Physiologically based pharmacokinetic/pharmacodynamic model to predict the effects of formulation and food on the pharmacokinetics and pharmacodynamics of esomeprazole

약물 제형과 음식물이 에스오메프라졸의 약동학과 약력학에 미치는 영향을 예측하는 생리학 기반 약동학/약력학 모델 구축

서울대학교 의과대학 임상약리학교실
김현철

2024 Population Approach Group in Korea

2024.12.18.

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Introduction

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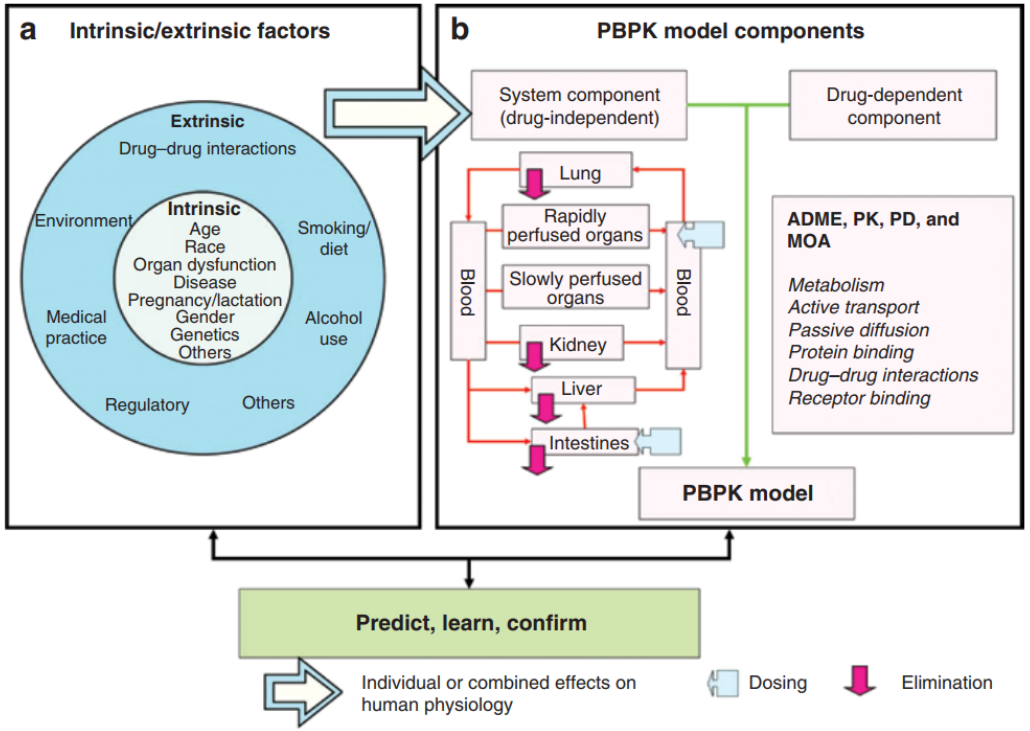
Physioloically based biopharmaceutics modeling (PBBM)

- Physiologically based pharmacokinetic (PBPK) absorption modeling
- Physiologically based absorption modeling
- PBPK modeling for biopharmaceutics applications



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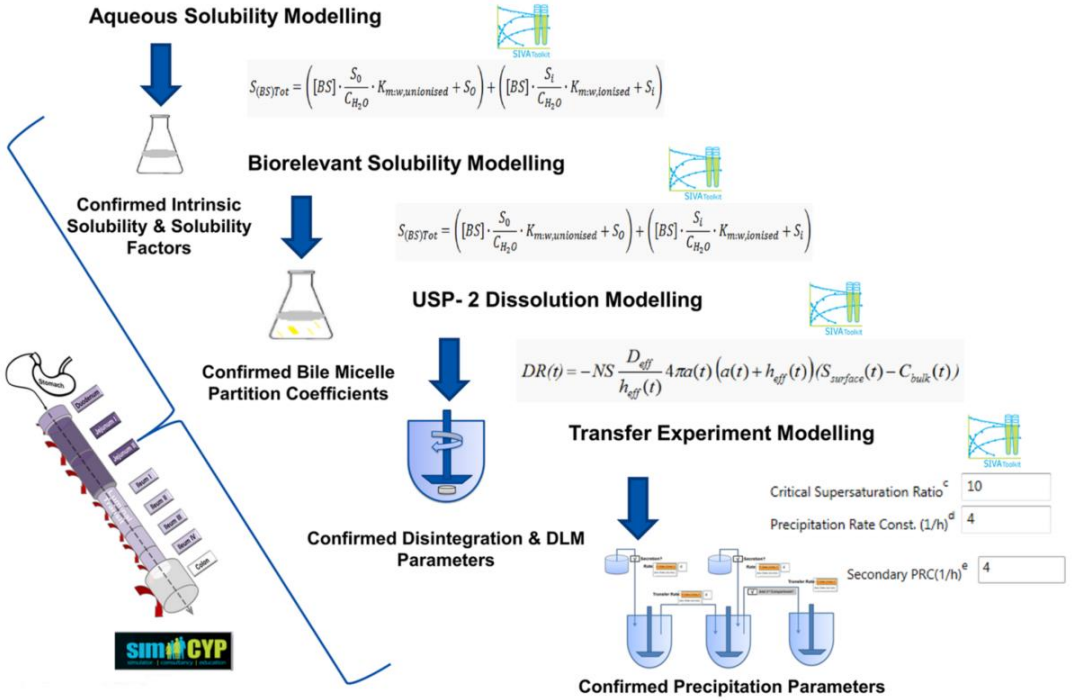
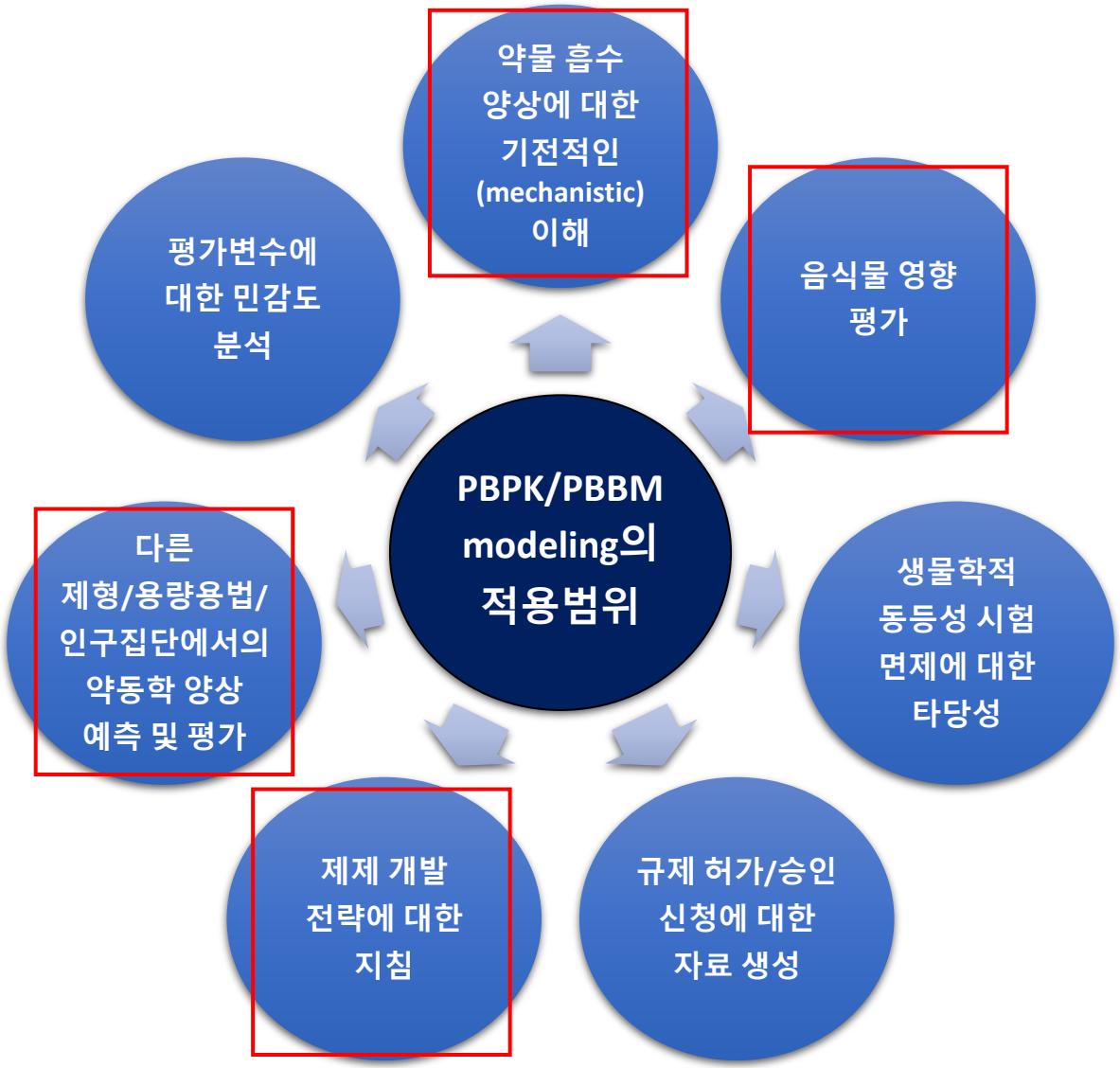


Figure 3. An integrated sequential *in vitro* modeling workflow followed within this research work.

Zhao, P., et al. "Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review." *Clinical Pharmacology & Therapeutics* 89.2 (2011): 259-267.
Pathak, Shriram M., et al. "Model-based analysis of biopharmaceutic experiments to improve mechanistic oral absorption modeling: an integrated in vitro in vivo extrapolation perspective using ketoconazole as a model drug." *Molecular pharmaceutics* 14.12 (2017): 4305-4320.

Physioloically based biopharmaceutics modeling (PBBM)



Yuvaneshwari, K., et al. "Applications of PBPK/PBBM modeling in generic product development: an industry perspective." *Journal of Drug Delivery Science and Technology* 69 (2022): 103152.

