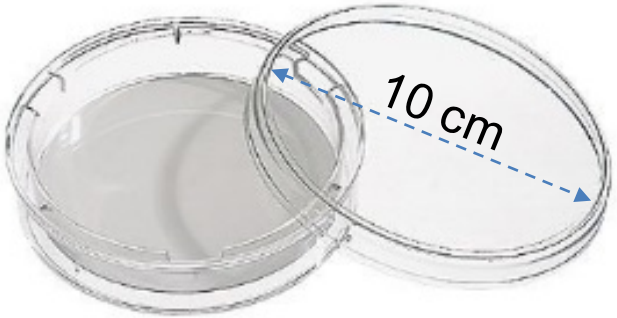
Discriminative *in vitro* dissolution testing for orally inhaled drug products

Tanswell-based system



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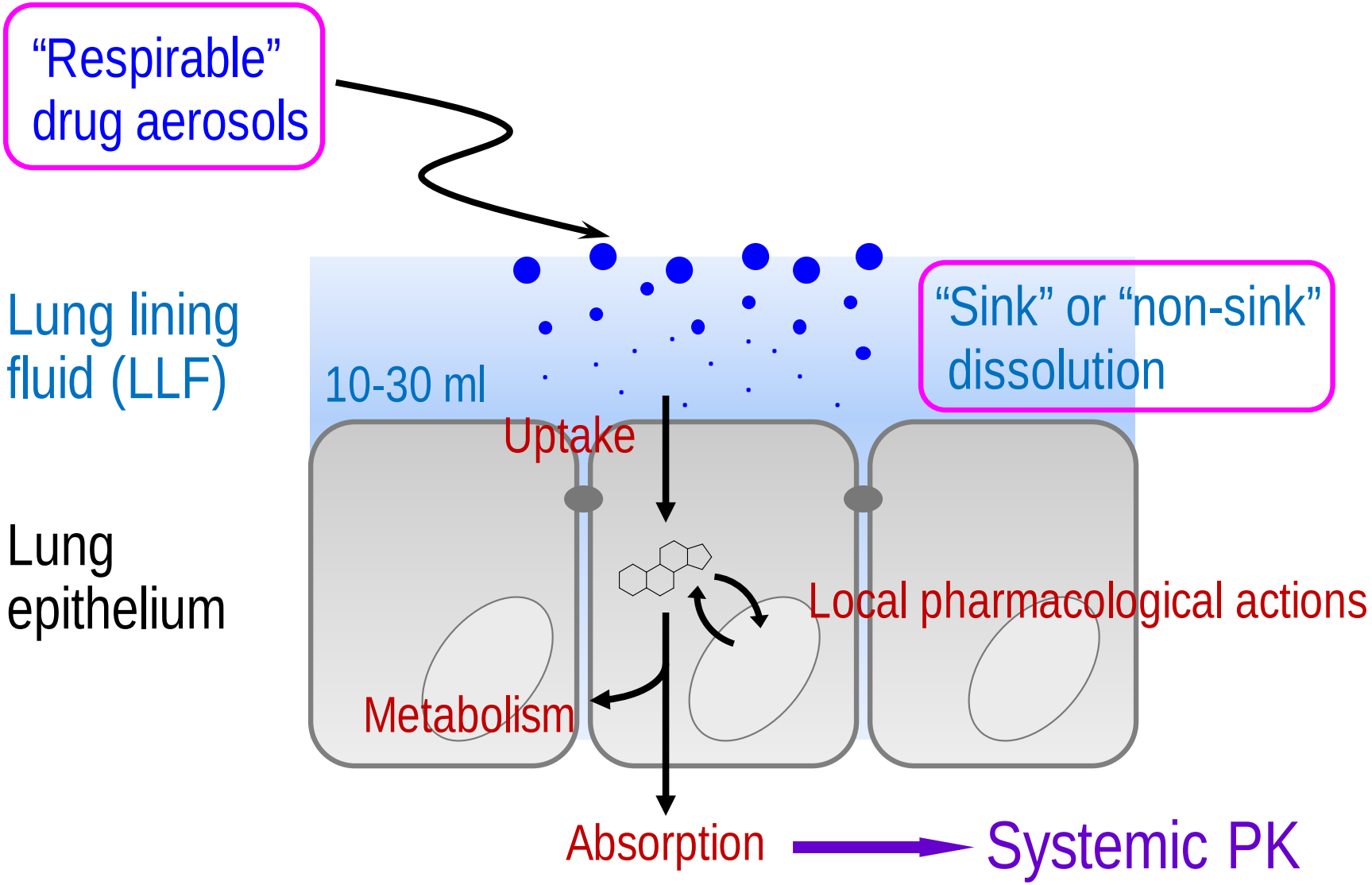
OIDP: deposition and disposition



Pulmonary *vs.* aqueous solubility

$$\frac{\text{“Respirable” dose}}{\text{10-30 ml of LLF volume}} \textit{ vs. } \text{Aqueous solubility (at ~pH 7)}$$

Corticosteroid (ICS)	Aqueous solubility	“Respirable” dose Dissolution	Estimated LLF concentration
Flunisolide	140 μg/ml	320 μg x ~25 %* “Sink”	3-8 μg/ml
Fluticasone propionate	0.14 μg/ml	220 μg x ~45 %* “Non-sink”	3-10 μg/ml

*% < 5 μm; Guo et al: AAPS PharmSciTech 14:1004-11 (2013)

Project goals & objectives

- Develop a discriminative dissolution test method for the “respirable” aerosol drugs of OIDPs
- Determine the fluid capacity-limited dissolution rates of the “respirable” ICS aerosol particles for commercial and investigational OIDPs
- Examine whether the *in vitro* dissolution rates are correlated/extrapolated with the lung absorption rates in humans for investigational OIDPs of fluticasone propionate (FP)

