



TOWARDS A CLASSIFICATION SYSTEM FOR PULMONARY DRUGS: SCOPE AND RELEVANCE

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IPAC-RS Symposium at RDD 2016

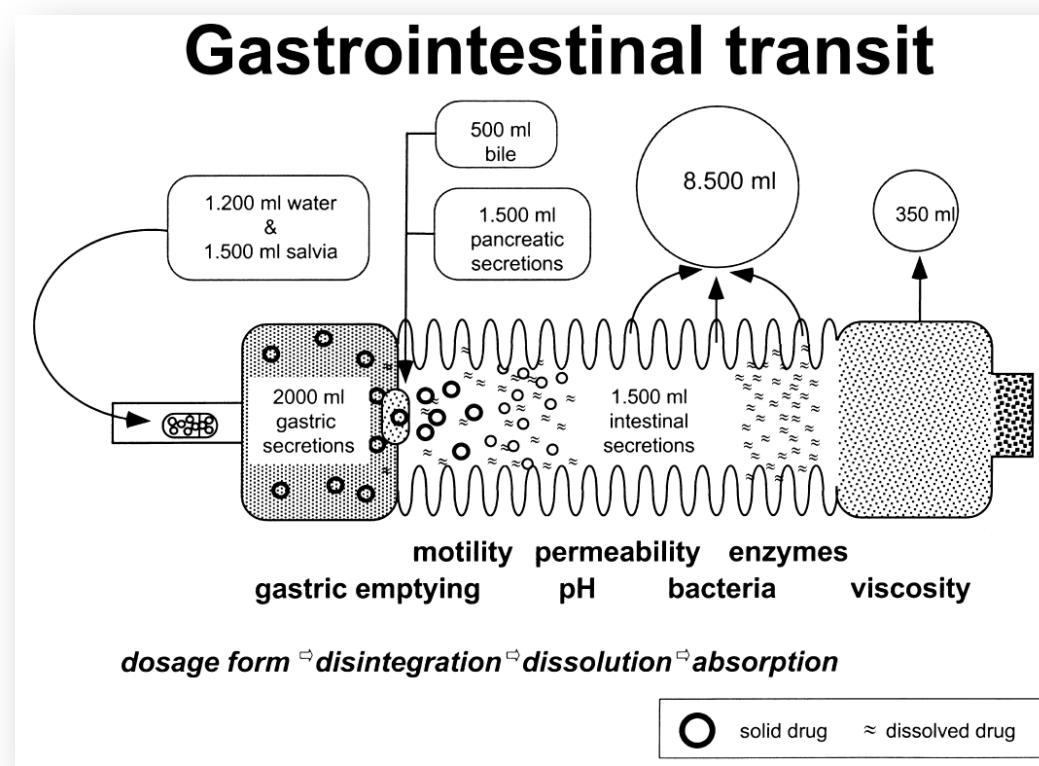
“Meeting the Quality Challenge for Orally Inhaled Drug Products”
Session 3: Biopharmaceutics – Predicting Performance in the Patient

OUTLINE

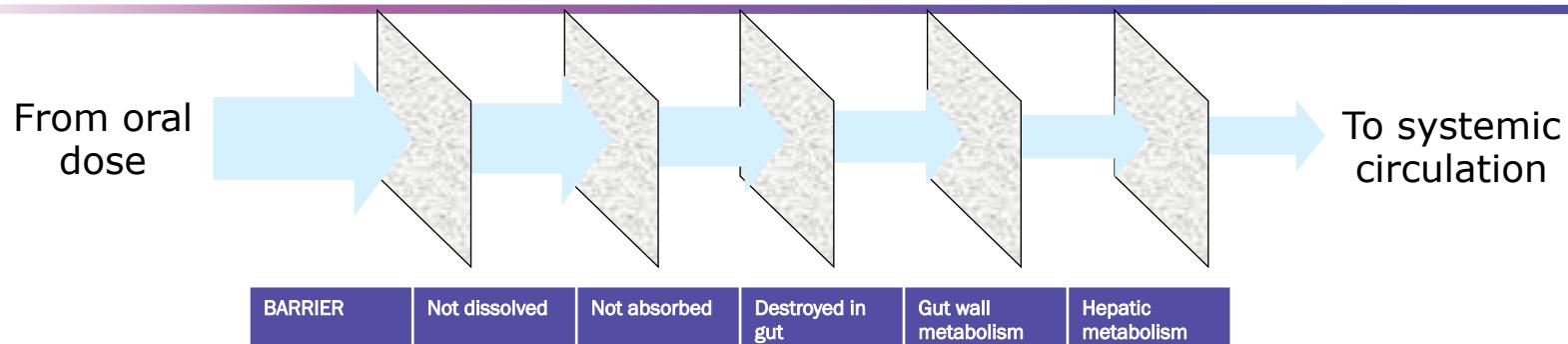
- Oral Drug Delivery Classification Approaches
- Molecular Properties of Pulmonary Drugs
- Classification Approaches for Pulmonary Drugs
 - Dose
 - Dissolution and Solubility
 - PK, Permeability, and Lung Residence Time
- Conclusions & Next Steps

ORAL DRUG CLASSIFICATION APPROACHES

Lipinski and BCS



WHY?



- Drug Discovery and Design Strategy
 - Dissolution
 - Solubility
 - Permeability/Absorption

- Product Development Strategy
 - Particle engineering
 - Excipient selection
 - Manufacturing technologies

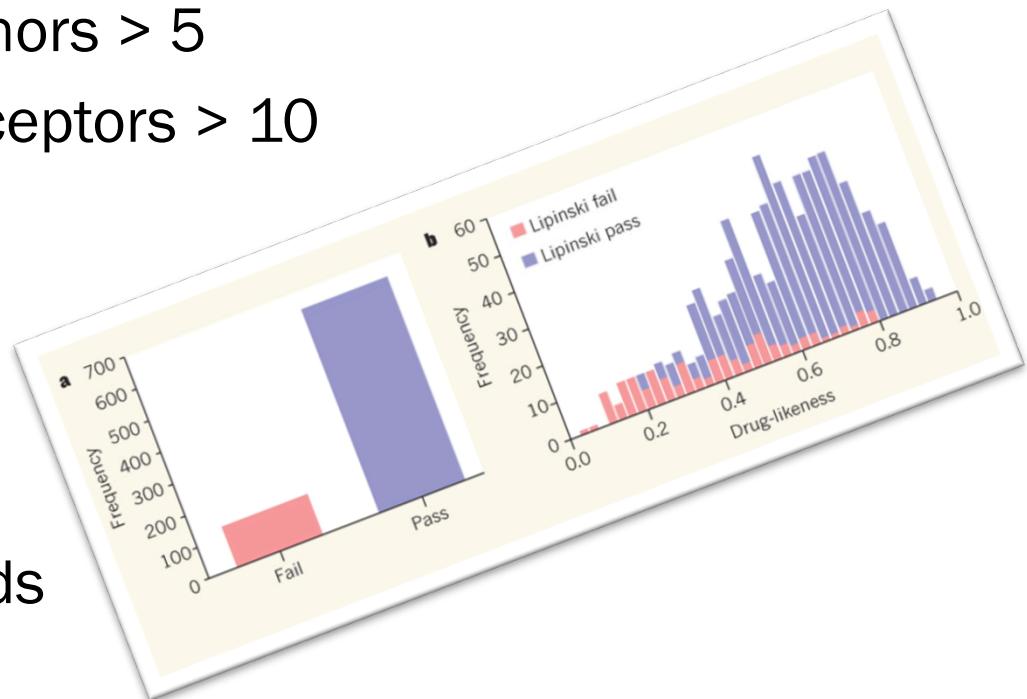
LIPINSKI'S RULE OF 5

○ Poor Absorption or Permeation:

- MW > 500
- Number of H-bond donors > 5
- Number of H-bond acceptors > 10
- Log P > 5