Esomeprazole

➢ Proton pump inhibitor (PPI)

- Gastric acid secretion ↓ → Medications for controlling acid-related disorders

Table 2. Pharmacokinetic Properties of Proton Pump Inhibitors

	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Bioavailability, %	30–40	64–90	80–85	-	77	52
Time to peak plasma level (tmax, hr)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
Protein binding, %	95	97	97	96	98	96.3
Half-life, hr	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19 CYP3A4	CYP2C19 CYP3A4	CYP2C19

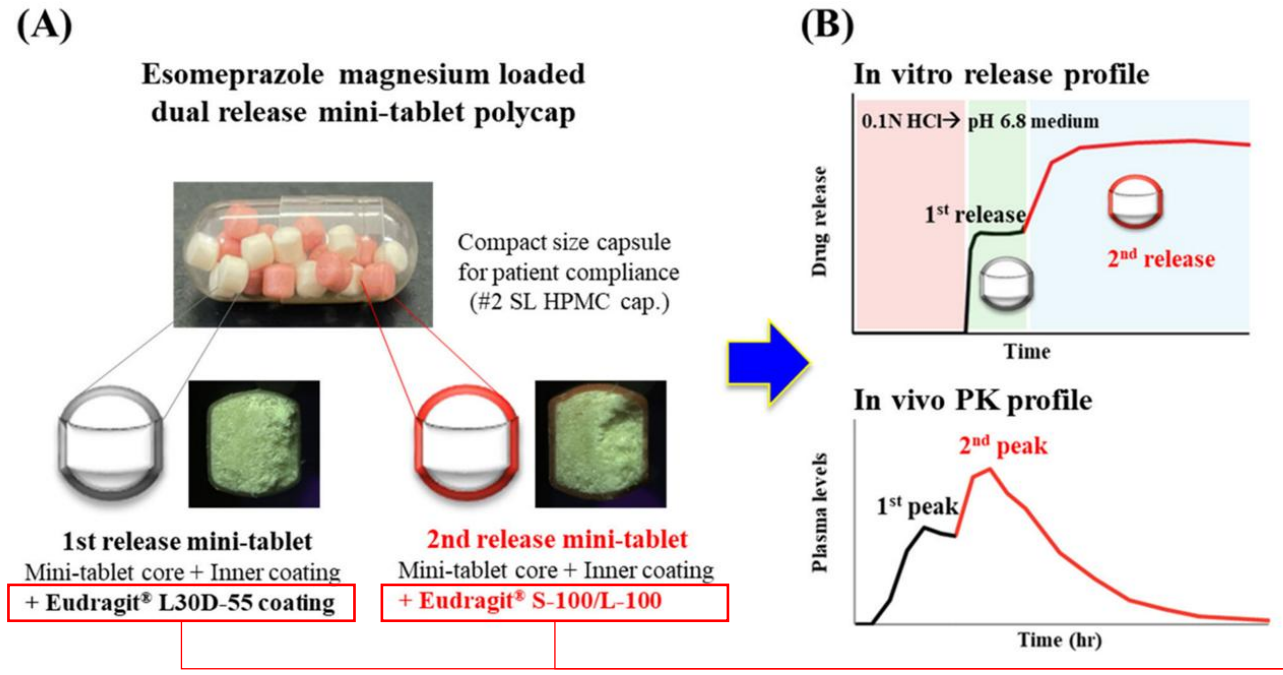
➢ Enteric-coated (EC) delayed-release formulation

- Common use for acid-labile PPIs to prevent degradation by gastric acid

Strand, Daniel S., Daejin Kim, and David A. Peura. "25 years of proton pump inhibitors: a comprehensive review." *Gut and liver* 11.1 (2017): 27.

Esomeprazole DR formulation

- New dual delayed-release (DR) capsule of esomeprazole
  - To extend the duration of gastric acid suppression, especially during the night-time



Eudragit grade	Solubility
Eudragit L30D-55	Soluble in intestinal fluid from pH 5.5
Eudragit L-100	Soluble in intestinal fluid from pH 6
Eudragit S-100	Soluble in intestinal fluid from pH 7

Figure 1. Schematic diagram of esomeprazole magnesium dual release mini-tablet polycap (DR polycaps). (**A**) image of DR polycaps. (**B**) In vitro release and in vivo pharmacokinetics profile of DR polycaps.

Kwon, Taek Kwan, et al. "Novel esomeprazole magnesium-loaded dual-release mini-tablet polycap: formulation, optimization, characterization, and in vivo evaluation in beagle dogs." *Pharmaceutics* 14.7 (2022): 1411.
Thakral, Seema, Naveen K. Thakral, and Dipak K. Majumdar. "Eudragit®: a technology evaluation." *Expert opinion on drug delivery* 10.1 (2013): 131-149.

Introduction
03

Clinical study 1 – Formulation comparison

DR: dual delayed-release
EC: enteric-coated

➢ Clinical study 1 of esomeprazole DR formulation

- To compare the pharmacokinetics (PKs) and pharmacodynamics (PDs) of the DR and EC formulations

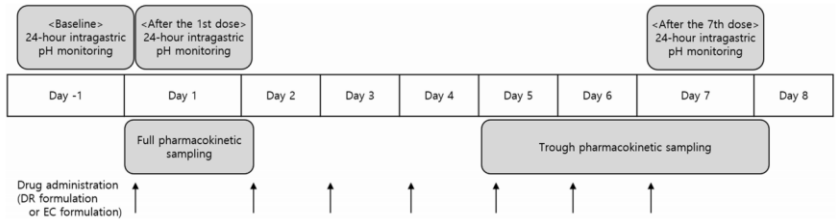


Figure 1 Study design in each period.
Note: There was a 7-day washout period between the two administration (DR formulation or EC formulation) periods.
Abbreviations: DR, dual delayed-release; EC, enteric-coated.

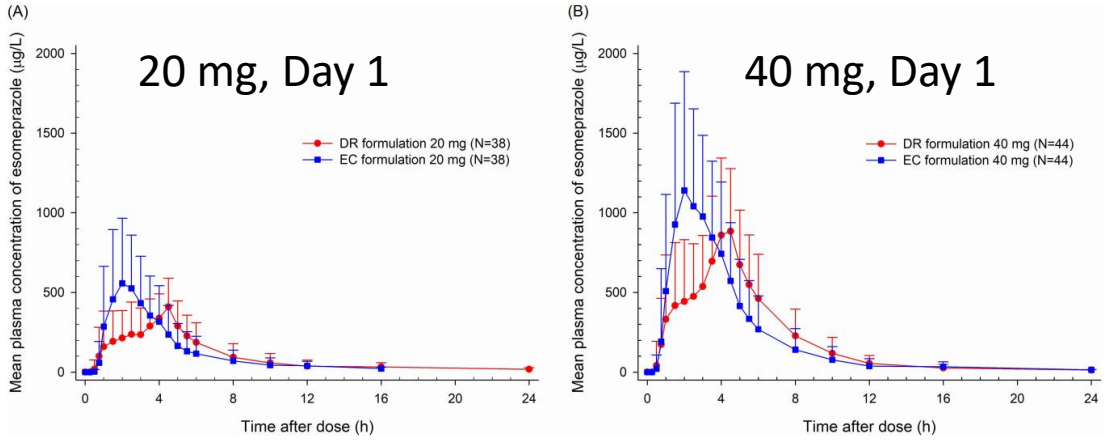


Figure 2 Mean plasma concentration-time profiles of esomeprazole for DR formulation or EC formulation after the 1st dose in (**A**) 20 mg and (**B**) 40 mg dose groups.
Note: The vertical bars represent standard deviation.
Abbreviations: DR, dual delayed-release; EC, enteric-coated.

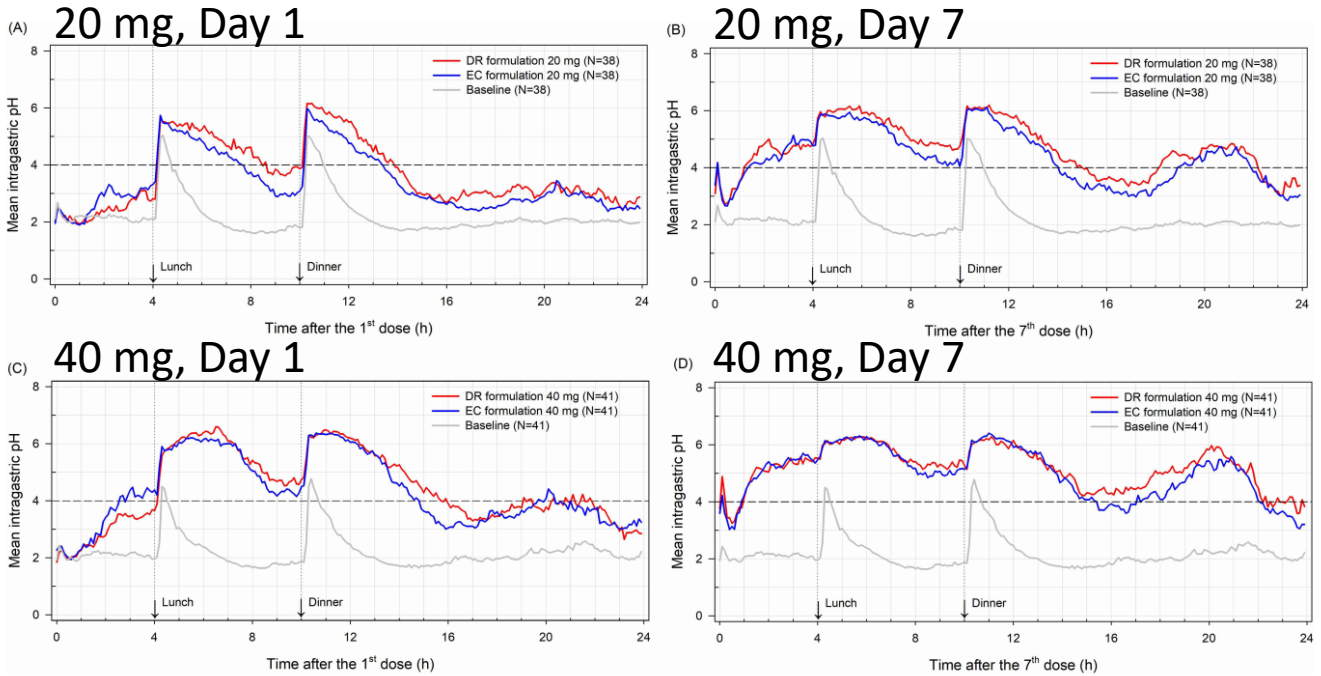


Figure 3 Mean intragastric pH-time profiles for DR formulation or EC formulation after (**A**) the 1st and (**B**) the 7th dose in 20 mg dose group and after (**C**) the 1st and (**D**) the 7th dose in 40 mg dose group.
Note: The gray line represents mean intragastric pH before the 1st dose of DR formulation or EC formulation as baseline.
Abbreviations: DR, dual delayed-release; EC, enteric-coated.

Kim, Hyun Chul, et al. "Pharmacokinetics and pharmacodynamics of Esomezol DR, a New Dual delayed-release formulation of Esomeprazole 20 mg or 40 mg, in healthy subjects." *Drug Design, Development and Therapy* (2023): 1115-1124.

Clinical study 2 – Food effect

DR: dual delayed-release

➢ Clinical study 2 of esomeprazole DR formulation

- To compare the pharmacokinetics (PKs) and pharmacodynamics (PDs) of the DR formulation in the fasted and fed states

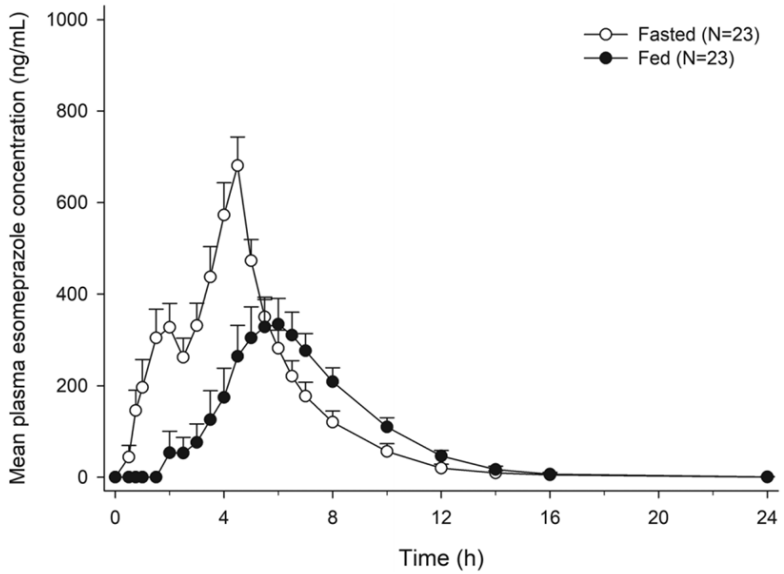


Figure 1. Mean plasma concentration–time profiles of esomeprazole after a single oral administration of 40-mg dual delayed-release formulation in a fasted or fed state. Bars represent standard errors.

