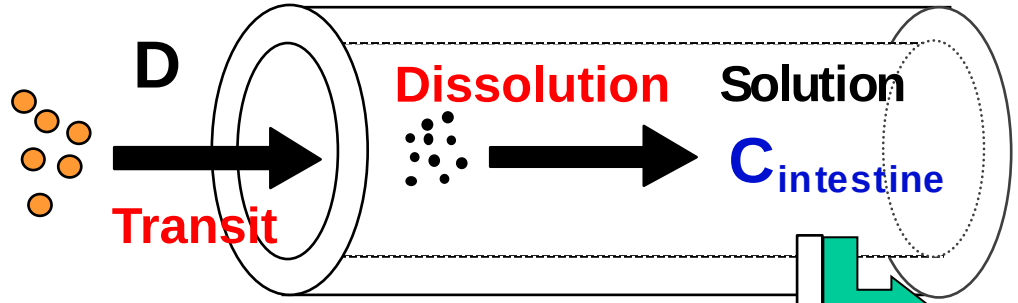
"Drug Dissolution in Oral Drug Absorption" workshop
The University of Maryland, Baltimore, Maryland, USA

Considering Free-Drug Concentrations in the GI Tract: Impact of Cyclodextrin and Food

Shinji Yamashita

Ritsumeikan University

Macroscopic analysis of drug absorption



Permeation (P_{eff})

1st-pass metabolism (Fg)

CL_{perm} = P_{eff} x surface area (SA)

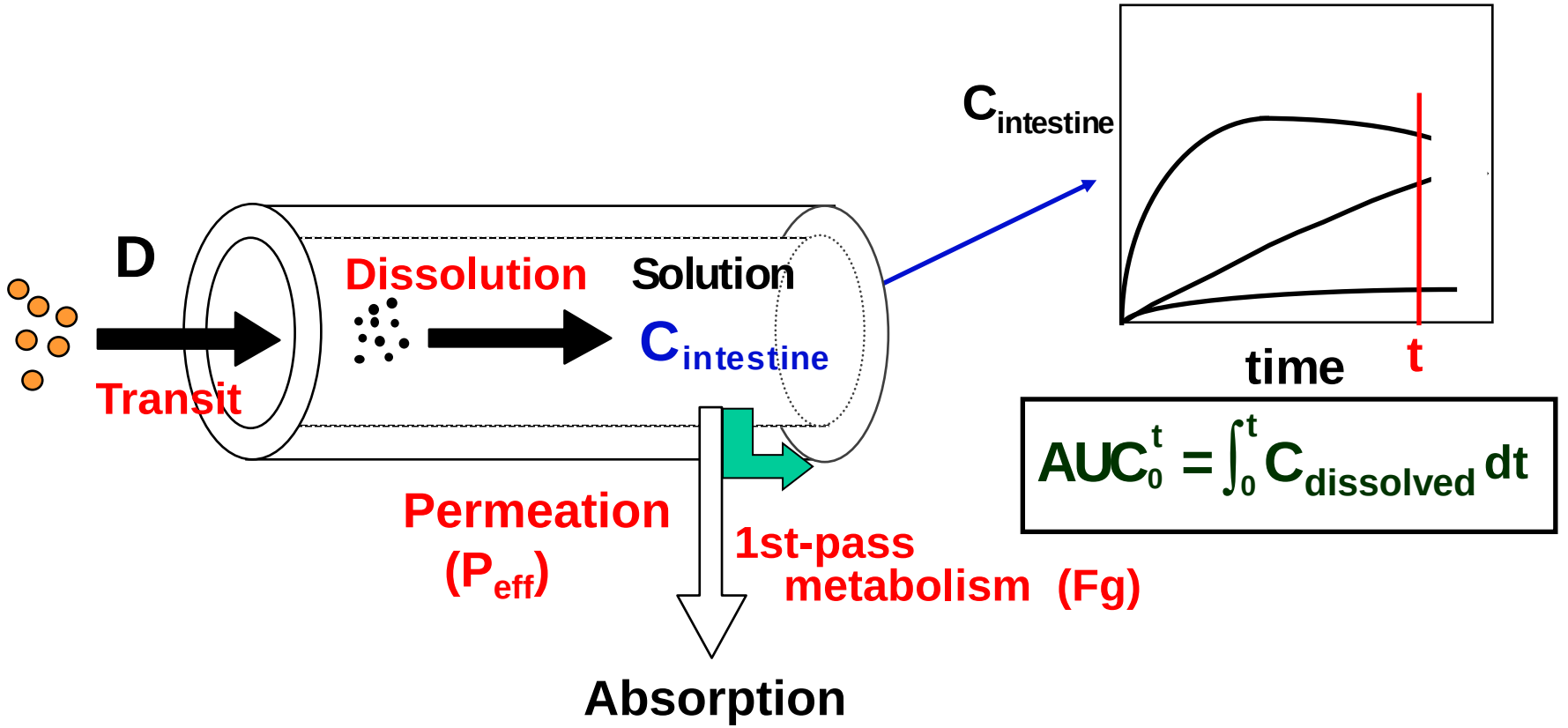
Absorption

Absorption rate = $C_{intetine}$ x CL_{perm}

= $C_{dissolved}$ x P_{eff} x SA

$C_{dissolved}$: total dissolved concentration of the drug in the intestine

Macroscopic analysis of drug absorption



$$AUC_0^t = \int_0^t C_{dissolved}\, dt$$

$$\text{Absorbed amount} = \frac{AUC_0^t \times P_{eff} \times SA}{Fa} \times Fg$$

Question to audience

Effective permeability（P_{eff}）

Q: Does P_{eff} in the human small intestine change with diet?

If so, what are the main reasons?

To understand the intent of this question, precise meaning of P_{eff} will be explained on the next slide.

Effective permeability（P_{eff}）

「A very easy theory of oral drug absorption」
by Dr. K. Sugano

Parameters for membrane structure

$$P_{eff} = \frac{PE}{\frac{1}{P_{UWL}} + \frac{1}{P_{ep}'}} = \frac{PE}{\frac{1}{\frac{D_{eff}}{h_{UWL}} + P_{WC}} + \frac{1}{Acc \cdot VE \cdot f_u \left(f_0 P_{trans0} + P_{para} \right)}}$$

Lipid membrane

Unstirred Water layer

Lipid membrane

Unstirred Water layer

Parameters related to the state of the drug molecule

P_{UWL}: 非撹拌水層（UWL）透過係数

P_{ep}: 消化管上皮膜透過係数（$P_{ep}' = AccVEf_uP_{ep}$, $P_{ep} = f_0P_{trans0}+P_{para}$）

P_{WC}: 水吸収に伴う非撹拌水層移行係数

$P_{trans,0}$: 非解離型分子種の固有受動拡散透膜過係数（リン脂質部分(transcelluler)の透過）

P_{para}: 細胞間隙経路透過係数（細胞と細胞の間にある隙間（paracelluler）の透過）

f_0: 非解離型分率 — Fraction of non-dissociated drug molecule

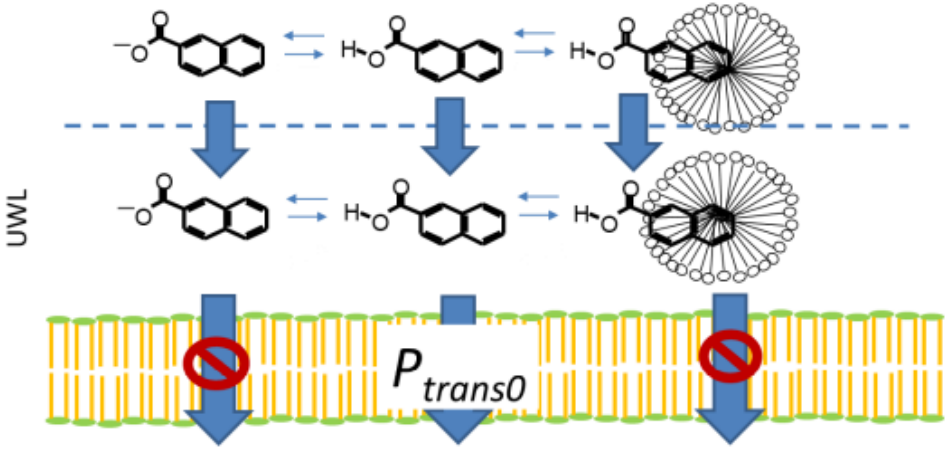
f_u: 胆汁ミセル非結合型分率 — Fraction of free drug molecule (unbound to bile acid micelles)

h_{UWL}: UWL の有効厚

PE: 襞構造による表面積拡大係数

VE: 絨毛構造による表面積拡大係数

Acc: 上皮膜へのアクセス率（ほぼ 1 として OK）



State of drug molecule and membrane permeation

Effective permeability（P_{eff}）

Food intake stimulates bile secretion and increases the total dissolved concentration of drugs ($C_{dissolved}$) by incorporating into bile acid micelles.

Drug molecule

However, when the undissolved (solid) drugs remain in the solution, free drug concentration remains unchanged and f_u (fraction of free drug molecules) decreases.

In many poorly soluble drugs, P_{eff} is reduced by food intake (compared to fasting) !