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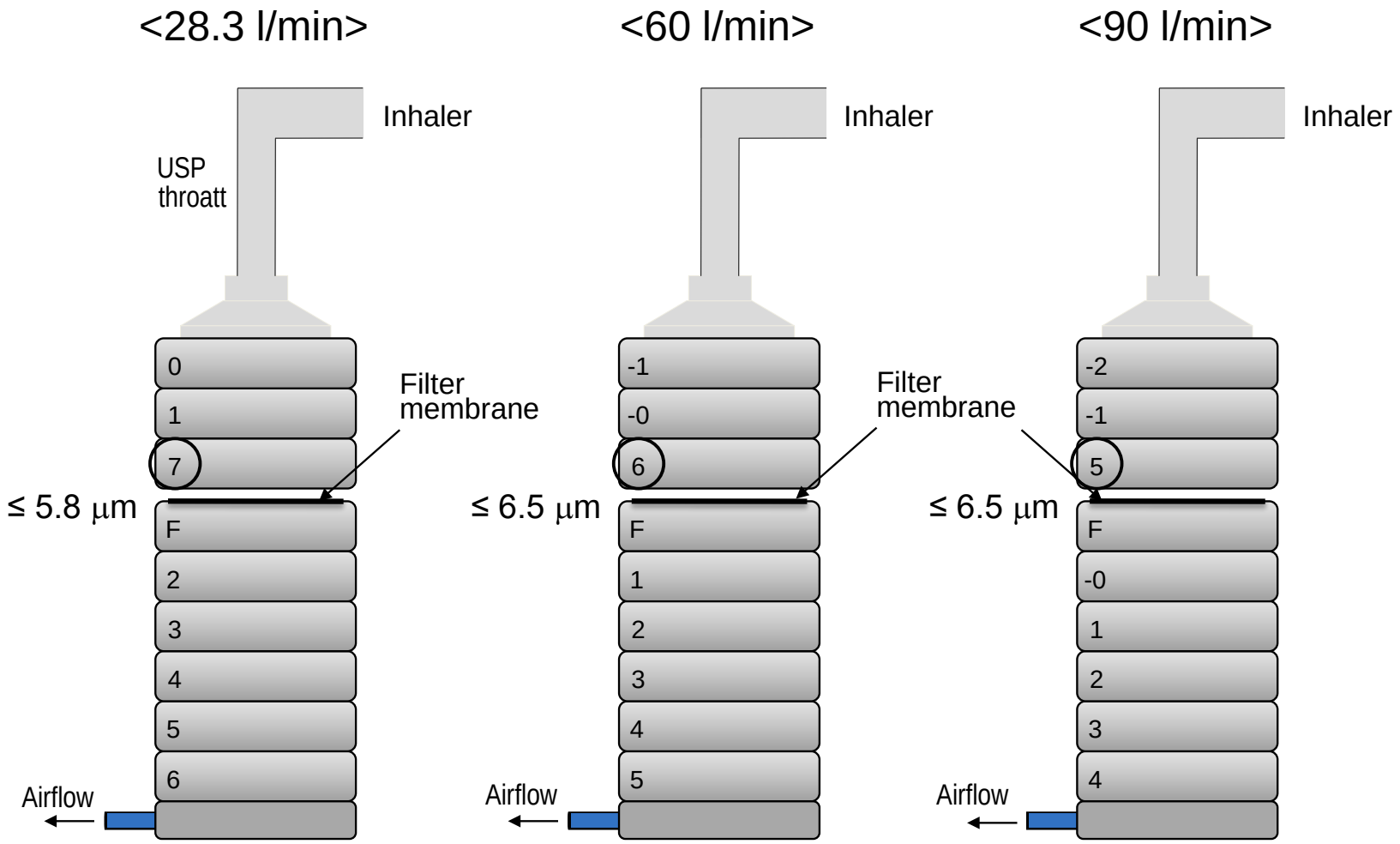
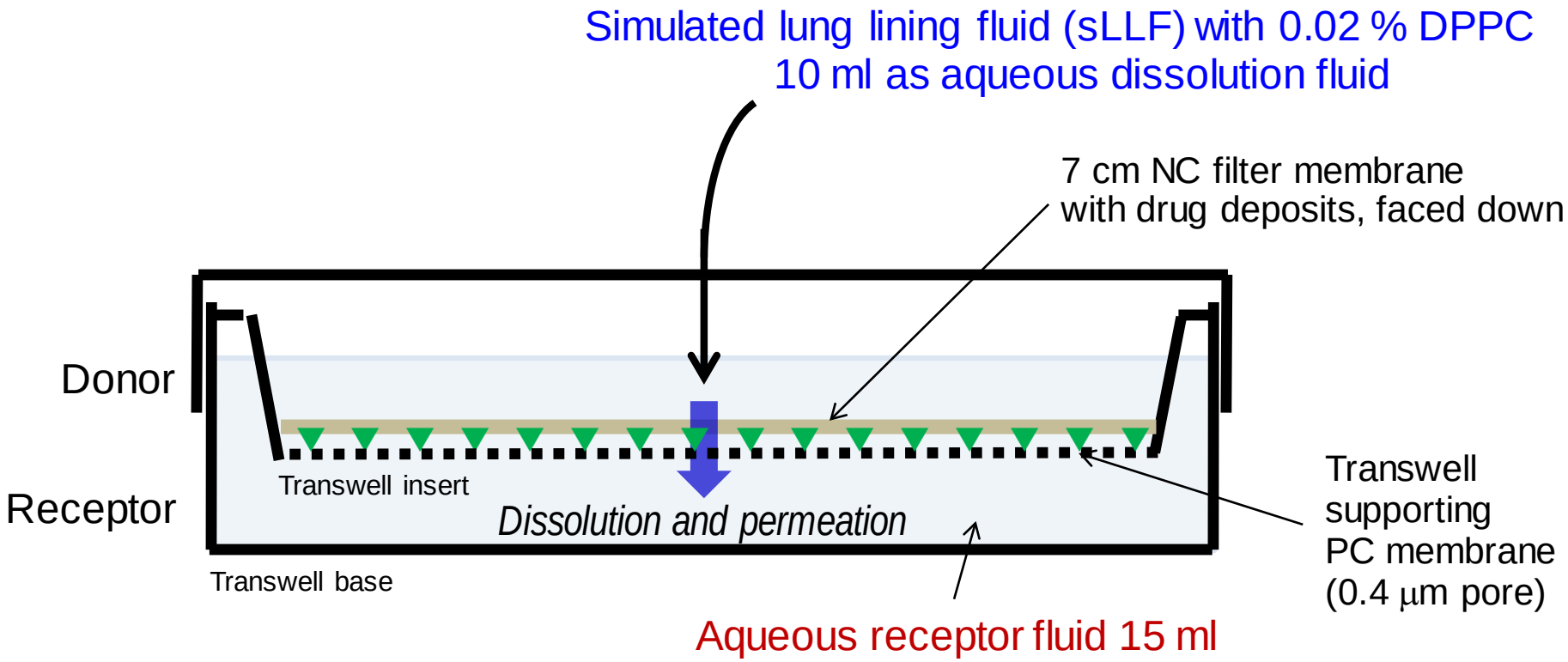
Modified ACI assembly for “respirable” aerosol collection

