# Measurement and prediction of human permeability: current best practices, regional differences and future developments

*Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls*
*CERSI Workshop, College Park, MD, September 23 2019*

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# Content

- Background
- Measurements and Predictions
- Regional differences
- Importance for drug product performance
- Future development

# Background

**Permeability**

- The reciprocal of the resistance for a molecule to move from point A to point B through a specified matrix.

**Permeability in a biopharmaceutical context** (generally)

- The ability for a drug to translocate a cell membrane or epithelial.
- Determined by a combination of processes and conditions.

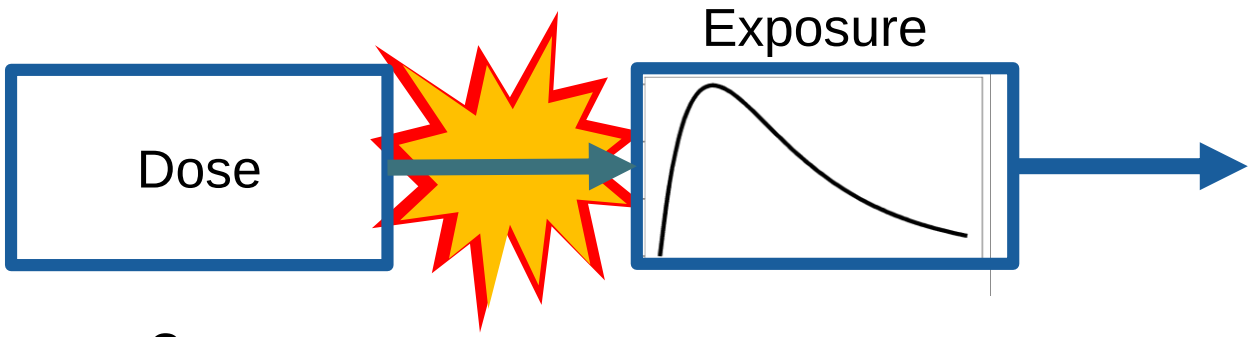
**Interpretation of permeability in a biopharmaceutical context**

- A characteristic that translate to a drugs potential to be absorbed.

# Background

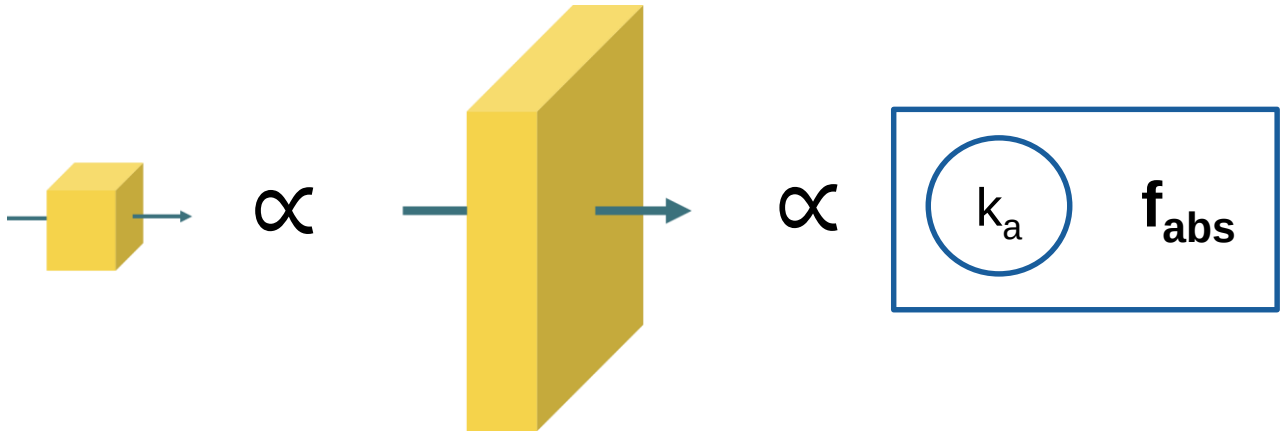
**What do we want?**

- To predict extent or rate of absorption




**By what means?**

- By accessible information/measurement and a direct approach for translation




*Info/experiment* *In vivo reference* *Clinic output*

# Background

**How do we achieve this in the best way** (i.e., best practice)

- Clear definitions
- Defined experimental conditions
- Defined constraints of assays, experimental procedures and correlations.
- Defined strategies for translation to in vivo conditions

# Background

## Permeability - Reference data

- Understand the reference data, the experimental settings, assumptions and calculations, AND how these relate to an in vivo situation.