Table 1. Pharmacokinetic Parameters of Esomeprazole After a Single Oral Administration of 40-mg Dual Delayed-Release Formulation in a Fasted or Fed State

Parameters	Fed (N = 23)	Fasted (N = 23)	GMR[a] (90%CI)
T_{max} (h)[b]	5.5 (2.0-10.0)	4.0 (1.0-5.0)	–
C_{max} (μg/L)	460 ± 329	768 ± 283	0.52 (0.39-0.67)
AUC_{last} (μg · h/L)	1851 ± 1585	2701 ± 1721	0.63 (0.51-0.79)
AUC_{inf} (μg · h/L)	1898 ± 1586	2745 ± 1722	–
$t_{1/2}$ (h)	1.5 ± 0.7	1.4 ± 0.5	–
CL/F (L/h)	31.6 ± 18.6	19.6 ± 10.7	–

AUC_{inf}, area under the plasma concentration–time curve from 0 to infinity; AUC_{last}, area under the plasma concentration–time curve from 0 to time of last measurable concentration; CI, confidence interval; CL/F, apparent total clearance; C_{max}, maximum concentration; GMR, geometric mean ratio; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration.
All values are presented as the mean ± standard deviation.
[a] GMR indicates the ratio of the geometric mean comparing the fed state to the fasted state.
[b] Values are presented as median (minimum-maximum).

Hwang, Sejung, et al. "Effect of Food on the Pharmacokinetics and Pharmacodynamics of a Novel Dual Delayed-Release Formulation of Esomeprazole in Healthy Subjects." *Clinical Pharmacology in Drug Development* 12.8 (2023): 839-844.

Purpose of research

- To **quantitatively** predict the **pharmacokinetics (PKs)** and **pharmacodynamics (PDs)** of the **enteric-coated (EC)** and **dual delayed-release (DR)** formulations of **esomeprazole magnesium trihydrate (EMT)** by using the PBPK/PD modeling framework

- To explore the **absorption parameters** that contribute to the **negative food effect of esomeprazole**

02
Methods

Methods
01

Mechanistic modeling for biopharmaceutic data

➢ **Experimental data** from in vitro solubility (aqueous & biorelevant) and dissolution measurements

➢ **In vitro solubility model**

- Simcyp in vitro analysis (SIVA) toolkit (version 5)
- Esomeprazole magnesium trihydrate (EMT)
  - ✓ Salt form to improve the low solubility of esomeprazole itself
  - ✓ Solubility product (K_{sp}) model
  - ✓ Two solid states model (Salt form & free form)

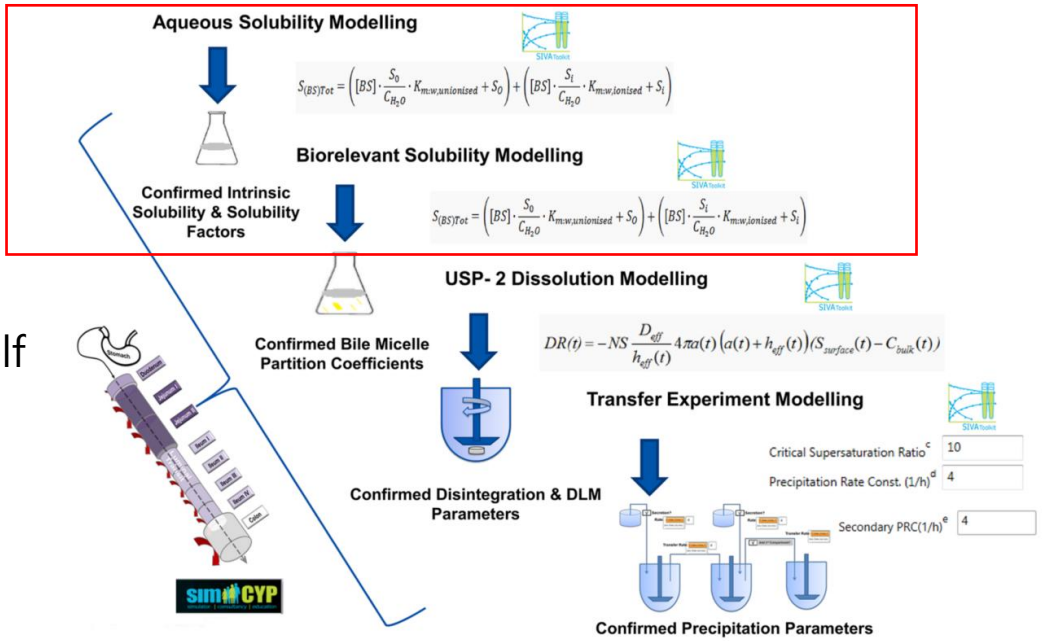
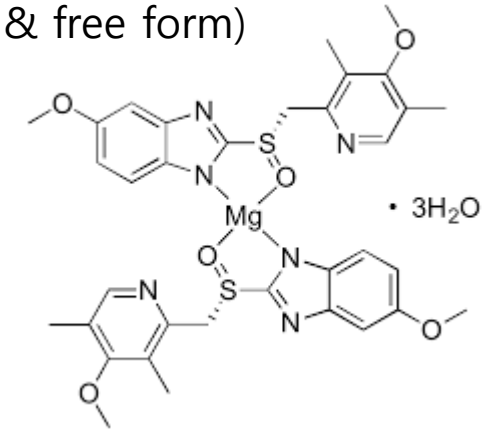


Figure 3. An integrated sequential *in vitro* modeling workflow followed within this research work.

Esomeprazole Magnesium Trihydrate	
에스오메프라졸마그네슘삼수화물	44.5mg
(에스오메프라졸(으)로서 40mg)	

<넥시움정 40 mg, 약학정보원>



<Esomeprazole magnesium trihydrate (EMT)>

Pathak, Shriram M., et al. "Model-based analysis of biopharmaceutic experiments to improve mechanistic oral absorption modeling: an integrated in vitro in vivo extrapolation perspective using ketoconazole as a model drug." *Molecular pharmaceutics* 14.12 (2017): 4305-4320.

Methods
01

Mechanistic modeling for biopharmaceutic data

DR: dual delayed-release
EC: enteric-coated

➢ In vitro dissolution model

- EC formulation
  - ✓ SIVA toolkit (Version 5)
  - ✓ Empirical first-order disintegration model

$$\%F_{disint,t} = \%F_{max} \cdot \left(1 - e^{-K_{d1} \cdot (t - t_{lag})}\right) when\ t > t_{lag}$$

$$\%F_{disint,t} = 0\ when\ t \leq t_{lag}$$

- $\%F_{disint,t}$: percentage disintegrated at time t
- $\%F_{max}$: the maximum extent of release assumed to be 100%
- K_{d1}: a first-order release constant
- t_{lag}: lag time

- DR formulation
  - ✓ Simcyp version 23R1
  - ✓ NONMEM (Version 7.5.1)
  - ✓ Pulse function

$$\%F_{released,t} = \%F_{max} \cdot \left(1 - f_1 \cdot e^{-\frac{(t - t_{lag1})^{\beta_1}}{\alpha_1}} - (1 - f_1) \cdot e^{-\frac{(t - t_{lag2})^{\beta_2}}{\alpha_2}}\right) \quad when\ t > t_{lag1}$$

$$\%F_{released,t} = 0\ when\ t \leq t_{lag1}$$

- $\%F_{released,t}$: the percentage released at time t
- f_1: the fraction of dose following the first part of the curve
- α_1 & β_1: Weibull scale and shape factors for the first fraction of dose
- t_{lag1}: lag time for the start of the first pulse
- α_2 & β_2: Weibull scale and shape factors for the second fraction of dose
- t_{lag2} lag time for the start of the second pulse from the start of the first pulse

Methods
02

Development of PBPK/PD models

➢ Korean population

- Based on 'Sim-Chinese Healthy Volunteers' population from the Simcyp version 23R1
- CYP2C19 phenotype frequency
- Liver density
- Hematocrit

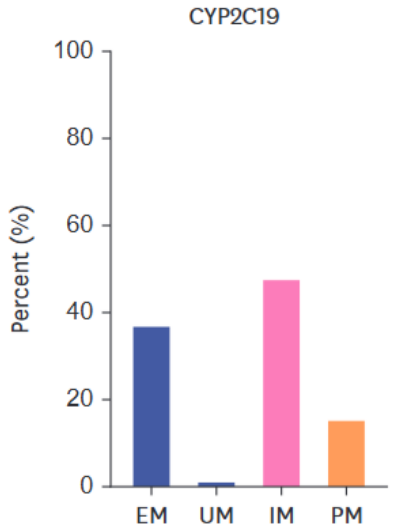
Table 4 The frequency of *CYP2C19* phenotypes by race[53,57,58]

Race	*CYP2C19* phenotype		
	PMs	IMs	UMs
Caucasian	1%–7%	25%	40%
Asian	13%–23%	50%	<5%
African American	1%–7%	30%	45%

Note: Patients without the PM, IM, or UM phenotype are presumably EMs.
Abbreviations: PMs, poor metabolizers; IMs, intermediate metabolizers; UMs, ultrarapid metabolizers.

Table 3. Phenotypes of clinically relevant DMET markers in Korean population (n = 1,012)

Gene*	Related drugs	Diplotype	Phenotype	Sample count (%)
CYP2C19	Amitriptyline, clopidogrel, citalopram, voriconazole	*1/*1	EM	372 (36.76)
		*1/*17	UM	9 (0.89)
		*17/*17	UM	1 (0.10)
		*1/*2A	IM	363 (35.87)
		*1/*2B	IM	0 (0.00)
		*1/*3	IM	106 (10.47)
		*2A/*17	IM	9 (0.89)
		*3/*17	IM	1 (0.10)
		*2A/*2A	PM	76 (7.51)
		*2A/*2B	PM	1 (0.10)
		*2A/*3	PM	62 (6.13)
		*3/*3	PM	12 (1.19)



Cavallari, Larisa H., Hyunyoung Jeong, and Adam Bress. "Role of cytochrome P450 genotype in the steps toward personalized drug therapy." *Pharmacogenomics and personalized medicine* (2011): 123-136.
Kim, Byungwook, et al. "Comprehensive analysis of important pharmacogenes in Koreans using the DMET™ platform." *Translational and Clinical Pharmacology* 29.3 (2021): 135.
Kim, Yun, et al. "Development of a Korean-specific virtual population for physiologically based pharmacokinetic modelling and simulation." *Biopharmaceutics & Drug Disposition* 40.3-4 (2019): 135-150.

