Computational oral absorption simulation: a theoretical framework and recent progresses

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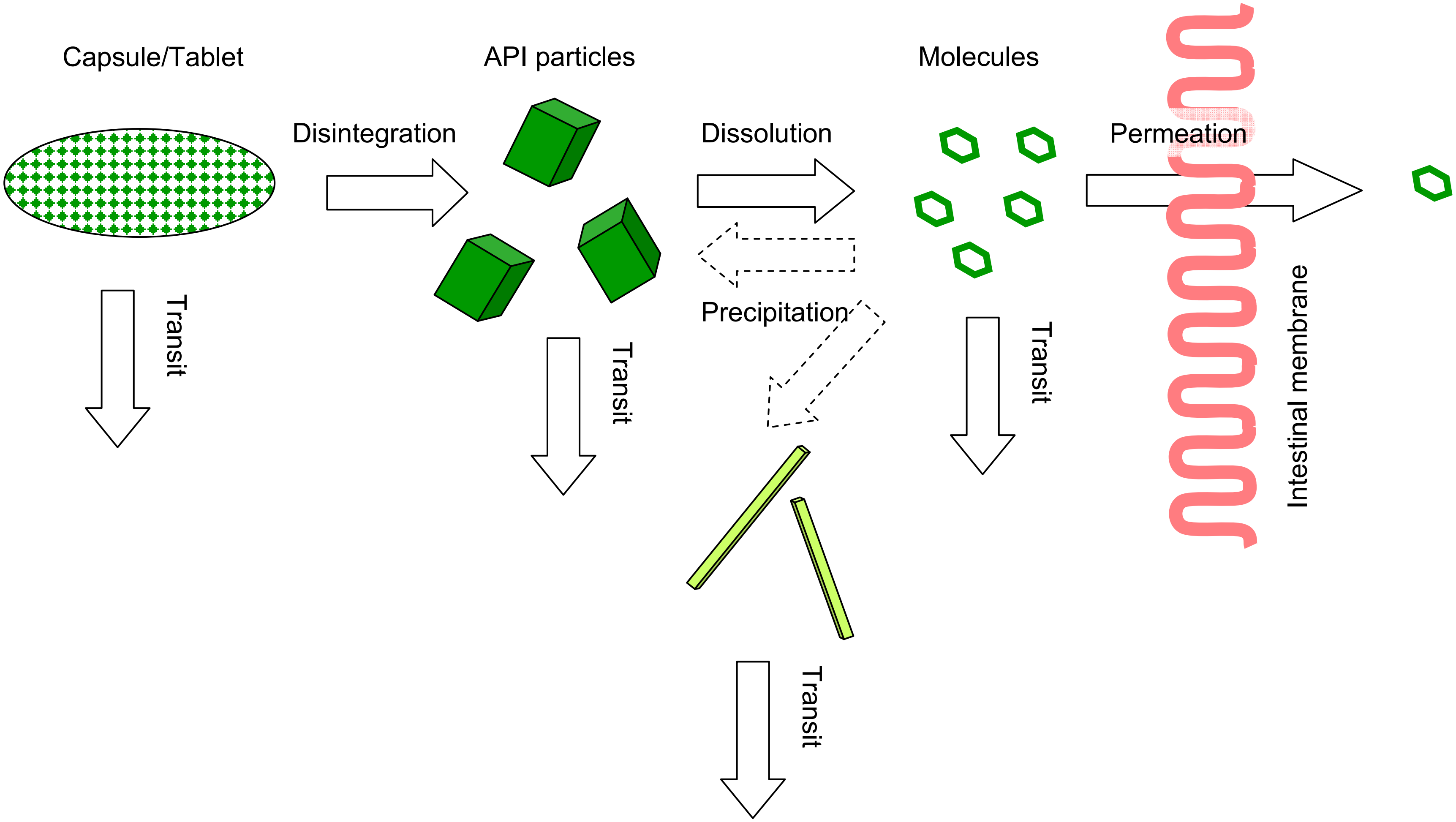
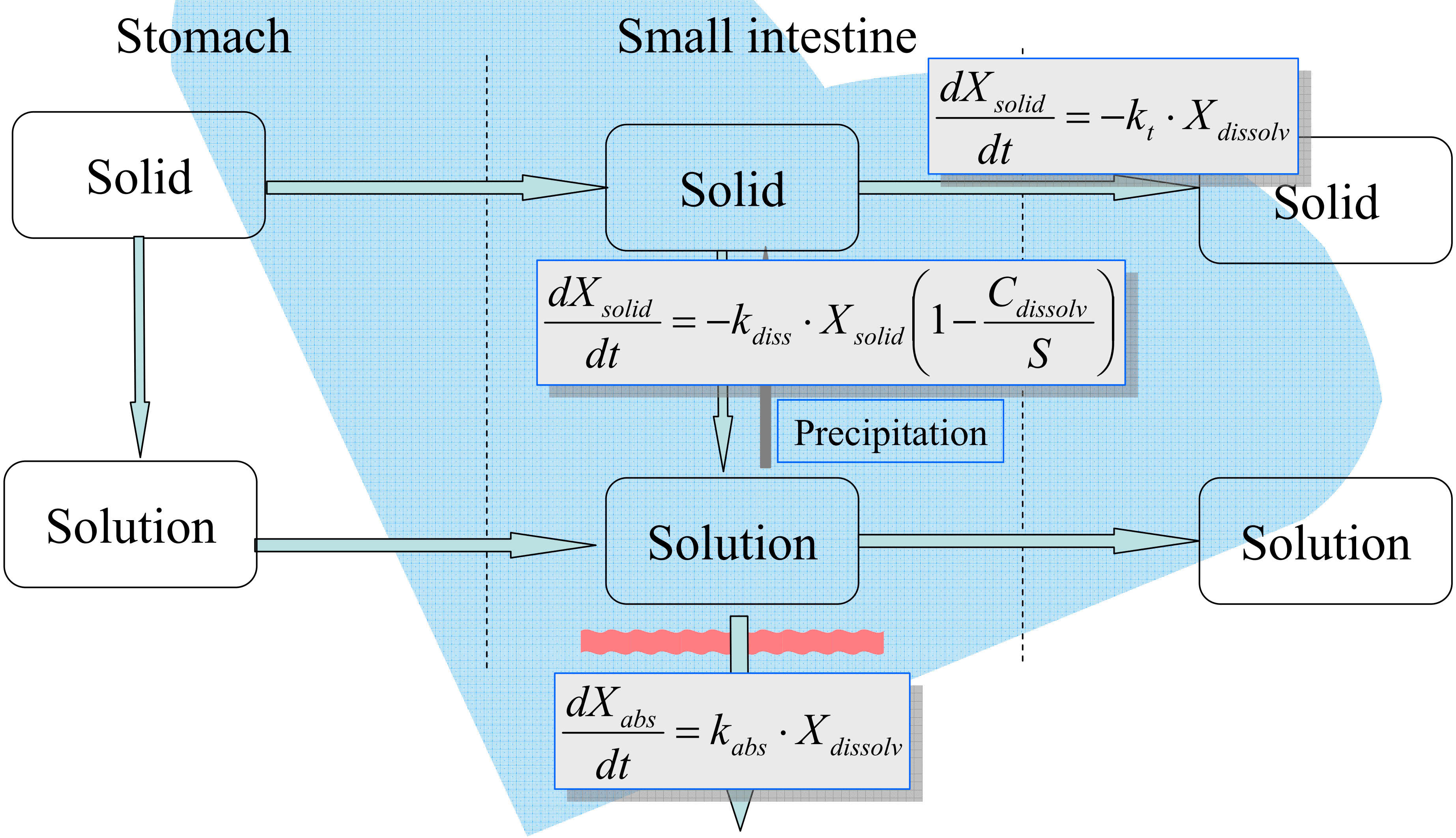
Oral absorption processes



Sugano, K. Expert Opin Drug Metab Toxicol 2009, 259-293

Central dogma



Stomach

Small intestine

$$\frac{dX_{solid}}{dt} = -k_t \cdot X_{dissolv}$$

Solid

Solid

Solid

$$\frac{dX_{solid}}{dt} = -k_{diss} \cdot X_{solid}\left(1-\frac{C_{dissolv}}{S}\right)$$