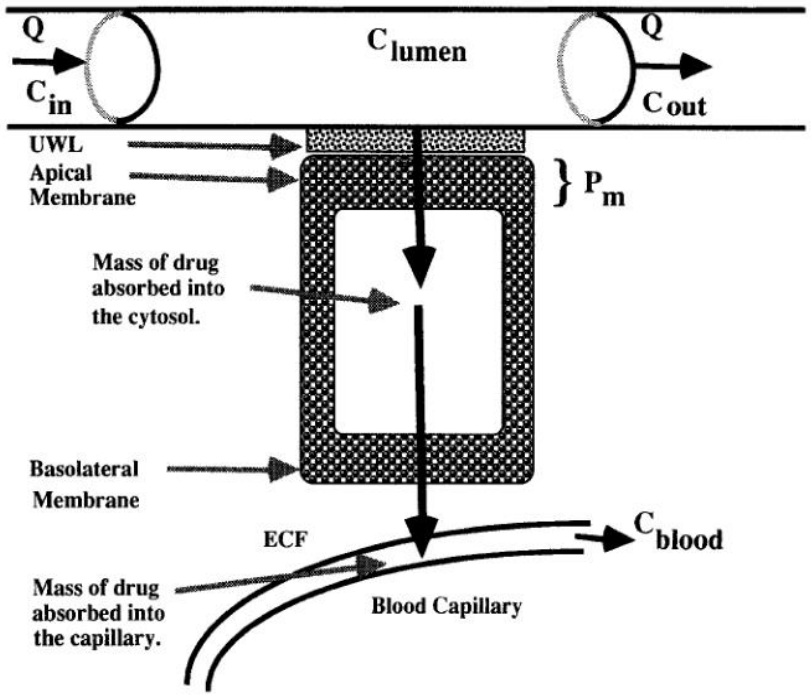



**Fig. 1.** Illustration of the different transport barriers a drug molecule has to pass during the intestinal absorption process (UWL: unstirred water layer, ECF: extracellular fluid, Pm: membrane permeability).

*Permeability and Clearance Views of Drug Absorption: A Commentary*
*Lennernäs et al. 1995.*

*"Transport to the membrane (aqueous permeation, e.g., diffusion and convection to the membrane), cell mucosa permeation including mucin and membrane translocation processes (passive and/or active transcellular transport or passive paracellular diffusion /convection), and perhaps transport through the cytosol, basolateral membrane, interstitial fluid, and capillary wall to the blood"*

# Background

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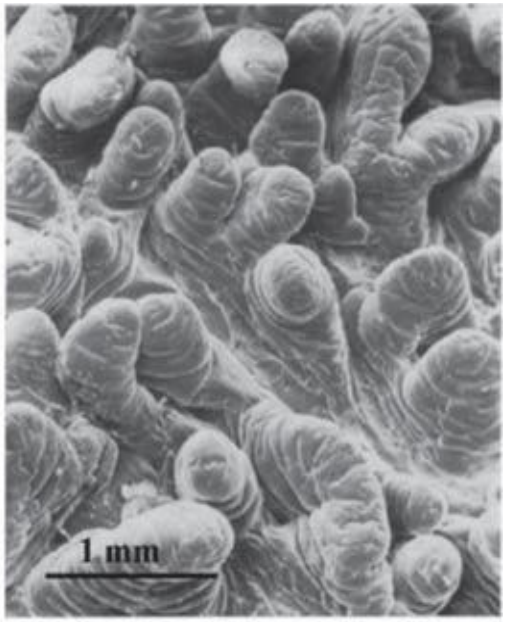
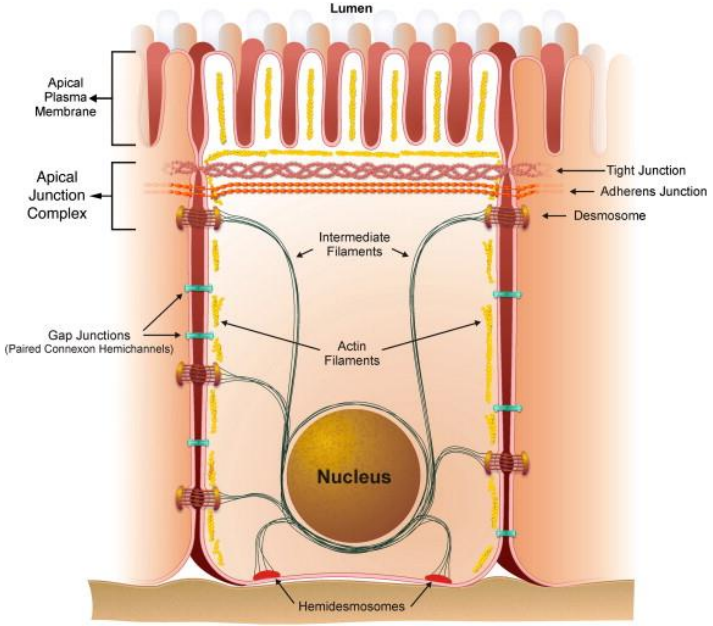
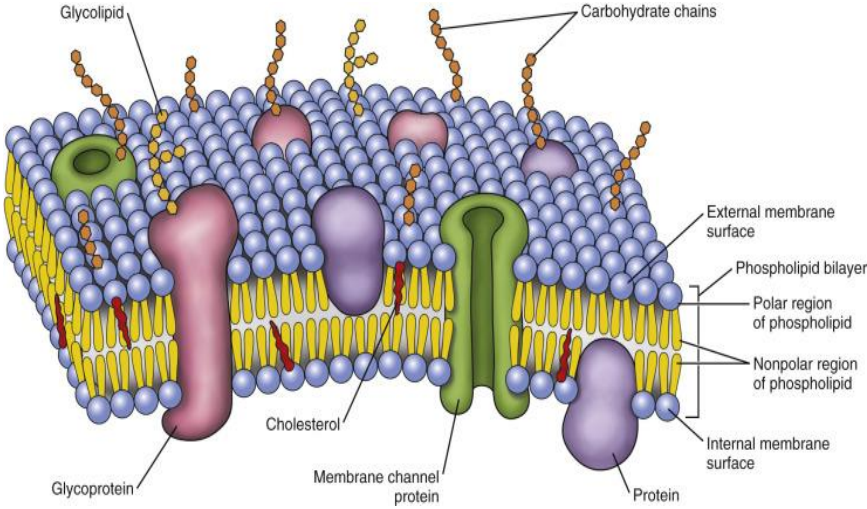



*Helander, et al. 2014*




*Guttman, et al. 2009*




*Miller, et al. 2017*

# Measurements and predictions

Confident measurements and predictions can only be done with understanding of the information at hand AND the reference data AND how these relate to an in vivo situation.