Effective permeability（P_{eff}）

「A very easy theory of oral drug absorption」
by Dr. K. Sugano

Parameters for membrane structure

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Unstirred Water layer

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P_{UWL}: 非撹拌水層（UWL）透過係数

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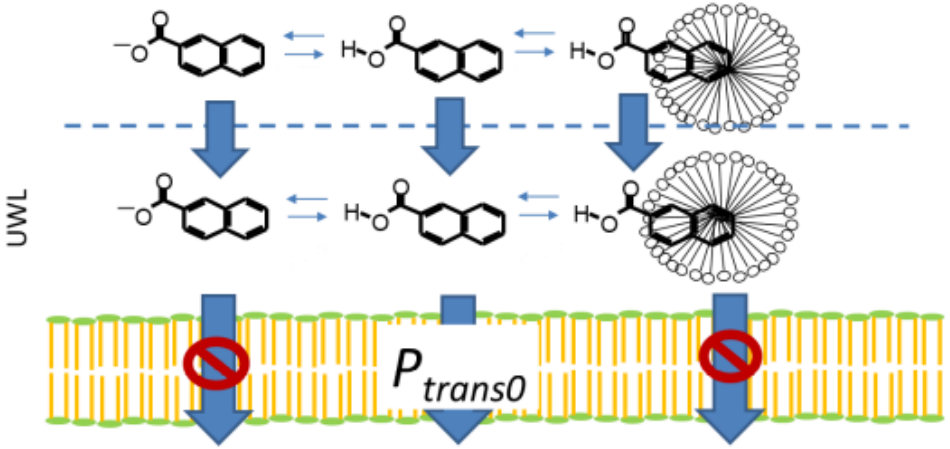
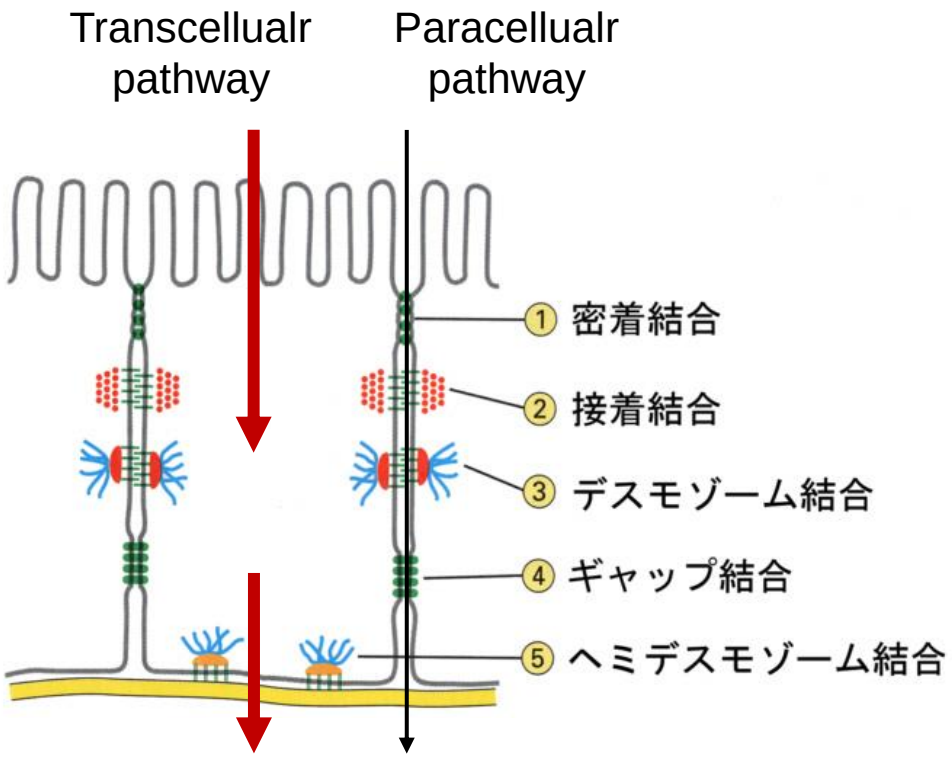


State of drug molecule and membrane permeation

Contribution of paracellular pathway to real drug absorption



- Oral absorption of Mannitol (MW 180) is less than 20% in human.
- Paracellualr permeability is restricted by the molecular size of the drug.

Contribution of paracellular pathway to real absorption of lipophilic and high MW (400<) drug is almost negligible.

Effective permeability（P_{eff}）

P_{eff} varies with membrane structures and the state of dissolved drug molecules.

→ Not a drug-intrinsic value (intrinsic membrane permeability is P_{trans0})

- P_{eff} may vary among animal species (rat, dog, human)
- In humans, for example, P_{eff} also changes when the concentration of bile acids changes before and after food intake.
- Even in the same human subject, calculation of drug absorption at the fed state using the P_{eff} value obtained at the fasted sate may give an incorrect answer.

Absorption rate = $C_{dissolved}$ x P_{eff} x SA

Membrane permeation rate of drugs

In the case the effect of UWL is negligible…

Intrinsic permeability of free and non-dissociated drug molecules to the lipid epithelial membrane

$$\text{Membrane permeation rate} = C_{dissolved} \times P_{eff} \times SA$$

$$= (f_0 f_u C_{dissloved} \times P_{trans0}) \times \text{Scaling factor}$$

Fraction of free drug molecule (unbound to bile acid micelles)

Fraction of non-dissociated drug molecule

including SA and other parameters of the membrane

To consider oral drug absorption, it is important to estimate the concentration of free (un-bound) and non-dissociated drug concentration dissolved in the gastrointestinal tract.

Case study in which

Joint research with Boehringer Ingelheim Co.

analysis of the concentration of free and non-dissociated drugs ($f_0 f_u C_{dissloved}$) on the surface of the gastrointestinal mucosa is important

Dr. Risa Aihara

ELSEVIER

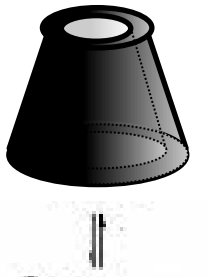
International Journal of Pharmaceutics

Volume 600, 1 May 2021, 120494

In vitro-in vivo correlation in the effect of cyclodextrin on oral absorption of poorly soluble drugs

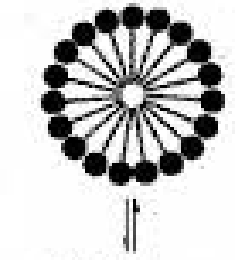
Risa Aihara [a], Roman Messerschmid [a], Masashi Mizoguchi [a], Koichi Wada [a], Keiko Minami [b], Haruki Higashino [b], Toshihide Takagi [b], Makoto Kataoka [b], Shinji Yamashita [b]

Oral formulation with Cyclodextrin（CyD）



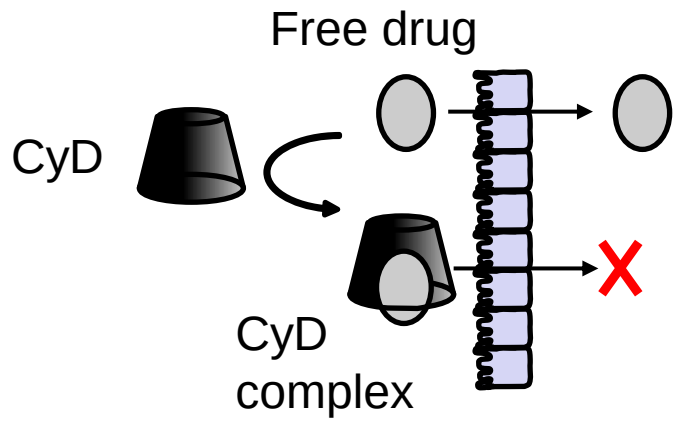
Drug molecule

Bile acid micelles



Drug molecule

Drug absorption from CyD including formulation – *basic understanding*



To design an effective formulation with CyD, amount of CyD contained in the formularion should be determined carefully.

［CyD］>>［Drug］　Excess amount of CyD ⇒　drug dissolves completely

- Total dissolved drug concentration（ $C_{dissloved}$ ）is constant（plateauing ）
- Free drug concentration decreases with increasing the amount of CyD
- Drug absorption possibly decreases due to the decrease in absorption rate

［CyD］< ［Drug］　⇒　Undissolved drug remains

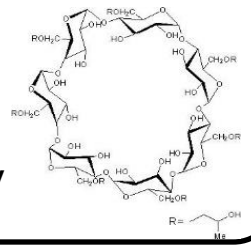
- Total dissolved drug concentration（ $C_{dissloved}$ ）increases with increasing the amount of CyD
- At the equilibrium state,　free drug concentration is kept constant regardless of the CyD amount（＝saturated solubility of the drug）
- Is drug absorption rate constant ?

In vitro study using μFlux system

Drug dissolution and membrane permeation were quantitatively evaluated from suspensions or solutions containing a fixed amount of drug (HP-βCyD concentration: 0-20%)

Hydroxy propyl -βCyD (HP-βCyD)

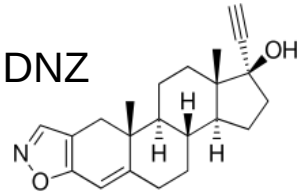
- hydrophilic (HP)
- already used clinically



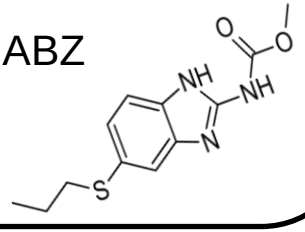
Danazol (DNZ)
Albendazole (ABZ)

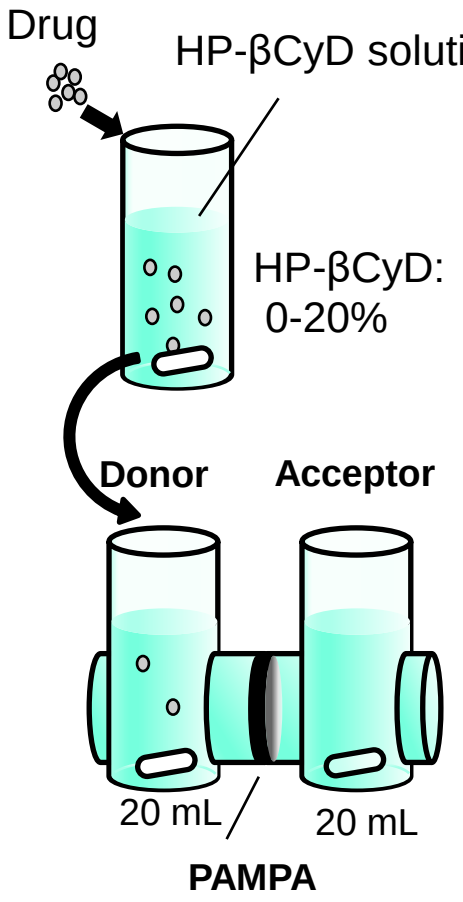
- BCS Class IIb
- HP-βCyD is reported to enhance the absorption in animals

