PHABIOC

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New analytical tools for drug discovery and drug development

- Gegründet im Februar 2023
  - Carsten Radtke
  - Jannik Jungmann
  - Erwin Quarder Systemtechnik GmbH (Serienproduzent)
  - Eike Kottkamp (strategische Beratung)
- Operativ tätig seit März 2023
- Unsere Idee:
  - Neuartige Multiwellplatten für Biotech/Pharma
  - Steigerung in Effizienz und Reproduzierbarkeit
  - Einfache Implementierung in Standardgeräte

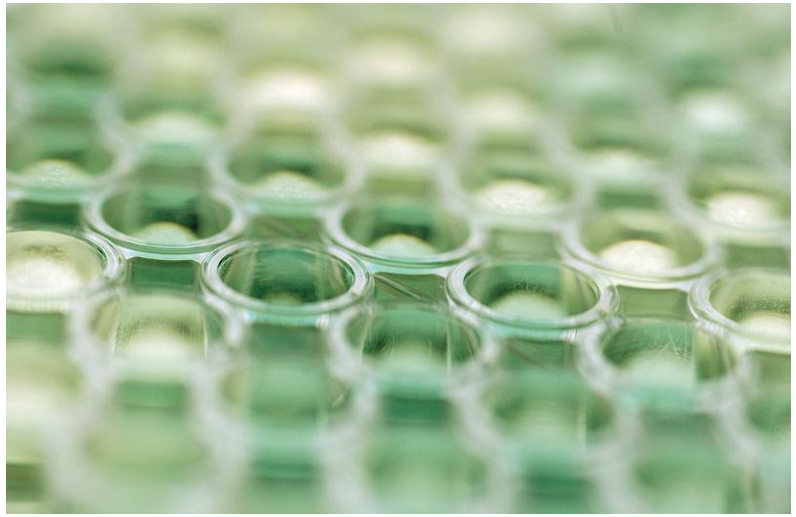
Büro in Karlsruhe

©Nathalie Zimmermann

Bundesministerium für Wirtschaft und Klimaschutz
eXIST Existenzgründungen aus der Wissenschaft
ESF Europäischer Sozialfonds für Deutschland
Europäische Union
Zusammen. Zukunft. Gestalten.

UV/Vis Spectroscopy in High-Throughput

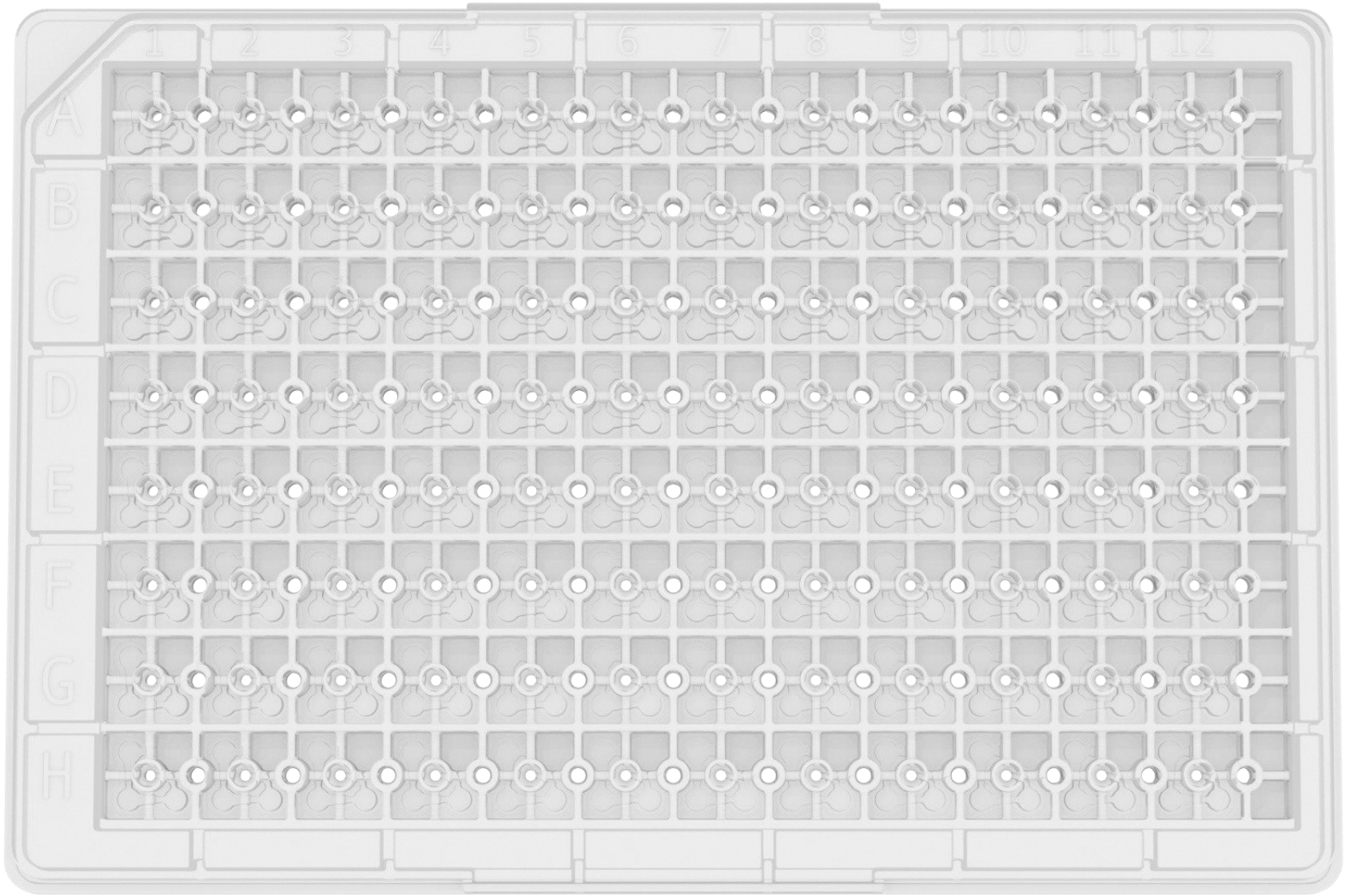
- Gold standard = Multiwell plates



- Limited concentration range
- Pipetting errors
- Liquid meniscus
- Alternatives not HT compatible or challenging implementation

