Special sites: dosing for infections in the lung

William Couet, PharmD - PhD

Copenhagen, 28 april 2015

- Aerosol delivery *vs* IV or oral administration?

- Higher local conc. / Lower systemic conc. ?

- Need for well controlled experiments

Main factors controlling antibiotics lung conc. ?

Pharm. Tech.

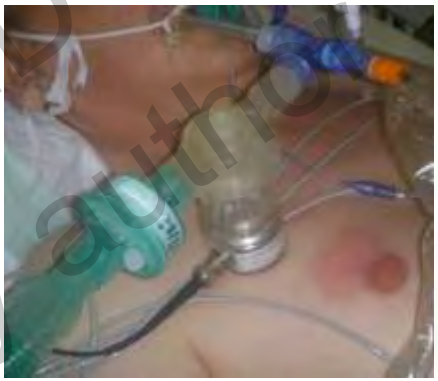
Drug Properties

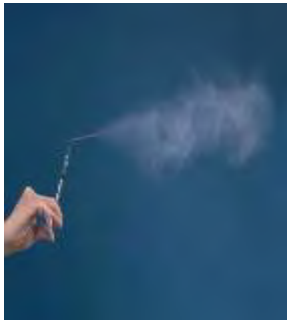
Human

Rats

Device

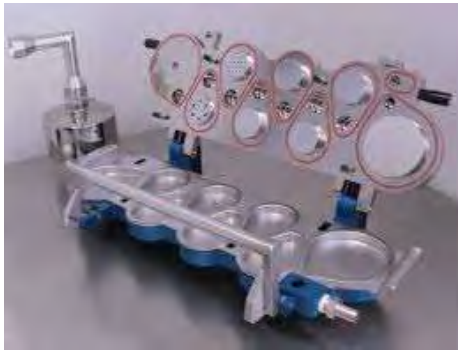
F = 10-20 %



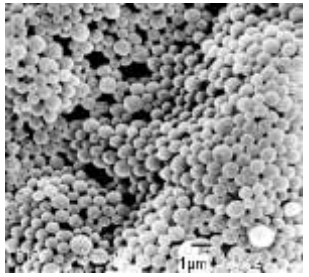


Penn Century
MicroSprayer IA-1B

F = 90-100 %



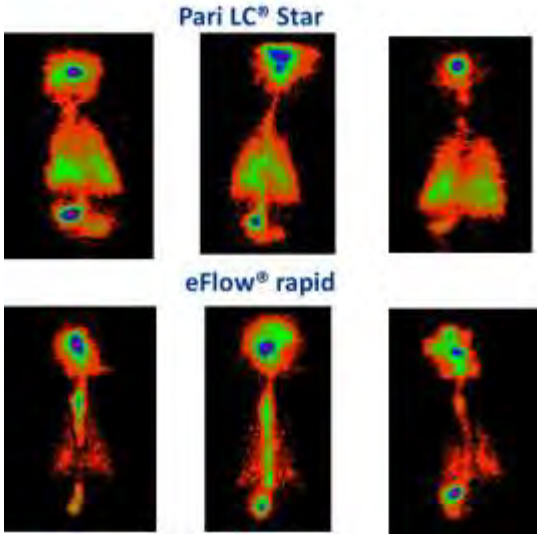
Formulation development



In-vitro

Deposition

In-vivo



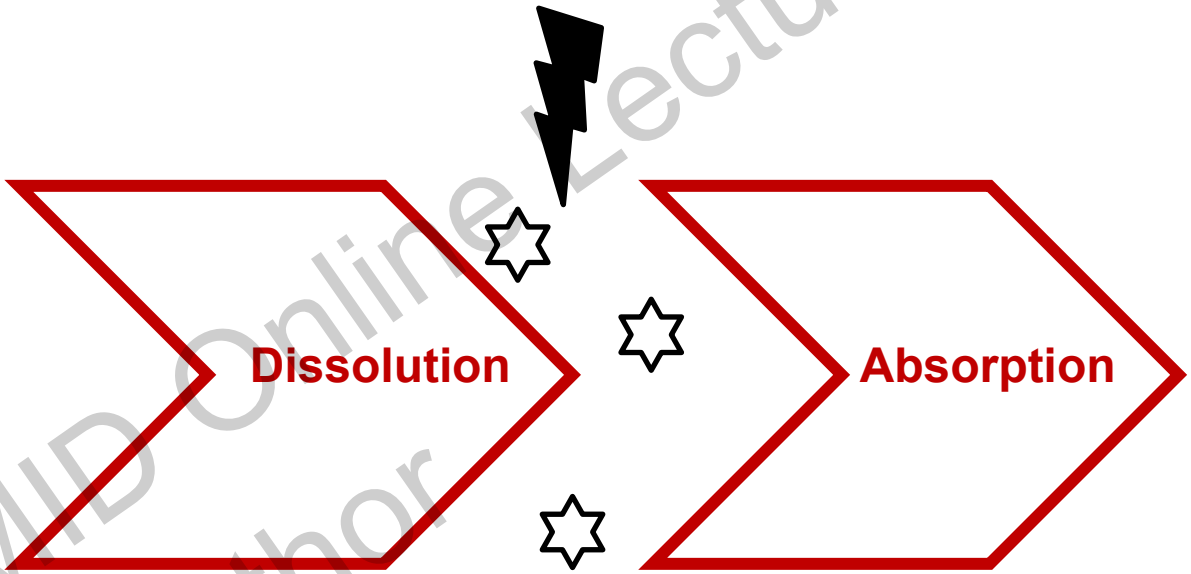
Pharm.Tech.

Drug properties

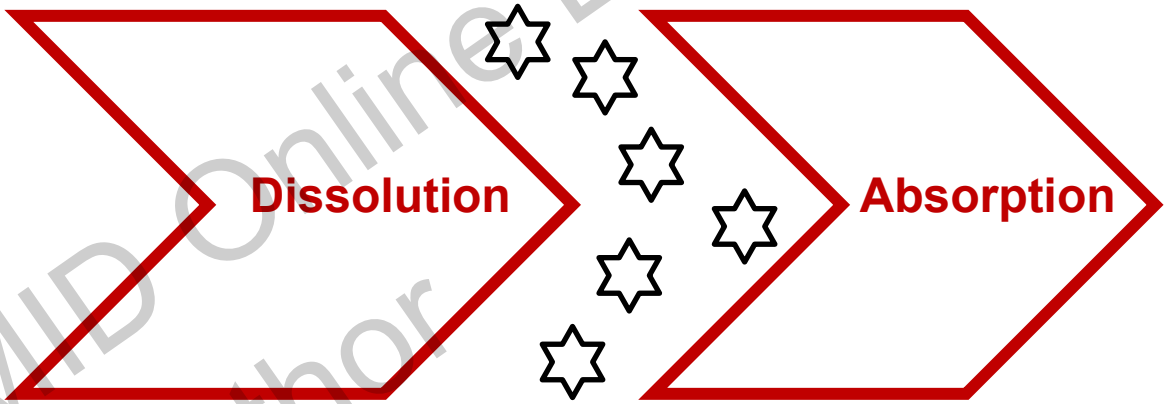
Solubility ***Permeability***

(ELF: 10 – 30 mL)

Antimicrobial effect within the lung (ELF)