DNZ



ABZ





μFlux system

① Prepare drug solution or suspension

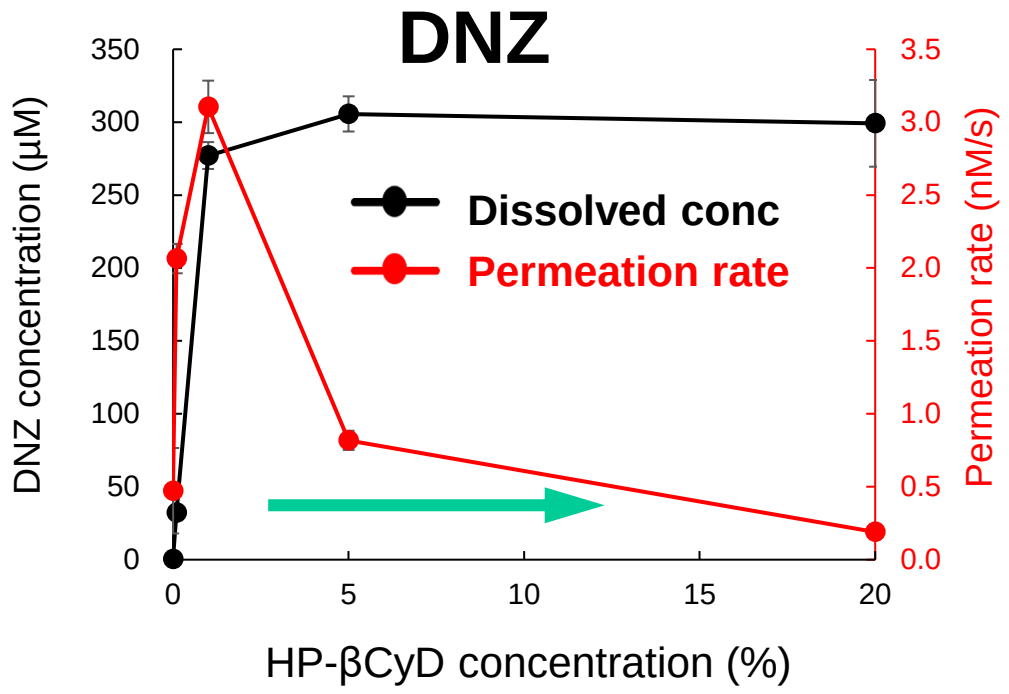
Drug is stirred for 2 hours in a solution containing HP-βCyD

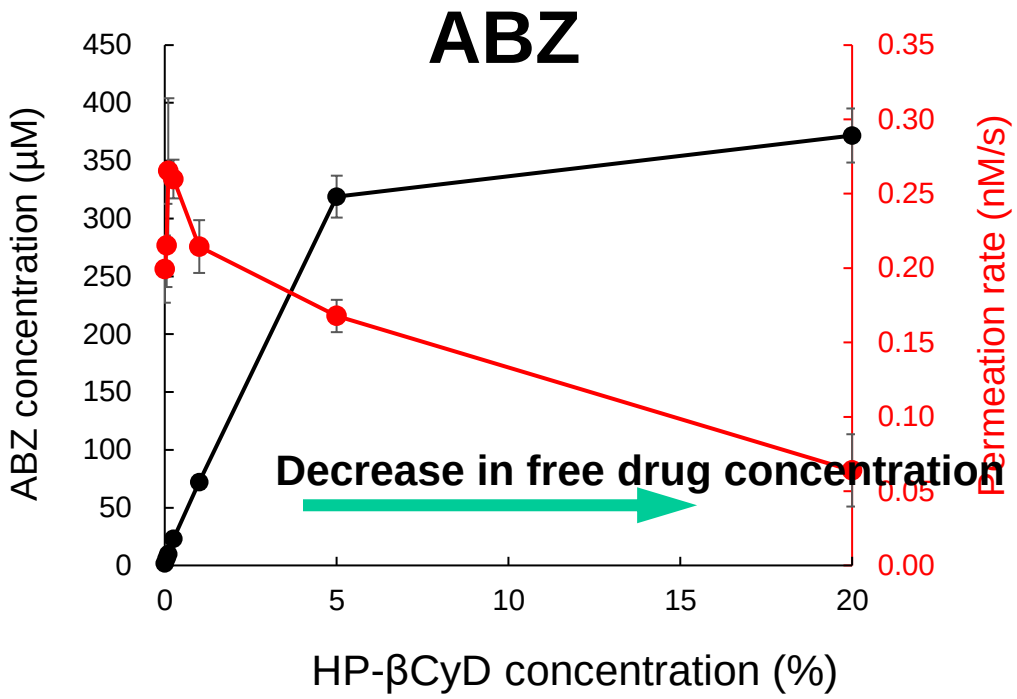
(Dissolution and inclusion reaction are in equilibrium)

② Start the experiment

③ Observe drug dissolution and permeation for 2 hours

Dissolved drug concentration and the membrane permeation rate





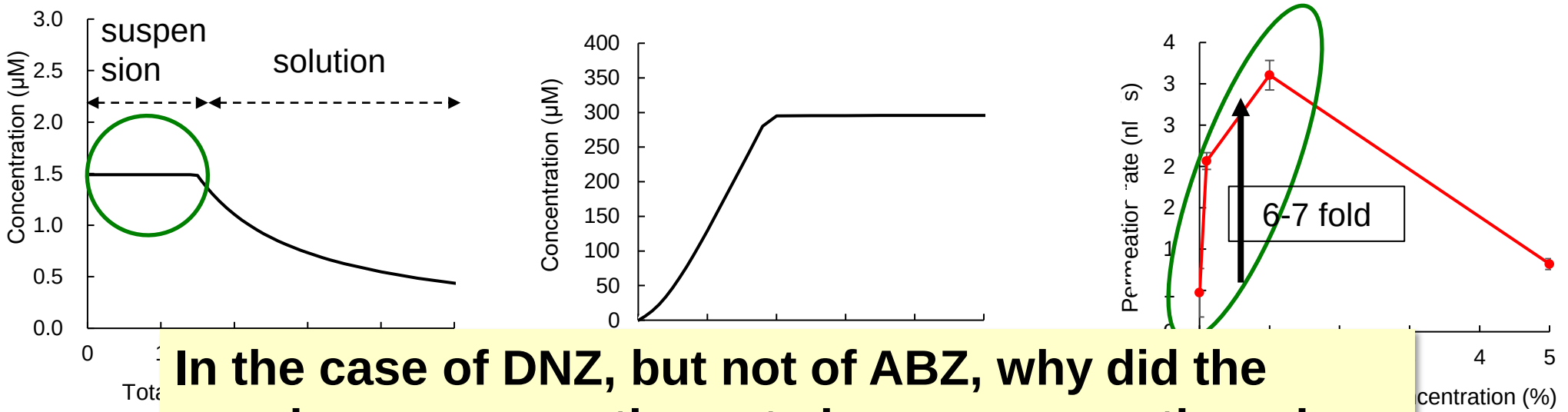
Dissolved conc: Elevated by HP-βCyD, with almost all drug dissolved at 1% (DNZ) and 5% (ABZ) or higher ($C_{dissolved}$)

Permeation rate: In DNZ, increased (about 6-7 fold) to 1% of HP-βCyD, then decreased.
In ABZ, almost no change (about 1.5-fold) until 5% HP-βCyD, then decreased.

Relation between drug concentration in the donor and membrane permeation rate

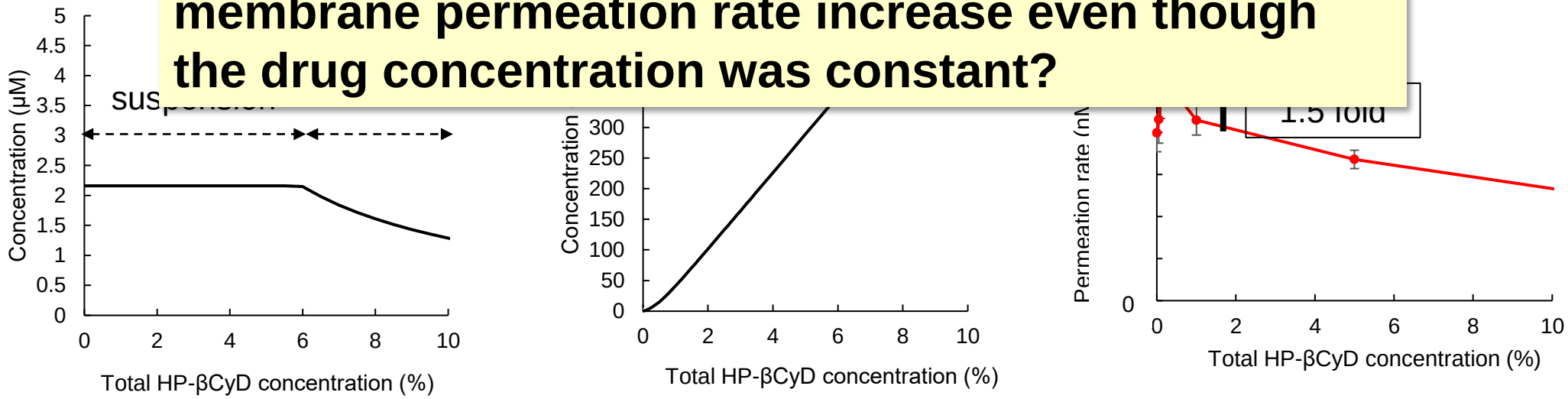
Free drug concentration | **Drug-HP-βCyD complex** | **Membrane permeation rate**

DNZ



In the case of DNZ, but not of ABZ, why did the membrane permeation rate increase even though the drug concentration was constant?

ABZ



Considering “rate-limiting process” of membrane permeation

Effective permeability（P_{eff}）

「A very easy theory of oral drug absorption」
by Dr. K. Sugano

$$P_{eff} = \frac{PE}{\frac{1}{P_{UWL}} + \frac{1}{P_{ep}'}} = \frac{PE}{\frac{1}{\frac{D_{eff}}{h_{UWL}} + P_{WC}} + \frac{1}{Acc \cdot VE \cdot f_u\left(f_0 P_{trans0} + P_{para}\right)}}$$

Lipid membrane

Unstirred Water layer

Lipid membrane

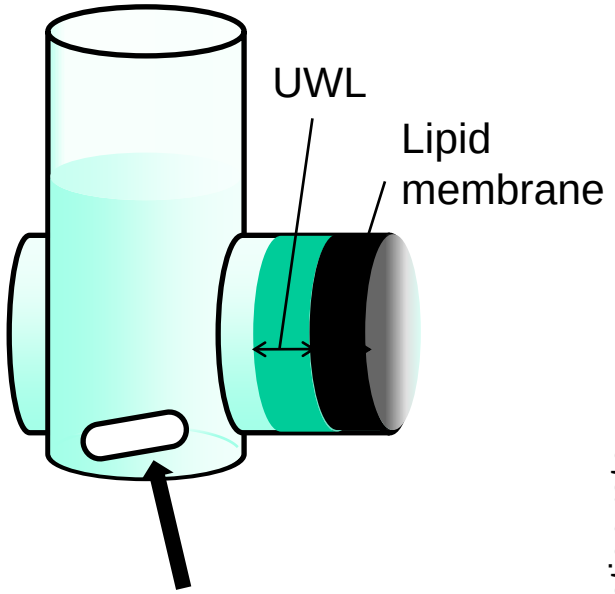
Unstirred Water layer

$P_{ep'} >> P_{UWL}$ Highly permeable drug

Diffusion of drug molecules in UWL rate limits the Membrane permeation **(UWL-limited)**

$$P_{eff} = \frac{PE}{\frac{1}{P_{UWL}}} = \frac{PE}{\frac{1}{\frac{D_{eff}}{h_{UWL}} + P_{WC}}}$$