Precipitation

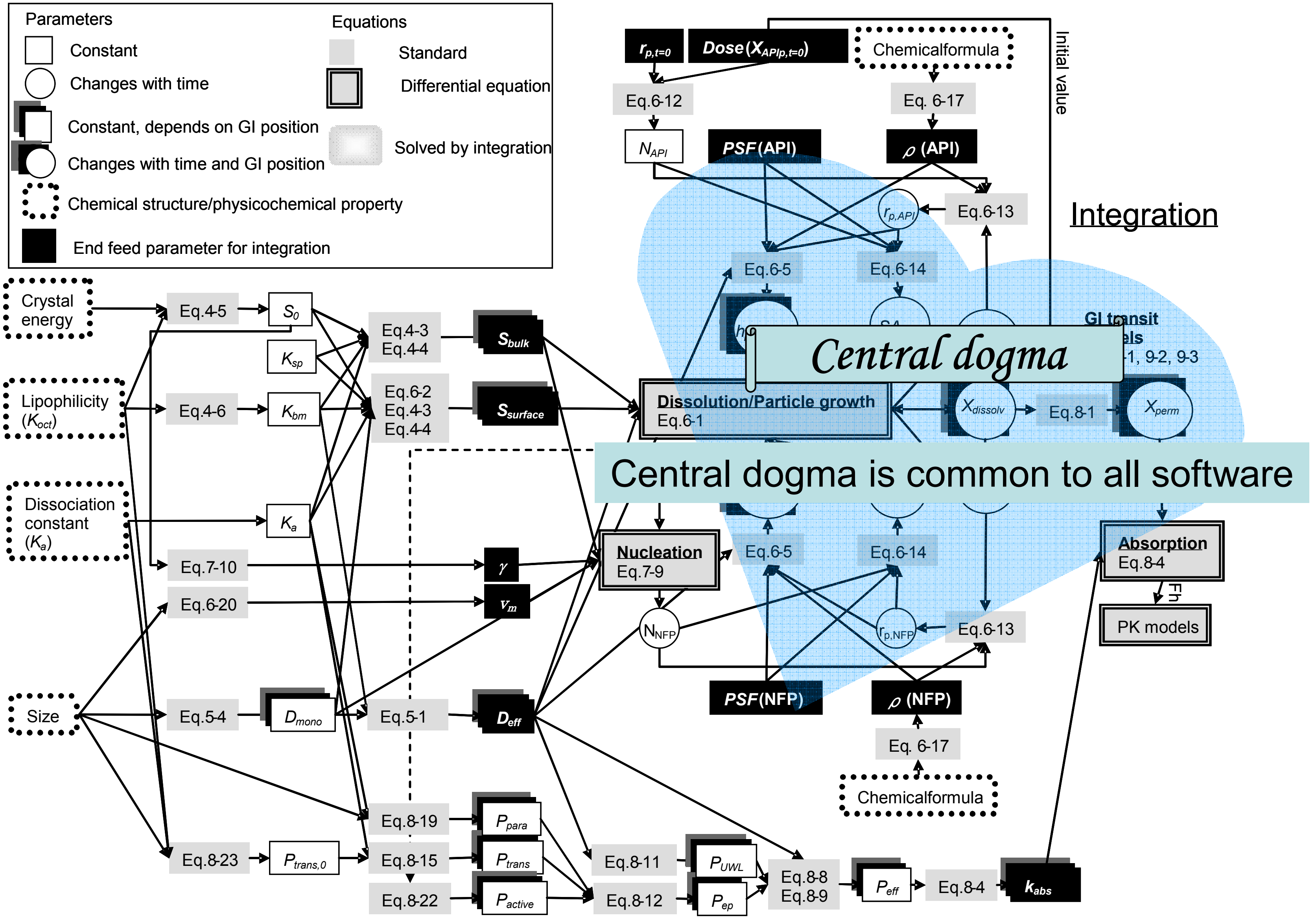
Solution

Solution

Solution

$$\frac{dX_{abs}}{dt} = k_{abs} \cdot X_{dissolv}$$

GUT framework

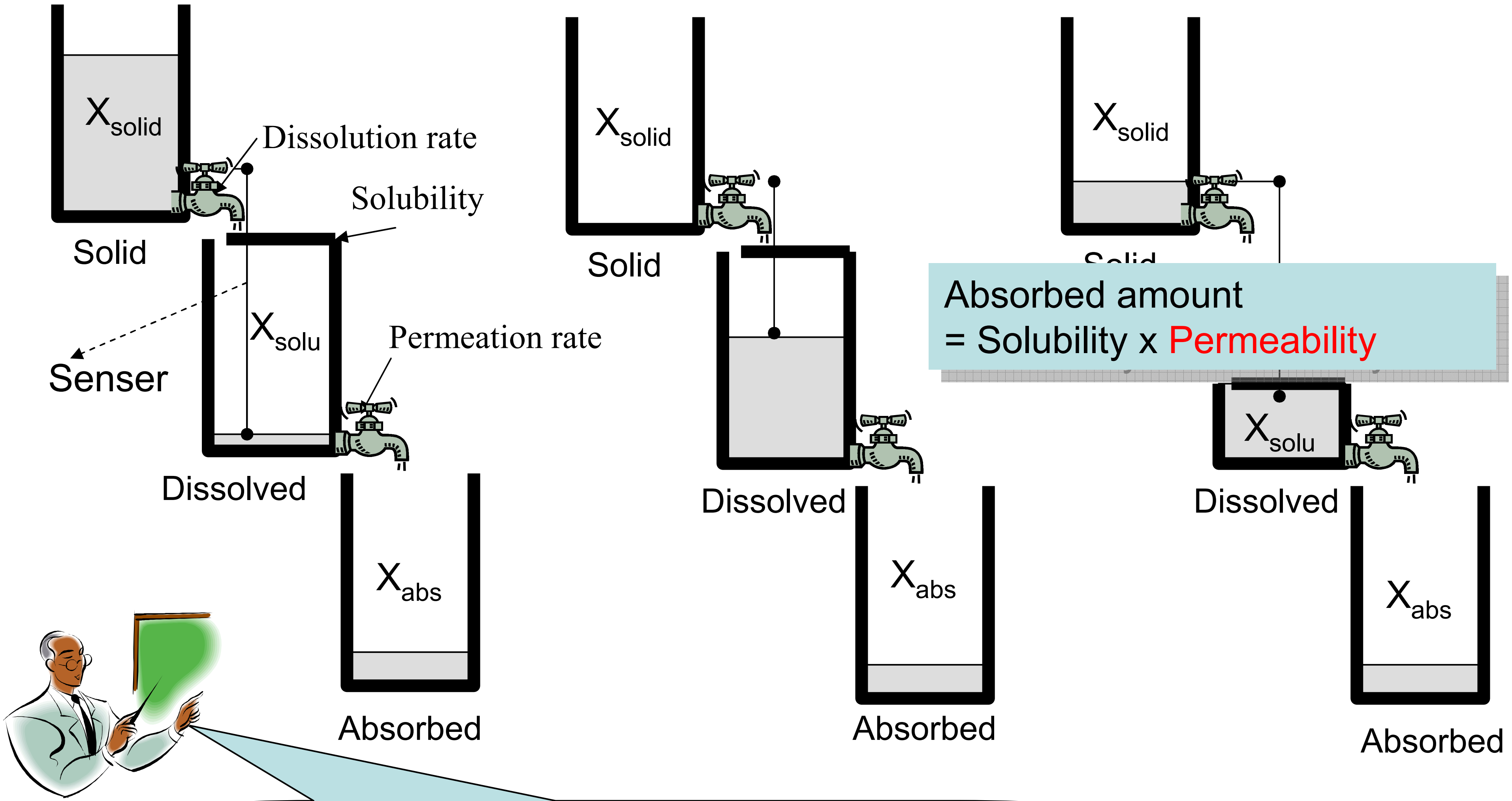


Central dogma is common to all software

Sugano, Exp. Opin. Drug Met Tox, 2009

Limiting process

(A) **Dissolution rate limited** (B) **Permeability limited** (C) **Solubility limited**

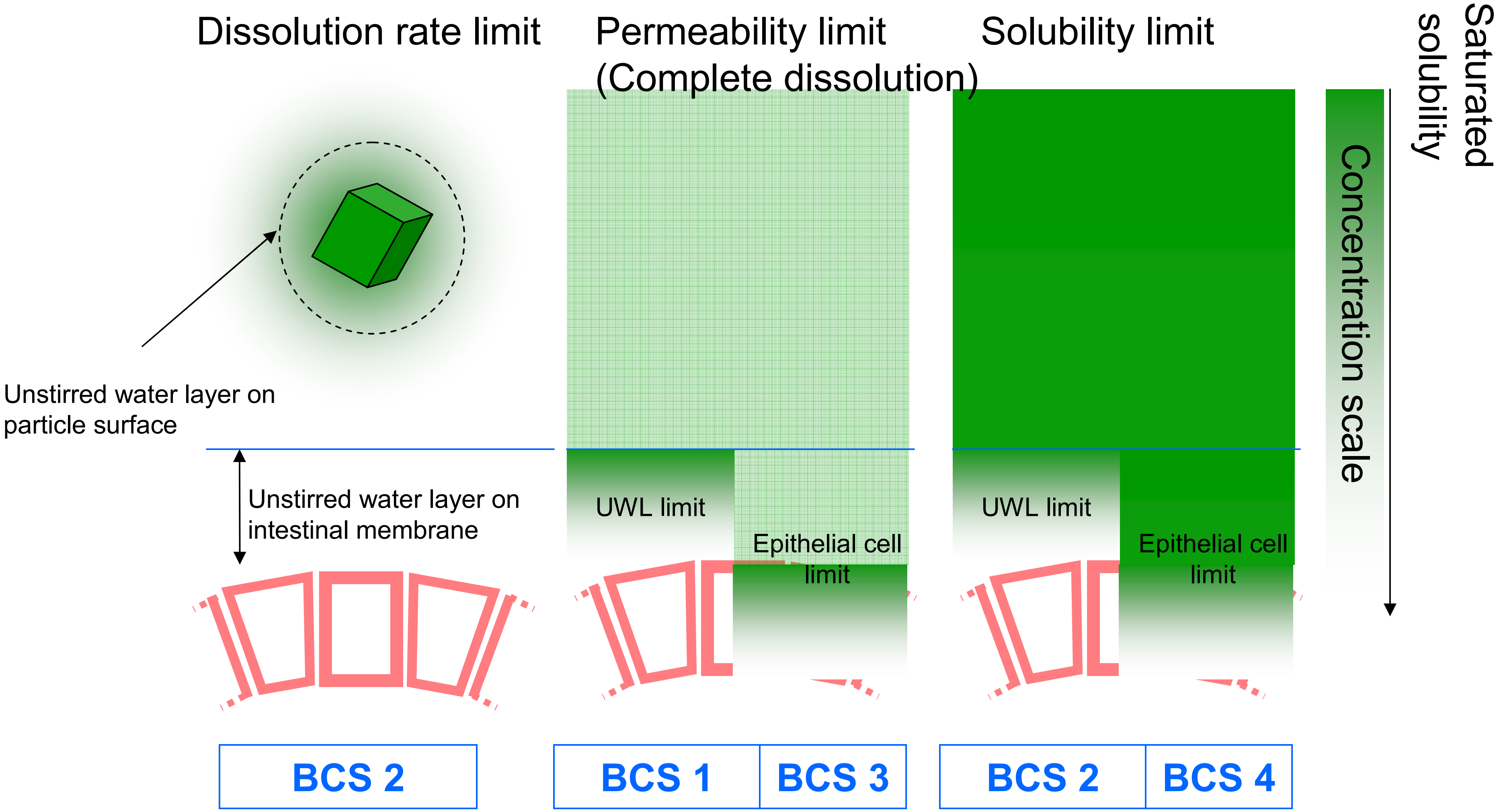


Absorbed amount
= Solubility x Permeability

Disso. limited and solubility limited are different!

Sugano et al, DMPK 2007 (4) 225-254

Rate limiting steps and concentration gradient



Dissolution rate limit

Permeability limit (Complete dissolution)

Solubility limit

Saturated solubility

Concentration scale

Unstirred water layer on particle surface

Unstirred water layer on intestinal membrane

UWL limit

Epithelial cell limit

UWL limit

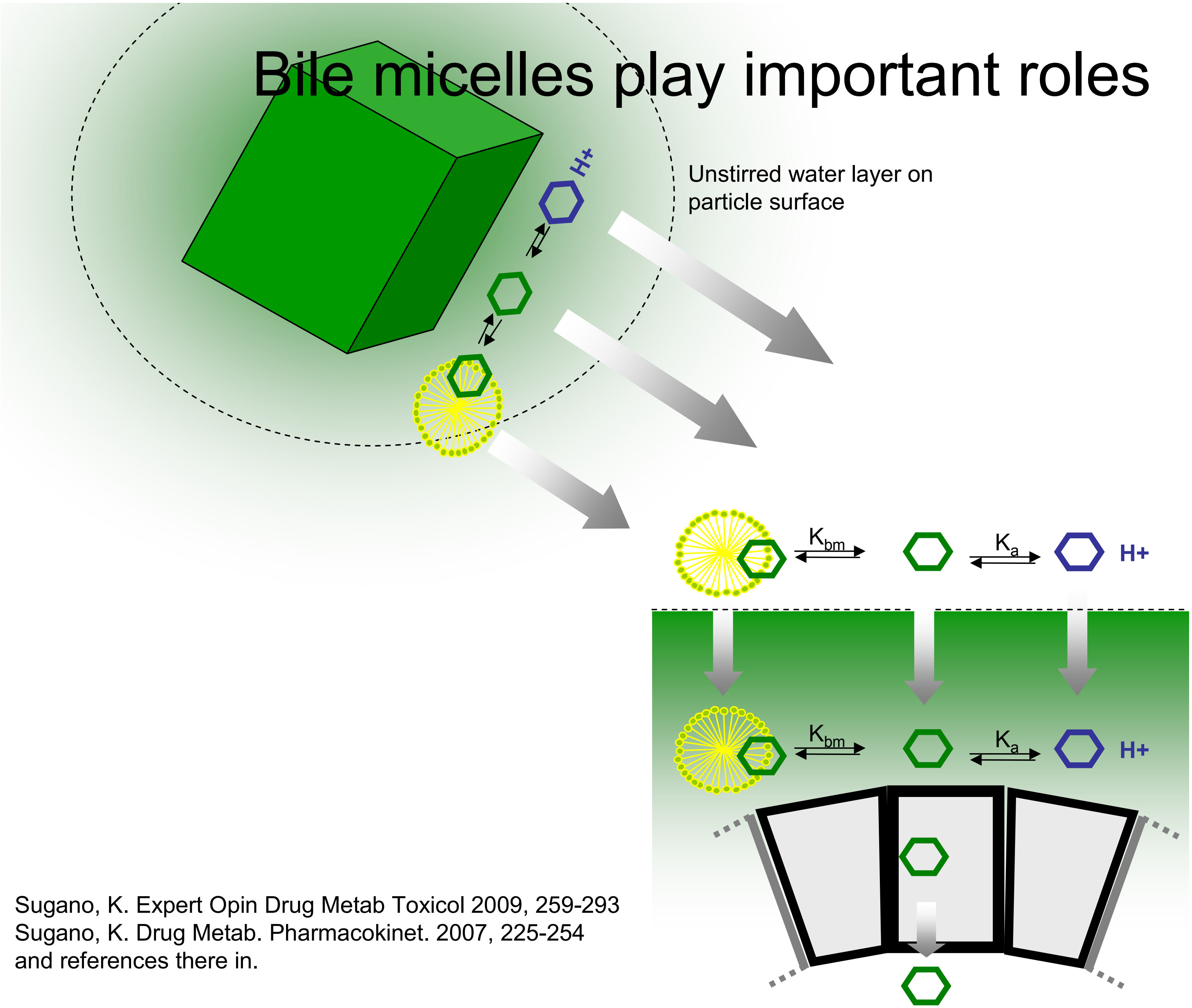
Epithelial cell limit

BCS 2

BCS 1 | **BCS 3**

BCS 2 | **BCS 4**

Bile micelles play important roles



Unstirred water layer on particle surface

Unstirred water layer on intestinal membrane

Epithelial cells at villi top

Sugano, K. Expert Opin Drug Metab Toxicol 2009, 259-293
Sugano, K. Drug Metab. Pharmacokinet. 2007, 225-254
and references there in.

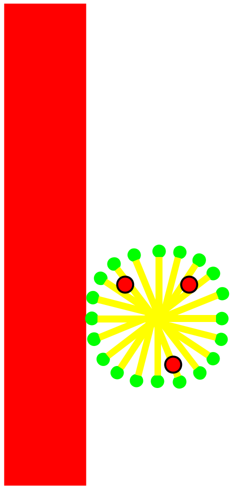
Contents

Nernst Brunner equation

$$\frac{dX}{dt} = SA \times \frac{D_{eff}}{h} \times \frac{S_{surface}}{S_{bulk}} \times \left(S_{bulk} - C_{bulk}(t)\right)$$

One assumption is that the pH is maintained by a feedback process in the GI tract.