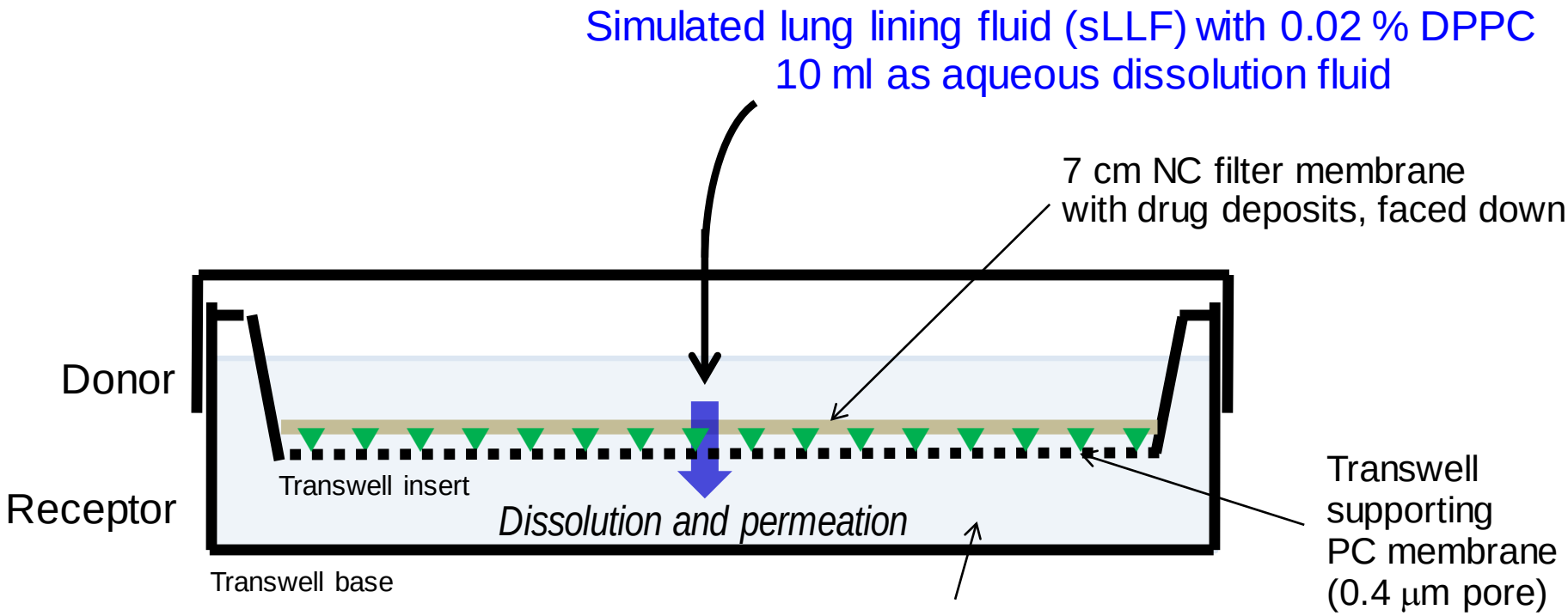


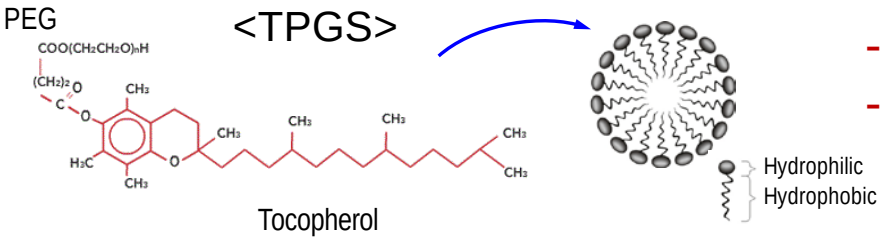
Transwell dish-based dissolution test for “respirable” aerosols



Placed in the incubator at 37 ^{o}C and near 100 %RH

Transwell dish-based dissolution test for “respirable” aerosols



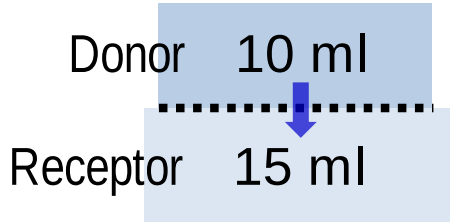


OIDPs and ICSs

ND: Not determined

Corticosteroid	Inhaler (MDI / DPI)	ACI flow rate [l/min]	Solubility [μg/ml] H_2O	1 % TPGS
Flunisolide (FN)	MDI	28.3	140	ND
Triamcinolone acetonide (TA)	MDI	28.3	26	ND
Budesonide (BD)	MDI DPI	28.3 60.0	15	ND
Fluticasone propionate (FP)	MDIs DPIs	28.3 60.0	0.14	20.7
Beclomethasone dipropionate (BDP)	MDI (CFC) MDI (HFA)	28.3 28.3	0.13	44.2
Mometasone fuorate (MF)	MDIs DPI	28.3 60.0	0.05	22.4
Ciclesonide (CIC)	MDI	28.3	0.03	17.0

<Transwell dish>



Sample analysis and data

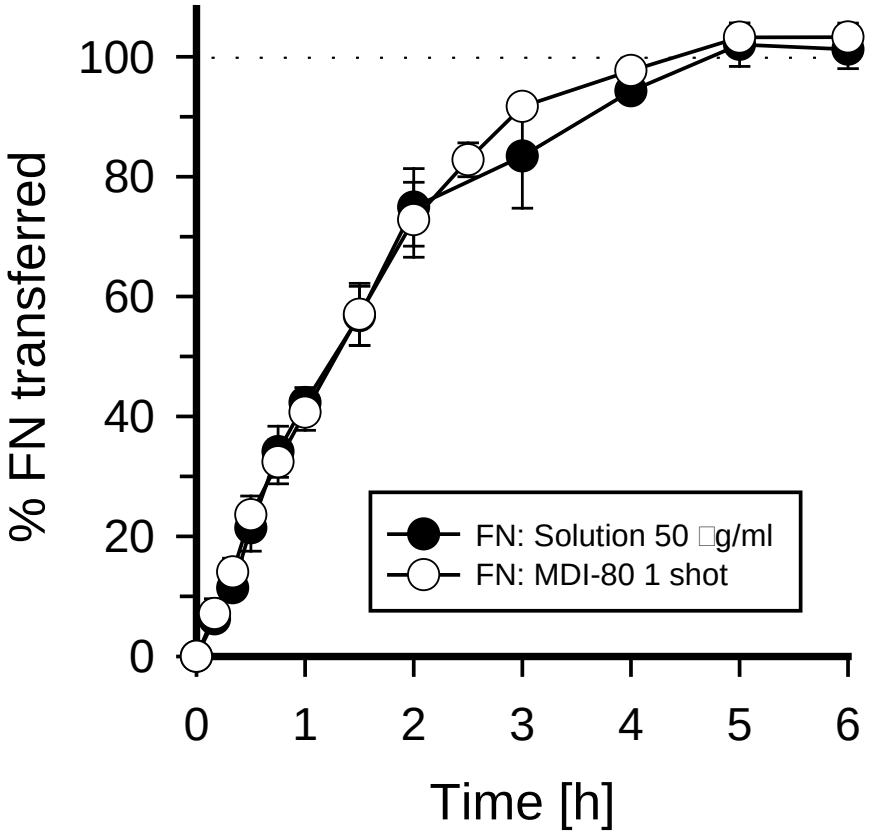
- HPLC-UV analysis to determine drug mass:
  - transferred to the receptor at each sampling time
  - remaining in the donor at the last sampling time
- Drug deposit = total drug mass recovered from the receptor and the donor at the last sampling time
- % Drug dissolved and transferred to the receptor

$$= \frac{\text{(Cumulative mass transferred to the receptor)}}{\text{(Transferrable drug mass)}} \times 100$$

