

2019 KSCPT Spring Meeting Pre-course Workshop

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

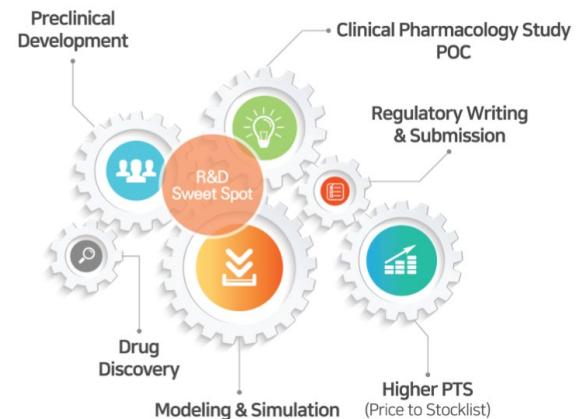
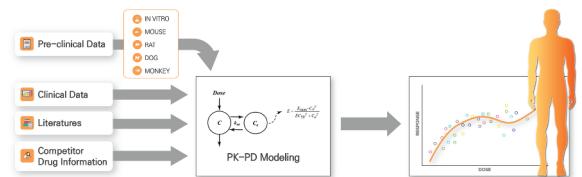


주요 *in vitro* 정보와 이를 활용한 인간 약동학 예측 이론

Suein Choi, MD
Resident

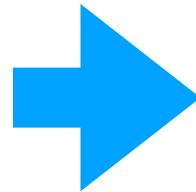
PIPET

Dept. of Clinical Pharmacology & Therapeutics /
The Catholic Univ. of Korea Seoul St.Mary's Hospital



What is Dallphin-AtoM

- Drugs with
- ALLometry and
- Physiology
- INside
- Animal to
- huMan



PBPK software for human
PK parameters prediction

using physicochemical
properties, in vitro and
animal PK data

Objective

In vitro data

LogP

C_b/C_p

f_u

pKa

P_{app}

CL_{met}

Animal in vivo PK

CL_h

V_c

V_p

CL_r

Q

Output

Human PK parameter

Clearance (CL)

Central volume (V_c)

Peripheral volume (V_p)

Intercompartment clearance (Q)

Absorption rate constant (k_a)

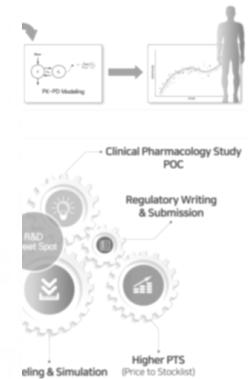
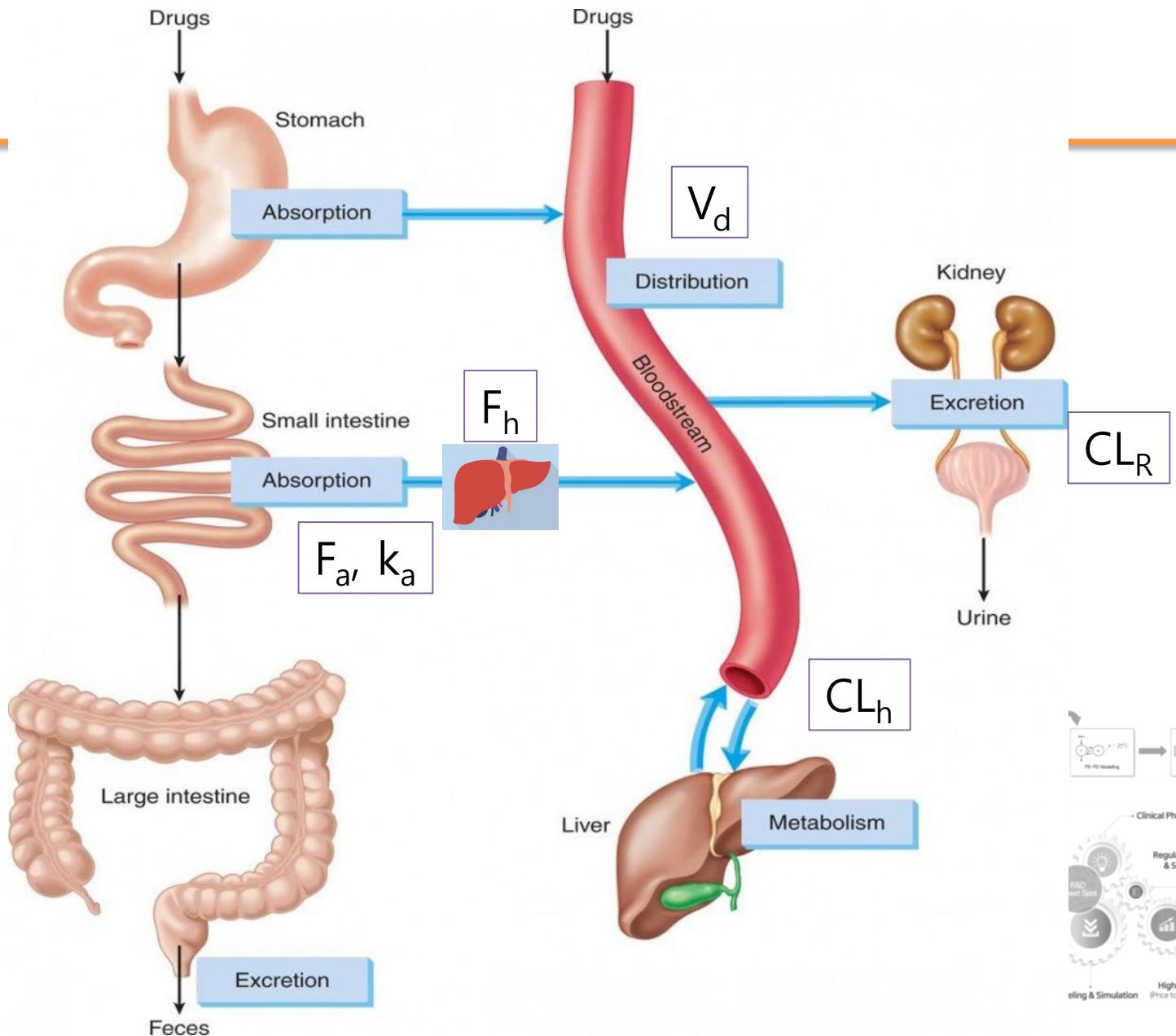
Bioavailability (F)

V_{ss}



Pharmacology Study





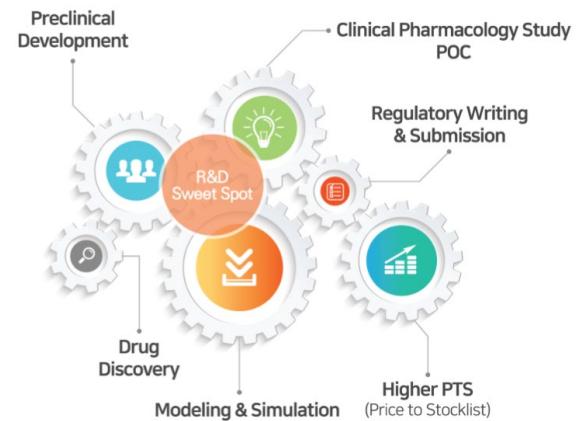
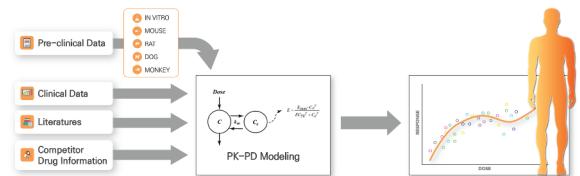
2019 KSCPT Spring Meeting Pre-course Workshop

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information



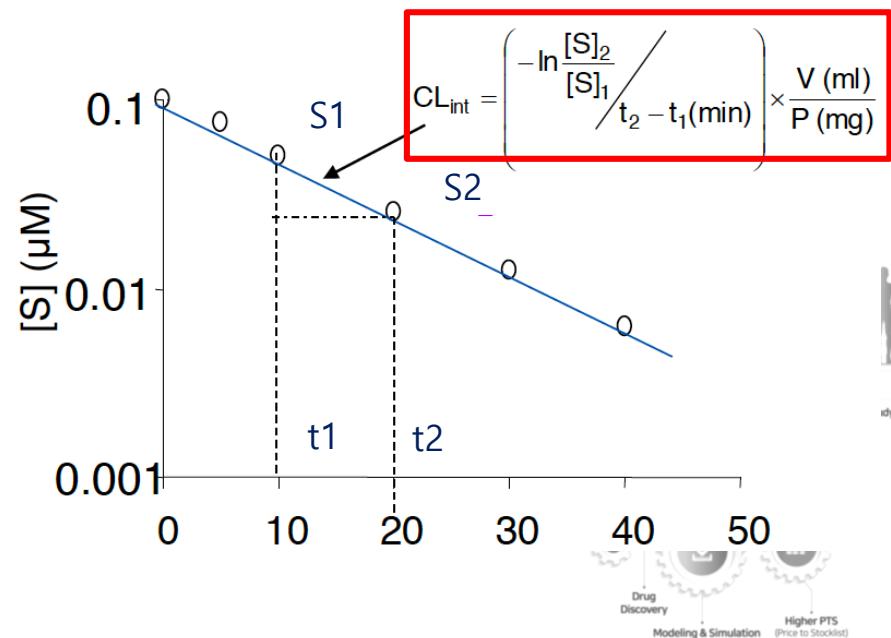
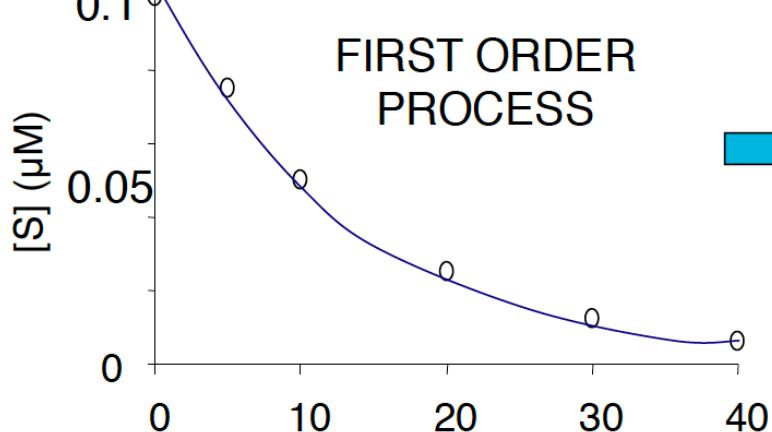
Clearance (CL)

Hepatic CL + Renal CL



Which *in vitro* system?