- Understand your information including the source of information
- Define the application
- Assess the level for translation
- Define the constraints and limitations
- Assess the expected predictive performance
- Continuously evaluate and re-calibrate

# Measurements and predictions

**Predictions based on Chemical descriptors and molecular properties**

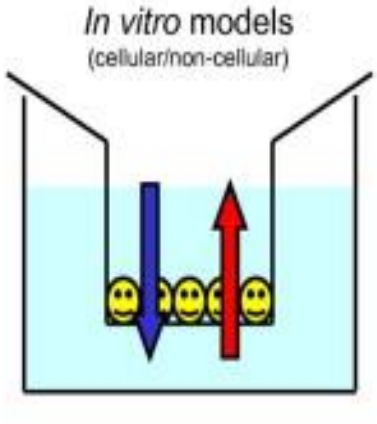
- Review the experimental data used

**Cell-based assays and excised tissue specimens**

- Review experimental setup and data analysis carefully

**Problems**

- Precipitation of drug
- Insufficient concentration
- Adsorption
- Accumulation
- Poor mass balance
- UWL
- Non-sink conditions
- Variability in $P_{app}$ values
- Effect of free and bound fraction of drug




**Solutions**

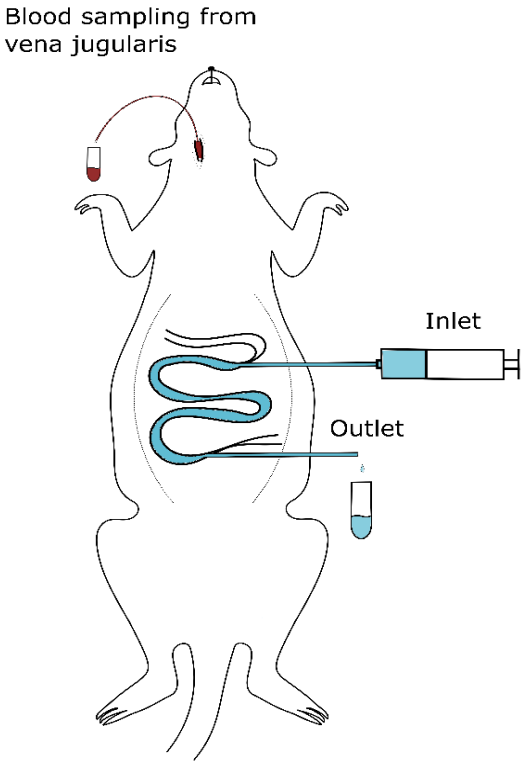
- Solubilising agents
- Bio-relevant media
- More sensitive analytical technique
- Bovine serum albumin
- Stirring
- Refined calculation of $P_{app}$
- Use flux values
- Reciprocal permeability

*Buckley et al. 2012*

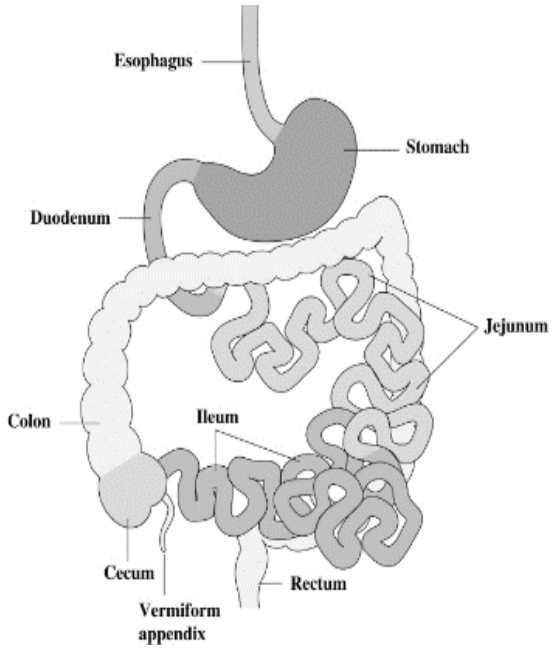
# Measurements and predictions

## Preclinical in-situ systems

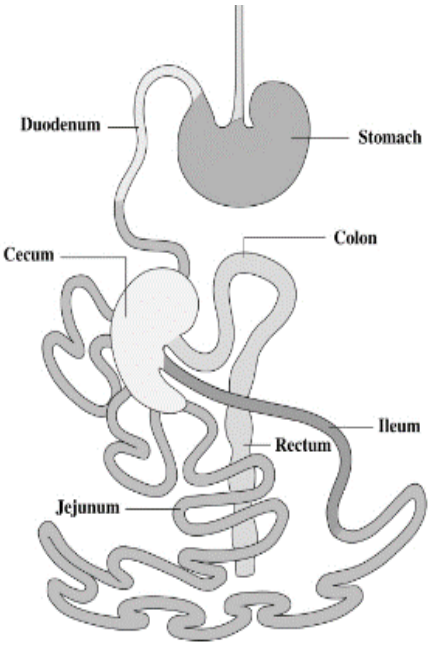
- Review experimental setup and data analysis carefully
- Species differences




Human




Rat




*DeSesso et al. 2001*

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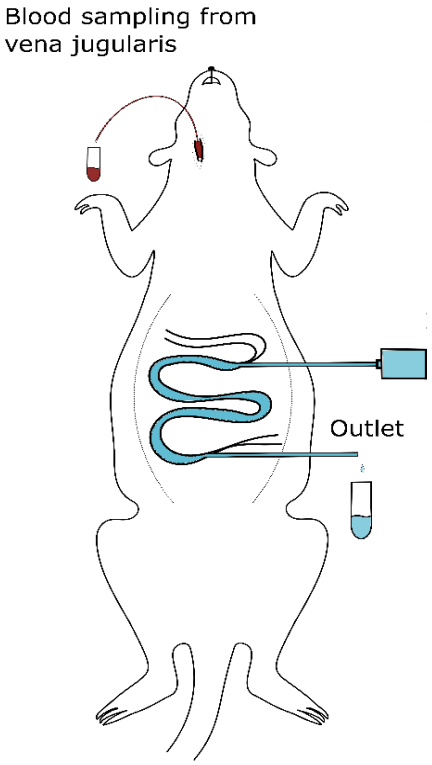


