Combined Dissolution/Permeation:

Input for Rationalized Drug Formulation Development

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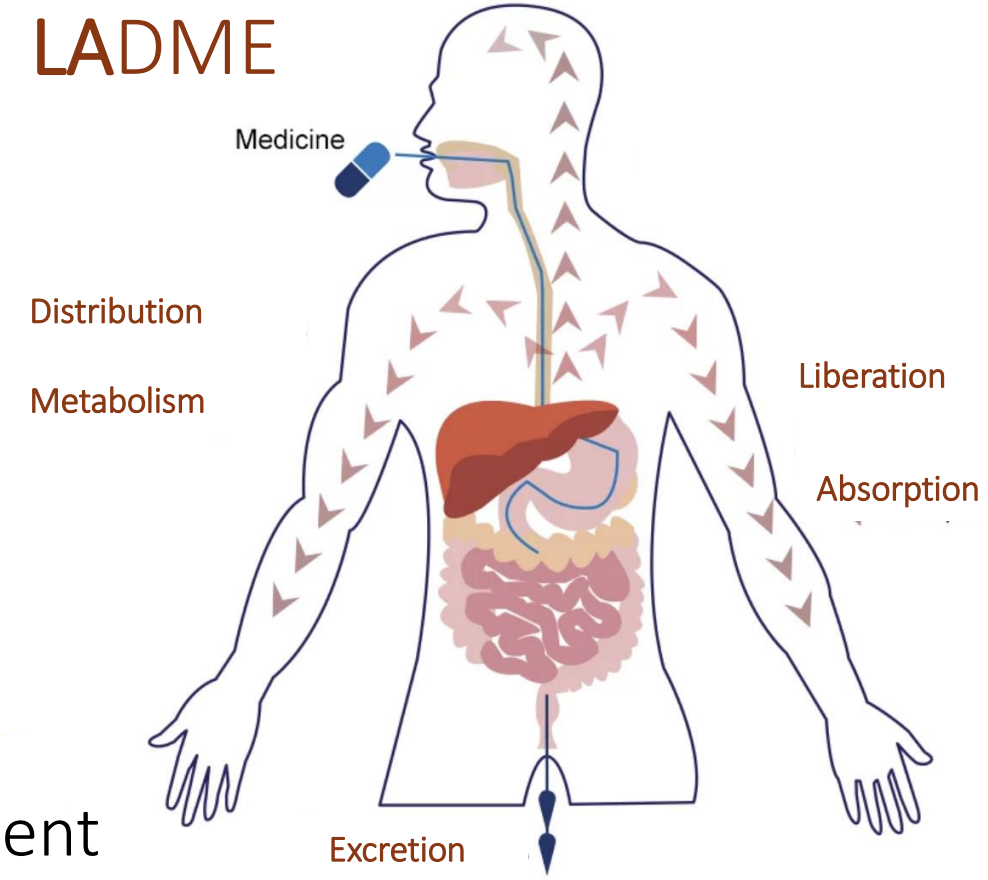
Outline: Combined Dissolution/Permeation

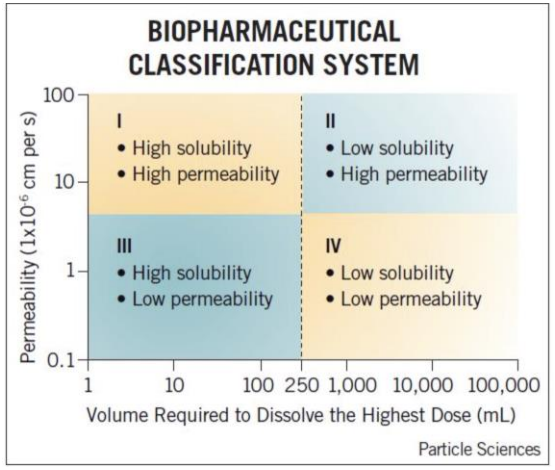
Why combine ?

Dynamic systems
(Supersaturation)

Barriers
Set-ups
Parameters
Implications for formulation development



Background



- In the past we have looked at drug solubility (dissolution) and (steady-state) permeability separately.
- This is inappropriate for most enabling formulations, because
  - not all dissolved states of a drug are equally prone to cross biological barriers
  - extent and duration of supersaturation may be affected by the presence of an absorptive sink
- To gain insight into the dynamic interplay between dissolution and permeation, we need to develop new tools for the performance ranking of enabling formulations.
- In cases, where the permeable fraction of drug (molecularly dissolved drug) is difficult to measure during the course of a dissolution experiment, D/P may serve as a alternative approach.

Ref: Buckley et al., Eur. J. Phar. Sci. 2013

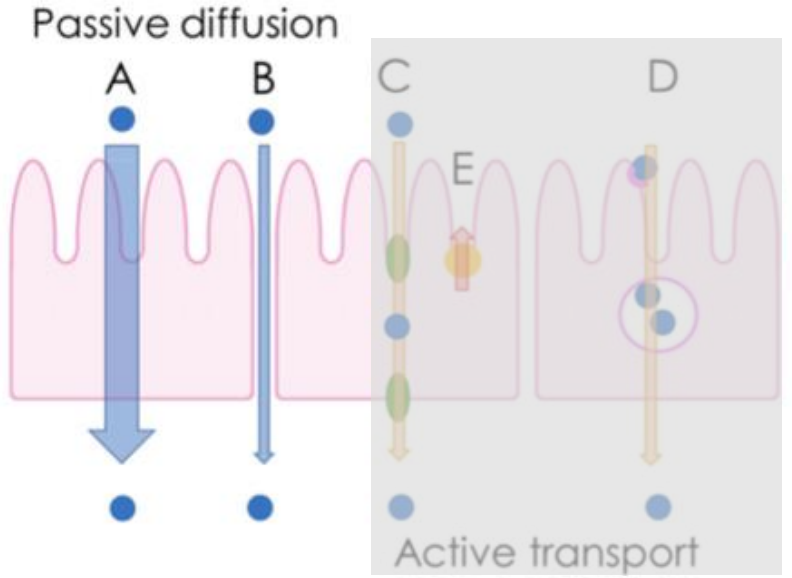
Background

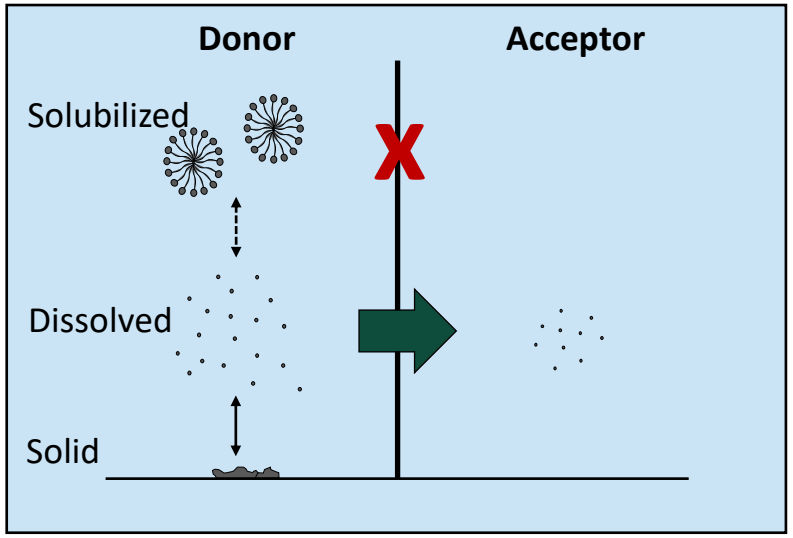
Diffusion

pH – dissociation of weak bases and acids

Supersaturation

- Degree of supersaturation :
  - Metastable supersaturated states
  - Spontaneous nucleation, precipitation
  - Replenishing the dissolution process from amorphous precipitate
  - Highly dynamic process
- Supramolecular assemblies affect supersaturation
  - Excipients: e.g. surfactants, polymers, complexing agents
  - Physiological: presence of bile salt micelles and mixed micelles
  - Food effect: change in composition; transit times
  - Digestion (lipolysis)
  - ….
- Supramolecular assemblies affect permeation





What is the Challenge ?

Example: Fenofibrate

Commercial Micro- vs. Nano products; bioequivalent

200 mg micro

$\hat{=}$

145 mg nano

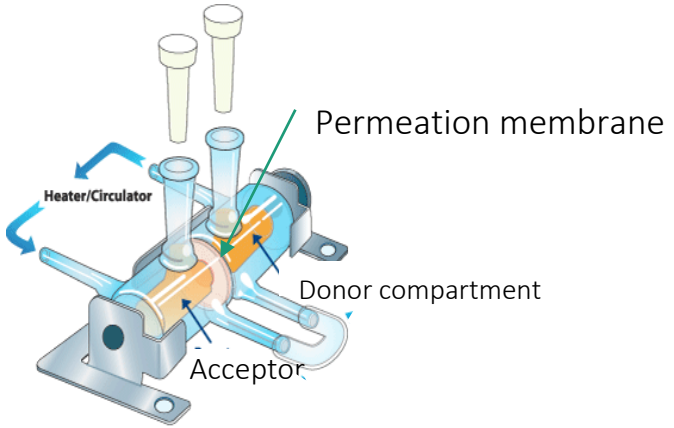
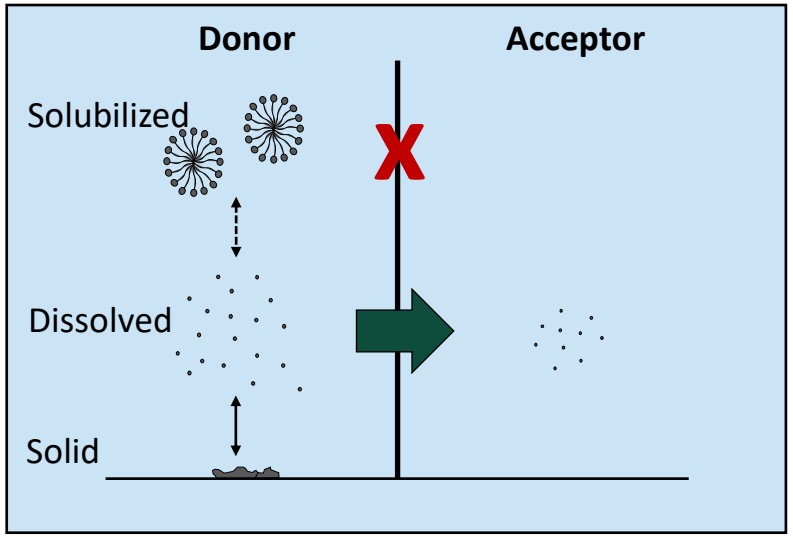


Figure: www.permegear.com

Dissolution/Permeation of Fenofibrate Nanoformulation



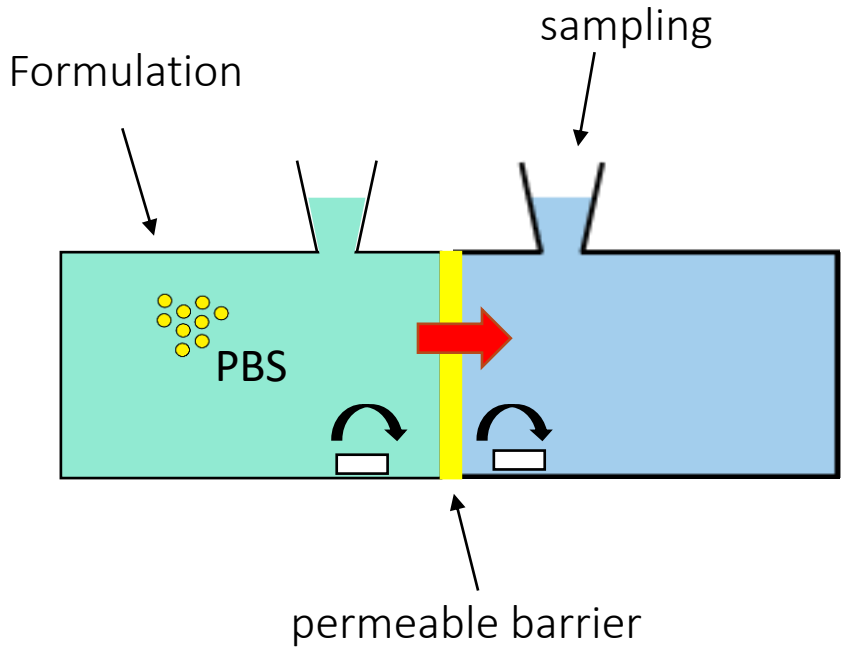
Solid state: Amorphous

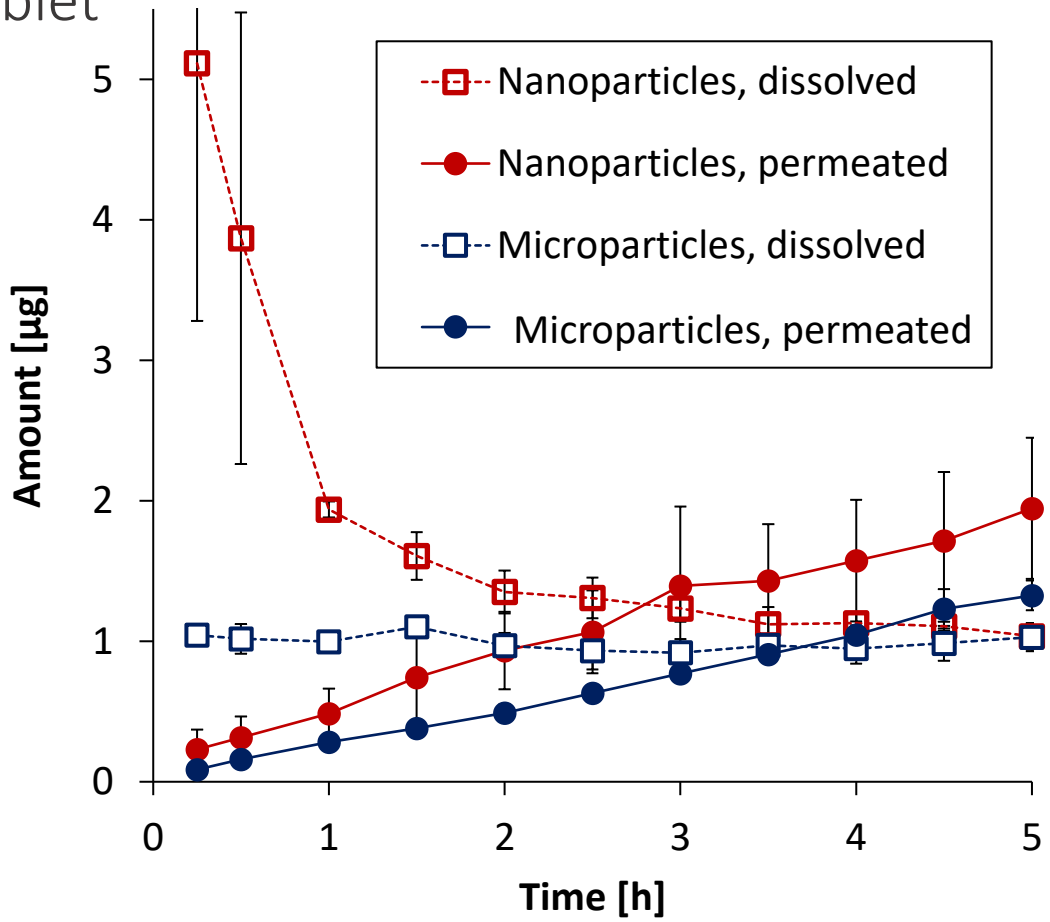
Hens, B., Brouwers, J., Corsetti, M., Augustijns, P., Eur. J. Pharm. Sci. 77(2015)40-47

Dissolution vs. Combined Dissolution/Permeation ?