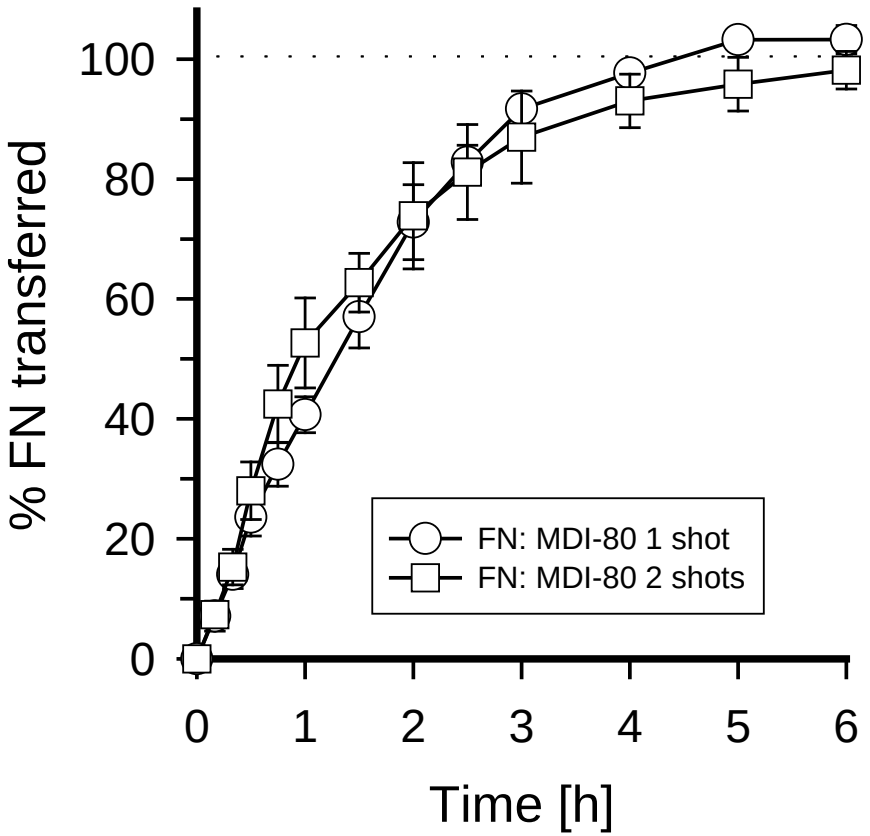
- FN, TA, BD: sLLF: drug deposit x 0.6
- FP, BDP, MF, CIC: sLLF + TPGS: drug deposit

Flunisolide (FN)