- Subcellular tissue fractions (HLM, HLC, HLS9)
- Recombinantly expressed system (rhCYP)
- Hepatocyte



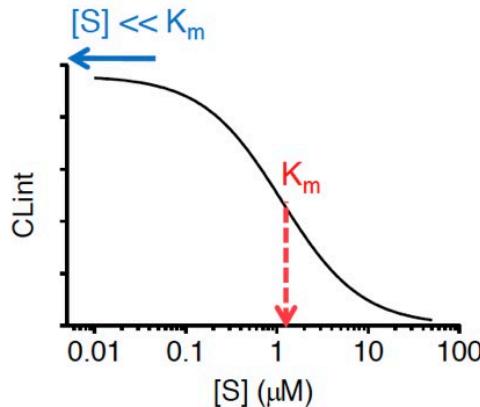
Determination of intrinsic clearance



$$CL_{U\text{int}} = CL_{\text{int}} / fu_{\text{inc}}$$

Nonspecific binding

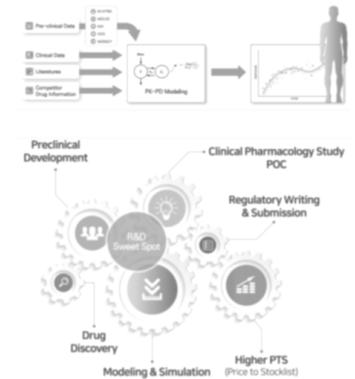
In vitro $CL_{U\text{int}}$



**Incubation conditions
(Time, [P] and [S]):**

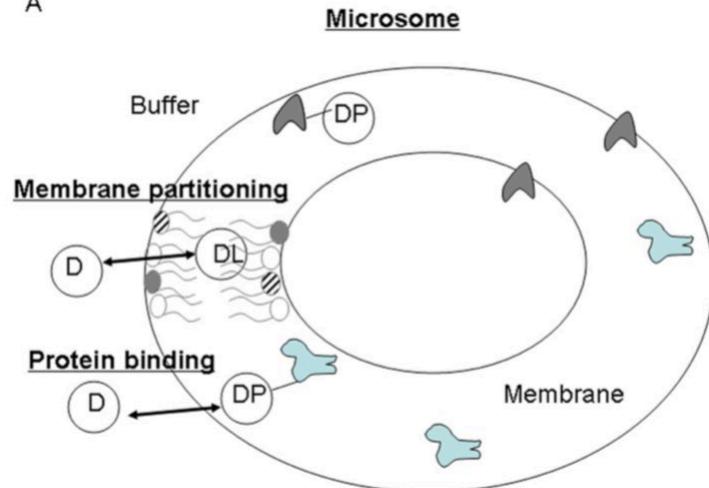
- $[S] \ll Km$
- Significant substrate loss ($> 20\%$)

- Binding is non-specific
- System is non-saturable microsome-buffer phase equilibrium



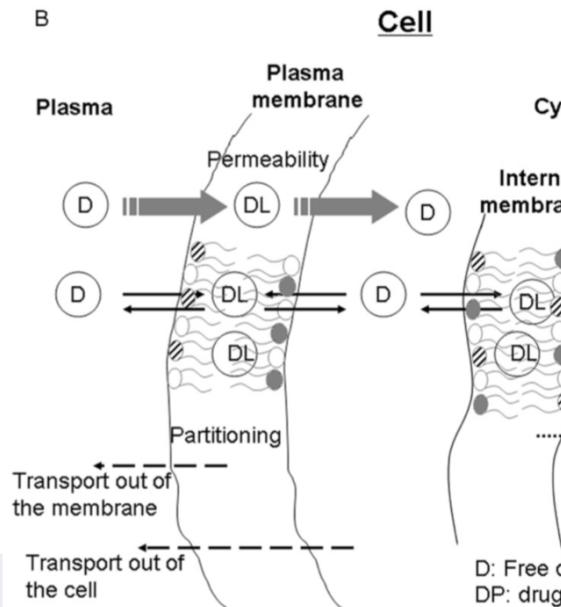
Nonspecific binding

A



$$fu_{inc(\text{microsome})} = 1/(1+P \cdot 10^{0.072*(\log P/D)^2 + 0.067\log P/D - 1.126})$$

B



D: Free drug
DP: drug bound to protein
DL: Drug partitioned into lipid

$$fu_{inc(\text{hepatocyte})} = 1/(1+125*V_R \cdot 10^{0.072*(\log P/D)^2 + 0.067\log P/D - 1.126})$$

Sequestration – CL underestimation

- Protein binding
- **Membrane partitioning – Hydrophobicity ($\log P/D7.4$)**
- Binding experimental apparatus

Hallifox and Houston (2006)

Drug Information PK-PD Modeling

Preclinical Development Clinical Pharmacology Study POC

R&D Project Management

Regulatory Writing & Submission

LogP for acidic/neutral drug
LogD7.4 for base drug

P for microsomal protein concentration

V_R for cell/incubation volume ratio

LogD7.4 prediction

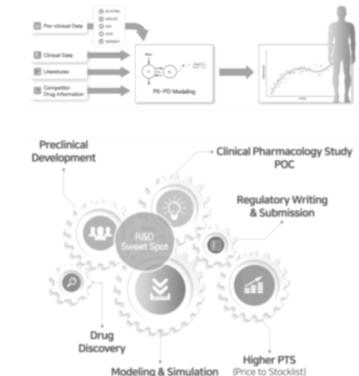
- Log P
- Log D – pH7.4 : Distribution coefficient at pH7.4 (pH dependent)

$$\log P_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}^{\text{un-ionized}}}{[\text{solute}]_{\text{water}}^{\text{un-ionized}}} \right)$$

$$\log D_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}^{\text{ionized}} + [\text{solute}]_{\text{octanol}}^{\text{un-ionized}}}{[\text{solute}]_{\text{water}}^{\text{ionized}} + [\text{solute}]_{\text{water}}^{\text{un-ionized}}} \right)$$

- LogD prediction using Henderson Hasselbach equation

- $\log D_{\text{acids}} \cong \log P + \log \left[\frac{1}{1 + 10^{pH - pK_a}} \right],$
- $\log D_{\text{bases}} \cong \log P + \log \left[\frac{1}{1 + 10^{pK_a - pH}} \right].$

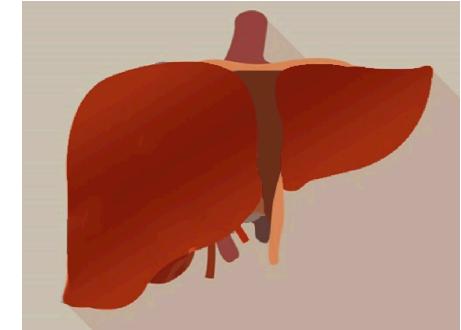


Scaling factor for human IVIVE



In vitro CL_{int}

CL_{int} per g Liver



CL_{int} per Liver

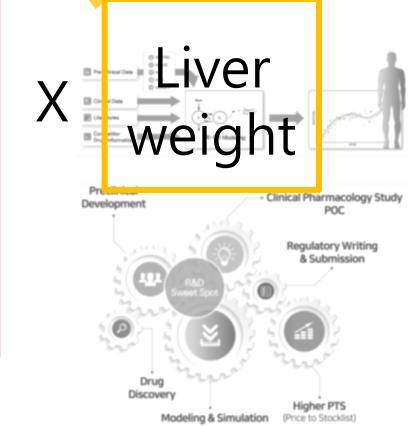
$$\text{Hepatocyte } \frac{\mu\text{L}/\text{min}}{10^6 \text{ cells}}$$
$$\text{Microsome } \frac{\mu\text{L}/\text{min}}{\text{mg protein}}$$

X

HPGL
(Hepatocytes per gram Liver)

X

MPPGL
(Microsome protein per g Liver)

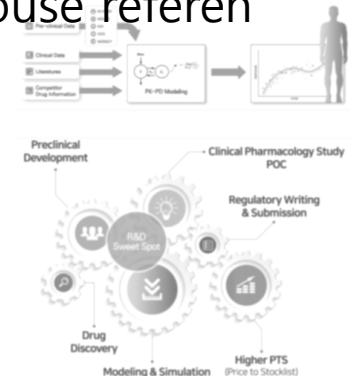


Passive clearance (CL_{pass})

$$CL_{pass} = P_{app} \times 2 \times SA_{HHEP} \rightarrow \text{MDCK-II cell Papp !!}$$
$$CL_{int,app} = (CL_{int,met} + CL_{int,bile}) \times \frac{CL_{int,uptake} + CL_{int,pass}}{CL_{int,met} + CL_{int,bile} + CL_{int,pass} + CL_{int,efflux}}$$

- Microsome : tends to overpredict the CL
(Passive clearance shall be applied)
- If MDCK-II cell Papp is not available,
Caco-2 cell Papp or logD7.4 value is used for prediction (In-house reference data)

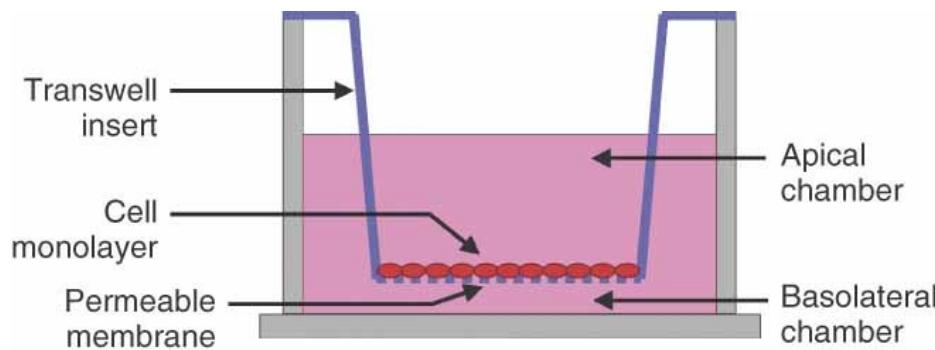
$$\begin{aligned} \log_{10}(CL_{pass}) &= \log D_{7.4} \times 0.6032 - 0.1509 \\ \log_{10}(P_{app}) &= \log D_{7.4} \times 0.4773 - 5.843 \end{aligned}$$



Rui Li, Yi-An Bi (2014)

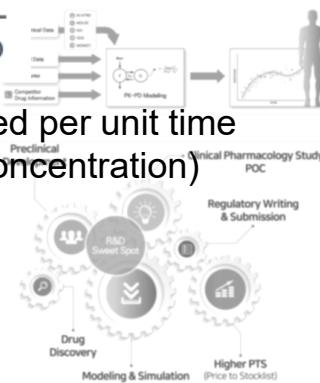
In vitro permeability models

Non-cellular systems	Cell model systems		
PAMPA	Caco-2	MDCK II	LLC-PK ₁
No transpoters	Relevant, variable tran sporter expression		Low endogenous transporters
High-throughput & re producible	Long cultivation, 14-2 8d	3 days	4-6 days



$$P_{app} = \frac{dQ}{dt} * \frac{1}{A * C_0}$$

dQ/dt : Mass removed per unit time
 C_0 : Force (driving concentration)
 behind the process
 A : Filter area



Lab-to-lab calibration (P_{app})

Table 3

P_{app} values of training set compounds from our laboratory and six different literature datasets.