Micro- and Nanoparticles from commercial tablet

Supersaturation for nanoformulation translates into better permeation



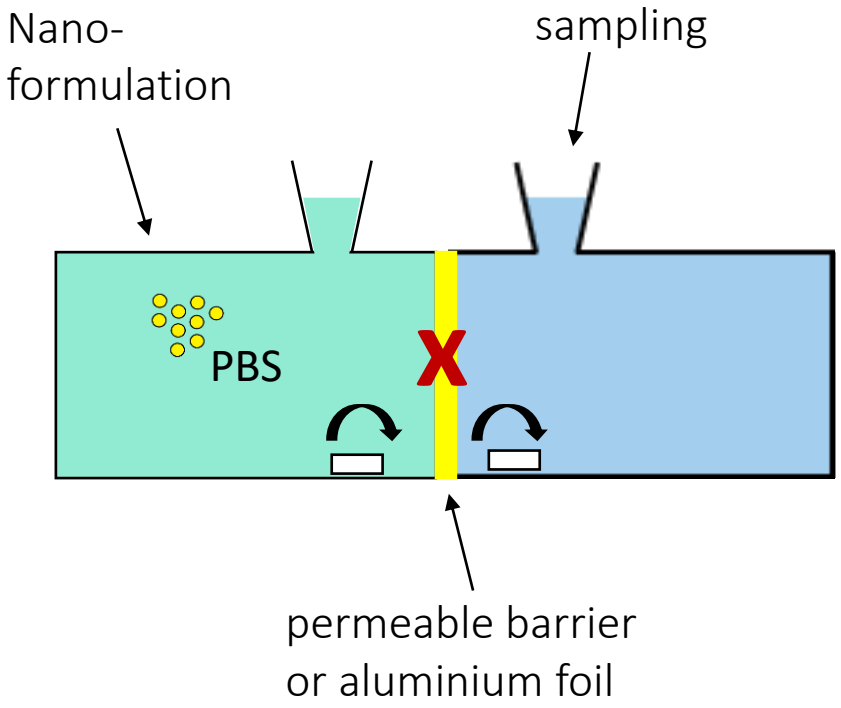


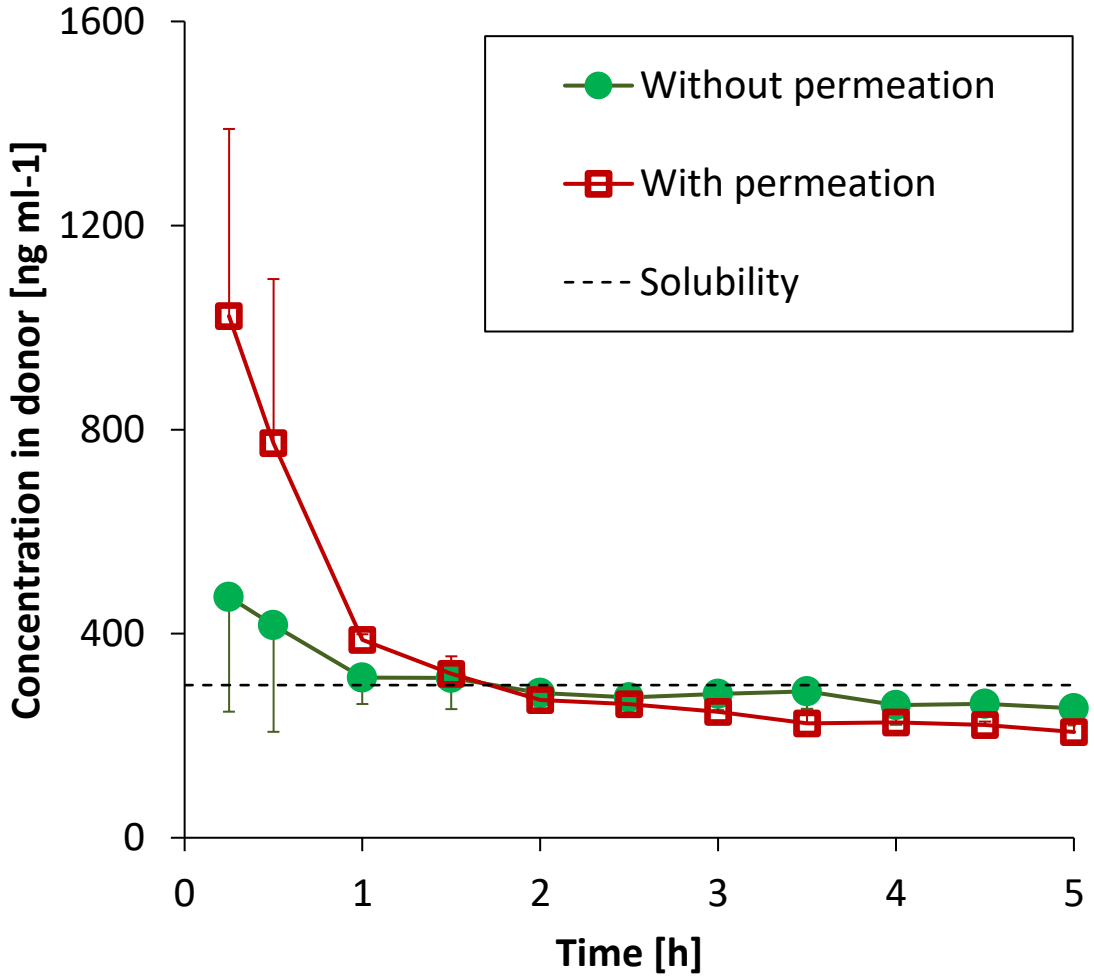
Sironi et al., Eur. J. Pharm. Sci. ., 96, 20-27 (2017)

Dissolution vs. Combined Dissolution/Permeation ?

Nanoparticles from commercial tablet

Supersaturation in the donor compartment decreases in absence of absortpive sink

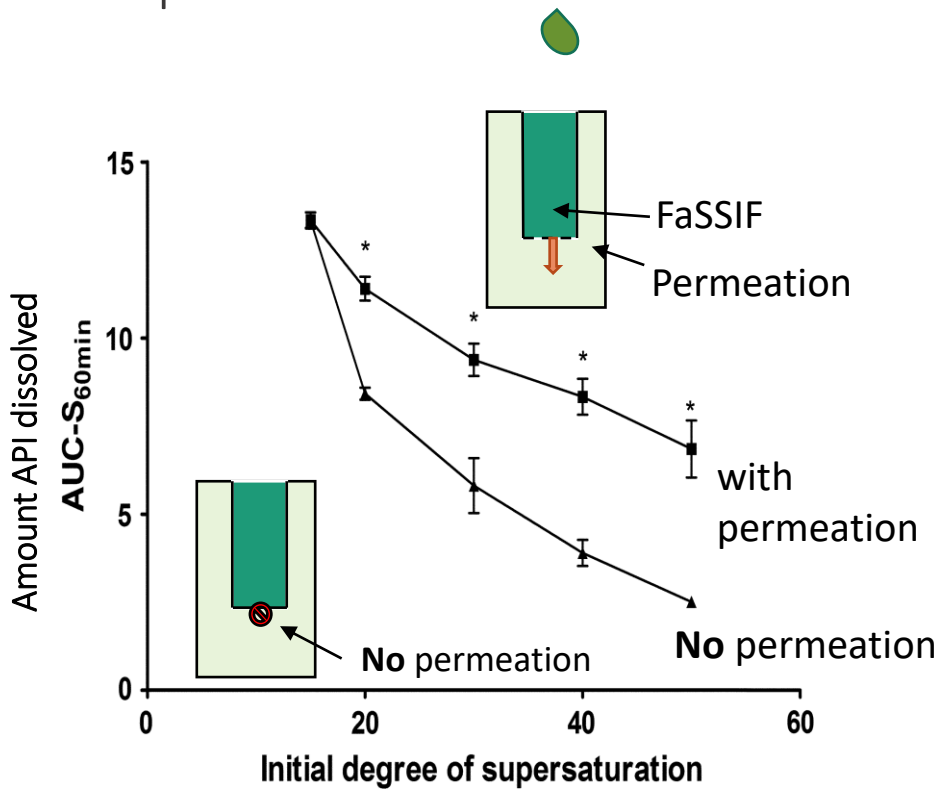




Sironi et al., Eur. J. Pharm. Sci. ., 96, 20-27 (2017)

Dissolution vs. Combined Dissolution/Permeation ?

Another similar example:
Nanoparticles from DMSO solution in situ



Bevernage et al., Eur.J.Pharm.Sci, 82, 424-428 (2012)

For supersaturating enabling formulations:

How to monitor
- Degree of Supersaturation
- Time course of Supersaturation ?

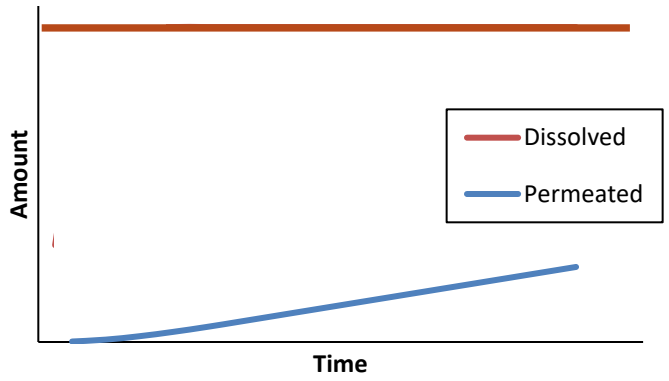
How to tune the supersaturation profile in order to mimic in vivo ?

From Permeability to Combined Dissolution/Permeation

In general : LADME

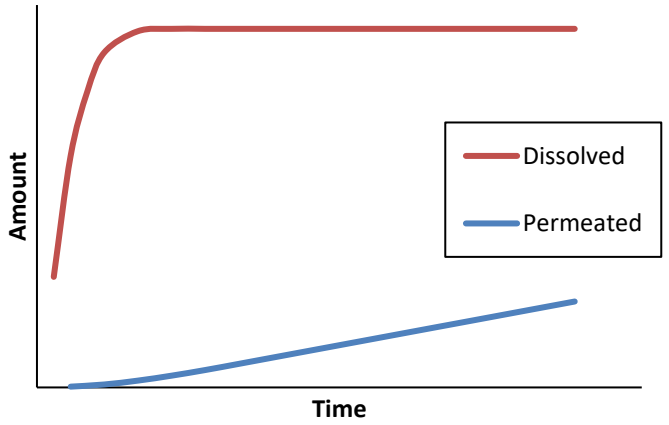
In supersaturating systems

Permeability



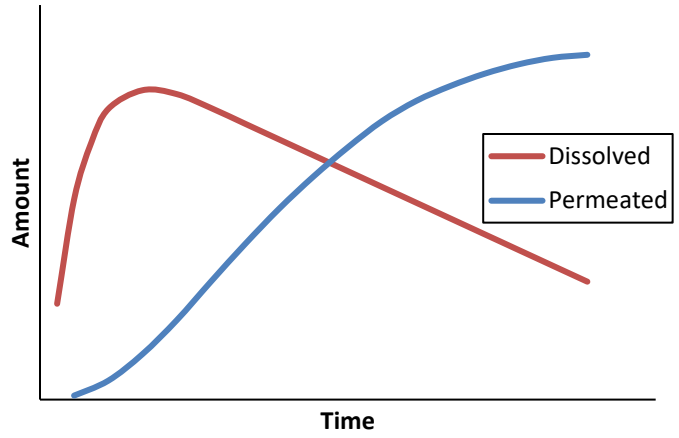
- Solution; c= constant
- Steady state flux, P_{app}

Dissolution/Permeation



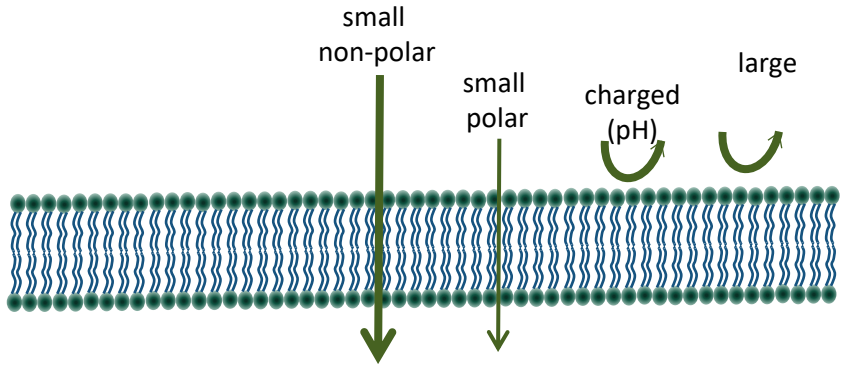
- Steady state flux
- Dissolution not affected

In vivo



- Dynamic flux
- Donor depletion

How to Increase Permeation Rate?



Permeation Rate depends on:

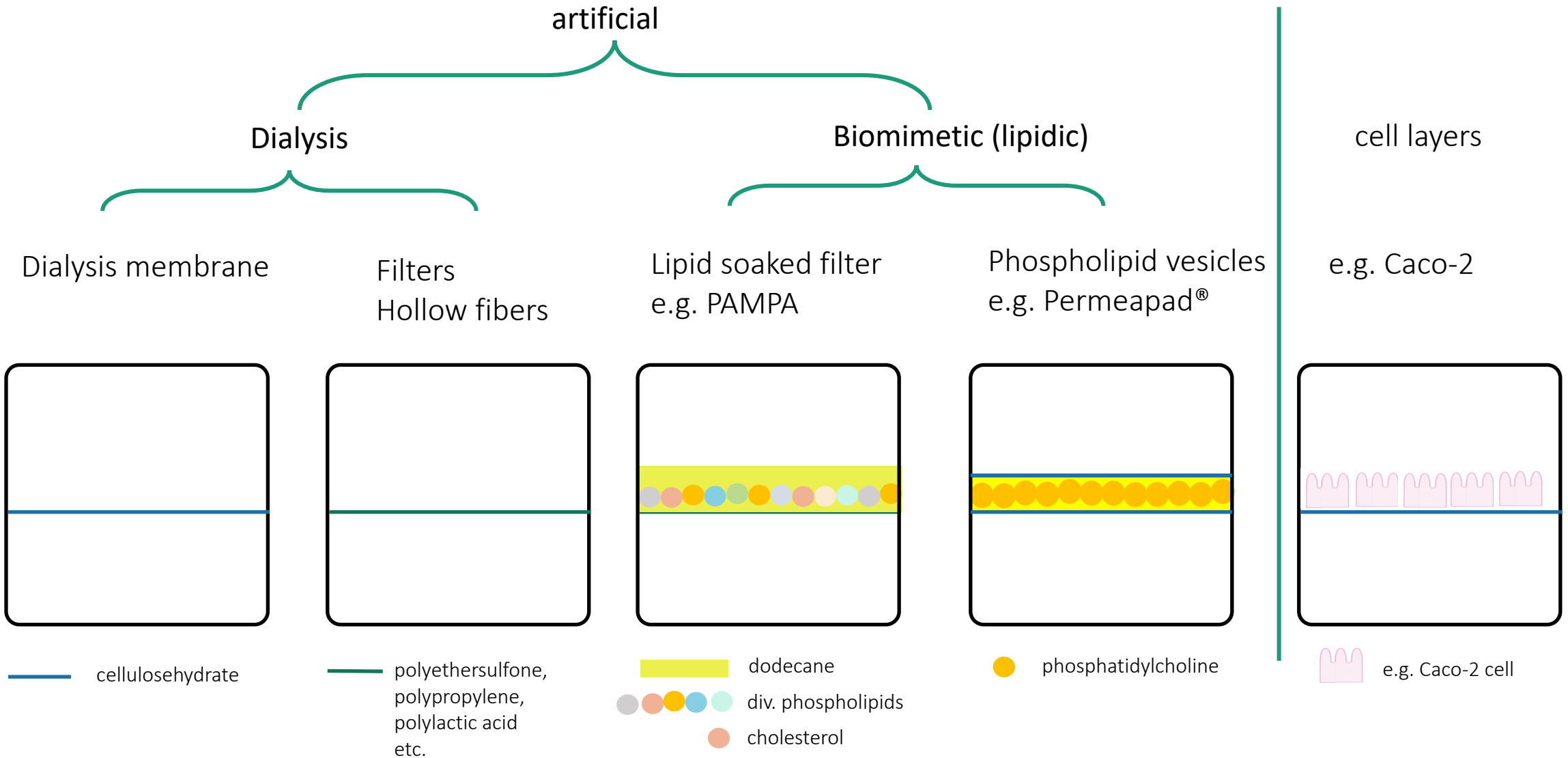
- Association state of the API:
  - Free fraction, solvation state (e.g. dissociation)
  - Polymer-associated,
  - Solubilized; (supramolecularly associated),
  - Phase separated (amorphous),
  - ….
- Dissolution Rate; replenishing from reservoirs

