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Drug permeability across biological barriers estimated by the PVPA

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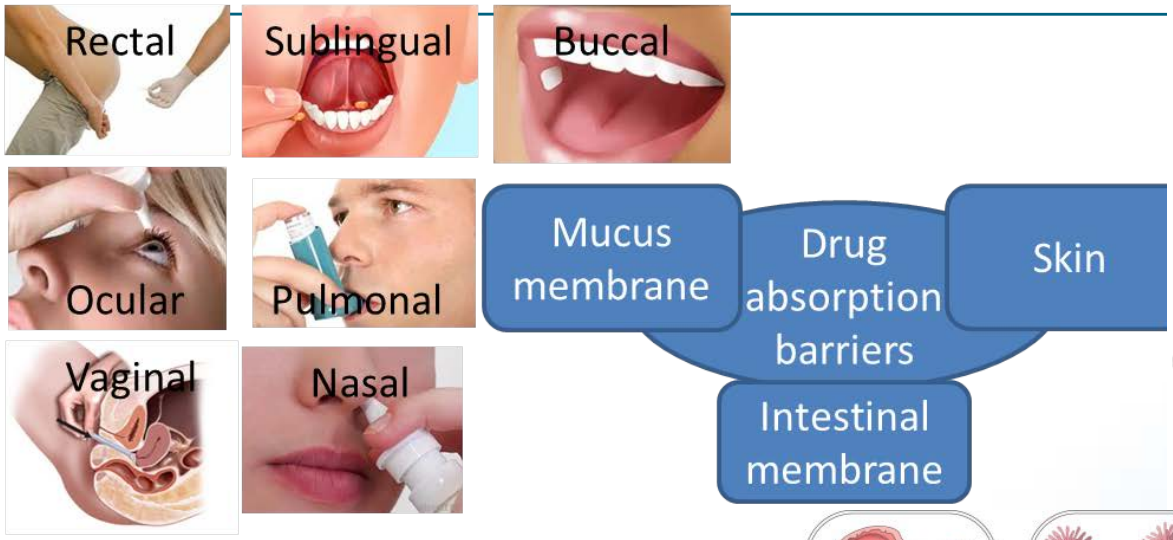
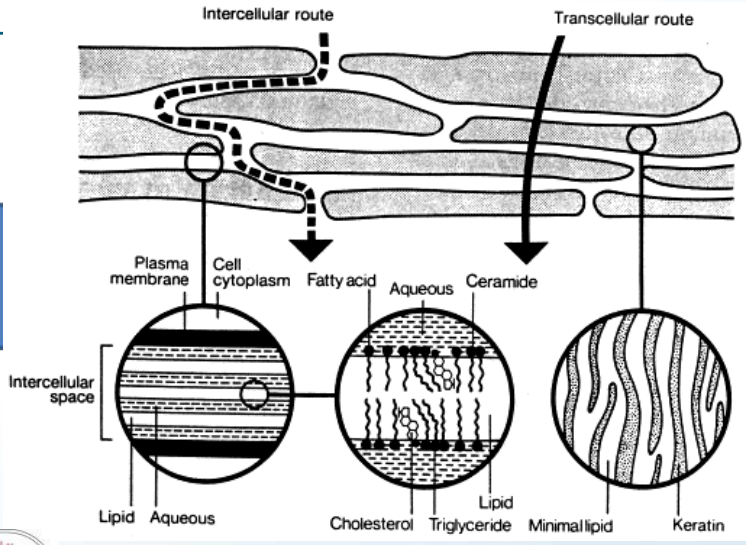
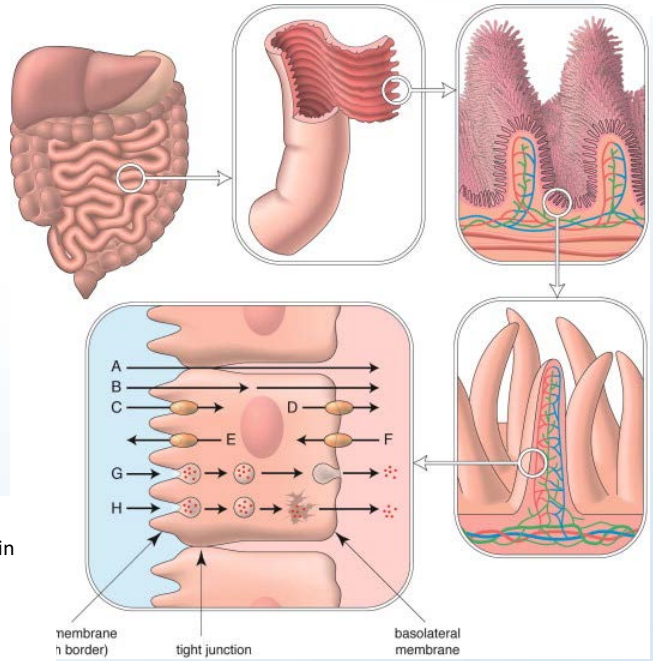
Norecopa's 10 year Anniversary
10 October 2017