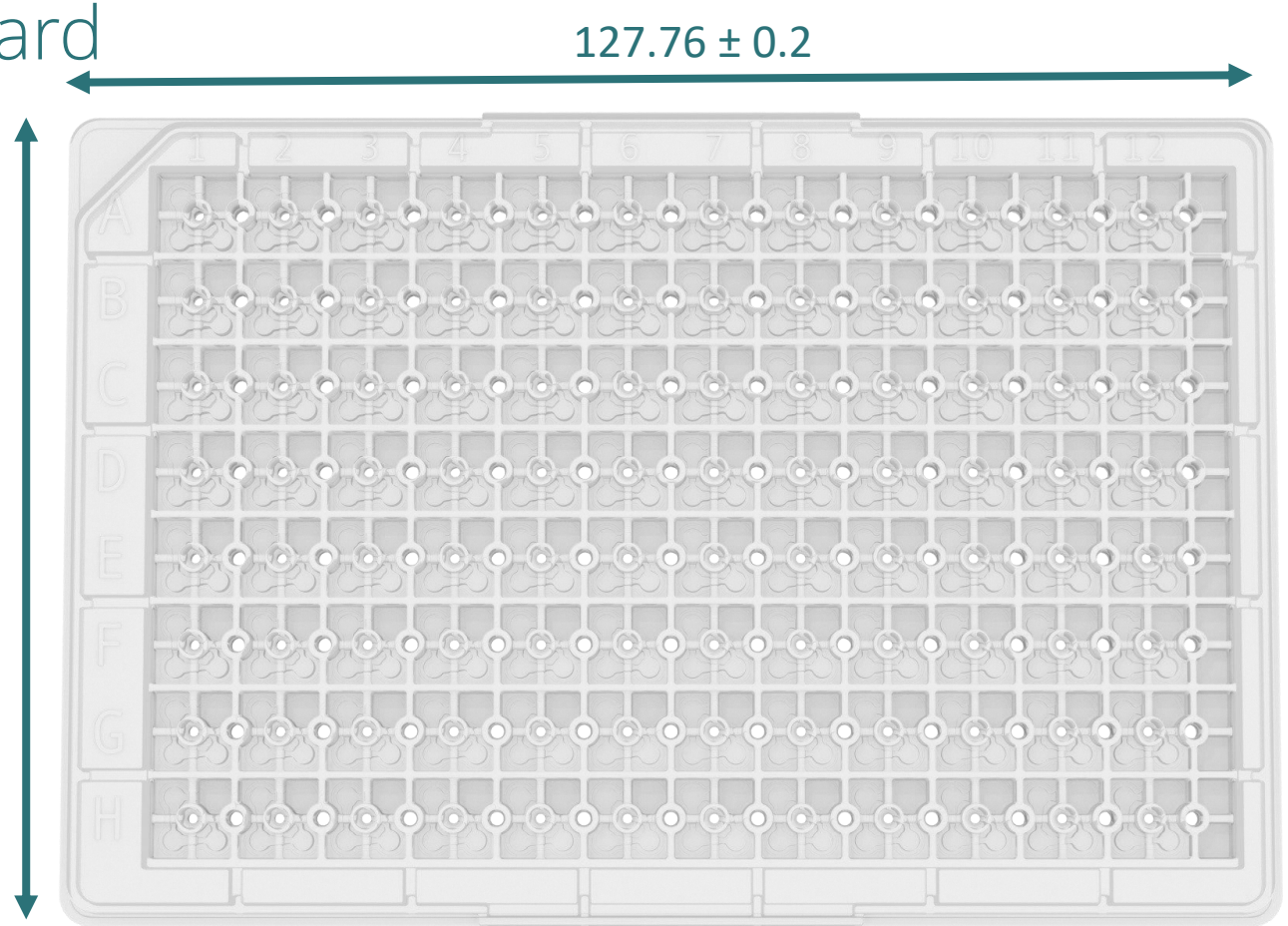
- High expenditure of time and material

SpecPlate



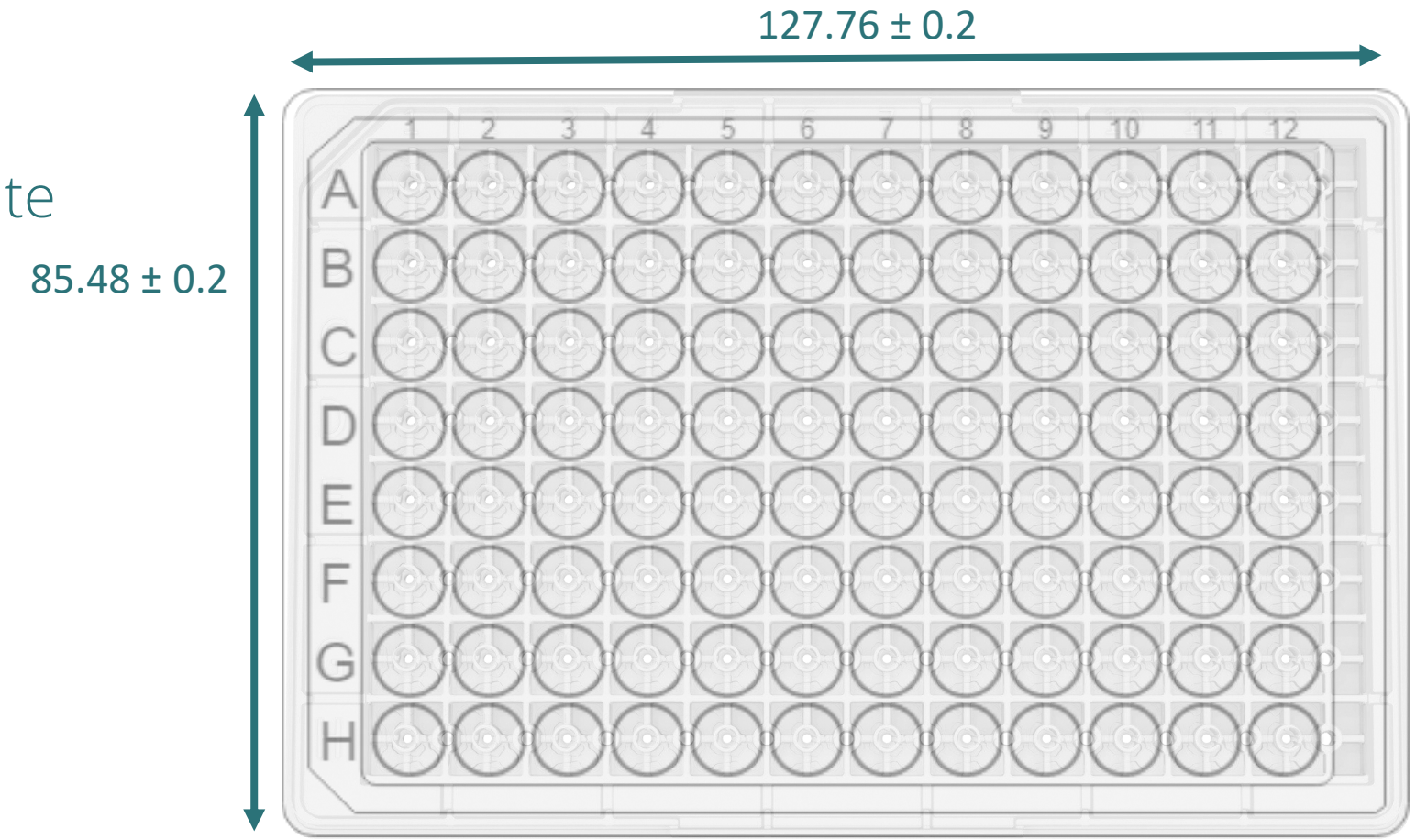
Design

- Conformity with SLAS standard
  - Society for lab automation
  - Handling like standard plates



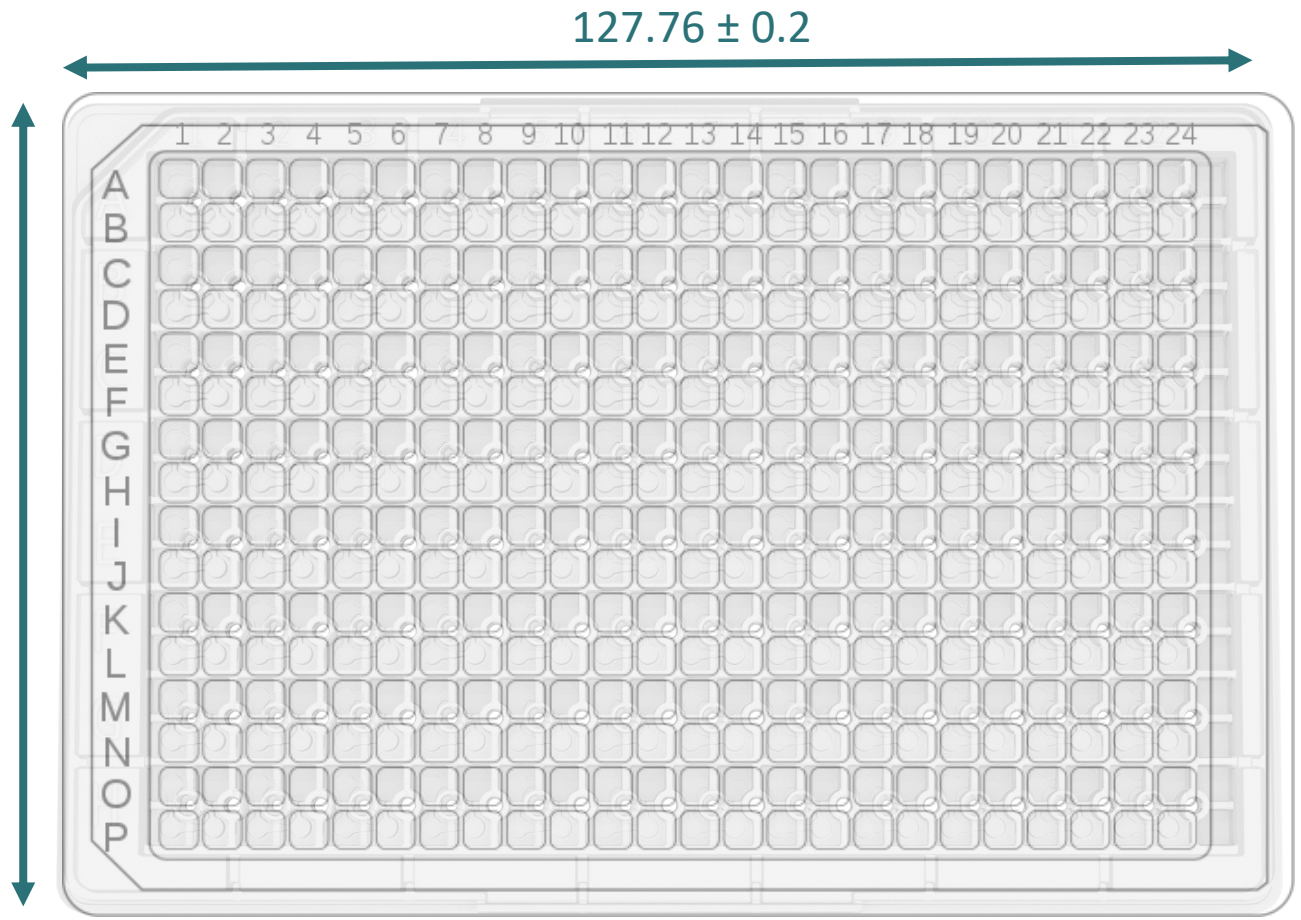
Design

- 96 structures
  - filling like 96 Well Plate



Design

- 4 measuring chambers
  - Measuring like 384 Well Plate



Design

- Conformity with SLAS standard
  - Society for lab automation
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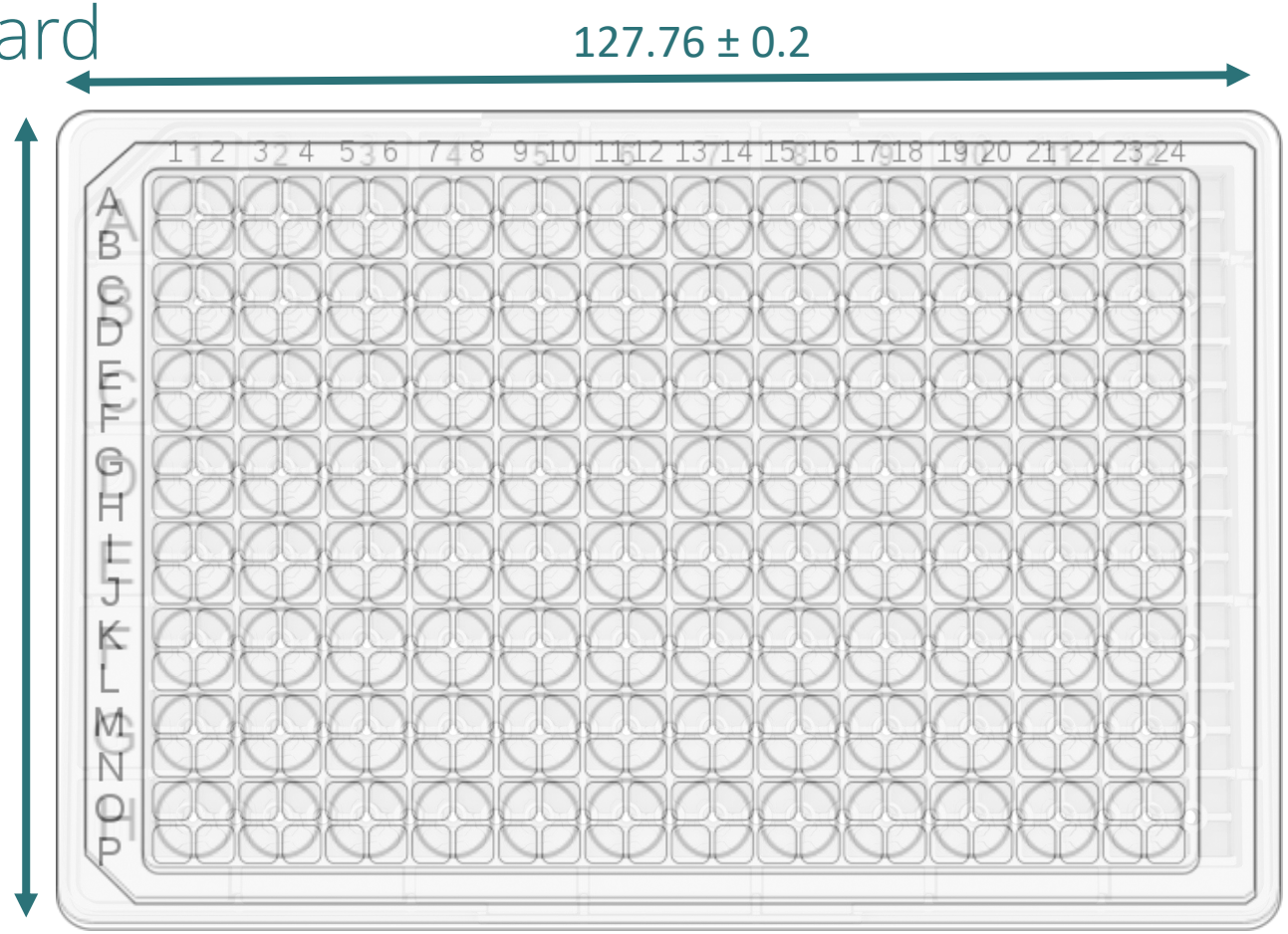
- 96 structures
  - filling like 96 Well Plate
- 4 measuring chambers
  - Measuring like 384 Well Plate