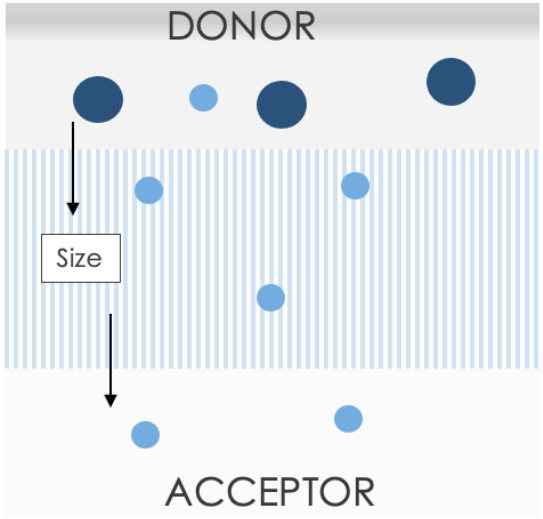
Adjustable Parameters for in vitro Models:

a) Barrier properties: Higher transmittance

b) Set-up: Increase barrier area as compared to volume of compartment

Permeation Barriers

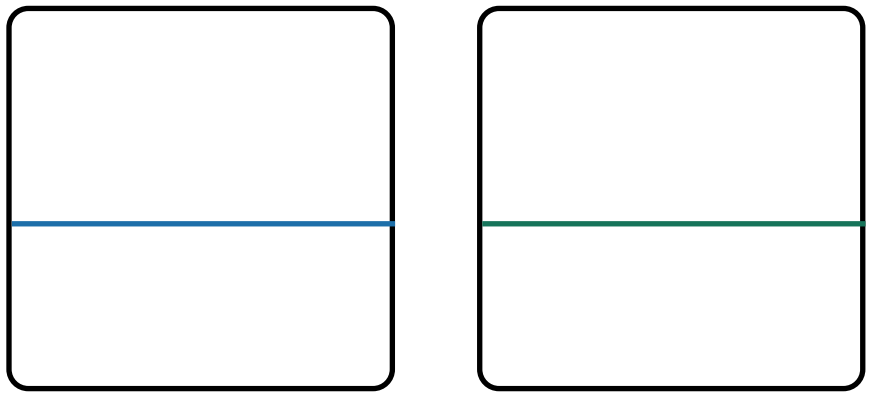




Barrier	Components	Reference(s)
AMI-system	regenerated cellulose (MWCO < 2 kDA)	Berben et al., 2018c
Permea- Plain	Cellulose hydrate (used in PermeaPlain plates®)	Jacobsen et al., 2019
PDMS membrane	Poly(dimethyl siloxane)	Garrett & Chemburkar, 1968; Sinko et al., 2017

Dialysis membrane

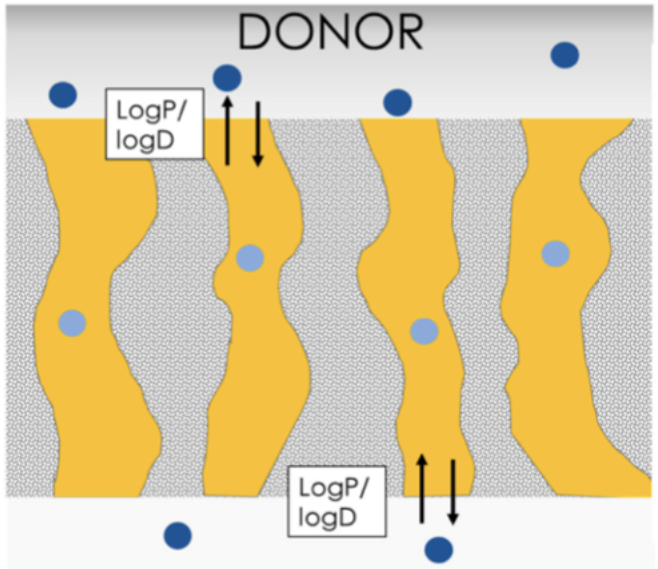
Filters
Hollow fibers



cellulosehydrate

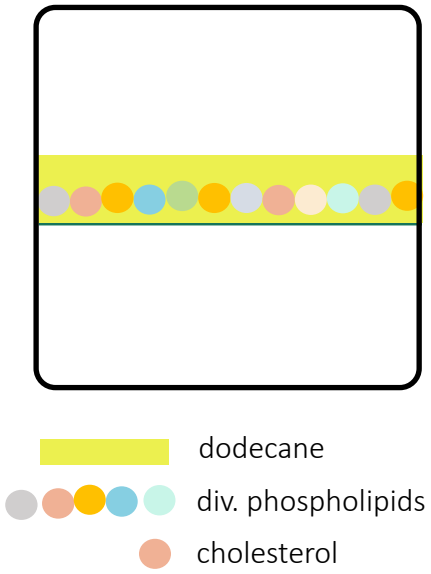
polyethersulfone,
polypropylene,
polylactic acid
etc.

- Transport according to size of molecules (solvated)
- Dissociation state disregarded

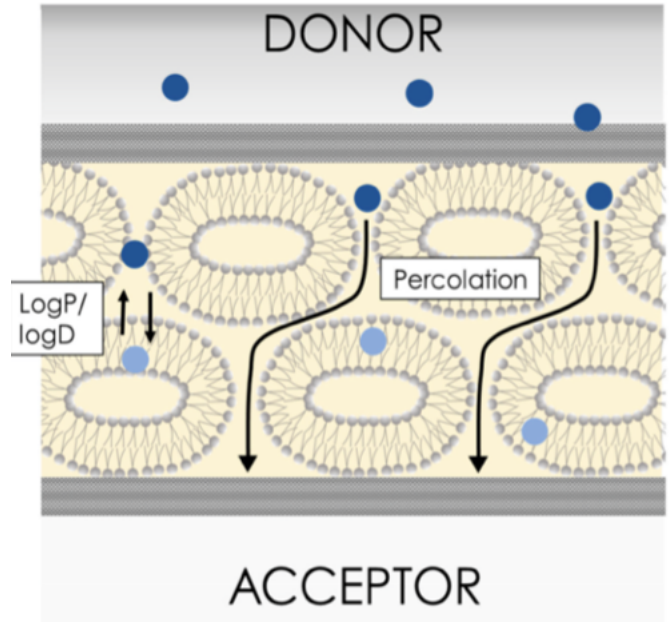


Barrier	Components	Reference(s)
PAMPA	Filter (e.g. hydrophobic PVDF), (phospho)lipids dissolved in organic solvent (e.g. 10% egg-lecithin in n-dodecane)	Avdeef et al., 2001; Kansy et al., 1998; Sugano et al., 2001; Zhu et al., 2002
Hexadecane (HDM) PAMPA	Polycarbonate filter, n-hexadecane	Wohnsland & Faller, 2001
Precoated PAMPA	PVDF filter, lipid/oil/lipid tri-layer	Chen et al., 2008

e.g. PAMPA

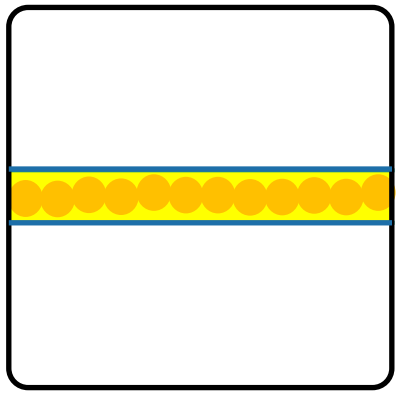


- Partitoning
- pH-dependent distribution
- Predicts lipophilic compounds better



Barrier	Components	Reference(s)
PVPA	Filter (mixed cellulose ester), liposomes (from e.g. egg phosphatidylcholine)**	Flaten et al., 2006; Naderkhani et al., 2014
Permeapad®	2 support sheets cellulose hydrate sandwich phospholipids (e.g. soy phosphatidylcholine)	di Cagno et al., 2015; Jacobsen et al., 2020b

Phospholipid vesicles
e.g. Permeapad®



phosphatidylcholine

Transport mechanism includes interaction with PL bilayers and aqueous spaces

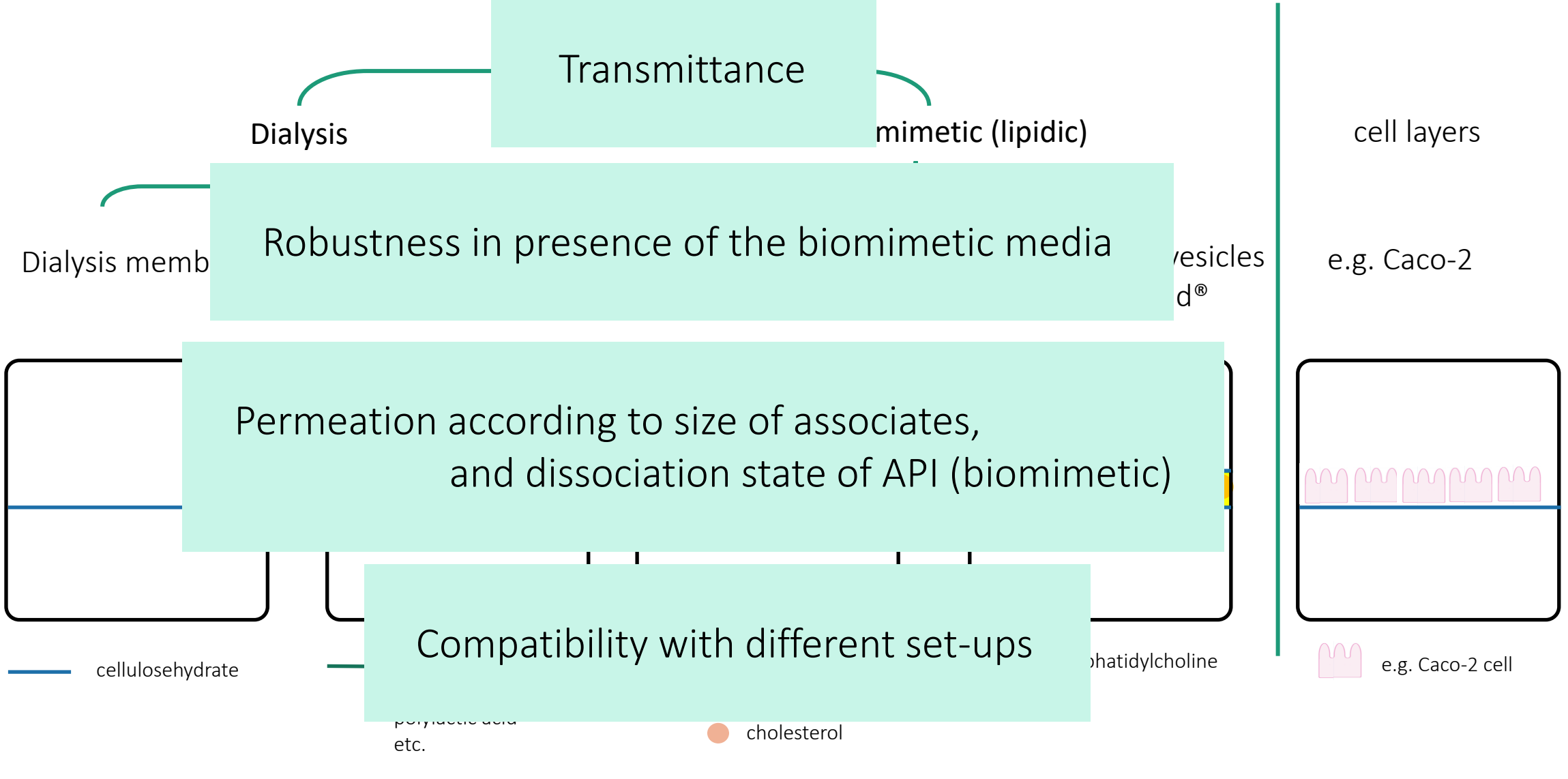
How to select a Permeation Barrier ?

Transmittance

Robustness in presence of the biomimetic media

Permeation according to size of associates,
and dissociation state of API (biomimetic)

Compatibility with different set-ups

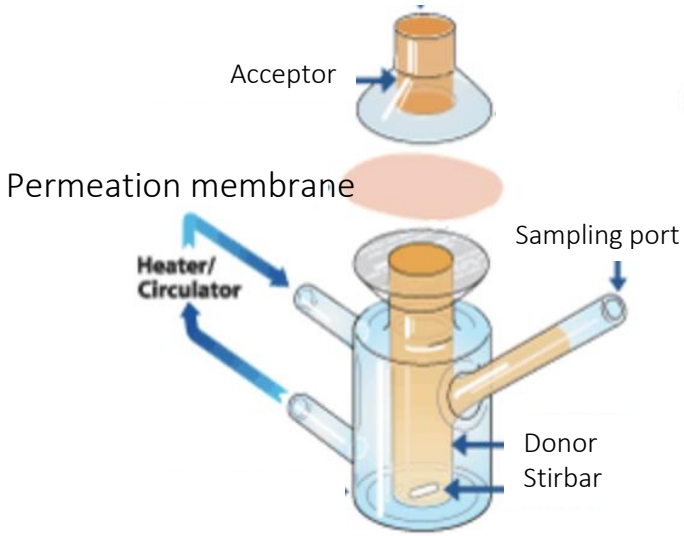


b) Set-ups: Classical Diffusion cells

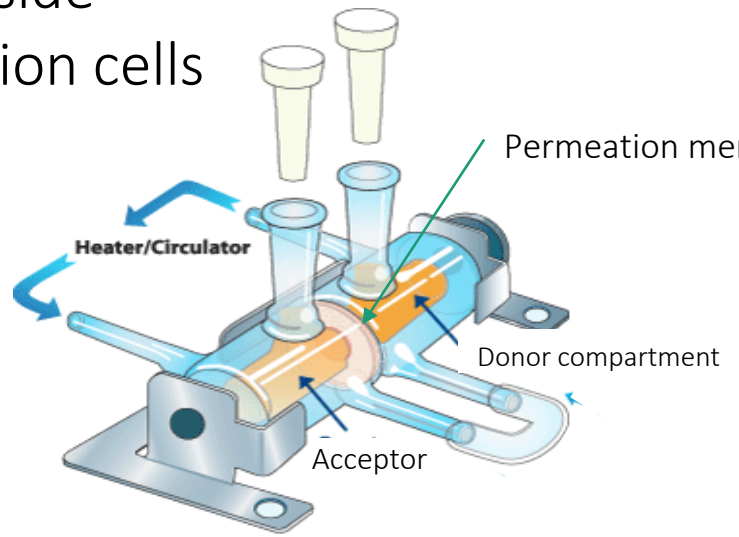
- Dissolution / Permeation

- Hydrodynamics /stirring
- Volumes
- Arrangement of sampling ports

Franz cells



Side-by-side
diffusion cells



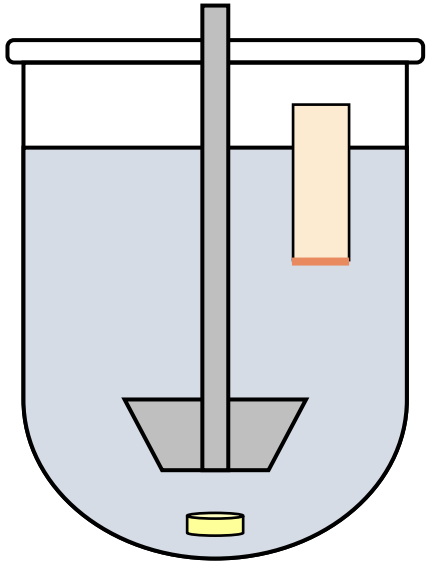
Figures: www.permegear.com

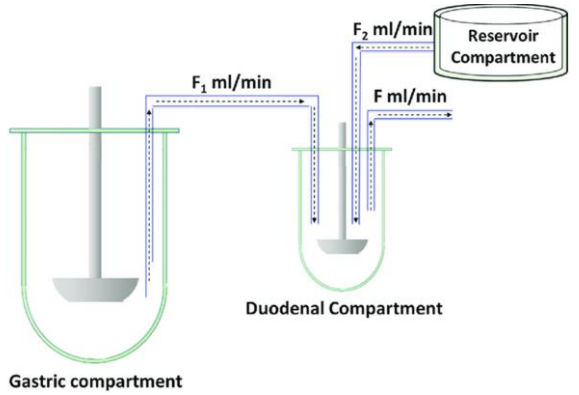
Set-ups:

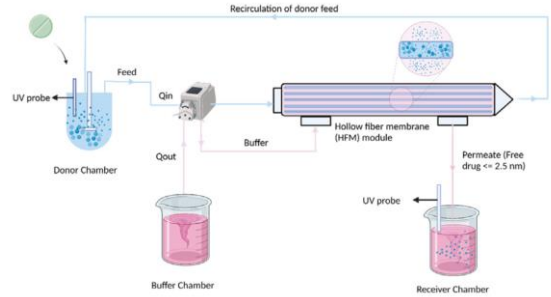
- Dissolution / Permeation

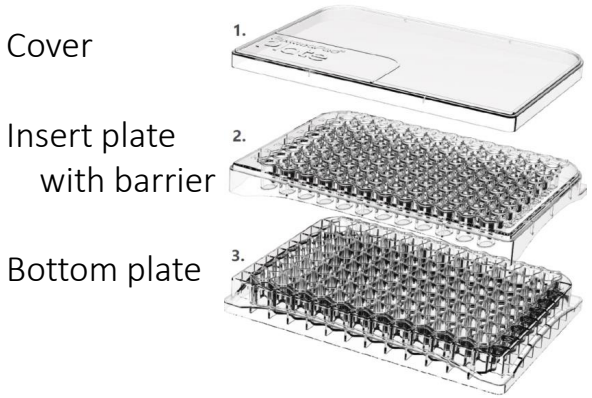
- Hydrodynamics
- A/V ratio

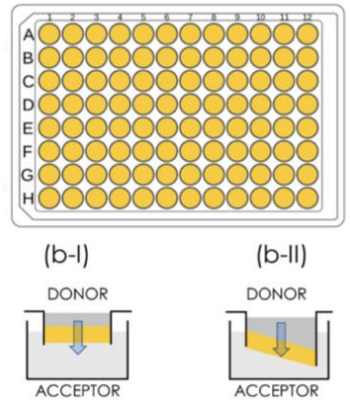
- closed compartment methods
- Half change methods
- Fluid flow through methods
- Microtiter plates



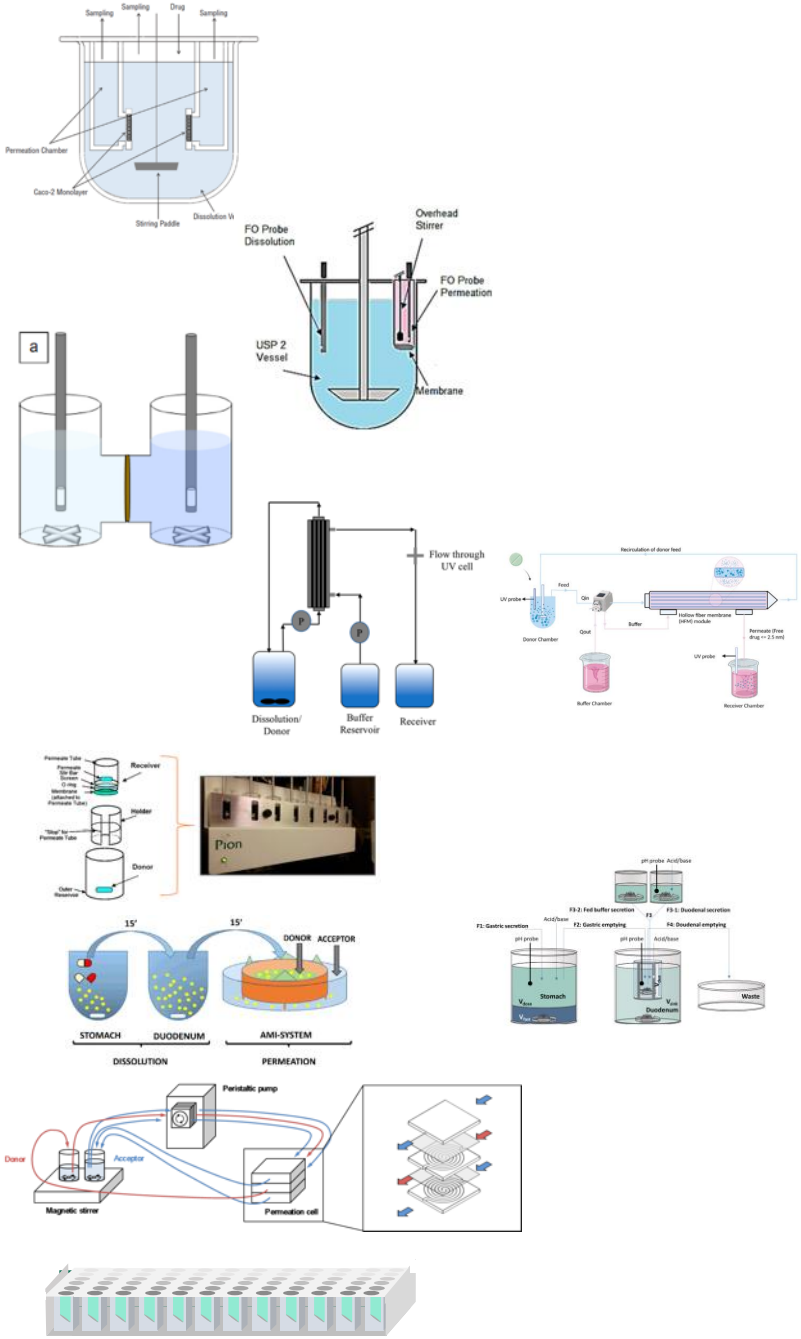








Setup	Reference	**Barrier**	**A [cm²]**	**V_{Donor} [mL]**	**A/V [cm⁻¹]**	**Sample**	**D/P set-up**
IDAS2	*Li et al. 2019*	Caco-2	2.26	500	**0.005**	Complete dosage form	Continuous
MacroFLUX™	*Borbás et al. 2018*	Lipid-soaked filter (PAMPA)	3.80	1062	**0.004**	Complete dosage form	Continuous
Microflux ™	*Tsinmann et al. 2018*	Lipid-soaked filter (PAMPA)	1.54	20	**0.08**	Down-scaled formulation	Continuous
Hollow fiber module	*Hate et al. 2019*	Dialysis principle	100	50	**2.00**	Complete dosage form	Continuous
Diamod®	*Moens et al., 2023*	Dialysis membrane	65	30	**2**	Complete dosage form	Continuous
TIM Tiny TIM	*Mármol et al., 2022*	Hollow fiber dialysis		55-300	**n/a**	Complete dosage form	Continuous
Vertical membrane flux cell	*Stewart et al. 2017*	Lipid-soaked filter (PAMPA)	4.90	5	**0.98**	Drug substance	Continuous
AMI-system	*Berben et al. 2018*	Dialysis membrane	4.91	0.7	**7.38**	Complete dosage form	Dis-continuous
PermeaLoop™	*Sironi et al. 2018*	Dialysis membrane / Permeapad	27.6	20	**1.38**	Downscaled formulation	Continuous
Permeapad® Plate; Plain Plate	*Jacobsen et al 2019*	Dialysis membrane / Permeapad	0.2	0.15-0.4	**1.33-0.5**	Downscaled dosage form	Continuous



How to select a set-up?

- Accroding to the objective of the study:

  Ranking of formulations or mechanistic understanding?

- Number of test parameters; number of experiments
- Compatibility of barriers with the different set-ups
- Compatibility with dosage form and preparation, e.g. lipolysis
- Propabability for non-specific adsorption of API to surfaces
- …

Case Study 1:

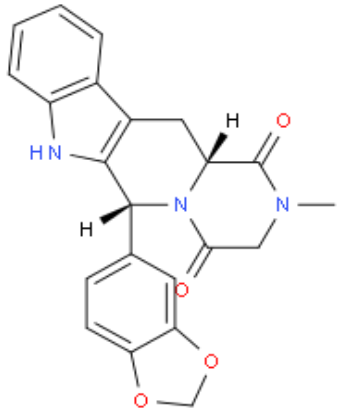
Combined Dissolution and Permeation
in preformulation /early formulation studies

Ranking of formulations

Case Study 1: Formulations of Amorphous Tadalafil

- In vivo bioavailability rat data:
  from Krupa et al. (2016)
- High-energy ball-milling for tadalafil amorphization
- Solid dispersion of tadalafil in Soluplus® (amphiphilic polymer)

Tadalafil:
MW 389.4 g/mol
logP: 2
BCS class II
Solubility ~ 2 µg/mL
not pH dependent



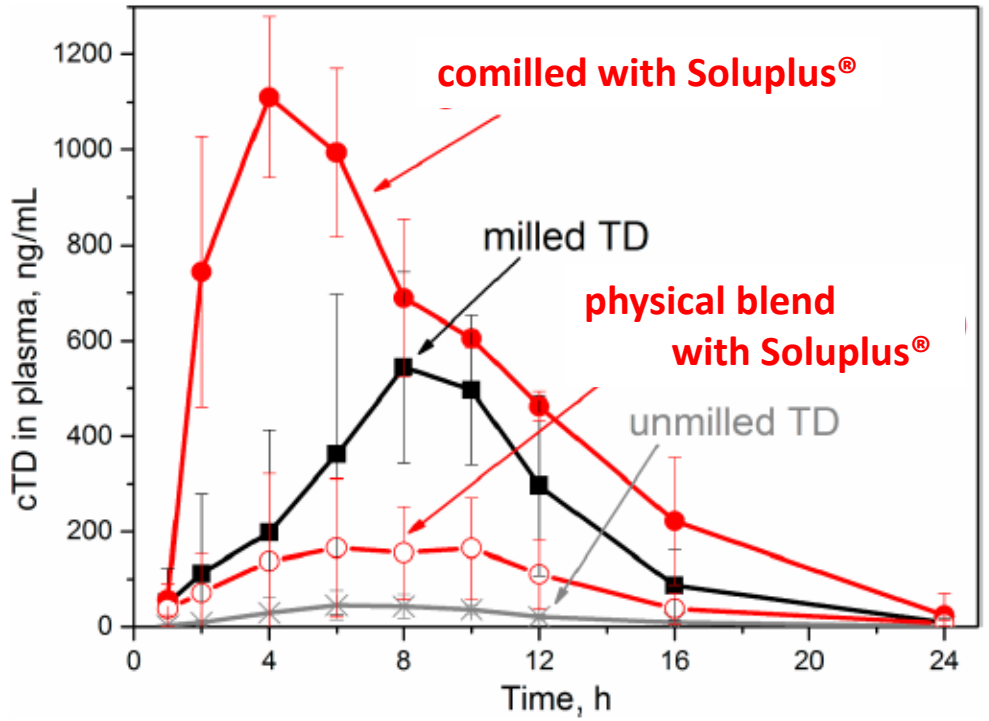
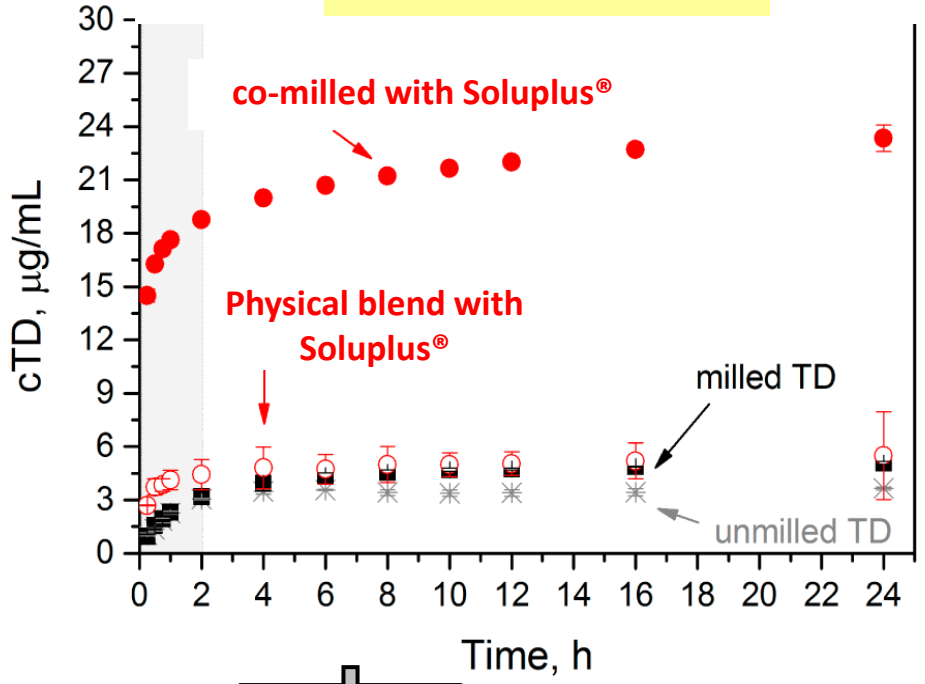


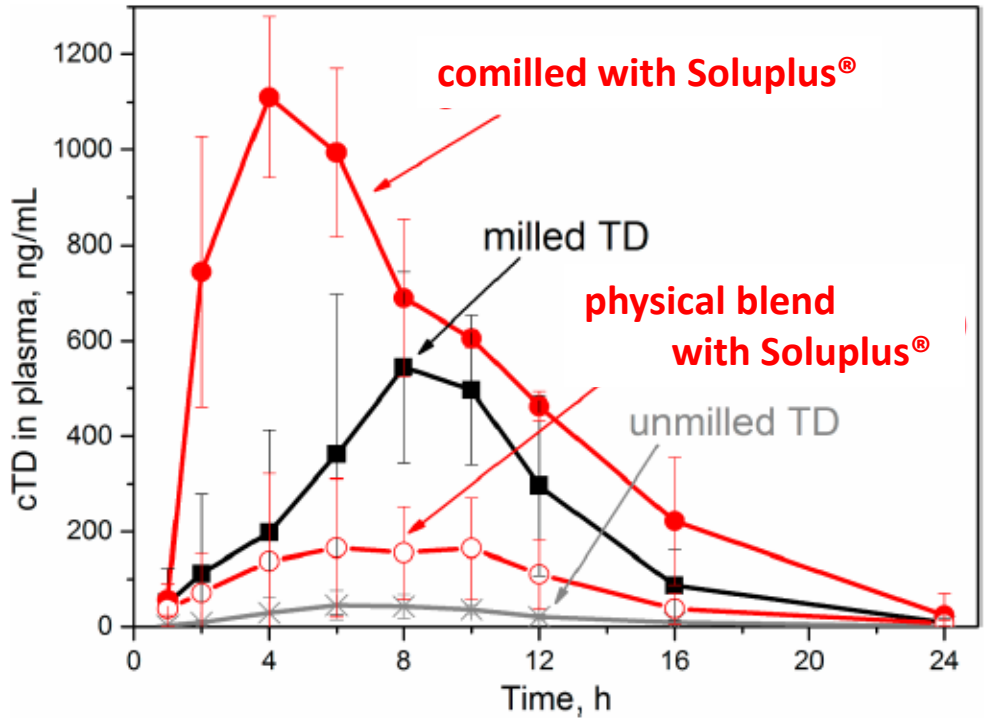
Figure 9. Rat plasma concentrations of TD as a function of time following oral administration of gelatin capsules containing TD (5 mg/kg) in the form of comilled glassy solution 0.1TD (red solid circles), milled amorphous TD (black solid squares), unmilled crystalline PM 0.1TD (red open circles), and unmilled crystalline TD (gray stars) (n = 4).