<Solution *vs.* Aerosol>

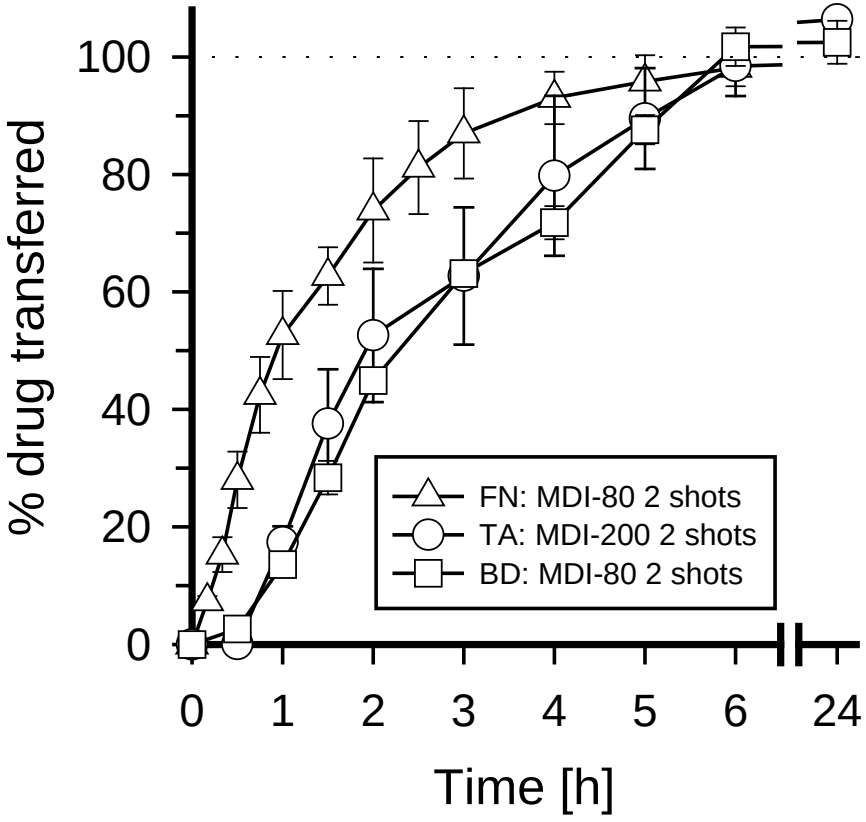


<Effect of aerosol mass>

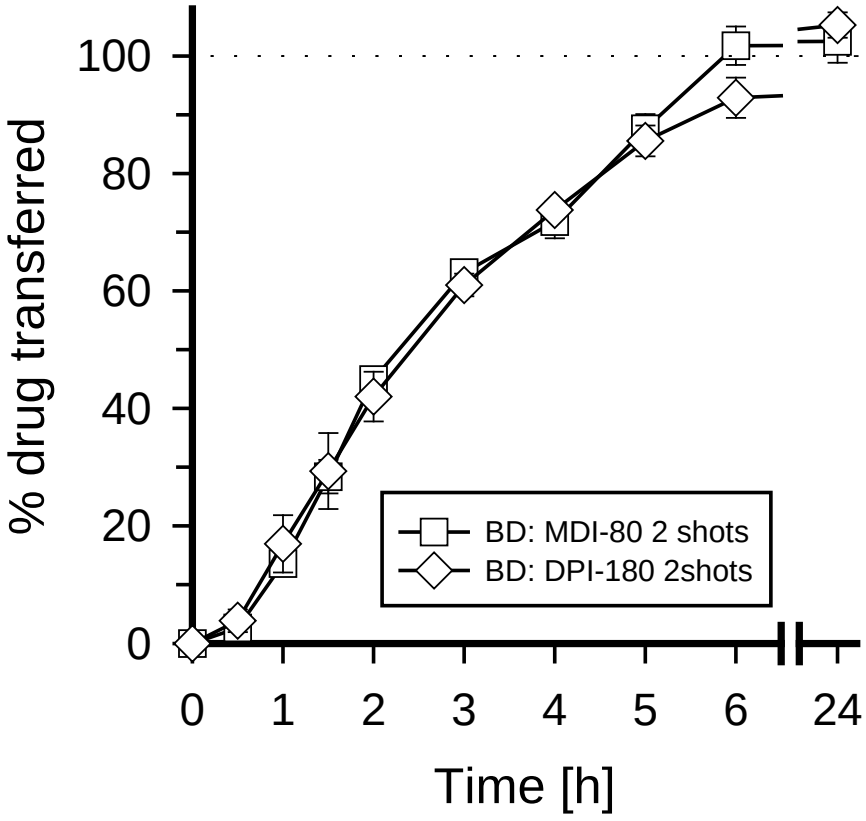


Triamcinolone acetonide (TA) and Budesonide (BD)

<FN *vs.* TA *vs.* BD aerosol>

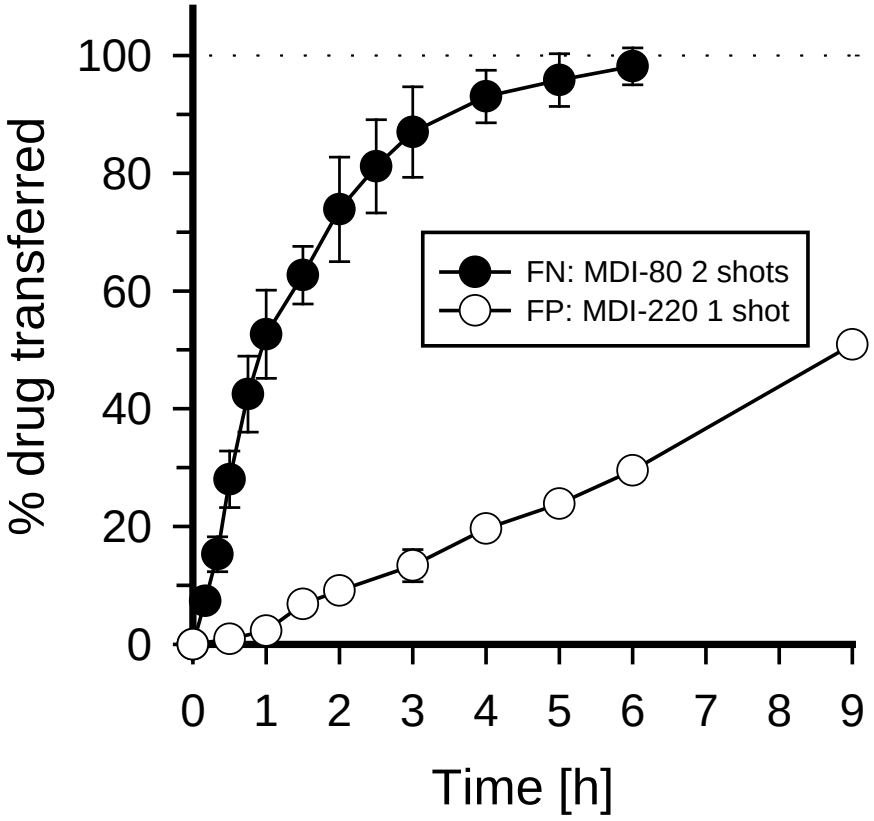


<BD: MDI *vs.* DPI>

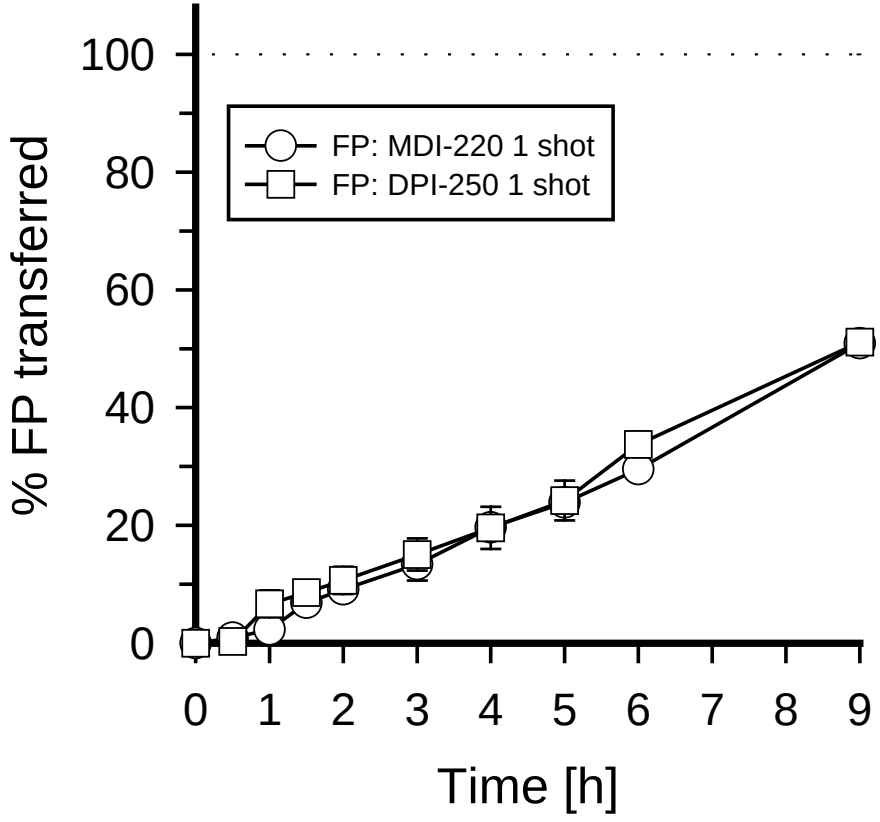


Fluticasone propionate (FP)