○ Benefits

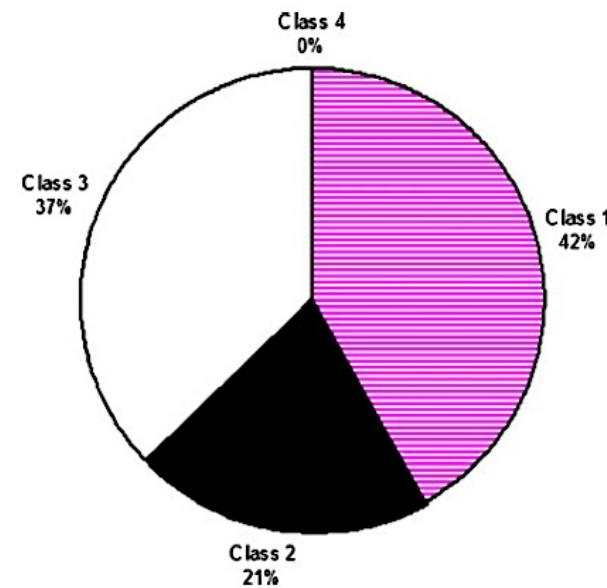
- Drug design and candidate selection
- “Drug-able” compounds



Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* 1997, 23, 3–25.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

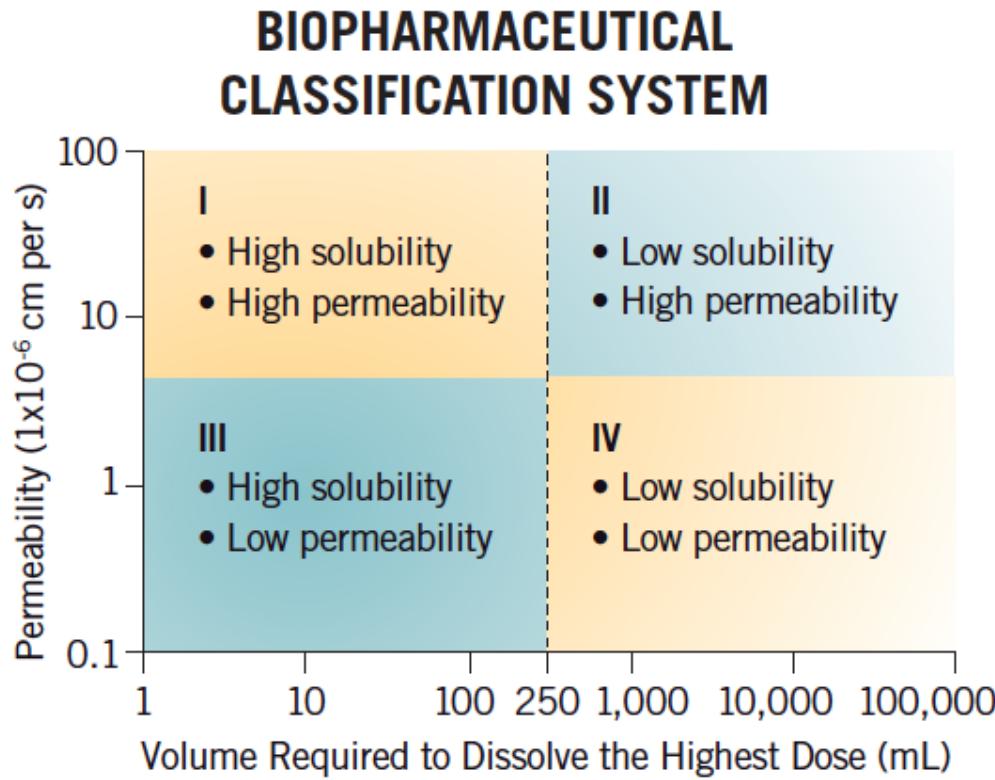
- The Biopharmaceutics Classification System (BCS), is a science-based classification system used and developed for orally-administered drugs.
- The BCS uses three simple, derived dimensionless numbers that take into account the dissolution, dose, and absorption for a particular drug substance.
- Using the **dissolution number**, **dose number**, and **absorption number**, one can predict if an orally administered drug will be solubility-limited or permeability-limited.



Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of *in vitro* Drug Product Dissolution and *in vivo* Bioavailability. *Pharm. Res.* 1995, **12**: 413-420.

Kasim, N. A.; Whitehouse, M.; Ramachandran, C.; Bermejo, M.; Lennernäs, H.; Hussain, A. S.; Junginger, H. E.; Stavchansky, S.A.; Midha, K. K.; Shah, V. P.; Amidon, G. L. *Mol. Pharm.* 2004, **1**, 85-96.

BCS FOR ORALLY ADMINISTERED DRUGS (giBCS)



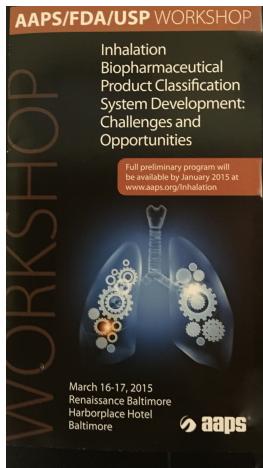
○ Benefits

- Drug discovery/design
 - Screening techniques
- Formulation strategies
 - Addressing the “lows”
- Biowaivers
 - BCS Class I
 - BCS Class III
- IVIVC Potential
 - BCS Class II
 - BCS Class I – potentially

FDA. Guidance for Industry Guidance for Industry Waiver of In Vivo Bioavailability and Bioequivalence Studies for IR Solid Oral Dosage Forms Based on BCS; 2015.

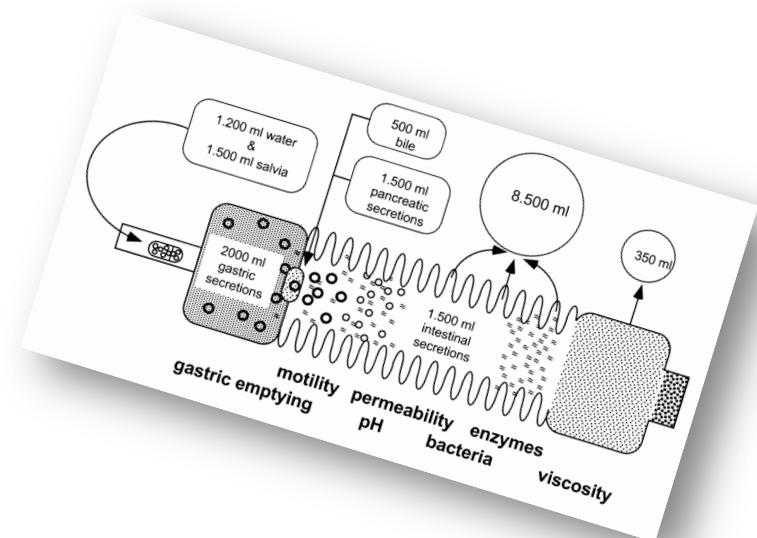
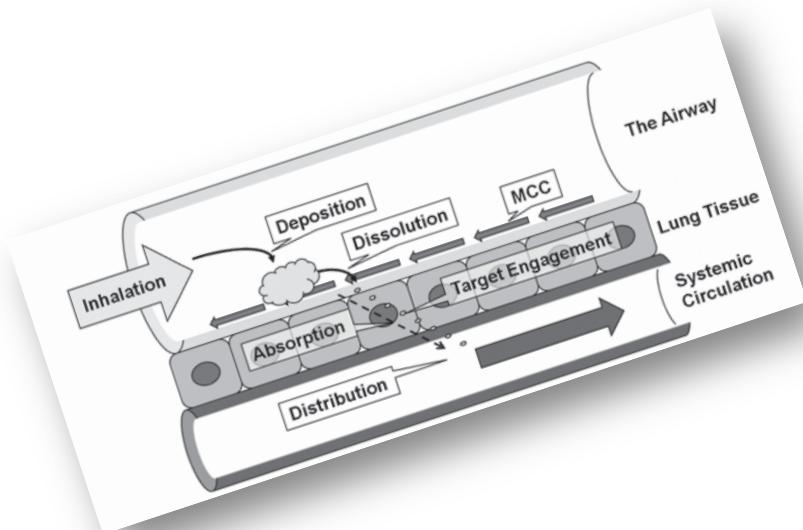
Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. *Pharm. Res.* 1995, 12, 413–420.

Yazdanian, M.; Glynn, S. L.; Wright, J. L.; Hawi, A. *Pharm. Res.* 1998, 15, 1490–1494.



TOWARDS A PULMONARY DRUG CLASSIFICATION SYSTEM

What can we learn from oral drug classification approaches



DESIRED PROPERTIES: ORAL VS. INHALED THERAPEUTICS

	Oral Drugs	Inhaled Drugs with Local Target
Distribution	Systemic	Local to Lung
Systemic absorption	Rapid	Low to None
Systemic Clearance	Slow	Rapid
Protein Binding or Retention Time	Low	High
Oral BA	High	Low

Adapted from Yeadon, M. Future Med. Chem. 2011, 3, 1581–1583.