Absorption barriers for the different drug administration routes

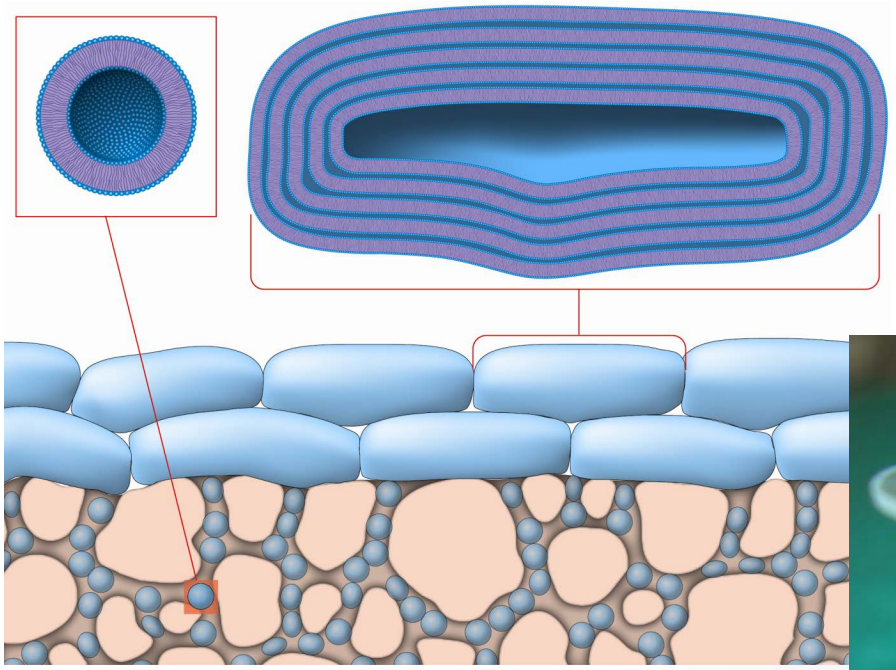






Colourbox.com
Junginger, H. E. et al, Visualization of drug transport across human skin and the influence of penetration enhancers, Drugs Pharm Sci, 1994, 62, 59-84.
Våbenø, J, Dipeptidomimetics as Pro-Moieties for hPEPT1 Targeted Prodrugs, PhD thesis, University of Tromsø, April 2004

Phospholipid Vesicle-based Permeation Assay (PVPA)



Flaten GE, The Phospholipid Vesicle-Based Barrier: A novel Method for Passive Drug Permeability Screening, PhD thesis, University of Tromsø, June 2007

- Link to the video about our research: https://www.youtube.com/watch?v=6mHkbzSYzMw

The PVPA for estimation of permeability

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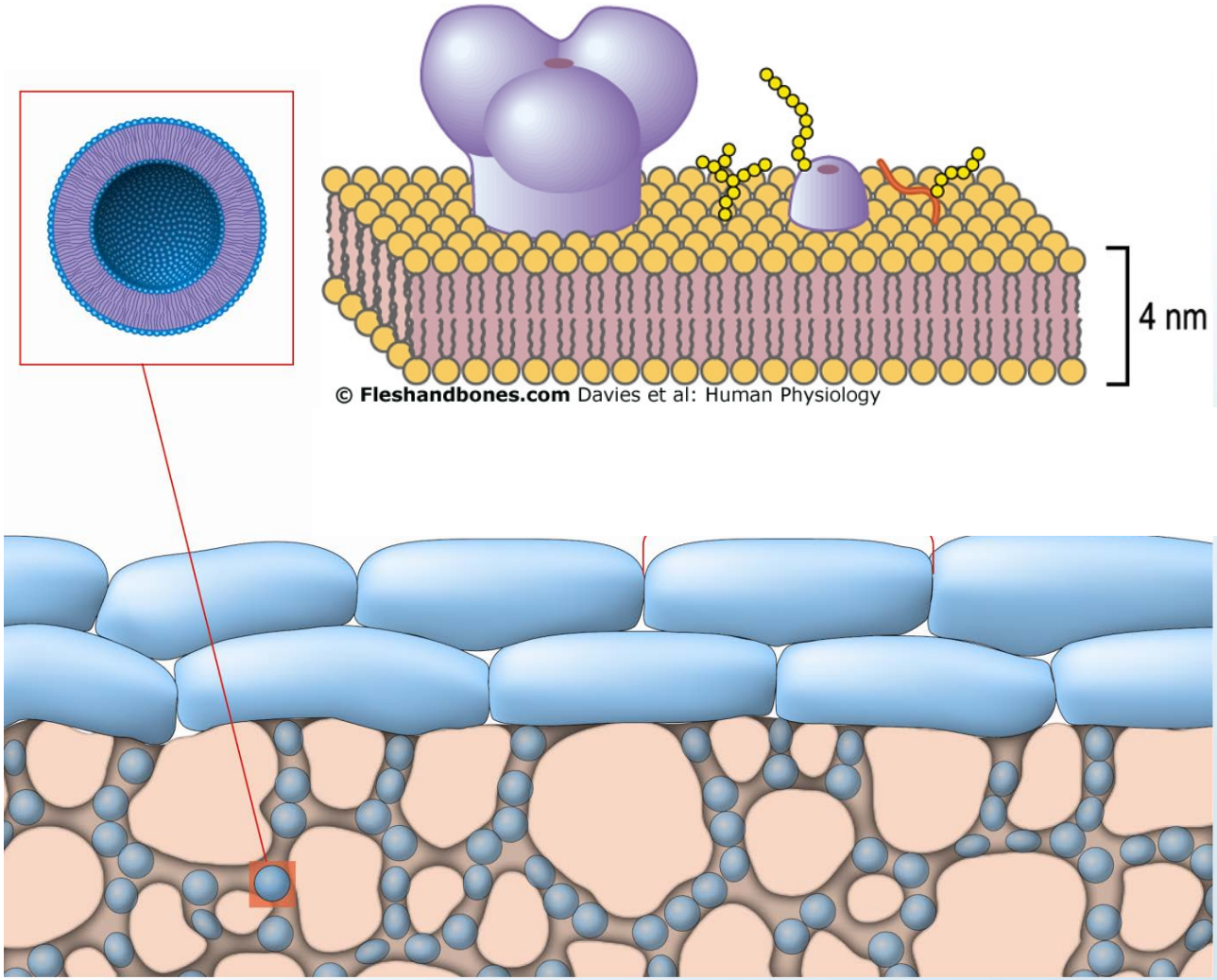
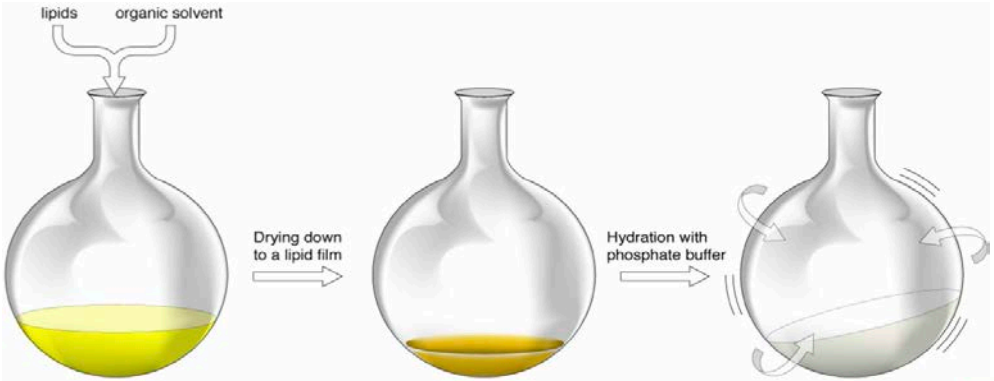
The PVPA for estimation of permeability