<FN *vs.* FP aerosol>

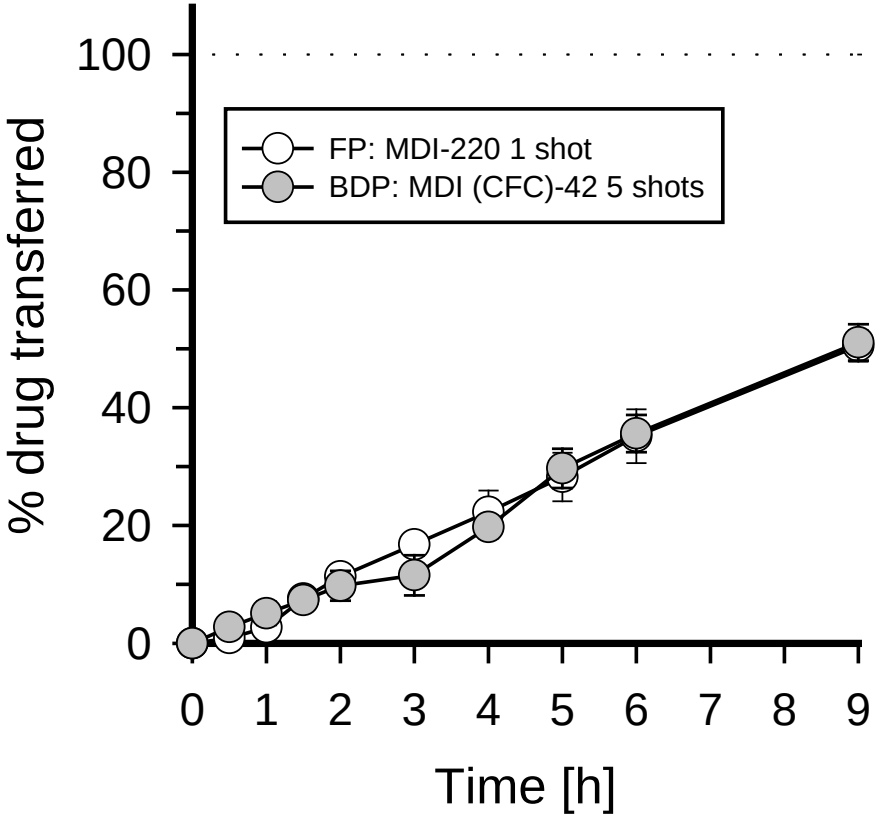


<MDI *vs.* DPI>

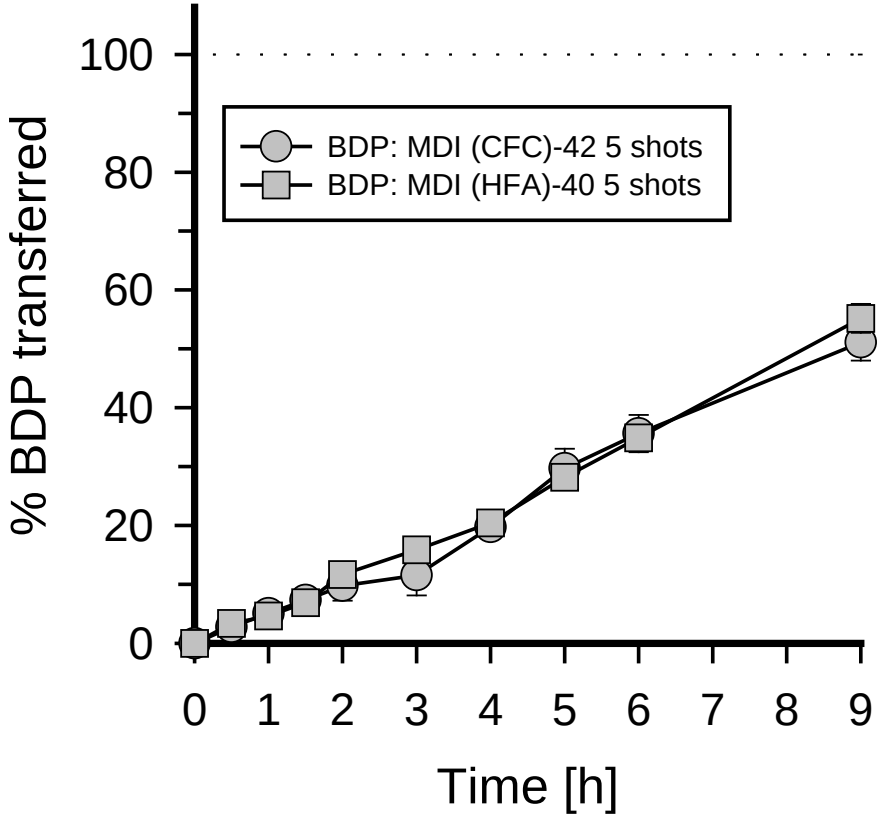


Beclomethasone dipropionate (BDP)