PHYSICOCHEMICAL PROPERTIES: ORAL VS. INHALED THERAPEUTICS

Class	Avg Mol. Weight (SD)	Avg. H-bond count (SD)	Avg. Polar Surface Area (Å ²) (SD)	Avg. Rotatable Bond Count (SD)
LABA	498 (80.29)	11.00 (2.12)	116.63 (28.53)	13.00 (4.30)
LAMA	385 (63.39)	3.50 (1.50)	43.15 (11.80)	6.00 (2.35)
MABA	717 (58.22)	12.82 (1.80)	148.5 (23.97)	16.73 (2.83)
PDE4 Muscarinic duals	691 (32.29)	11.25 (1.30)	122.50 (9.66)	12.25 (1.30)
Phosphate prodrugs	969 (102.88)	13.20 (2.48)	173.00 (31.72)	26.2 (2.32)
Oral	305 (91.00)	6.04 (2.92)	60.37 (32.27)	4.70 (2.69)
Inhaled	370 (103.00)	8.31 (3.25)	89.20 (38.65)	5.10 (2.76)

Selby, M. D.; de Koning, P. D.; Roberts, D. F. Future Med. Chem. 2011, 3, 1679–1701.

INHALED VS. ORAL DRUG PROPERTIES

“Compounds administered via the inhaled/intranasal routes have a higher polar surface area, a higher molecular weight, and trend towards lower lipophilicity, when compared with their orally administered counterparts.”

Ritchie TJ, Luscombe CN, Macdonald SJF. Analysis of the calculated properties of respiratory drugs: can we design for inhaled drugs yet? *J. Chem. Inf. Model.* 49(4), 1025–1032 (2009).

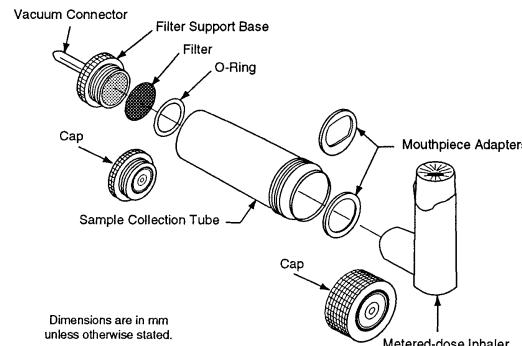
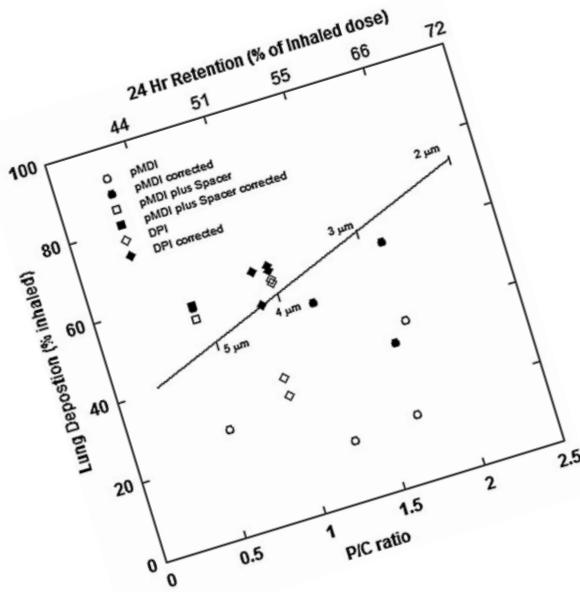
CONCLUSION

the desired properties of inhaled therapeutics are different from oral therapeutics

- ❖ Pulmonary Dose
- ❖ Pulmonary Dissolution and Solubility
- ❖ Pulmonary Residence Time and PK

THE PULMONARY DOSE AND DOSE NUMBER

Delivered dose is an important CQA for inhaled drugs along with aerodynamic particle size and distribution.

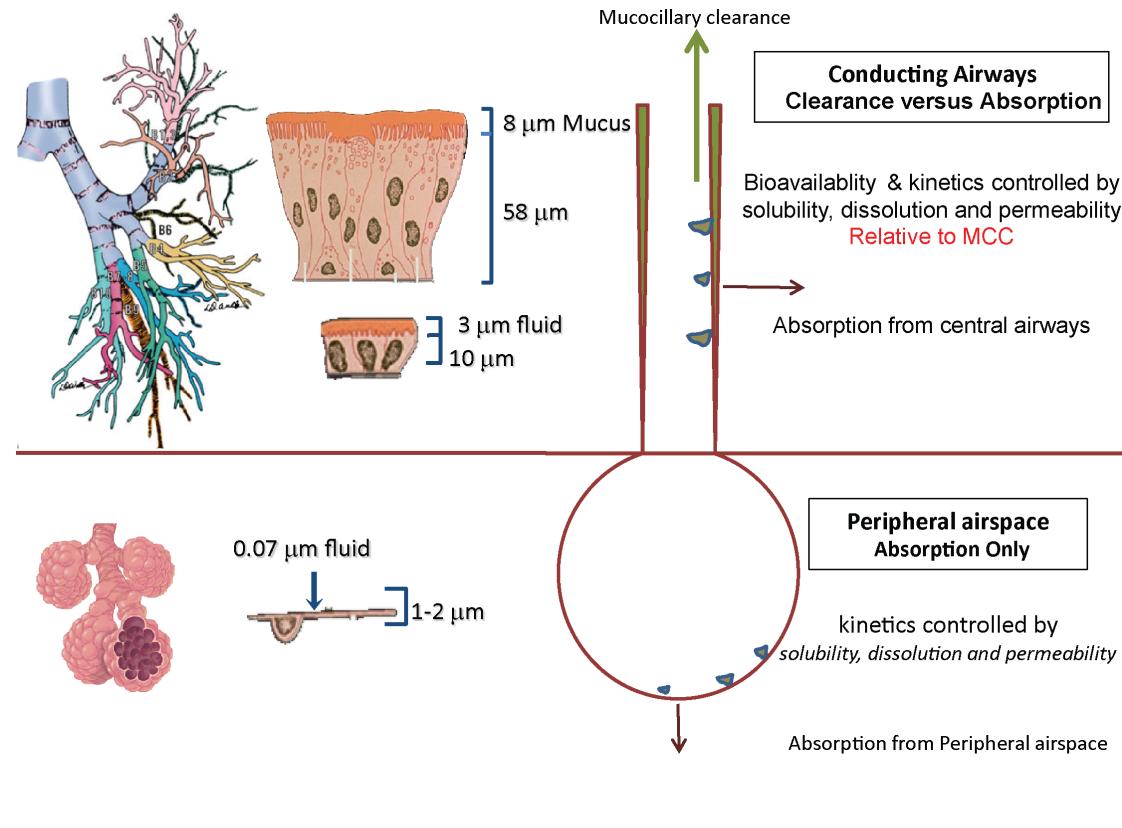
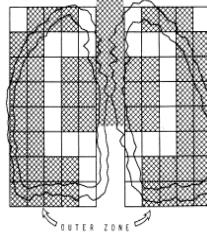


THE PULMONARY DOSE

- Clinical safety and efficacy of inhaled drugs are influenced by the total aerosolized dose delivered to the lungs and by the aerodynamic particle size distribution.
 - The lung dose is less than the amount of drug in the dosage unit and is dependent upon the device used and the patient.
 - Both dose content uniformity and aerodynamic particle size distribution are CQAs for inhaled drugs.
 - The deposition patterns impact the fate of the inhaled dose.

REGIONAL DEPOSITION PATTERNS AND DOSE

- Inhaled dose is “pre-filtered” by mouth and oropharynx
- Peripheral deposition of this “true” dose is approximately 40-60%.
- “True” aerosol lung dose:
 - 50% central
 - 50% peripheral



Hastedt, J. E.; Bäckman, P.; Clark, A. R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P. J.; Lehr, C.-M.; Mauser, P.; McConville, J.; Niven, R.; Sakagami, M.; Weers, J. G. *AAPS Open* 2016, 2, 1.

Clark, A. R. Understanding Penetration Index Measurements and Regional Lung Targeting. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2012, 179–187.