Compounds	Apparent permeability coefficient ($P_{app} \times 10^{-6}$ cm/s)						
	Our laboratory	Alsenz et al. ^a	Irvine et al. ^a	Li et al. ^a	Zhu et al. ^a	Skolnik et al. ^a	Kerns et al. ^a
Antipyrine	11.32	54.3	150	35.7	28.2	–	12
Furosemide	0.25	0.31	0.14	1.3	0.12	1.29	0.086
Hydrochlorothiazide	0.37	0.42	0.92	1.5	0.51	1.81	0.75
Ketoprofen	10.53	24.36	93	34.7	–	18.49	20
Metoprolol	8.19	31.77	140	33.2	23.7	17.74	2.3
Naproxen	12.71	53.07	–	33.8	39.5	31.07	28
Propranolol	11.28	47.2	110	39.4	41.9	21.29	3.3
Ranitidine	0.37	0.67	–	2.1	0.49	2.51	0.47
Terbutaline	0.27	1.71	0.41	0.8	0.38	2.38	–
Verapamil	9.67	44.67	–	45.7	–	22.68	2.4
RMSE ^b	–	0.480	0.581	0.459	0.395	0.301	0.260

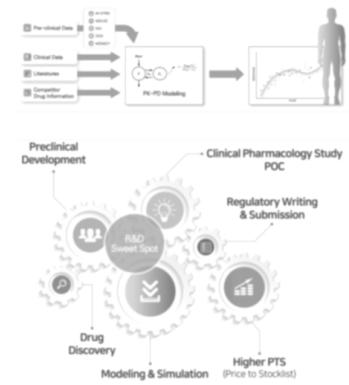
^a Values from Refs. [1–5,7].

^b Root mean square error between each set of P_{app} values and experimental results from our laboratory.

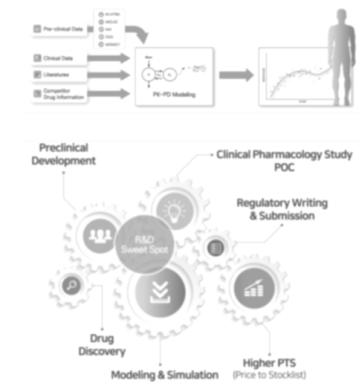
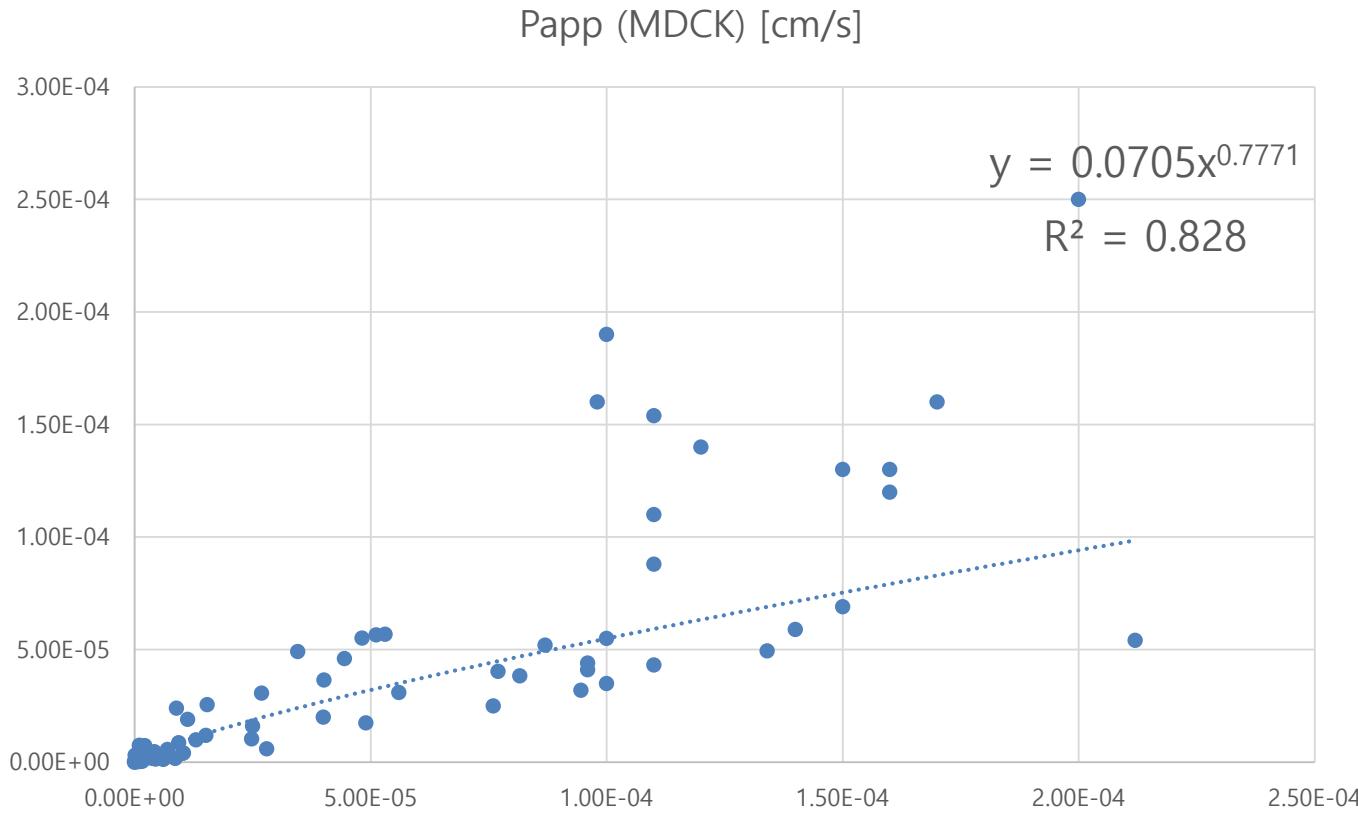
- Calibrator
 - Propranolol
 - Atenolol

$$P_{app(\text{corrected})} = P_{app(\text{measured})} \times$$

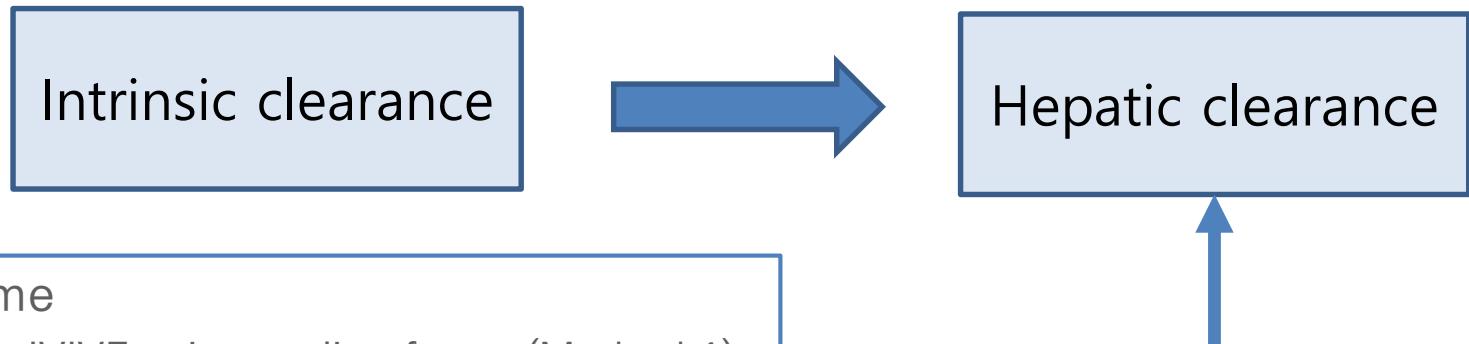
$$\frac{P_{app(\text{calibrator, reference})}}{P_{app(\text{calibrator, measured})}}$$



Prediction of MDCK-II cell P_{app}

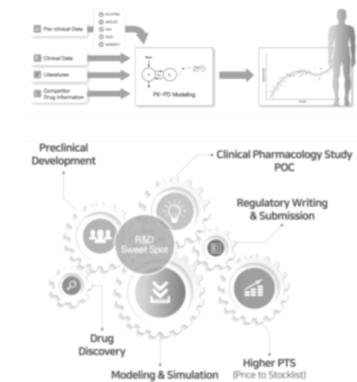


Intrinsic hepatic clearance

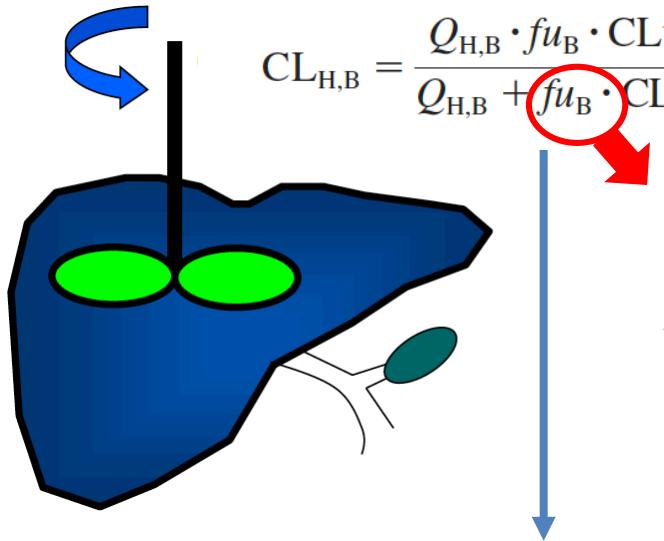


- Microsome
 - Direct IVIVE using scaling factor (Method 1)
 - Passive clearance applied (Method 2, 3)
- Hepatocyte
 - Direct IVIVE using scaling factor

