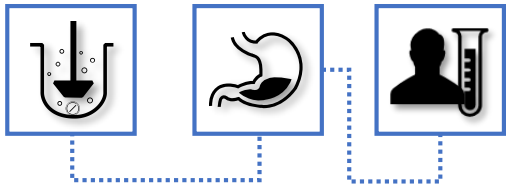
Establishment of novel IVIVC model combined with DoE for the development of extended-release formulation: from formulation composition to in vivo pharmacokinetics



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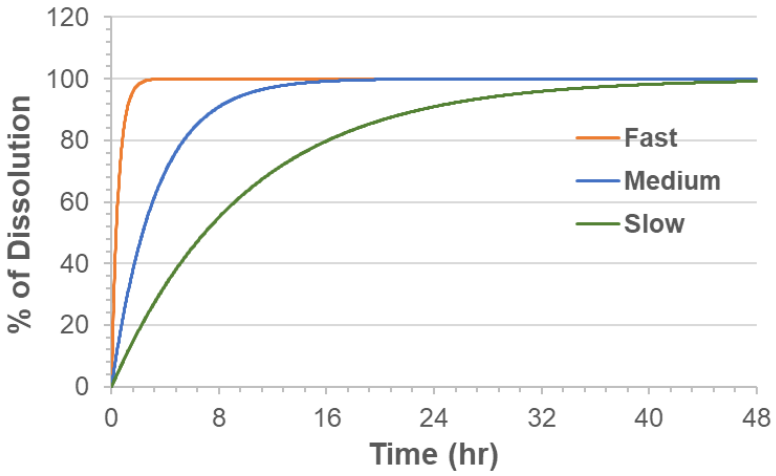
신 범 수

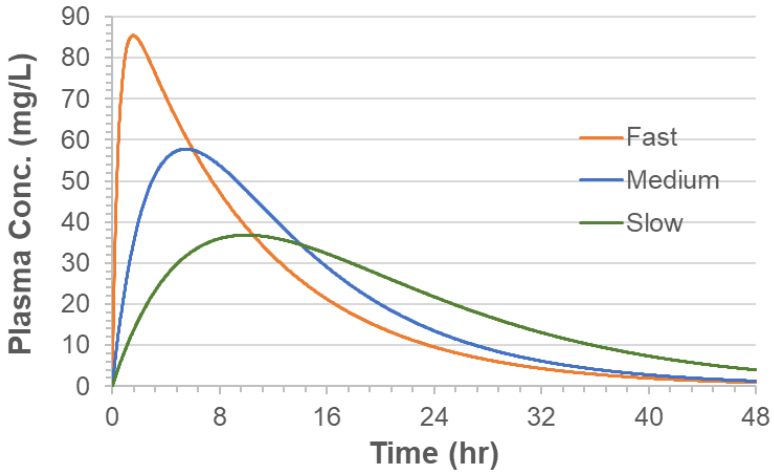
What is “Extended Release Formulation”?

Extended Release Formulations

Extended-release dosage formulations are dosage forms designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects.



Dissolution profiles
in vitro



Plasma concentration vs. time profiles
in vivo

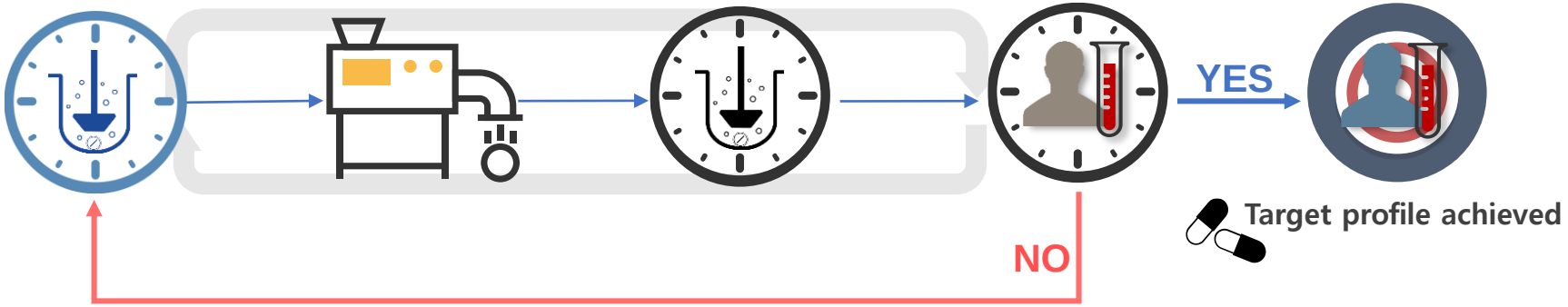
Development process of the extended release (ER) formulations