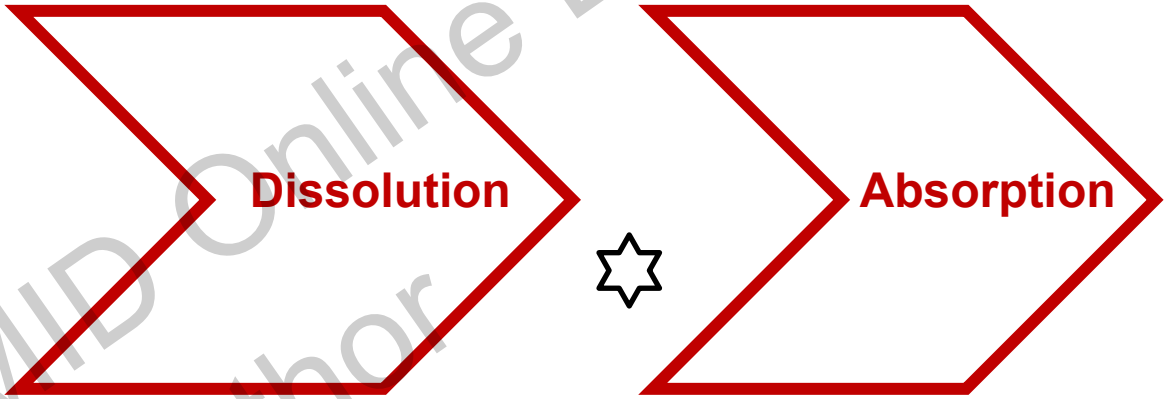


Dissolution Rate >> Absorption Rate

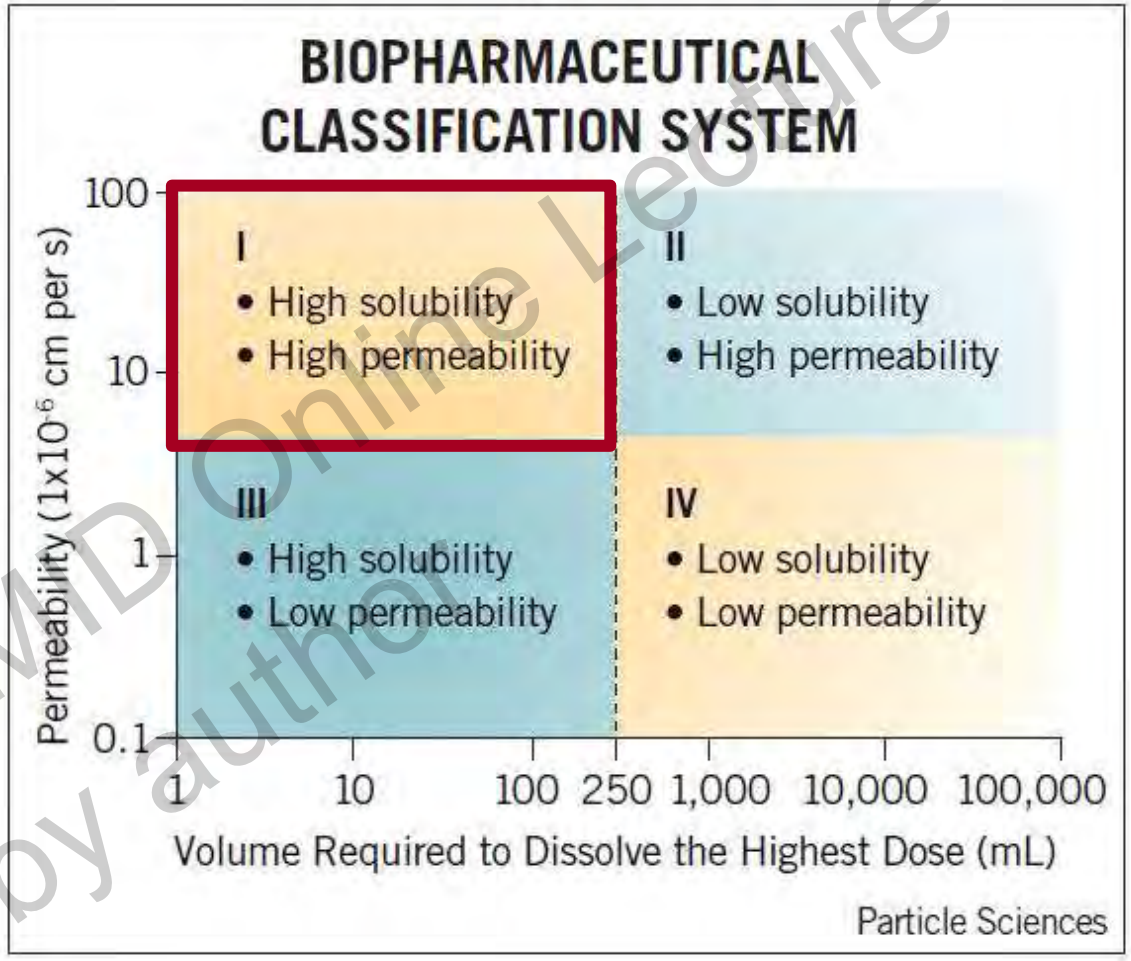


***High* concentration**

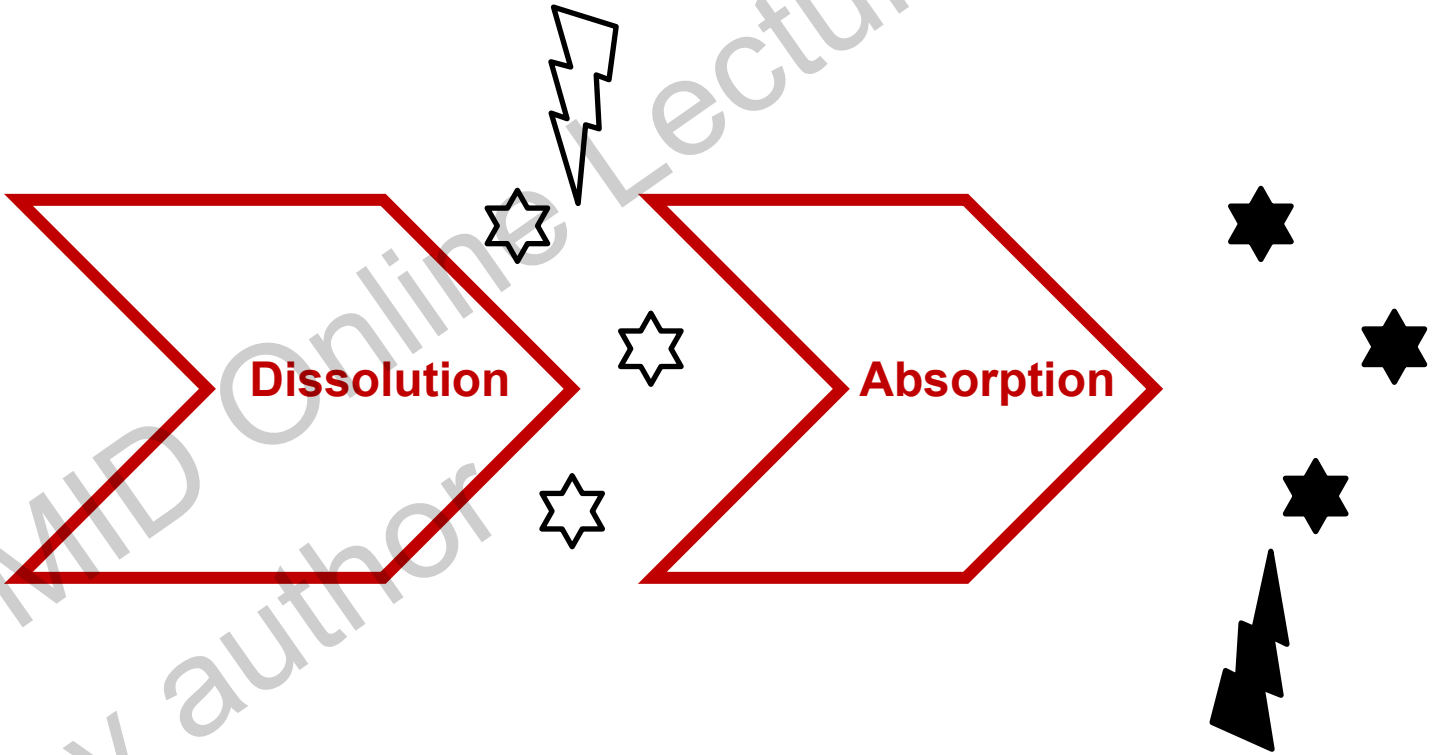
Dissolution Rate << Absorption Rate

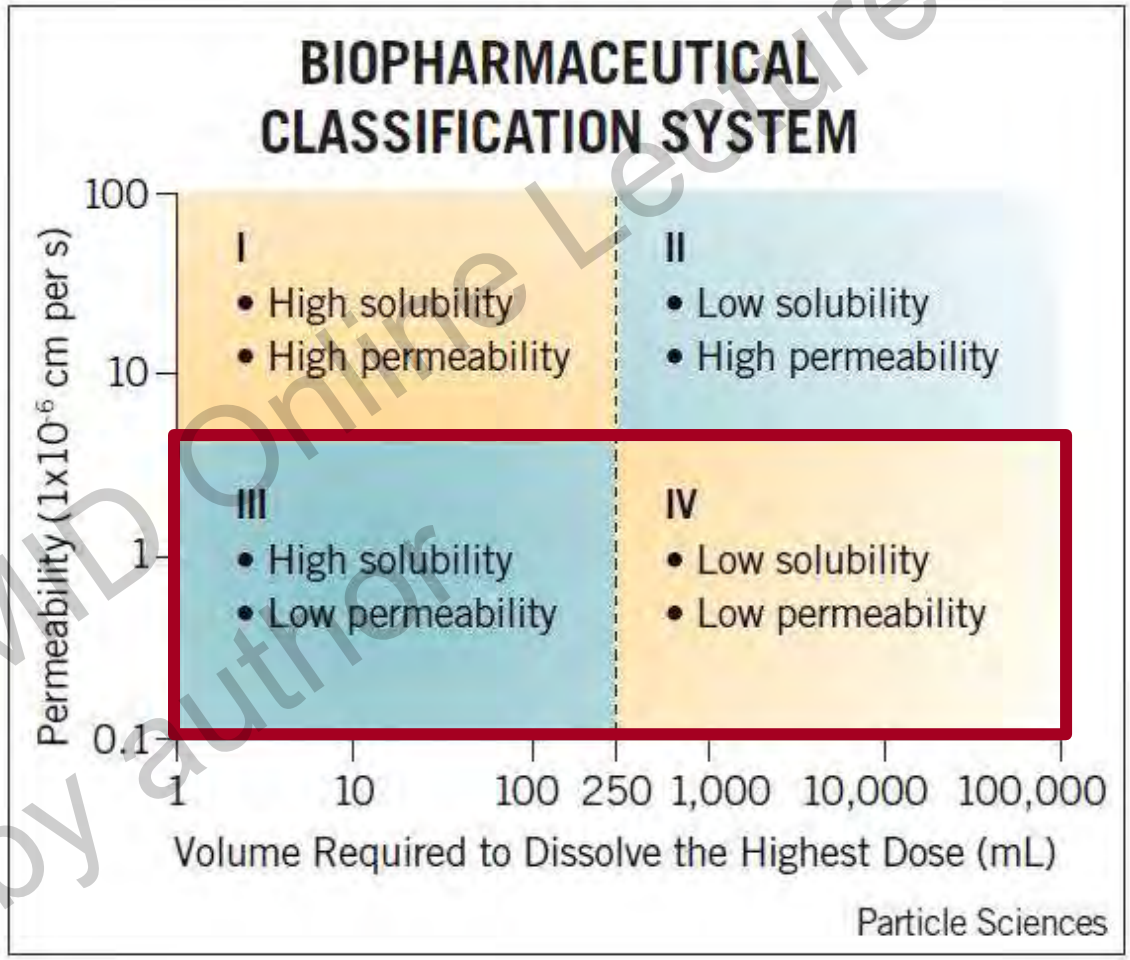


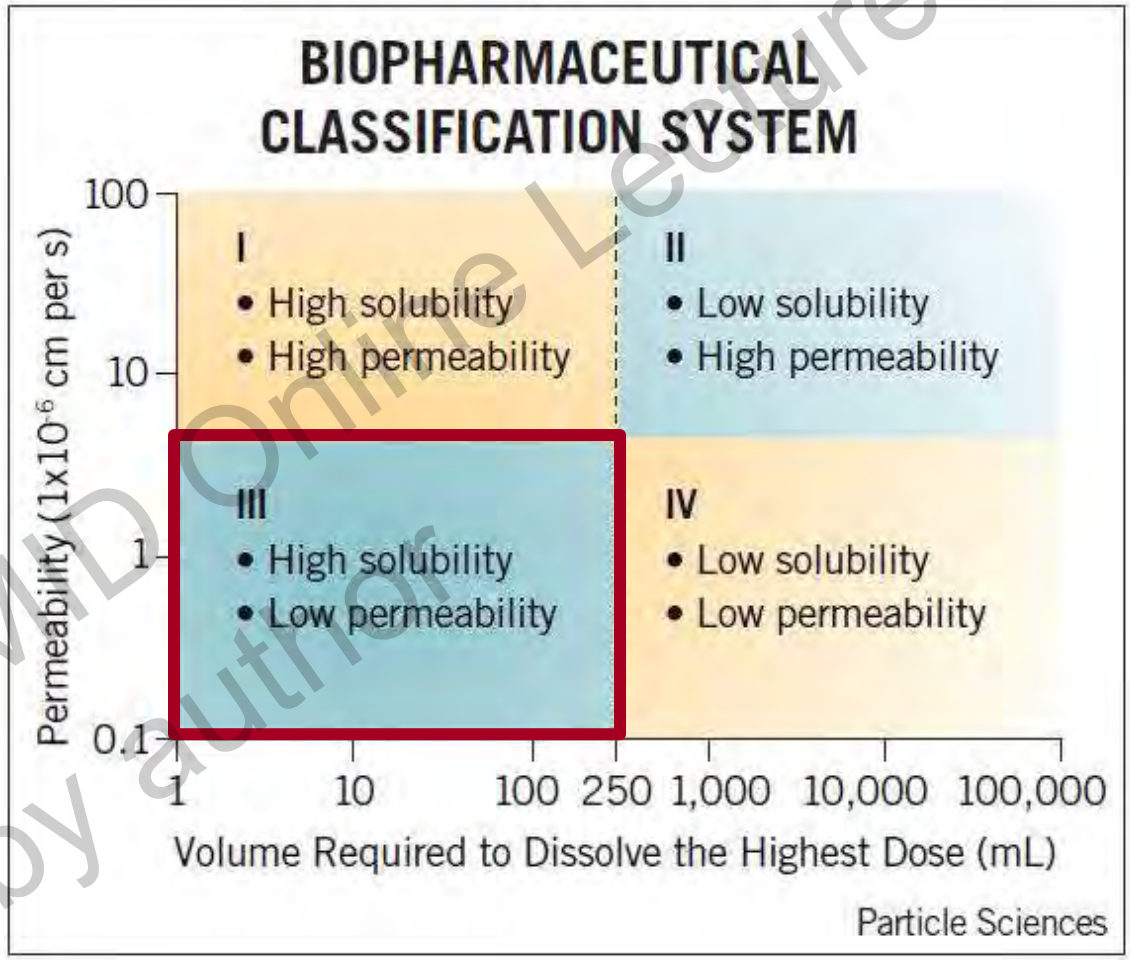
***Low* concentration**



BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	







Question: Would that be useful to consider a Biopharmaceutical Classification for nebulized antimicrobial agents ?

- Aerosol delivery *vs* IV or oral administration?

- Higher local conc. / Lower systemic conc. ?

- Need for well controlled experiments

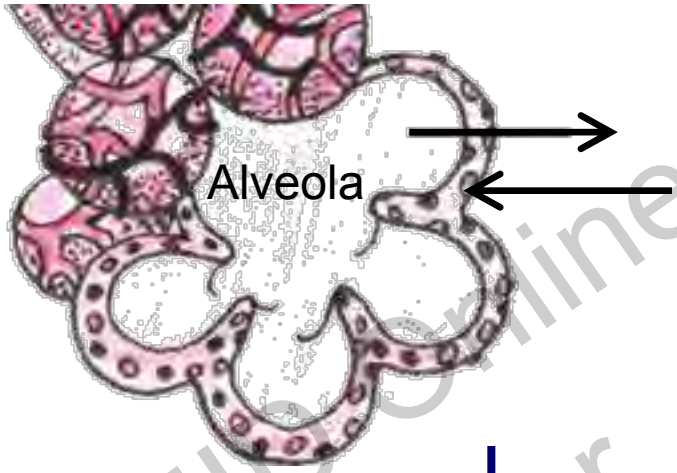