Observed/Predicted ratio of hepatic clearance in rat



Hepatic clearance : Well-stirred model



$$CL_{H,B} = \frac{Q_{H,B} \cdot f_u \cdot CL_{u,int,H}}{Q_{H,B} + f_u \cdot CL_{u,int,H}}$$



$$CL_H = \frac{Q_{H,B} \cdot f_u \cdot CL_{u,int,H}}{Q_{H,B} + f_u \cdot CL_{u,int,H}/(C_B/C_P)}$$

$$= f_u/[C_B/C_P] = f_u/(B:P \text{ Ratio})$$

Assumed to be same as

$$C_{u, \text{ plasma}}/C_{\text{total(blood)}} = C_{u, \text{liver}} / C_{\text{total(blood)}}$$

Used for prediction of hepatic bioavailability

Q_H : Hepatic blood flow

$f_u/[C_B/C_P]$: Fraction of unbound in blood

$CL_{u,int}$: Unbound intrinsic clearance



Renal clearance

- Direct correlation corrected by plasma protein binding & Kidney blood flow

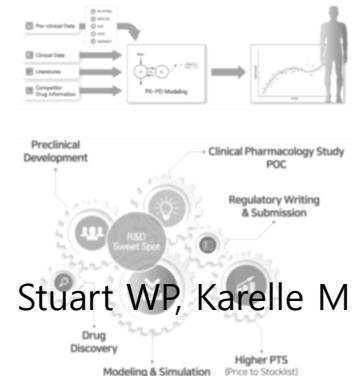
$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

- Simple allometry (Body weight)

$$CLr = a(W)^b$$

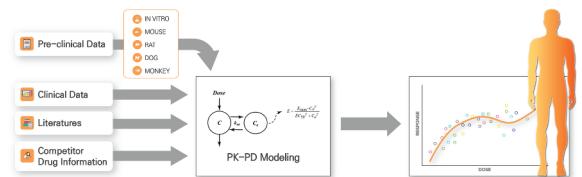
- Mahmood's renal clearance scaling method (GFR, KBF, Body weight, Kidney weight)

$$SSF = \frac{(\text{Glomerular filtration} \times \text{kidney blood flow})}{(\text{body weight} \times \text{kidney weight})}$$



Distribution (V_{ss})

Mechanistic prediction



Partition coefficient of tissues ($K_{\text{tissue:plasma}}$)

$$K_{Tp} = \frac{C_{\text{total}, T}}{C_{\text{total}, p}}$$

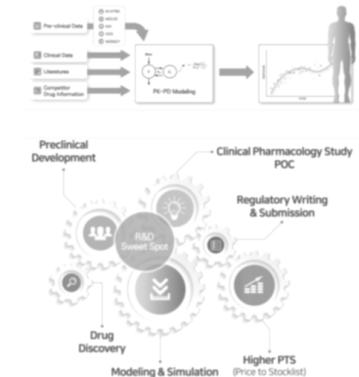
- Ratio of tissue total concentration and plasma total concentration

$$K_{p-\text{lean tissues}} = \frac{[P_{o:w-pH7.4}(V_{nl} + 0.3V_{ph}) + V_w/fu_t + 0.7V_{ph}]_{-\text{tissue}}}{[P_{o:w-pH7.4}(V_{nl} + 0.3V_{ph}) + V_w/fu_p + 0.7V_{ph}]_{-\text{plasma}}}$$

Phospholipid : 30% neutral lipid, 70% water

$$K_{p-\text{adipose}} = \frac{[D_{vo:w-pH7.4}(V_{nl} + 0.3V_{ph}) + V_w/fu_t + 0.7V_{ph}]_{-\text{tissue}}}{[D_{vo:w-pH7.4}(V_{nl} + 0.3V_{ph}) + V_w/fu_p + 0.7V_{ph}]_{-\text{plasma}}}$$

$$\boxed{\log K_{vo:w} = 1.115 \log P_{o:w} - 1.34}$$



Patrick Poulin , Sean Ekins, Frank-Peter Theil (2011)

Partition coefficient of tissues ($K_{\text{tissue:plasma}}$)

- Poulin & Theil

$$K_{p-\text{lean tissues}} = \frac{\left[P_{o:w-pH7.4} (V_{nl} + 0.3V_{ph}) + V_w + 0.7V_{ph} \right]_{-\text{tissue}}}{\left[P_{o:w-pH7.4} (V_{nl} + 0.3V_{ph}) + V_w + 0.7V_{ph} \right]_{-\text{plasma}}} * f_{u_p} / f_{u_t}$$

$$K_{p-\text{adipose}} = \frac{\left[D_{vo:w-pH7.4} (V_{nl} + 0.3V_{ph}) + V_w + 0.7V_{ph} \right]_{-\text{tissue}}}{\left[D_{vo:w-pH7.4} (V_{nl} + 0.3V_{ph}) + V_w + 0.7V_{ph} \right]_{-\text{plasma}}} * f_{u_p} / f_{u_t}$$

- Rodgers and Rowland (Ionized form – Unionized form)

$$K_{pu-\text{lean tissues}} = \frac{(1 + X*f_{iw}) + K_{AP}*C_{AP}*X + P_{o:w-pH7.4}*V_{nl} + (0.3P_{o:w-pH7.4} + 0.7)*V_{ph}}{1 + Y} + F_{ew}$$

$$K_{pu-\text{adipose}} = \frac{(1 + X*f_{iw}) + K_{AP}*C_{AP}*X + K_{vo:w-pH7.4}*V_{nl} + (0.3K_{vo:w-pH7.4} + 0.7)*V_{ph}}{1 + Y} + F_{ew}$$

Rodgers and Rowland

$$C_{u, \text{iwT}} = [B]_{u, \text{iwT}} + [BH^+]_{u, \text{iwT}}$$

For very weak monoprotic bases:

$$X = 1 + 10^{pK_a - pH_w}$$

$$Y = 1 + 10^{pK_a - pH_p}$$

For monoprotic acids:

$$X = 1 + 10^{pH_w - pK_a}$$

$$Y = 1 + 10^{pH_p - pK_a}$$

For neutrals, since there is no ionization:

$$x = y = 1$$

$$K_{Tp\mu} = \frac{Xf_{iwT}}{Y} + f_{ewT} + \left(\frac{P_{ow} \times f_{nlT} + (0.3P_{ow} + 0.7) \times f_{nplT}}{Y} \right) + \frac{1}{f_{up}} - 1 - \left(\frac{P_{ow} \times f_{nlpT} + (0.3P_{ow} + 0.7) \times f_{nplp}}{Y} \right) \times \frac{[\text{protein}]_T}{[\text{protein}]_p}$$

TRUDY RODGERS, MALCOLM ROWLAND
(2006)

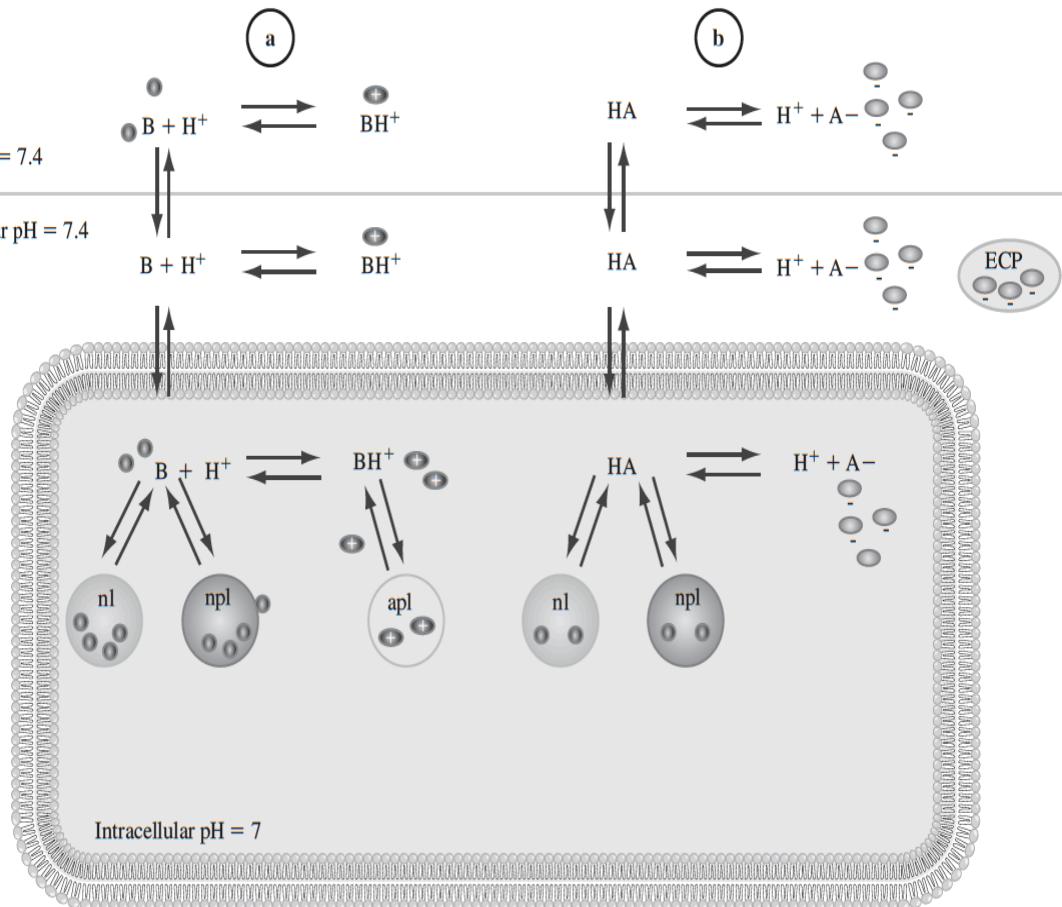


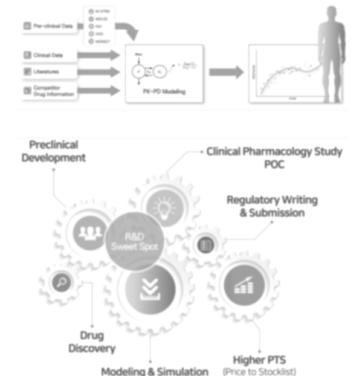
Figure 5.6. Binding of (a) moderate to strong bases to intracellular neutral lipids (nl), neutral phospholipids (npl) and acidic phospholipids (apl) and (b) acids to nl, npl, and albumin. Weak bases also bind to albumin. Lipophilic neutrals on the other hand bind to extracellular lipoproteins (ECP).