1 Designing drug dissolution

2 Formulation

3 In vitro dissolution

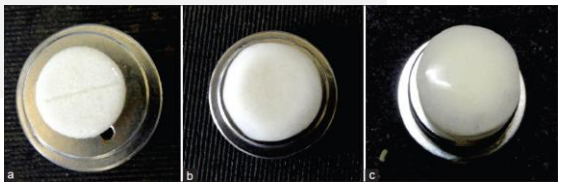
4 In vivo pharmacokinetics



Expensive and time-consuming process

Formulation strategies of ER formulations

- Hydrophilic/inert matrix system (HPMC)
- Coated particles
- Osmotic pump
- Ion-exchange resins

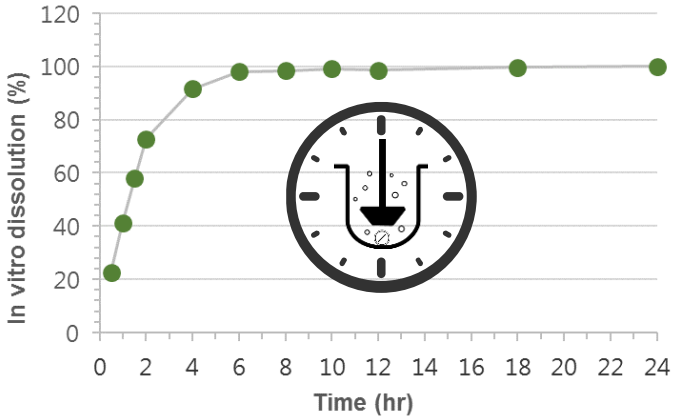


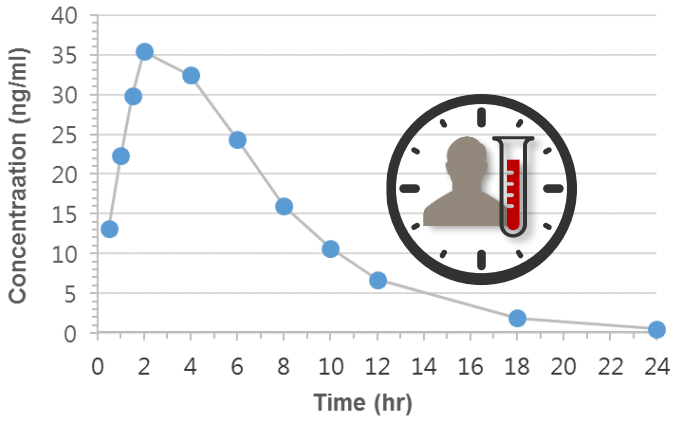
What is “In Vitro-In Vivo Correlation (IVIVC)”?

US FDA definition of IVIVC

A predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response

Application 1: Prediction of PK profile from dissolution pattern





In vitro property: Dissolution

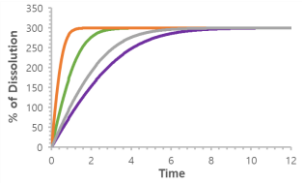
In vivo response: PK profile

Application 2: Design the optimal dissolution pattern for the desired PK profile

Application of IVIVC
for the development of extended release (ER) formulations

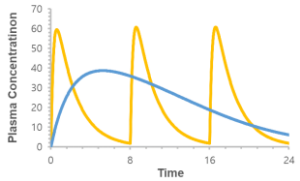
Increases success rate, Saves time and cost