AAC
Journals.ASM.org

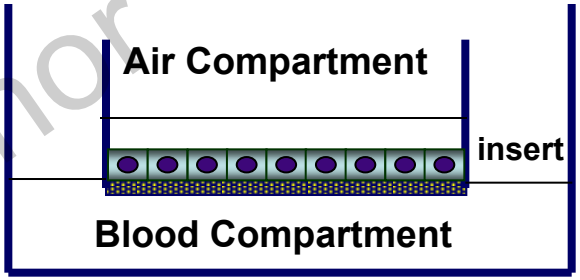
Biopharmaceutical Characterization of Nebulized Antimicrobial Agents in Rats: 1. Ciprofloxacin, Moxifloxacin, and Grepafloxacin

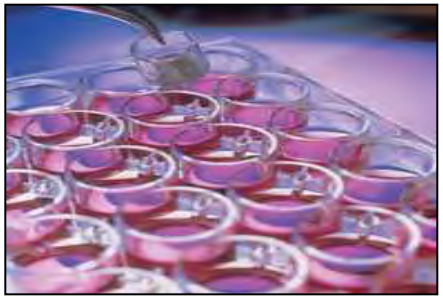
Aline Vidal Lacerda Gontijo,[a,c,d] Julien Brillault,[a,c] Nicolas Grégoire,[a,c] Isabelle Lamarche,[a,c] Patrice Gobin,[a,b] William Couet,[a,b,c] Sandrine Marchand[a,b,c]

Inserm U1070, Pôle Biologie Santé, Poitiers, France[a]; Service de Toxicologie-Pharmacocinétique, CHU de Poitiers, Poitiers, France[b]; Université de Poitiers, UFR Médecine-Pharmacie, Poitiers, France[c]; CAPES Foundation, Ministry of Education of Brazil, Brasília, Brazil[d]