Diffusion coefficient



D_{mono}

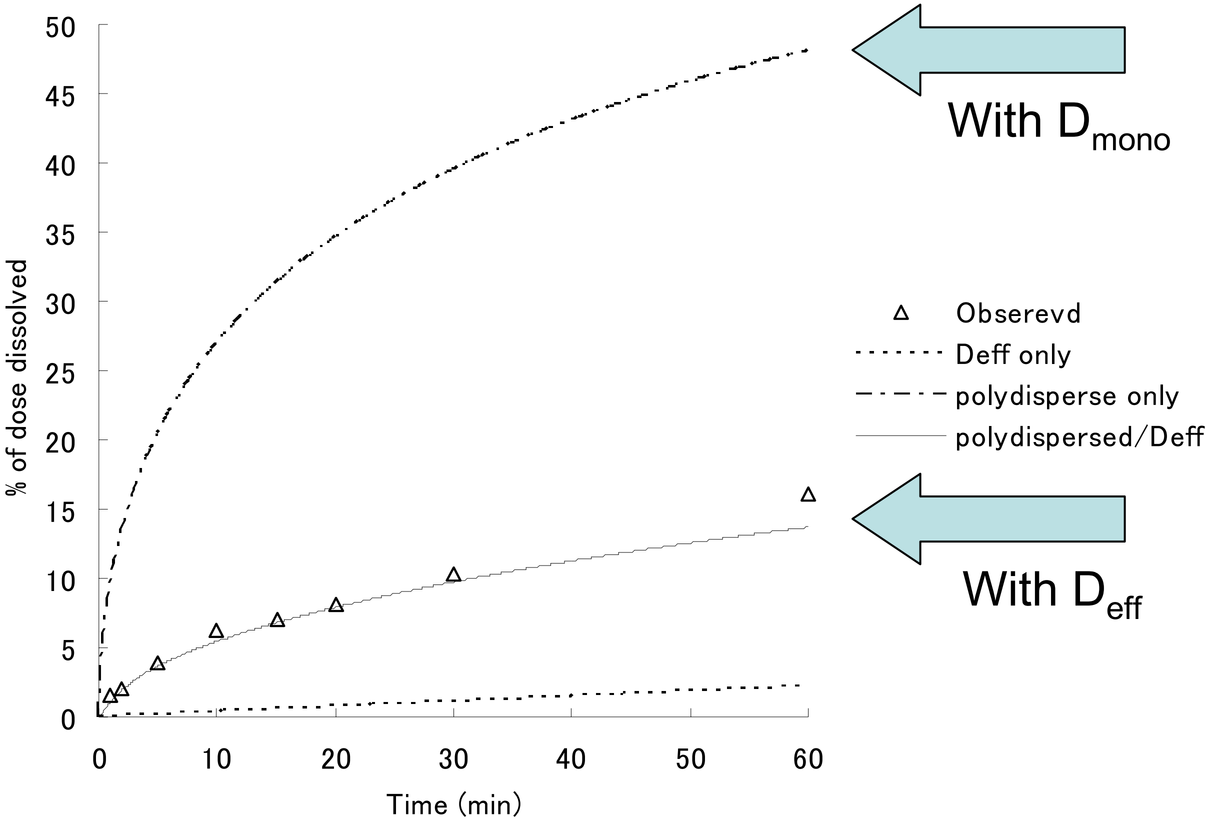
Since the free fraction is different **in the stomach and small intestine, the diffusion coefficient is different.**

$$D_{eff} = D_{mono} \cdot f_{mono} + D_{mic} \cdot f_{mic}$$

f_{mono}: fraction of free monomer drug
f_{mic}: fraction of aggregate bound drug

Naylor LJ, Bakatselou V, Dressman JB 1993. Pharm. Res. 10(6):865-870.
Balakrishnan A, Rege BD, Amidon GL, Polli JE 2004. J. Pharm. Sci. 93(8):2064-2075.

Validation: Dissolution test



With D_{mono}

With D_{eff}

Danazol
FaSSIF
Mini vessel (50 mL)
50 rpm
1 mg dose

A. Okazaki, T. Mano, K. Sugano, JPS 2008, 1843

In vivo evidence: Felodipine

Buffer	1 ug/mL
FaSSIF$_{dog}$	77 ug/mL (TC/EL : 5 mM/1.25 mM)
D_{mono}	7.0×10^{-6} cm^2/sec
D_{eff}	0.64×10^{-6} cm^2/sec
P_{eff}	0.48×10^{-4} cm/sec*
Intestinal fluid volume	36 mL* (= 250 mL in humans)

* These have little effect on Fa% in the case of dissolution rate limited absorption.

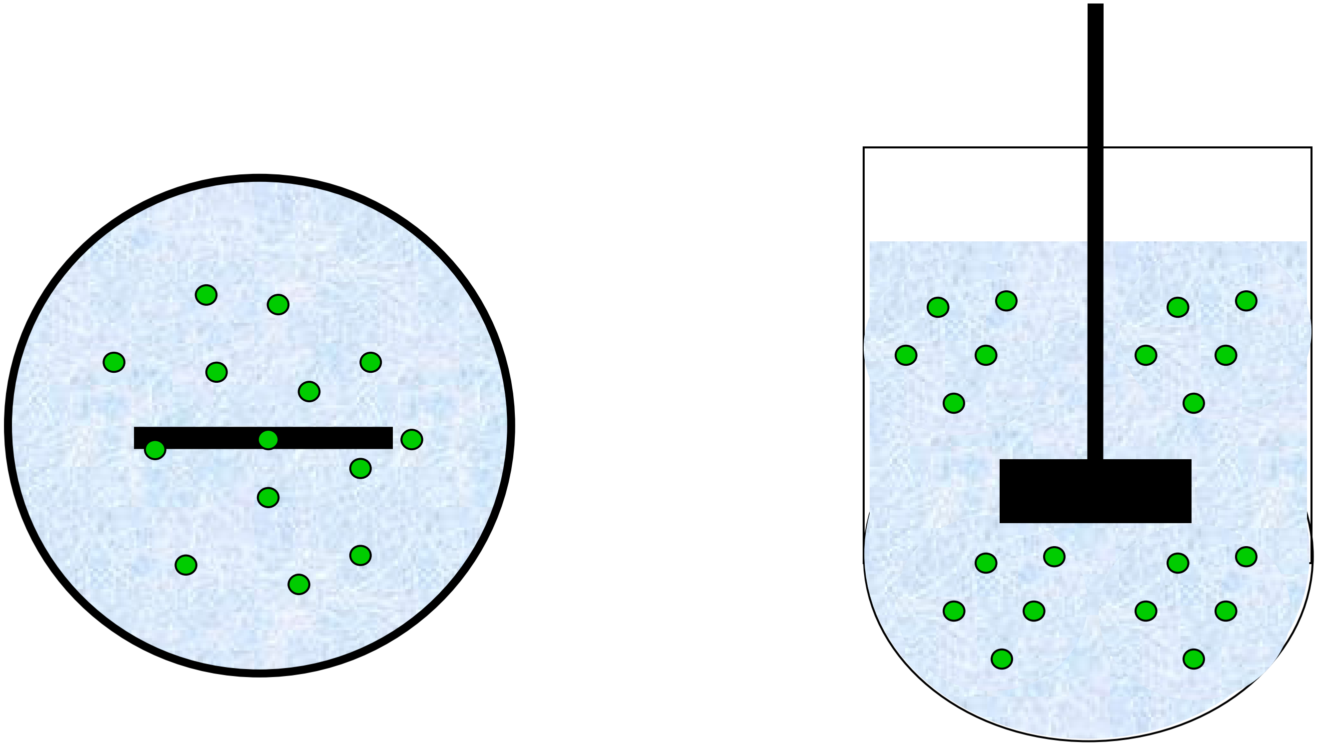
Dog (Labrador)
Suspension 0.33 mg/kg dose

Observed AUC and simulation results

	AUCobs* (ug/L/h)	AUC ratio	Sim. Fa% ratio	
			D_{mono}	D_{eff}
solution	33.9 +-15.2	-	-	-
125 um	1.7 +- 0.5	**0.05**	0.35	**0.08**

Scholz, A., Abrahamsson, B., Diebold, S.M., Kostewicz, E., Polentarutti, B.I., Ungell, A.-L. and Dressman, J.B., Pharm. Res., 19: 42-46 (2002).
Sugano, K. Chemistry and Biodiversity 2009, in press.

Floating particle



The *relative* velocity is not so large.

Fluid dynamics theory

$$\frac{dX}{dt} = D \times \frac{Sh}{d_p} \times S \times \left(Cs - C_{bulk}(t)\right) \qquad h = \frac{d_p}{Sh}$$

Ranz–Marshall correction

$$Sh = \underline{2} + \underline{0.6\,\mathrm{Re}^{1/2}\; Sc^{1/3}}$$

Asymptotic diffusion term
(Curvature effect)

Effect of flow
around a particle

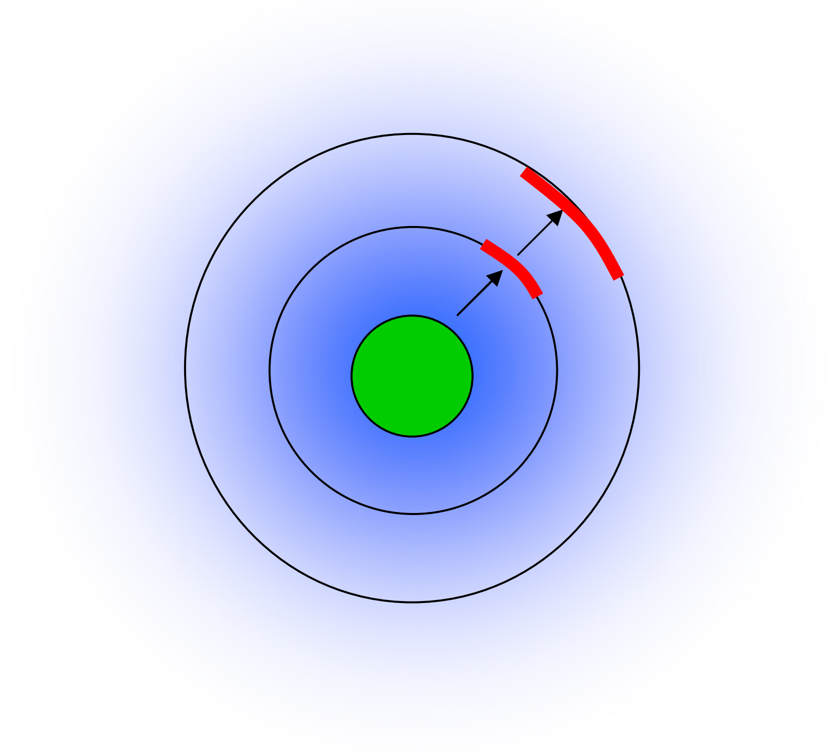
Sh: Sherwood number
Re: Reynolds number
Sc: Schemit number

d_p: particle diameter
v_p: *relative* flow speed around a particle
μ: kinematic viscosity

$$Re_p = \frac{v_p \cdot d_p}{\mu} \qquad Sc = \frac{\mu}{D}$$

Harriott P 1962. Mass transfer to particles: Part 1. AICH E J. 8(1):93-102.