ESTIMATED DOSE NUMBERS – BCS APPROACH

$$Do = DoseNumber = \frac{Mo / Vo}{C_s}$$

Dose adjusted for device and estimated deposition pattern
(P/C)

$$Mo = \text{central lung dose} = M_{nom} \times \eta_{lung} \times \eta_{central}$$

$$Vo = \text{volume} = 10ml$$

$$C_s = \text{solubility in water}$$

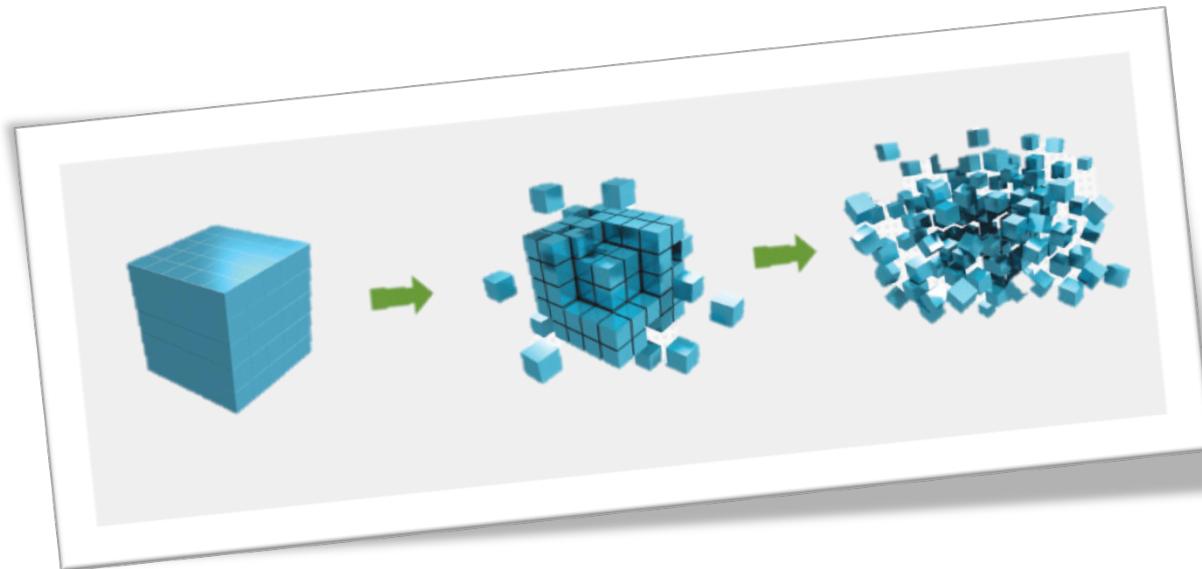
If Do is < 1, the delivered dose is assumed to be fully dissolved

Drug	Class	Do
Amphotericin B	AB	150
Fluticasone propionate	ICS	27
Beclomethasone dipropionate	ICS	15
Ciprofloxacin betaine	AB	12
Mometasone furoate	ICS	3
Tobramycin sulfate	AB	0.1
Salmeterol xinafoate	LABA	0.005
Albuterol sulfate	SABA	0.0001
Ipratropium bromide	SAMA	0.00002
Formoterol fumarate	LABA	0.00001
Tiotropium bromide	LAMA	0.00001

Adapted from J. Weers, AAPS/FDA/USP iBCS Workshop, March 2015.

PARTICLE DISSOLUTION IN THE LUNG

There are no regulatory requirements or USP techniques for dissolution testing of inhaled drugs. It is not considered a CQA for inhaled drug products.



IMPACT OF SOLUBILITY ON PARTICLE DISSOLUTION – ICS DRUGS

There is a good correlation between Do and MDT for ICS drugs

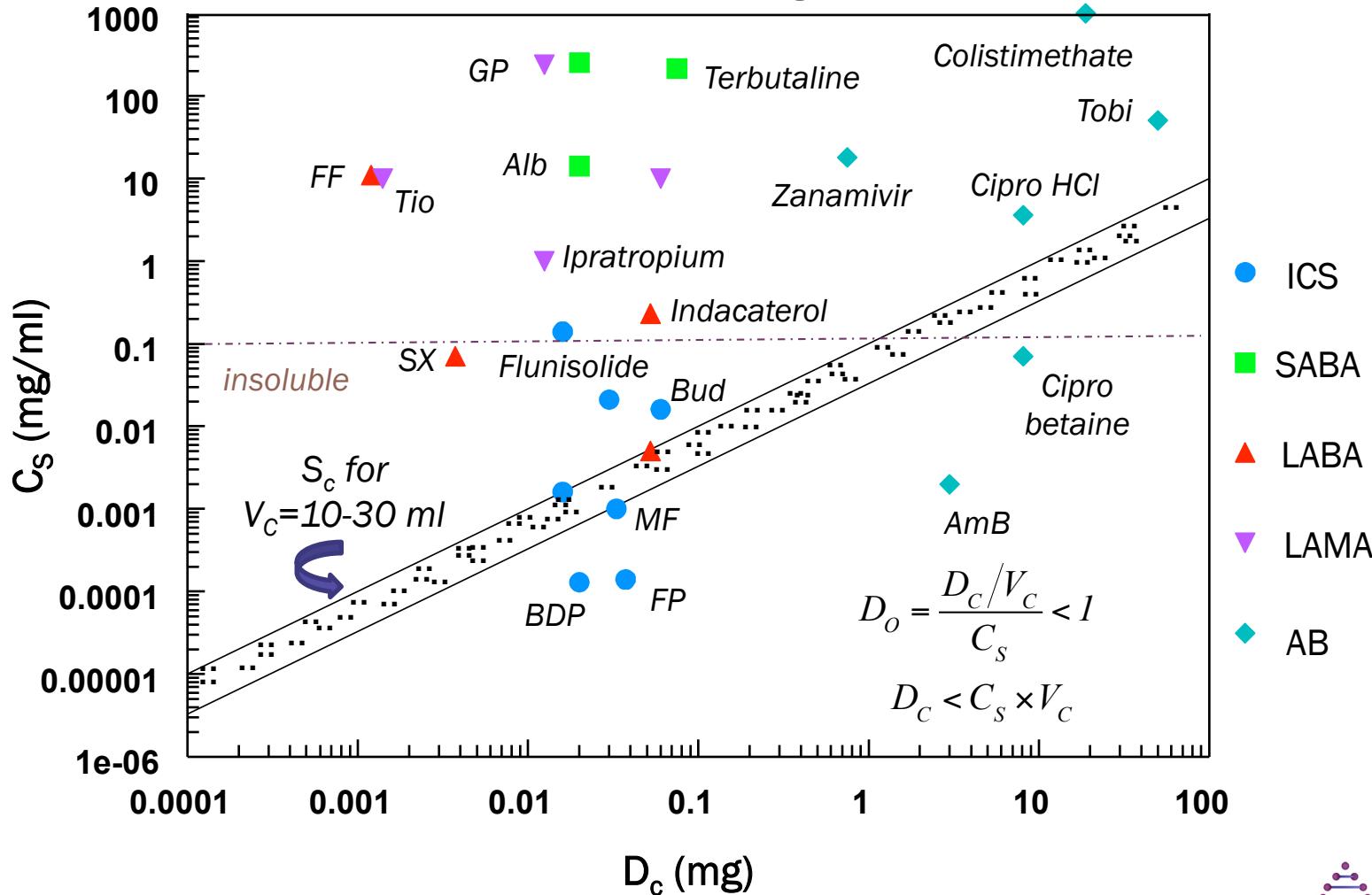
ICS	C_s ($\mu\text{g}/\text{ml}$)	Do	Mean Dissolution Time (hr)
Fluticasone propionate	0.14	27	>8
Beclomethasone dipropionate	0.13	15	>5
Budesonide	16	0.375	~ 0.1
Flunisolide	140	0.01	< 0.03

Source: Högger P, Bonsmann U, Rohdewald P. Efflux of glucocorticoids from human lung tissue to human plasma in vitro [Abstract P1735]. Eur Respir J 1994;7:382s.

Adapted from Hastedt, J. E.; Bäckman, P.; Clark, A. R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P. J.; Lehr, C.-M.; Mauser, P.; McConville, J.; Niven, R.; Sakagami, M.; Weers, J. G. AAPS Open 2016, 2, 1.