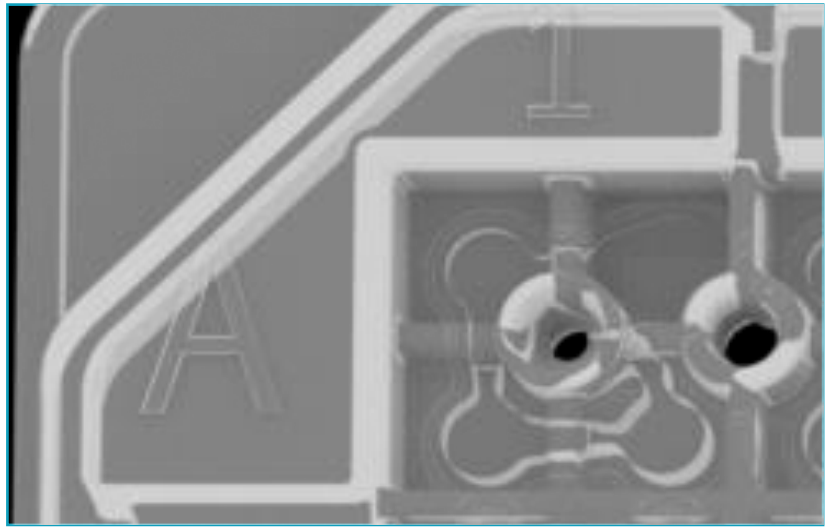


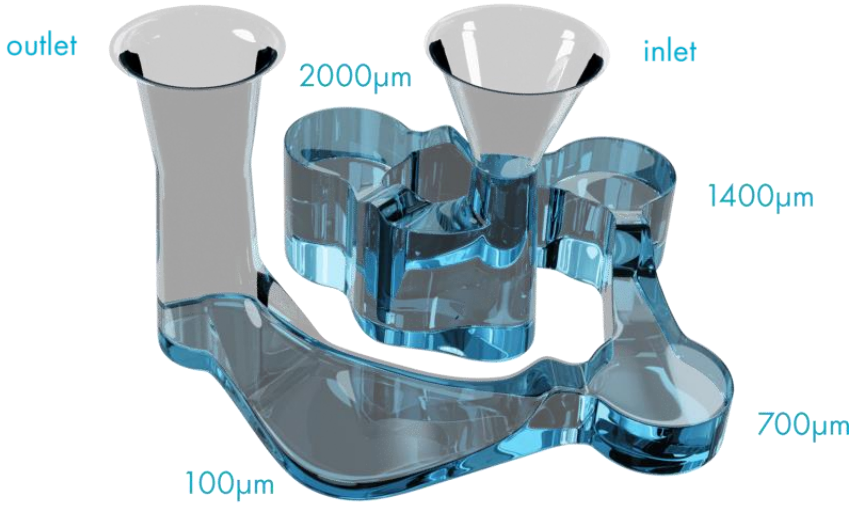
Compatible instruments

- SpecPlate is compatible with all common devices
  - Liquid handler capable of handling 96 Well plates
  - Plate Reader capable of reading 384 Well plates

- Compatibility already tested
  - Tecan Evo (8 pipettes setup)
  - Tecan Fluent (96 pipettes setup)
  - Eppendorf ep5070 (8 pipettes setup)
  - Plate Reader from Tecan and BMG

96 measuring structures



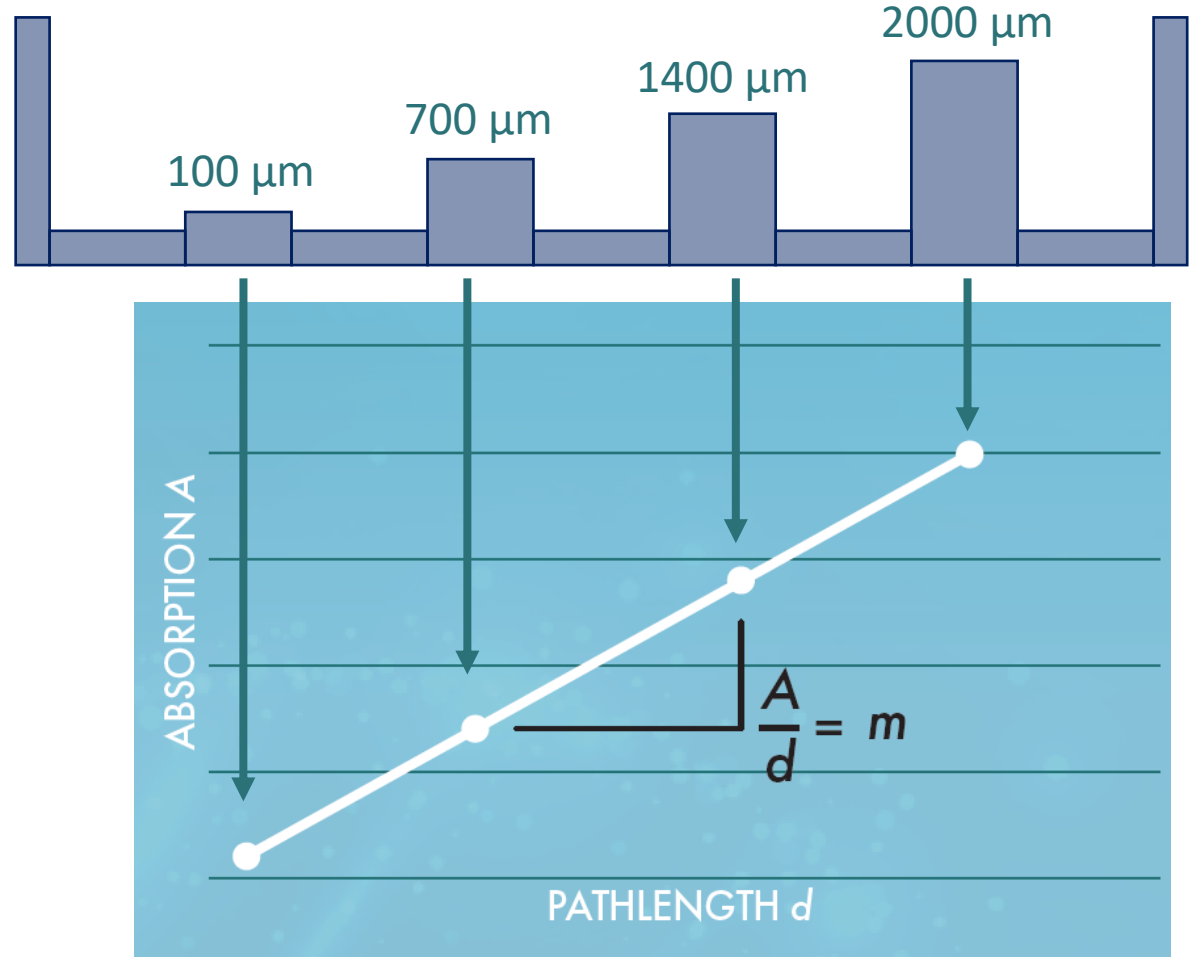


- Defined pathlengths
  - 2000, 1400, 700, 100 µm
  - No liquid meniscus
- Broad concentration range
- Sample volume: 36 µL

$$E_\lambda = \log_{10}\left(\frac{I_0}{I_1}\right) = \varepsilon_\lambda \cdot c \cdot d$$

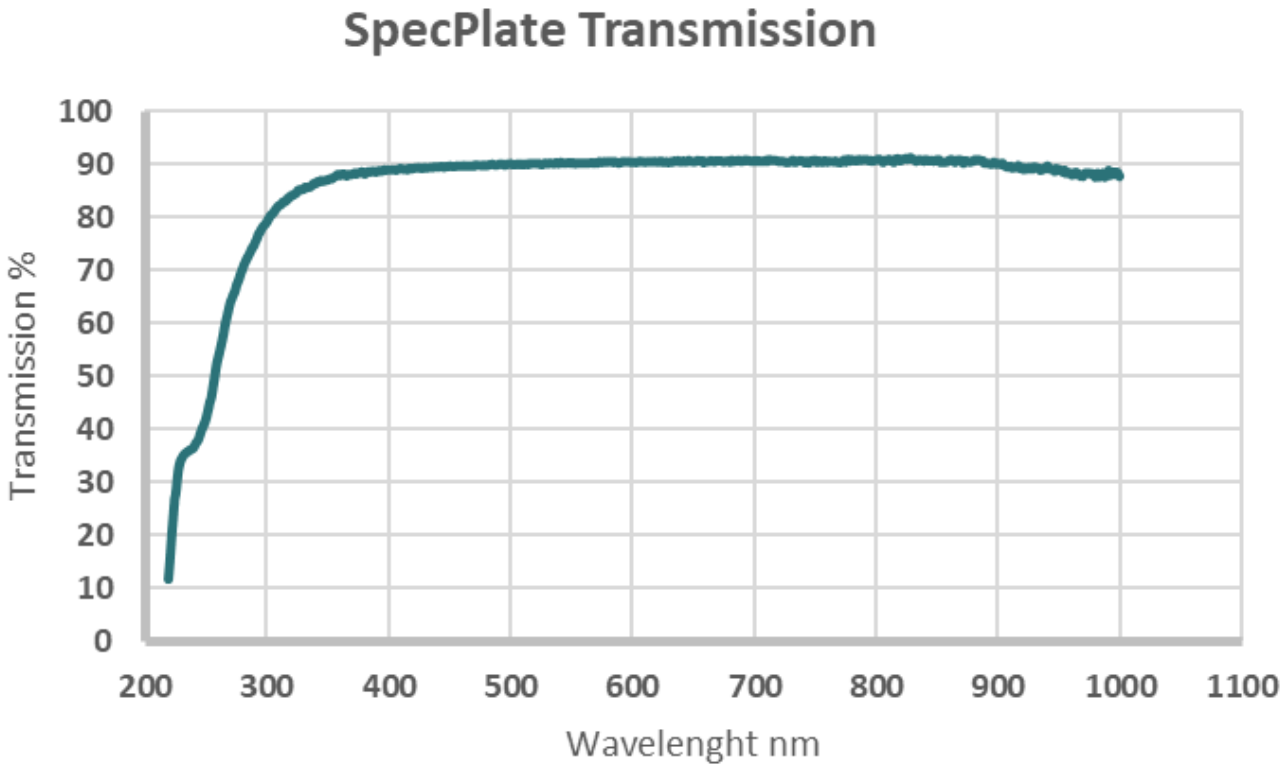
Slope method

- Increasing measurement precision
  - $c = m/\varepsilon_\lambda$



Material

- COC
  - Cyclic olefin Copolymer
- Exeptional optical properties
  - High UV transmission
- Suited to injection molding