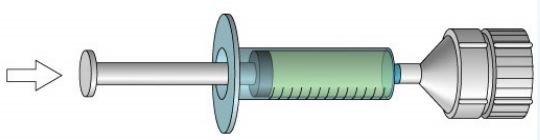


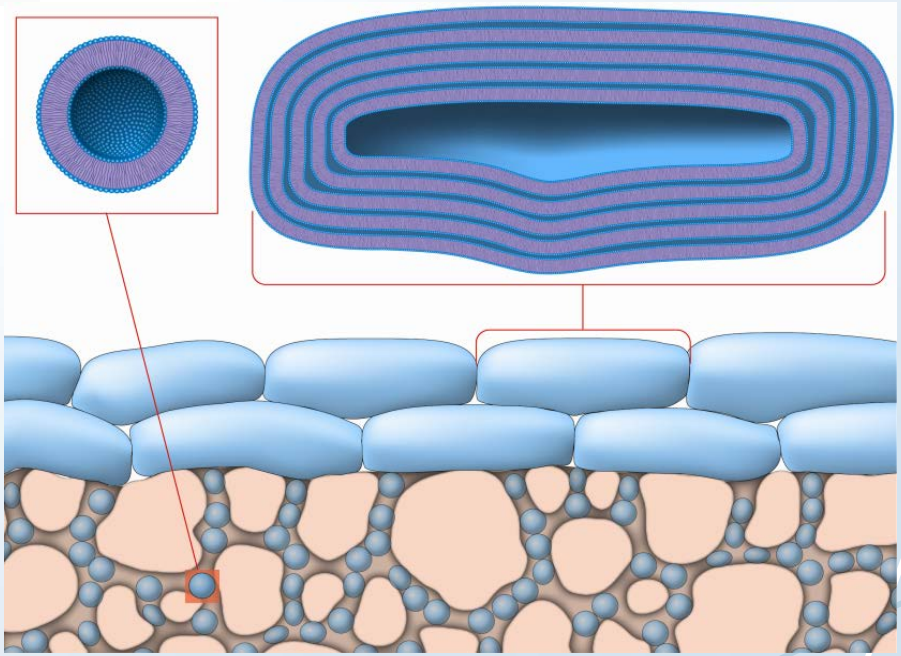
Liposomes could be seen as a model for the cell because of their structural similarities

Flaten GE, The Phospholipid Vesicle-Based Barrier: A novel Method for Passive Drug Permeability Screening, PhD thesis, University of Tromsø, June 2007