1) In-vitro experiments using Calu-3 cells







Epithelial cells : thigh junctions

Efflux transport systems: **P-gp**

(Brillault et al., AAC 2009)

2) Standardized in-vivo protocol in rats

- **Routes of administration:**
  - Nebulization

    and
  - IV infusion

Penn Century
MicroSprayer IA-1B

2) Standardized in-vivo protocol in rats

- **Routes of administration:**
  - Nebulization
  - IV infusion

MicroSprayer IA-1B

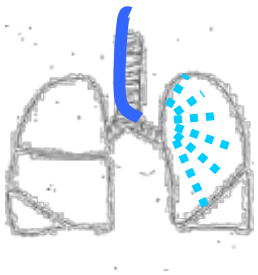
- **Simultaneous sampling** (5 time points x 6 rats)
  - Blood (intra-cardiac puncture)

2) Standardized in-vivo protocol in rats

- **Routes of administration:**
  - Nebulization
  - IV infusion

MicroSprayer IA-1B

- **Simultaneous sampling (5x6)**
  - Blood (intracardiac puncture)
    and
  - BAL (1 mL NaCL 0.9% - 37°C)
    to limit cell lysis



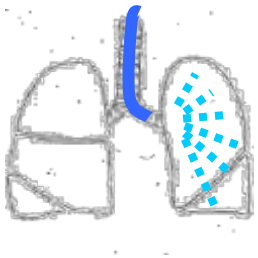
⇨ **ELF conc**

2) Standardized in-vivo protocol in rats

- **Routes of administration:**
  - Nebulization
  - IV infusion

MicroSprayer IA-1B

- **Simultaneous sampling (5x6)**
  - Blood (intracardiac puncture)
  - BAL (1 mL NaCL 0.9% - 37°C)



⇨ **ELF conc**

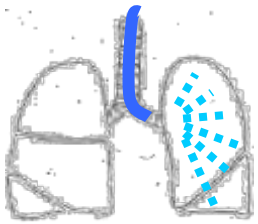
- **LC-MS/MS assay**

2) Standardized in-vivo protocol in rats

- **Routes of administration:**
  - Nebulization
  - IV infusion

MicroSprayer IA-1B

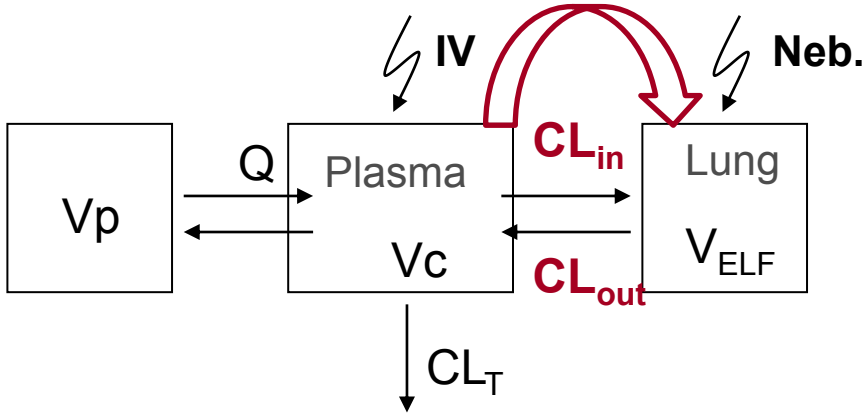
- **Simultaneous sampling (5x6)**
  - Blood (intracardiac puncture)
  - BAL (1 mL NaCL 0.9% - 37°C)



ELF conc

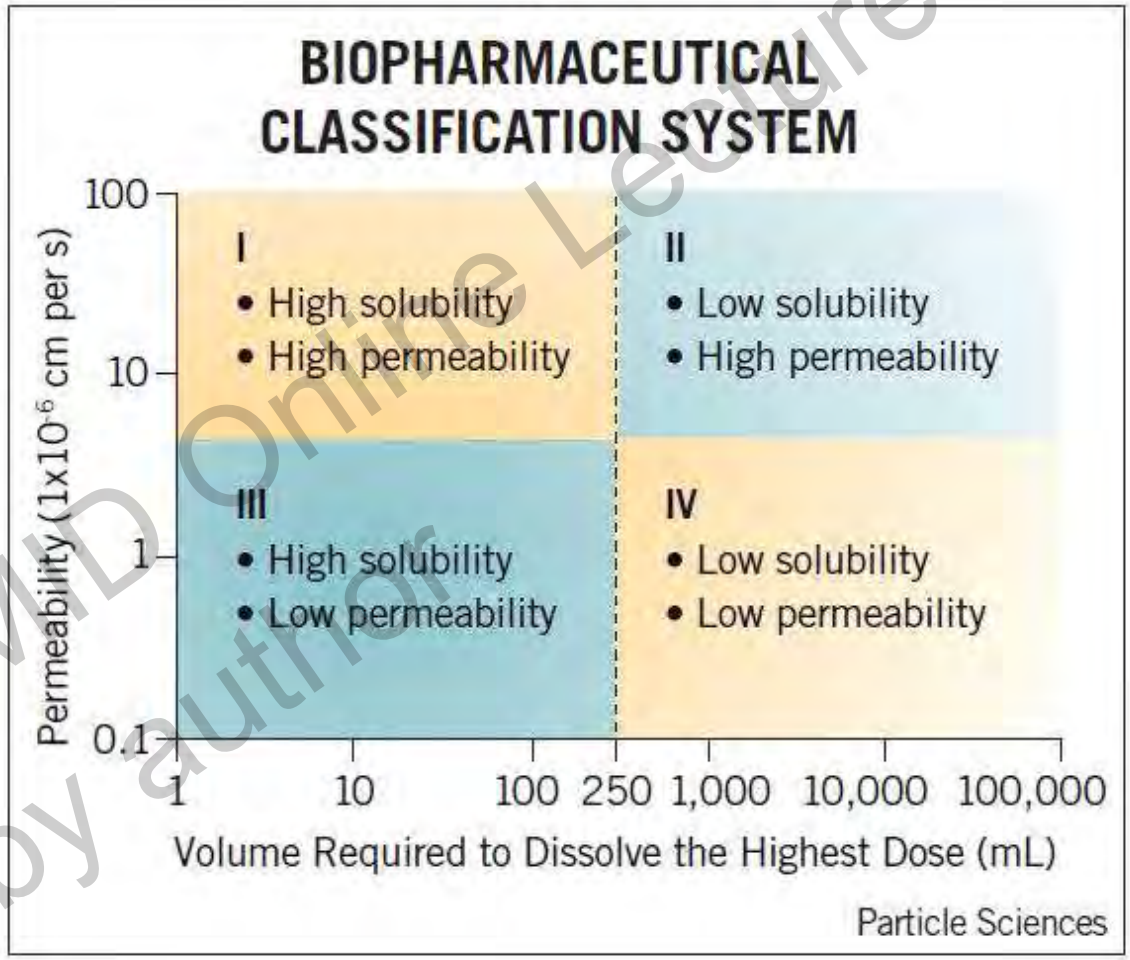
- **LC-MS/MS assay**

- **Simultaneous PK modeling**



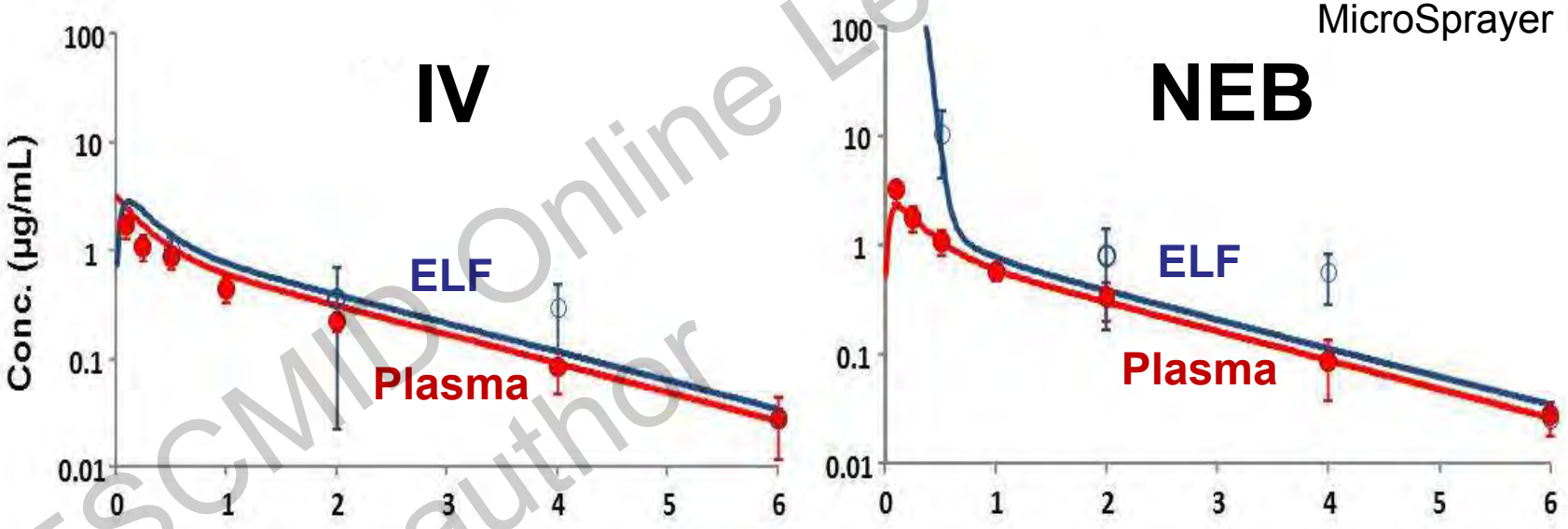
	Solubility (water, $mg.mL^{-1}$)	Log P
CIP	1,35	-0,81
MOX	0,168	-0,5
COL	0,238	-8,1
AZT	0,0429	-3,1
TOB	53,7	-6,3