Krupa, A., Descamps, M., Willart, J.F., Strach, B., Wyska, E., Jachowicz, R., Danede, F., 2016:
High-Energy Ball Milling as Green Process To Vitrify Tadalafil and Improve Bioavailability. Molecular Pharmaceutics 13, 3891-3902.

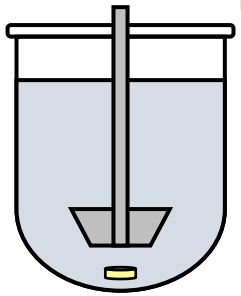
Case Study 1: Formulations of Amorphous Tadalafil

in vitro dissolution





Dissolution Apparatus 2



-> poor prediction

Krupa, A., Descamps, M., Willart, J.F., Strach, B., Wyska, E., Jachowicz, R., Danede, F., 2016:
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Case Study 1:

Combined Dissolution and Permeation
in preformulation /early formulation studies

Formulation screening

“black box”:

Permeated amount
after fixed time interval

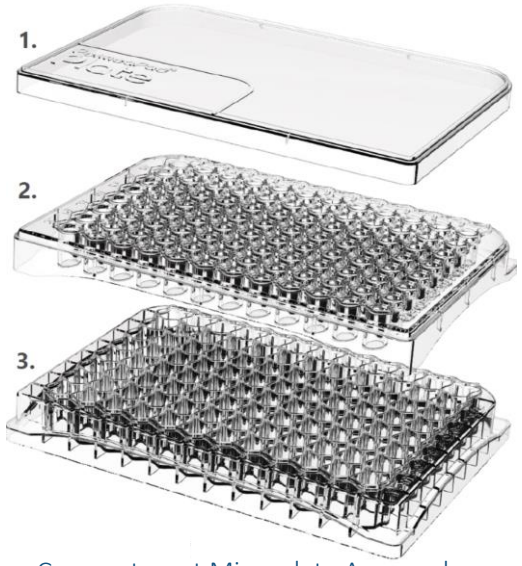
Permeation-”plain” plate : dialysis principle

Microtiter plates

Cover

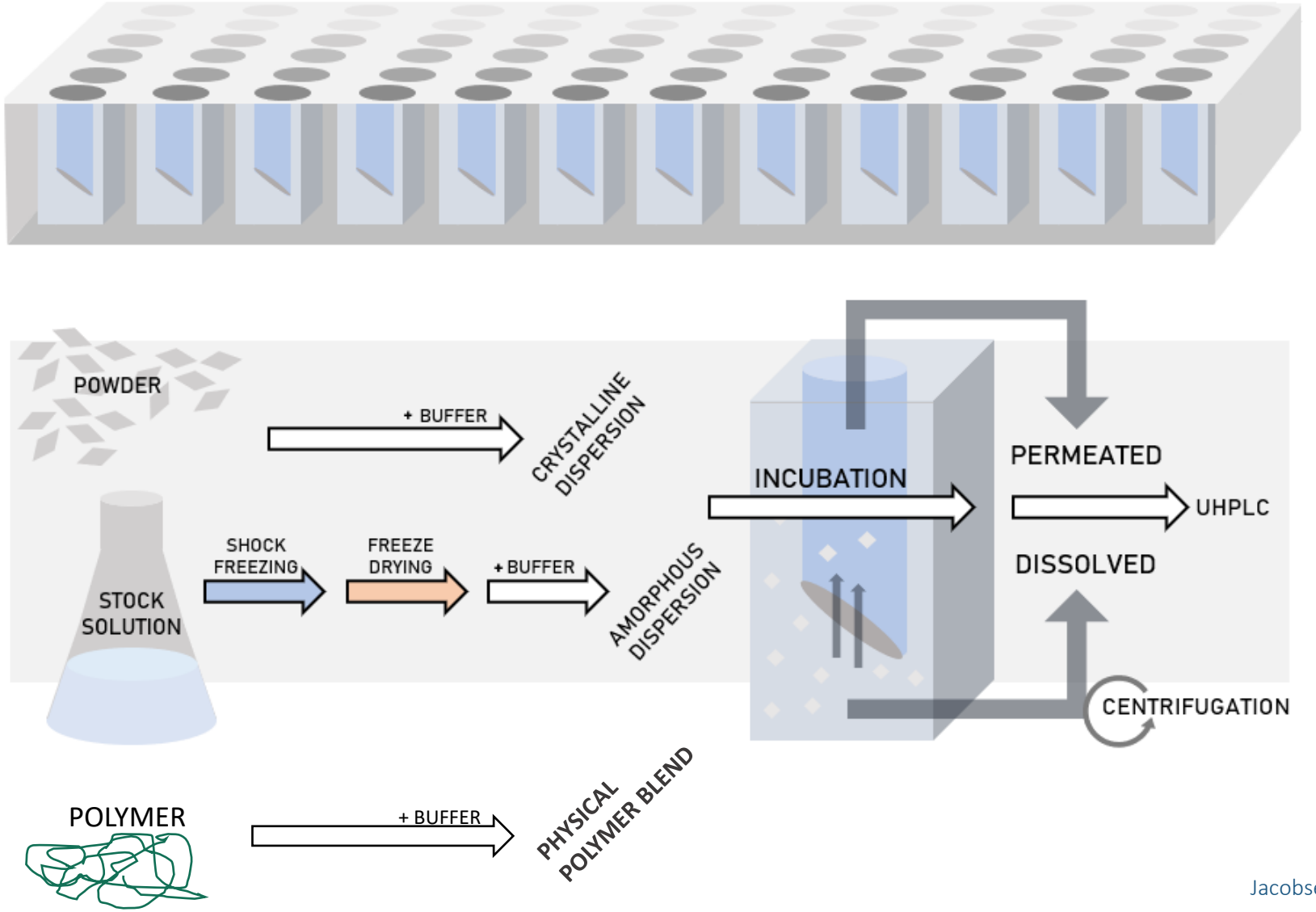
Insert plate
with barrier

Bottom plate



Jacobsen AC, Krupa A, Brandl M, Bauer-Brandl A: High-Throughput Dissolution/Permeation Screening—A 96-Well Two-Compartment Microplate Approach, Pharmaceutics, May 2019, 10.3390/pharmaceutics11050227

Case Study 1: Preparation of Formulations



Jacobsen et al., Pharmaceutics, 2019.

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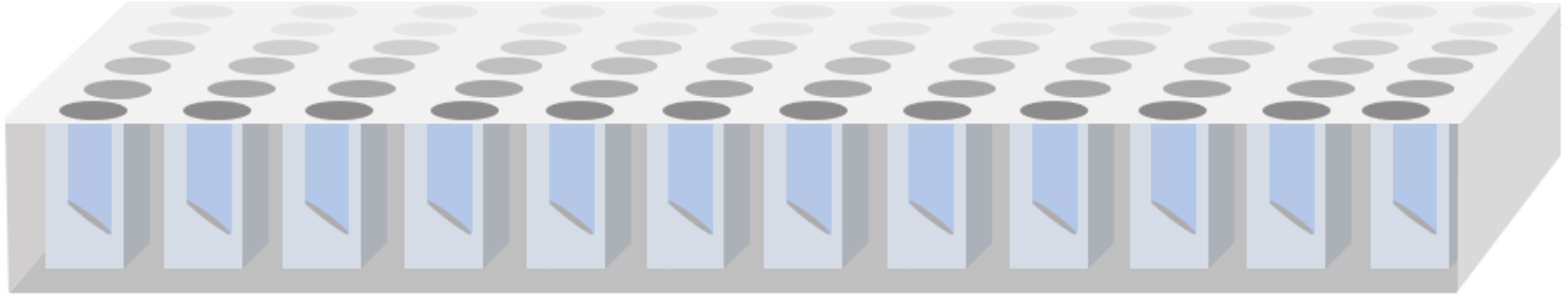
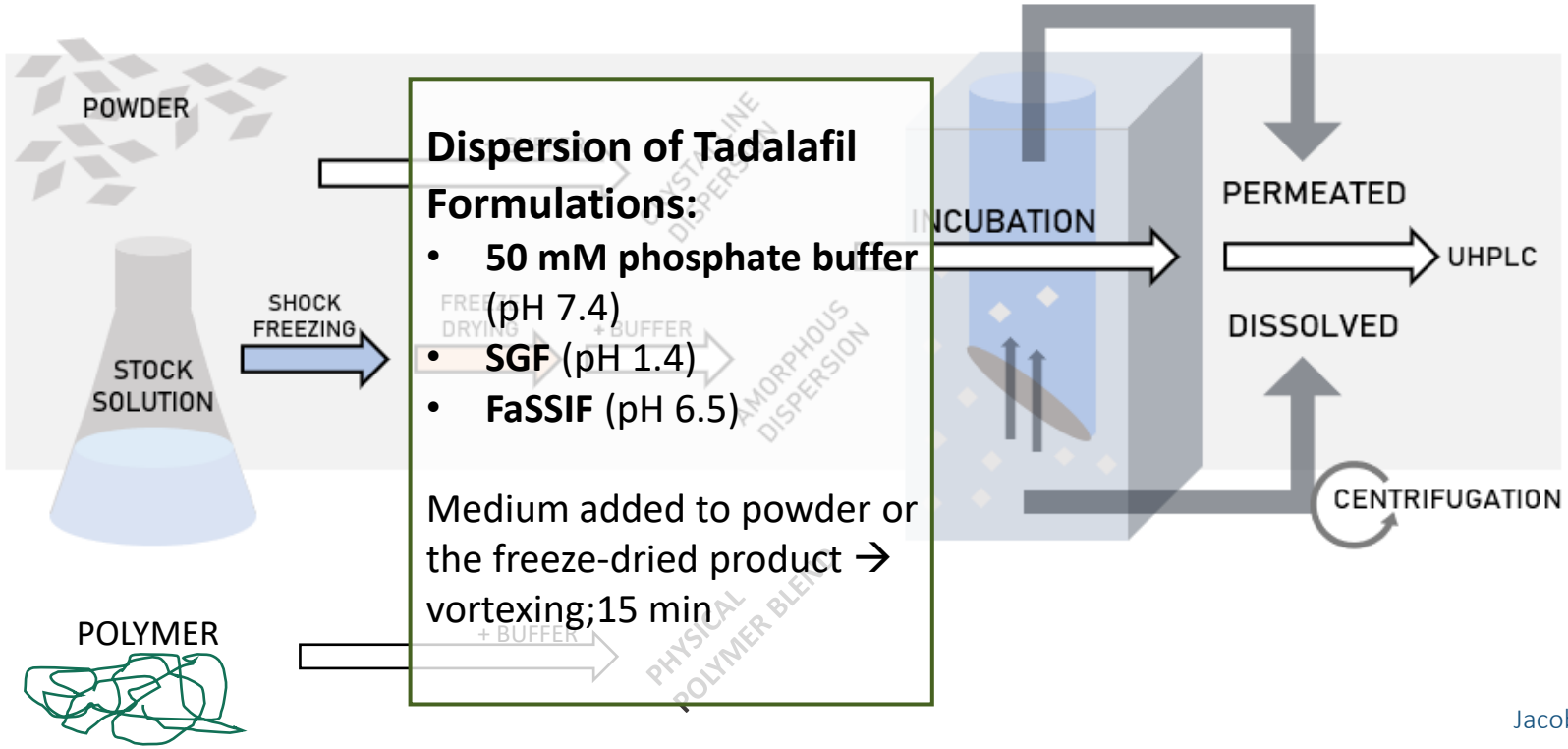
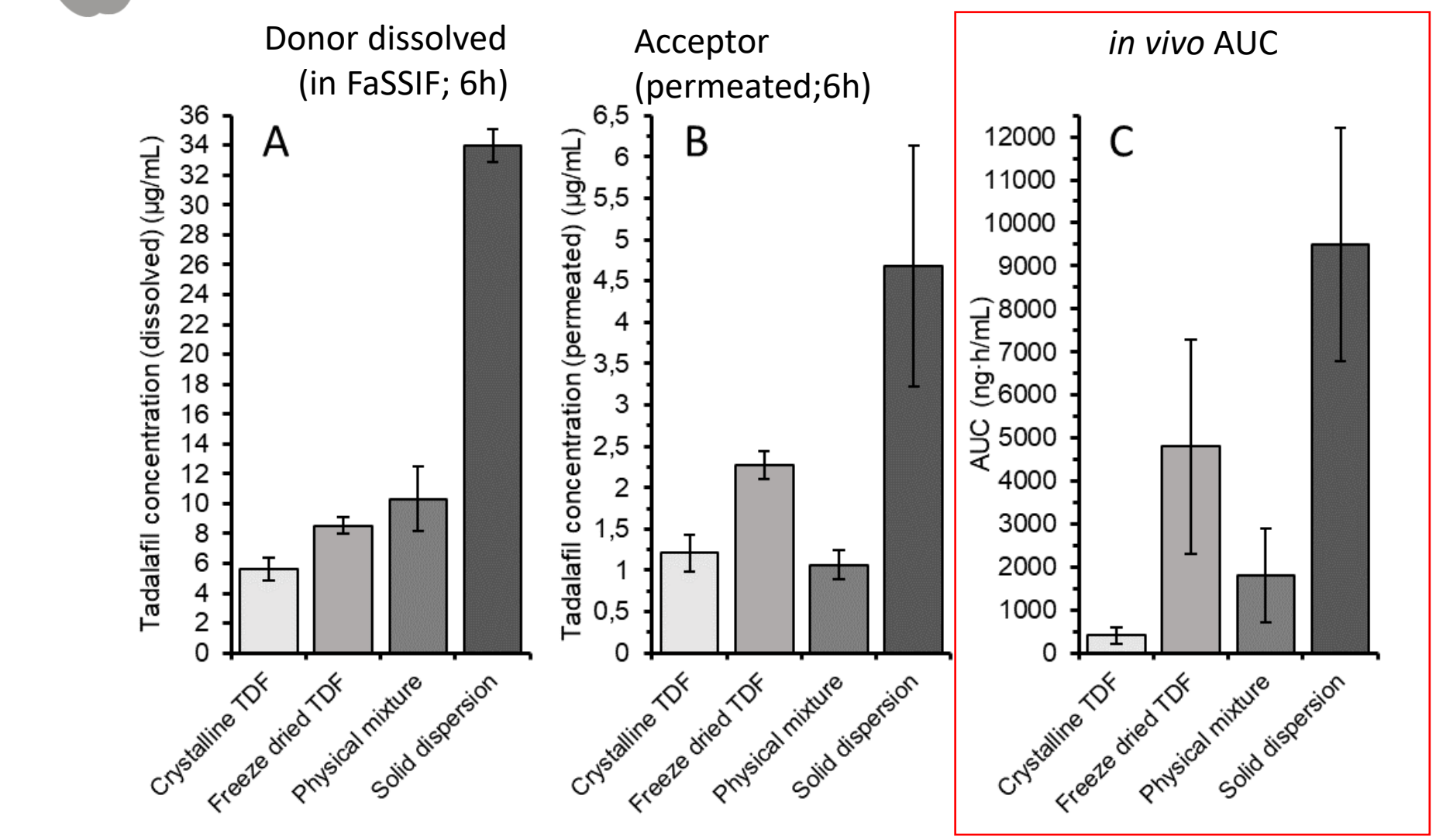
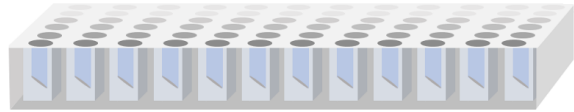




Jacobsen et al., Pharmaceutics, 2019.