Preparation of the PVPA barriers



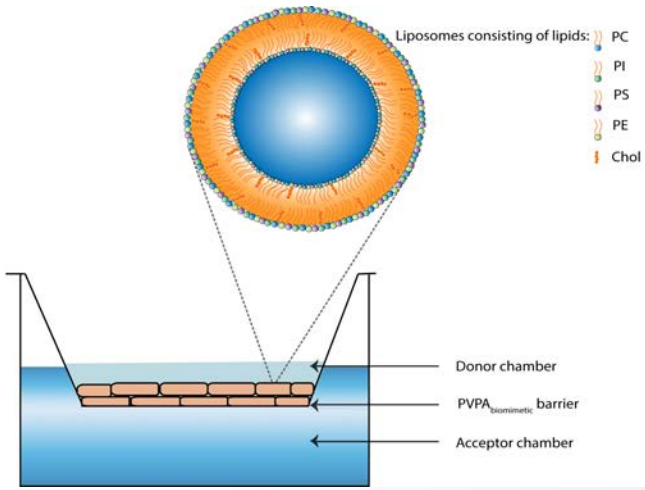


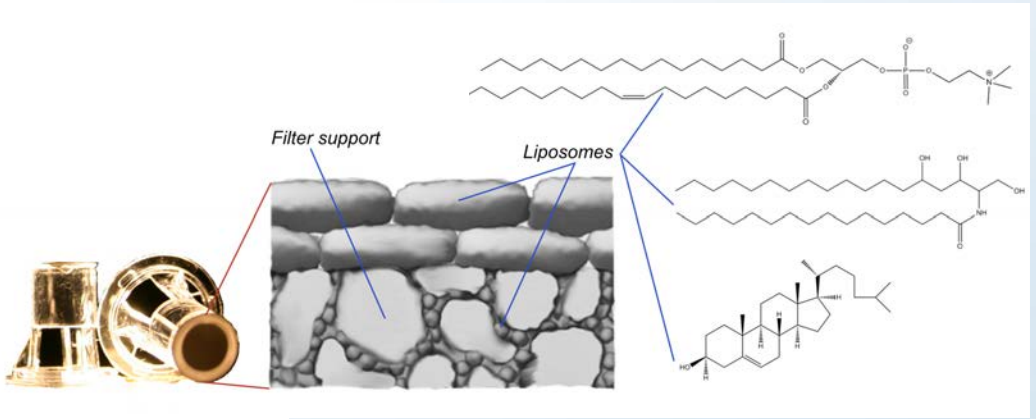


Modified from Flaten GE, The Phospholipid Vesicle-Based Barrier: A novel Method for Passive Drug Permeability Screening, PhD thesis, University of Tromsø, June 2007

Aim

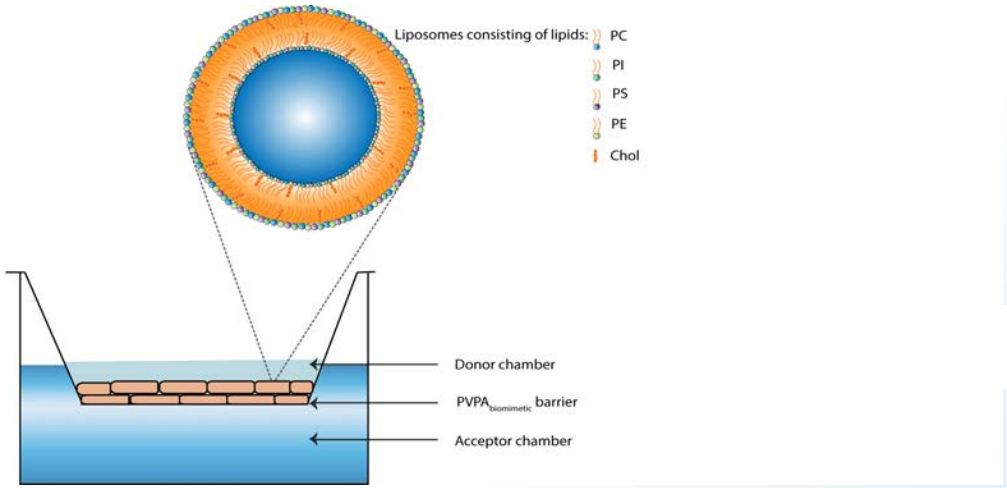
- The aim was to elucidate the PVPA's ability to mimic the stratum corneum (SC) and the intestinal epithelia more closely by changing the lipid composition of the barriers to resemble the lipid composition *in vivo*.





Naderkhani E, Vasskog T, Flaten GE. Biomimetic PVPA in vitro model for estimation of the intestinal drug permeability using fasted and fed state simulated intestinal fluids. Eur J Pharm Sci 2015;73:64-71..
Engesland A, Skar M, Hansen T, Skalko-Basnet N, Flaten GE. New applications of phospholipid vesicle-based permeation assay: permeation model mimicking skin barrier. J Pharm Sci 2013;102:1588-600.

