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
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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 translates to a drug's 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

Exposure

Dose

Info/experiment \( \propto \) In vivo reference \( \propto \) Clinic output

\( k_a \) \( f_{abs} \)

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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.

“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

Permeability - Reference data

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

Helander, et al. 2014


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

Buckley et al. 2012
Measurements and predictions

Preclinical in-situ systems

- Review experimental setup and data analysis carefully
- Species differences

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DeSesso et al. 2001
Measurements and predictions

Preclinical in-situ systems

- Review experimental setup and data analysis carefully
- Species differences

Roos et al. 2017

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

Roos et al. 2017
Measurements and predictions

**Preclinical in-situ systems**

- Review experimental setup and data analysis carefully
- Species differences

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

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Regional permeability

What do we know?
Permeability is generally lower in the large intestine (LI) compared to the small intestine (SI).

Direct correlation between permeability in SI and LI is weak.

Sjögren et al. 2015
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

Lennernäs et al. 1995.
Importance for drug product performance

Formulation ingredients affecting permeability (abs. modifying excipients)
Importance for drug product performance

Formulation ingredients affecting permeability (abs. modifying excipients)

Enalaprilat

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