Case Study 1: Comparison to in vivo Data





Dissolution is not predictive- even in biomimetic media.

Amount of API permeated is predictive (ranking of formulations).

Jacobsen et al., Pharmaceutics, 2019.

How to select a D/P method?

Ranking of formulations

"Black box":
anaylse amount permeated only

High throughput screening HTS

- Balance rates of dissolution and depletion
  - API properties
  - Excipient properties
- Which barrier?
  Which experimental conditions?
- Key influence parameters

Mechanistic understanding

Input for choice of formulations

- Follow permeation over time
- In depth analysis of supersaturation states, equilibria in the donor
- Follow exchange rates
- Analytical tools?
- Prediction & modelling

Case Study 2:

Combined Dissolution and Permeation
Enabling Formulation Screening
using side-by-side diffusion cell and Permealoop™

Reverse engineering approach

Formulation optimization

Case Study 2: Permealoop™ Surface pH-modified Dipyridamole Formulations

Preparation of granules:

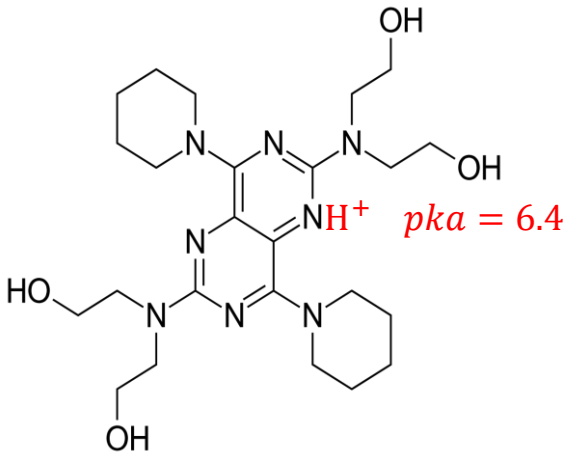
Fumaric acid
Dipyridamole
Mannitol

→ Addition of HPC solution and 70% ethanol q.s.

→ 500µm sieve

→ 60°C, 2h

→ Particles passing 125µm sieve are discarded



$pka = 6.4$

Table 6 Compositions of prepared granules and physical mixture

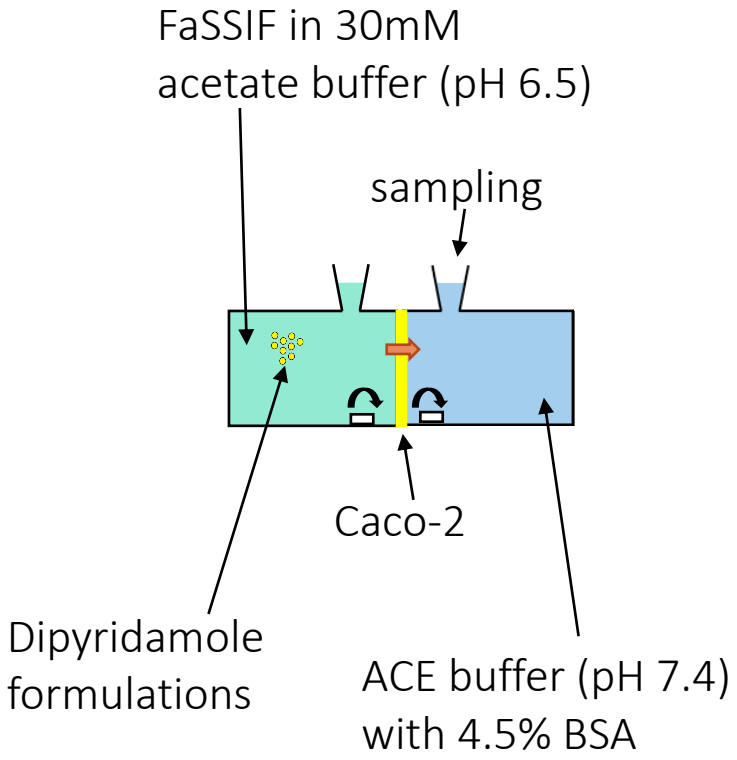
API:acid ratio	1:0	1:0.5	1:1	1:2	1:1
Wet granulation?	yes	yes	yes	yes	no (PM)
Dipyridamole (mass, %)	29.85	29.85	29.85	29.85	29.85
Mannitol (mass, %)	69.65	54.75	39.8	9.95	39.8
Fumaric acid (mass, %)	0	14.90	29.85	59.7	29.85
HPC (mass, %)	0.5	0.5	0.5	0.5	0.5
Total (mass, %)	100	100	100	100	100

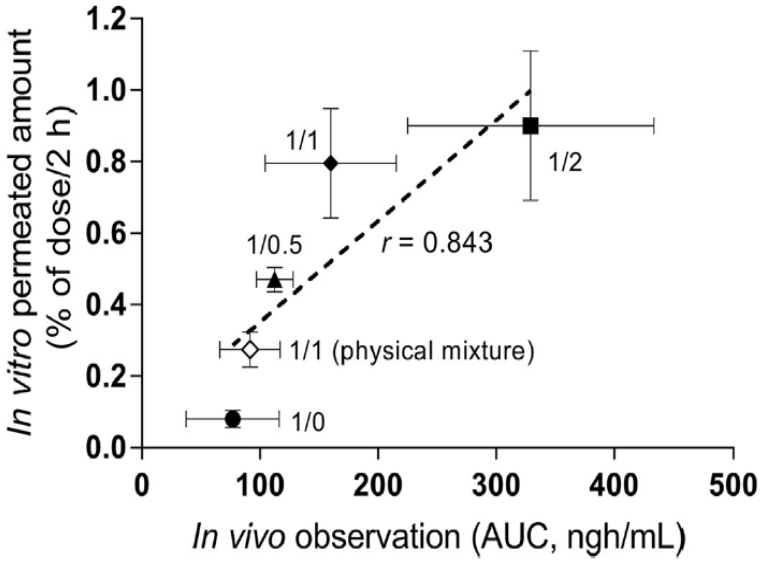
Eriksen et al., Eur J Pharm Sci 2020

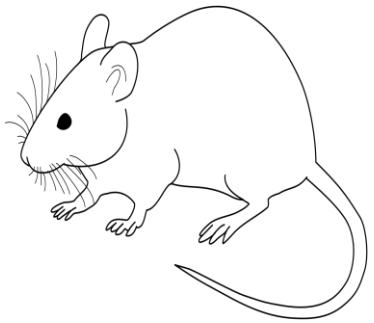
Case Study 2: References for Dipyridamole Formulations: D/P and in vivo absorption

Dipyridamole properties:
*Solubility pH 4.0: 490µg/mL
*Solubility pH 6.5: 5µg/mL
*Solubility pH 7.4: 3µg/mL
LogP: 4.1
BCS: II

*Sieger et al., EJPS, 105, 82-90 (2017)





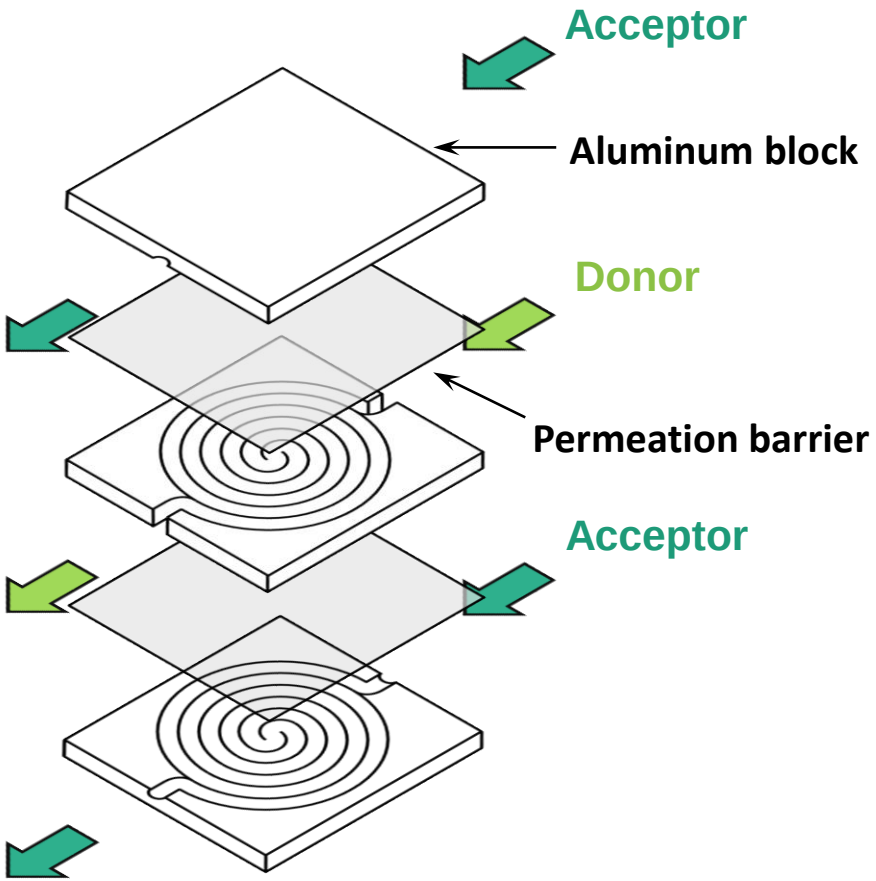


Mizoguchi et al., Journal of Pharmaceutical Sciences, 107 (9) 2404-2410 (2018)

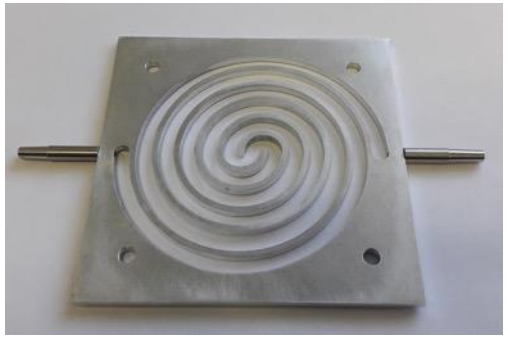
Case Study 2: PermeaLoop™

Permeation setup with high area-to-volume ratio

→ Small-scale flow-through dissolution/permeation studies



Permeation area:	27.6 cm^2
Donor volume:	20 mL
Area/volume:	**1.38 cm^{-1}**



Middle compartment (donor)

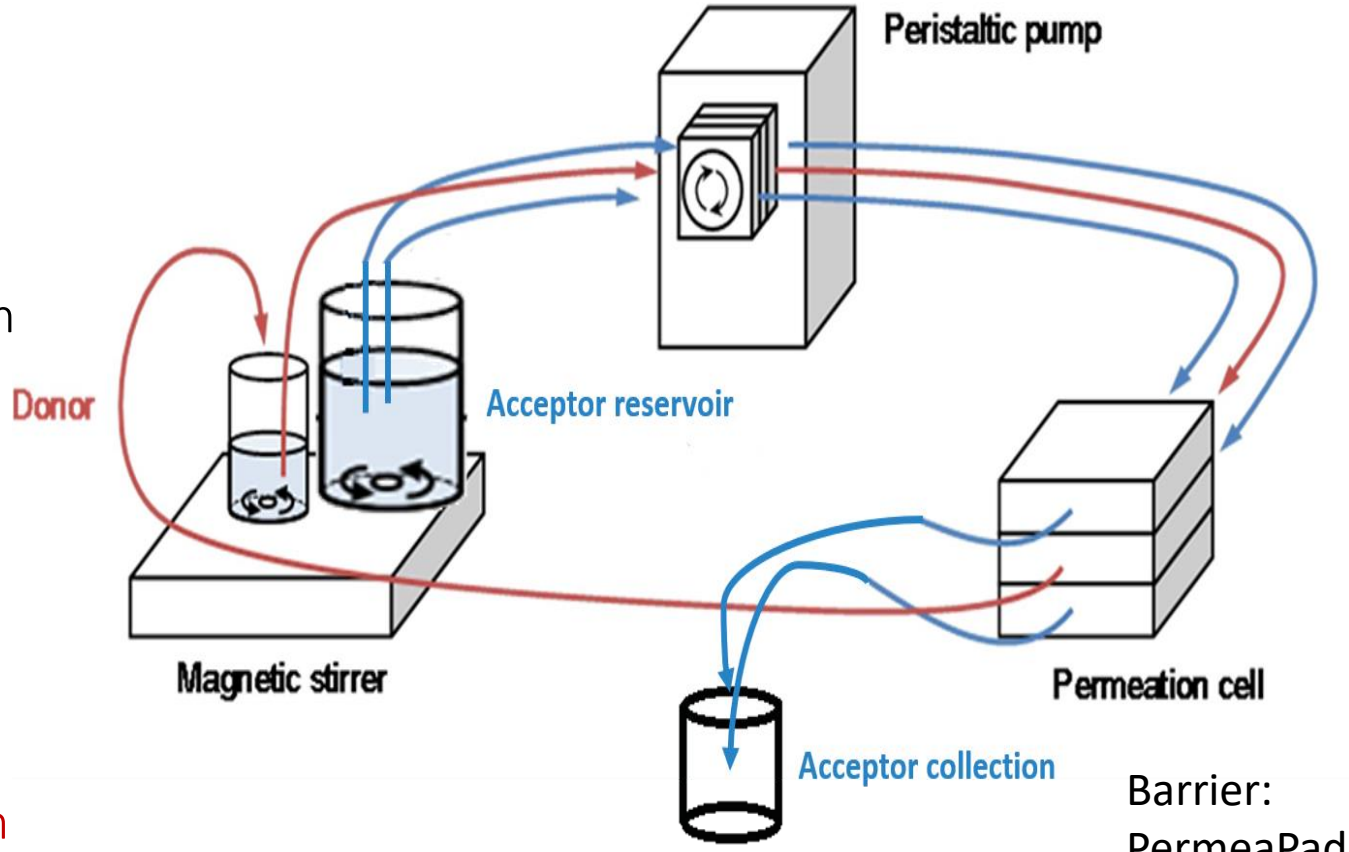
Figure: D. Sironi

Case Study 2: PermeaLoop™ Set-up

Donor flowrate: 1mL/min

Acceptor flowrate: 0.25mL/min
or 1mL/min

Temperature: 37ºC



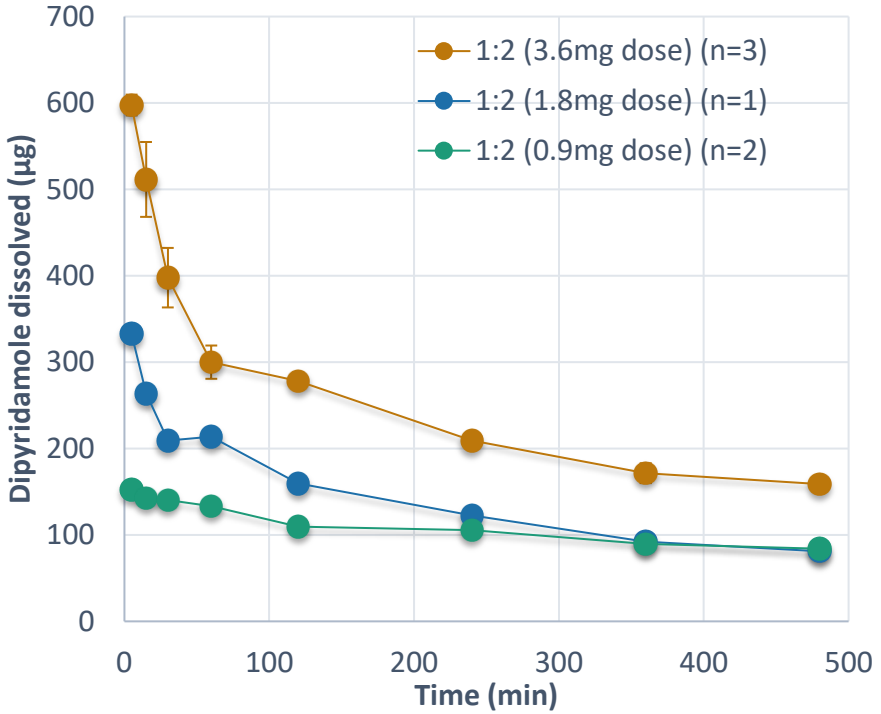
Donor medium:
75µg/mL Dipyridamole solution
in 50mM Phosphate-citrate buffer pH 4
Acceptor medium:
50mM Phosphate-citrate buffer pH 4