Use Cases

- UV/Vis absorbance measurements
  - Quantification of proteins and nucleic acid
  - Concentration Range 0.5 – 100 mg/mL Lysozyme
- Colorimetric assays
- Fluorescence methods in testing phase

SpecPlate properties

- Increased measurement precision
  - Slope method
- Eliminated influence of liquid meniscus
  - Closed channel structure
- Reduced influence of pipetting errors
  - no dilutions, closed chambers
- Wide concentration range
  - Defined pathlengths
- Completely HT compatible
  - SLAS standards

Current status

- Start-up grant from Nov 22 – Oct 23

- Preparing serial production
  - Estimated start of production End of Q2 2023

- Current batch of functional samples is under evaluation
- Next batch of functional samples
  - End of January

- Planning of various application notes
- Looking for potential users
  - Cooperations, Application Notes, Publications

PHABIOC

PermeaPad®

Major barriers

[1] Use of Permeapad® for prediction of buccal absorption: A comparison to *in vitro*, *ex vivo* and *in vivo* method

Hanady Ajine Bibi [a], René Holm [b,1], Annette Bauer-Brandl [a,*]

[a] University of Southern Denmark, Campusvej 55, DK-5230 Odense, Denmark
[b] Biologics and Pharmaceutical Science, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark

[3] Validation and testing of a new artificial biomimetic barrier for estimation of transdermal drug absorption

Greta Camilla Magnano [a,b,*], Stefania Sut [c], Stefano Dall'Acqua [c], Massimiliano Pio Di Cagno [d], Luke Lee [e], Ming Lee [e], Francesca Larese Filon [a], Beatrice Perissutti [b], Dritan Hasa [b], Dario Voinovich [b]

[2] New biomimetic barrier Permeapad™ for efficient investigation of passive permeability of drugs

Massimiliano di Cagno [a,*], Hanady A. Bibi [b], Annette Bauer-Brandl [b]

[a] Drug Transport and Delivery Research Group, Department of Pharmacy, Arctic University of Norway, Tromsø, Norway
[b] Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Odense, Denmark

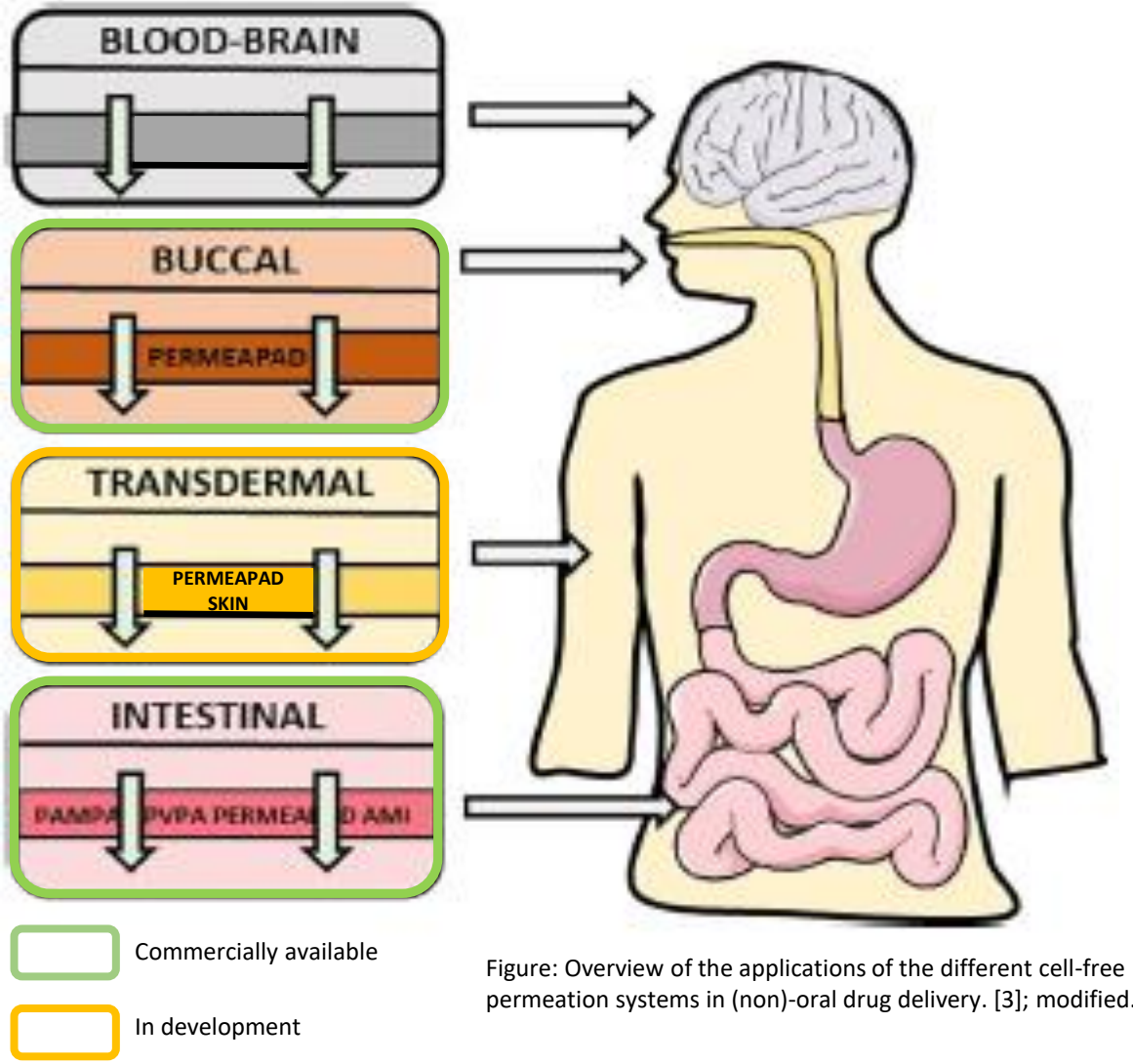
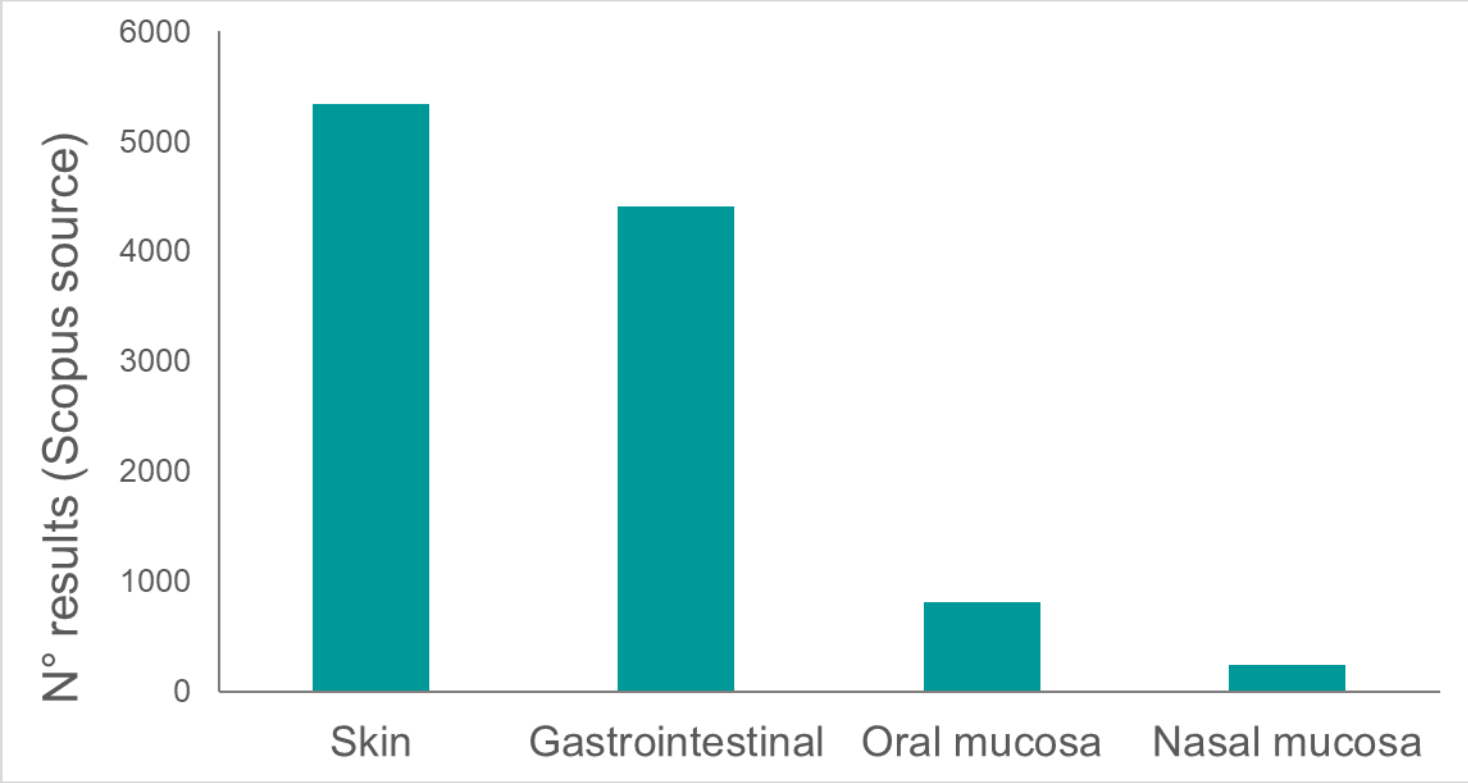
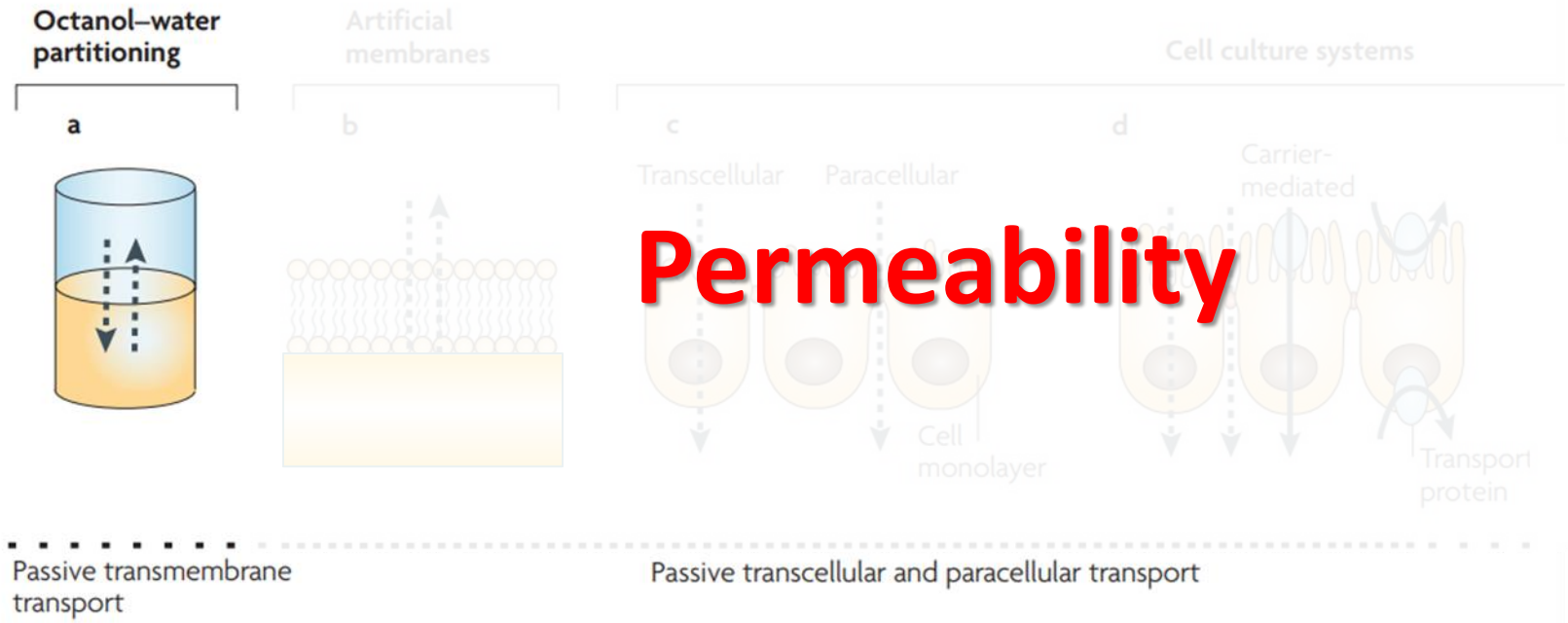