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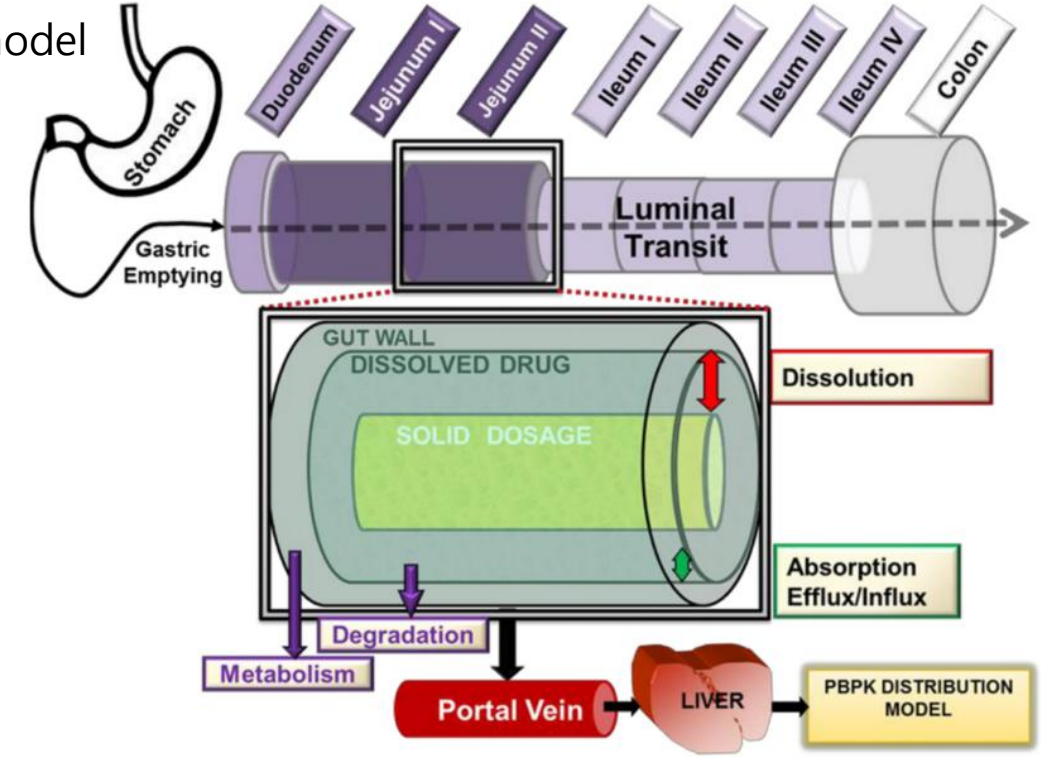
Methods
02

Development of PBPK/PD models

➢ Absorption

- Simcyp V23R1 library "SV-Esomeprazole"
- Advanced dissolution, absorption, and metabolism (ADAM) model
  - ✓ Unstirred boundary layer (UBL) fluid volume option
- Food staggering model for food effect assessment
  - ✓ Advanced bile dynamics
  - ✓ Advanced fluid volume dynamics
- Permeability
  - ✓ **Colon absorption rate scalar: 0.1**



Pathak, Shriram M., et al. "Model-based analysis of biopharmaceutic experiments to improve mechanistic oral absorption modeling: an integrated in vitro in vivo extrapolation perspective using ketoconazole as a model drug." *Molecular pharmaceutics* 14.12 (2017): 4305-4320.

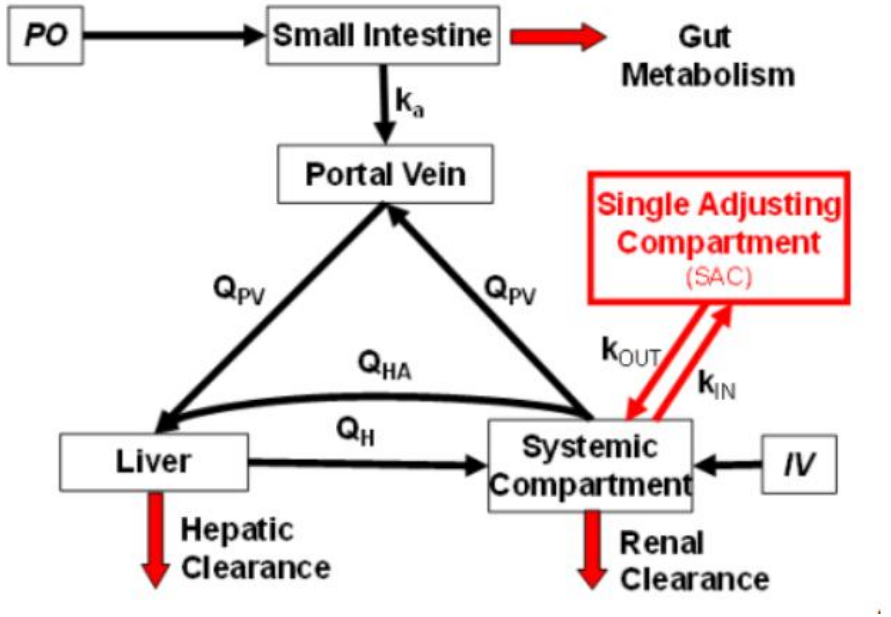
Methods
02

Development of PBPK/PD models

➢ Distribution

- Minimal PBPK distribution model
- V_{sac} parameter estimated from the observations
- Other parameters
  - ✓ Simcyp V23R1 library "SV-Esomeprazole"

$$V_{SYS} = V_{ss} - V_H - V_{SAC}$$



➢ Elimination and interaction

- Elimination parameters (CL_{int}) of CYP2C19 and CYP3A4
  - ✓ Simcyp V23R1 library "SV-Esomeprazole"
- Time-dependent inhibition of CYP2C19
  - ✓ Inactivation rate of CYP2C19 ($k_{inact,CYP2C19}$)
    : sum of $k_{inact,CYP2C19}$ of hydroxyomeprazole and 5-O-desmethylomeprazole
  - ✓ Half maximal inactivation (K_{app}): parameter estimated from the observations

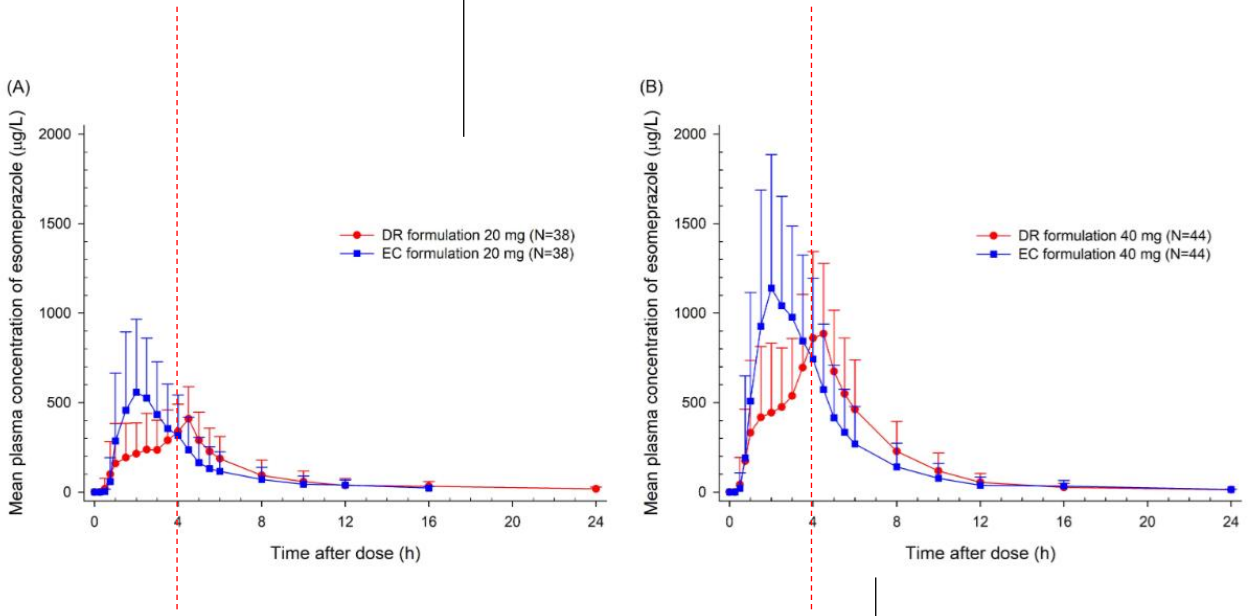
Pathak, Shriram M., et al. "Model-based analysis of biopharmaceutic experiments to improve mechanistic oral absorption modeling: an integrated in vitro in vivo extrapolation perspective using ketoconazole as a model drug." *Molecular pharmaceutics* 14.12 (2017): 4305-4320.

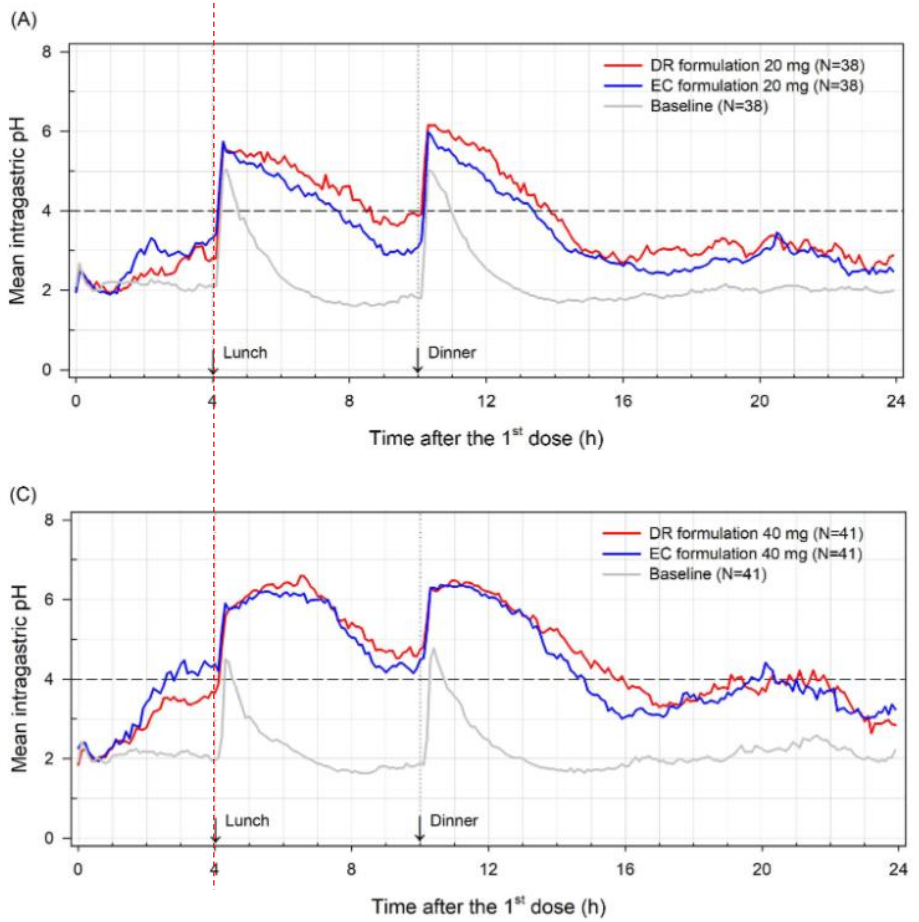
Methods
02

Development of PBPK/PD models

➢ PK/PD relationship

- **Formulation-specific pharmacodynamic parameters**
- **Observations from 4 to 24 hours on day 1**





Kim, Hyun Chul, et al. "Pharmacokinetics and pharmacodynamics of Esomezol DR, a New Dual delayed-release formulation of Esomeprazole 20 mg or 40 mg, in healthy subjects." *Drug Design, Development and Therapy* (2023): 1115-1124.