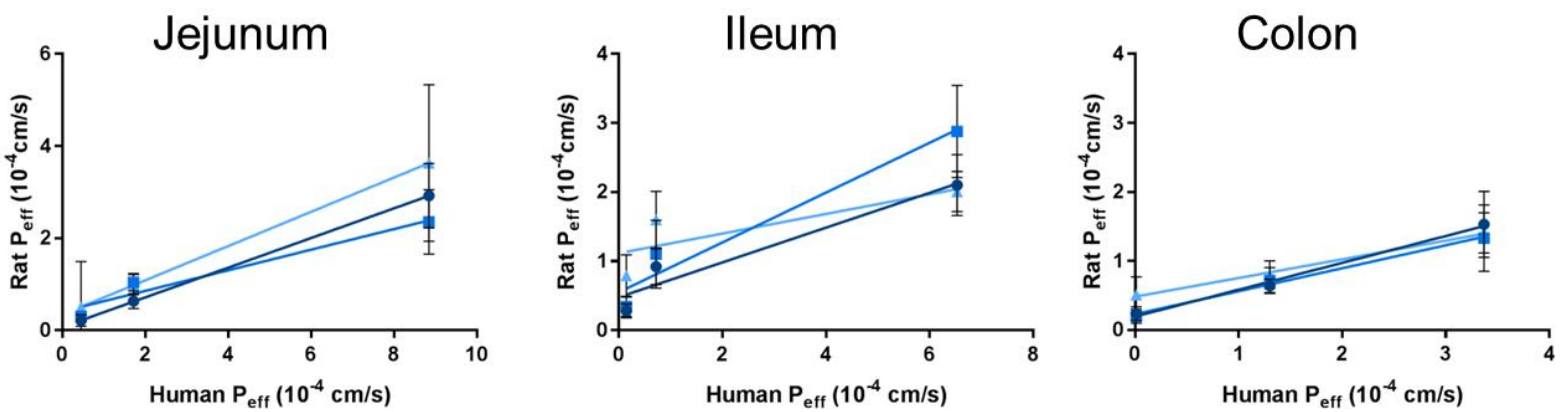


atenolol, metoprolol and ketoprofen
perfusate pH 6.5 (low/high I) and pH 7.4

*Roos et al. 2017*

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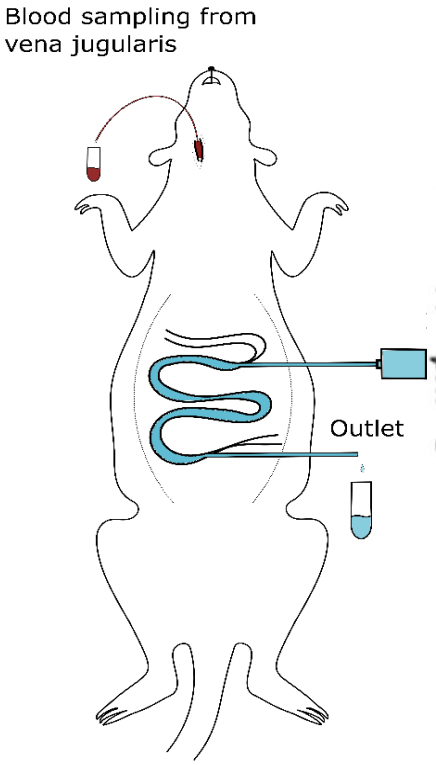
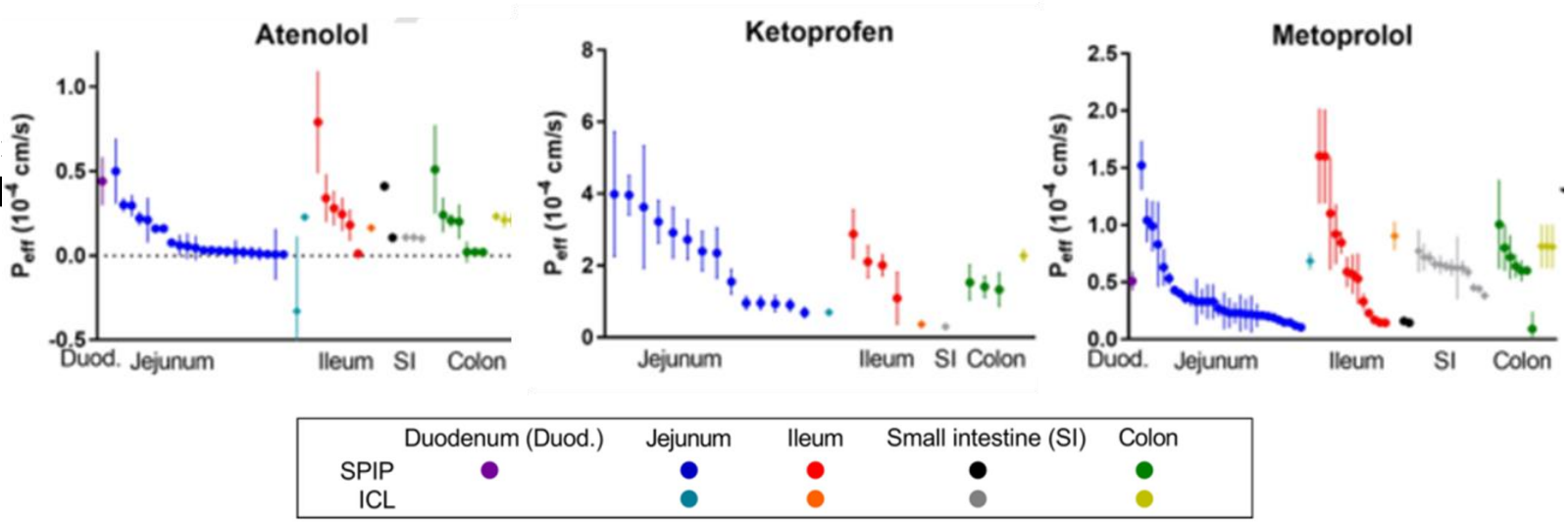