Asymptotic diffusion term



As the distance from the surface increases, the available space for diffusion increases.
Therefore, even *without any flow* aroud the particle, dissolution occurs.
(If the h in NBE as a real one, h is infinite and dissolution rate would be zero. The h in NBE is NOT a real thickness (a conceptual one from the view point of dimension.))

$$Sh = 2$$

therefore

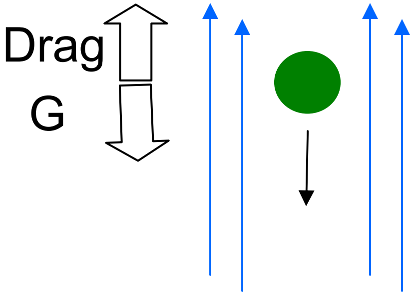
$$h = \frac{d_p}{2} = r_p$$

Relative flow around a particle

$$v_{rel} = \sqrt{v_t^{\ 2} + v_m^{\ 2}}$$

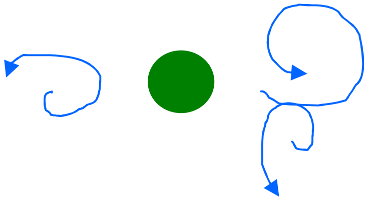
(A) Terminal velocity (v_t)

The effect of particle density



(B) Microeddy effect (v_m)

The effect of agitation strength (rpm)

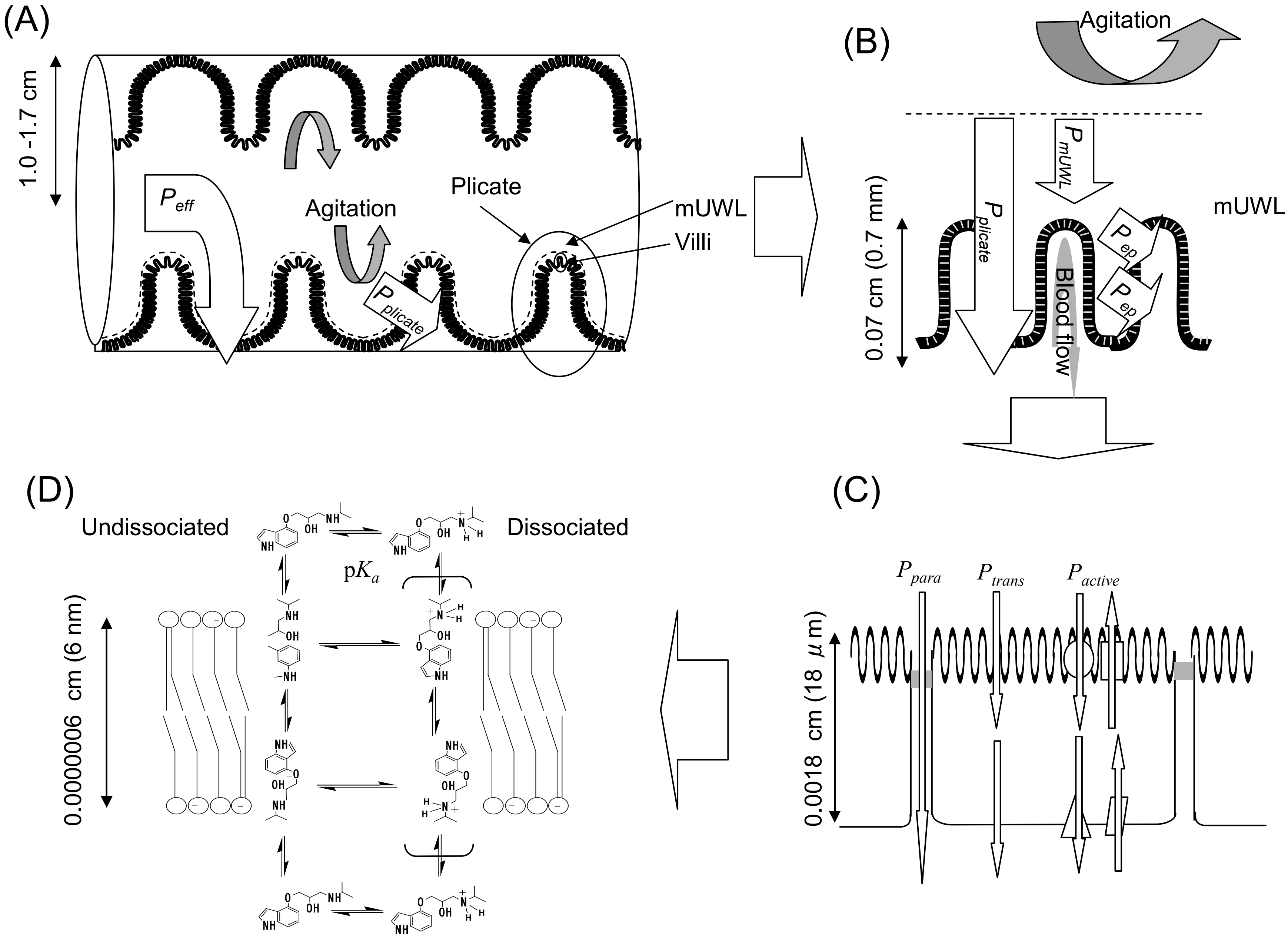


Levins, D. M.; Glastonbury, J. R., Mass transfer. Trans. Inst. Chem. Eng. 1972, 50, (2), 132-46.
Sugano K, 2008. Int. J. Pharm. 73-77.

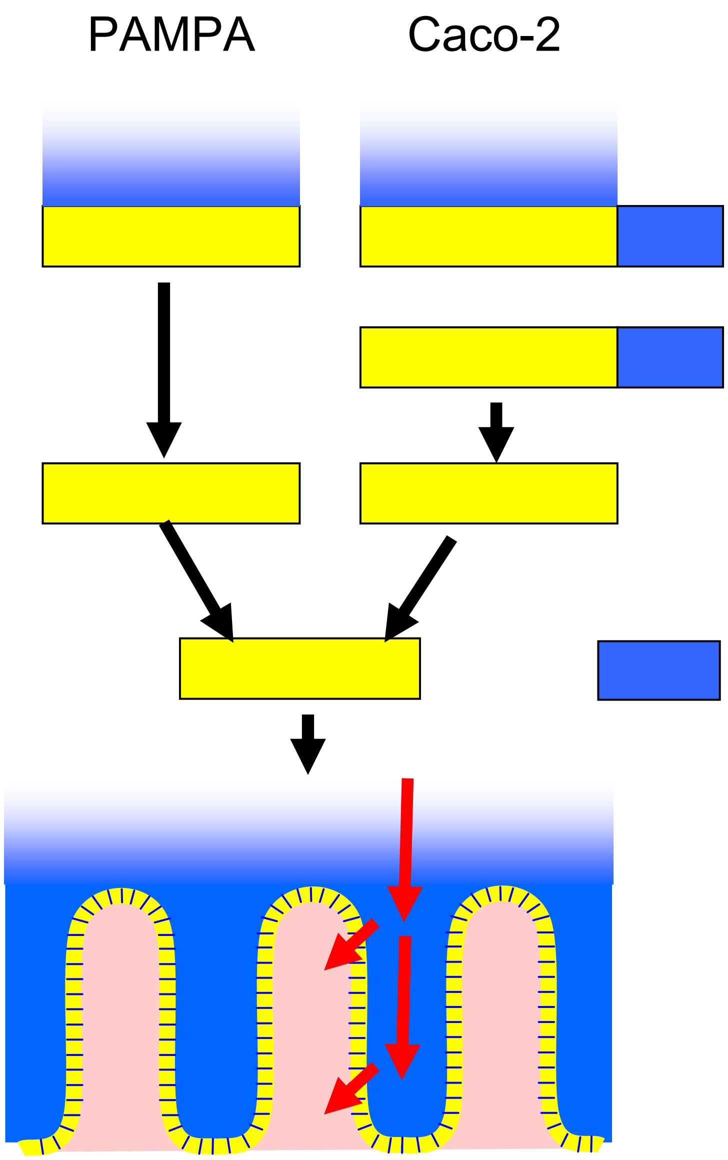
Contents

- Central Dogma
  - Three limiting cases
- Dissolution
  - Bile micelle effect
  - Hydrodynamics
- Permeation
  - Paracellular
  - Unstirred water layer
- Food effect
  - Bile micelle effect
    - UWL limited case
    - Epithelial membrane limited case

Fold (Plica), villi, and microvilli



P_{eff} estimation scheme from Caco-2 and PAMPA



(1) Subtract UWL

(2) Subtract P_{para} of Caco-2

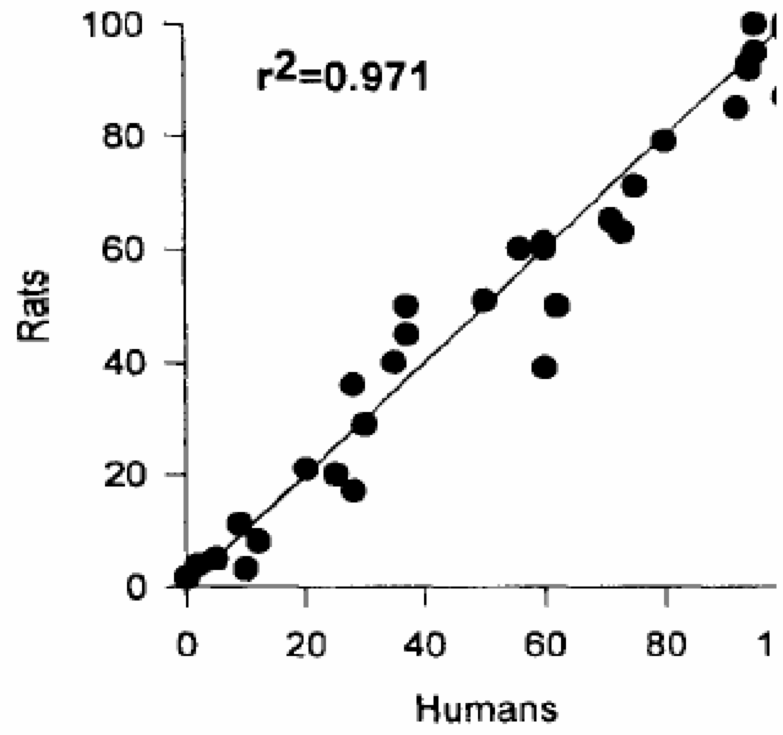
(3) pH correction for transcellular pathway
(pH partition theory)

(4) Add P_{para} of humans

(5) Surface expansion by fold and villi
(6) Calculate the surface accessibility
(7) Add UWL

- Paracelluar
Dog > Human ≈Rat > Caco-2
Negatively charged (basic compound selective)
- pH
- UWL
Caco-2>> Human > Dog (?)
- FE
Human 3, Rat 1

Animal – Human correlation for *permeability limited* compounds-observed



Due to a larger paracellular pathway permeation in dogs.

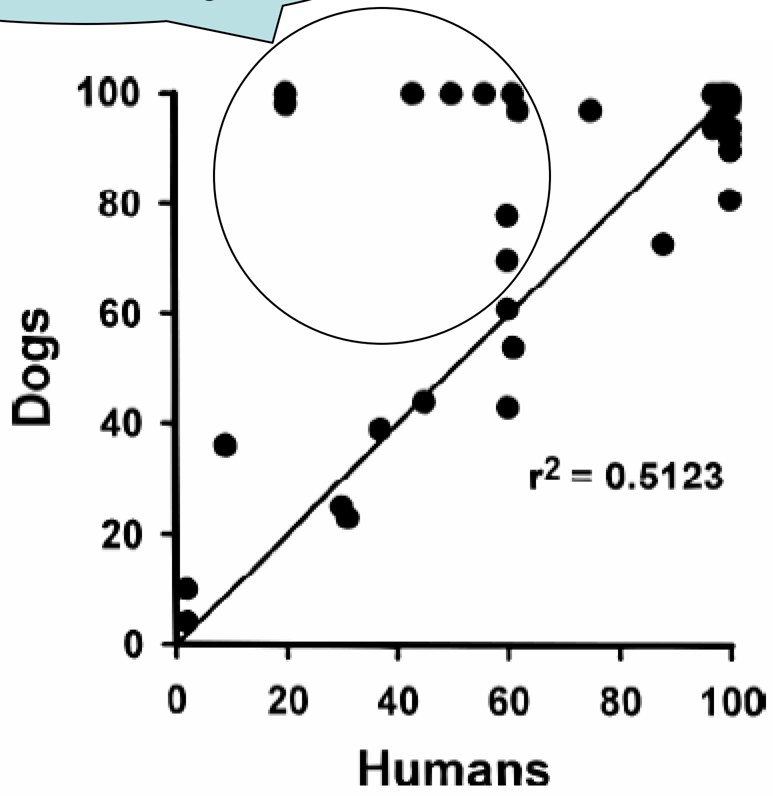
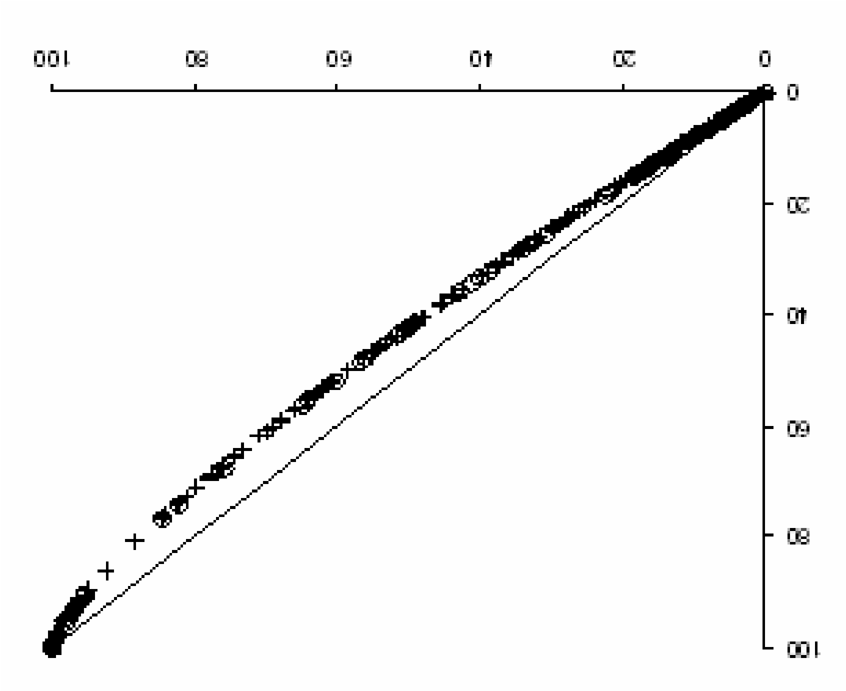


Fig. 1. Correlation of percent of oral dose absorbed between humans and dogs for the 43 drugs with a regression equation of $F_{dog} = 0.6341$ $F_{human} + 35.29$ ($p < 0.0001$). The straight line has a slope of one.