Biomimetic modelling of intestinal epithelia

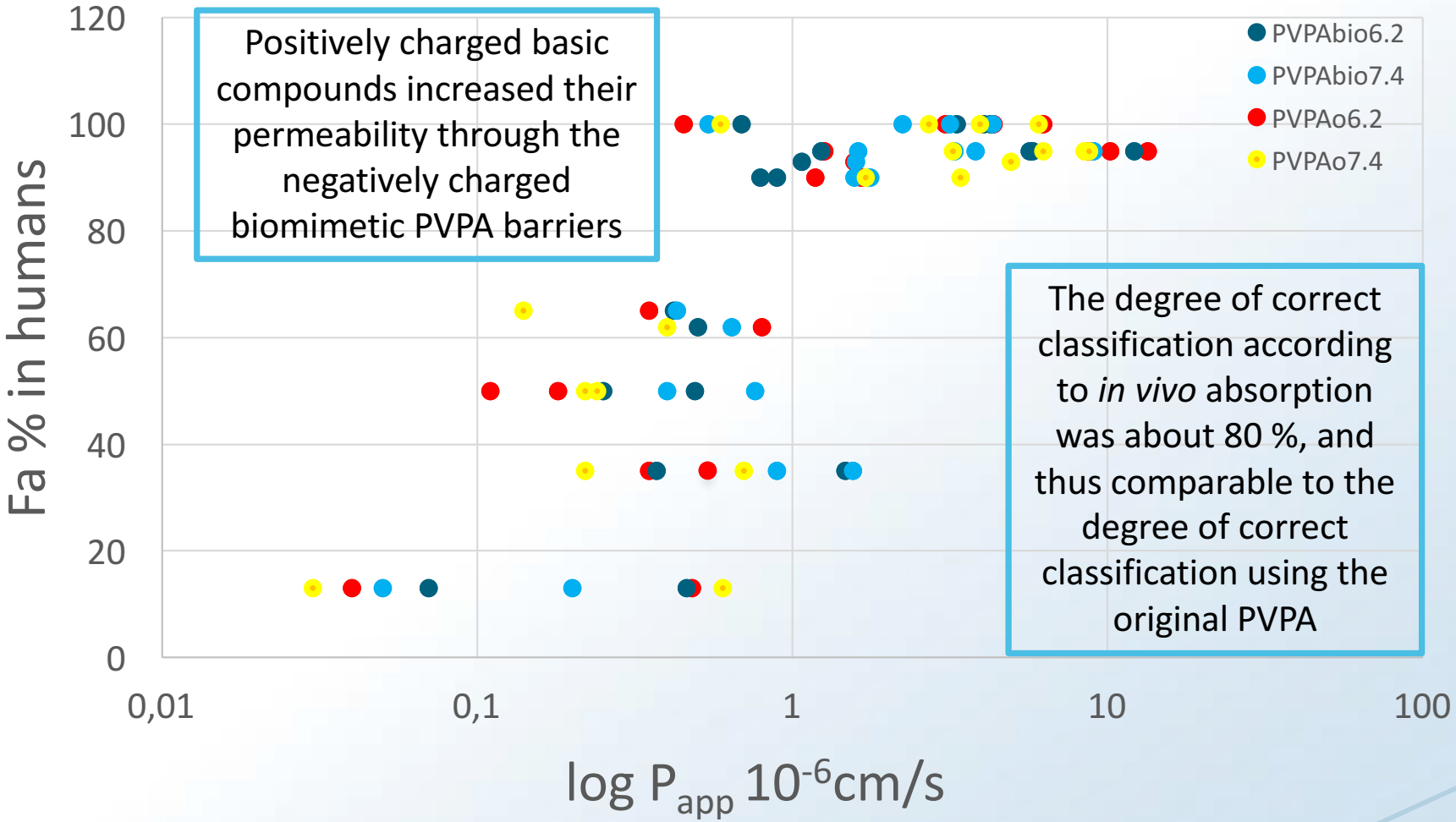


- The original PVPA consists of liposomes from egg phospholipids → changes in the lipid composition for the biomimetic PVPA: phosphatidylcholine (PC, 26%), phosphatidylethanolamine (PE, 26.5%), phosphatidylserine (PS, 7%), phosphatidylinositol (PI, 7%) and cholesterol (33%)
- Changes in lipid composition → changes in preparation process

*all percentages are in w/w

Naderkhani E, Vasskog T, Flaten GE. Biomimetic PVPA in vitro model for estimation of the intestinal drug permeability using fasted and fed state simulated intestinal fluids. Eur J Pharm Sci 2015;73:64-71.
Naderkhani E, Isaksson J, Ryzhakov A, Flaten GE. Development of a Biomimetic Phospholipid Vesicle-based Permeation Assay for the Estimation of Intestinal Drug Permeability. J Pharm Sci 2014;103:1882-90.

Correlation between fraction absorbed (Fa) *in vivo* and P_{app} from original PVPA and biomimetic PVPA



Naderkhani E, Isaksson J, Ryzhakov A, Flaten GE. Development of a Biomimetic Phospholipid Vesicle-based Permeation Assay for the Estimation of Intestinal Drug Permeability. J Pharm Sci 2014;103:1882-90.

Challenge: Poorly water soluble drugs

- Poor aqueous solubility of drug candidates
  → problems according to permeability and bioavailability
- Important that *in vitro* assays are able to handle this challenge in permeability testing
- Relevant **additives** and biorelevant **donor media**

Compatibility with tensides and co-solvents

- Co-solvents ethanol, DMSO and PEG 400 as well as the surfactants Poloxamer 188 and Span 20 did not induce any significant change in calcein permeability.
- Tween 80, Brij 35 and Cremophor EL were also found compatible based on no change in electrical resistance
- Triton X, included as a reference due to its known efficiency in solubilizing phospholipids, was found compatible with the model
- Huge improvement compared to the original PVPA

Naderkhani E, Isaksson J, Ryzhakov A, Flaten GE. Development of a Biomimetic Phospholipid Vesicle-based Permeation Assay for the Estimation of Intestinal Drug Permeability. J Pharm Sci 2014;103:1882-90.

Biorelevant donor media - FaSSIF and FeSSIF

- Biomimetic PVPA is compatible in the presence of FaSSIF (fasted state simulated intestinal fluid) and FeSSIF (fed state simulated intestinal fluid) in respect to calcein permeability, electrical resistance and no release of phospholipids.

- The permeability of BCS class II (low solubility, high permeability) and III (high solubility, low permeability) drugs were differently affected in the presence of the biorelevant media, with more pronounced effect on the class II drugs.

Naderkhani E, Vasskog T, Flaten GE. Biomimetic PVPA in vitro model for estimation of the intestinal drug permeability using fasted and fed state simulated intestinal fluids. Eur J Pharm Sci 2015;73:64-71.