Unbound fraction in tissue

$$fu_t = 1 / \left(1 + \left(\left(\left(1 - fu_p \right) / fu_p \right) * R \right) \right)$$

- R : Average values of the tissue interstitial fluid-to-plasma ratio of albumin and lipoproteins

(R=0.5 for lean tissues, R=0.15 for adipose tissue)



V_{ss} prediction

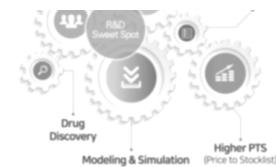
$$V_{ss} = V_p + \sum (V_t \times K_{pt})$$

Table A1

Physiological input parameters related to prediction methods of human V_{ss} . Values were reproduced from Poulin and Theil (2009).

Tissues	Tissue composition for human (fraction of tissue wet weight)							Tissue volume (l/kg) (V_t)
	Water (V _w)	Neutral lipids (V _{nl})	Neutral phospholipids (V _{ph})	Extracellular water (f _{ew})	Intracellular water (f _{iw})	Acidic phospholipids (mg/g) (C _{AP})	Albumin and lipoprotein ratio (R)	
Plasma	0.95	0.0032	0.0021	–	–	–	–	0.0450
Adipose	0.15	0.79	0.002	0.135	0.017	0.40	0.15	0.1490
Bone	0.45	0.074	0.0011	0.10	0.346	0.67	0.50	0.0976
Brain	0.78	0.051	0.0565	0.162	0.62	0.40	0.50	0.0213
Gut	0.76	0.0487	0.0163	0.282	0.475	2.41	0.50	0.0264
Heart	0.78	0.0115	0.0166	0.32	0.456	2.25	0.50	0.0044
Kidneys	0.76	0.0207	0.0162	0.273	0.483	5.03	0.50	0.0044
Liver	0.73	0.0348	0.0252	0.161	0.573	4.56	0.50	0.0360
Lungs	0.78	0.003	0.009	0.336	0.446	3.91	0.50	0.0131
Muscle	0.71	0.022	0.0072	0.079	0.63	2.42	0.50	0.4841
Skin	0.67	0.0284	0.0111	0.382	0.291	1.32	0.50	0.0804
Spleen	0.79	0.0201	0.0198	0.207	0.579	3.18	0.50	0.0029
Thymus	0.78	0.0168	0.0092	0.15	0.626	2.3	0.50	0.00056
Blood cells	0.63	0.0012	0.0033	–	0.603	0.57	–	0.0347

Patrick Poulin , Sean Ekins, Frank-Peter Theil (2011)



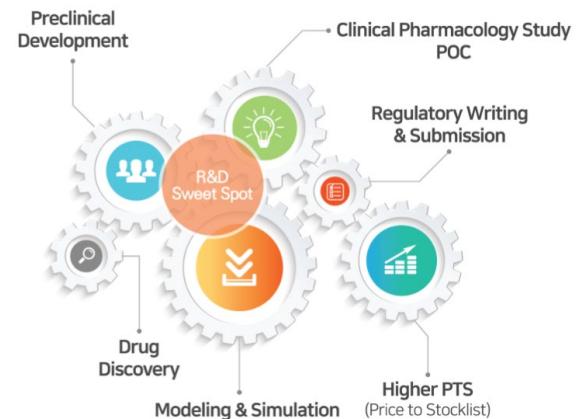
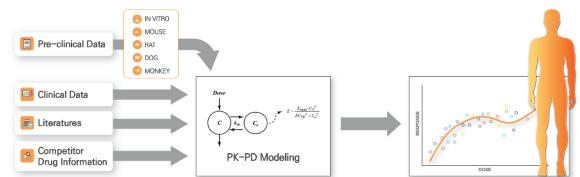
2019 KSCPT Spring Meeting Pre-course Workshop

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

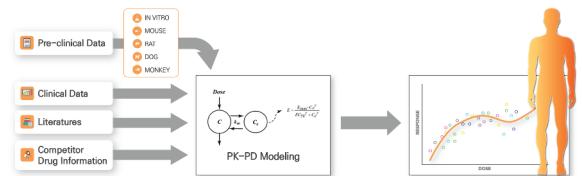


Absorption

k_a, F



Absorption rate constant (k_a)



Absorption rate constant

$$k_{a,eq} = \frac{P_m S}{V_c}$$

P_m : drug permeability across intestinal mucosa (Caco-2 Papp)
 S : absorptive surface area

$$\frac{dM_{pl}}{dt} = k_a M_{pl}$$

Absorption phase : absence of elimination

$$\frac{dM_i}{dt} = -k_d M_i$$

$$\rightarrow k_d = \frac{P_m S}{V_i} \quad K_d : \text{Disappearance rate constant}$$

$$-\frac{dM_i}{dt \times S} = P_m C_i = P_m \frac{M_i}{V_i}$$

$$-\frac{F_{FP} \times dM_i}{dt} = \frac{dM_{pl}}{dt}$$

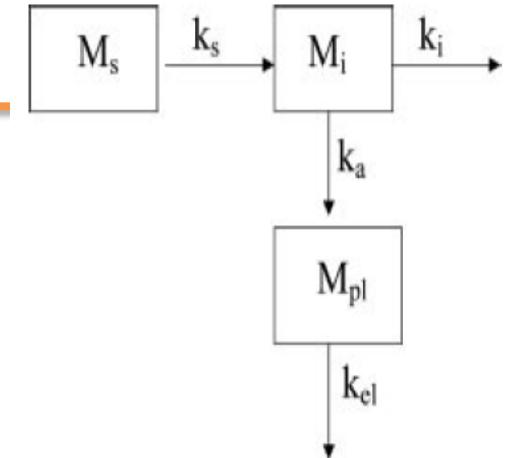
F_{FP} : First-pass extraction ($= F_g \times F_h$)



$$k_a = \frac{P_m S}{V_c} \times \frac{F_{FP} C_i}{C_{pl}} = 1 \text{ at equilibrium solution}$$

(Independent of drug concentration changes in intestine and plasma)

Helen H. Usansky (2005)



Absorption–Disposition kinetic model
(First order)

k_s : Gastric emptying
 k_i : Intestinal transit
 k_a : Absorption
 k_{el} : Elimination

$$\frac{dM_s}{dt} = -k_s M_s$$

$$\frac{dM_i}{dt} = k_s M_s - (k_i + k_a) M_i$$

$$\frac{dM_{pl}}{dt} = k_a M_i F_{FP} - k_{el} M_{pl}$$

Central volume (V_c)

- PBPK approach

$$V_{ss} = V_p + \sum (V_t \times K_{pt}) \quad \longrightarrow \quad V_c = V_{pl} + \sum_{i=1}^n K_{pl:Ti} V_{ti}$$

Well-perfused organ for V_c
(Lung, Kidney, Liver, spleen, heart, plasma, brain)

- Allometric approach



Helen H. Usansky (2005)

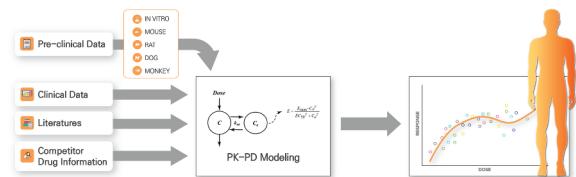
2019 KSCPT Spring Meeting Pre-course Workshop