Compilation of published rat intestine permeability measurements in-situ

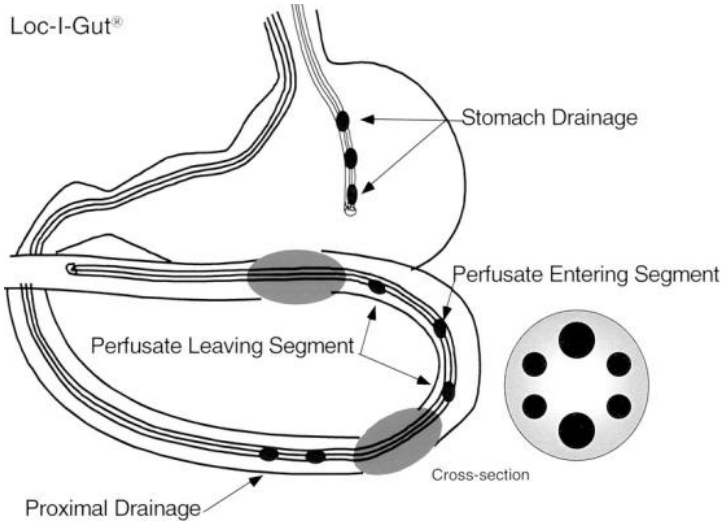


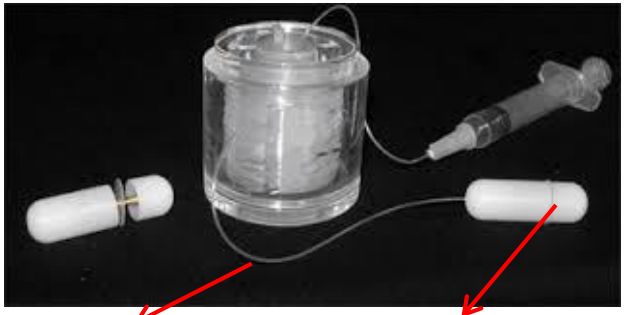

*Dubbelboer et al. 2019*

# Measurements and predictions

**Human in vivo permeability**

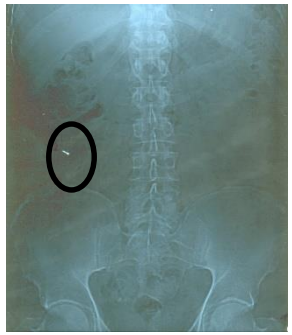
- Perfusion of segment– *traditional reference*
- Local drug administration - deconvolution of plasma conc.-time profile
  - Enables regional measurements



Diameter 0.6 mm

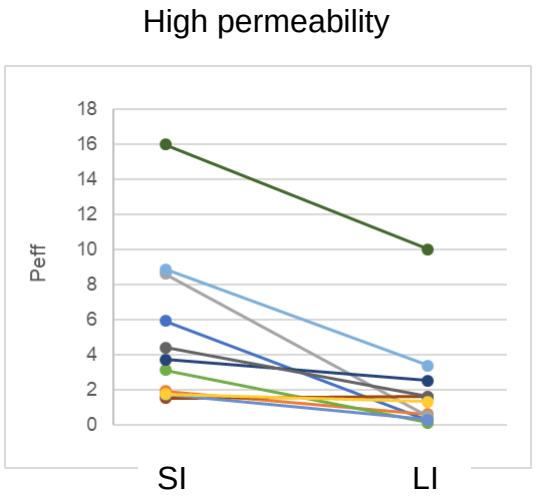
Size 30 * 10 mm

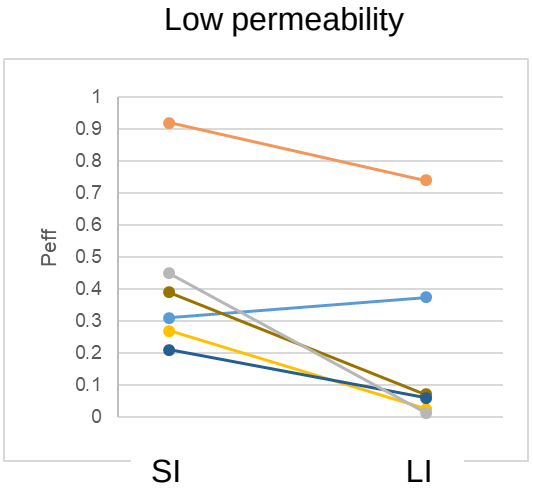


# Regional permeability

**What do we know?**

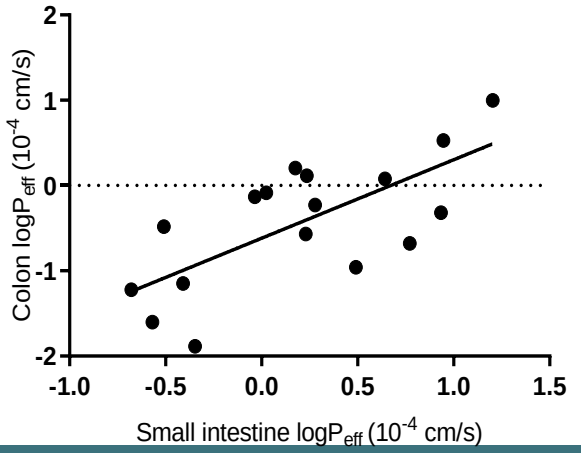
Permeability is generally lower in the large intestine (LI) compared to the small intestine (SI).