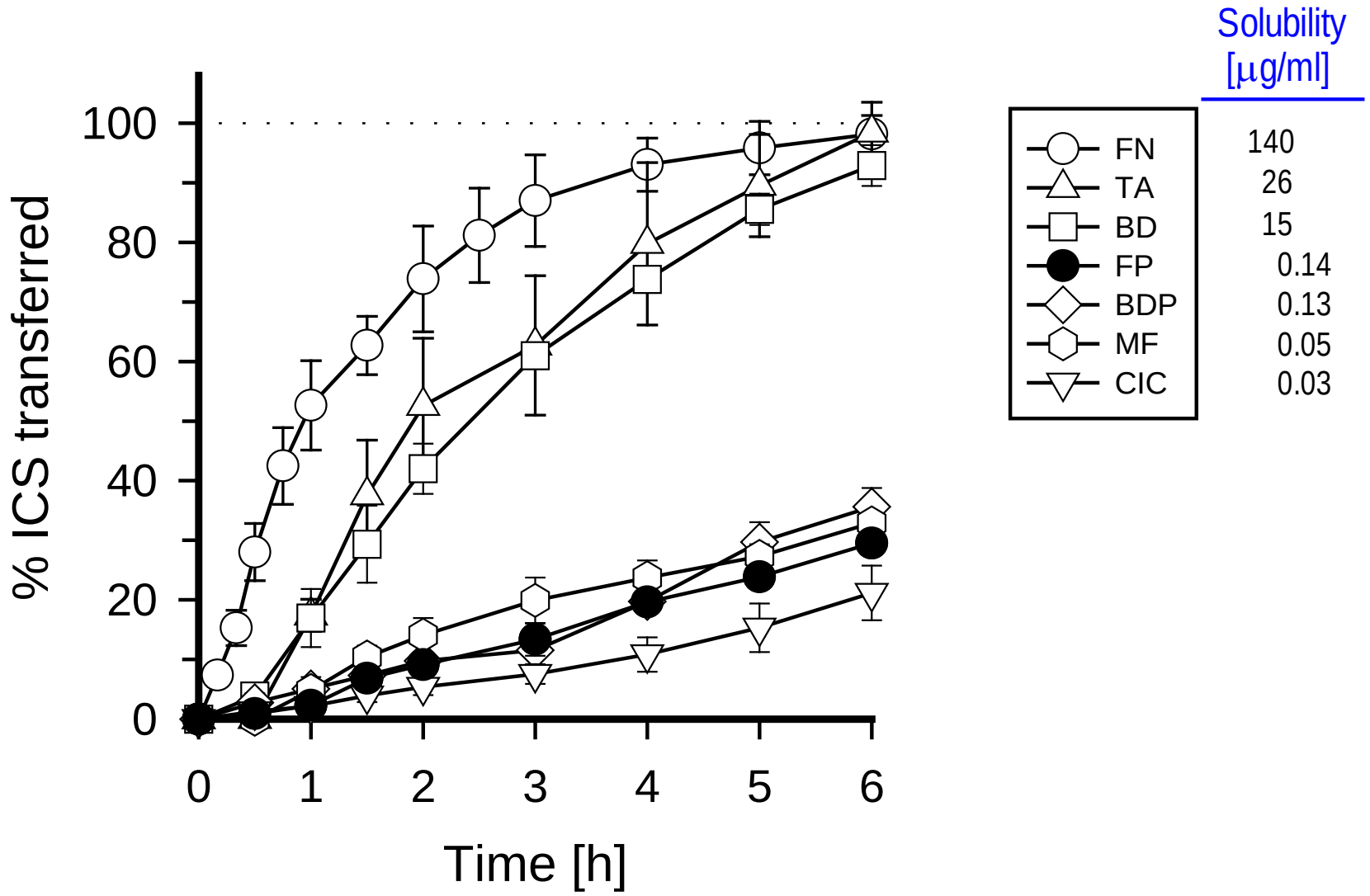
<FP *vs.* BDP>



<MDI: CFC *vs.* HFA>



Across-ICS comparison



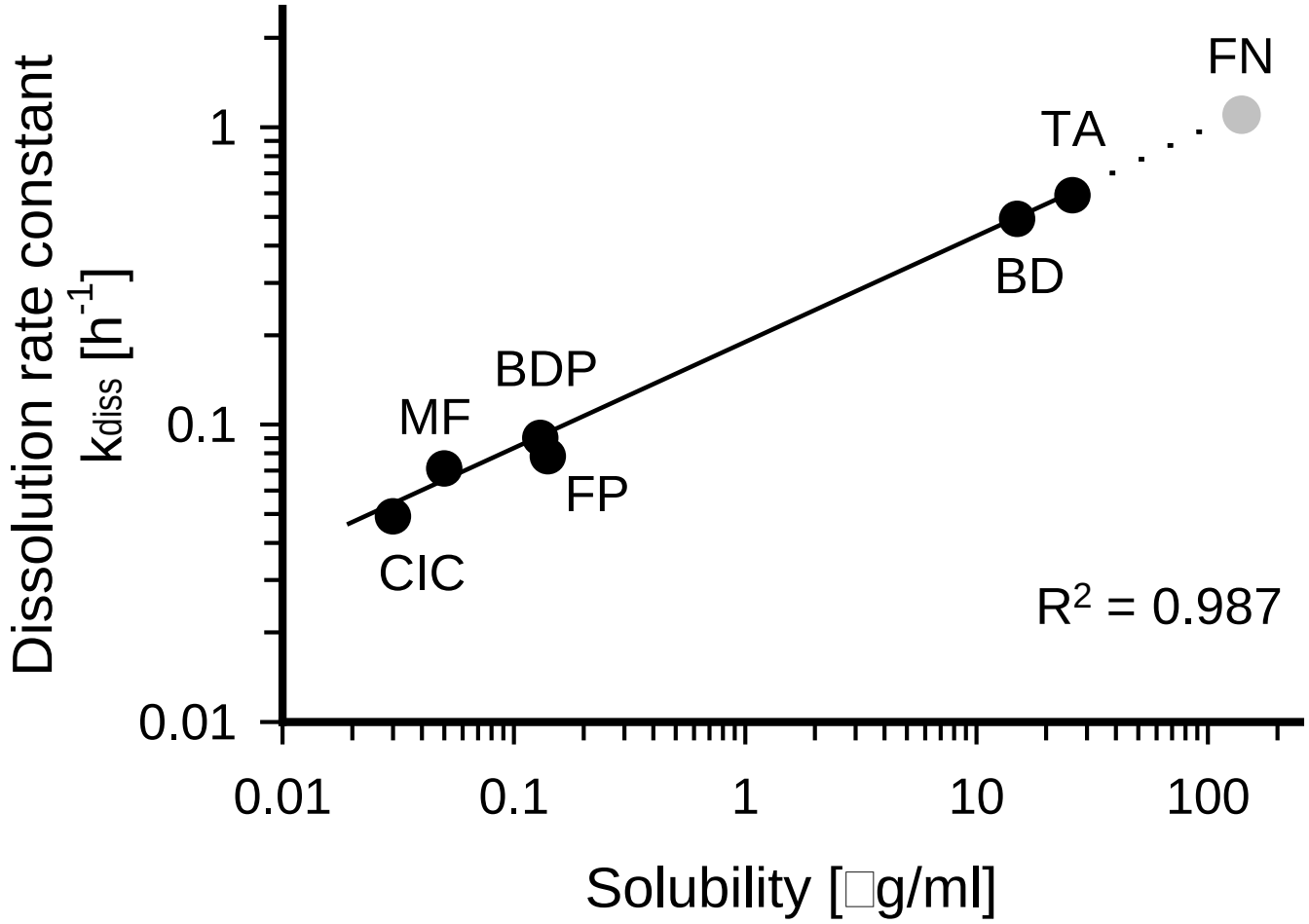
Profile analysis for k_{diss} estimation

- Assumptions:
  - Two sequential first-order processes of dissolution and permeation
  - Dissolution rate constants (k_{diss}) can be separated from permeation rate constants [reflected by FN and held consistent across ICSs], based on the additivity of their MRT* or 1/k