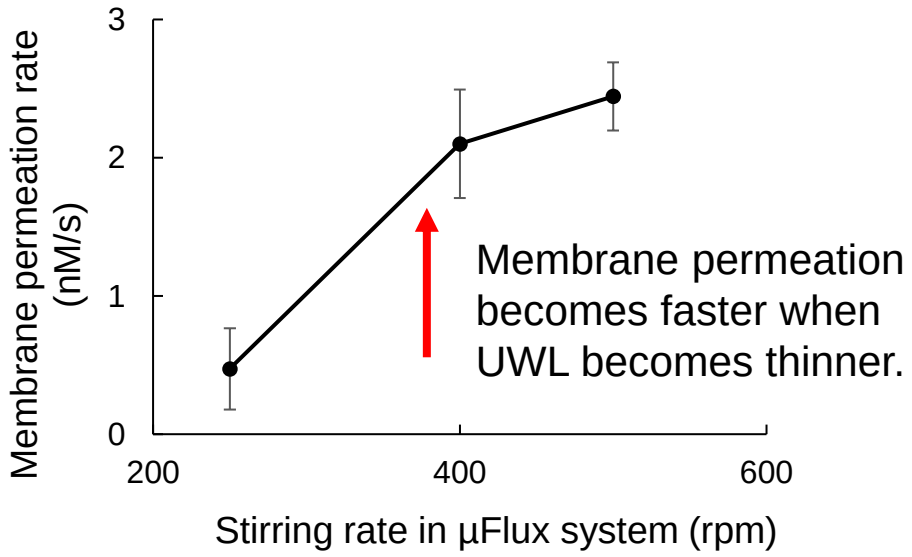
Rate limiting process in membrane permeation



increase the stirring rate

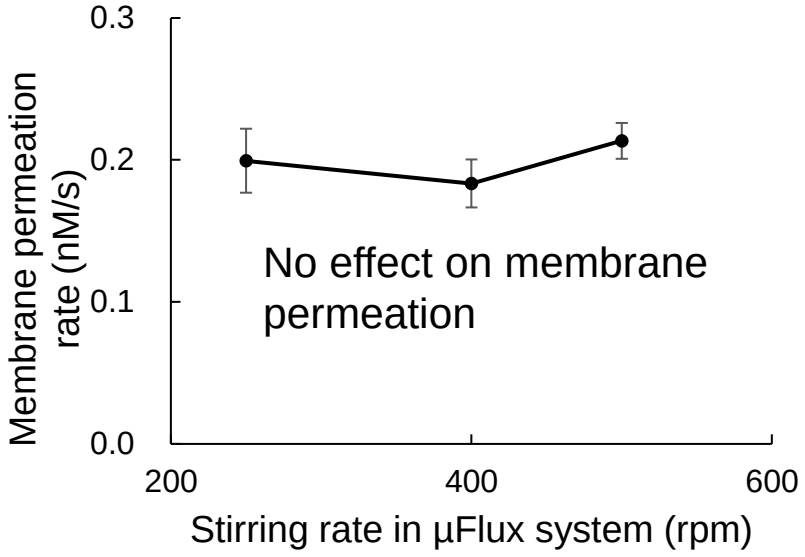
UWL limited permeation

DNZ



Membrane limited permeation

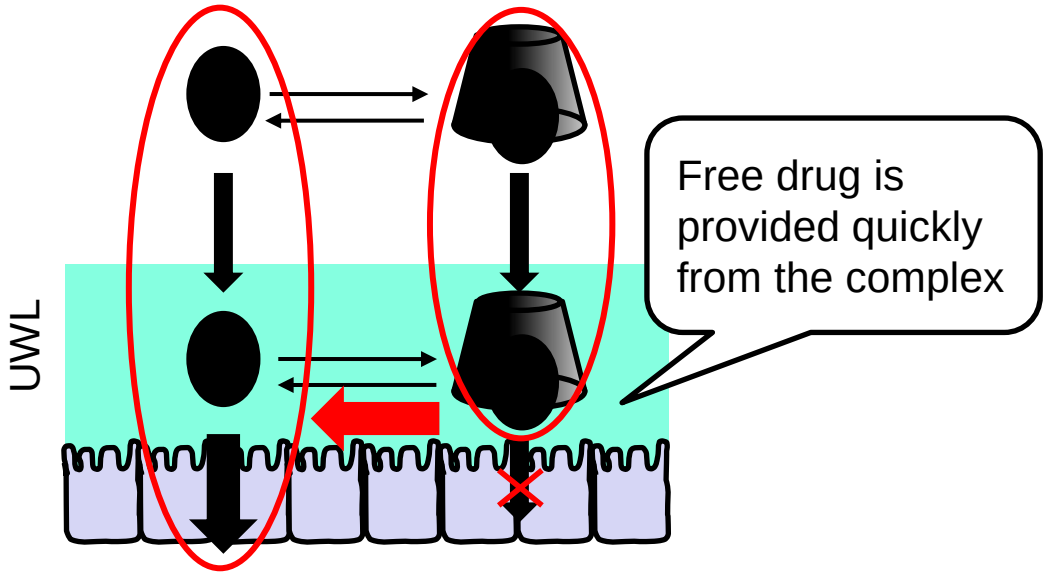
ABZ



Effect of HP-βCyD on the membrane permeation of DNZ and ABZ

HP-βCyD-drug complex can diffuse into UWL Environ. Sci. Technol. 39, 6123-6129

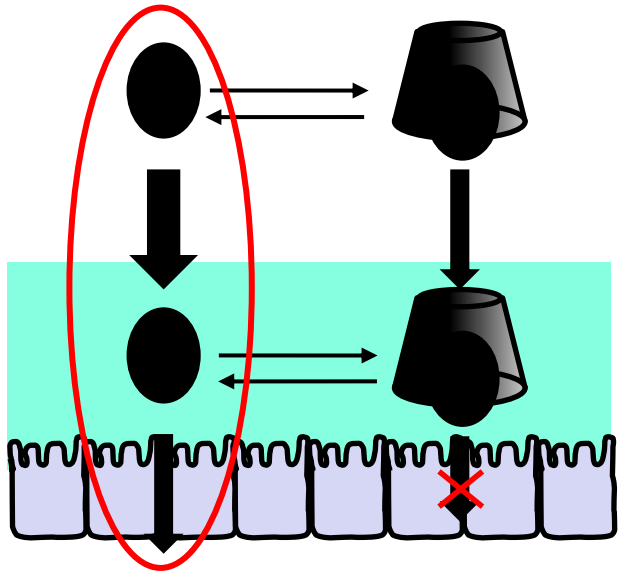
DNZ：UWL limited



Membrane permeation rate depends on both free and CyD-complexed drug concentration