Figure: Overview of the applications of the different cell-free permeation systems in (non)-oral drug delivery. [3]; modified.

Which biological barriers are the most relevant?



Permeability for IVIVC



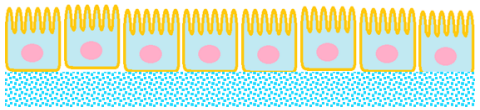
Adapted from Sugano, k. et al. Drug Discover. 9: 597-614(2010). DOI: https://doi.org/10.1038/nrd3187

„Permeability is an important parameter in drug discovery and development as it is the best parameter available in order to make predictions on bioavailability of a chemical entity or enabling formulation
Cellular based models can account for both passive and facilitated transport (i.e. active) whereas artificial membrane-based models account only for passive“

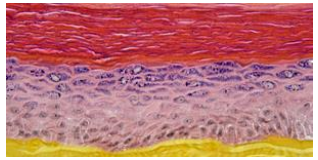
Commercially available barriers/systems

Biological

Caco-2 (and others)



EpiSkin™



https://www.episkin.com/Episkin

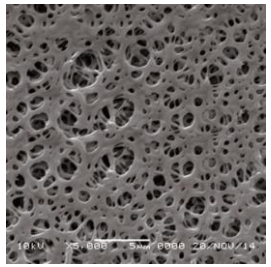
Ex-vivo tissue

Often used in EU

https://www.alibaba.com/product-detail/Good-Price-Poland-Pig-Ears-Pork_50030878089.html

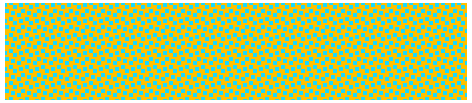
Artificial

Strat-M®

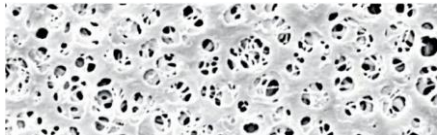


http://www.gvs.com/product-family/170/819/

PAMPA

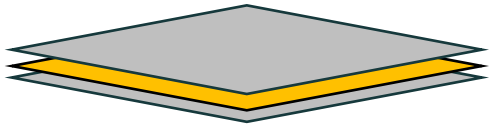


PBM

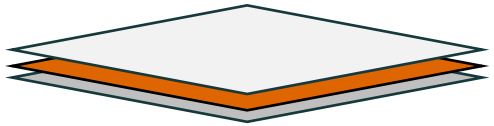


Biomimetic

PermeaPad® GIT

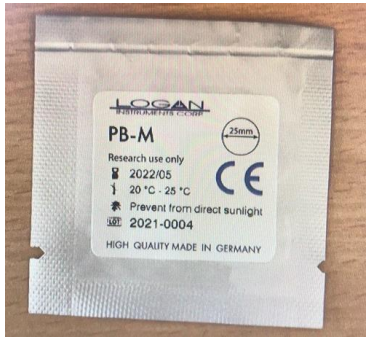


PermeaPad® Skin

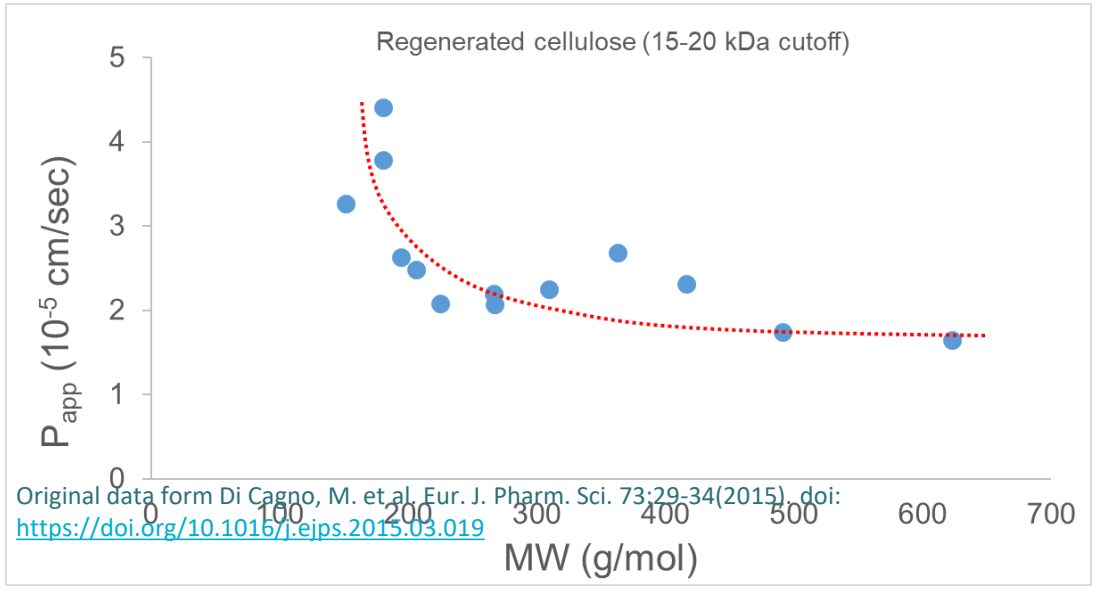


PBM – Permeation Barrier Membrane

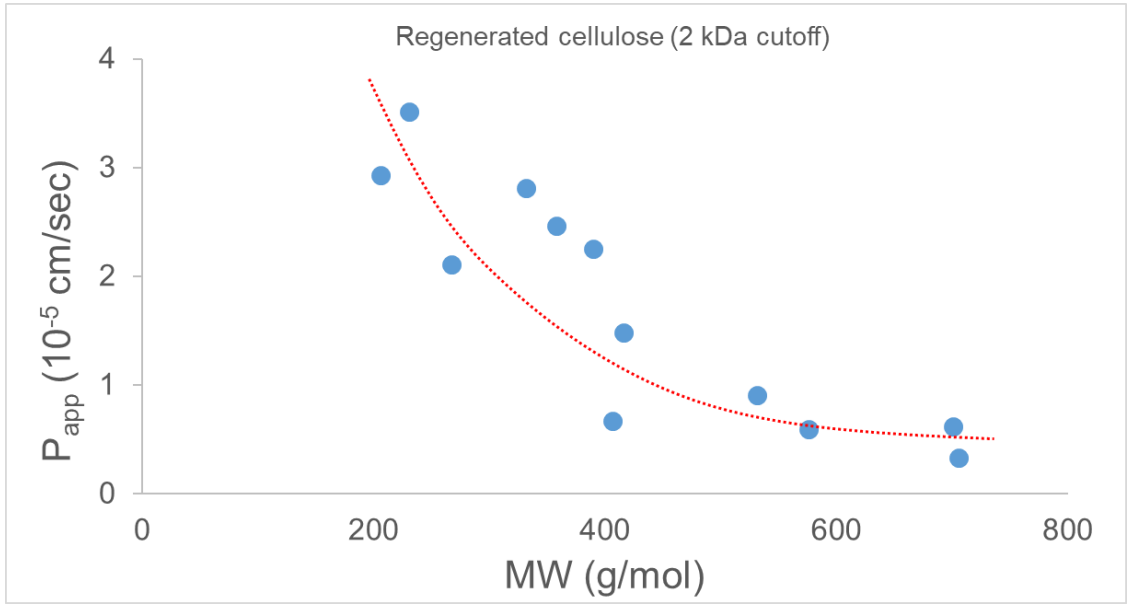
For IVRT



Regenerated cellulose is not biomimetic



Original data form Di Cagno, M. et al. Eur. J. Pharm. Sci. 73:29-34(2015). doi: https://doi.org/10.1016/j.ejps.2015.03.019

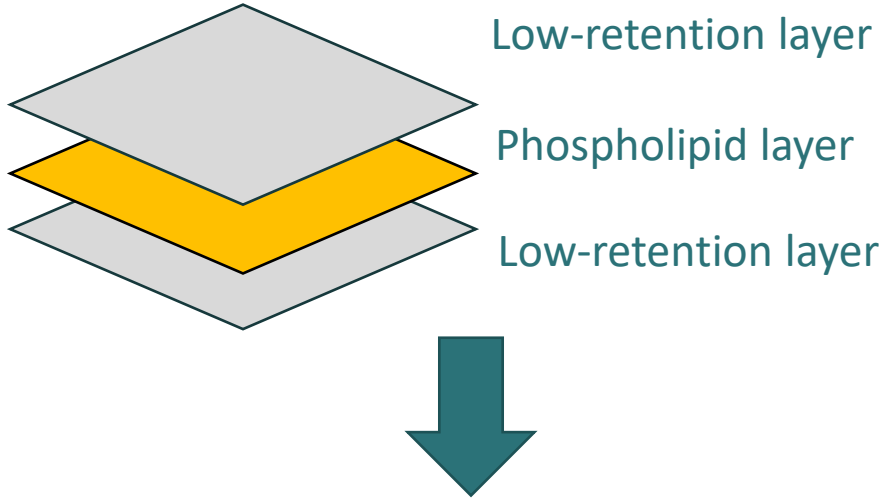


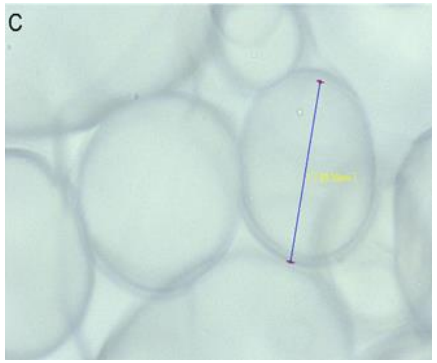
Original data from Berben, P. er al. J Pharm Sci. 107:250-256(2018). doi: https://doi.org/10.1016/j.xphs.2017.08.002