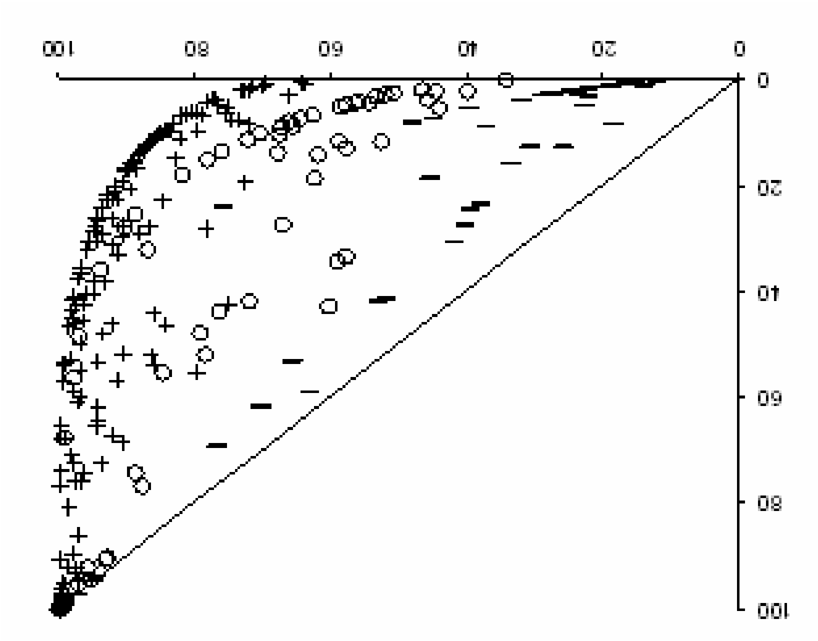
Chiou et al., Pharm Res 1998, 15, (11), 1792-1795.
Chiou et al., Pharm Res 2000, 17, (2), 135-140.

Simulation

Rat

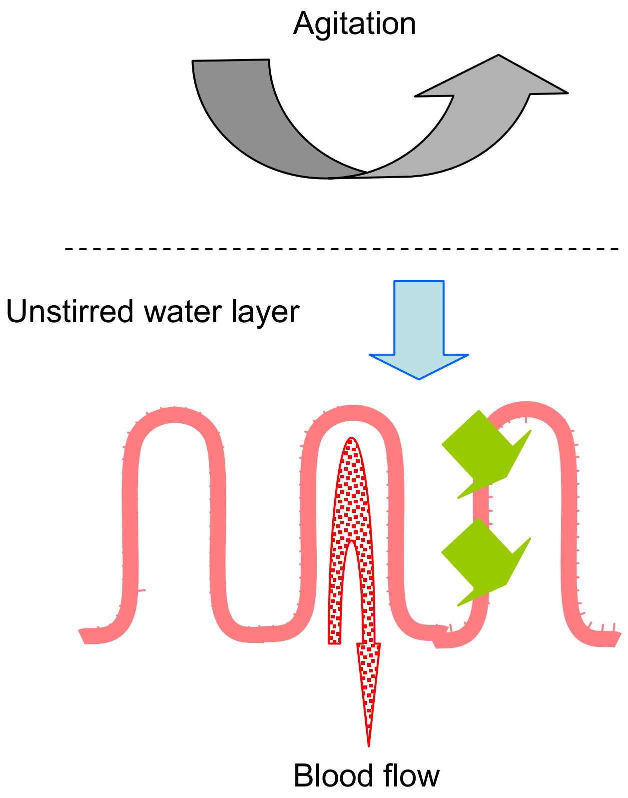


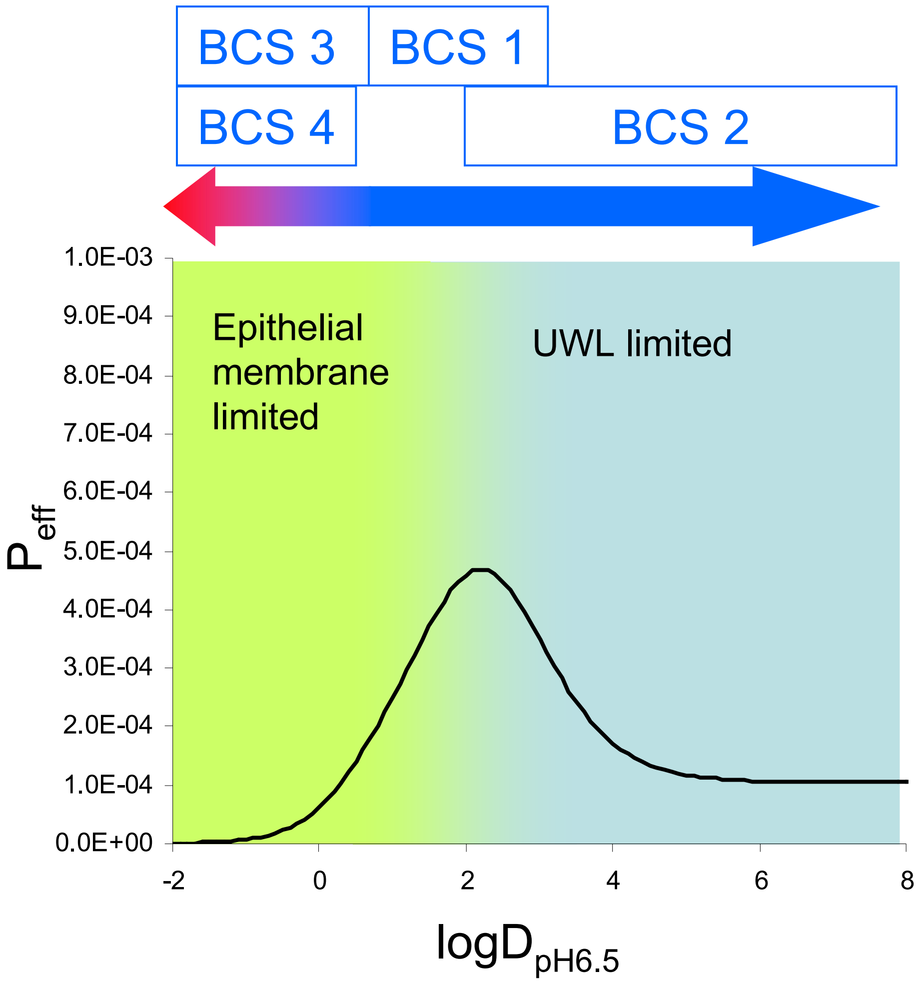
Dog



Sugano, K., Int J Pharm 2009

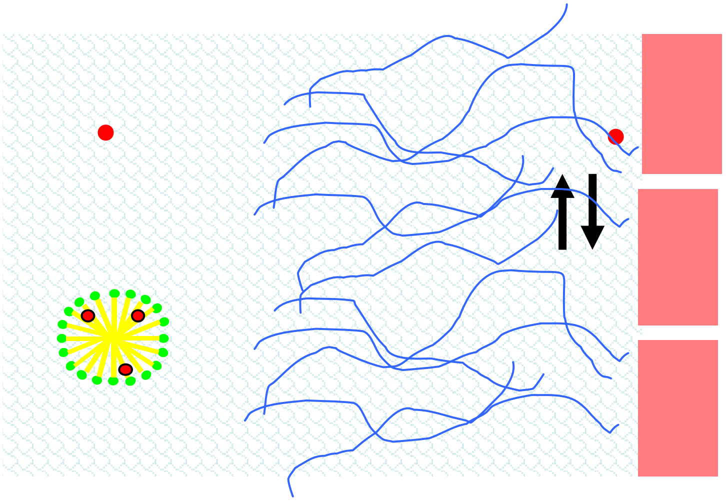
For some low solubility compounds, UWL could limit the permeability





Passing through the UWL

Unstirred water layer (mucus)



D_{mono}

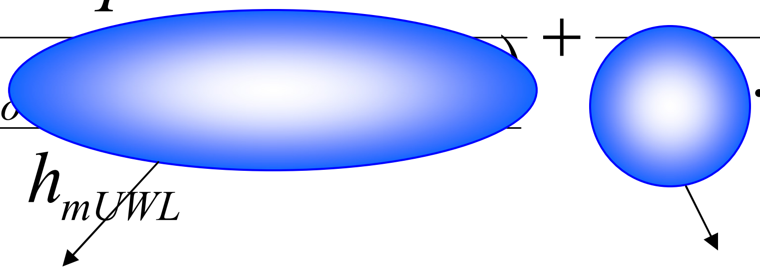
D_{mic}

$$P_{eff} \approx \frac{A' \, D_{eff}}{h_{eff}} + P_{WC}$$

Equation to take bile micelles into account

- Published in *1982* by Greg Amidon, Norman Ho and William Higuchi.

$$P_{app} = \frac{1}{\frac{1}{\frac{D_{mono}\cdot f_{mono}}{h_{mUWL}}} + \frac{1}{\cdot P_{membrane}}}$$



Diffusion of bile micelles in UWL

Free fraction at membrane surface

For P_{eff} calculation we can modify it to

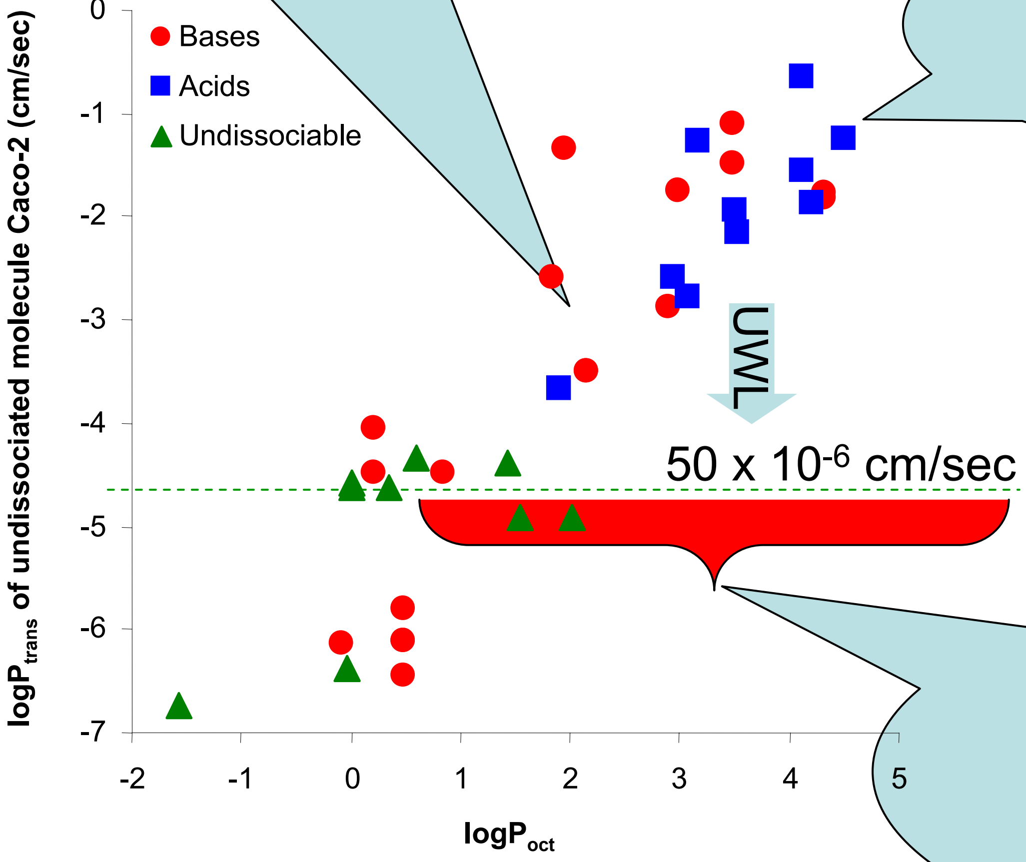
$$P_{eff} = \frac{1}{\frac{1}{\frac{D_{mono}\cdot f_{mono} + A'\cdot D_{bm}\cdot\left(1 - f_{mono}\right)}{h_{mUWL}} + P_{WC}} + \frac{1}{f_{mono}\cdot P_{ep}\cdot Acc\cdot VE}}\cdot PE$$

Sugano, K. Int J Pharm 2009, 116–122.