IMPACT OF SOLUBILITY AND DOSE ON PARTICLE DISSOLUTION IN THE CENTRAL AIRWAYS

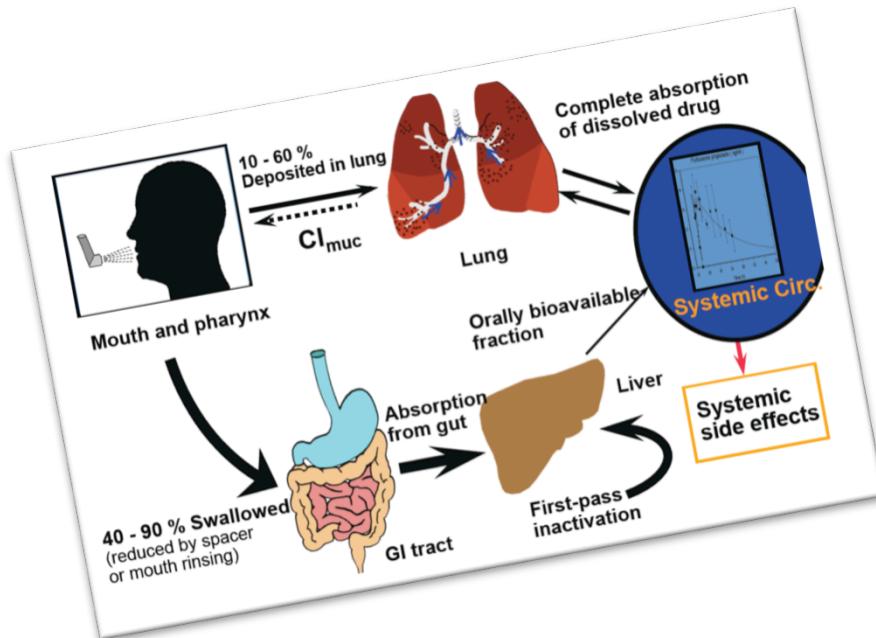
Dissolution becomes important for drugs that are considered “insoluble”



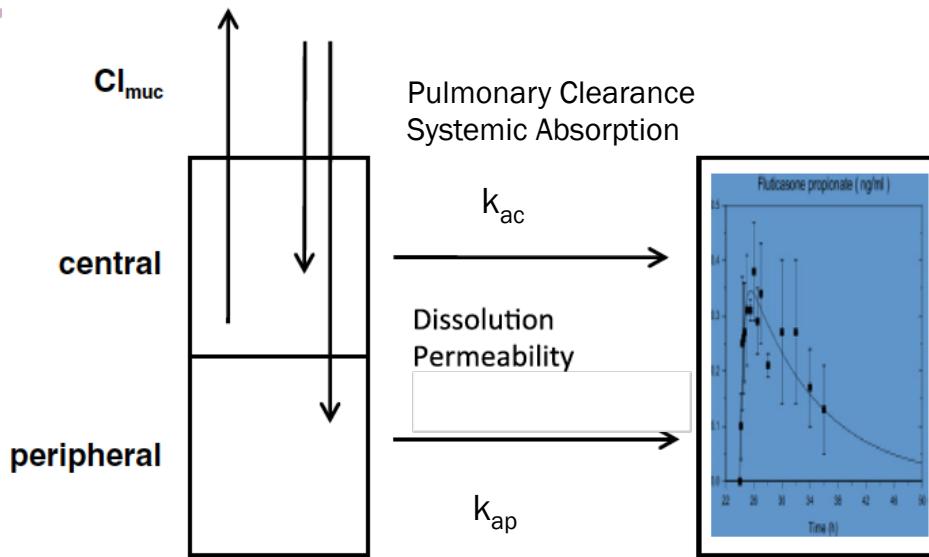
Adapted from Hastedt, J. E.; Bäckman, P.; Clark, A. R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P. J.; Lehr, C.-M.; Mauser, P.; McConville, J.; Niven, R.; Sakagami, M.; Weers, J. G. AAPS Open 2016, 2, 1.

PHARMACOKINETICS, PERMEABILITY, AND LUNG RESIDENCE TIME

The Fate of Inhaled Drugs

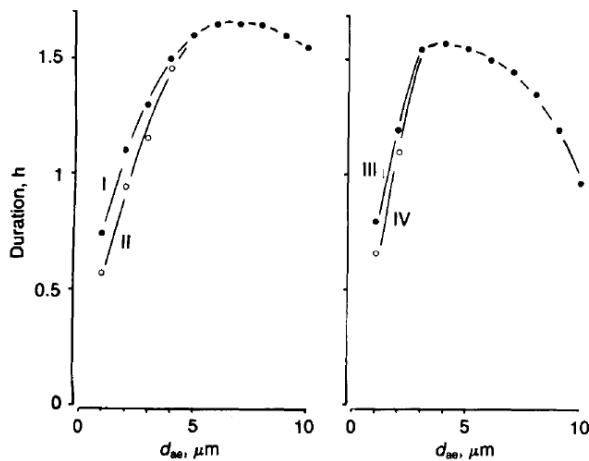


UNDERSTANDING PK, PERMEABILITY, AND RESIDENCE TIME

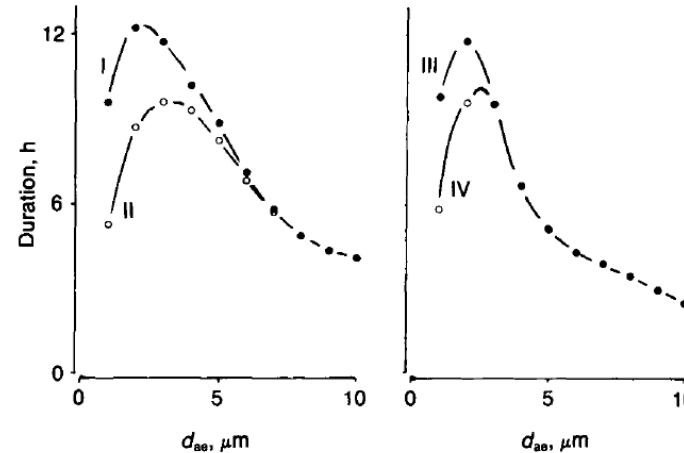


Cl_{sys}

Adapted from: Hochhaus, G.; Horhota, S.; Hendeles, L.; Suarez, S.; Rebello, J. AAPS J. 2015.



Soluble and highly permeable

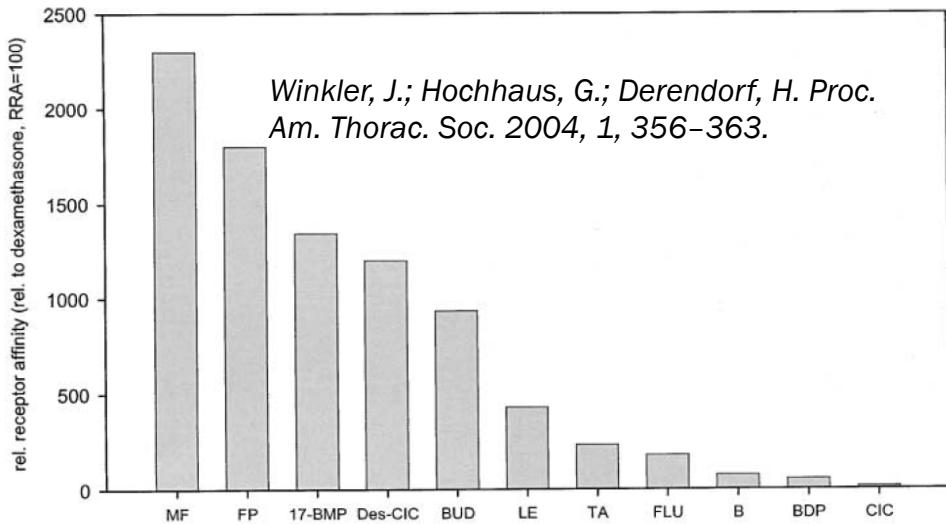
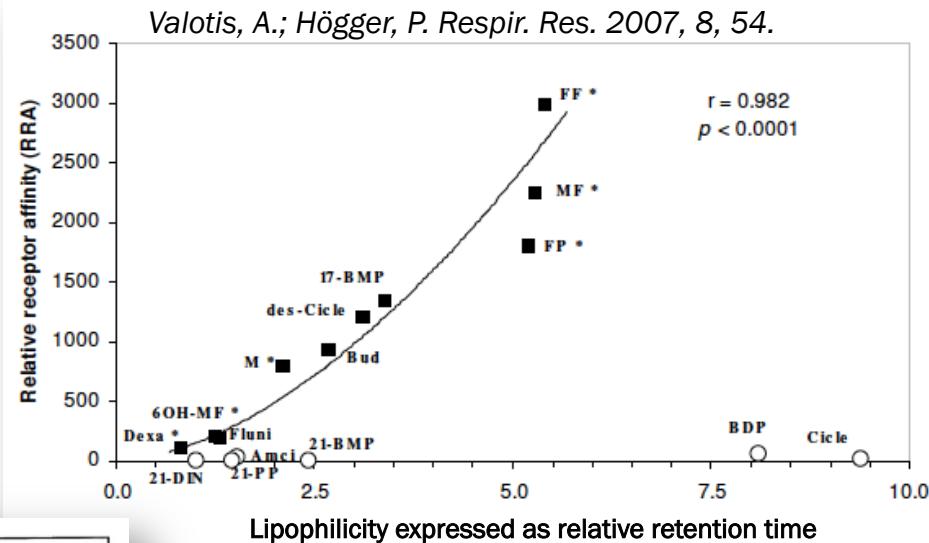


Insoluble and low permeability

Byron, P. R. J. Pharm. Sci. 1986, 75, 433–438.