	Solubility (water, mg.mL^{-1})	Log P	Permeability Papp (10^{-6} cm.s^{-1})
CIP	1,35	-0,81	0.7 ± 0.02
MOX	0,168	-0,5	5 ± 0.2
COL	0,238	-8,1	0.04 ± 0.02
AZT	0,0429	-3,1	0.07 ± 0.02
TOB	53,7	-6,3	NA



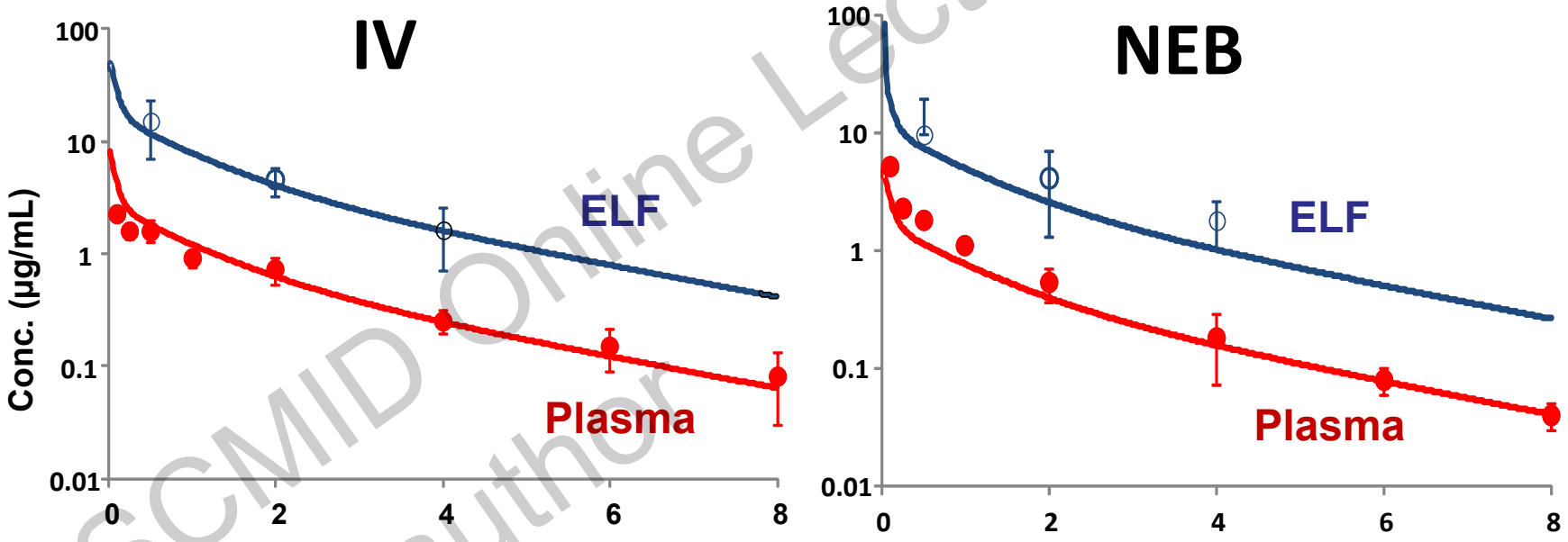
Class I: a) Ciprofloxacin

Penn Century
MicroSprayer IA-1B



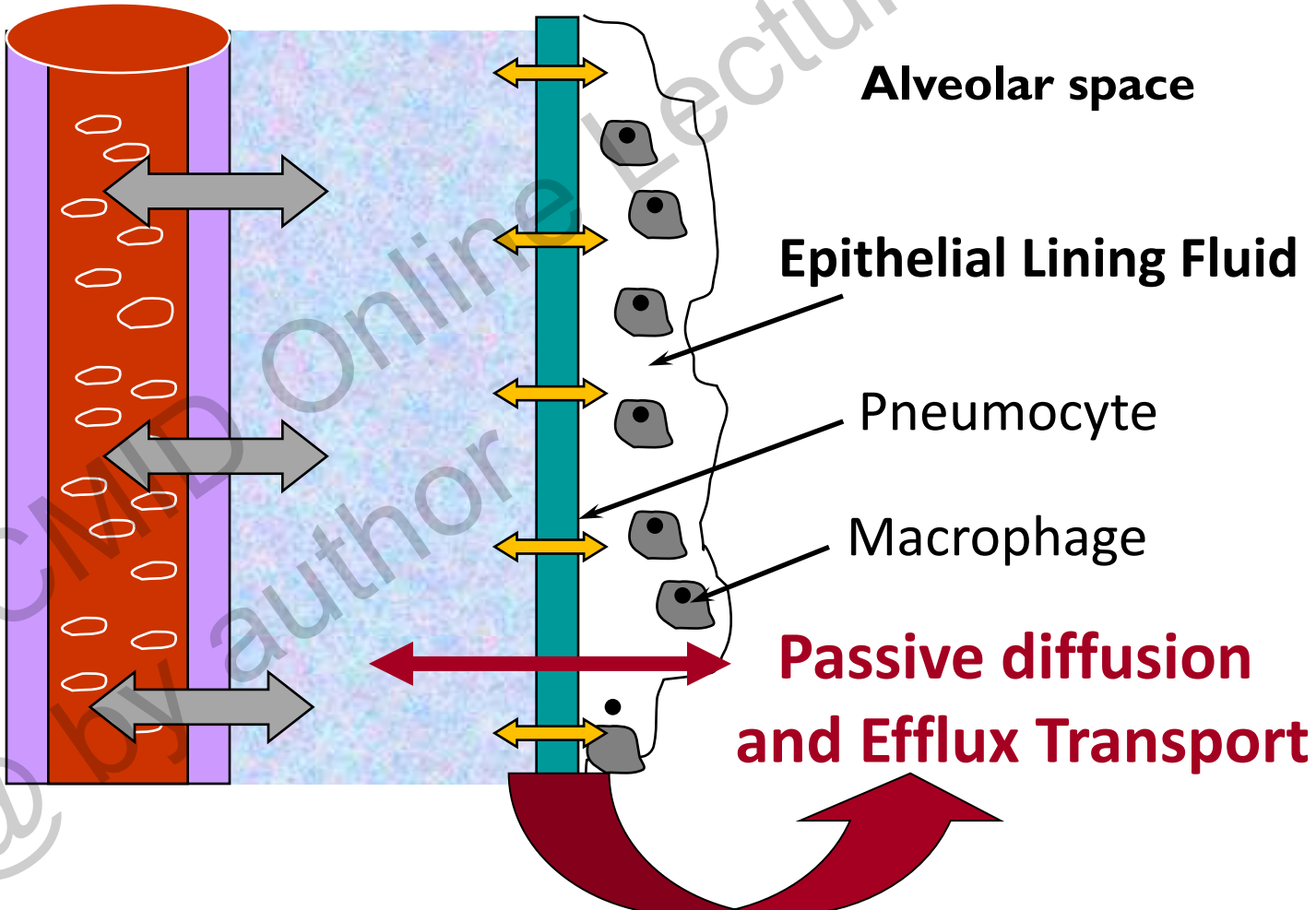
(Gontijo et al., AAC 2014)