$\log P_{oct}$ vs $\log P_{ep}$

lculated from pH – P_{app} profile

The slope is almost 1.
As $\log P_{oct}$ increase 1 unit, P_{ep} increases 10 fold.



At logP = 4, permeability increase 10000 fold if UWL could be removed.

Upper limit by the UWL without vigorous stirring

In most low solubility compounds, the true membrane permeability is masked by the UWL (Slope ~ 1 relationship can not be observed) .

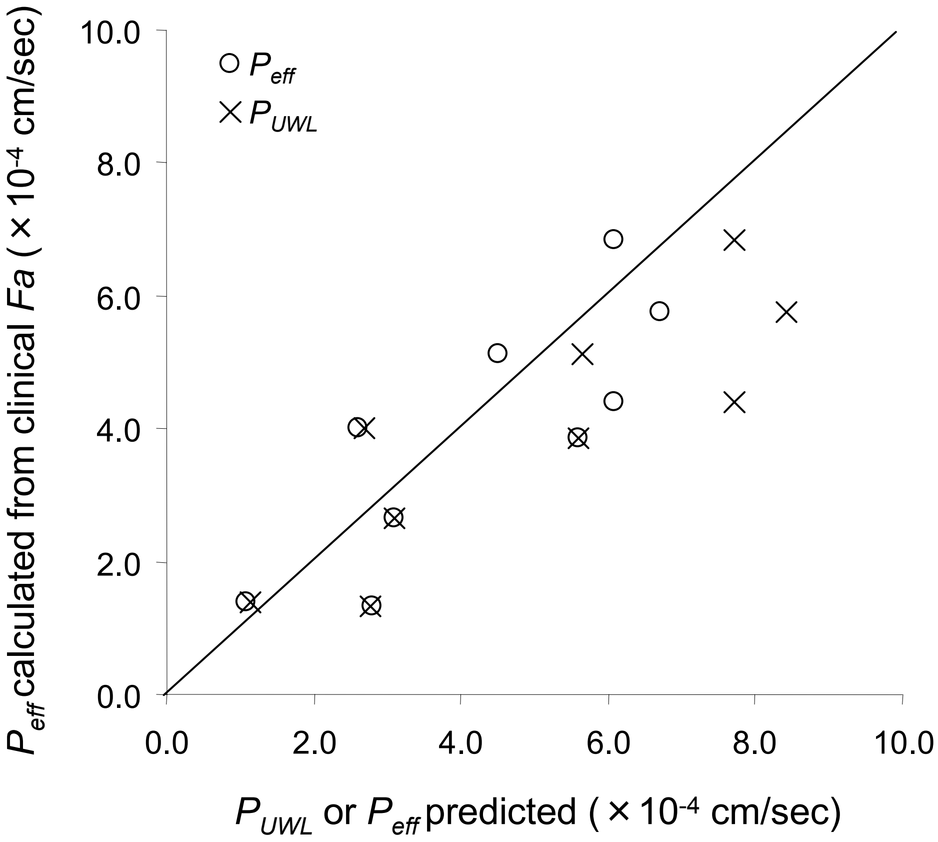
A. Avdeef, P. Artursson, S. Neuhoff, L. Lazorova, J. Grasjoe, S. Tavelin, Eur. J.

K. Sugano Int J Pharm 2009, 368, 116–122

S. Yamashita, EJPS, 2000 , 195

Kyoung-Jin Lee, EJPS 2005, 193

UWL – bile micelle model



$$P_{eff} = \frac{1}{\frac{1}{\frac{D_{mono}\cdot f_{mono}}{h_{mUWL}} + P_{WC}} + \frac{1}{\cdot P_{trans,0}\cdot Acc\cdot VE}}\cdot PE$$

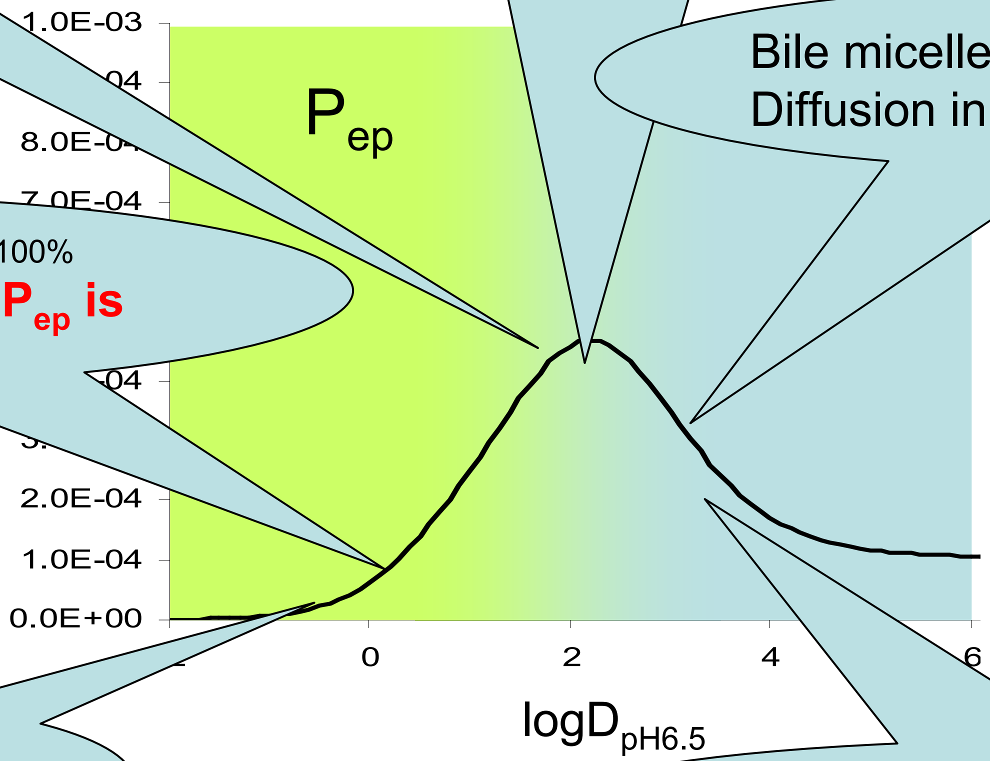
Sugano, K. Chemistry and Biodiversity 2009, in press.

P_{eff} – logDoct

Lipophilicity of oral drugs ran limiting step

$_{ep}$ being always

dominant.



UWL starts to limit P_{eff}

UWL being dominant.

Bile micelle binding ↑
Diffusion in UWL ↓

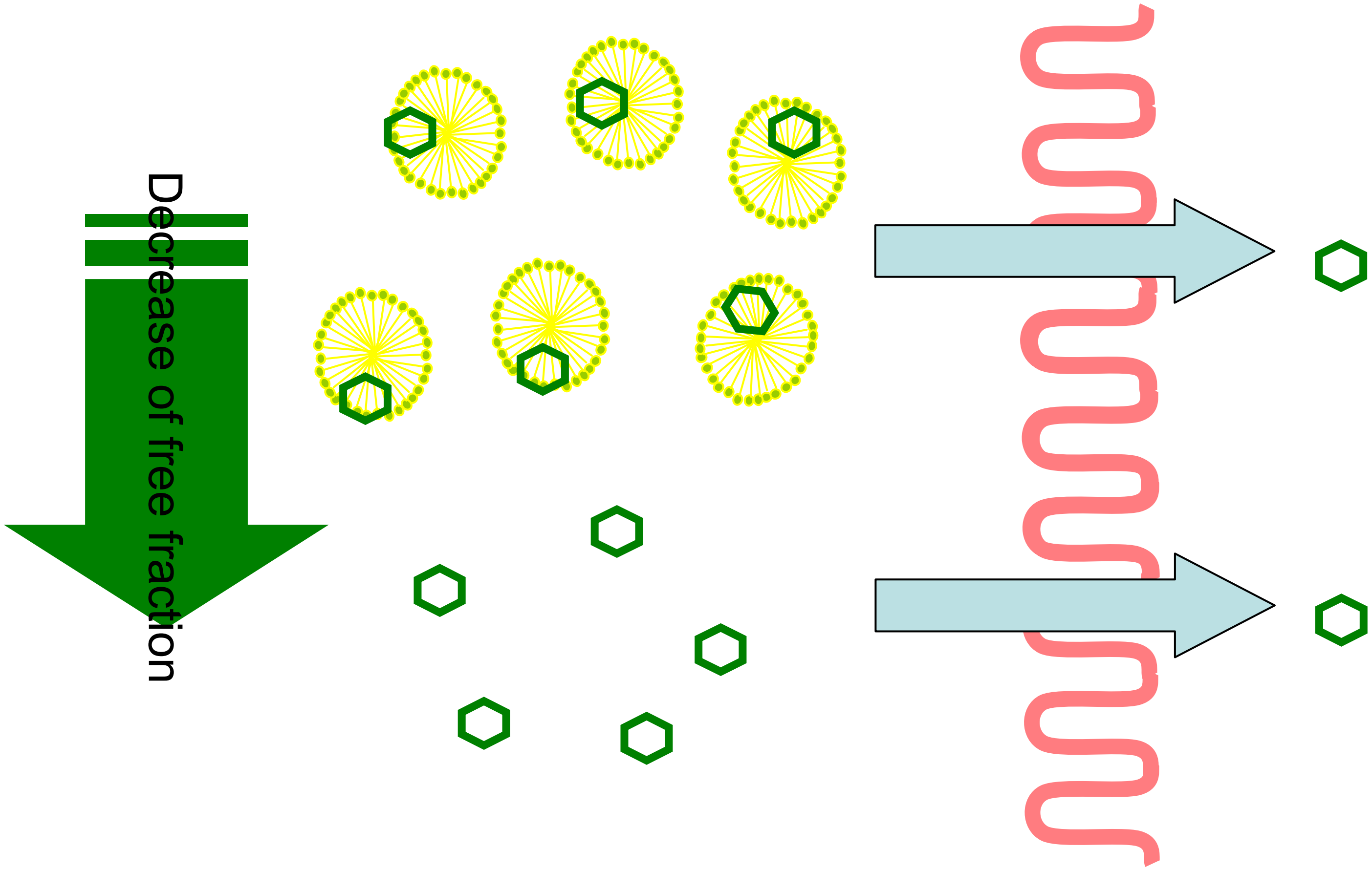
P_{eff} = 1 – 2 x 10^{-4} cm/sec = Fa% 100%
Below this permeability (so BCS III)、**P_{ep} is very important**.

P_{ep} increases as lipophilicity increases,

In this range、**UWL is important**

Contents

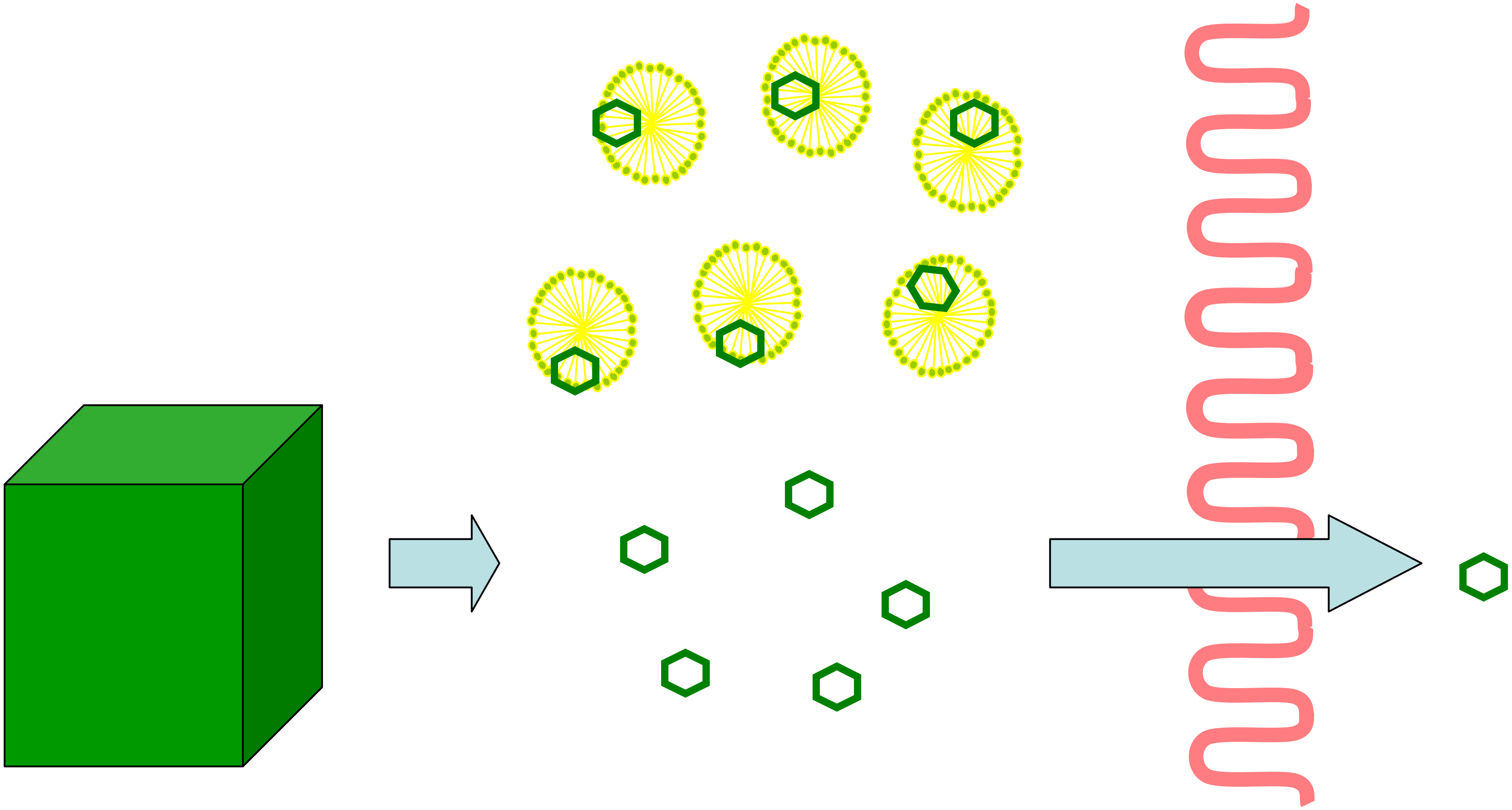
“Bile micelles decrease the absorbed amount for permeability limited case.”