RELATIVE RECEPTOR AFFINITIES – ICS DRUGS

Residence time is dependent upon receptor binding for ICS drugs



PLASMA LEVELS AND LOCALLY ACTING INHALED DRUGS

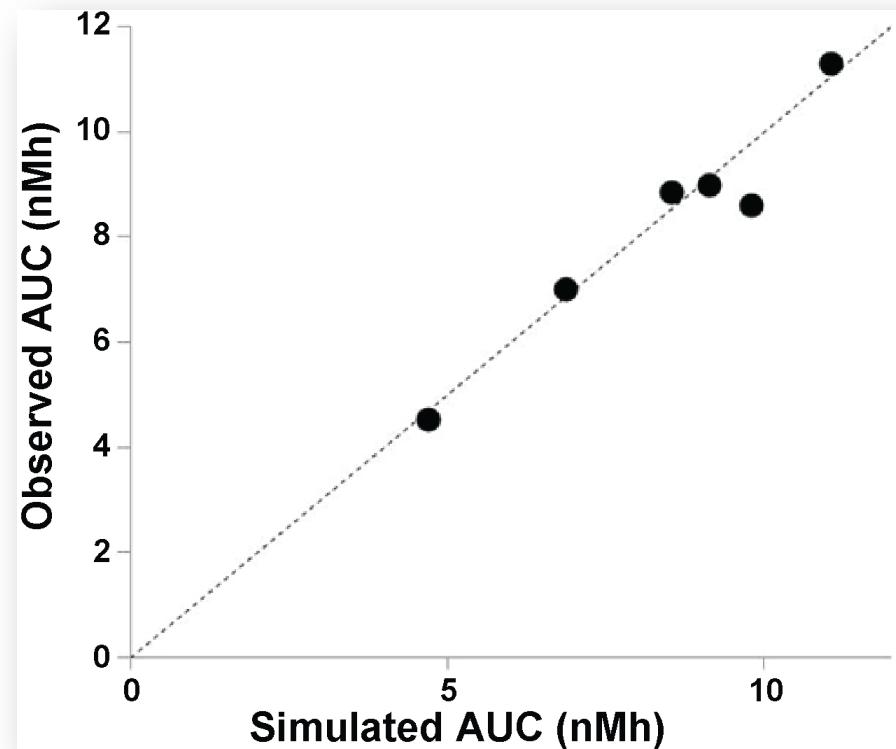
“Ideally, clinical pharmacokinetic (PK) data are used to develop a pharmacokinetic/pharmacodynamic (PK/PD) model but, for inhaled compounds, plasma levels do not reflect the pharmacodynamically relevant concentrations, but rather the spillover of drug from the effect compartment.”

Sykes, D. A.; Charlton, S. J. *Br. J. Pharmacol.* 2012, 165, 2672–2683.

CASE STUDY: COMPUTER MODELING

Mechanistic computer modeling using deposition, dissolution, clearance, absorption and systemic disposition for an SGRM in healthy volunteers shows promise.

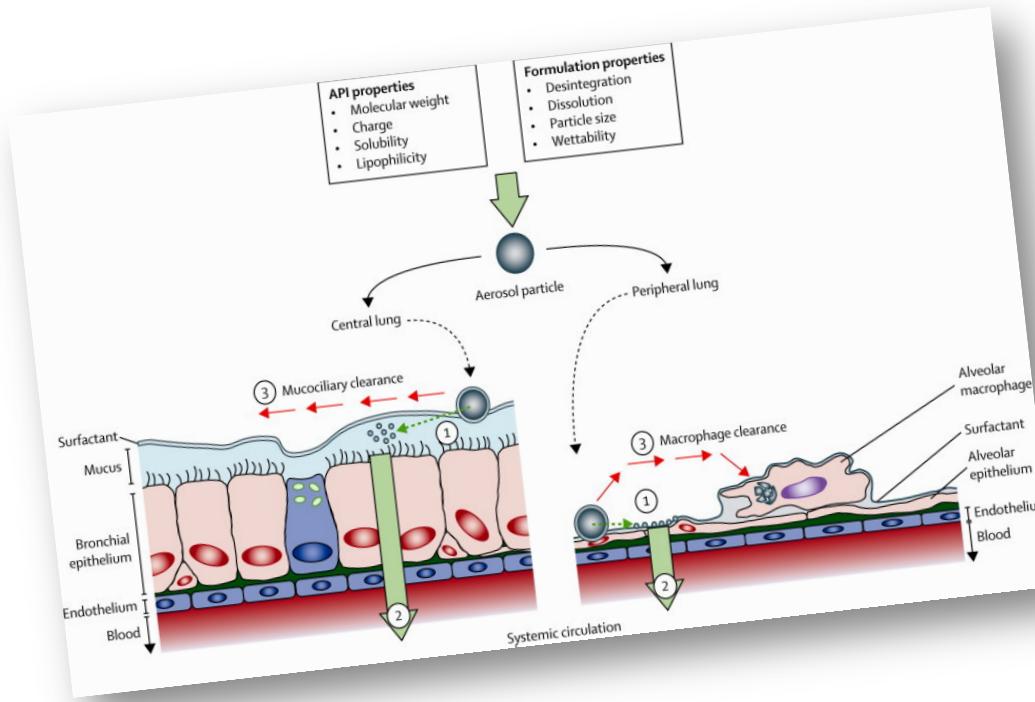
Successful modeling is dependent upon an understanding of biorelevant physicochemical properties, drug deposition patterns, and lung physiology.



Modified from Olsson & Bäckman, RDD 2014, Fajardo, Puerto Rico, 2014, pages 287-294.

iBCS OPPORTUNITIES AND CHALLENGES

Conclusions and Next Steps



CONCLUSIONS: THE LUNG IS A BUCKET

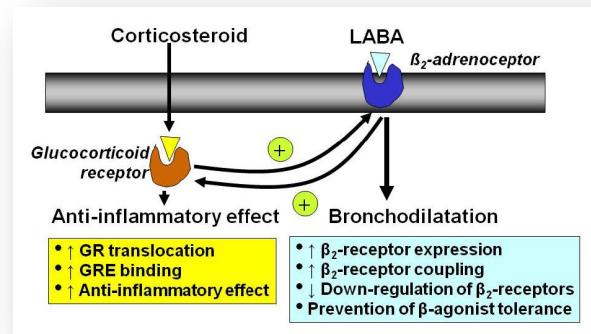
- Most drugs designed for the pulmonary route are larger and have a higher polar surface area than orally administered drugs.
 - Clearance mechanisms are dependent upon deposition
- Higher receptor affinity increases lung residence time and minimizes the impact of dissolution rate on efficacy.
 - e.g., fluticasone propionate
- Overall fraction absorbed is not relevant for orally inhaled pulmonary drugs with local receptors/activity.
 - Understanding receptor binding, protein binding, and residence time are all critical parameters



CONCLUSIONS: DISSOLUTION, DOSE, AND RESIDENCE TIME

- Dose number can be calculated using giBCS parameters and dose can be defined by using the “pre-filtered” aerosol deposition pattern.
- Dissolution rate:
 - If the dissolution time is greater than the residence time, then either a depot of drug remains in lung or the undissolved drug is cleared.
 - If the dissolution time is less than the residence time, then complete dissolution occurs.
- Residence time is a variable and cannot be defined using a giBCS approach.

$$t_{i-res} \neq \frac{\pi R^2 L}{Q}$$



NEXT STEPS: SCOPE AND RELEVANCE

- Scope and Relevance:

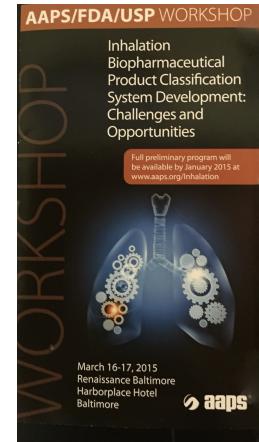
- Provide information for drug discovery chemists and formulators/engineers.
- Characterization model will require a multi-faceted approach and will be derived from first principles.
 - Biorelevant dose, solubility, dissolution, residence time/receptor binding.
 - Focus on locally acting therapeutics and exclude antibiotics, systemic and protein therapeutics.