Summary biomimetic PVPA for intestinal site

- good correlation with *in vivo* data on the fraction absorbed in humans
- maintain integrity to a higher extent in presence of FaSSIF and FeSSIF as well as tensides and co-solvents compared to the original PVPA
- improved storage stability
- next step: is the model suitable in formulation optimization?

PVPA model mimicking skin, why?

- Human skin is exposed to various chemicals and drugs in our daily life
- A simplified method based on artificial membrane barriers would enable us to test and evaluate various drugs and formulations at en early development stage
- Avoid excessive use of animals and human models

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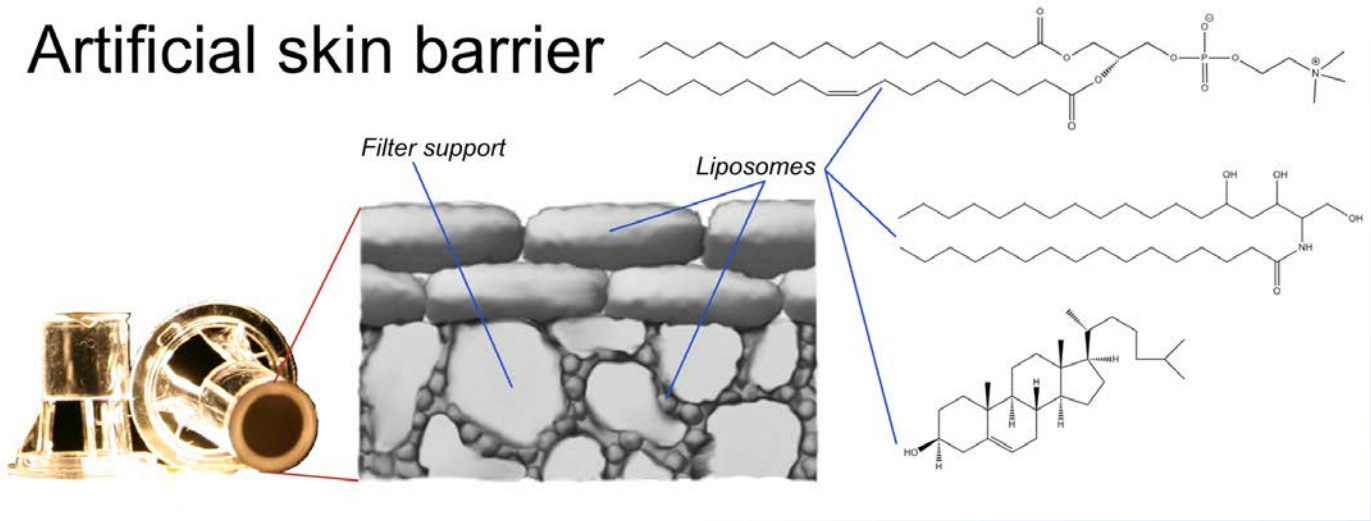
PVPA models mimicking skin

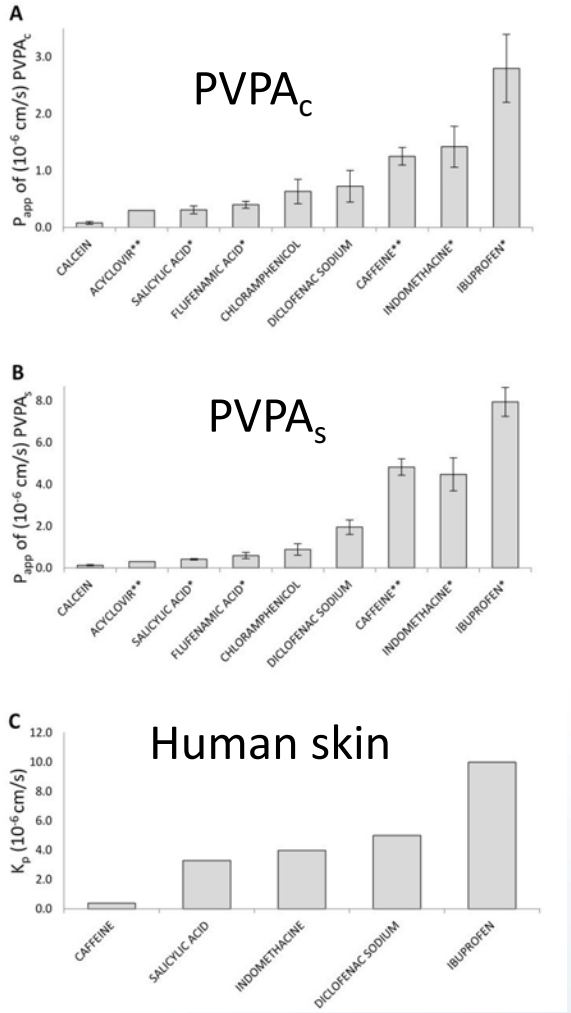


- The original PVPA consists of liposomes from egg phospholipids (E-80) → changes in the lipid composition:*
  - $PVPA_c$: E-80 (77%) and cholesterol (23%)
  - $PVPA_s$: E-80 (50%), ceramides (27.5%), cholesterol (12.5%), cholesteryl sulphate (2.5%), and palmitic acid (7.5%)
- Changes in lipid composition → changes in preparation process