*Sjögren et al. 2015*

Direct correlation between permeability in SI and LI is weak.



# Regional absorption

**What is the overall concern?**

- LI is a black box for absorption – erratic
- Absorption in LI is generally lower than in SI – inadequate

**What are observations telling us?**

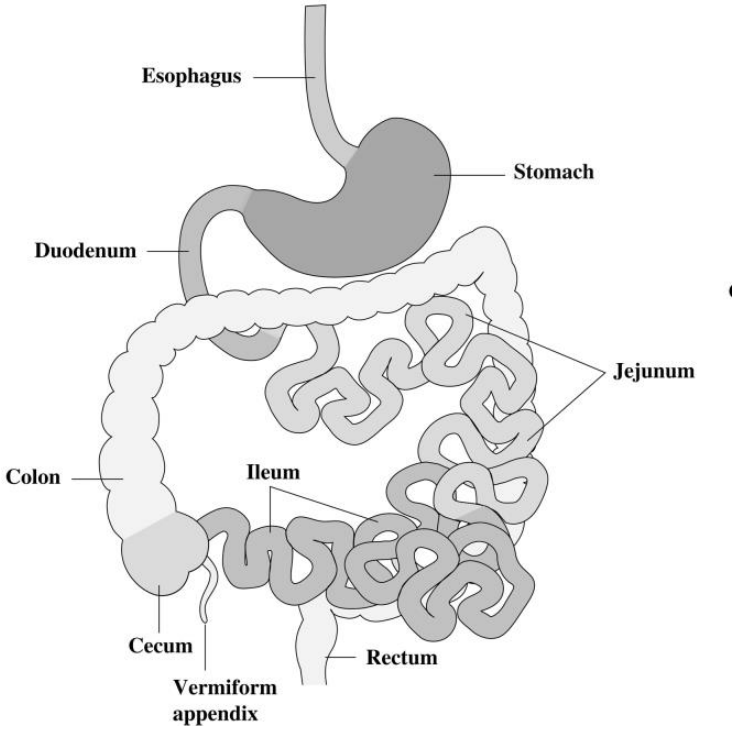
- Yes, absorption from LI is slower and less than in SI.
- Current knowledge indicates that the permeability generally is lower.
- Yet, some drugs are readily absorbed in LI.
- ER formulations releasing in colon can perform adequately for high permeably drugs while poorly permeable drugs generally will not.

- However, residence time in LI is much longer than in SI.
- Is the reduced extent of absorption in LI only caused by a reduction in permeability?

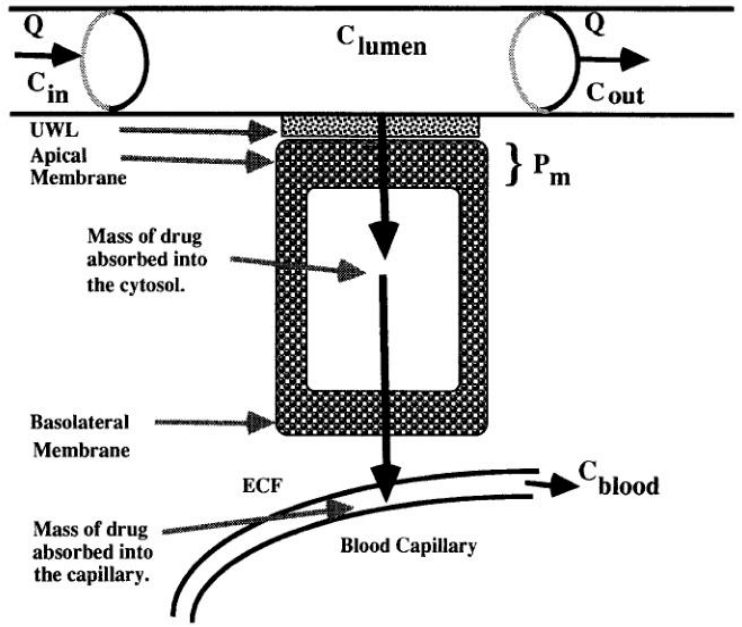
# Importance for drug product performance

**Regional differences in permeability**

- Release/dissolution in regions where permeability is sufficiently high.
- Sensitive to formulation changes/variations