- Challenges:

- Biorelevant testing and characterization techniques.
- Limited data – the number of pulmonary therapeutics is small compared to oral therapeutics.

ACKNOWLEDGEMENTS

- AAPS INTFG EC and Members
- AAPS/FDA/USP Workshop planning committee members, presenters, and participants
 - Gordon Amidon, Per Bäckman, Andy Clark, Bill Doub, Tony Hickey, Guenther Hochhaus, Phil Kuehl, Claus-Michael Lehr, Pete Mauser, Jason McConville, Ralph Niven, Masahiro Sakagami, Jeff Weers, Jayne Hastedt
- IPAC-RS
- AAPS Open article
 - <http://aapsopen.springeropen.com/articles/10.1186/s41120-015-0002-x>





giBCS DIMENSIONLESS NUMBERS

Parameter	giBCS
Dose Number	$Do = \frac{M_o/V_o}{C_s}$
Dissolution Number	$Dn = t_{res} \cdot \frac{3DC_s}{\rho r_0^2} = \frac{t_{res}}{t_{diss}}$ $t_{diss} = \frac{r_0^2 \rho}{3DC_s}$
Absorption Number	$An = t_{res} \cdot \frac{P_{eff}}{R} = \frac{t_{res}}{t_{abs}}$ $t_{abs}^{-1} = k_{abs} = \left(\frac{S}{V}\right) P_{eff}$
Residence Time	$t_{res} = \frac{\pi R^2 L}{Q}$

SOLUBILITY-LIMITED DRUGS AND BCS

- Bioavailability of Class II compounds are limited by their dissolution rate and dose.
- Bioavailability of Class IV molecules are limited by their dissolution rate and permeability.

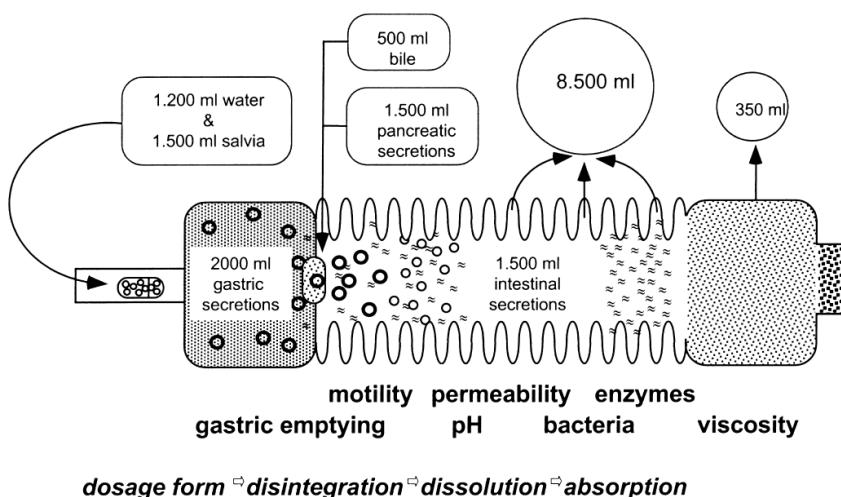


Table 1

BCS classification of drugs and in vitro/in vivo correlation expectations for immediate release products based on the biopharmaceutics class^a

Class	Solubility	Permeability	IVIVC expectation
I	High	High	IVIVC if the dissolution rate is slower than the gastric emptying rate, otherwise limited or no correlation
II	Low	High	IVIVC expected if the in vitro dissolution rate is similar to the in vivo dissolution rate, unless the dose is very high
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution rate
IV	Low	Low	Limited or no IVIVC expected

BCS AND FORMULATION APPROACHES

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	<ul style="list-style-type: none"> 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 luminal concentration	
4	Low	Low	Combine 2 and 3	

THE RULE OF FIVE FOR NON-ORAL ROUTES

- When considering systemic delivery, the rule of 5 is overly restrictive and should not be used to predict non-oral drug candidates, especially for inhalation and transdermal routes.
- Almost all current inhalation drugs adhere to the Rule of Five – probably due the small number of pulmonary drugs

Table I Modified Rule of Five for FDA-Approved Non-Oral Drugs Generated by the Bootstrap Method

Administration route	MW (Da)	# of H donors	# of H acceptors	log P
Ophthalmic	500 ^a	3	8	4.2
Inhalation	500 ^a	4	10 ^a	3.4
Transdermal	335	2	5	5.0 ^a

Choy, Y. Bin; Prausnitz, M. R. *Pharm. Res.* 2011, 28, 943–948.

COMPOSITION OF LUNG LINING FLUID

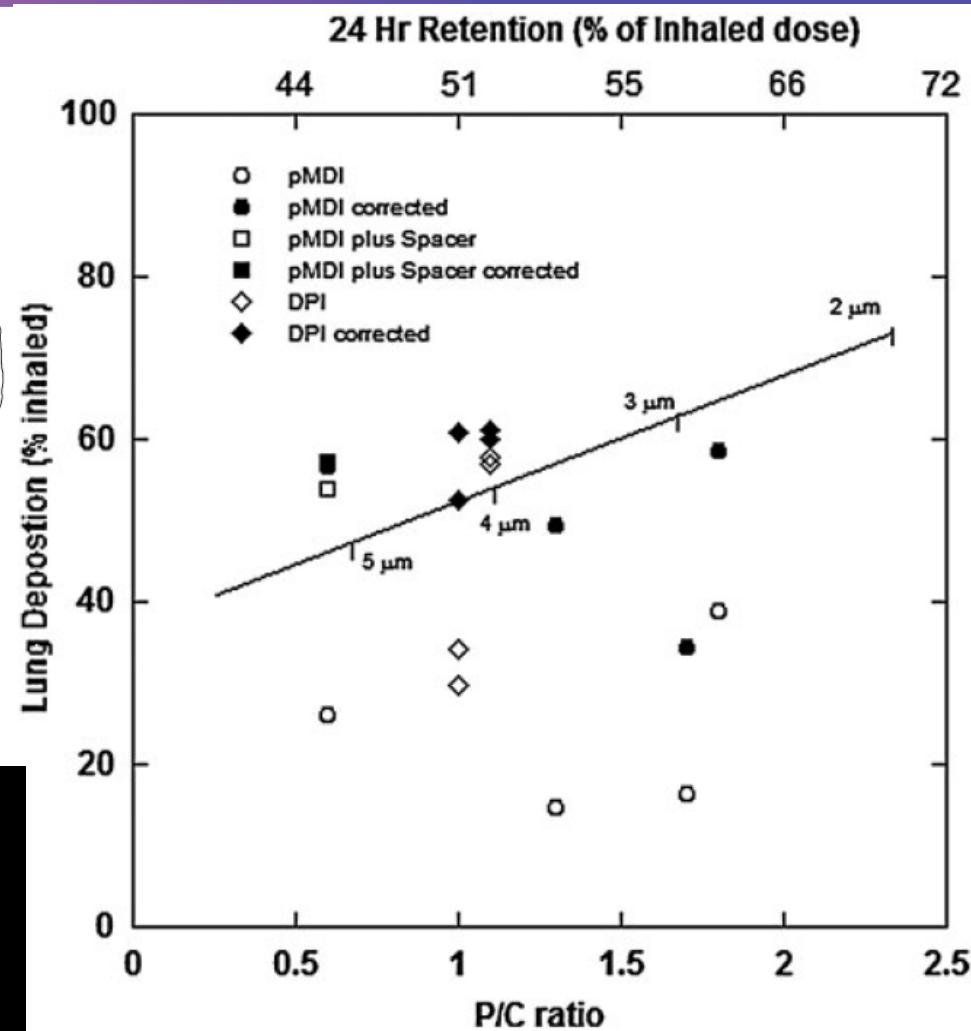
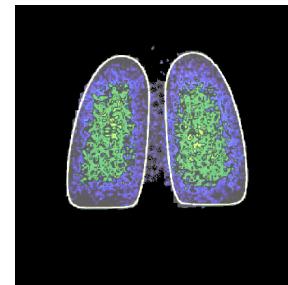
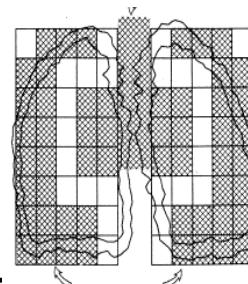
Table 3 Composition of lung lining fluid in conducting airways and respiratory zone (from (Eixarch et al. 2010) and (Hastedt 2014))