“Reason for negative food effect in BCS III compounds”

“Free fraction!”

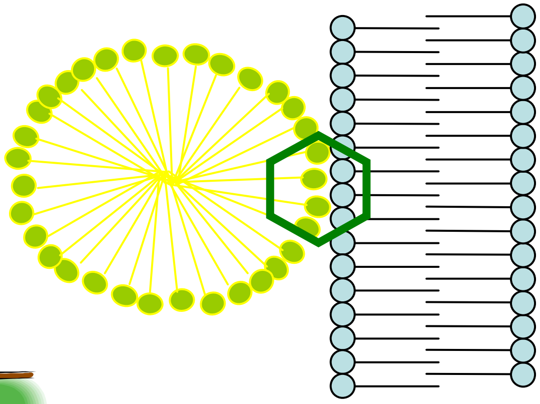
“Bile micelles increase oral absorption for a solubility limited case.” It’s a mystery!



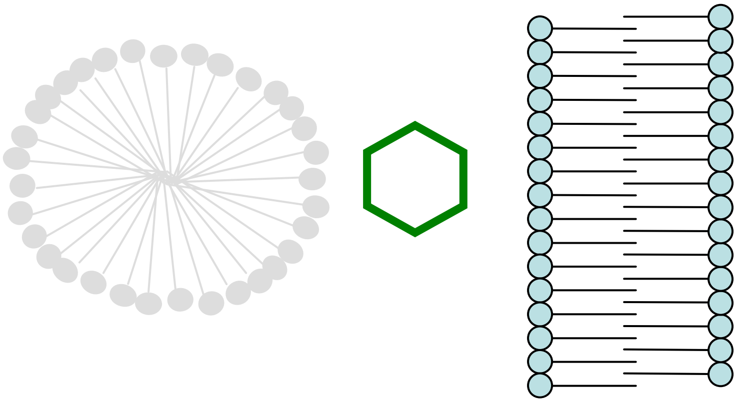
Bile micelles DON’T increase the free monomers.
Why bile micelles increase the absorbed amount?

It’s a mystery!

- I think many scientists noticed this mystery.
- Two *NEW hypothesis* suggested?
  - Molecules directly transfer from the bile micelles to the epithelial membrane
  - As bile micelles degrade and absorbed at the membrane surface, the compounds are released.



Collisional transfer?



Release at the surface?

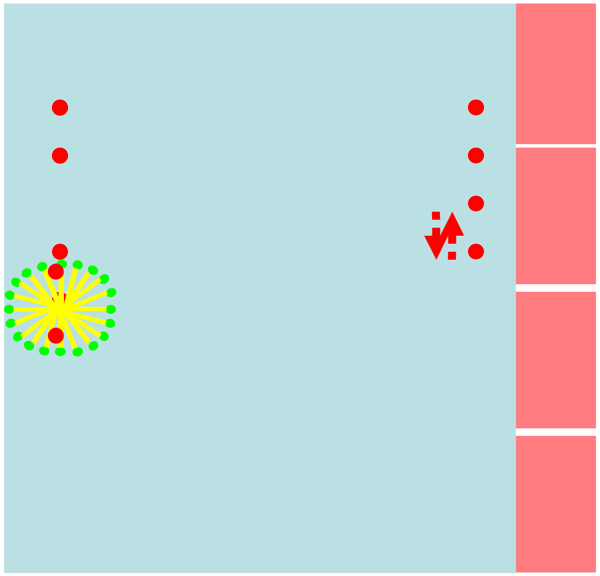
Hung on a minute, Kiyo. Before introducing a new mechanism, let’s re-consider the current mechanism!.

Passing through the UWL

Permeability limited

$P_{UWL} > P_{ep}$

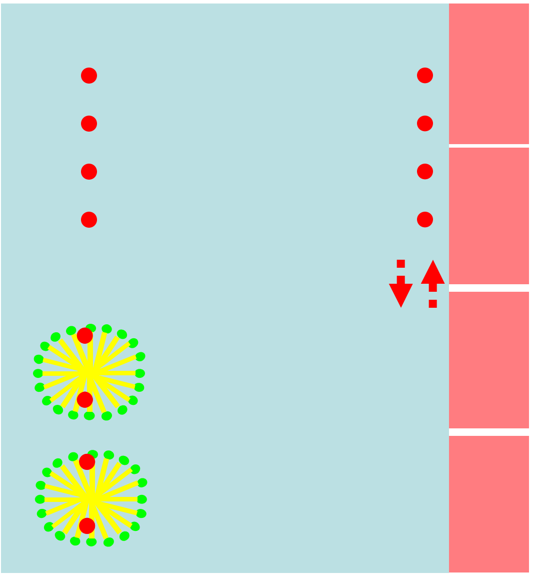
Fasted 4 → Fed 2



Solubility/epithelial perm. limited

$P_{UWL} > P_{ep}$

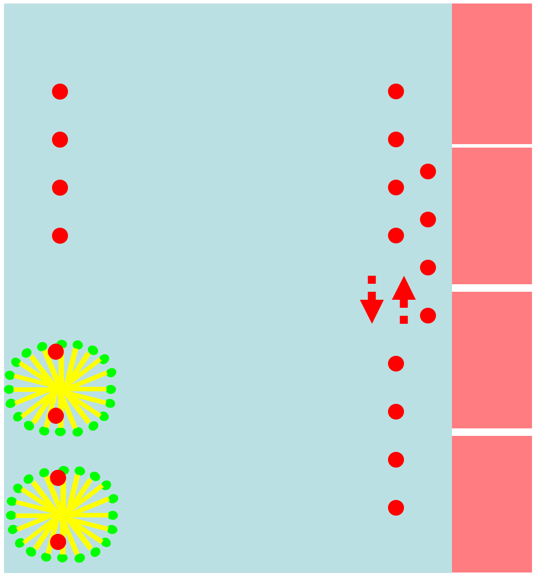
Fasted 4 → Fed 4



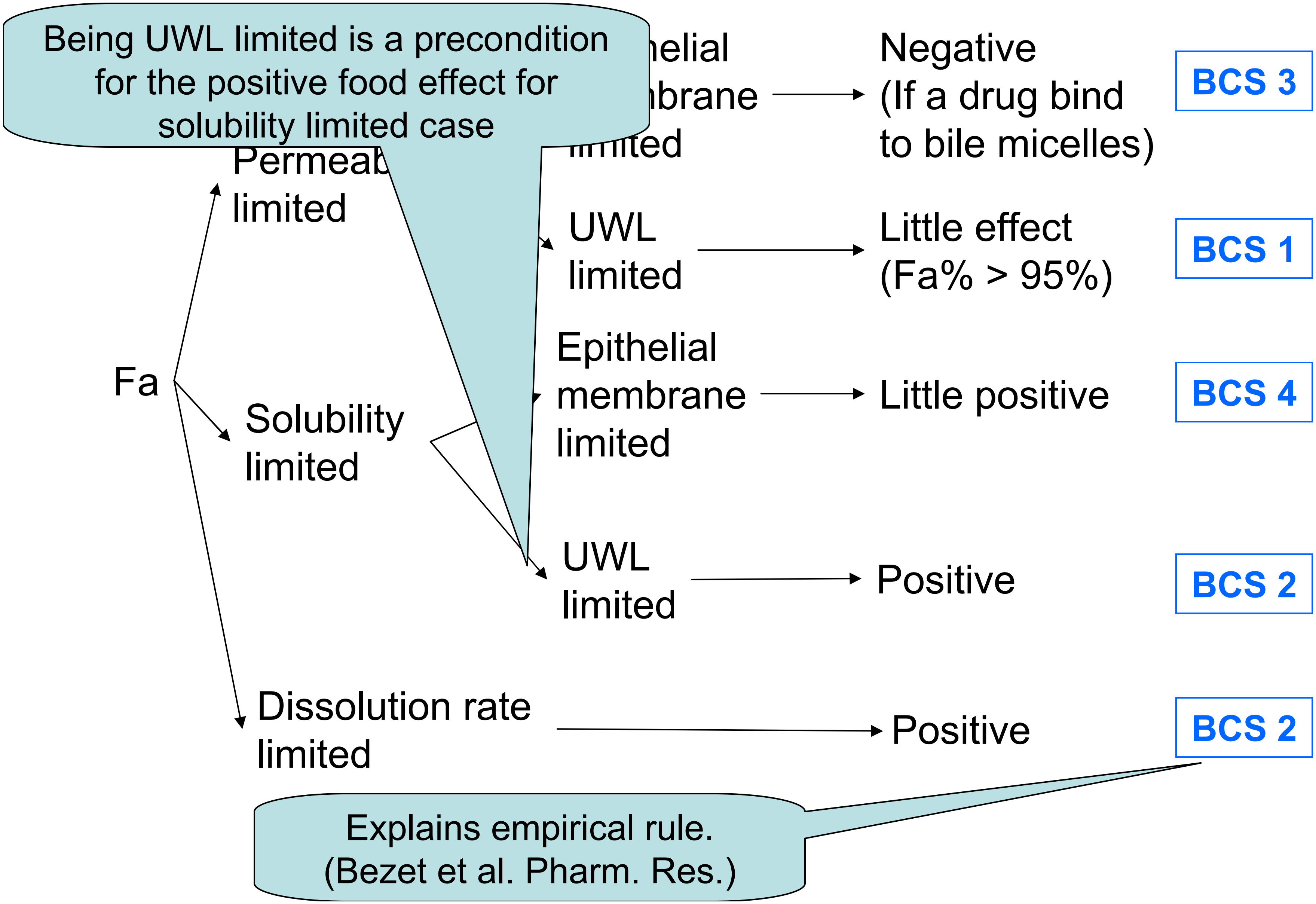
Solubility/UWL perm. limited

$P_{UWL} < P_{ep}$

Fasted 4 → Fed 8



Food effect and free fraction



Being UWL limited is a precondition for the positive food effect for solubility limited case

Fa

Permeab
limited

helial
brane
limited → Negative (If a drug bind to bile micelles) **BCS 3**

UWL limited → Little effect (Fa% > 95%) **BCS 1**

Solubility limited

Epithelial membrane limited → Little positive **BCS 4**

UWL limited → Positive **BCS 2**

Dissolution rate limited → Positive **BCS 2**

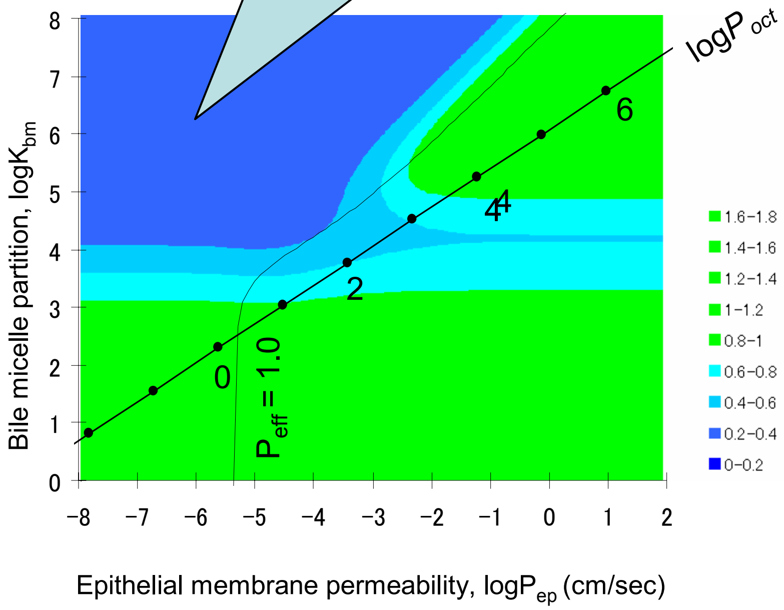
Explains empirical rule.
(Bezet et al. Pharm. Res.)