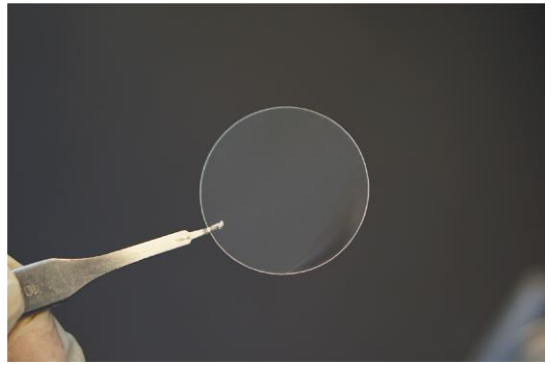
PermeaPad® GIT

Biomimetic barrier for measuring permeability of new chemical entities and enabling formulation to **predict the *in vivo* performance**

- The barrier is composed of 2 low-retention layers comprising and one lipoidal layer
- Commercially available (pads for standard diffusion cells or 96-multiwell plate)
- Ideal for high-throughput screening (HTS) of new chemical entities but also for studying enabling formulation
- High chemical and mechanical resistance
- It accounts also for paracellular transport →







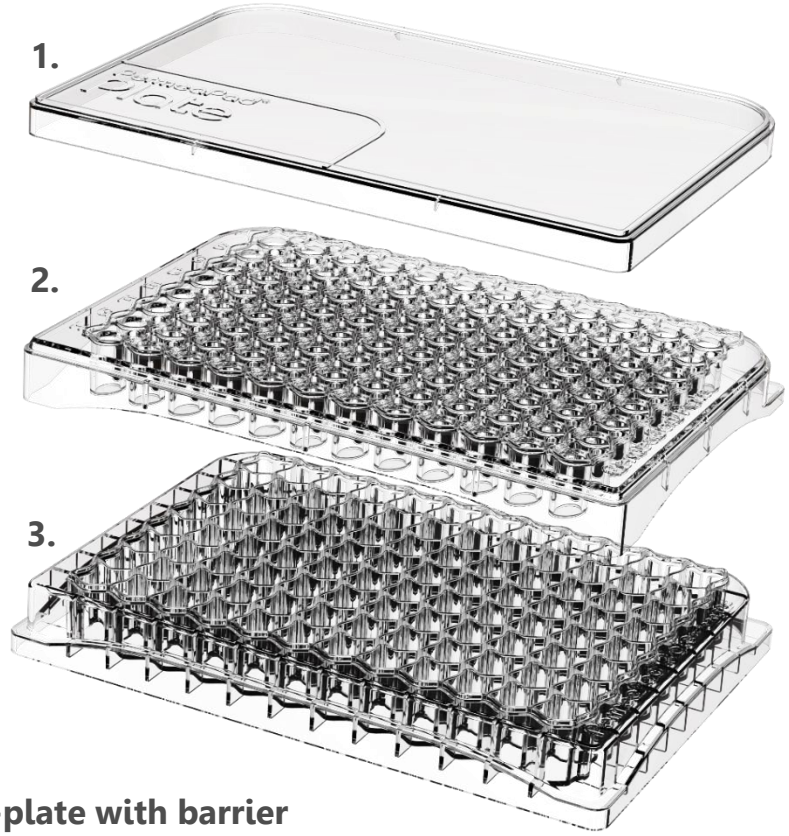
PermeaPad® GIT

PermeaPad® Barrier

Side-by-side diffusion cells (e.g. Ussing chambers)

Vertical diffusion cells (e.g. Franz cells)

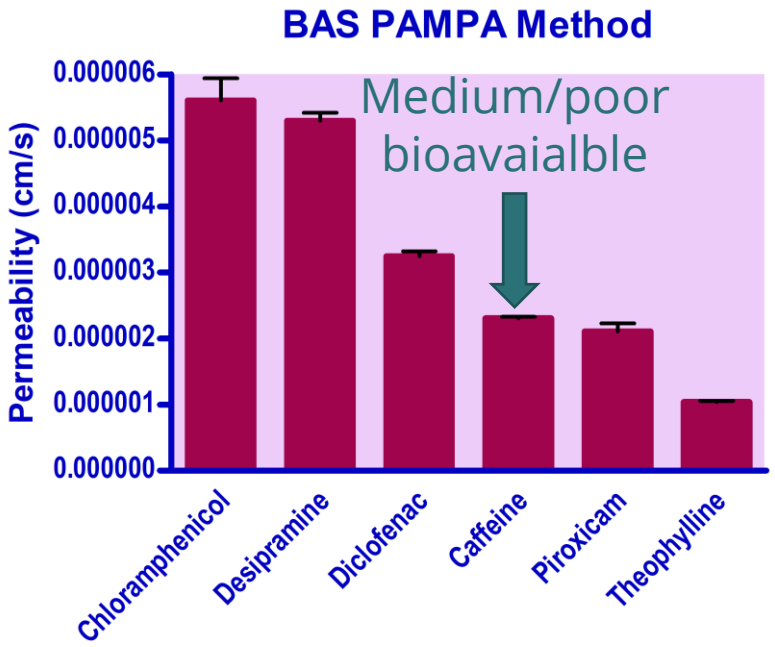
PermeaPad® Plate



1: Cover
2: Insert-plate with barrier
3: Bottom plate

Prediction of API/NCE bioavailability

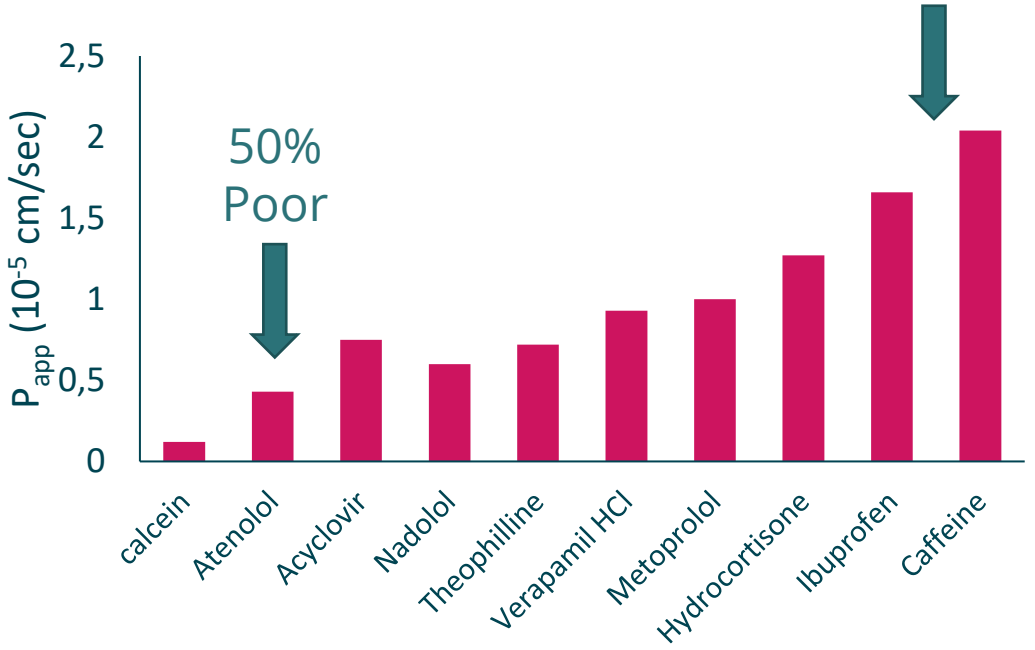
PAMPA



https://www.bioassaysys.com/services/pampa-permeability-service.html

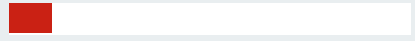
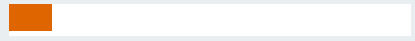
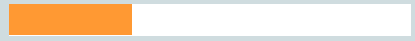
PermeaPad® GIT

Caffeine and Ibuprofen oral bioavailability is 100%



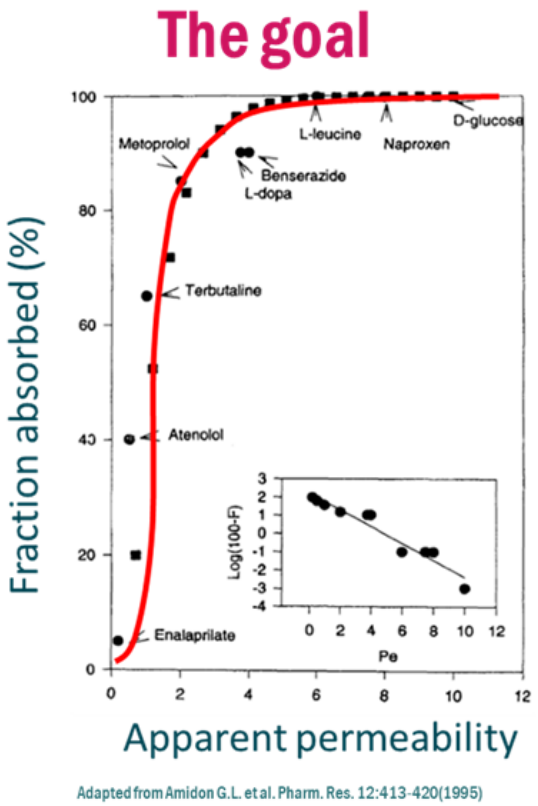
di Cagno M. et al. Eur. J. Pharm. Sci. 73:29–34(2015). DOI: https://doi.org/10.1016/j.ejps.2015.03.019