$$\frac{1}{k_{app,ICS}} = \frac{1}{k_{app,FN}} + \frac{1}{k_{diss,ICS}}$$

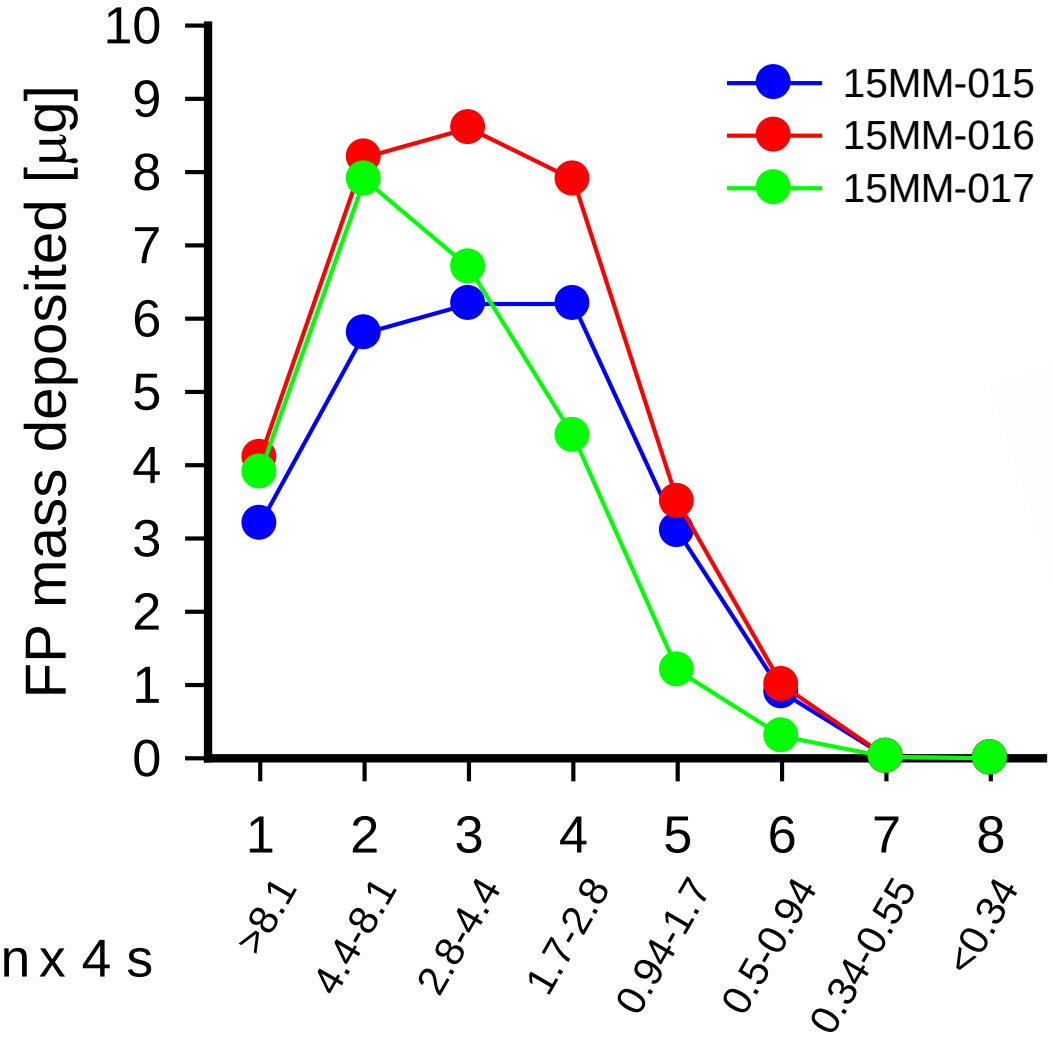
*MRT: mean residence time

k_{diss} correlation with solubility

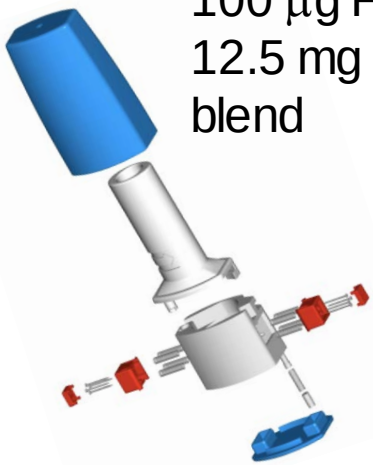


FDA OGD-FPs from DPI

	FPD < 5 μm [μg]	MMAD [μm]
15MM-015	22.5±0.9	3.41
15MM-016	29.2±1.5	3.54
15MM-017	20.6±1.1	4.38



60 l/min x 4 s

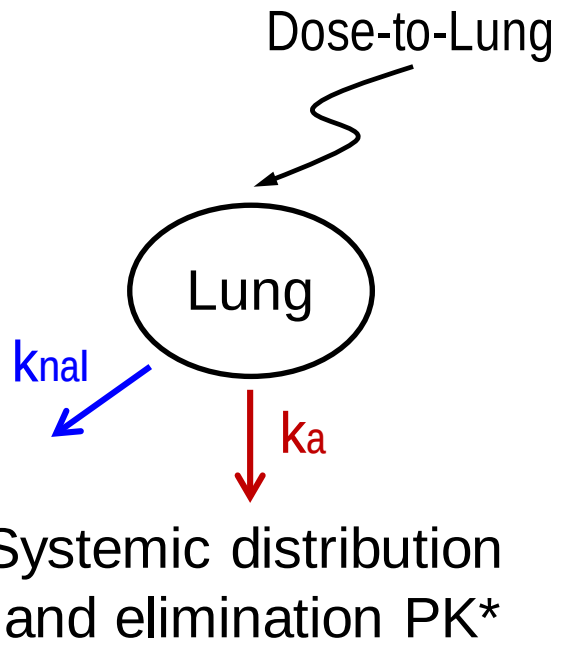


100 μg FP in 12.5 mg lactose blend

Redrawn with the data provided by University of Bath

On-going and future work

- Dissolution profile determination for the "respirable" aerosols of 3 OGD-FPs from DPI and estimation of their k_{diss} values
- Lung disposition modeling analysis for 3 OGD-FPs from DPI with their systemic pharmacokinetic (PK) profiles
- Correlation between *in vitro* k_{diss} and *in vivo* k_a



*Sakagami: RDD 2014 143-153 (2014)

Conclusions

- Discriminative *in vitro* dissolution test method for the “respirable” drug aerosols of OIDPs yielded different dissolution rates among ICSs
- The first-order dissolution rate constants were correlated with the solubility, yet indistinguishable for a given ICS among commercial OIDPs
- The method may be useful to examine “non-sink” dissolution rates for the “respirable” aerosols of poorly soluble “soft” ICSs (e.g., FP) for the bioequivalence (BE) assessment

Thoughts and future directions

- "Non-sink" dissolution rate assessment should be unique and relevant to *in vivo*
- "Sink" dissolution may still occur for prodrug ICSs with poor solubility (BDP and CIC) due to local metabolism

ICS	Solubility [μg/ml]	Mean absorption time* [h]	ICS type
FP	0.14	5.3-7.1	"Soft" drug
BDP	0.13	0.6	Prodrug
MF	0.05	4.1	"Soft" drug
CIC	0.03	0.5	Prodrug

*Whelan et al., 2006; Möllmann et al., 2001; Sahasranaman, 2004; derived from Nave, 2010

- Dissolution for differently micronized FP (e.g., D_{50} = 2 *vs.* 4 μm) would be of interest

Acknowledgements

<Funding>

- FDA Research Project Cooperative Agreement
  - 1U01FD004941-01

<VCU>

- Hua Li, BS
- Jurgen Venitz, MD, PhD

<FDA>

- Bhawana Saluja, PhD
- Renishkumar Delvadia, PhD
- Abir Absar, PhD