Food effect on P_{eff} and *Fa*

Negative food effect when the dose number is less than 1.

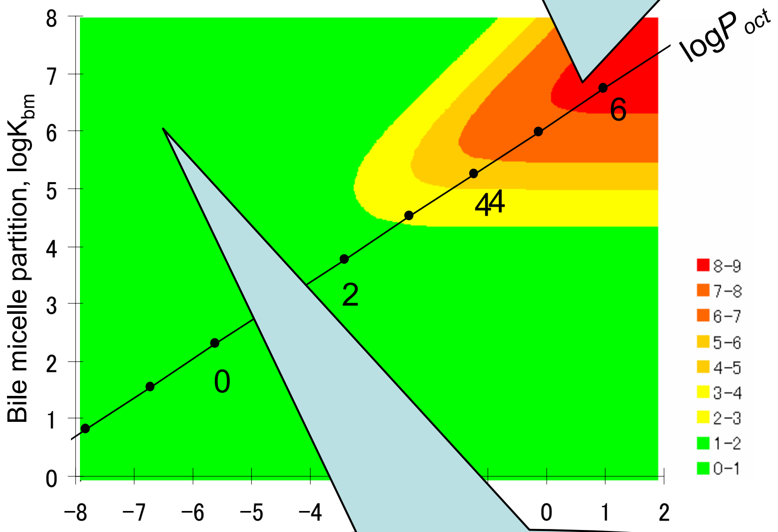
(A) P_{eff} ratio

solubility limitation)



Positive food effect: Increase of solubility exceeds decrease of diffusion in the UWL

(B) max. *Fa* ratio (solubility



Increase of solubility and decrease of free fraction at membrane surface cancels out

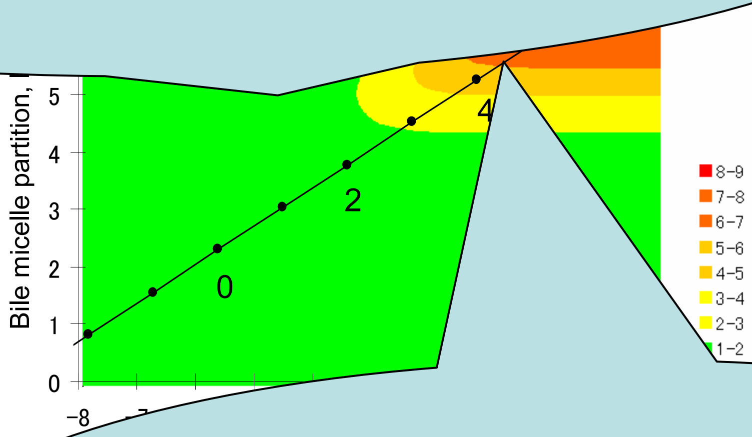
$$\frac{P_{eff,fed}}{P_{eff,fasted}}$$

$$Fa\ ratio = \frac{P_{eff,fed} \cdot S_{dissol,fed}}{P_{eff,fasted} \cdot S_{dissol,fasted}}$$

Sugano, K. Chemistry and Biodiversity 2009, in press.

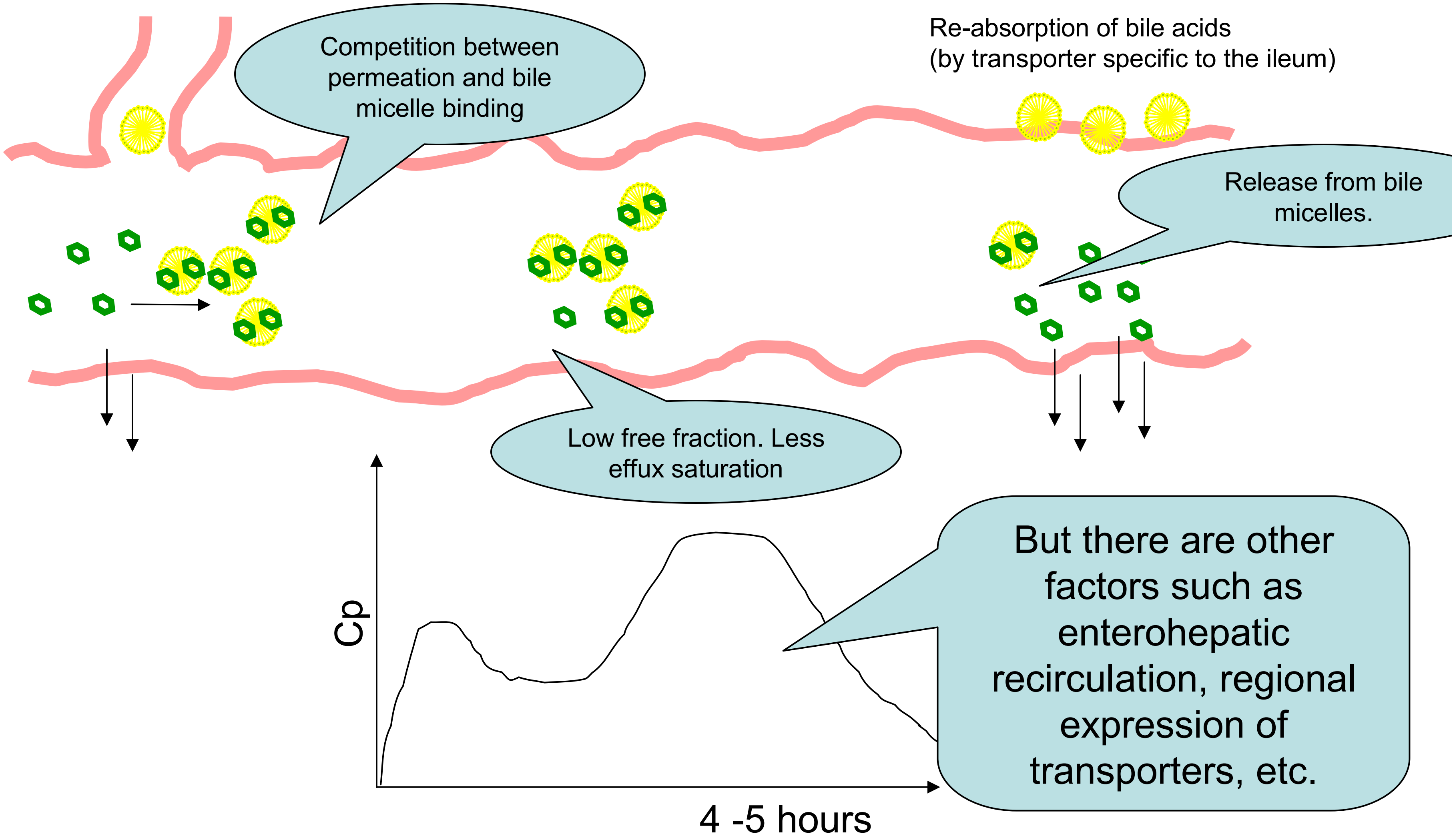
Examples

Pranlukast Solubility-epi. perm. limtied (BCS 4)
FaSSIF 0.09 mg/mL
FeSSIF 0.80 mg/mL (**x 8** of FaSSIF)
Little food effect (**only1.3 fold increase, Fa** 13-15%)
(@ 112.5 mg)



Danazol Solubility-UWL perm. limtied (BCS 2)
FaSSIF 0.018 mg/mL
FeSSIF 0.047 mg/mL (**x 2.5** of FaSSIF)
Positive food effect **3-4 fold** increase
(@ 100 mg)

Negative food effect and bimodal peak by bile micelle binding



Competition between permeation and bile micelle binding

Re-absorption of bile acids
(by transporter specific to the ileum)

Release from bile micelles.

Low free fraction. Less effux saturation

But there are other factors such as enterohepatic recirculation, regional expression of transporters, etc.

Lennernaes et al., Pharm Res 1993, 10, (6), 879-83.

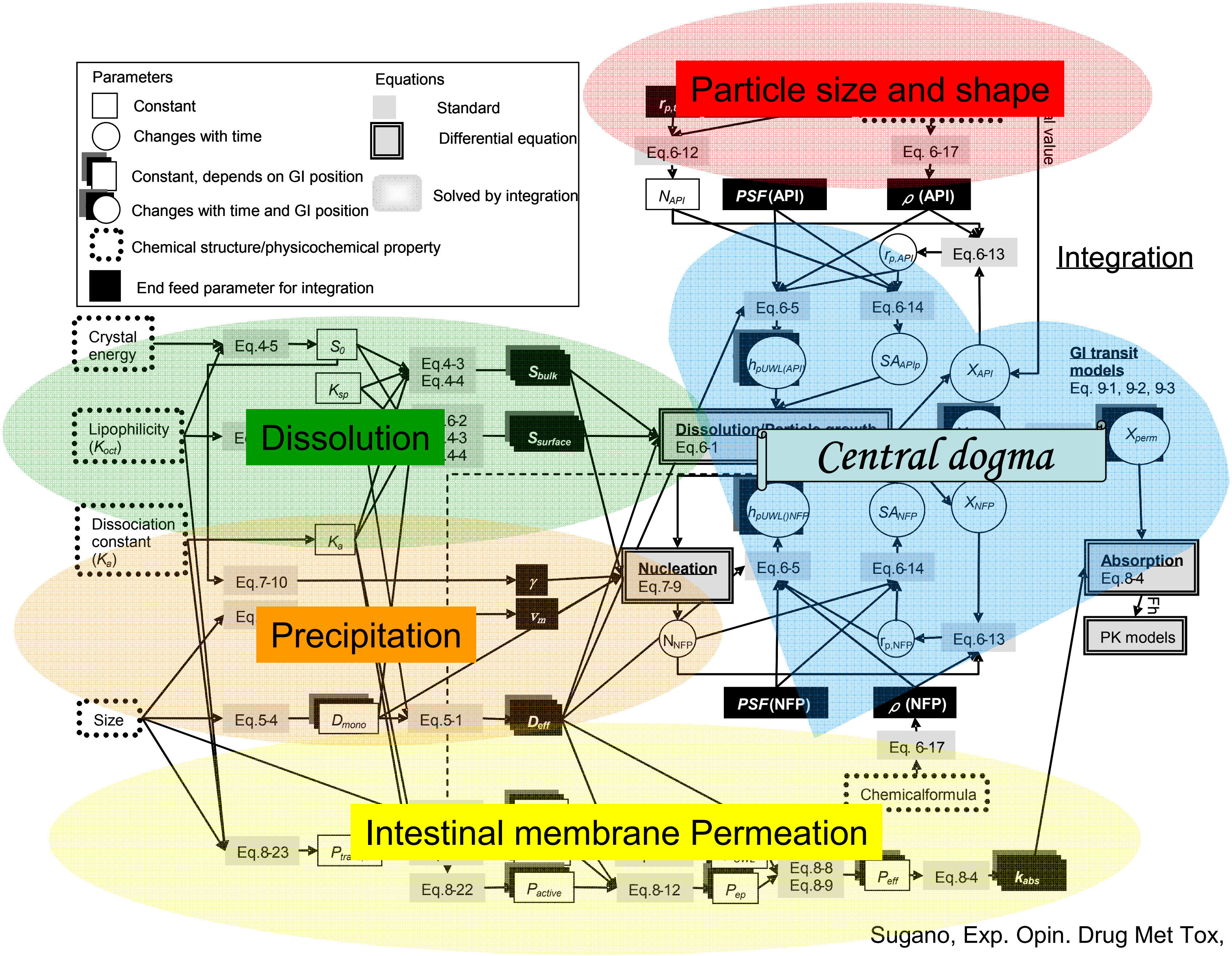
Summary

- Central Dogma
  - Three limiting cases: Perm./Disso./Sol.
- Dissolution
  - Bile micelle effect: Slow diffusion
  - Hydrodynamics: Particles flow. Asymptotic diff.
- Permeation
  - Paracellular: Dog
  - Unstirred water layer: important when logD > 1.5
- Food effect
  - Bile micelle effect: free fraction
    - Sol.-UWL limited case: positive (bile mic. pass UWL)
    - Sol.-Epithelial membrane limited case: little food effect
    - Perm. limited case: negative (if a drug binds to bile micelles)

If I select one key word from this presentation, it is

FREE FRACTION

GUT framework



Sugano, Exp. Opin. Drug Met Tox, 2009

Thank you for your patience.