Methods
03

Verification & modification of PBPK/PD models

➢ EC formulation

Dose (mg)	Study	State	Day
40	Hyun Chul Kim, et al.	Fasted	1
	Sungyeun Bae, et al.	Fasted	1
			7
	Hae Won Lee, et al.	Fasted	1
			5
		Fed	1
			5
20	Hyun Chul Kim, et al.	Fasted	1
	Sungyeun Bae, et al.	Fasted	1
			7

➢ DR formulation

Dose (mg)	Study	State	Day
40	Hyun Chul Kim, et al.	Fasted	1
	Sejung Hwang, et al.	Fasted	1
		Fed	1
20	Hyun Chul Kim, et al.	Fasted	1

DR: dual delayed-release
EC: enteric-coated

Kim, Hyun Chul, et al. "Pharmacokinetics and pharmacodynamics of Esomezol DR, a New Dual delayed-release formulation of Esomeprazole 20 mg or 40 mg, in healthy subjects." *Drug Design, Development and Therapy* (2023): 1115-1124.
Bae, Sungyeun, et al. "Comparative pharmacokinetics/pharmacodynamics of fixed-dose combination of esomeprazole and calcium carbonate (AD-206) to the conventional esomeprazole." *Drug Design, Development and Therapy* (2021): 5099-5108.
Lee, Hae Won, et al. "Pharmacokinetics and pharmacodynamics of YYD601, a dual delayed-release formulation of esomeprazole, following single and multiple doses in healthy adult volunteers under fasting and fed conditions." *Drug Design, Development and Therapy* (2023): 619-634.

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Methods

03

Verification & modification of PBPK/PD models

➢ Parameter estimation using the observed data

- If the predicted PK profiles and parameter values were not close to the observed data
- If no data were available

➢ Simulation

- 10 trials depending on the number, age, and sex of subjects in each study
- Evaluation by comparing the predicted plasma concentration-time profiles with the observed data in each study
- If the ratio of predicted to observed PK parameters of T_{max}, AUC, and C_{max} is within two-fold range

03
Results

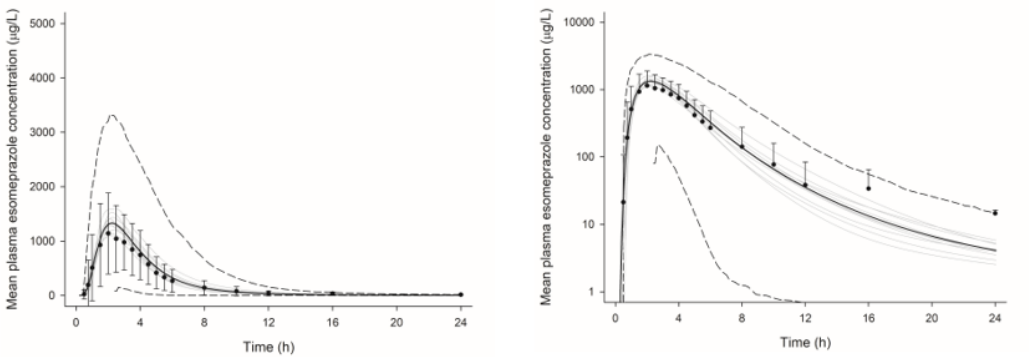
Results
02

Pharmacokinetic predictions of PBPK/PD model

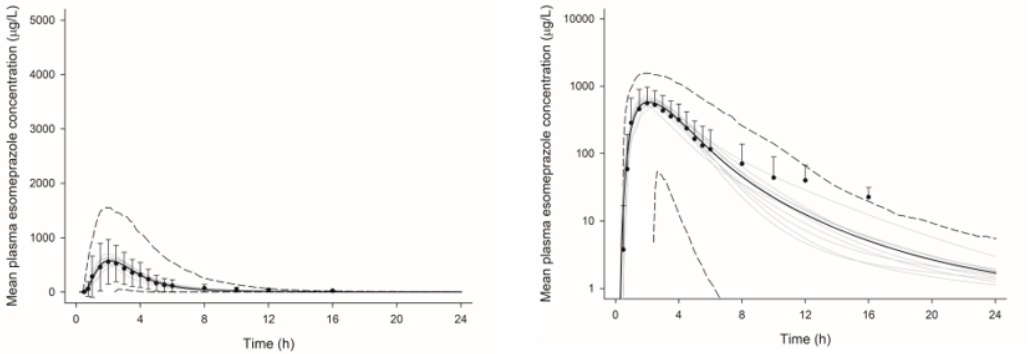
➢ Final PBPK/PD model predicted the observed data of the EC and DR formulations.

DR: dual delayed-release
EC: enteric-coated

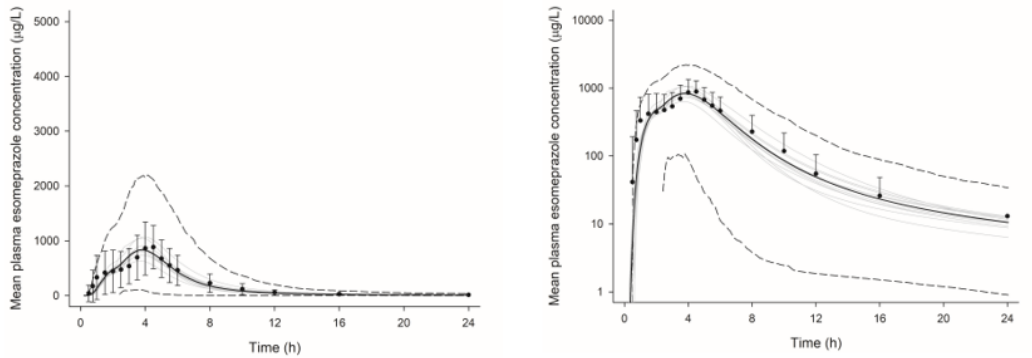
(A) EC formulation 40 mg



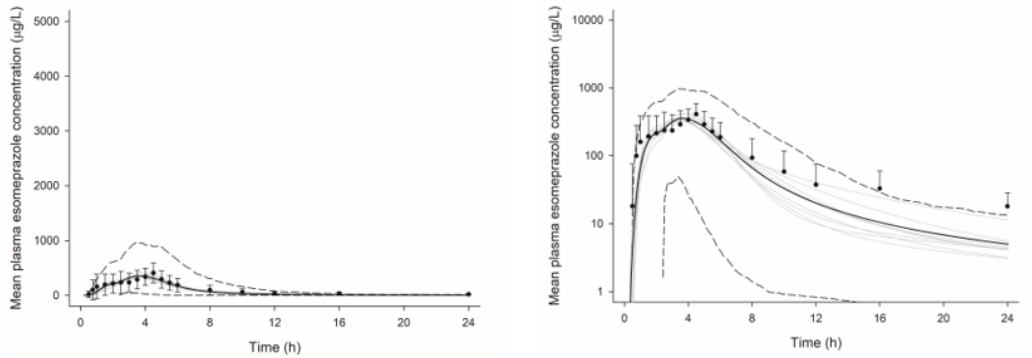
(B) EC formulation 20 mg



(A) DR formulation 40 mg



(B) DR formulation 20 mg



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Results
02

Pharmacokinetic predictions of PBPK/PD model

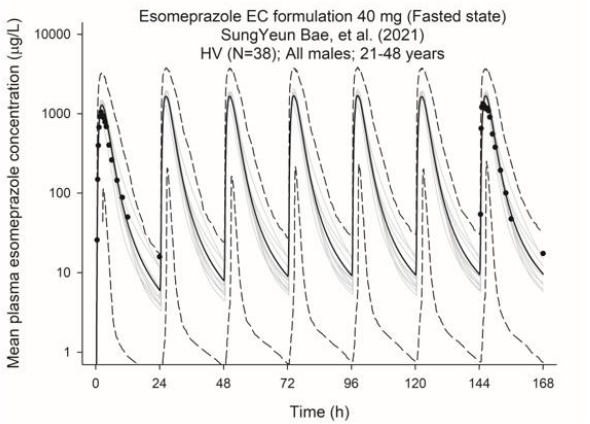
DR: dual delayed-release
EC: enteric-coated

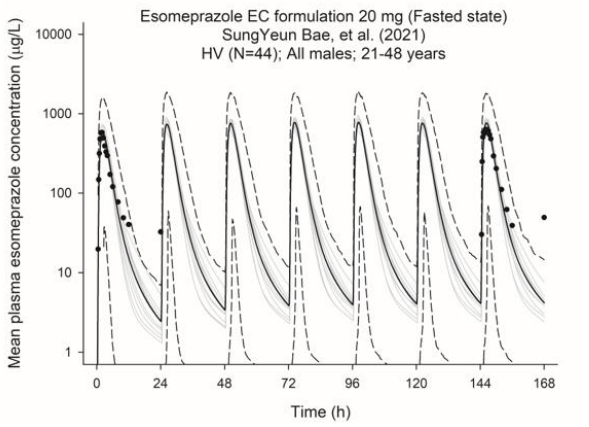
➢ Each simulated profile adequately represented other clinical results of esomeprazole.