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

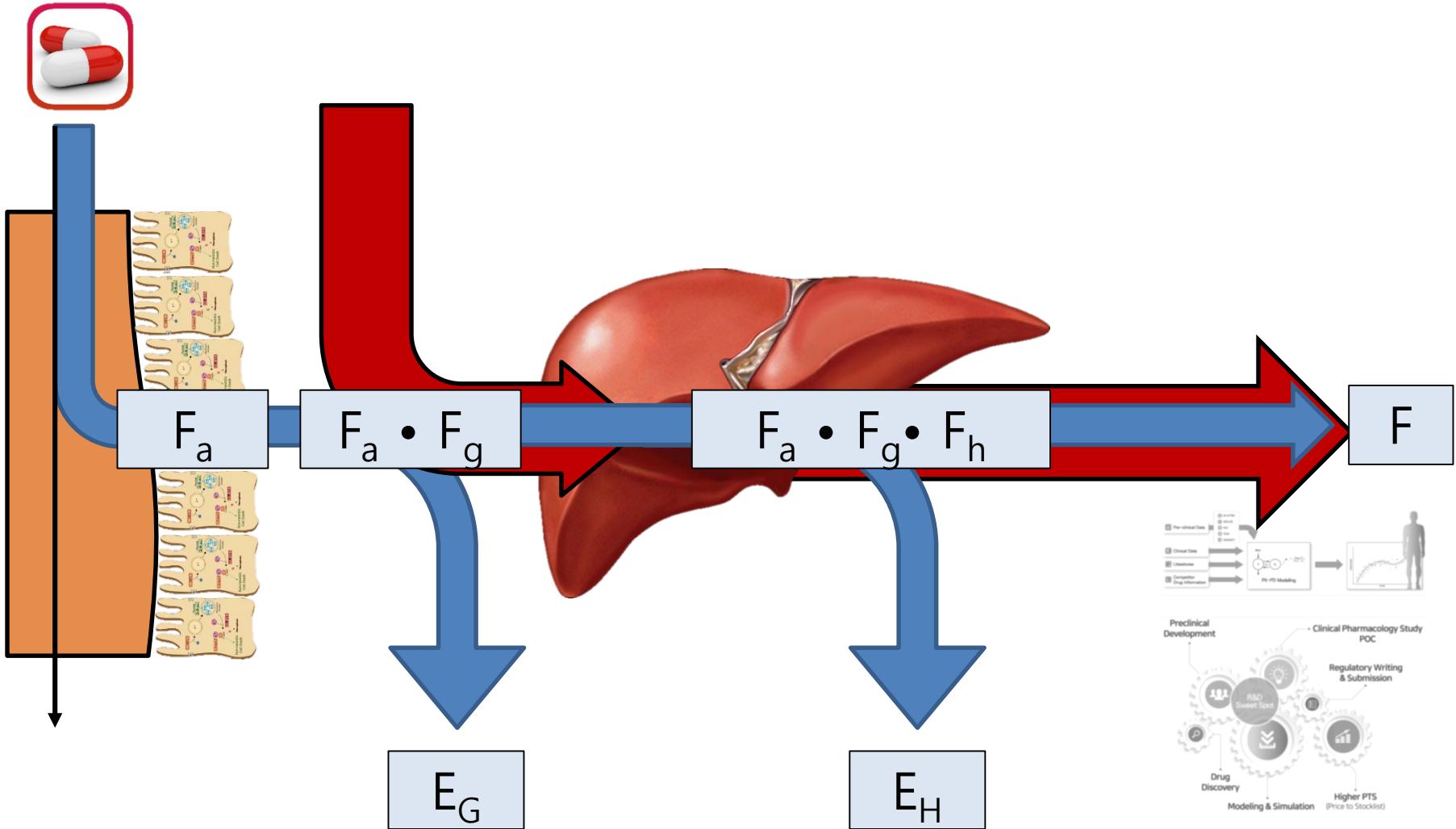


Absolute bioavailability (F)

$$F_a \times F_g \times F_h$$

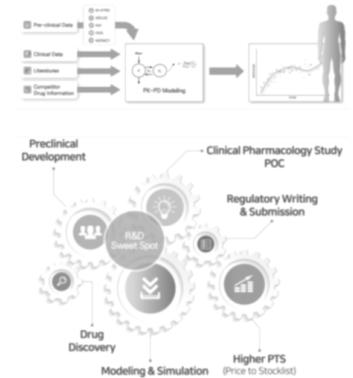


First pass effect



F_a (Fraction absorbed)

- Caco-2 cell (P_{app}) – Effective permeability
- Absorption rate constant
- PSA



F_a (Fraction absorbed)

- Caco-2 cell (Papp) – Effective permeability
- Absorption rate constant
- PSA

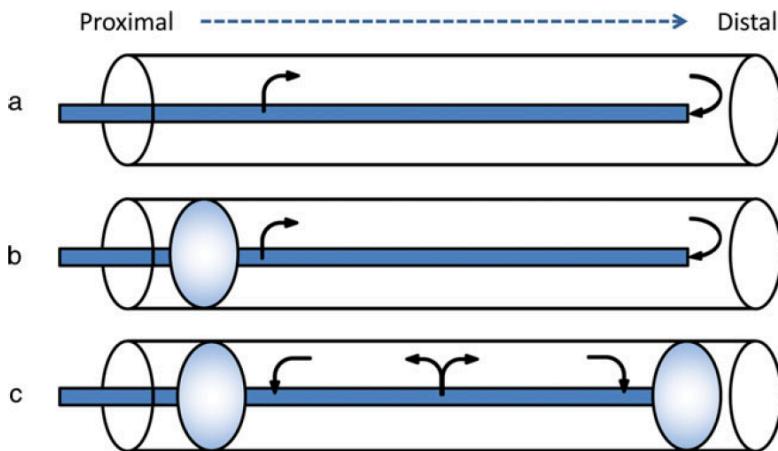
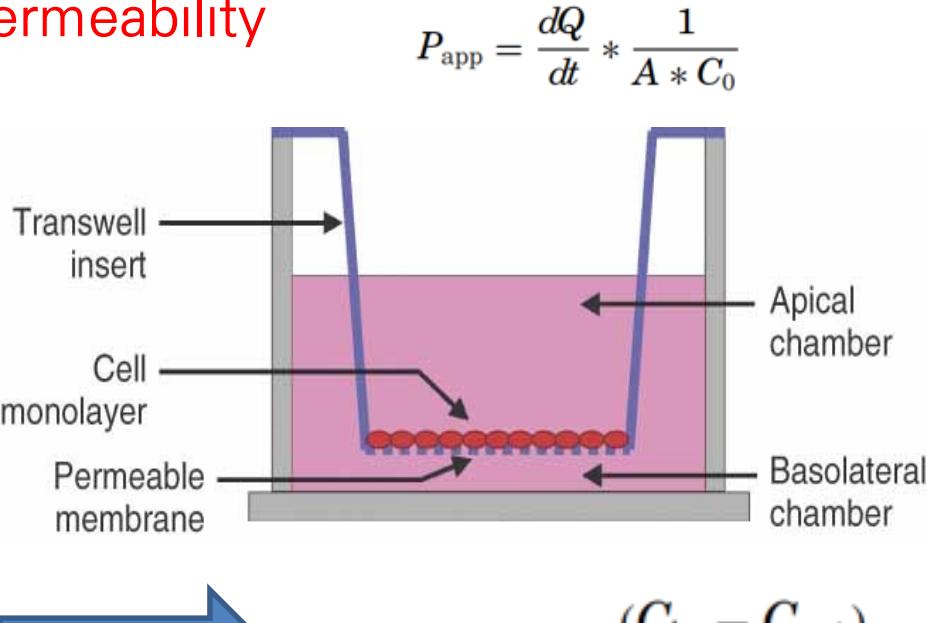


Figure 2. Schematic presentation of the clinical intestinal perfusion models. (a) The open perfusion system. (b) The proximal balloon perfusion system. (c) The double-balloon perfusion system.

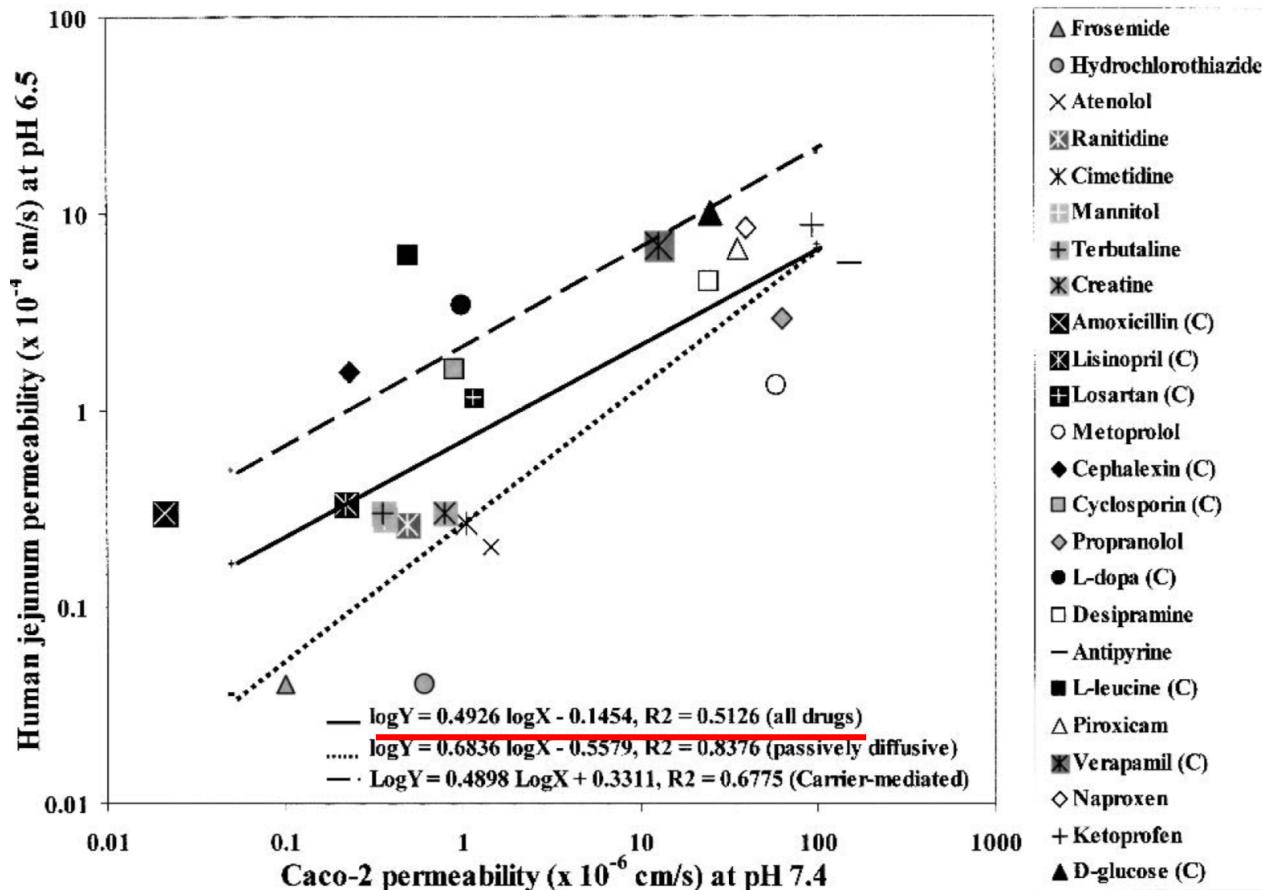


$$P_{\text{app}} = \frac{dQ}{dt} * \frac{1}{A * C_0}$$



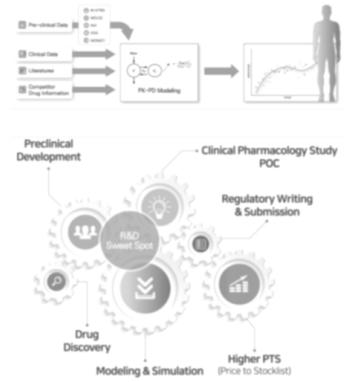
Effective permeability (P_{eff})