Barrier:
PermeaPad®

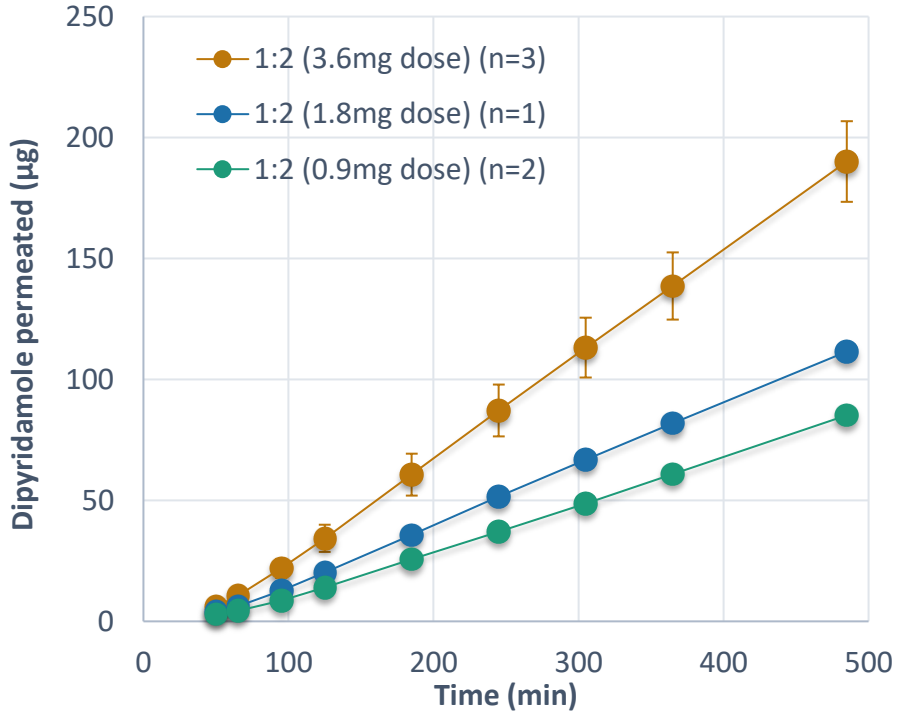
Case Study 2: D/P Profiles of Formulations: Doses

Different doses of 1:2 API:acid dipyridamole granules

Dissolved



Permeated

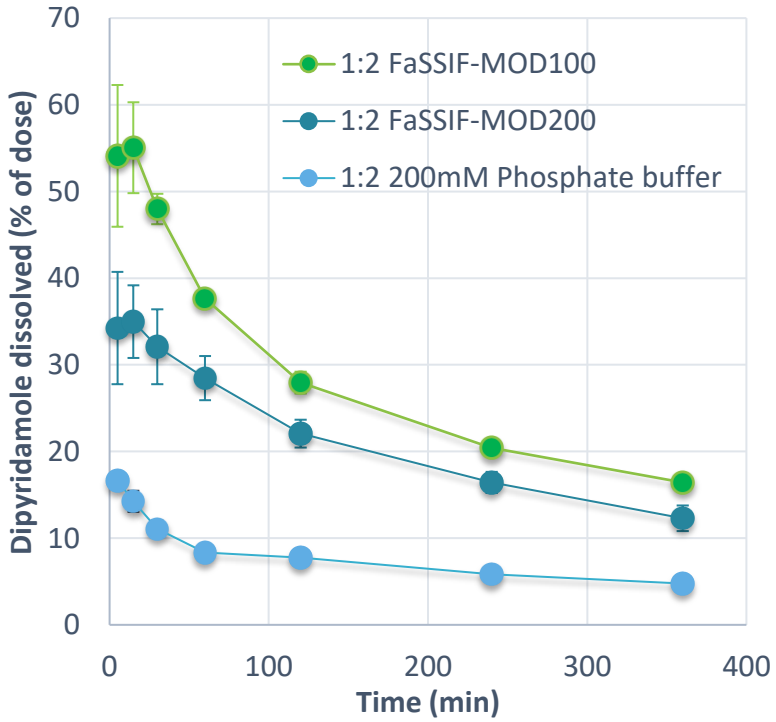


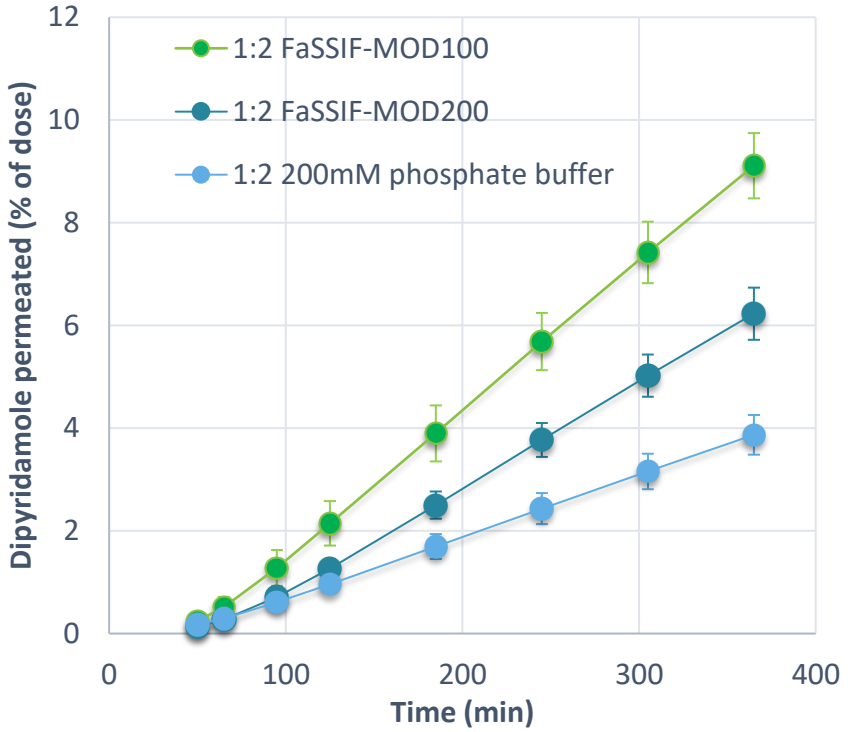
Donor: 200 mM phosphate buffer pH 6.5 ; Acceptor: 0.2% TPGS in 200 mM phosphate buffer pH 6.5
Dose: 3.6 mg; 1.8 mg; 0.9 mg mean±SD (n=3) for 3.6mg; others: n=1

Eriksen, B.J., Master thesis, SDU, 2020

Case Study 2: D/P Profiles of Formulations: Media

various donor media

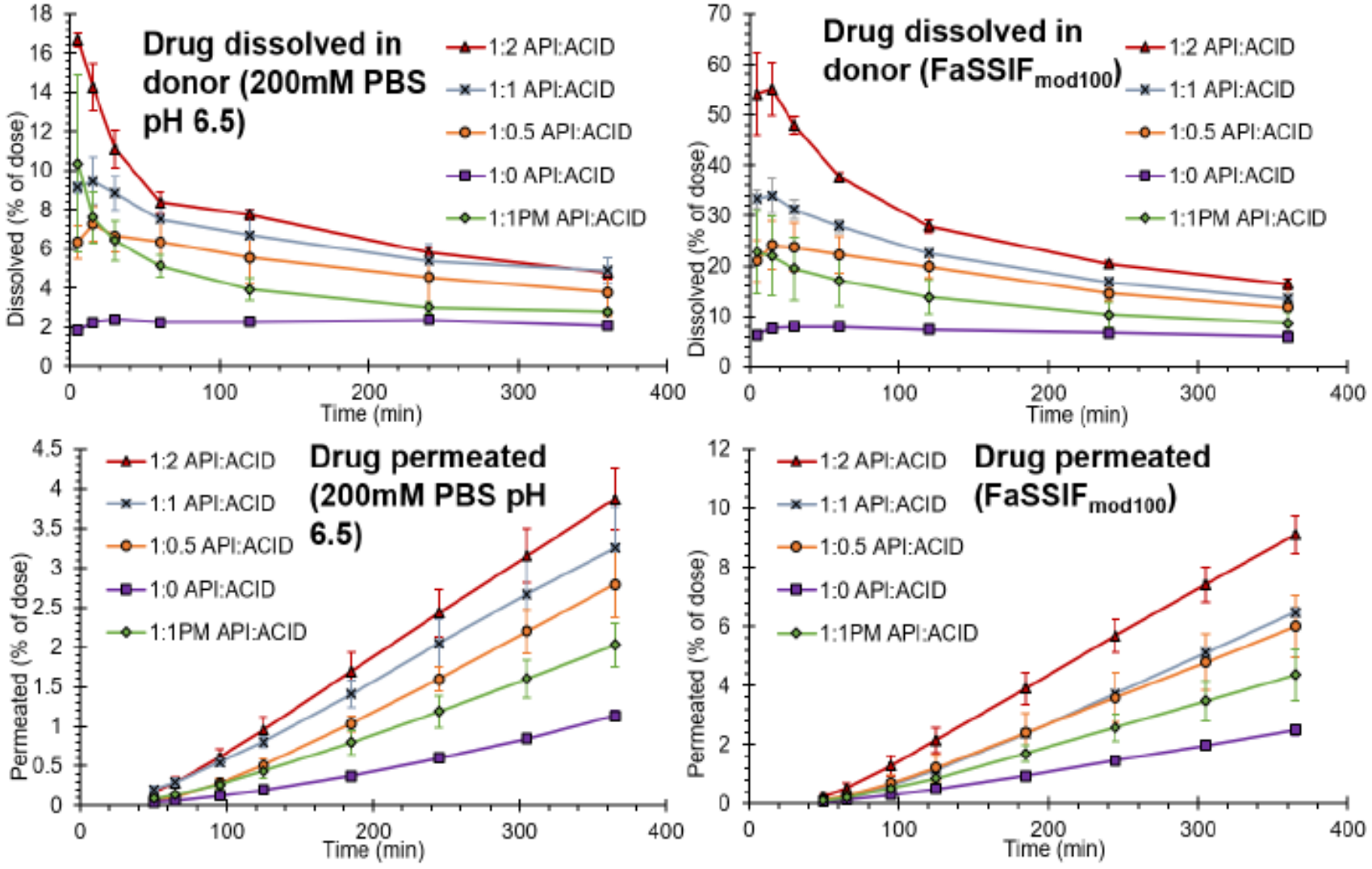




Dissolution profiles and permeation profiles of 1:2 API:acid dipyridamole granules in various donor media.
Acceptor medium 0.2% TPGS in pH 6.5 phosphate buffer; osmolality corresponding to the donor. mean±SD (n=3).

Eriksen, B.J., Master thesis, SDU, 2020

Case Study 2: D/P Profiles of Formulations:



Different dipyridamole formulations

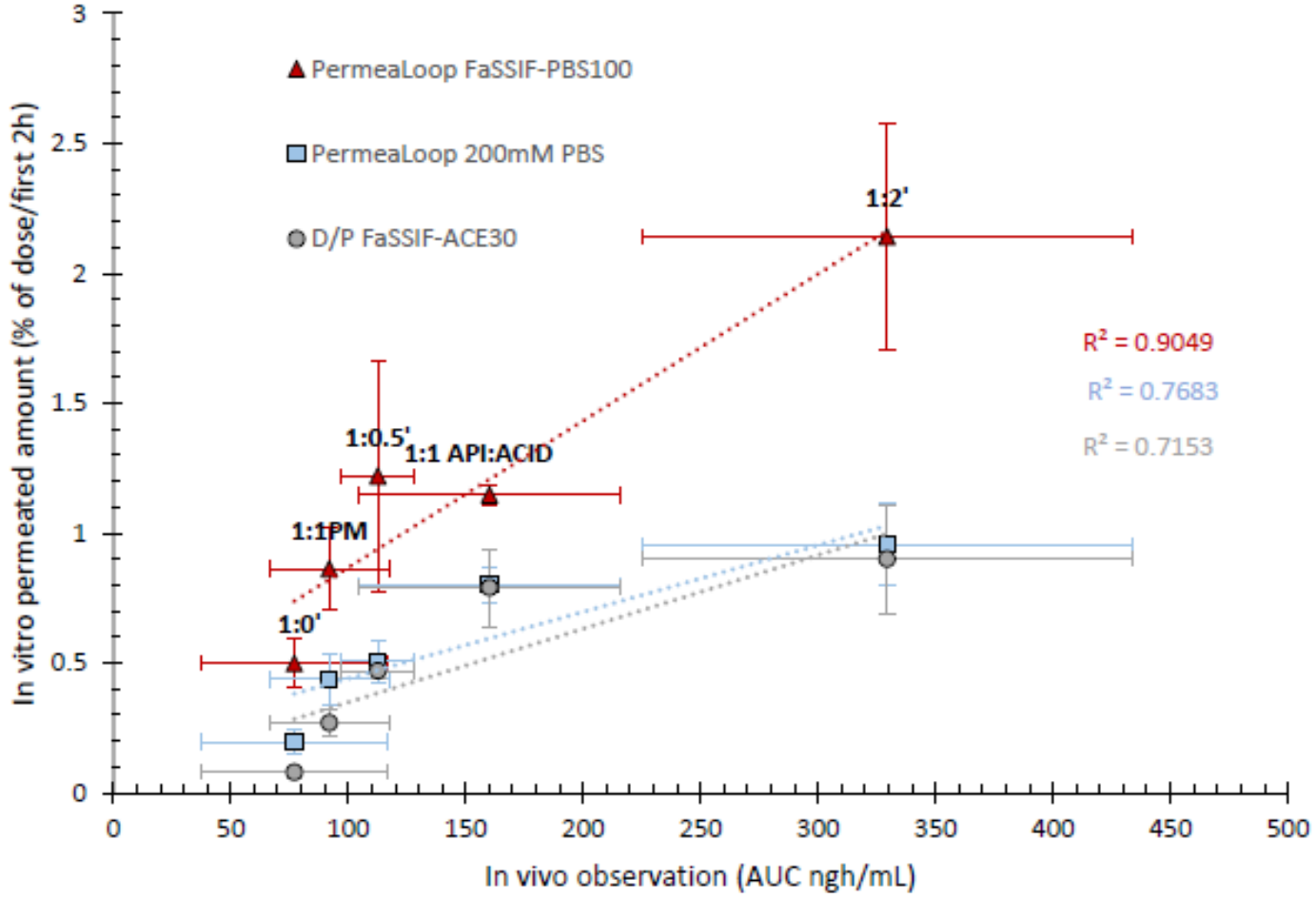
Donor:
A,B: PBS pH 6.5
C,D: FaSSIF mod pH 6.5

Acceptor:
PBS pH 6.5 + 0.2% TPGS
Isoosmotic

mean±SD (n=3).

Eriksen et al., Eur J Pharm Sci, 2020

Case Study 2: IVIVR: permeated vs. absorbed



Correlations:
in-vivo data and D/P results from Mizoguchi et al., 2018.
mean±SD
(in-vitro n=3, in-vivo n=4).