- With time-dependent inhibition of CYP2C19 during the multiple doses of esomeprazole
- In both fasted and fed states

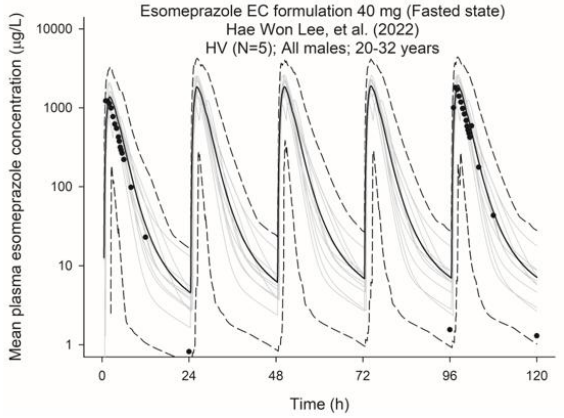
➢ EC formulation

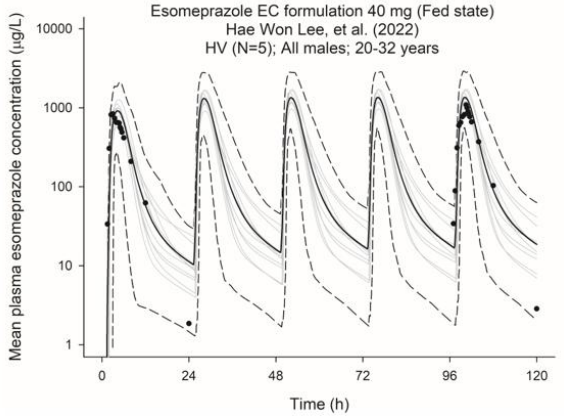
(A) SungYeun Bae, et al. (2021)





(B) Hae Won Lee, et al. (2022)





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Results
02

Pharmacokinetic predictions of PBPK/PD model

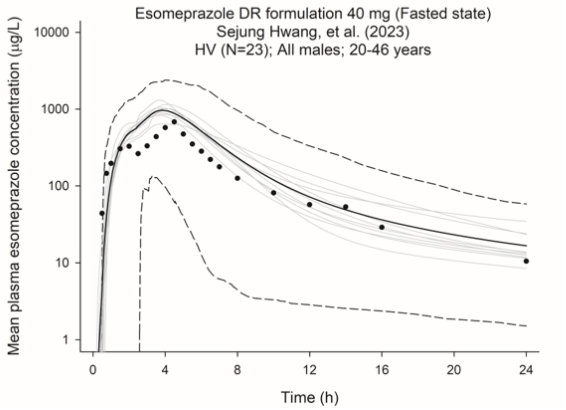
DR: dual delayed-release
EC: enteric-coated

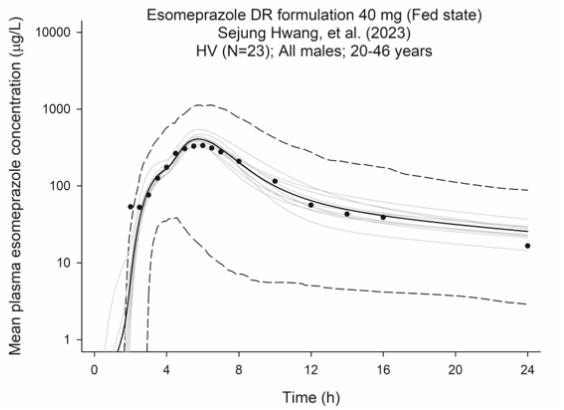
➢ Each simulated profile adequately represented other clinical results of esomeprazole.

- In both fasted and fed states

➢ DR formulation

(C) Sejung Hwang, et al. (2023)





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Results
02

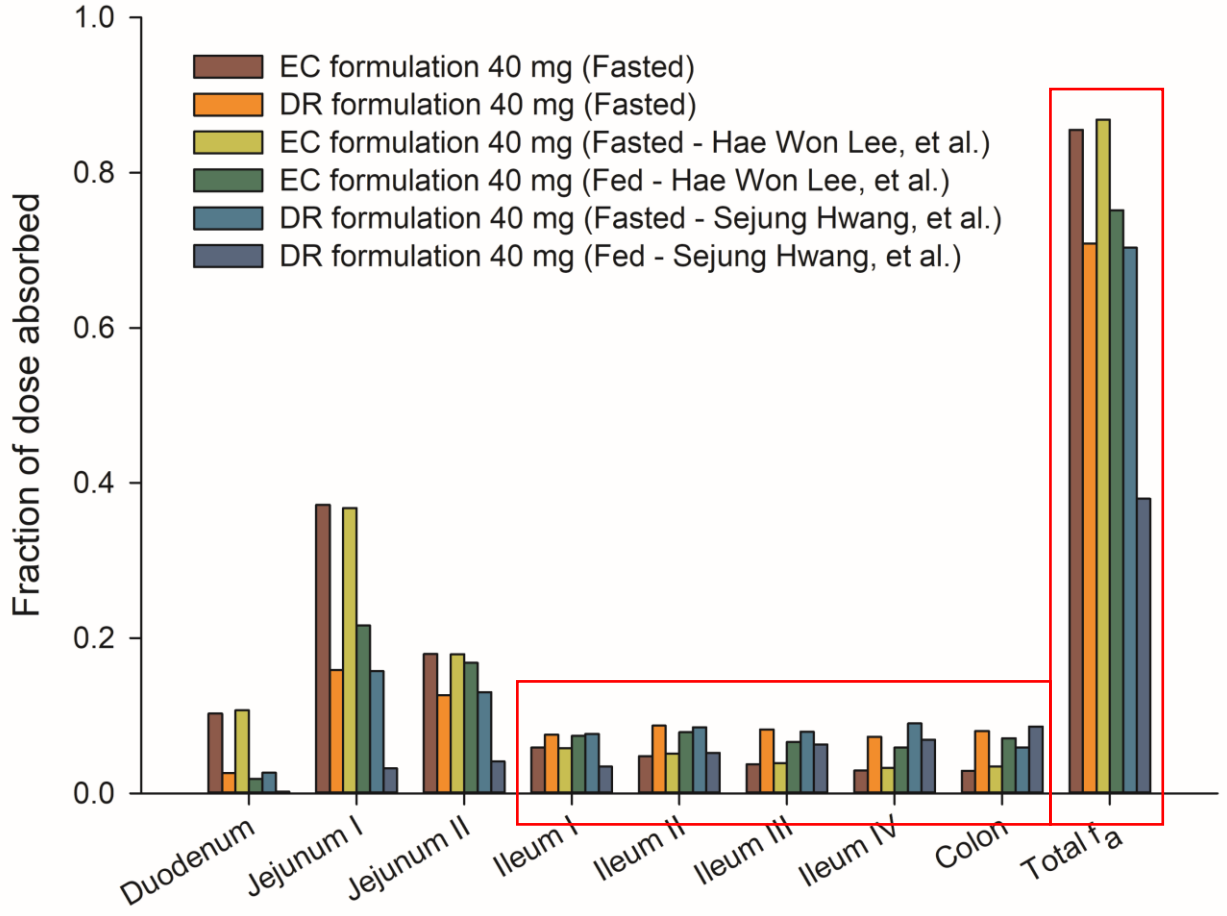
Pharmacokinetic predictions of PBPK/PD model

DR: dual delayed-release
EC: enteric-coated

➢ Fraction absorbed from regional gastrointestinal (GI) segments

- Total absorbed fraction
  : EC formulation > DR formulation
  : Fasted state > Fed state

- Fraction absorbed from the distal GI tract
  : EC formulation < DR formulation
  : Fasted state < Fed state



04
Discussion

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Discussion
02

Negative food effect of esomeprazole

- The food staggering model could not capture the negative effect of food on the PKs of esomeprazole. (physiology or dissolution)
- Food viscosity can delay not only drug dissolution but also tablet disintegration.
  - Mechanism of disintegration
    - ✓ Swelling, liquid penetration
      : one of the key factors in the disintegration process
    - ✓ Higher viscosity, slower disintegration

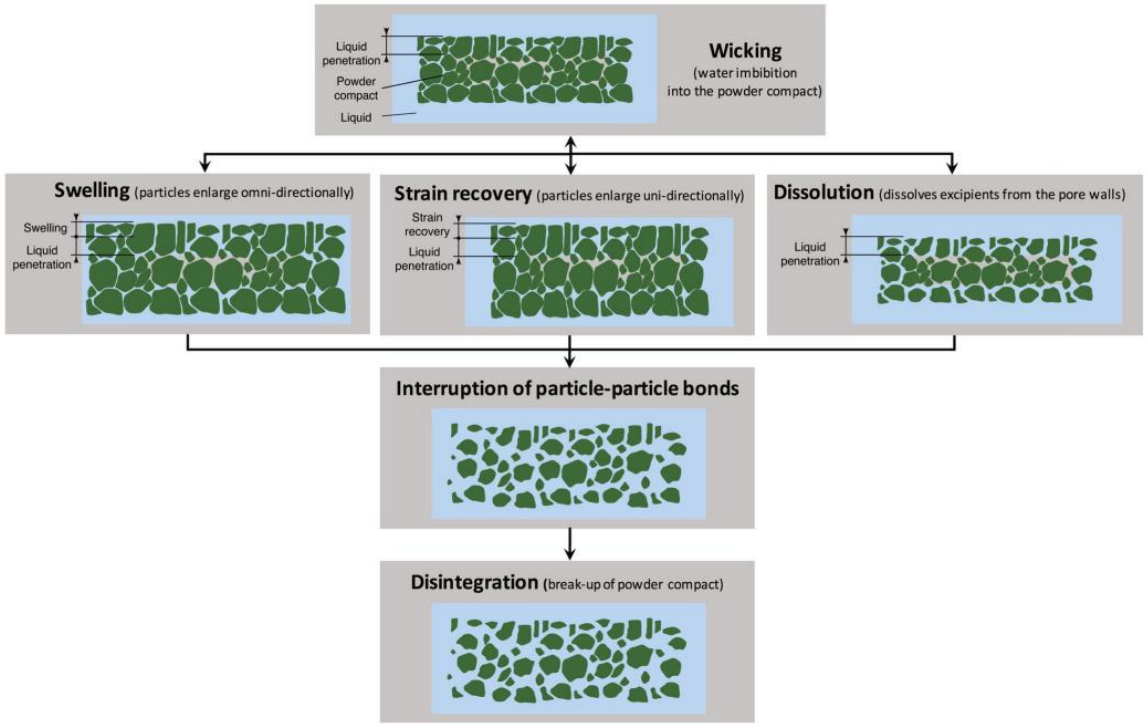

Fig. 3 Overview of mechanisms involved in disintegration of pharmaceutical powder compacts.

Markl, Daniel, and J. Axel Zeitler. "A review of disintegration mechanisms and measurement techniques." *Pharmaceutical research* 34.5 (2017): 890-917.

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Discussion
02

Negative food effect of esomeprazole

➢ Food viscosity can delay not only drug dissolution but also tablet disintegration.