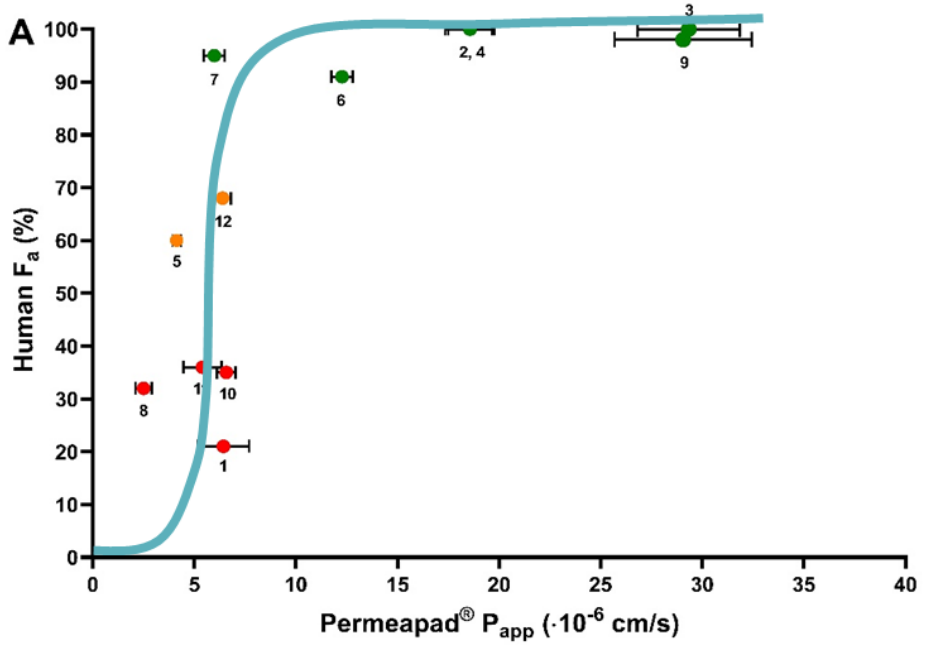
Performance

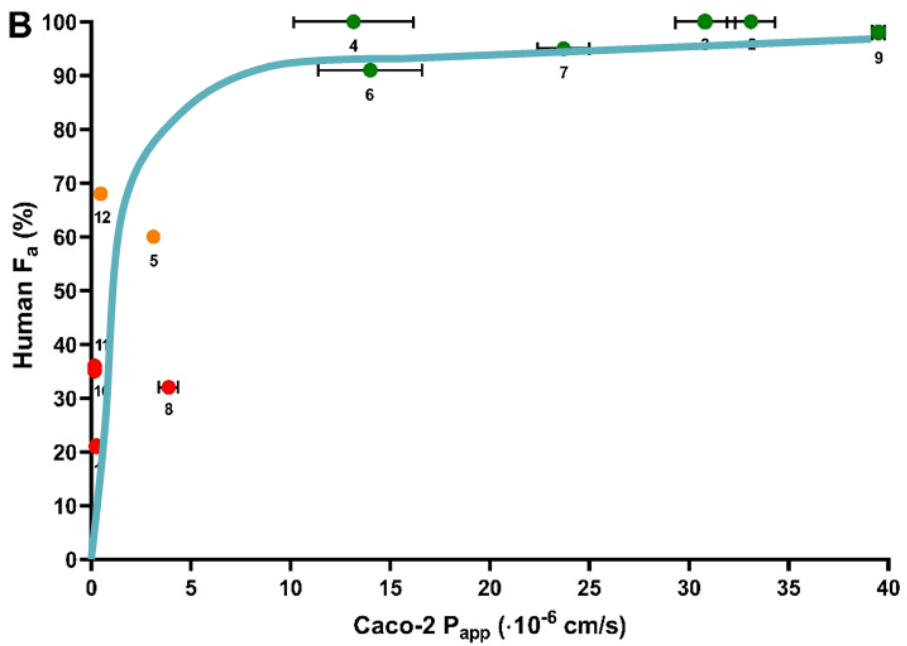
	PermeaPad®	PAMPA	Caco-2
Mechanical resistance			
Chemical resistance			
Reproducibility			
Time-effectiveness			
Cost-effectiveness			
Predictability			
Usage with enabling form			

Cremophor RH; Solutol HS; Triton-X

PermeaPad® GIT Plate

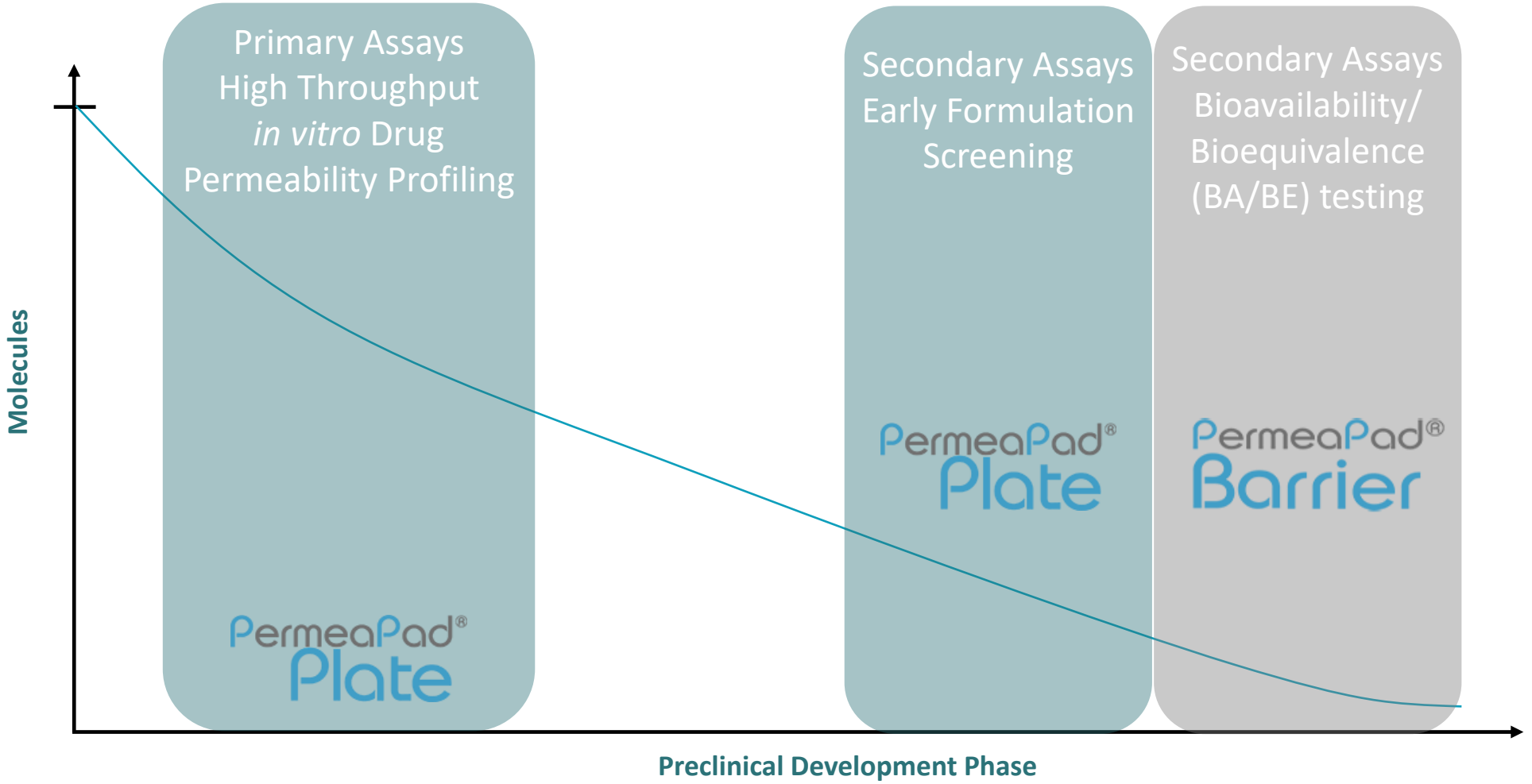






The fraction absorbed in human (Fa) plotted against the apparent permeability (Papp) of the model compounds determined in A) the Permeapad® Plate model or B) the Caco-2 model [4]

When to apply GIT permeation tests?

