosal membrane. If the strategy is to use an excipient with a potential to affect the processes determining the rate and/or extent of the intestinal drug absorption, it is defined as an absorption-modifying excipients (AME). These pharmaceutical excipients may act as AMEs, depending on the amounts applied, and accordingly influences bioequivalence assessment of innovative and generic drug products, as well as enable oral delivery of peptides and oligonucleotides. This review discusses the mechanisms by which AMEs increase drug absorption, and especially permeation step. The focus is on the most recent data regarding how AMEs can be evaluated in preclinical models, with an emphasis on in situ and in vivo intestinal absorption models. The in vivo predictive value of those models is reviewed for five factors of clinical relevance for the intestinal absorption performance: (a) effect and response rate of AMEs, (b) mucosal exposure time and intestinal transit of AMEs, (c) intraluminal AME dilution and proximal state, (d) mucosal recovery and safety, and (e) variability in the effects of the AMEs. We argue that any preclinical investigations of AMEs that fail to consider these processes will ultimately be of limited clinical value and add little to our understanding of how excipients affect intestinal drug absorption.


pharmaceutics

MDPI

Article

The In Vivo Effect of Transcellular Permeation Enhancers on the Intestinal Permeability of Two Peptide Drugs Enalaprilat and Hexarelin

David Dahlgren [1], Markus Sjöblom [2], Mikael Hedeland [3,4] and Hans Lennernäs [1,*]

[1] Department of Pharmacy, Uppsala University, Uppsala 751 23, Sweden; david.dahlgren@farmaci.uu.se
[2] Department of Neuroscience, Uppsala University, Uppsala 751 23, Sweden; Markus.Sjoblom@neuro.uu.se
[3] Department of Medicinal Chemistry, Uppsala University, Uppsala 751 23, Sweden; mikael.hedeland@ilk.uu.se
[4] National Veterinary Institute (SVA), Uppsala 751 89, Sweden
* Correspondence: hans.lennernas@farmaci.uu.se; Tel.: +46-184714317

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Abstract: Permeation enhancers like sodium dodecyl sulfate (SDS) and caprate increase the intestinal permeability of small model peptide compounds, such as enalaprilat (349 Da). However, their effects remain to be investigated for larger low-permeability peptide drugs, such as hexarelin (887 Da). The objective of this single-pass perfusion study in rat was to investigate the effect of SDS at 5 mg/mL and of caprate administered at different luminal concentrations (5, 10, and 20 mg/mL) and pH (6.5 and 7.4). The small intestinal permeability of enalaprilat increased by 8- and 9-fold with SDS at 5 mg/mL and with caprate at 10 and 20 mg/mL but only at pH 7.4, where the free dissolved caprate concentration is higher than at pH 6.5 (5 vs. 2 mg/mL). Neither SDS nor caprate at any of the investigated luminal concentrations enhanced absorption of the larger peptide hexarelin. These results show that caprate requires doses above its saturation concentration (a reservoir suspension) to enhance absorption, most likely because dissolved caprate itself is rapidly absorbed. The absent effect on hexarelin may partly explain why the use of permeation enhancers for enabling oral peptide delivery has largely failed to evolve from in vitro evaluations into approved oral products. It is obvious that more innovative and effective drug delivery strategies are needed for this class of drugs.

In vivo PE studies:

- Effect in different species and models
  - Rat, dog, SPIP, intestinal bolus
- Concentration and pH
  - Caprate, SDS, chitosan, EDTA etc.
- Mucosal exposure time-dependence
- Variability in effect
- Effect on peptides with different properties
  - Enalaprilat and hexarelin
- Food effects
  - FaSSIF and FeSSIF
- Safety/mucosal recovery
- **Effect in the colon**

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Permeation enhancers in the colon

pharmaceutics

MDPI

Article

Regional Intestinal Drug Permeability and Effects of Permeation Enhancers in Rat

David Dahlgren [1], Maria-Jose Cano-Cebrián [2], Tobias Olander [1], Mikael Hedeland [3,4], Markus Sjöblom [5] and Hans Lennernäs [1,*]

1 Department of Pharmacy, Division of Biopharmaceutics, Uppsala University, 752 36 Uppsala, Sweden; david.dahlgren@farmaci.uu.se (D.D.); olander92@hotmail.com (T.O.)
2 Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia, 46010 València, Spain; Maria.Jose.Cano@uv.es
3 Department of Medicinal Chemistry, Analytical Pharmaceutical Chemistry, Uppsala University, 752 36 Uppsala, Sweden; mikael.hedeland@ilk.uu.se
4 Department of Chemistry, Environment and Feed Hygiene, National Veterinary Institute (SVA), 751 89 Uppsala, Sweden
5 Department of Neuroscience, Division of Physiology, Uppsala University, 752 36 Uppsala, Sweden; Markus.Sjoblom@neuro.uu.se
* Correspondence: hans.lennernas@farmaci.uu.se