→ **Increased by HP-βCyD**

ABZ：Membrane limited

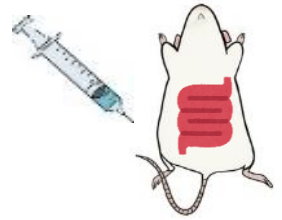


Membrane permeation rate depends only on the free drug concentration

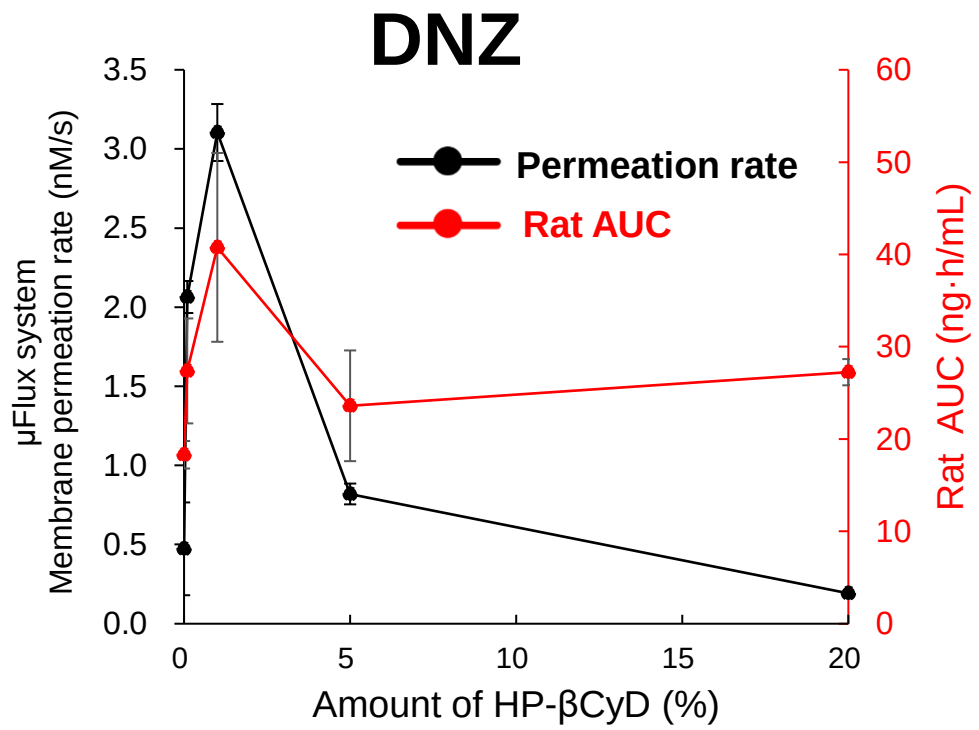
→ **No effect by HP-βCyD**

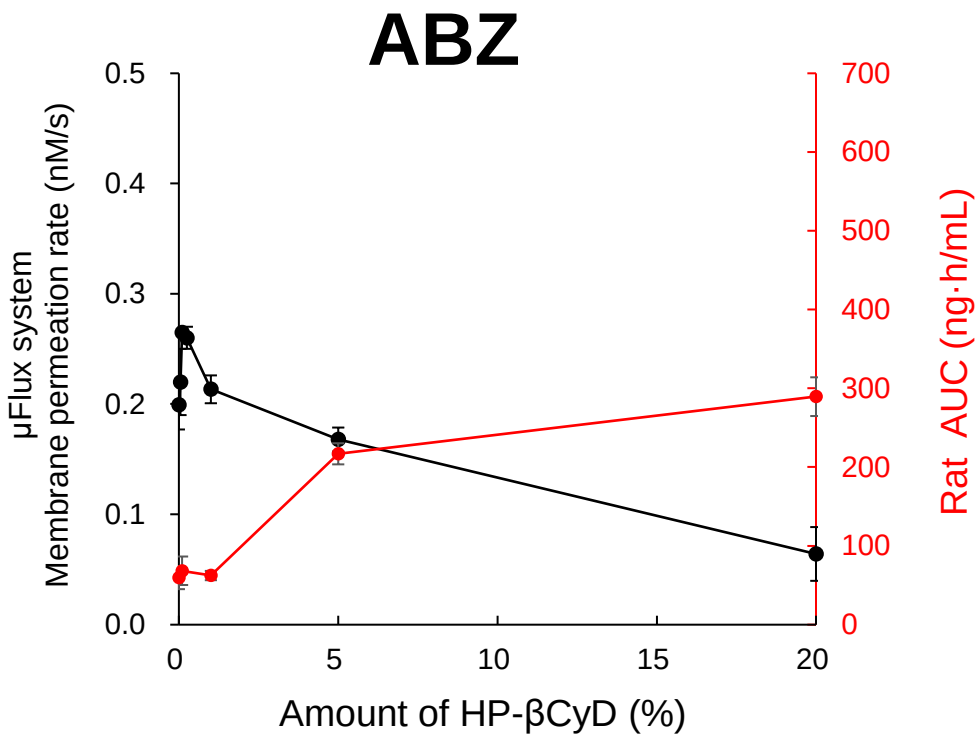
IVIVC (μFlux system and rat)

In vivo study
SD rat ♂
（250～300 g)



Compare the membrane permeation rate in μFlux system with the absorbed amount (AUC) in rat





Good IVIVC

1% HP-βCyD gave the maximum values for permeation and AUC.

Poor IVIVC

HP-βCyD increased the absorption due to the increase in dissolution rate of ABZ.

Case study

more complicated case – food effects on CyD containing formulation

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Dr. Keiko Minami

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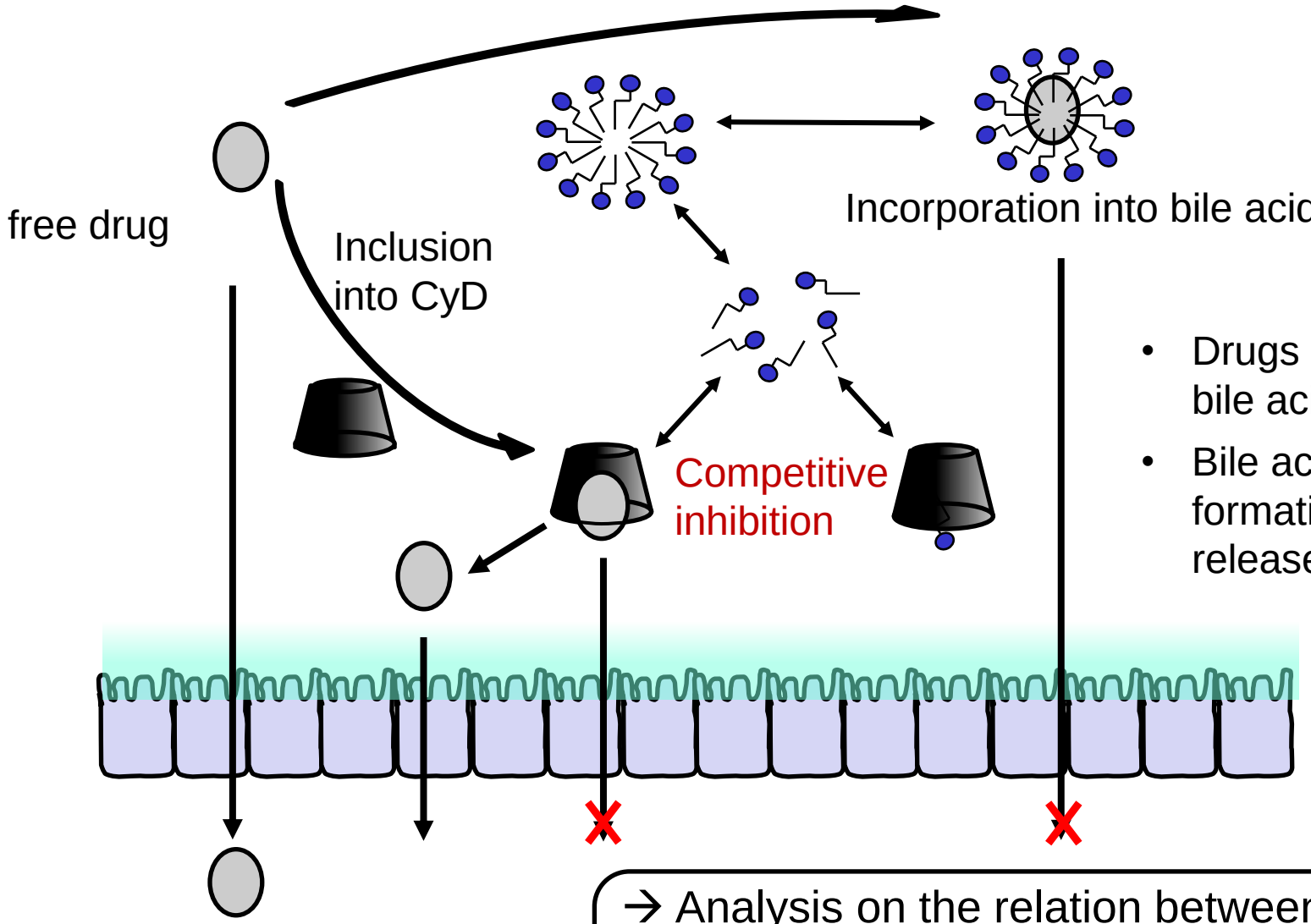
Journal of Drug Delivery Science and Technology

Volume 73, July 2022, 103440

Mechanistic analysis for positive and negative food effects on oral absorption of poorly soluble drugs from cyclodextrin containing formulations: Study with a mini-scale *in vitro* system

Risa Aihara [a] [1] ✉, Keiko Minami [b, 1], Roman Messerschmid [a], Koichi Wada [a], Toshihide Takagi [b], Shinji Yamashita [b]

Possible effects of food intake (secretion of bile acid) on oral drug absorption from CyD containing formulation



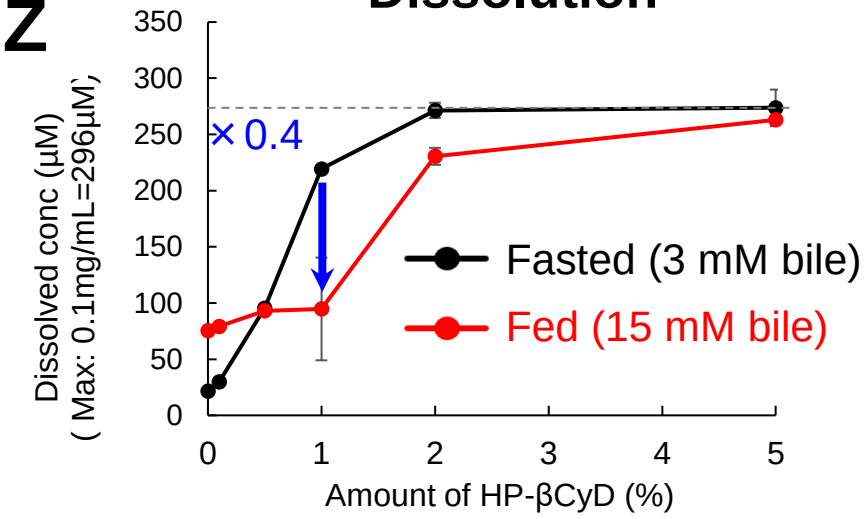
- Drugs can interact with both CyD and bile acid micelles.
- Bile acid inhibits the drug-CyD complex formation competitively leading to the release of free drug molecules.

→ Analysis on the relation between CyD amount (%) and food effect on oral drug absorption.

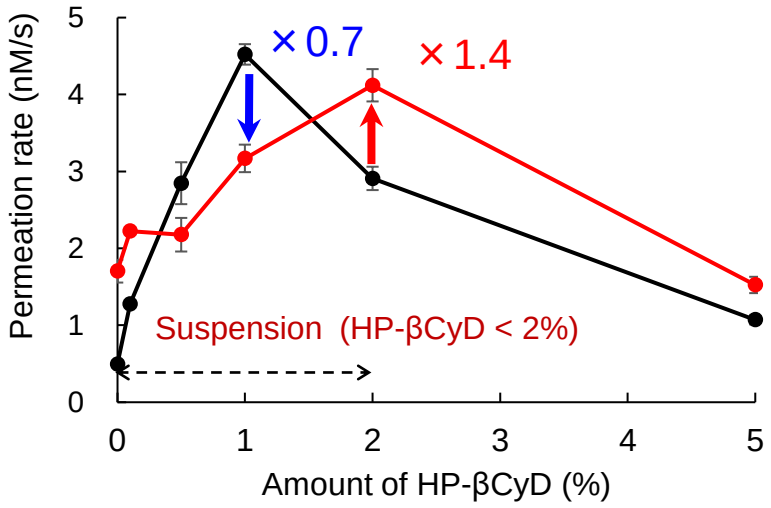
Effect of HP-βCyD on the dissolution and permeation of drugs in μFlux system