*DeSesso et al. 2001*

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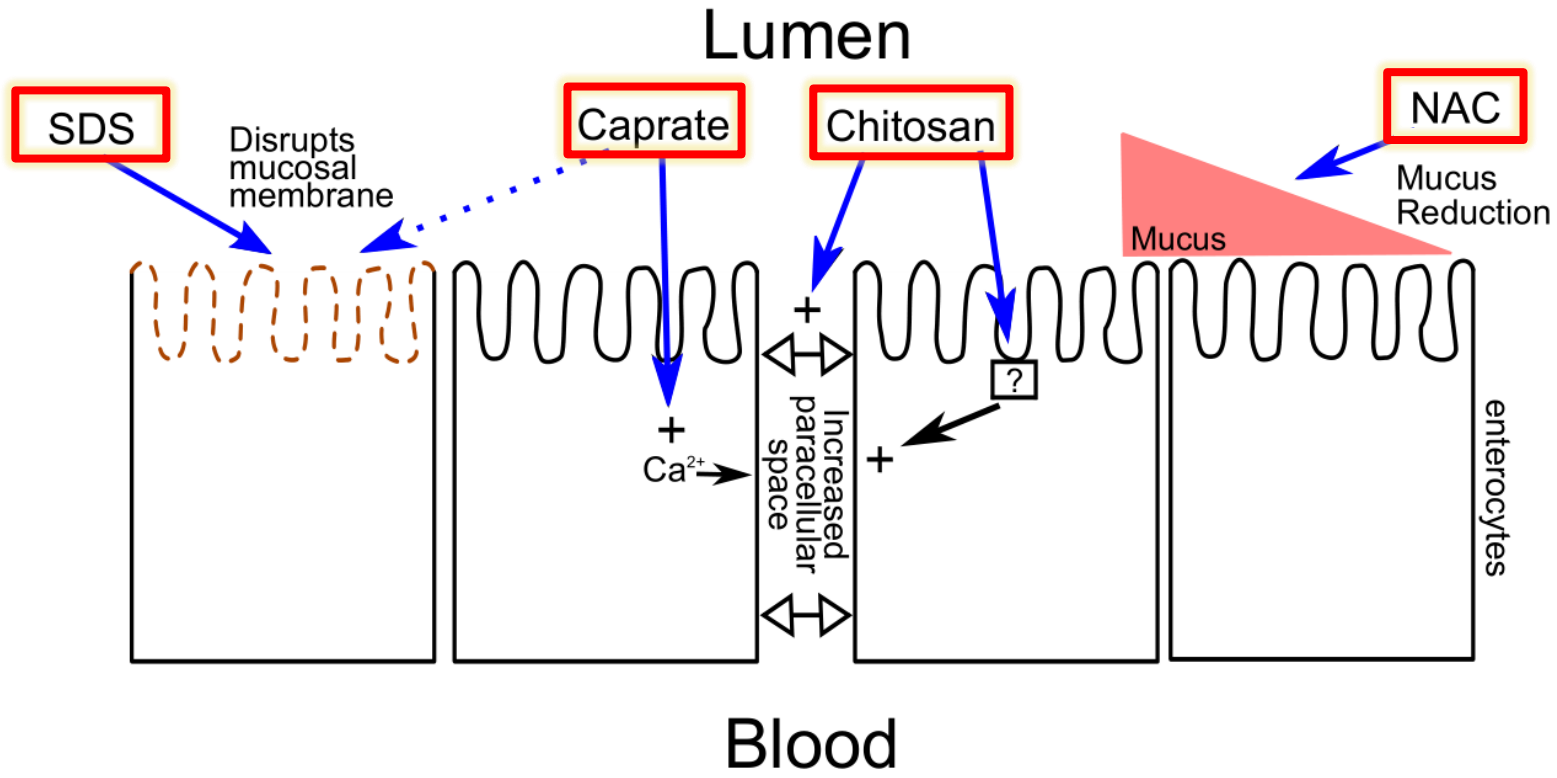
*Lennernäs et al. 1995.*

# Importance for drug product performance

**Formulation ingredients affecting permeability (abs. modifying excipients)**



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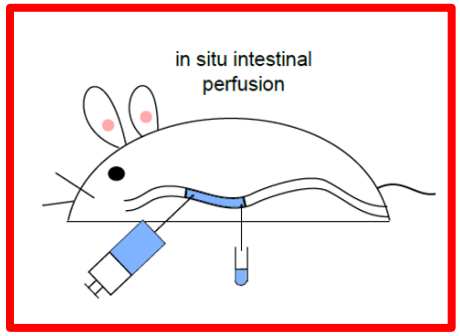
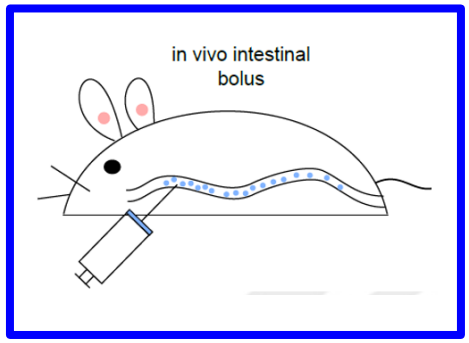
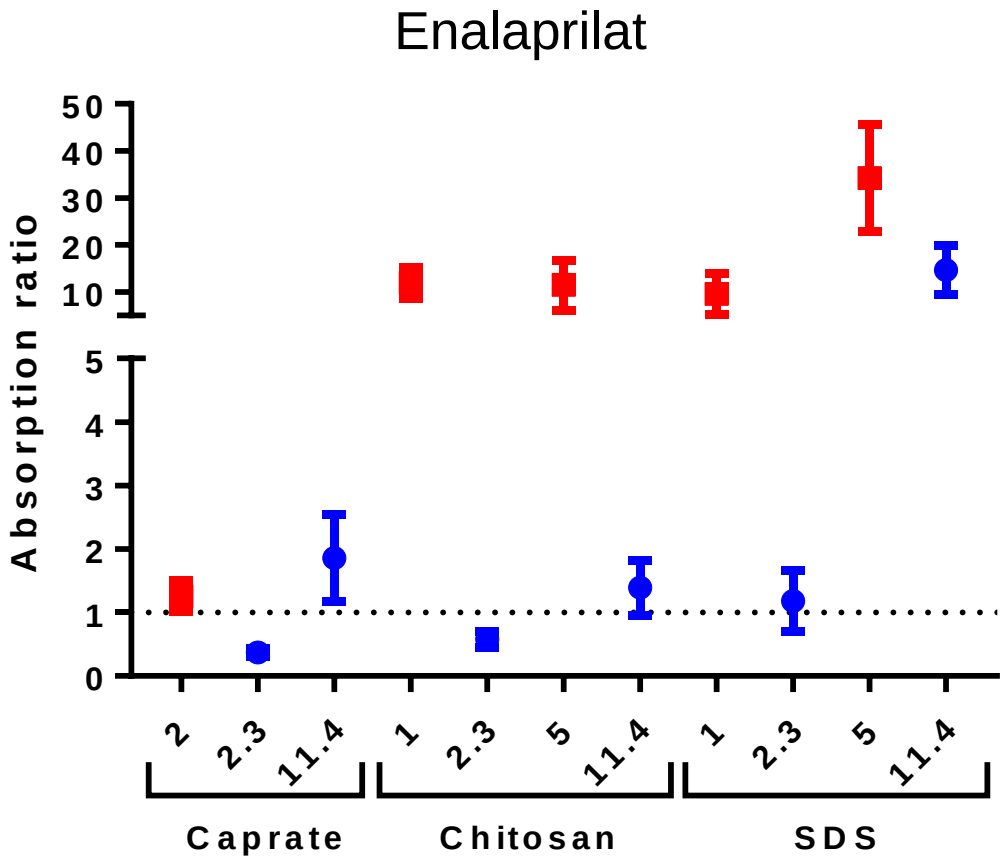