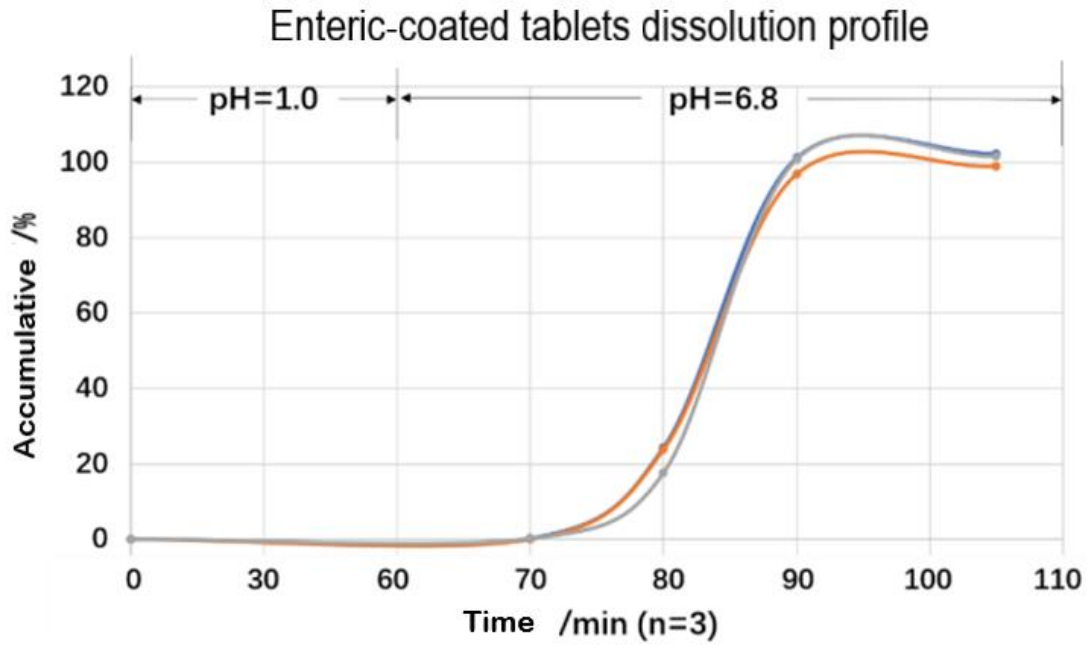


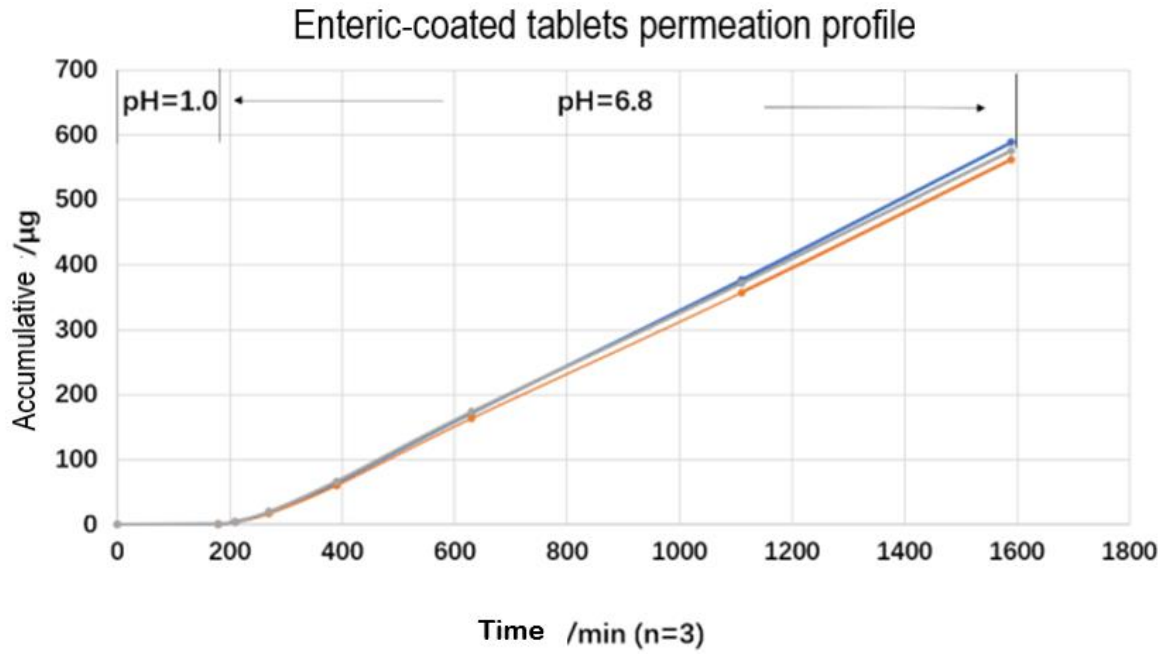
Dissolution and Permeation

PermeaPad® GIT Barrier + PERMETRO System

Dissolution and Permeation

PermeaPad® GIT Barrier + PERMETRO System



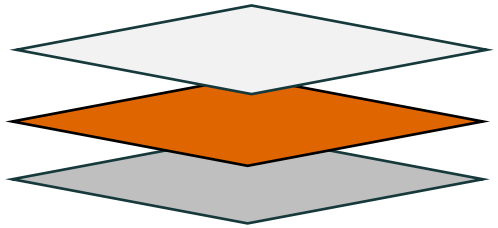


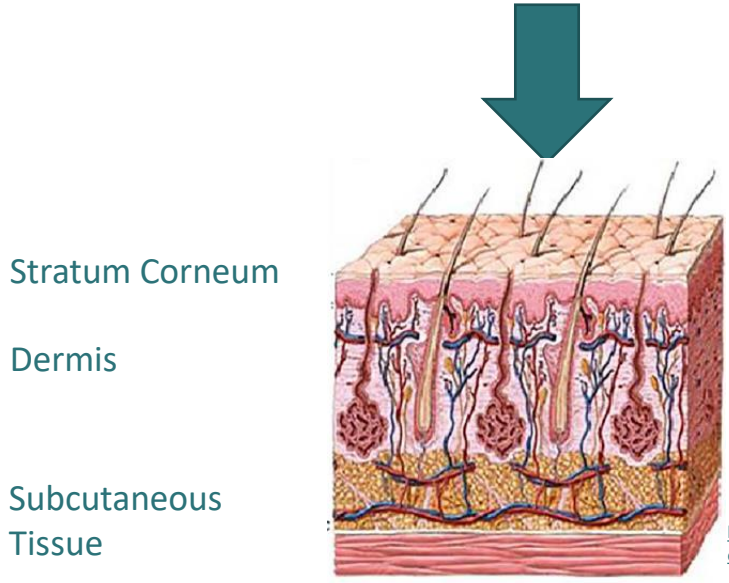
Dissolution & Permeation profile of control release formulations with food effect

PermeaPad® Skin

Biomimetic barrier for measuring permeability of new chemical entities and enabling formulation to **predict the *in vivo* performance**

- The barrier is composed of one filter layer (top; donor site) a skin mimicking lipid layer (ceramides, cholesterol and squalene) and a cellulose layer (bottom; acceptor site)
- Commercially available Q2 2023 (pads for standard diffusion cells)
- High and positive correlation with porcine skin
- Low variability





https://www.sciencedirect.com/science/article/abs/pii/S0378517318300413?via%3Dihub

Excellence fit for IVPT

PermeaPad® Skin Barrier + LOGAN SYSTEM 913A-12

LOGAN SYSTEM 913A-12 Automated Water Jacket Diffusion Cell Sampling System for Cream / Ointments / Gel / Micro Needle…

PermeaPad® Skin

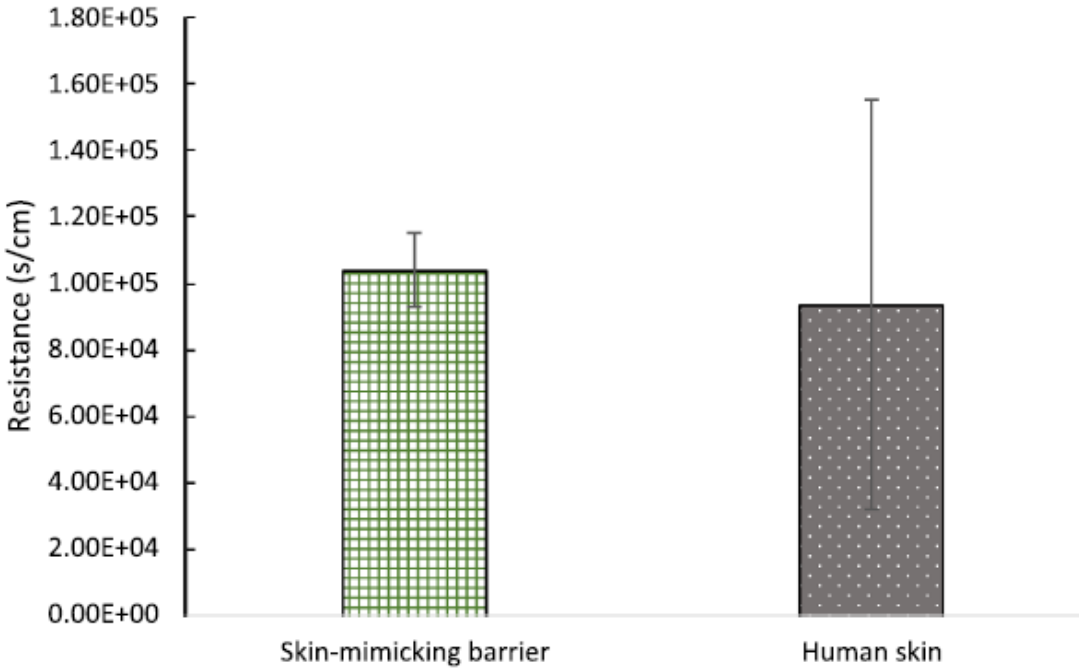


Figure: Resistance (R) to penetration offered by the skin-mimicking barrier (SMB) and human skin to diclofenac permeation. Human skin R values were obtained from the literature (https://doi.org/10.1208/pt0804094) [3]

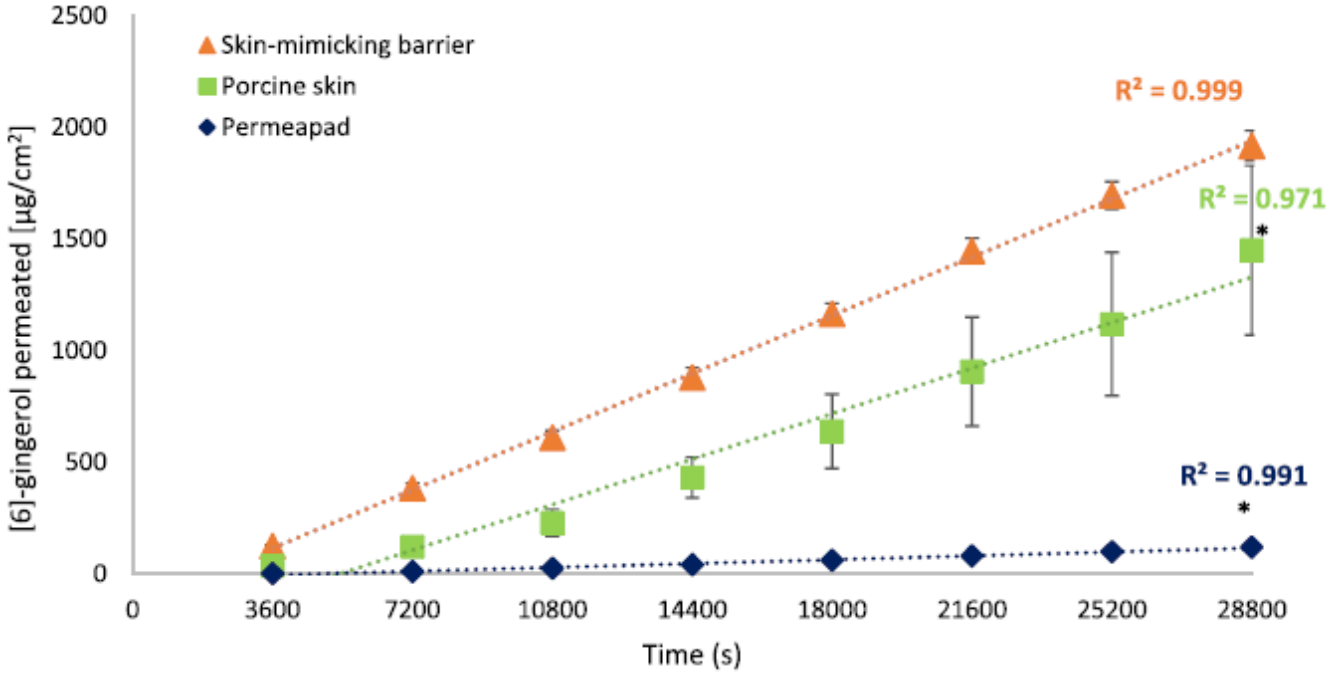


Figure: [6]-gingerol amount (µg/cm²) that permeated in the receptor fluid at specific extraction times through SMB, PermeaPad®, and porcine skin. Values are normalized by the thickness of the SMB and expressed as mean ± SE (n = 6). Asterisk (*) indicates statistically significant differences between SMB and the other two tested membranes ($p < 0.05$). [3]

Conclusions

- Apparent permeability should be considered as a qualitative parameter rather than a quantitative parameter
- in vitro non-cellular models can provide useful information in preformulation stage and also at formulation stages
- It is important to apply these assays in a rational way, knowing what you are actually measuring (avoiding “blindly” measuring)
- When enabling formulations are investigated, consider to apply non-linear data fitting approach → PHABIOC can consult you with your data analysis

Gefördert durch:

Bundesministerium
für Wirtschaft
und Klimaschutz

aufgrund eines Beschlusses
des Deutschen Bundestages

Thank you!

PHABIOC GmbH
info@phabioc.com

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Venture Cup
PHABIOC
Gewinner Konzeptphase 2023

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