DNZ

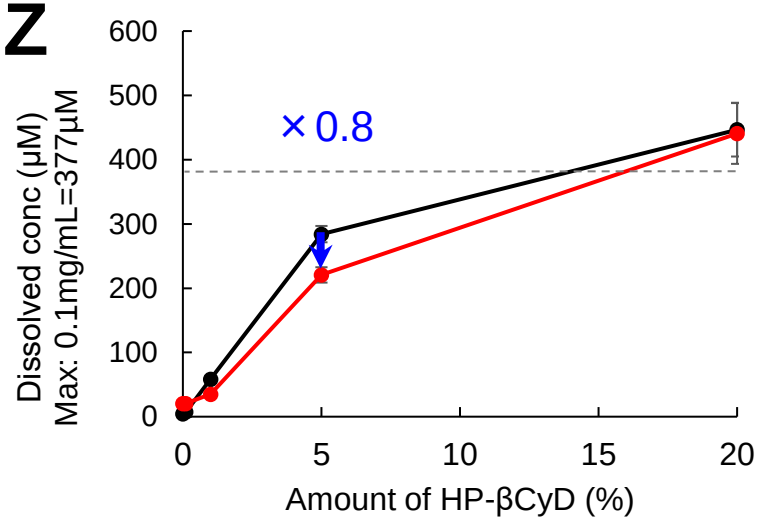
Dissolution

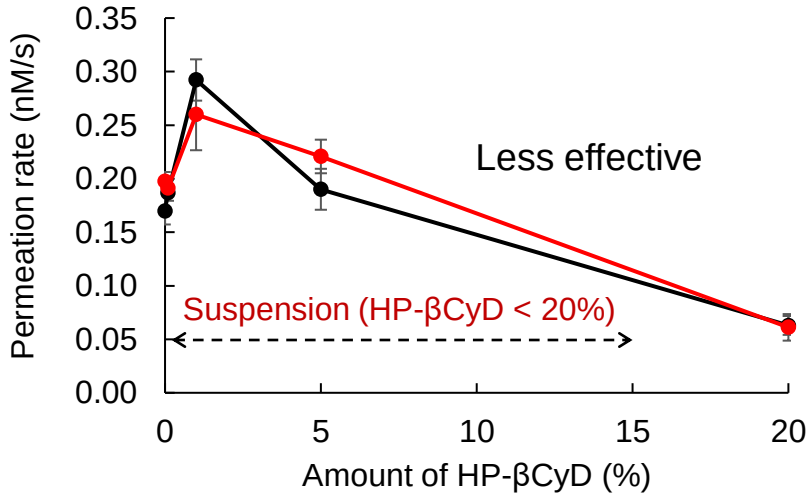


Membrane permeation



ABZ





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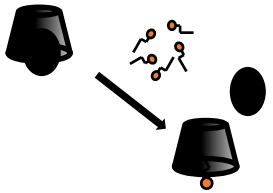


Fed condition

- Dissolution
  decrease at 1% HP-βCyD
- Permeation
  decrease at 1% HP-βCyD
  increase at 2% HP-βCyD

Analysis based on the chemical equilibrium theory

Simulating [free drug], [Drug-CyD] and [Drug-bile micelle] concentration at various HP−βCyD amount (%)

Complexation constant

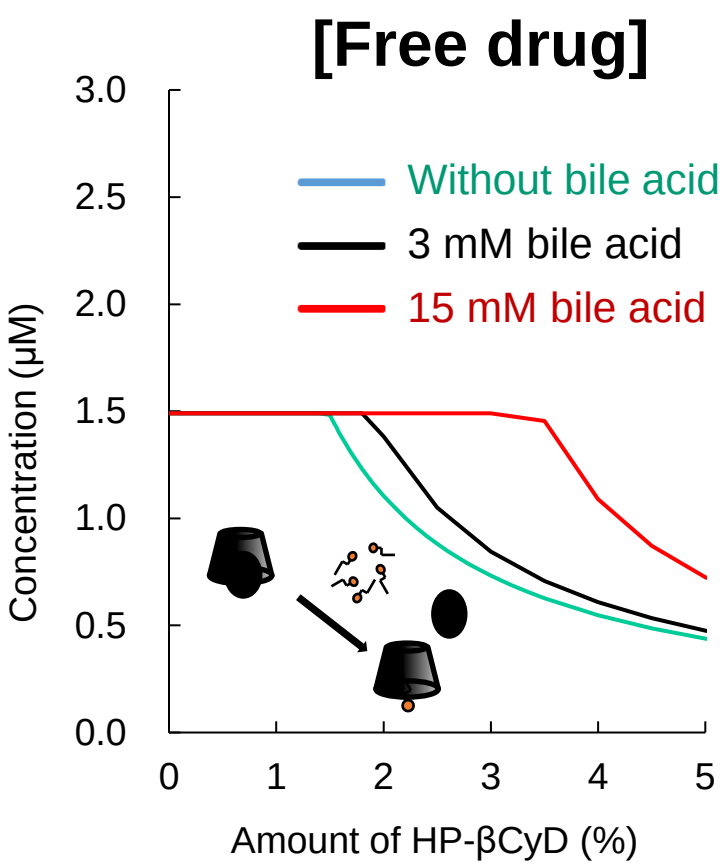
$$K_{D:CyD} = \frac{[D:CyD]}{[D][CyD]}$$ Drug and HP−βCyD

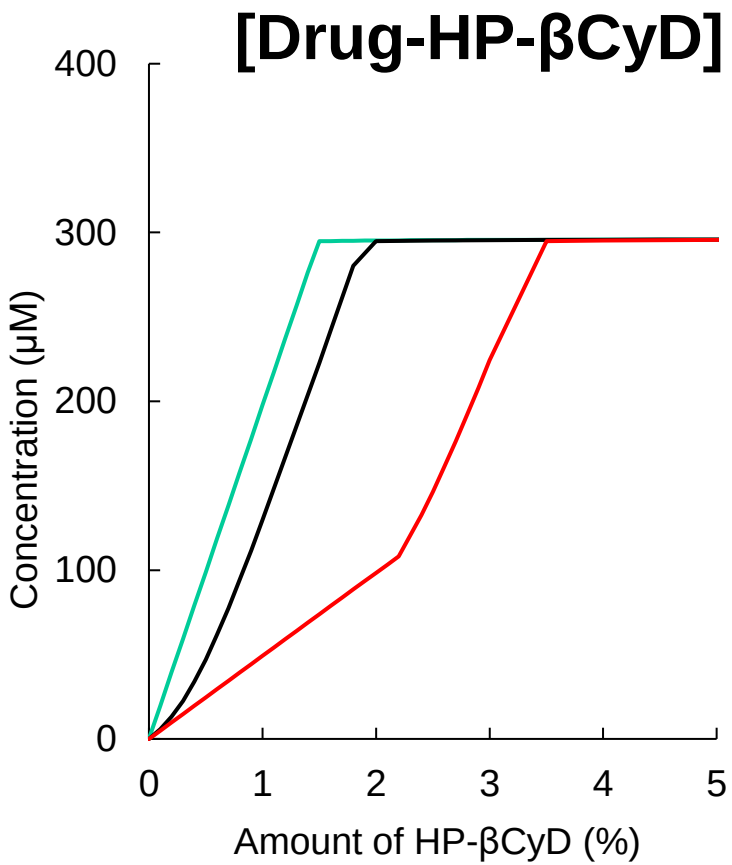
$$K_{BS:CyD} = \frac{[BS:CyD]}{[BS][CyD]}$$ Bile acid monomer and HP−βCyD

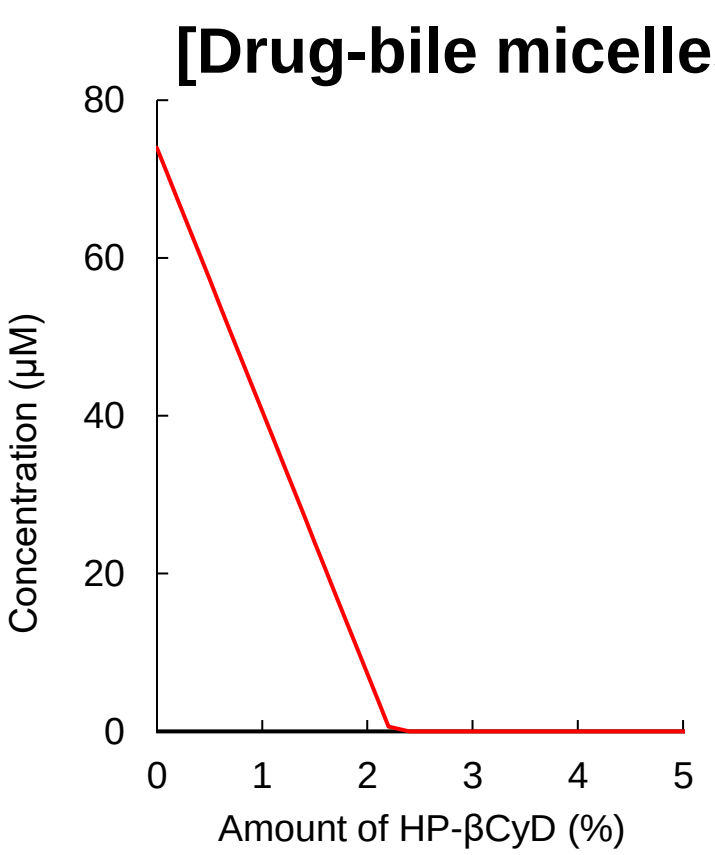
Partition constant

$$K_{BS:D} = \frac{[D:BS]/(n\cdot[M_n])}{[D][Water]}$$ Drug and Bile acid micelles

State of dissolved drug (DNZ)





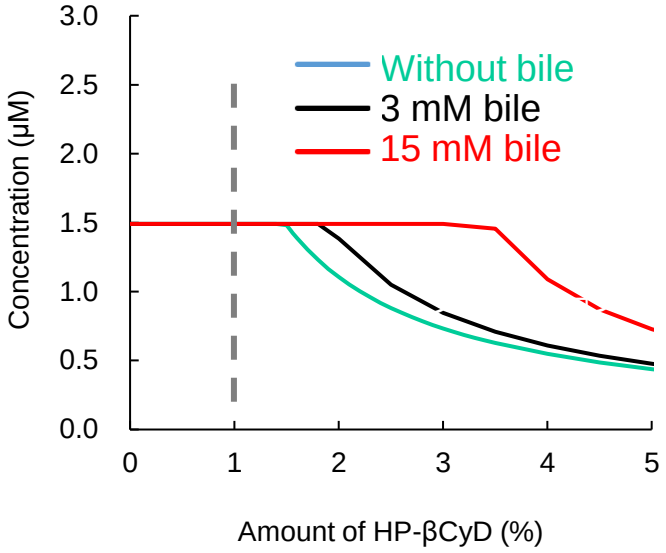


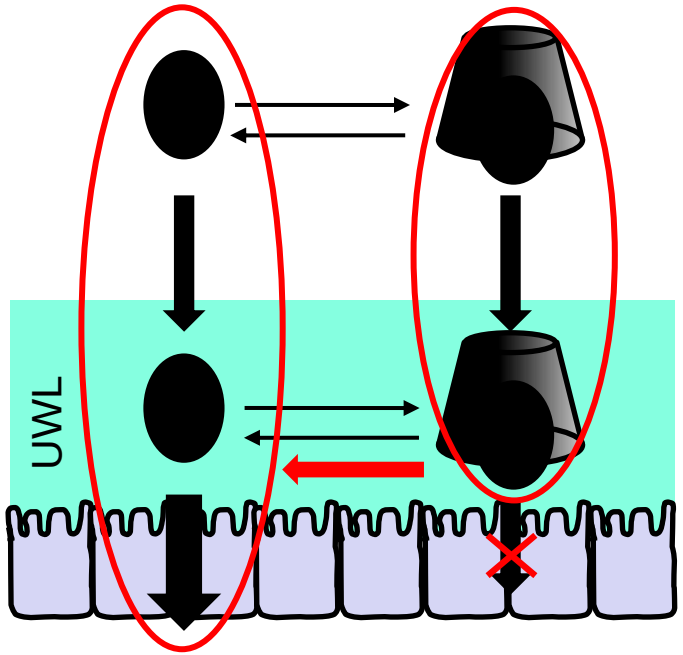
Consider the effect of drug-CyD-bile acid interactions on membrane permeation of DNZ.