	Conducting airways	Respiratory Zone
Principal lining fluid	Mucus	Surfactant
Composition of fluid layer	1 % inorganic salts 1 % proteins 2 % glycoproteins (mucins) 1 % lipids 95 % water	85 % phospholipids 5 % cholesterol 10 % surfactant proteins (e.g., SP-A, SP-B, SP-C, SP-D)
Layer thickness	3–15 µm (decreases in thickness in lower airways)	~0.07 µm
Approximate volume	10–30 ml	7–20 ml

Hastedt, J. E.; Bäckman, P.; Clark, A. R.; Doub, W.; Hickey, A.; Hochhaus, G.; Kuehl, P. J.; Lehr, C.-M.; Mauser, P.; McConville, J.; Niven, R.; Sakagami, M.; Weers, J. G. *AAPS Open* 2016, 2, 1.

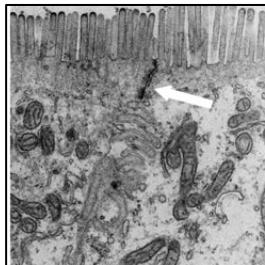
REGIONAL DEPOSITION & PARTICLE SIZE

- The mouth and oropharynx “prefilter” the aerosol.
- P/C of 1 is a reasonable first approximation for modeling regional deposition of dose.
- For “true” aerosol lung dose:
 - 50% central
 - 50% peripheral

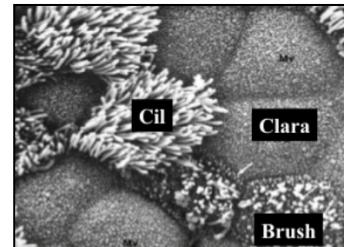


PERMEABILITY MODELS

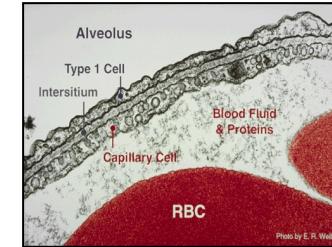
	Cell Culture Model
GI	
Intestines	Caco-2
Lung	
Central Airways – ciliated bronchial	Calu-3 16HBE14o
Peripheral Airways – alveolar, type I	pAEpC



Caco-2

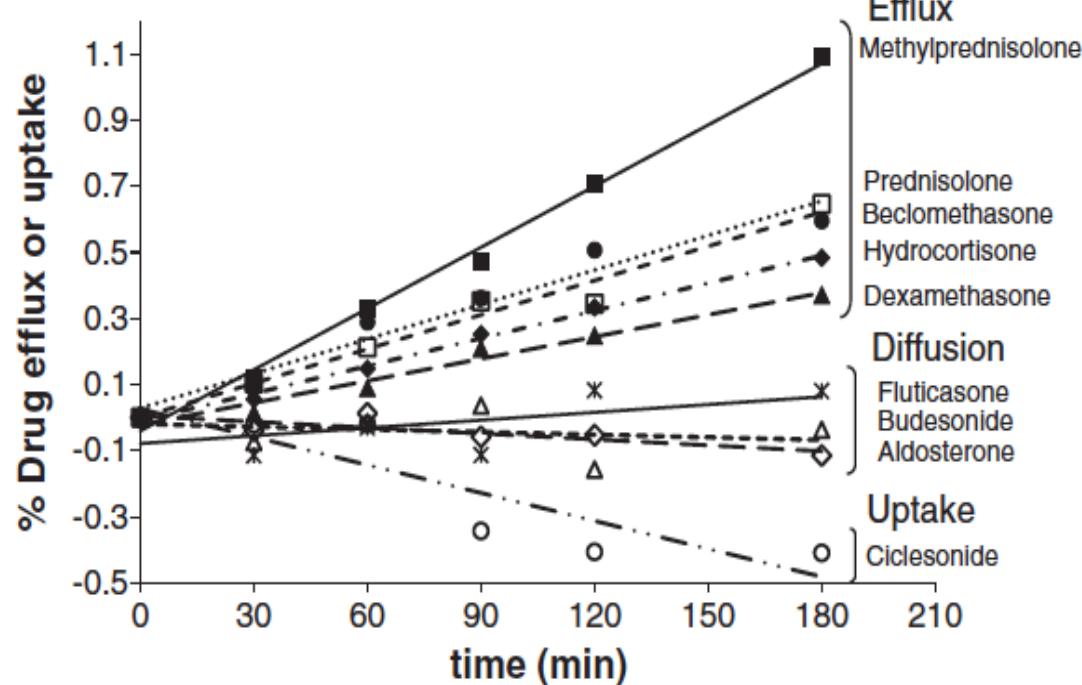


Calu-3



pAEpC

Crowe, A.; Tan, A. M. *Toxicol. Appl. Pharmacol.* 2012, 260, 294–302.



PHARMACOKINETICS AND PHARMACODYNAMICS OF INHALED CORTICOSTEROIDS (ICS)

TABLE 1. PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF INHALED AND INTRANASAL CORTICOSTEROIDS

Corticosteroid	RRA	F_{oral} (%)	fu (%)	CL (L/h)	Vd_{ss} (L)	$t_{1/2}$	Ref.
						elim./(h)	
MF	2,300	< 1	1–2	54	—	5.8	11, 13, 23, 55
FP	1,800	< 1	10	66–90	318–859	7–8	12, 21, 57, 63, 64, 68
BDP	53	15–20	13	150	20	0.5	12, 22, 24, 58
17-BMP	1,345	26	—	120	424	2.7	12, 22
B	76	—	—	—	—	—	12
CIC	12	< 1	< 1	152	207	0.36	14, 25, 54, 65, 71
Des-CIC	1,200	< 1	< 1	228	897	3.4	14, 25, 54, 65, 71
BUD	935	11	12	84	183–301	2.8	12, 26, 69
LE	430	—	10*	63*	37*	2.8*	15, 61
TA	233	23	29	37	103	2.0	12, 28, 60
FLU	180	20	20	57	96	1.3	12, 27, 59, 70

Definition of abbreviations: 17-BMP = beclomethasone monopropionate; B = beclomethasone; BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; CL = clearance; Des-CIC = des-ciclesonide; FLU = flunisolide; F_{oral} = oral bioavailability; FP = fluticasone propionate; fu = fraction unbound; LE = loteprednol etabonate; MF = mometasone furoate; RRA = relative receptor affinity; TA = triamcinolone acetonide; Vd_{ss} = volume of distribution at steady state, $t_{1/2}$ = half-life.

* In dogs.

Oral BA is low and compounds are highly bound.

SOLUBILITY AND DOSE: INHALED THERAPEUTICS ARE HYDROPHOBIC POTENT DRUGS

Class	Drug	Mol Wt (g/mol)	Max Dose (mcg)	Aqueous Solubility (mcg/mL)	Log P	$V_{(sol)}$ @ (mL)
ICS	Budesonide	430.5	720	16	2.8	45
	Fluticasone propionate	500.6	1000	0.14	4.1	7143
	Beclomethasone dipropionate*	521	640	0.13	1.3	4923
	Mometasone furoate	521.4	880	0.1	4.5	8800
	Ciclesonide*	540.7	640	0.09	5.3	7046
LABA	Salmeterol xinafoate	603.7	50	80	3.9	0.63
	Indacaterol maleate	508.6	75	230	3.3	0.33
	Formoterol fumarate	840.9	40	11,000	1.6	0.0036

*Prodrugs

@Based on maximum dose – not lung dose