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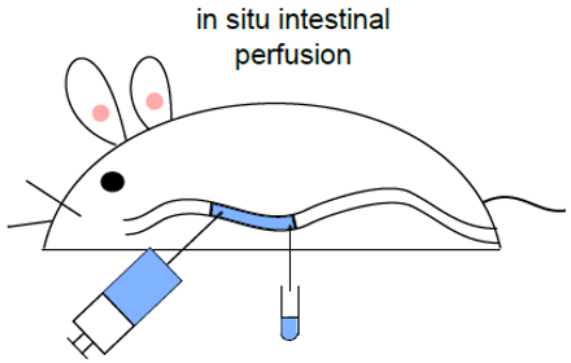
check for updates



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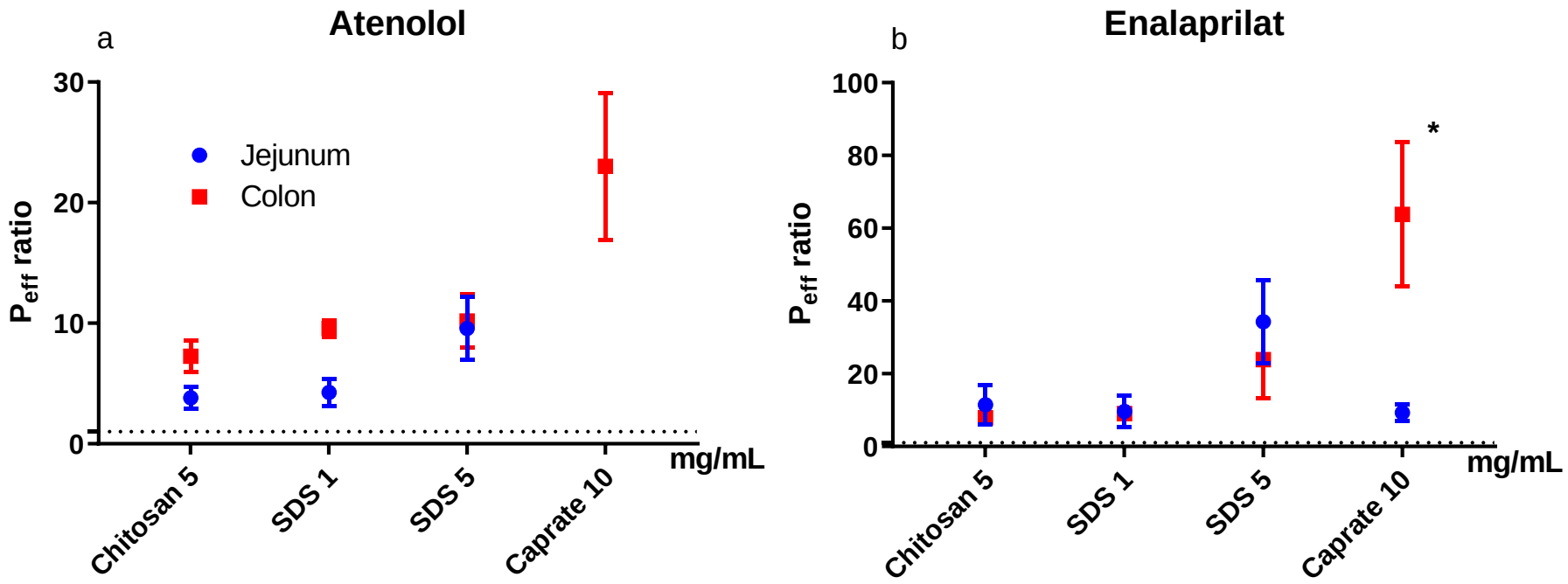
Permeation enhancers in the colon



Generally, no added effect of PEs in colon on drug permeability

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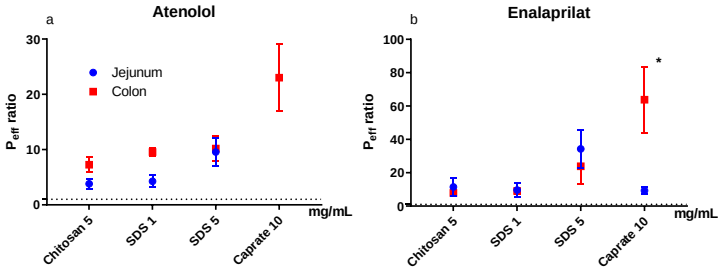
Permeation enhancers in the colon