1% of HP-βCyD

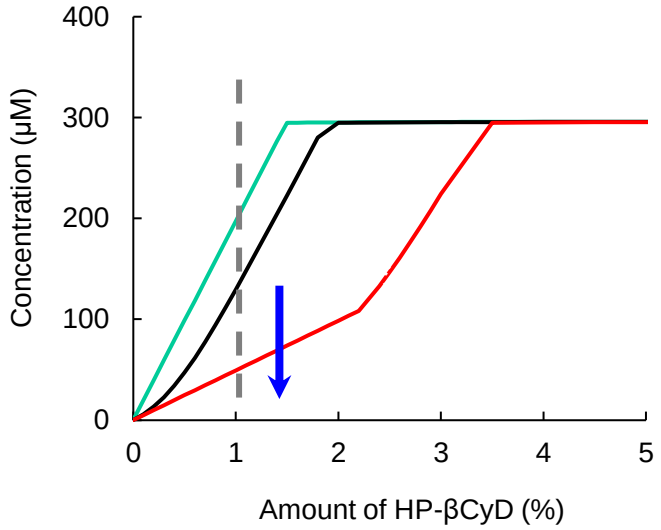
- Free drug concentration was constant in all conditions (suspension).
- Concentration of Drug-CyD complex decreased
- Permeation of DNZ decreased at Fed condition (×0.7)

Free drug





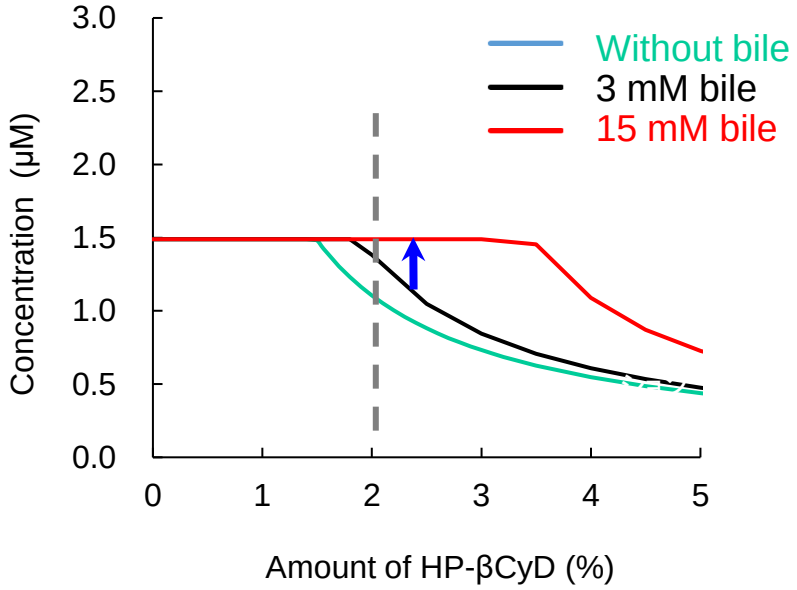
Drug-CyD complex

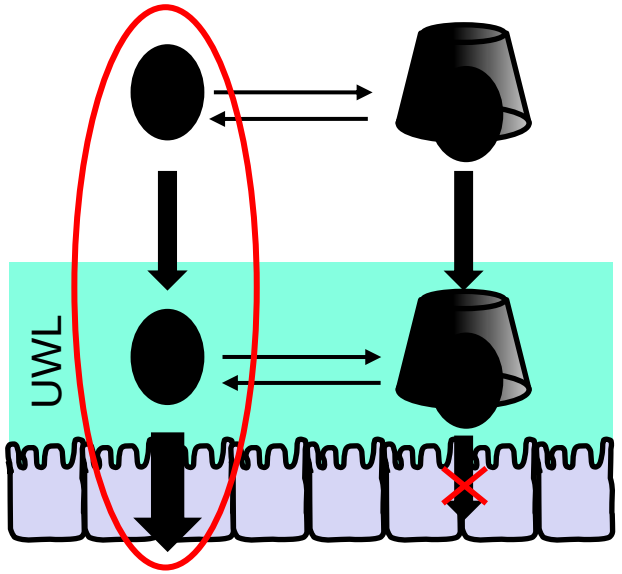


Because membrane permeation of DNZ is UWL limited and depends on both free and CyD complexed drug concentration, decrease in complex concentration may cause the decrease in permeation rate at 1% amount of HP-βCyD.

2% of HP-βCyD

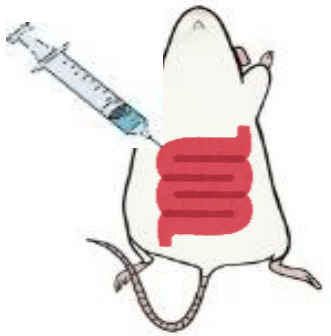
- DNZ dissolved completely in Fasted but not in Fed condition. Therefore free drug concentration was higher in Fed condition than in Fasted.
- Permeation of DNZ increased at Fed condition (×1.4)

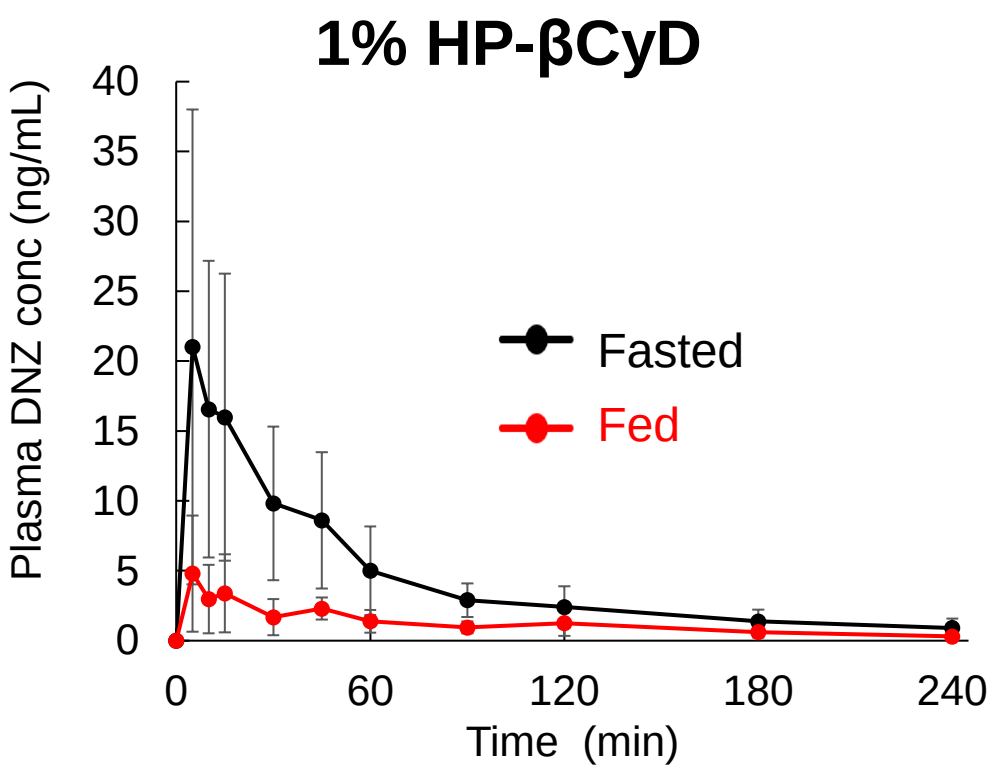


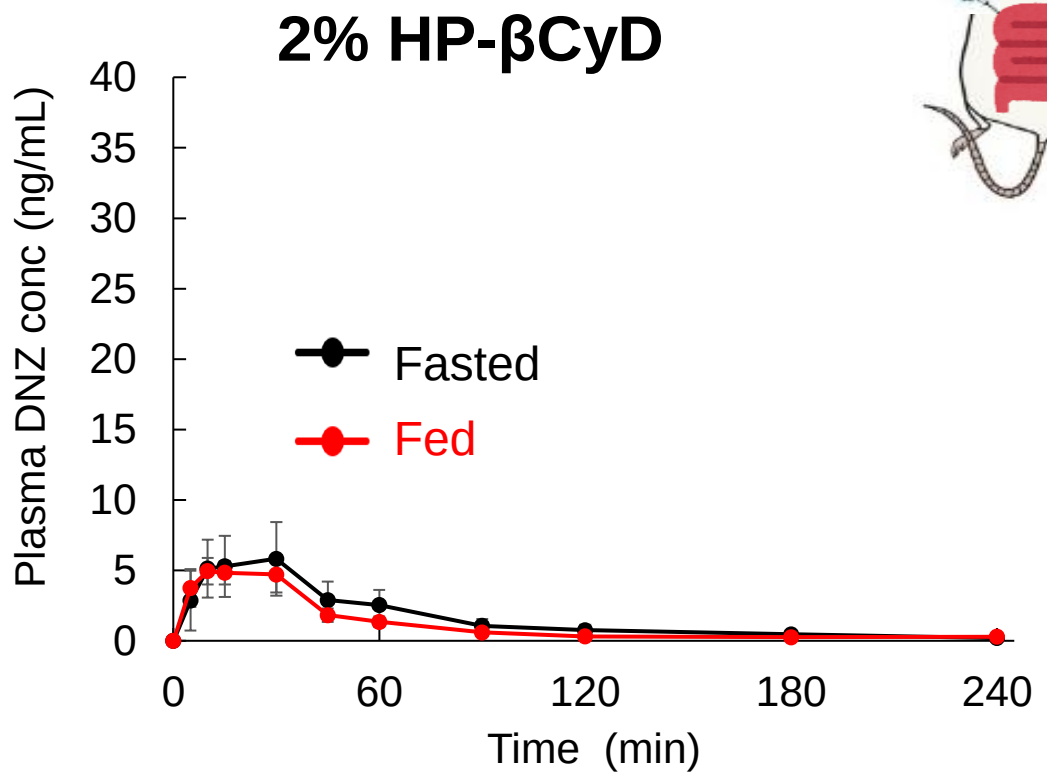


Higher concentration of free drug resulted in the faster permeation rate at Fed condition (15 mM bile acid) than at Fasted.