Class I: b) Moxifloxacin

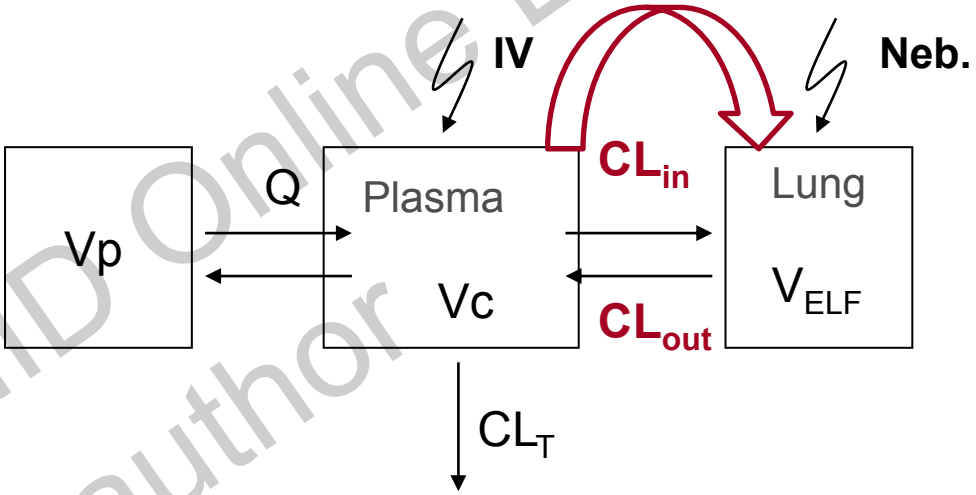


(Gontijo et al., AAC 2014)

Class I antibiotics: FQs

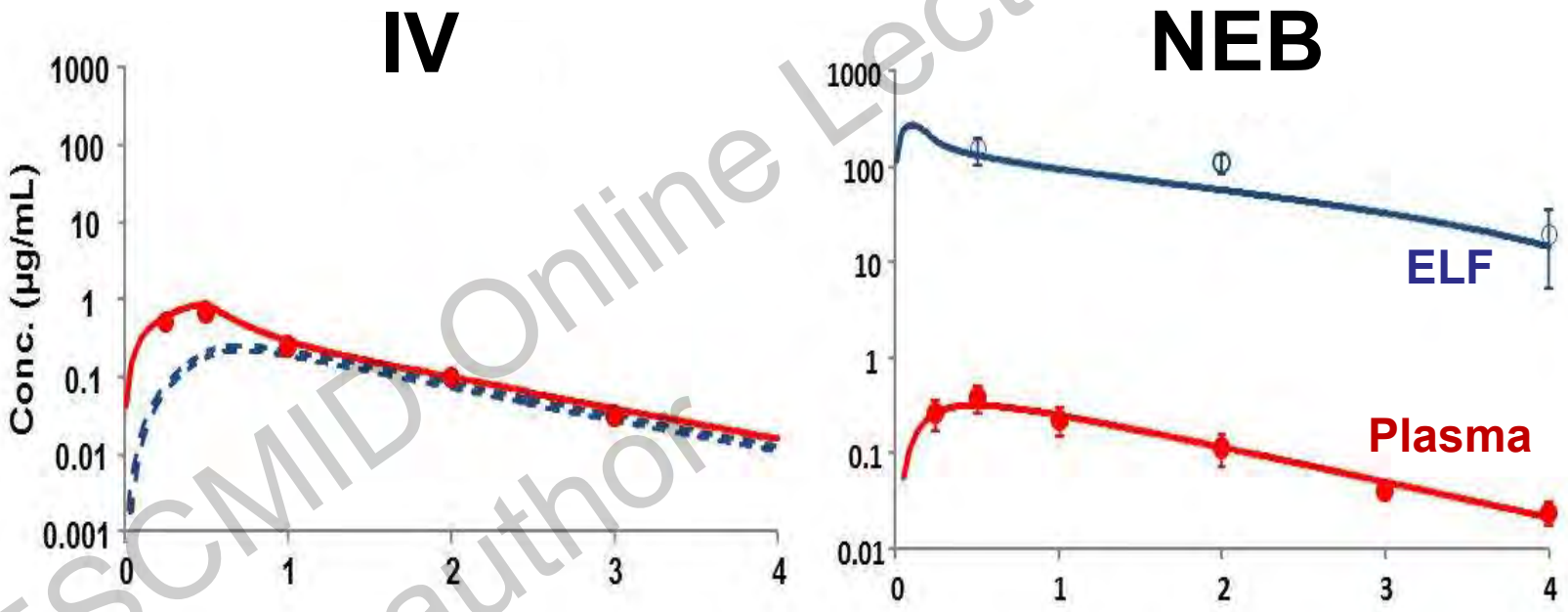


Active efflux: P-gp



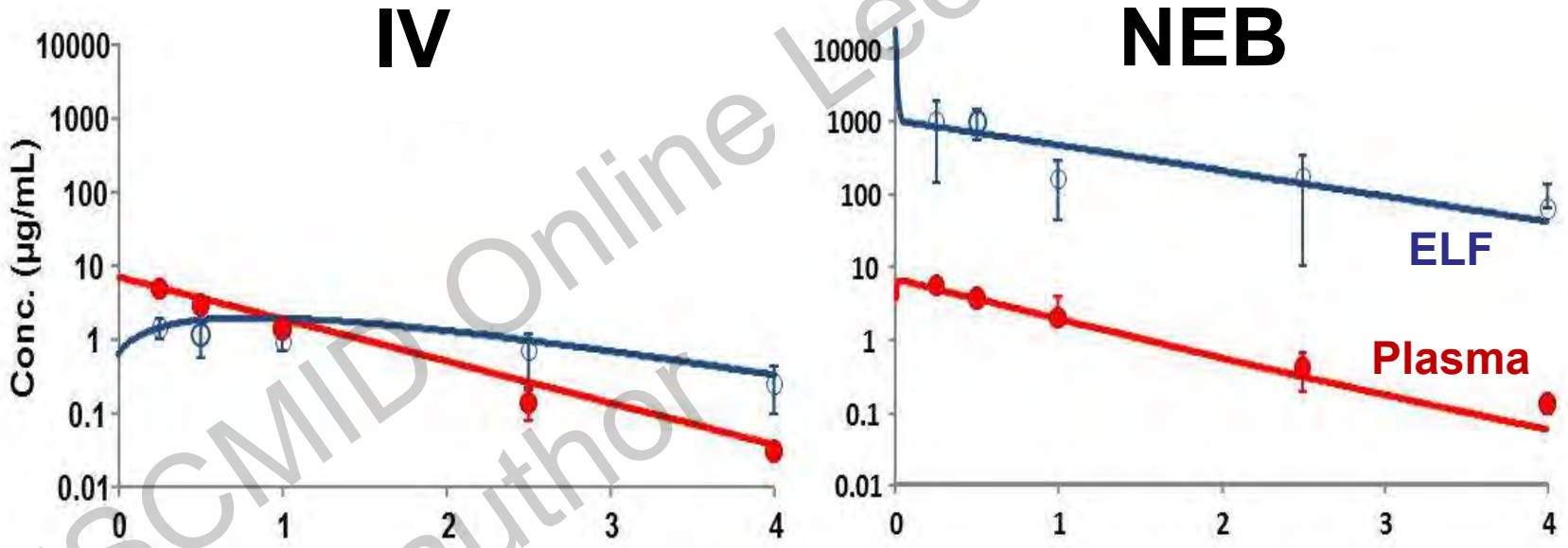
	Solubility (water, mg.mL^{-1})	Log P	Permeability Papp (10^{-6} cm.s^{-1})
CIP	1,35	-0,81	0.7 ± 0.02
MOX	0,168	-0,5	5 ± 0.2
COL	0,238	-8,1	0.04 ± 0.02
AZT	0,0429	-3,1	0.07 ± 0.02
TOB	53,7	-6,3	NA