- Trospium chloride

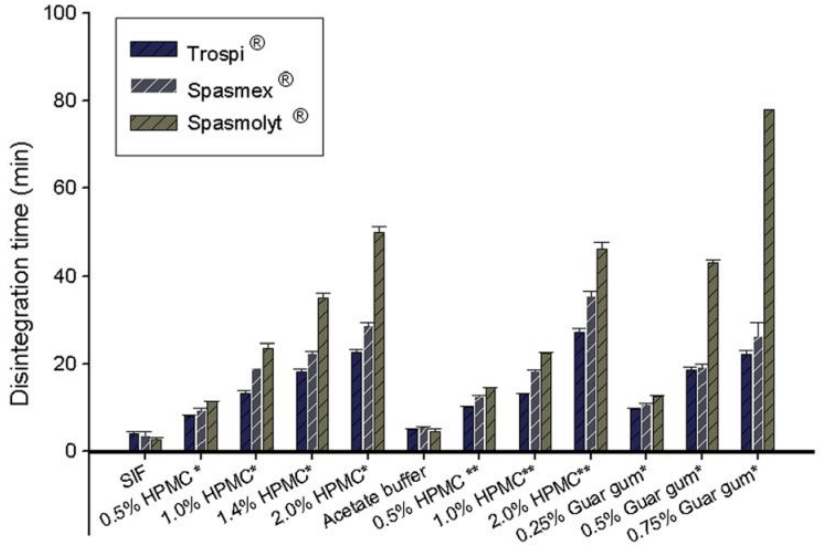
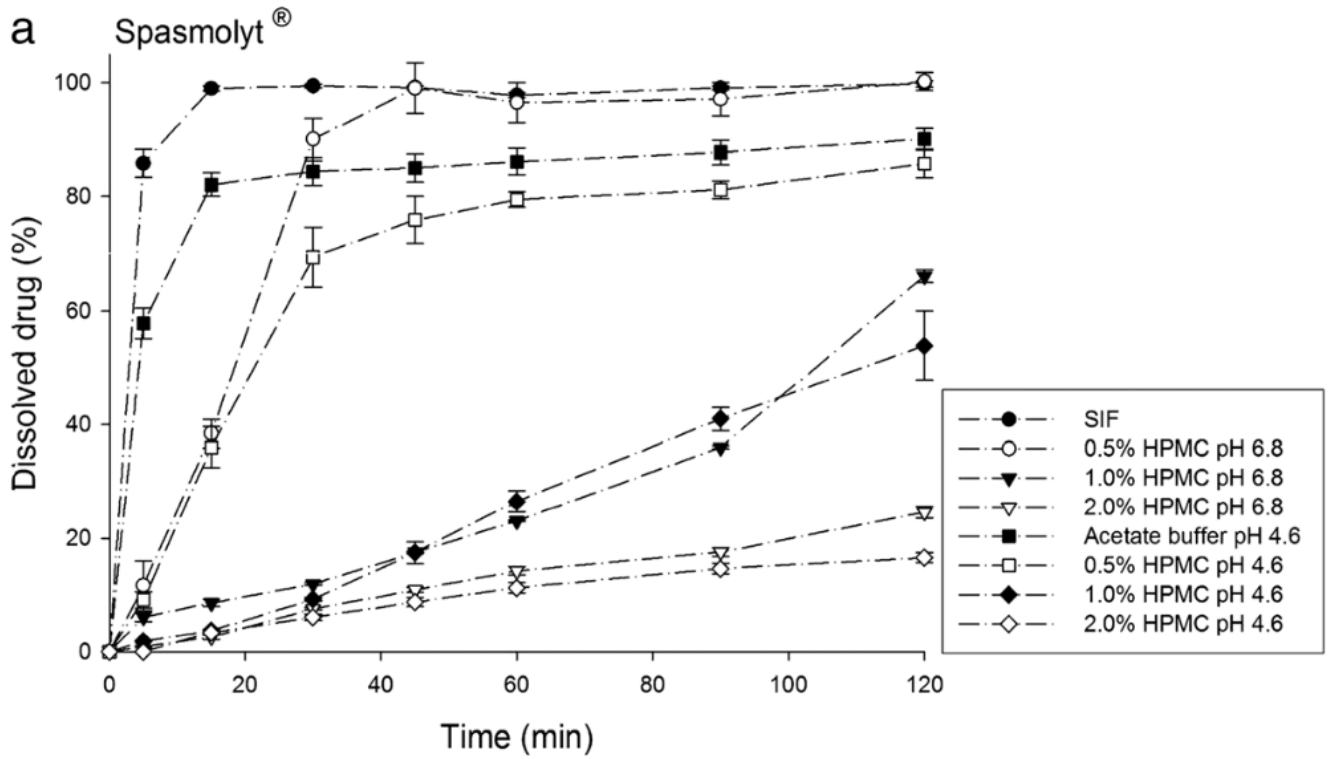


Figure 3. Disintegration times of various trospium chloride products in different disintegration media. The effects of increasing media viscosity on disintegration times were in all cases significant ($p < 0.05$), whereas the effect of change of pH for HPMC solutions at the same concentrations of VEA was insignificant ($p > 0.05$). *pH 6.8; **pH 4.6



Radwan, Asma, Gordon L. Amidon, and Peter Langguth. "Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity." *Biopharmaceutics & drug disposition* 33.7 (2012): 403-416.

Discussion

02

Negative food effect of esomeprazole

➢ Food viscosity can delay not only drug dissolution but also tablet disintegration.

- Ciprofloxacin

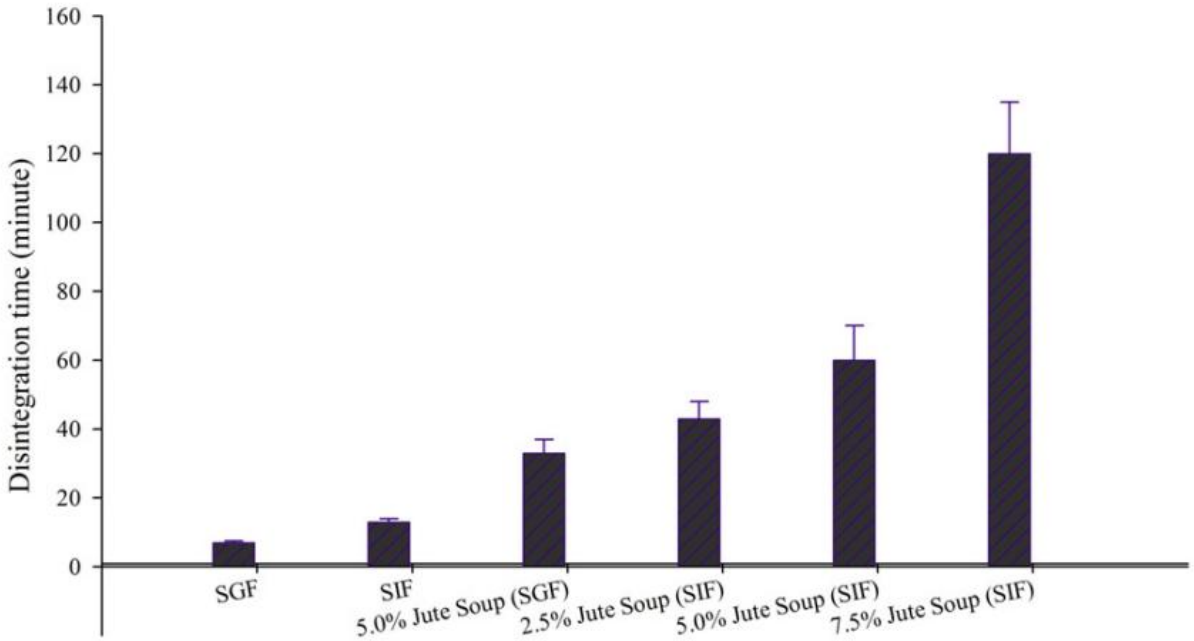


Fig. 2. Disintegration time (min) for ciprofloxacin tablet in the various media.

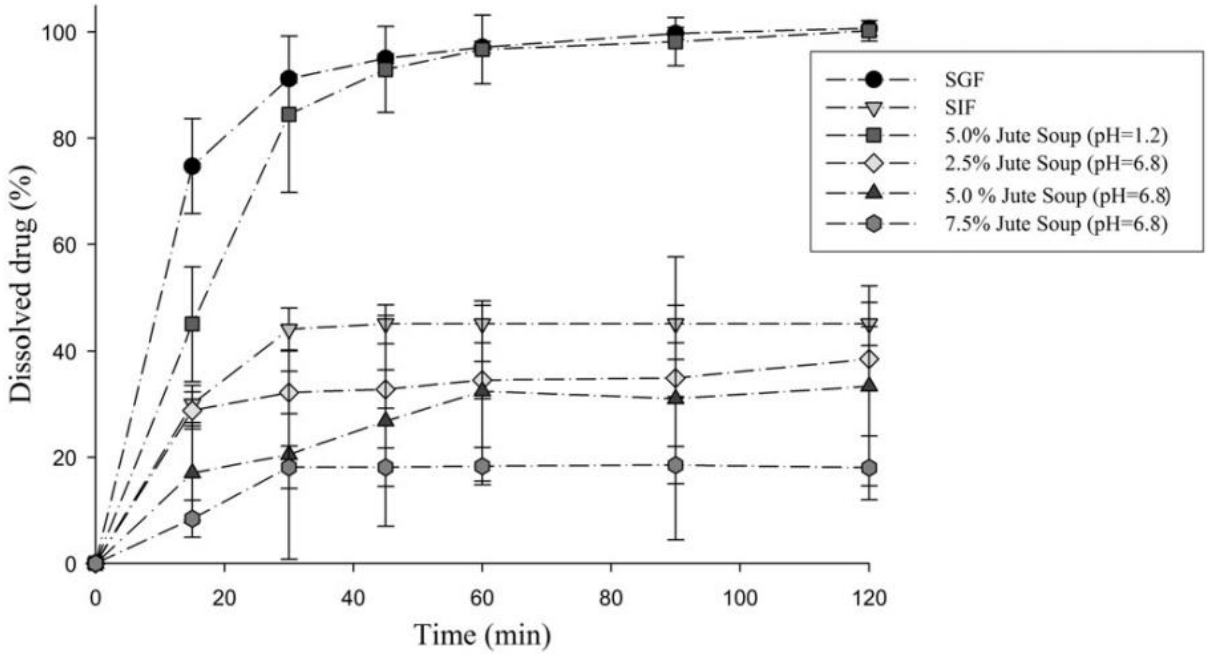


Fig. 3. Dissolution profile of ciprofloxacin at two pHs, with *C. olitaruis* leaves and without soup.

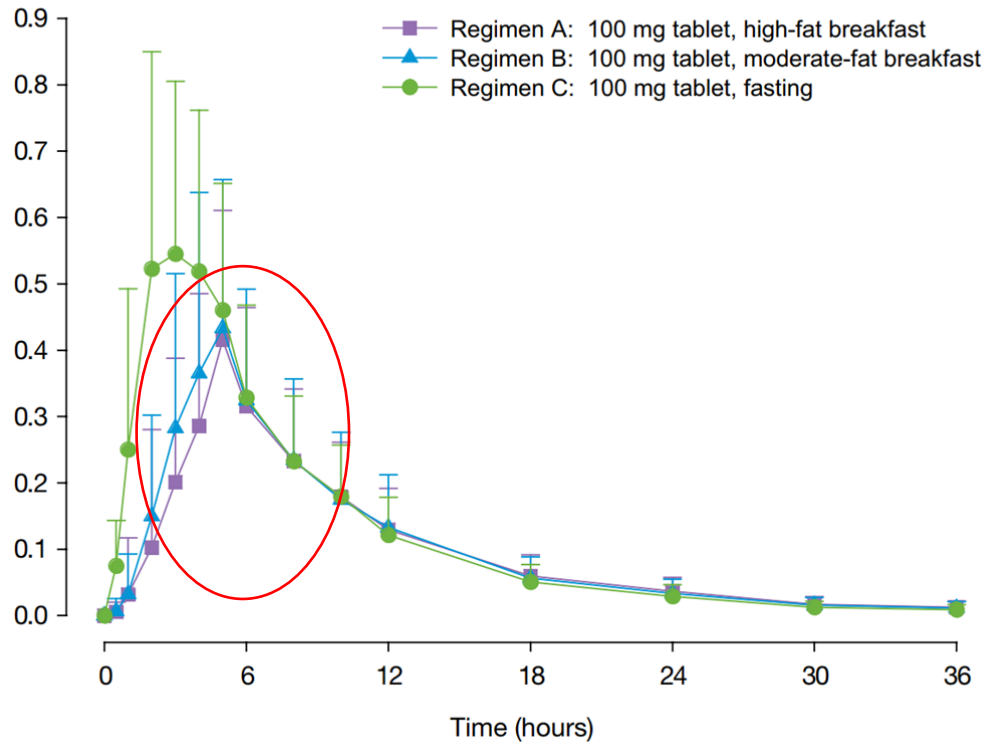
Radwan, Asma, et al. "Food effect: The combined effect of media pH and viscosity on the gastrointestinal absorption of ciprofloxacin tablet." *European Journal of Pharmaceutical Sciences* 101 (2017): 100-106.