$$\text{Log}(P_{eff}) = 0.4926 * \text{Log}(P_{app}) - 0.1454$$



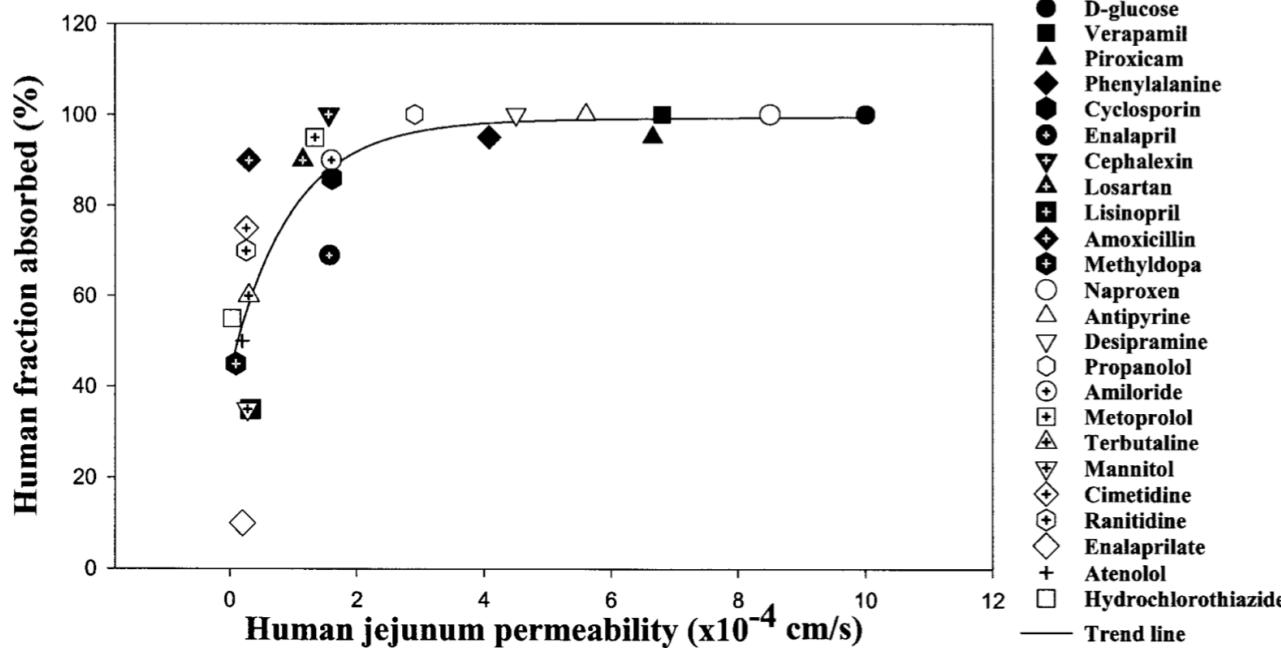
- Passively diffused
- Carrier-mediated

Duxin Sun, Hans Lennernas (2002)



Effective permeability (P_{eff})

$$F_a = 1 - e^{\left(\frac{-2P_{eff} \cdot T_{res}}{R}\right)}$$



Tres : transit time in human small intestine (3h)
R : the radius of human small intestine (2cm)

Duxin Sun, Hans Lennernas (2002)

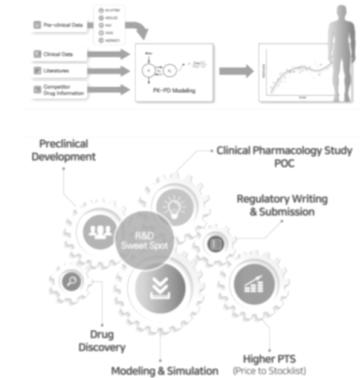
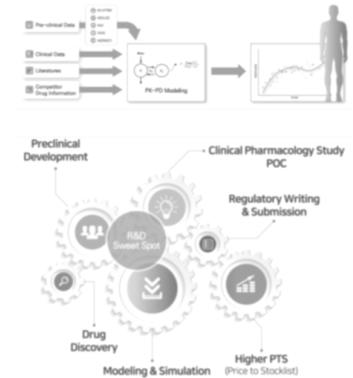


Fig. 7. Prediction of drug fraction absorbed using human jejunum permeability. Drugs are labeled with different symbols. Closed symbols are carrier-mediated absorbed drugs, while open symbols are passively absorbed drugs.

F_a (Fraction absorbed)

- Caco-2 cell (P_{app}) – Effective permeability
- Absorption rate constant
- PSA



F_a (Fraction absorbed)

- Caco-2 cell (P_{app}) – Effective permeability
- Absorption rate constant
- PSA



$$AUC = \int_0^\infty C dt = \lim_{s \rightarrow 0} \bar{C}$$

$$AUC_{i.v.} = \frac{D_{i.v.}}{V_d k_{el}}$$

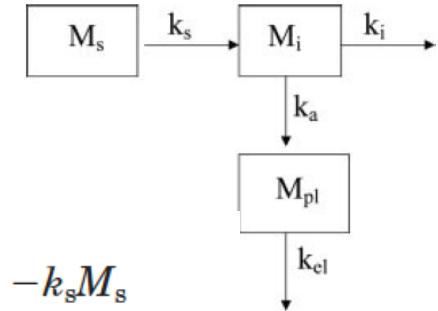
$$AUC_{oral} = \frac{k_{a,eq} F_{FP} D_{oral}}{V_d k_{el}(k_i + k_{a,eq})}$$

$$F_{oral} = \frac{AUC_{oral} D_{i.v.}}{AUC_{i.v.} D_{oral}} = \frac{k_{a,eq} F_{FP}}{k_i + k_{a,eq}}$$

$$F_{oral} = F_a \times F_{FP}$$

$$F_a = \frac{k_{a,eq}}{k_i + k_{a,eq}}$$

Helen H. Usansky (2005)



$$\frac{dM_s}{dt} = -k_s M_s$$

$$\frac{dM_i}{dt} = k_s M_s - (k_i + k_a) M_i$$

$$\frac{dM_{pl}}{dt} = k_a M_i F_{FP} - k_{el} M_{pl}$$

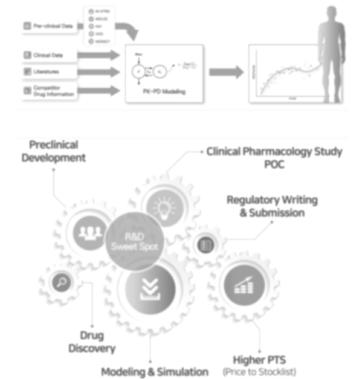


$$K_i = 5.025 * 10^{-3} \text{ min}^{-1}$$

S: the absorptive surface area of human intestine = 200 m²
 Ki : 1/the transit time in human small intestine (199 min)

F_a (Fraction absorbed)

- Caco-2 cell (P_{app}) – Effective permeability
- Absorption rate constant
- PSA



PSA

- Dynamic polar surface area (A^2)
~ Hydrogen bond
 - Dynamic molecular surface properties
: 3-dimensional shape of molecule +
Conformational flexibility
- Transcellular transport

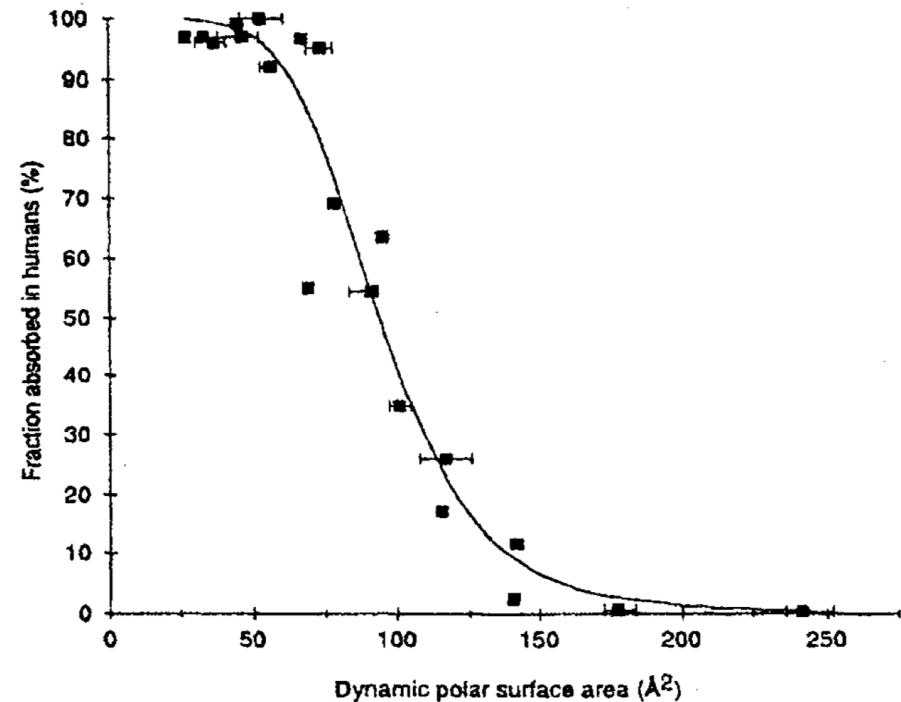
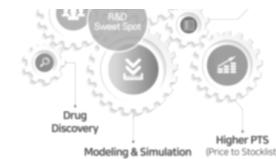


Fig. 1. Sigmoidal relationship between PSA_d of the 20 structurally diverse model drugs and absorption in humans after oral administration. PSA_d is presented as the dynamic mean value and the range of all low energy conformations.

$$Fa = 1 - \text{PSA}^{5.45}/(102^{5.45} + \text{PSA}^{5.45})$$

Katrin P, Patric S (1997)



F_g (fraction escaping gut clearance)

- Q_{gut} model

$$F_G = \frac{Q_{\text{Gut}}}{Q_{\text{Gut}} + fu_{\text{Gut}} \cdot CL_{\text{int,g}}}$$

$$Q_{\text{Gut}} = \frac{CL_{\text{perm}} \cdot Q_{\text{ent}}}{Q_{\text{ent}} + CL_{\text{perm}}}$$