Class III: a) Colistin

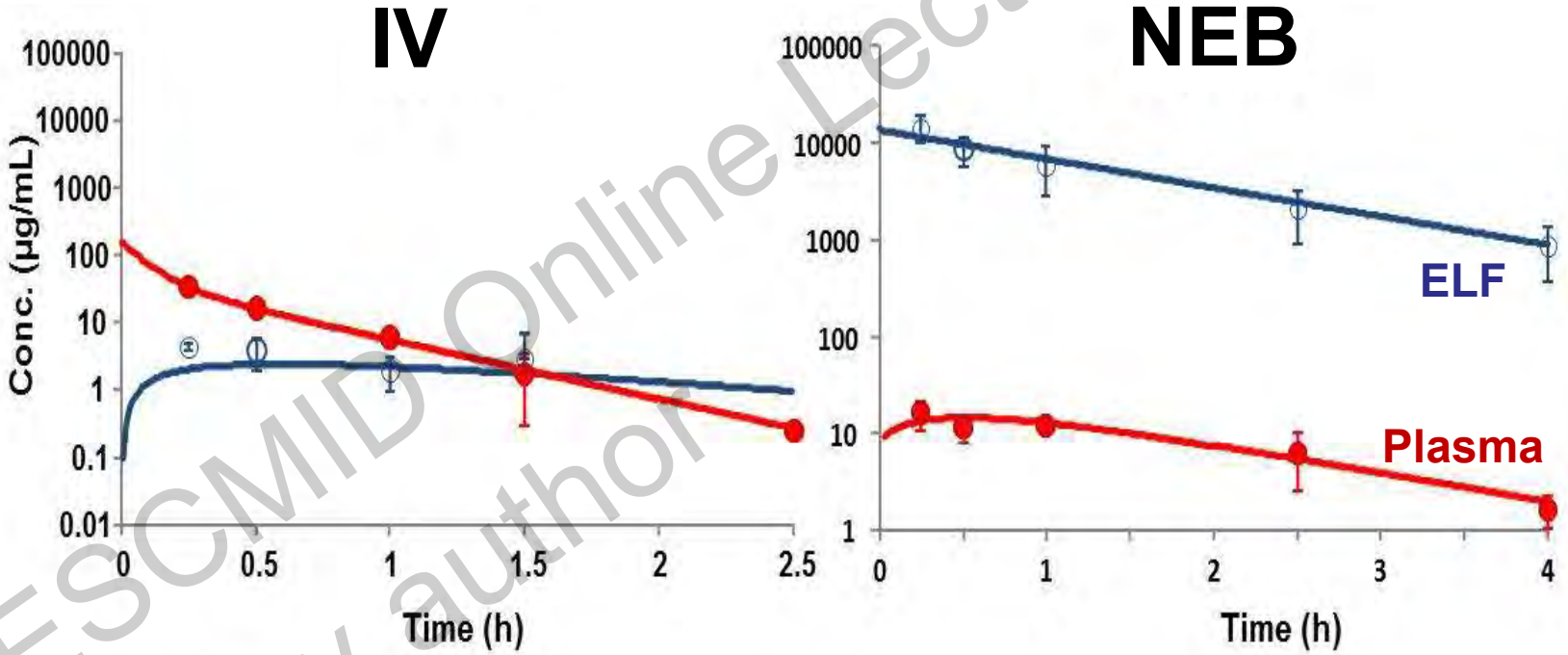


(Gontijo et al., AAC 2014)

Class III: b) Tobramycin



Class III: c) Aztreonam



Therapeutic Availability

$$TA = \frac{(AUC\ ELF_{0.5-t}/Dose)_{nebulized}}{(AUC\ ELF_{0.5-t}/Dose)_{IV}}$$

	Solubility (water, mg.mL^{-1})	Log P	Permeability Papp (10^{-6} cm.s^{-1})	TA
CIP	1,35	-0,81	0.7 ± 0.02	**1,2**
MOX	0,168	-0,5	5 ± 0.2	**0,95**
COL	0,238	-8,1	0.04 ± 0.02	**636**
AZT	0,0429	-3,1	0.07 ± 0.02	**545**
TOB	53,7	-6,3	NA	**191**

Drug Targeting Index

$$DTI = \frac{\left(\frac{AUC\ ELF_{0.5-t}/Dose}{AUC\ Plasma_{0.5-t}\ /Dose}\right)_{nebulized}}{\left(\frac{AUC\ ELF_{0.5-t}/Dose}{AUC\ Plasma_{0.5-t}\ /Dose}\right)_{IV}}$$

	Solubility (water, mg.mL^{-1})	Log P	Permeability Papp (10^{-6} cm.s^{-1})	TA	DTI
CIP	1,35	-0,81	0.7 ± 0.02	**1,2**	**1,2**
MOX	0,168	-0,5	5 ± 0.2	**0,95**	**1**
COL	0,238	-8,1	0.04 ± 0.02	**636**	**760**
AZT	0,0429	-3,1	0.07 ± 0.02	**545**	**180**
TOB	53,7	-6,3	NA	**191**	**183**

Limits

Data obtained in healthy rats…..

…that should not be used directly to make predictions in patients

But…

- Differences in permeability between antibiotics must be taken into consideration at early stage of development (Go / No-Go)

- Easy to predict from Log P and to estimate *in vitro* (Calu-3)

- Would be nice to get a threshold value

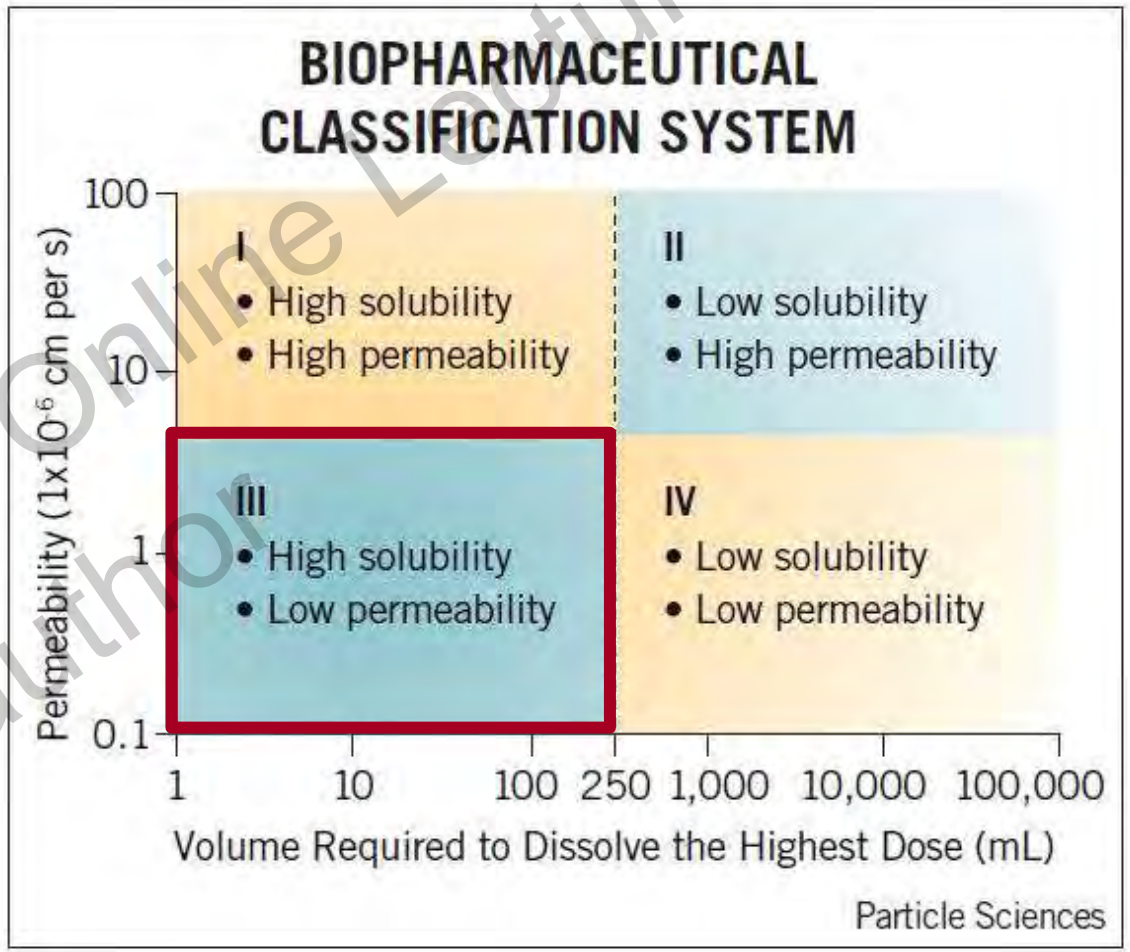
Effect of solubility remains to be investigated (PK-PD)