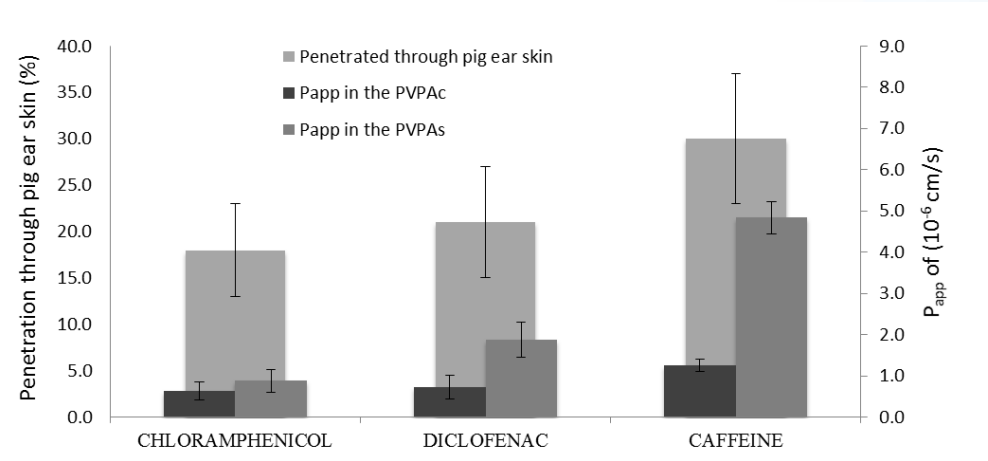
*all percentages are in w/w

Engesland A, Skar M, Hansen T, Skalko-Basnet N, Flaten GE. New applications of phospholipid vesicle-based permeation assay: permeation model mimicking skin barrier. J Pharm Sci 2013;102:1588-600.

Correlation between the PVPA models and skin of human and animal origin



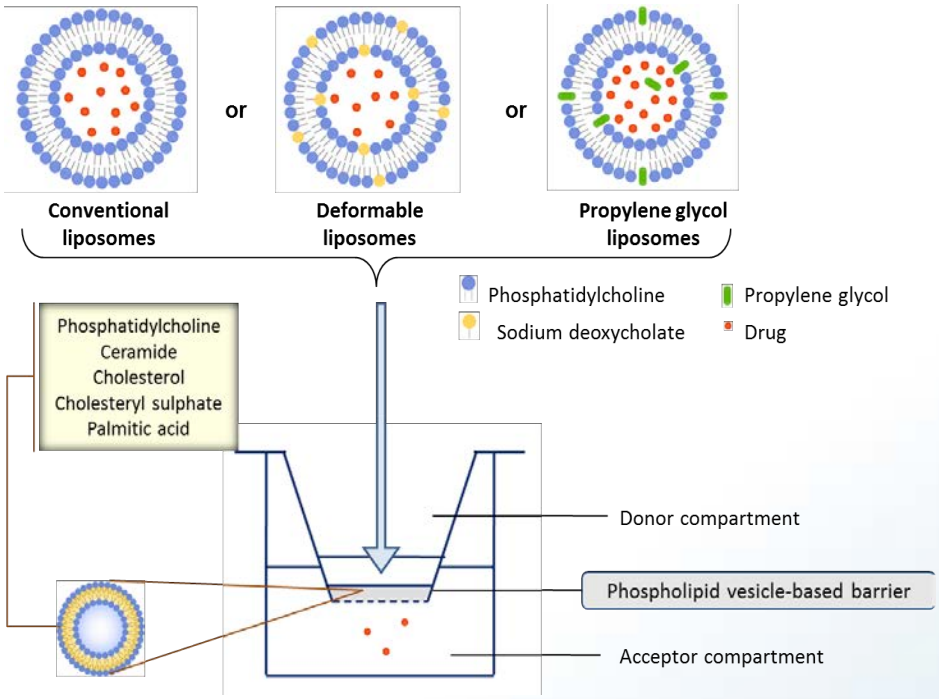
Permeability of selected compounds in A) the PVPA$_c$, B) the PVPA$_s$ and C) the human skin.

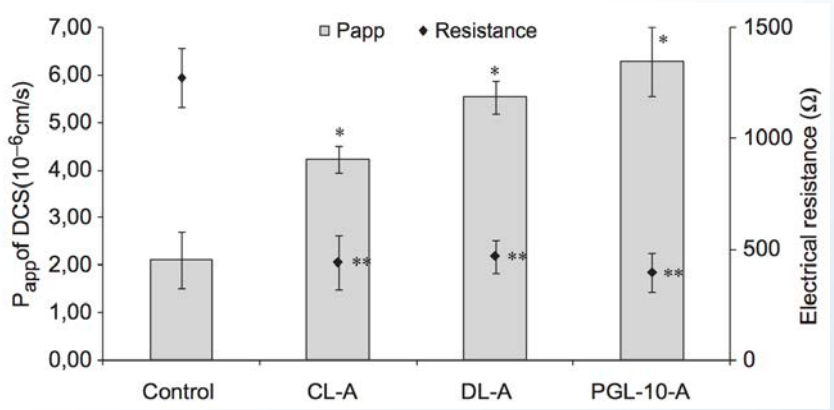


Rank orders of permeability of selected drugs were found to be the same in all the models