Eriksen et al., Eur J Pharm Sci 2020

Case Study 3:

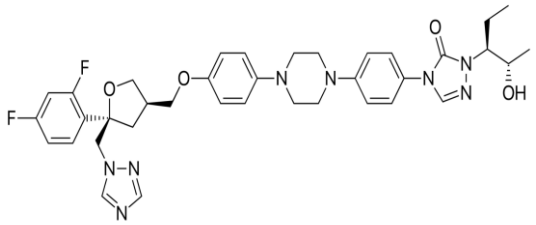
Combined Dissolution and Permeation
for commercial drug products

comparing set-ups : µFlux™ and Permealoop™

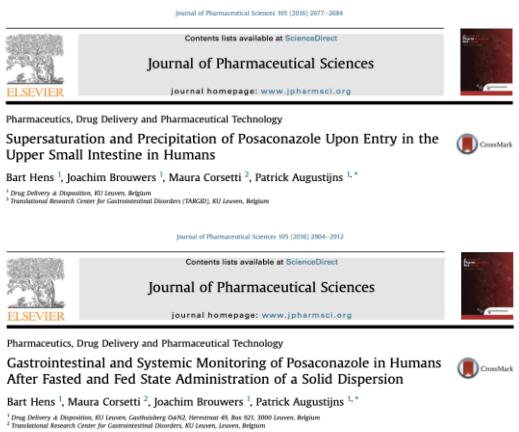
Reverse engineering approach

Case Study 3: IVIVR comparing set-ups

µFLUX™ and PermeaLoop™



Posaconazole
MW: 700 g/mol
logP: 4.6
pKa: 3.6 and 4.6
BCS Class II
oral bioavailablity < 50%



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journal homepage: www.jpharmsci.org
Pharmaceutics, Drug Delivery and Pharmaceutical Technology
Supersaturation and Precipitation of Posaconazole Upon Entry in the Upper Small Intestine in Humans
Bart Hens [1], Joachim Brouwers [1], Maura Corsetti [2], Patrick Augustijns [1,*]

Journal of Pharmaceutical Sciences 105 (2016) 2904–2912
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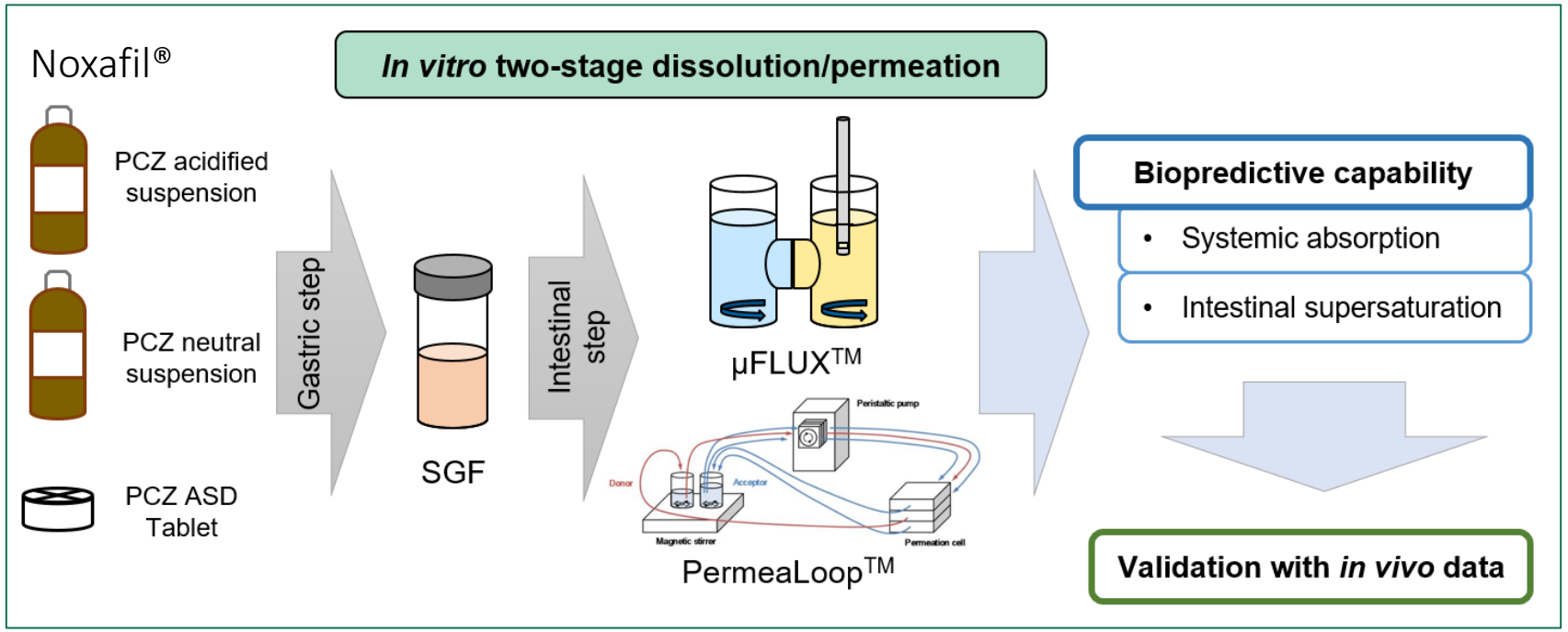
Pharmaceutics, Drug Delivery and Pharmaceutical Technology
Gastrointestinal and Systemic Monitoring of Posaconazole in Humans After Fasted and Fed State Administration of a Solid Dispersion
Bart Hens [1], Maura Corsetti [2], Joachim Brouwers [1], Patrick Augustijns [1,*]



Suspension given with acidified water leads to higher plasma exposure
Tablet (ASD) leads to supersaturation in jejunum

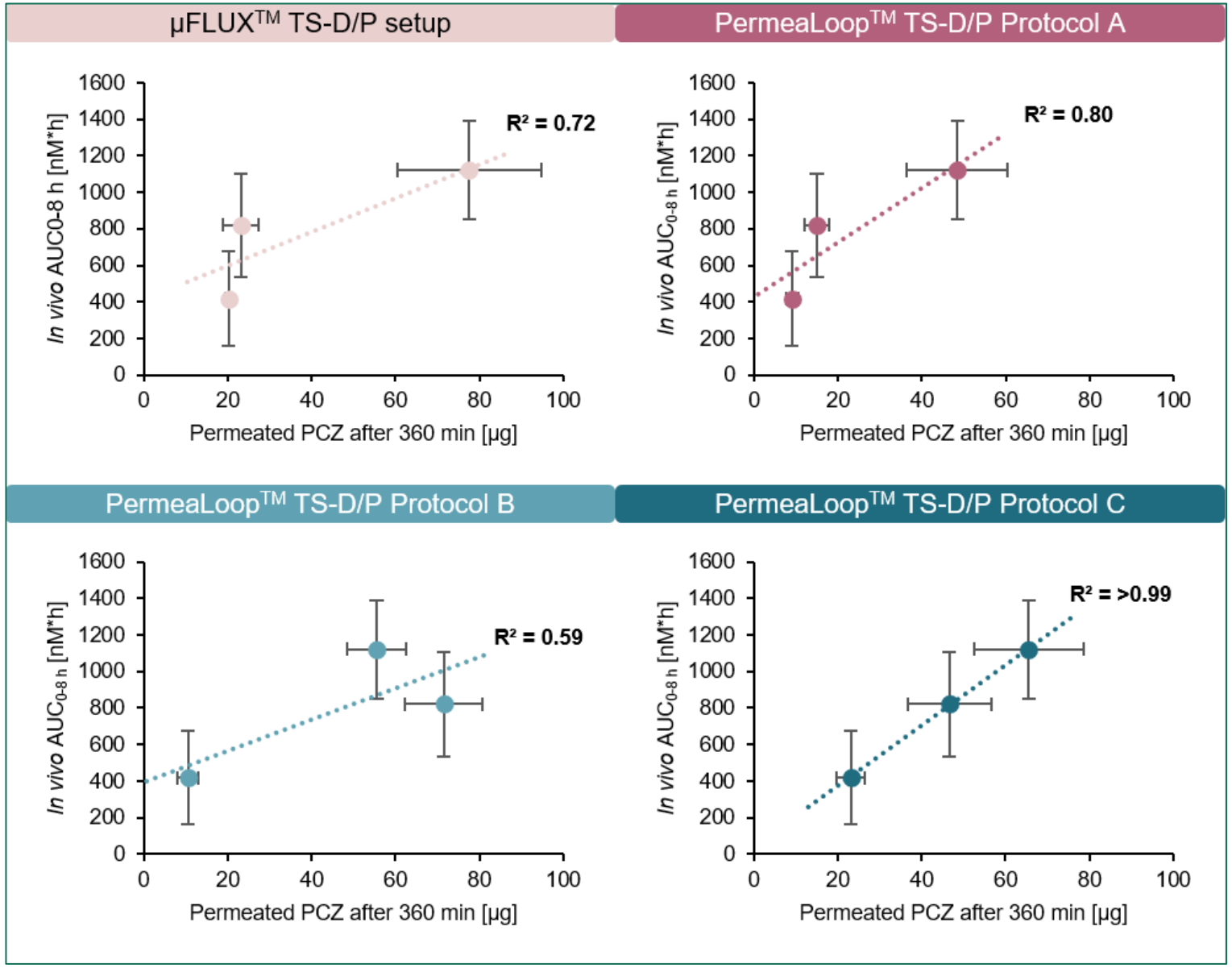
Hens et al., J. Pharm. Sci 2016; a, b

Holzem et al., EJPS, 2022

Case Study 3:

IVIVR for experimental data from
µFLUX™ and PermeaLoop™ and in vivo data

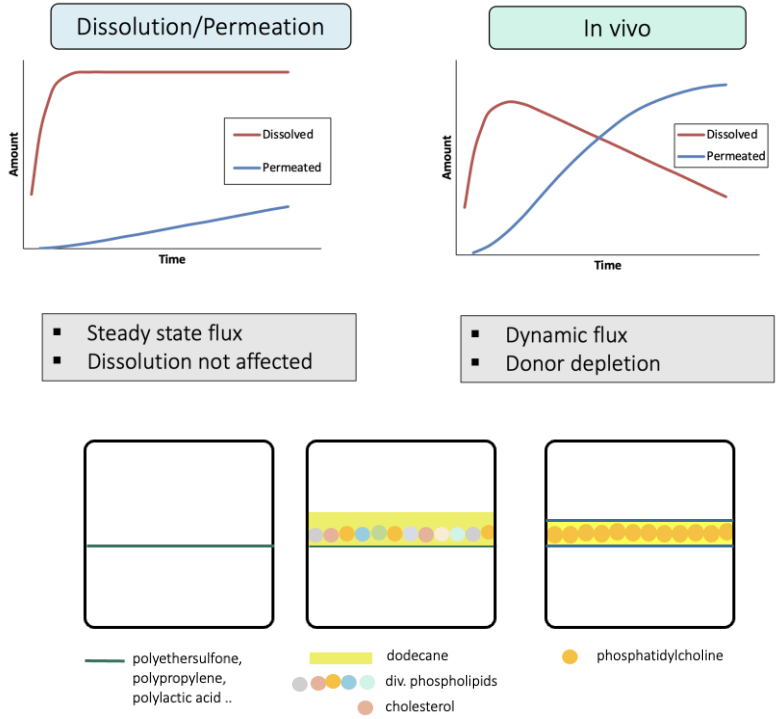
The permeated in vitro amount for acidified suspension,
neutral suspension,
aliquot of the ASD tablet
plotted vs.
$AUC_{0\text{-}8\ h}$ in vivo
Data from Hens et al. (Hens et al., 2016a, Hens et al., 2016b).

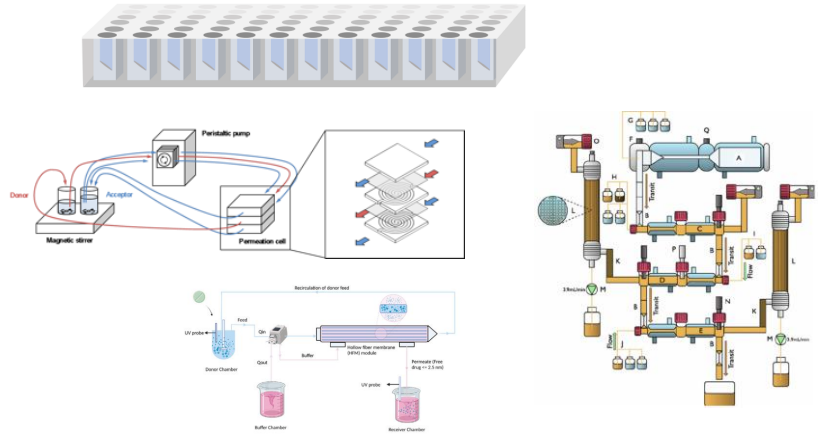


Holzem et al., EJPS, 2022

Key Messages

- Dissolution/Permeation to capture depletion of donor compartment by permeation (absorption)
- For drugs/enabling formulations with dissociation state changing, a (lipidic) biomimetic barrier is required
- Balance the rates of dissolution and permeation by choice of barrier and setup (A/V ratio) as well as experimental conditions
- Dynamic D/P scenario with mutual influence of dissolution and permeation cannot be achieved with classical D/P setups (due to low A/V ratio)
- Microtiterplate set-ups can be used for HTS
- Recent additions to the D/P –toolbox with high A/V ratios are promising for mechanistic studies





Collaborators ans Sponsors

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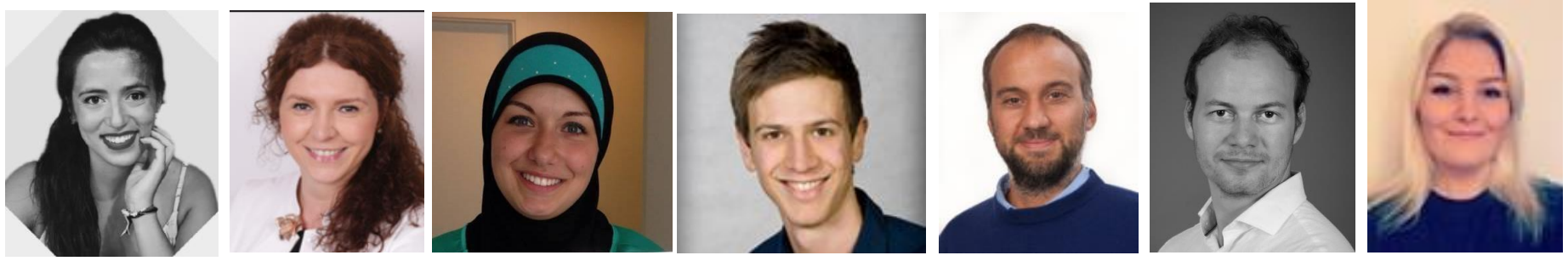

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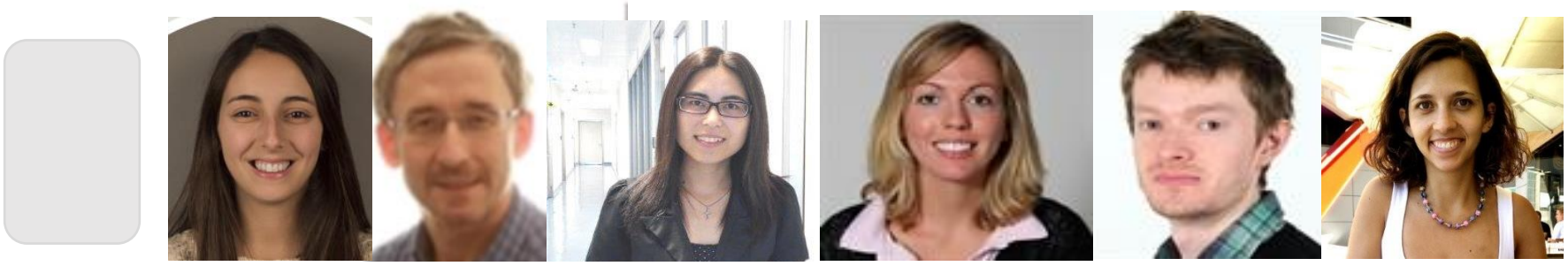

M. Cjajkowski P. Nunes P Stein S. Fong K. Frank (Schäfer) S. Buckley M.João Gomes

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Further reading

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Any questions?

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