Cmax / MIC

Solution

Dry powder

Figure 1

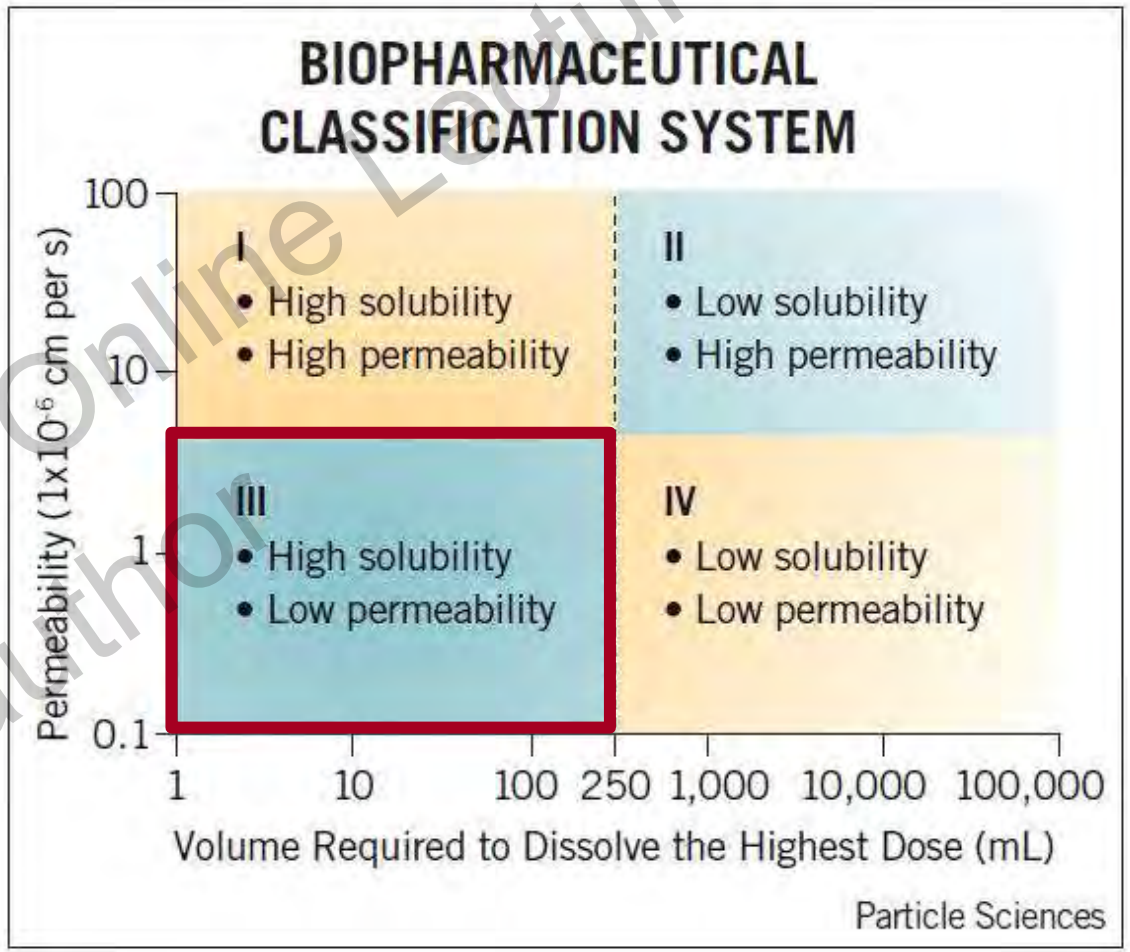


Effect of solubility remains to be investigated (PK-PD)

tmax / MIC

Sustained release formulation

Figure 1



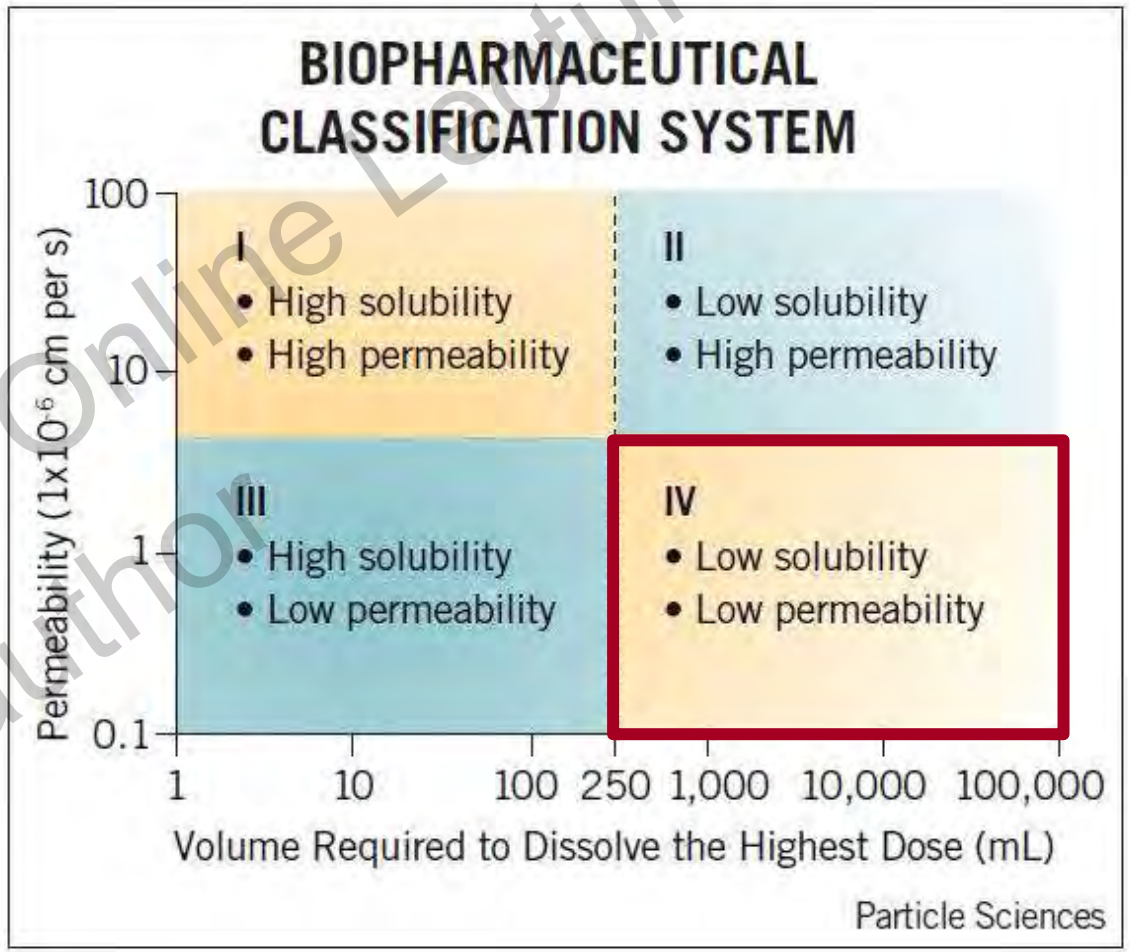
Effect of solubility remains to be investigated (PK-PD)

tmax / MIC

Increase solubility

Cyclodextrin ?

Figure 1



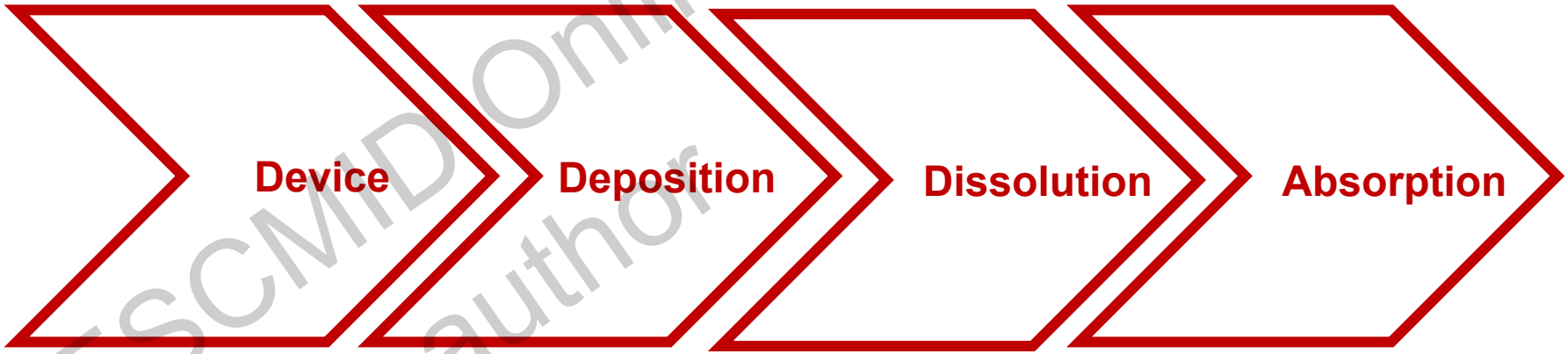
Question: **Would that be useful to consider a Biopharmaceutical Classification for nebulized antimicrobial agents ?**

YES

March 16–17, 2015
AAPS on Inhalation Product Biopharmaceutical Classification
Cosponsored by FDA, USP
Renaissance Baltimore Harborplace Hotel

CONCLUSION

Pharm.Tech. **Drug Properties**



Solubility ***Permeability***