- CYP3A substrate

F_G : Intestinal availability

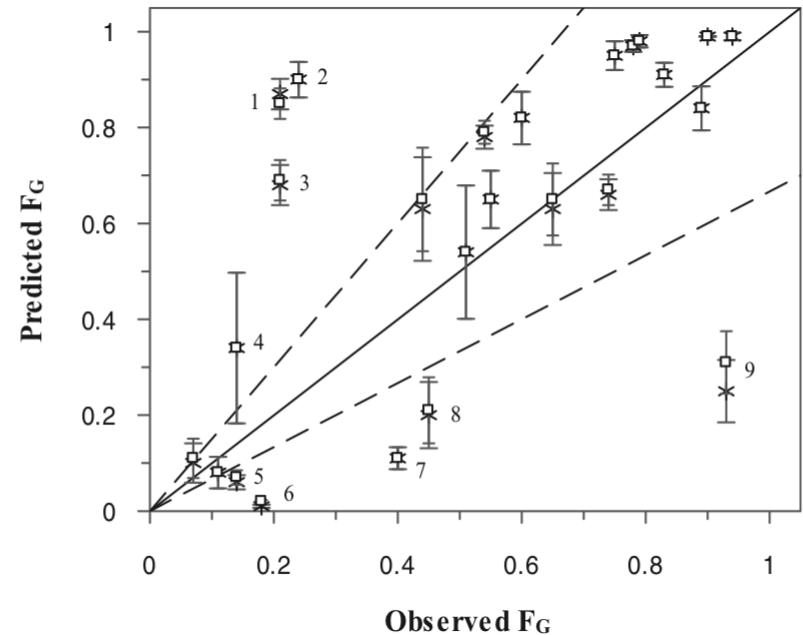
Q_{ent} : Mucosal epithelial blood flow (L/h) ~ 18L/h

CL_{int} : Unbound intrinsic clearance (microliters per minute per picomole CYP3A)

fu_{Gut} : Fraction unbound in the enterocytes (=1)

CL_{perm} : Permeability clearance (L/h)

(Product of intestinal surface area and apparent permeability = SA * Papp(Peff))



Fixed to 1



Michael Gertz, Anthony Harrison (2010)

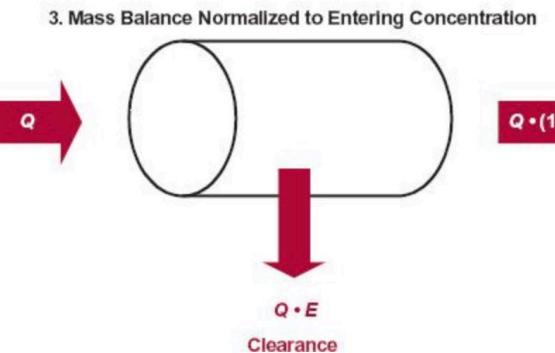
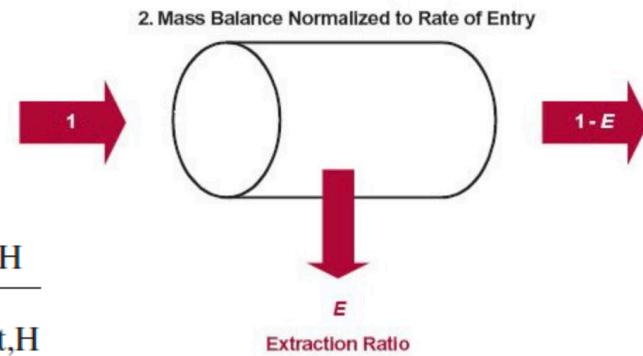
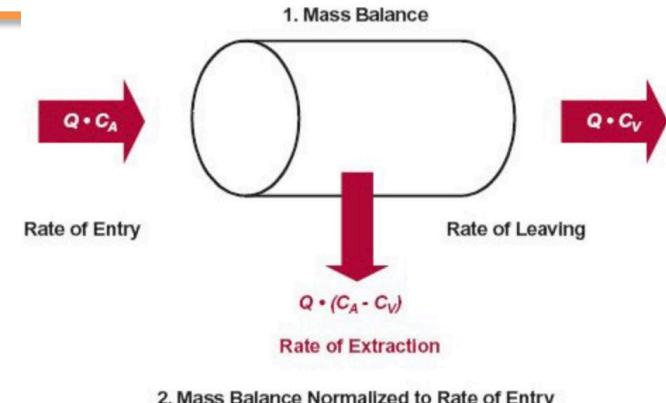
F_h (Fraction escaping hepatic clearance)

- Paired to hepatic blood clearance

$$CL_{H,B} = \frac{Q_{H,B} \cdot fu_B \cdot CLu_{int,H}}{Q_{H,B} + fu_B \cdot CLu_{int,H}}$$

- $F_h = 1 - \text{Extraction ratio}$ = $1 - CL_{H,B}/Q_{H,B}$

$$= 1 - \frac{fu_B \cdot CLu_{int,H}}{Q_{H,B} + fu_B \cdot CLu_{int,H}}$$



Objective

In vitro data

LogP

C_b/C_p

f_u

pKa

P_{app}

CL_{met}

Animal in vivo PK

CL_h

V_c

V_p

CL_r

Q

Output

Human PK parameter

Clearance (CL)

Central volume (V_c)

Peripheral volume (V_p)

Intercompartment clearance (Q)

Absorption rate constant (k_a)

Bioavailability (F)

V_{ss}

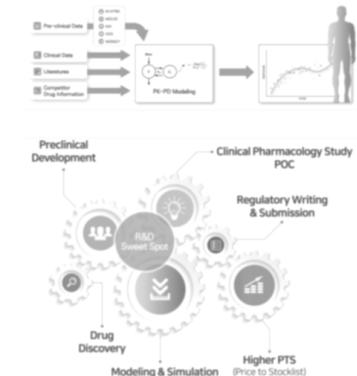


Pharmacology Study



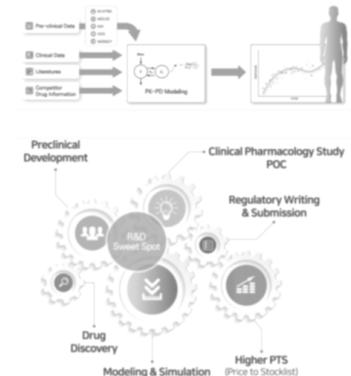
Reference

- SIMCYP Workshop (2017, Busan)
- Bittermann, K., & Goss, K. U. (2017). Predicting apparent passive permeability of Caco-2 and MDCK cell-monolayers: A mechanistic model. *PLoS One*, 12(12)
- Dahlgren, D., Roos, C., Sjogren, E., & Lennernas, H. (2015). Direct In Vivo Human Intestinal Permeability (P_{eff}) Determined with Different Clinical Perfusion and Intubation Methods. *J Pharm Sci*, 104(9), 2702–2726.
- Graham, H., Walker, M., Jones, O., Yates, J., Galetin, A., & Aarons, L. (2012). Comparison of in-vivo and in-silico methods used for prediction of tissue: plasma partition coefficients in rat. *J Pharm Pharmacol*, 64(3), 383–396.
- Jones, R. D., Jones, H. M., Rowland, M., Gibson, C. R., Yates, J. W., Chien, J. Y., Poulin, P. (2011). PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 2: comparative assessment of prediction methods of human volume of distribution. *J Pharm Sci*, 100(10), 4074–4089
- Kilford, P. J., Gertz, M., Houston, J. B., & Galetin, A. (2008). Hepatocellular binding of drugs: correction for unbound fraction in hepatocyte incubations using microsomal binding or drug lipophilicity data. *Drug Metab Dispos*, 36(7), 1194–1197.
- Li, R., Bi, Y. A., Lai, Y., Sugano, K., Steyn, S. J., Trapa, P. E., & Di, L. (2014). Permeability comparison between hepatocyte and low efflux MDCKII cell monolayer. *AAPS J*, 16(4), 802–809.
- Nagar, S., & Korzekwa, K. (2012). Commentary: nonspecific protein binding versus membrane partitioning: it is not just semantics. *Drug Metab Dispos*, 40(9), 1649–1652.
- O'Hagan, S., & Kell, D. B. (2015). The apparent permeabilities of Caco-2 cells to marketed drugs: magnitude, and independence from both biophysical properties and endogenous similarities. *PeerJ*, 3, e1405.
- Paine, S. W., Menochet, K., Denton, R., McGinnity, D. F., & Riley, R. J. (2011). Prediction of human renal clearance from preclinical species for a diverse set of drugs that exhibit both active secretion and net reabsorption. *Drug Metab Dispos*, 39(6), 1008–1013.



Reference

- Yang, J., Jamei, M., Yeo, K. R., Rostami-Hodjegan, A., & Tucker, G. T. (2007). Misuse of the well-stirred model of hepatic drug clearance. *Drug Metab Dispos*, 35(3), 501–502.
- Berezhkovskiy, L.M. (2005). Volume distribution at steady state for a linear pharmacokinetic system with peripheral elimination, *Journal of pharmaceutical sciences*, 93(6) 1628–1640
- Palm, K., Stenberg, P., Luthman, K., Artursson, P. (1997). Polar molecular surface properties predict the intestinal absorption of drugs in human, *Pharmaceutical research*, 14(5) 568–571
- Lee, J.B., Zhair, A., Taha, D.A., Zang, Z., Kagan, L., Kim, T.H., Kim, M.G., Yun, HY, fischer, P. M., Gershkovich, Pavel. (2017), Quantitative analysis of lab-to-lab variability in caco-2 permeability assays, *Eur J Pharm Biopharm*, 114(5) 38–42
- Poulin, P., Ekins, S., & Theil, F. P. (2011). A hybrid approach to advancing quantitative prediction of tissue distribution of basic drugs in human. *Toxicol Appl Pharmacol*, 250(2), 194–212.
- Rodgers, T., Leahy, D., & Rowland, M. (2005). Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci*, 94(6), 1259–1276.
- Usansky, H. H., & Sinko, P. J. (2005). Estimating human drug oral absorption kinetics from Caco-2 permeability using an absorption-disposition model: model development and evaluation and derivation of analytical solutions for $k(a)$ and $F(a)$. *J Pharmacol Exp Ther*, 314(1), 391–399.



2019 KSCPT Spring Meeting Pre-course Workshop

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information



경청해 주셔서 감사합니다.

주요 *in vitro* 정보와
이를 활용한 인간 약동학 예측 이론