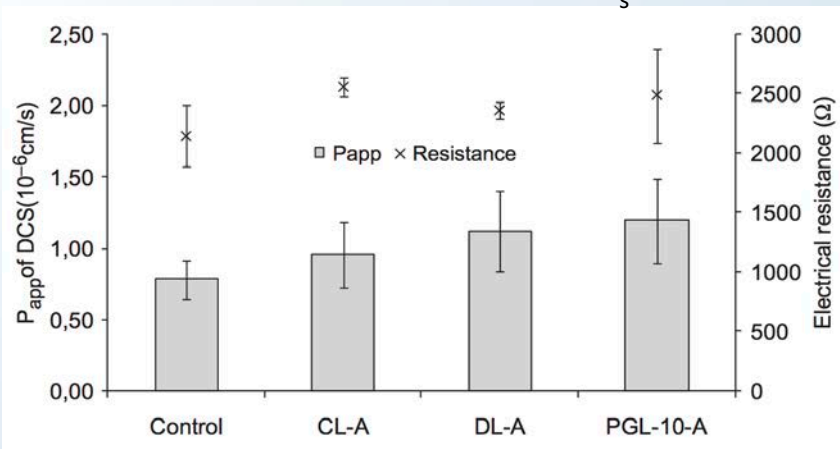
Engesland A, Skalko-Basnet N, Flaten GE. *In vitro* models to estimate drug penetration through the compromised *stratum corneum* barrier. Drug Dev and Pharm **2016**, 42:11, 1742-1751,

The PVPA models in formulation development of liposomes for (trans)dermal drug delivery





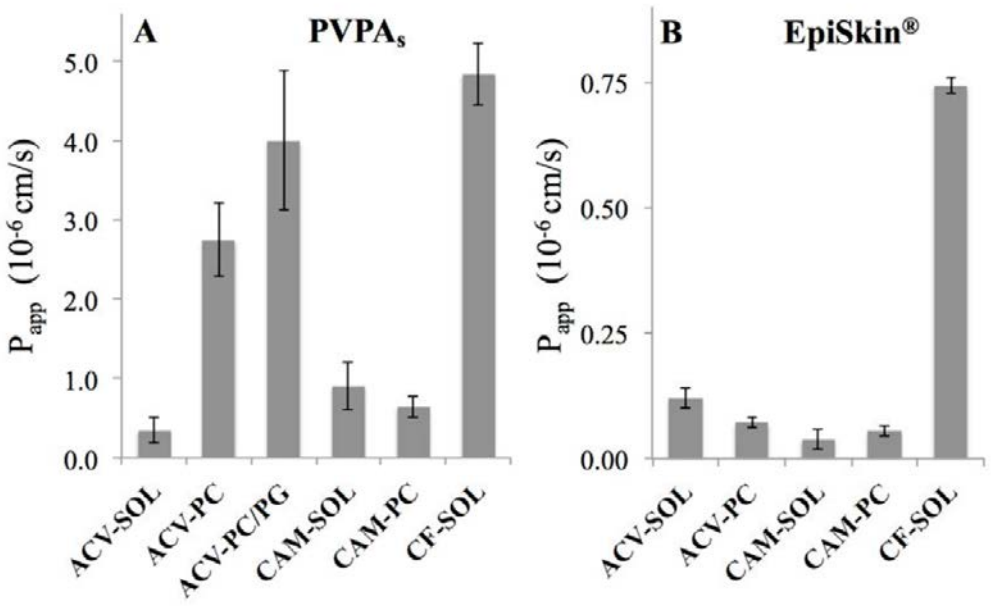
The permeability of DCS from the liposomal formulations on $PVPA_s$



The permeability of DCS from the liposomal formulations on $PVPA_c$

Palac Z, Engesland A, Flaten GE, Skalko-Basnet N, Filipovic-Grcic J, Vanic Z. Liposomes for (trans)dermal drug delivery: the skin-PVPA as a novel *in vitro stratum corneum* model in formulation development. J. Liposome Res 2014;24:313-322

How is PVPA performing compared to EpiSkin®?



Permeability of ACV, CAM and CF in solutions (SOL) and liposomal formulations (PC or PC/PG) in the PVPA$_s$ (A) and the EpiSkin® (B) models.

- EpiSkin® detected only small differences between the drugs in solution and formulations.
- In contrast with EpiSkin®, which is limited by a 3-day testing window, PVPA$_s$ barriers can be stored frozen for up to 2 weeks.
- The PVPA models are thus more cost effective and efficient than the EpiSkin® model.

Engesland A, Skalko-Basnet N, Flaten GE. PVPA and EpiSkin® in Assessment of Drug Therapies Destined for Skin Administration. J Pharm Sci 2014;104:1119-27.
Engesland A, PhD thesis, In vitro permeation model for health and compromized skin: The Phospholipid vesicle-based permeation assay (PVPA) for skin applications, University of Tromsø, March 2015

Conclusions

- PVPA models mimicking the SC and the intestinal epithelia have successfully been established

- Biomimetic PVPA's robustness and compatibility with the biorelevant media FaSSIF and FeSSIF as well as solubilizers is making it a promising alternative for estimation of drug permeability also for poorly soluble drugs →promising *in vitro* intestinal permeability model for use in drug development.

- The PVPA models for SC have shown the potential to provide permeation predictions when investigating drugs, formulations or cosmeceuticals intended for skin administration → reduce the time and cost as well as especially the use of animal testing

- The PVPA is representing an interesting and useful extension of the toolbox of *in vitro* permeability assays running in a medium- to high-throughput format.

Acknowledgements

- Former PhD students Dr André Engesland and Dr Elenaz Naderkhani

- PhD student Margherita Falavigna
- Stud. Pharm. Mette Klitgaard (University of Copenhagen) and Christina Brase (University of Braunschweig)
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Thank you for your attention!