Discussion
03

Colonic absorption

- Understanding colonic absorption is important in the delayed absorption process such as modified release (MR) formulation or food effect.
  - Several PBPK modeling studies have assumed negligible colonic absorption.
  - E.g., Ritonavir 100 mg film-coated tablet
    → Colonic absorption scalar: 0.1

Figure 1. Ritonavir Plasma Concentration-Time Profile



CE Klein, et al. "The Effect of Food on Ritonavir Bioavailability Following Administration of Ritonavir 100 mg Film-Coated Tablet in Healthy Adult Subjects" *https://www.natap.org/2008/InterHIV/InterHIV_46.htm*.

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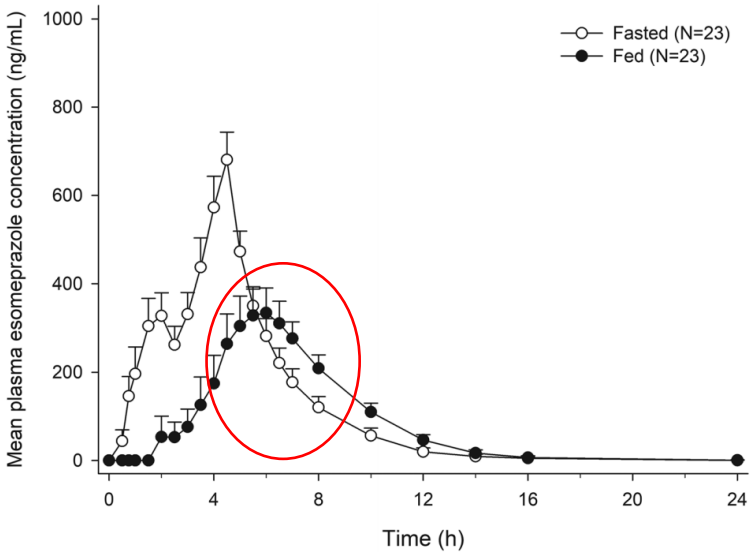
Discussion

03

Colonic absorption

- Physiological transit time of oral drug
  - From stomach to colon: 4 – 10 hours
- DR and EC formulation in the fed state



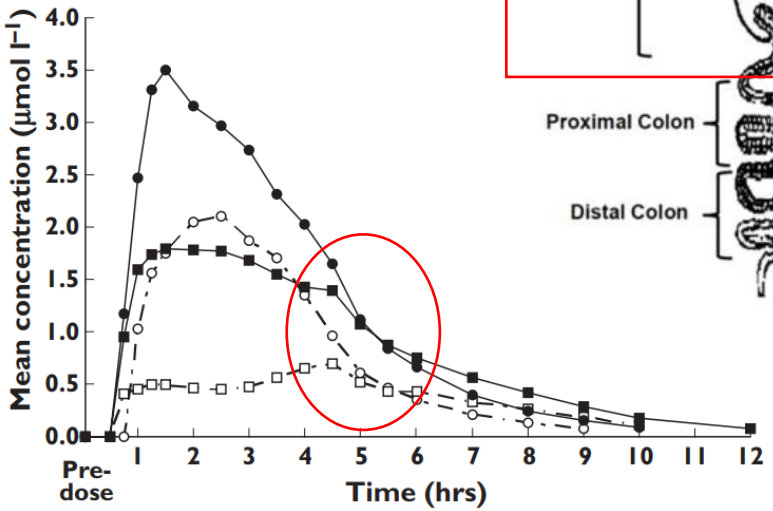
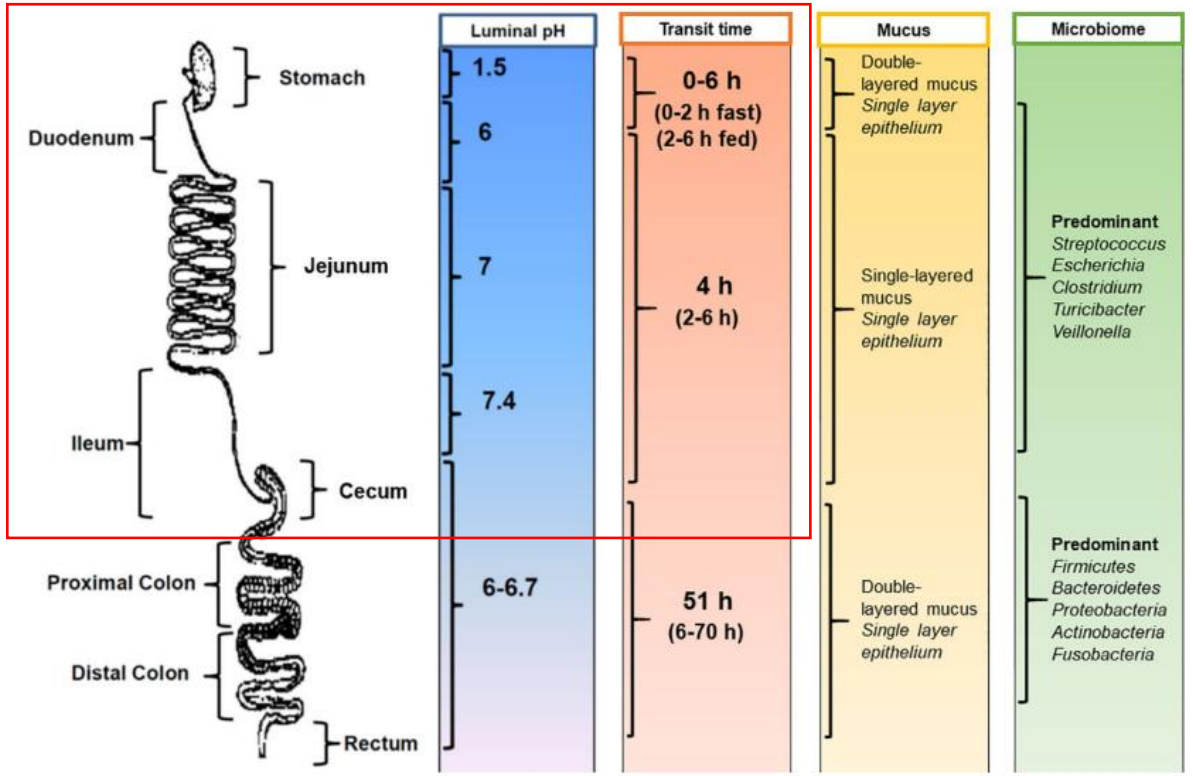


Figure 1

Mean plasma esomeprazole concentration *vs.* time on days 1 and 5 for subjects ($N = 44$) eating 15 min (fed) or 4 h (fasting) after esomeprazole administration. (-○-, Day 1 Fasting; -□-, Day 1 Fed; -●-, Day 5 Fasting; -■-, Day 5 Fed)



Hwang, Sejung, et al. "Effect of Food on the Pharmacokinetics and Pharmacodynamics of a Novel Dual Delayed-Release Formulation of Esomeprazole in Healthy Subjects." *Clinical Pharmacology in Drug Development* 12.8 (2023): 839-844.
Sostek, Mark B., Yusong Chen, and Tommy Andersson. "Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole." *British journal of clinical pharmacology* 64.3 (2007): 386-390.
Hua, Susan. "Advances in oral drug delivery for regional targeting in the gastrointestinal tract-influence of physiological, pathophysiological and pharmaceutical factors." *Frontiers in pharmacology* 11 (2020): 524.

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05
Conclusion

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Conclusion

01

Physioloically based biopharmaceutics modeling (PBBM)

Yuvaneshwari, K., et al. "Applications of PBPK/PBBM modeling in generic product development: an industry perspective." *Journal of Drug Delivery Science and Technology* 69 (2022): 103152.

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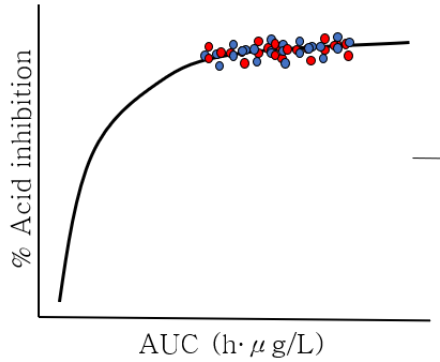
Conclusion
02

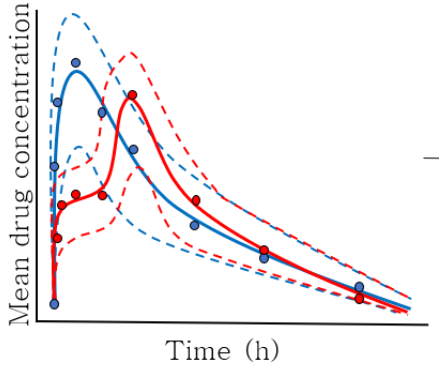
Application of PBPK/PD model

PBPK/PD model application

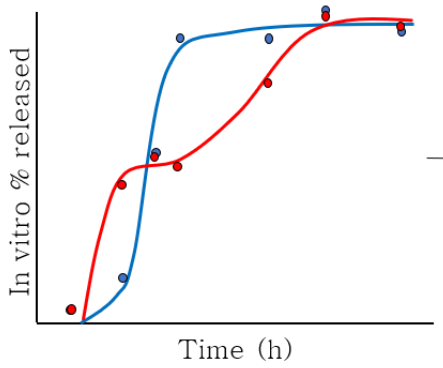
Formulation development and optimization



<PK/PD relationship>



<Appropriate PK profile>



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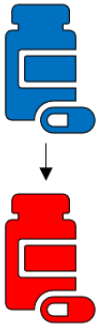
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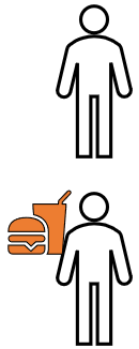
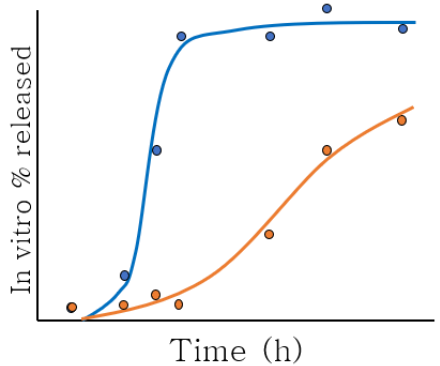
Prediction of food effect


<Physiological changes by food>



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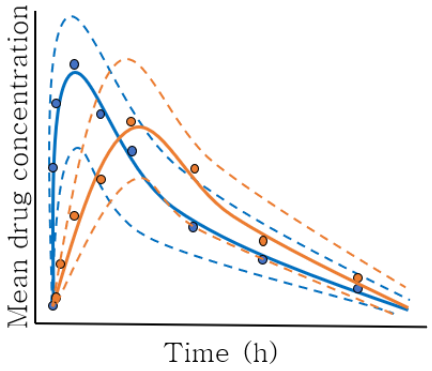

<Effect of food on PK profile>

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감사합니다.

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