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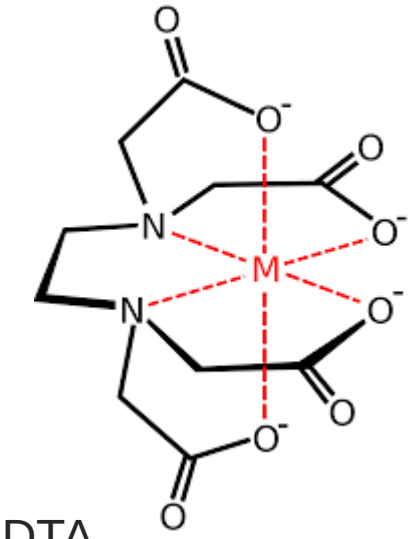
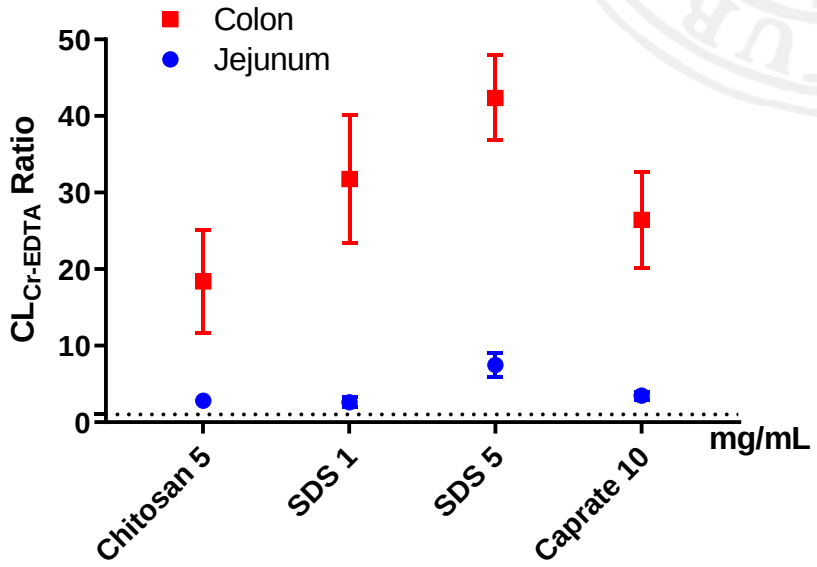


Cr-EDTA
clinical barrier markler



Substantial leakage of Cr-EDTA in colon

Based on these rat data - the risks of using PE in the colon seems to outweigh the gain

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Summary and conclusions

Reference human colonic drug P_{eff} data - for the first time

The **rat and dog jejunum** predicts human jejunal permeability well

The **dog colon** is useful, but more permeable than the human colon to low permeability drugs

The **rat colon** is not suitable for predicting human colonic permeability

We still need a good preclinical model for predicting human regional permeability

The risks of using PE in the colon seems to outweigh the gain

Thanks for your attention

david.dahlgren@farmbio.uu.se

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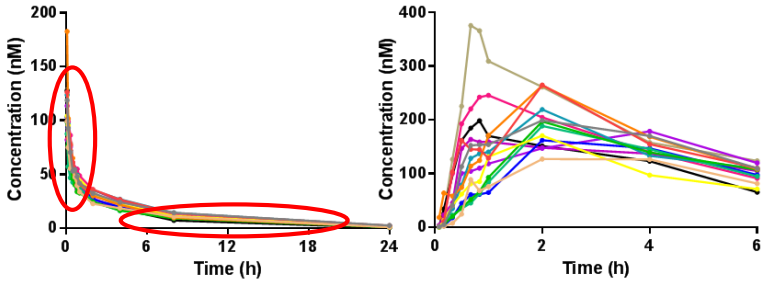
Bolus drug solution administration
IV and intraluminal



Elimination Distribution

Deconvolution

Luminal input rate (mg/s)

First pass metabolism corection

$$E_H = \frac{CL_H}{Q_H}$$

Luminal absorption rate (mg/s)

Intestinal drug conc.

Luminal Clearance (cm^3/s)

Luminal Clearance (cm^3/s) / surface area (cm^2)

Effective permeability (cm/s)

Administred intraluminal drug solution (mL)

Administered drug solution assumed to reside as a water pocket

Surface area available for absorption (cm^2)

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