IVIVC (μFlux system and rat)







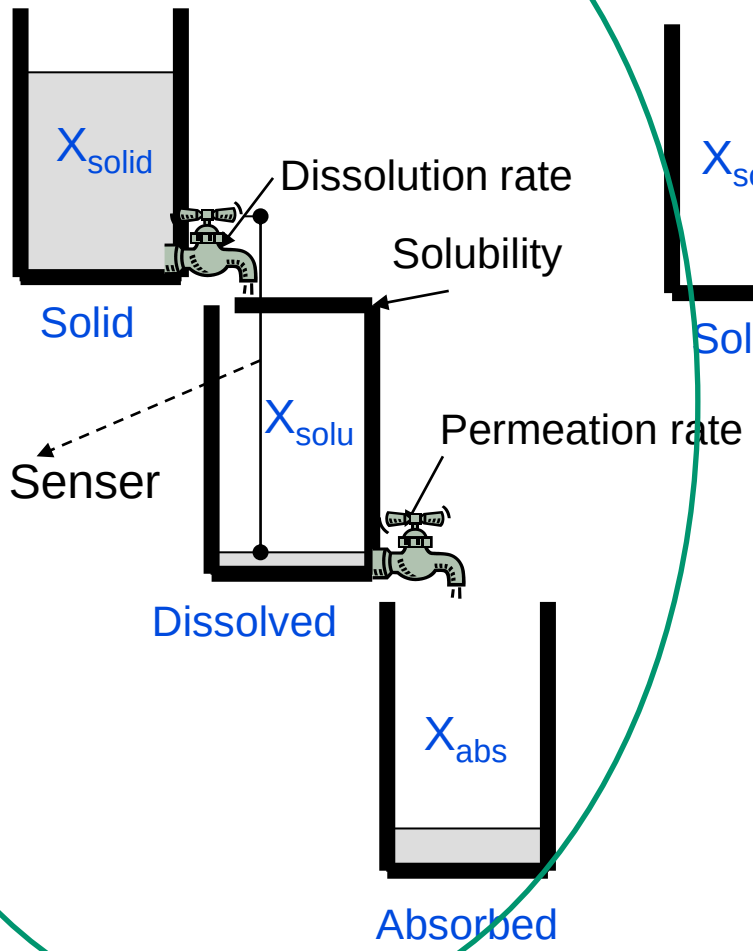
Effect of food intake (high bile acid concentration)

Amount of HP-βCyD	1%	2%
In vitro permeation	decrease	increase
In vivo AUC	decrease	No effect

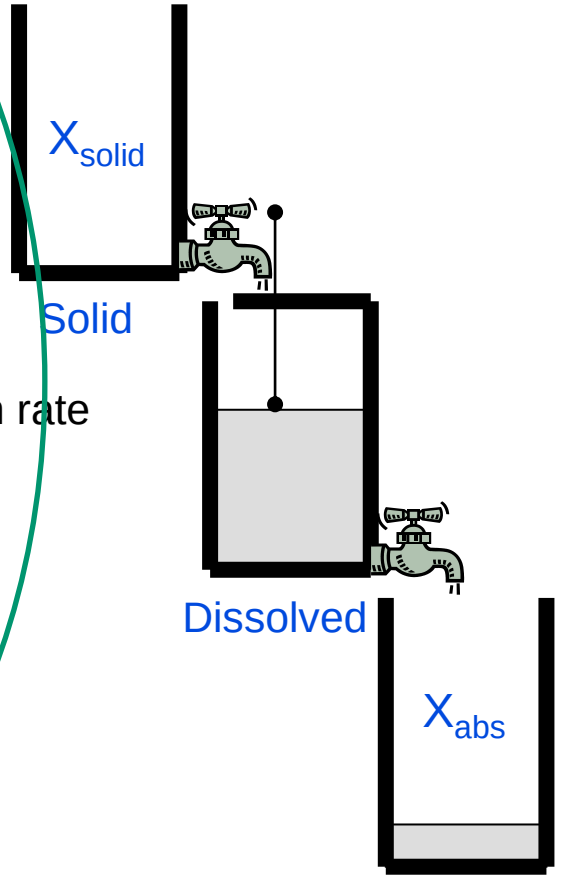
Why not match?

Rate limiting process of oral drug absorption

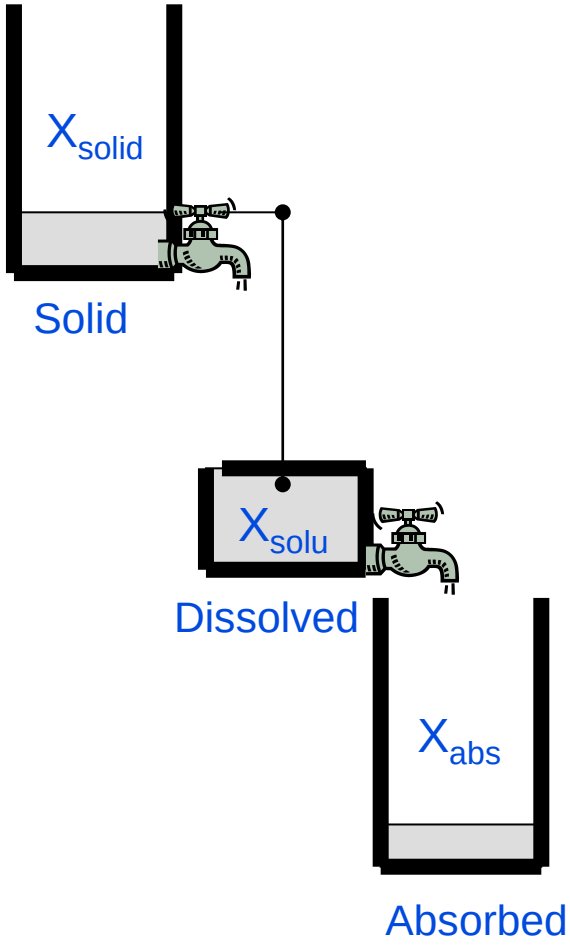
(A) Dissolution rate



(B) Permeability



(C) Solubility-permeability



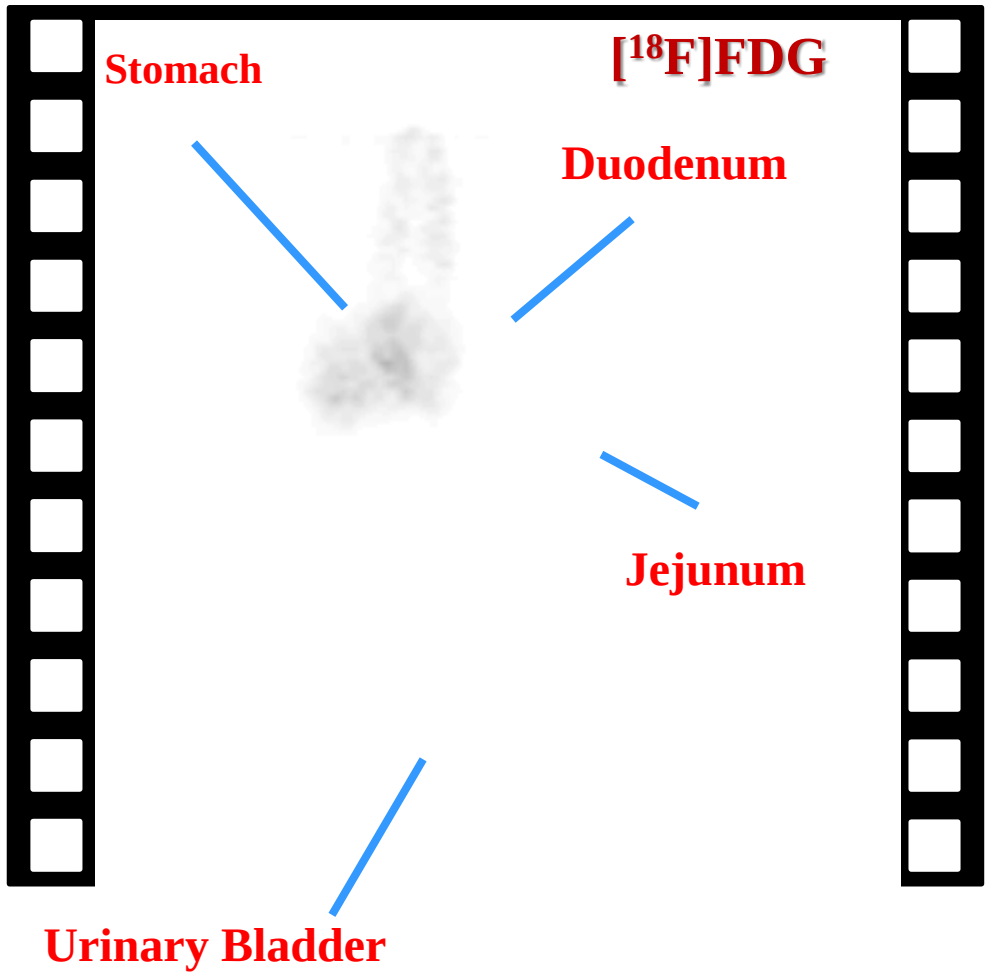
L. Yu, 1999, 1883
Sugano et al, DMPK 2007, 225

My conclusion is….

Drug absorption process after oral administration is quite complicated and hard to predict all processes correctly. Concept of "rate limiting process" is useful to make it simple.

However, regardless of the rate limiting process, at first, free drug concentration profile at the surface of the intestinal membrane should be estimated to predict the drug absorption.

GI transit and absorption of orally administered drug (PET imaging, rat)



Kataoka M, et al., Pharm Res. 2012. 29(9):2419-31

Acknowledgment

Risa Aihara (Boehringer Ingelheim Japan, Inc.)
Keiko Minami (Setsunan University)

Kiyohiko Sugano (Ritsumeikan University)

Boehringer Ingelheim Japan, Inc.
Koichi Wada
Roman Messerschmid

Setsunan University
Makoto Kataoka
Toshihide Takagi