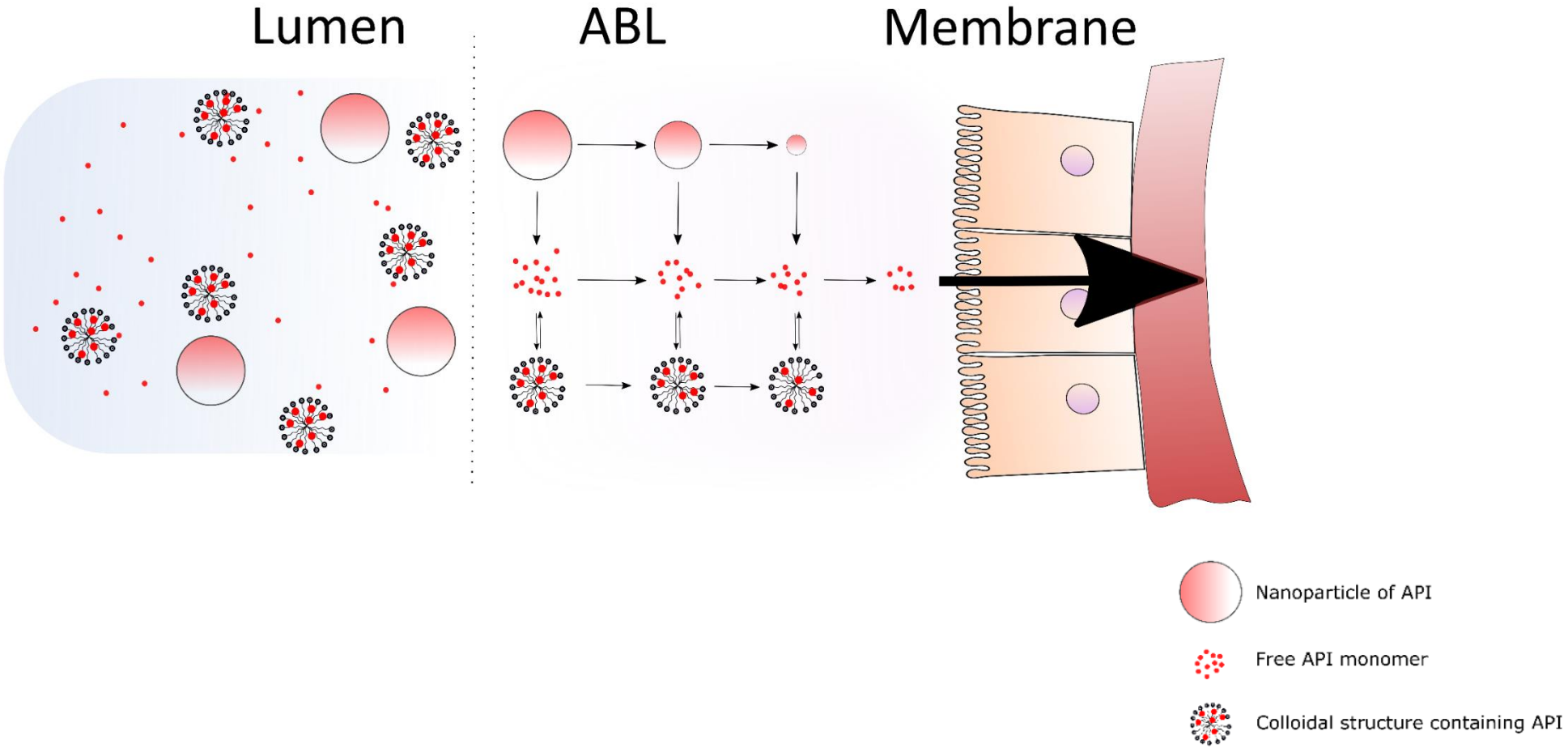




*Dahlgren et al. 2018*

# Importance for drug product performance

**Formulation designs with effect on permeability (e.g., particle drifting theory)**



# Future development

**Increase knowledge**

Additional measurements and deeper understanding

- Regional differences
- Physiological conditions and processes
- Formulation dependencies

**Apply knowledge**

- Improve assays and experimental procedures
- Implement knowledge to stipulate application based best practices

# Thank you for your attention