Optimized dissolution



IVIVC

Target PK profile

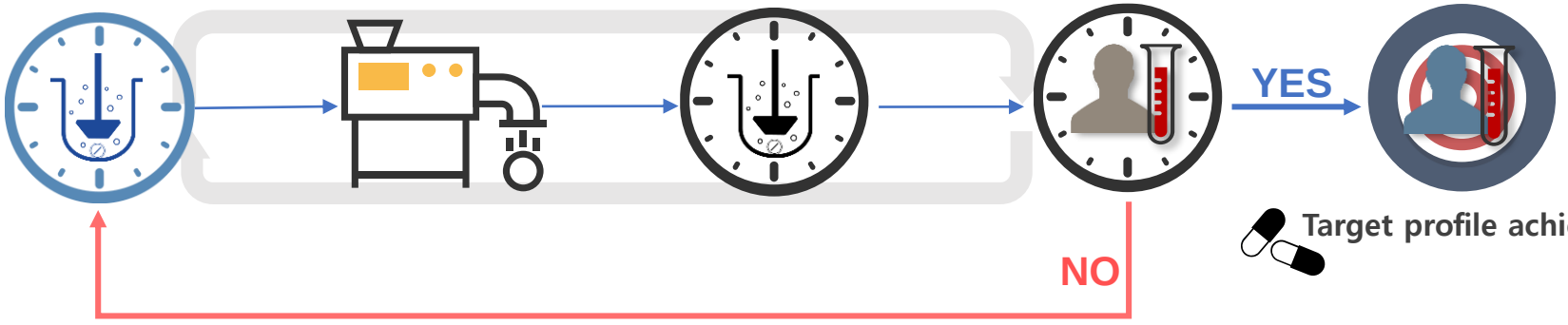


1 Designing drug dissolution

2 Formulation

3 In vitro dissolution

4 In vivo pharmacokinetics

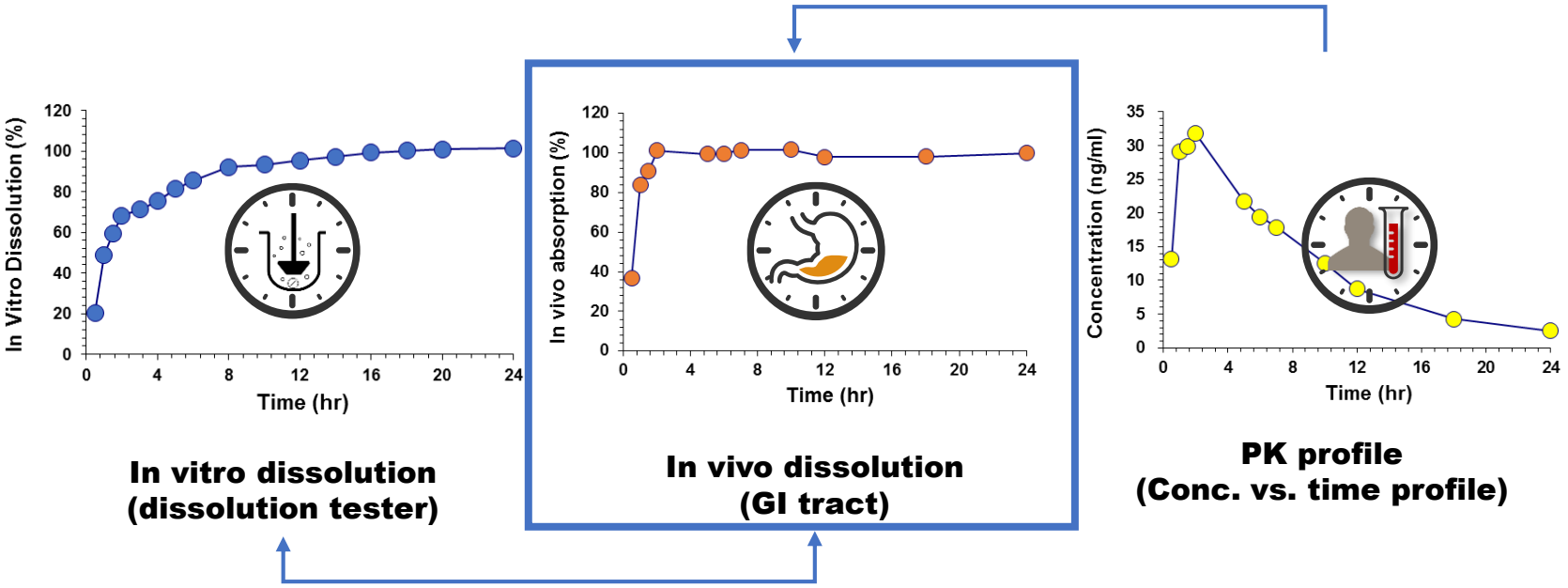


Expensive and time consuming process

Process of establishing in vitro-in vivo correlation (IVIVC)

Step1. Prediction of in vivo dissolution profile in the GI tract from plasma concentration-time profile

- Wagner-Nelson
- Loo-Riegelman
- Numeric deconvolution



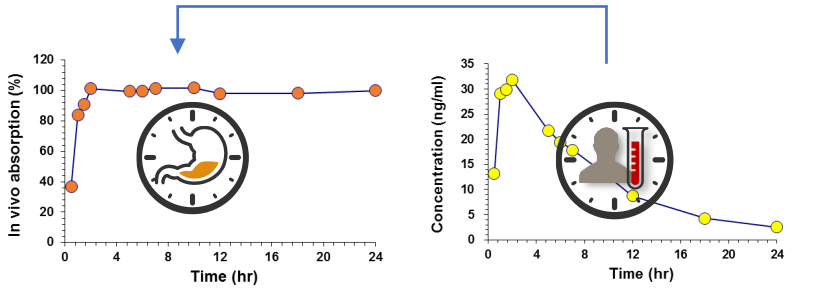
Step2. Correlation between in vitro dissolution and in vivo dissolution

- Mathematical conversion (in vivo dissolution ←→ in vitro dissolution)
- Optimize the in vitro dissolution condition to mimic in vivo condition in the GI tract

Limitation of the conventional IVIVC approach

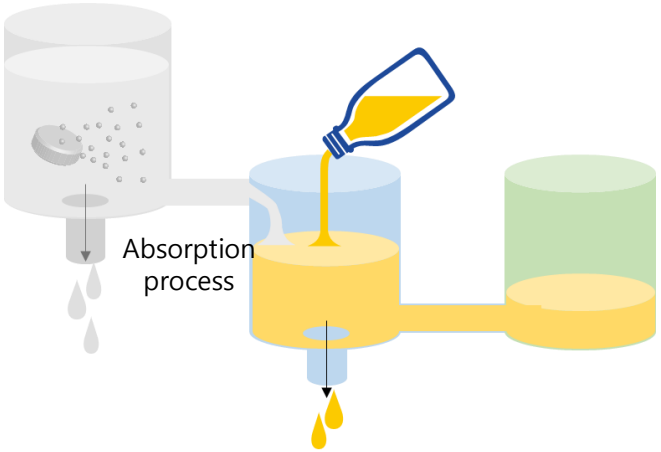
Step 1. (The most critical step)

Prediction of in vivo dissolution profile in the GI tract from plasma concentration-time profile



In vivo dissolution (GI tract)

PK profile (Conc. vs. time profile)



Assuming complete absorption of the drug after dissolution without absorption process

- Conventional methods assume all dissolved drug is completely absorbed without any limitation
  → thus only can be applied for BCS I and II drugs,
  → cannot describe complex physiological absorption process.
- Conventional IVIVC method cannot describe complex systemic drug disposition such as nonlinear PK or EHC which are frequent cases.

! Novel IVIVC approach may be necessary to improve predictability of in vivo drug performance and to expand application of IVIVC

Development of novel physiologically relevant IVIVC model

Case study 1 (Loxoprofen)

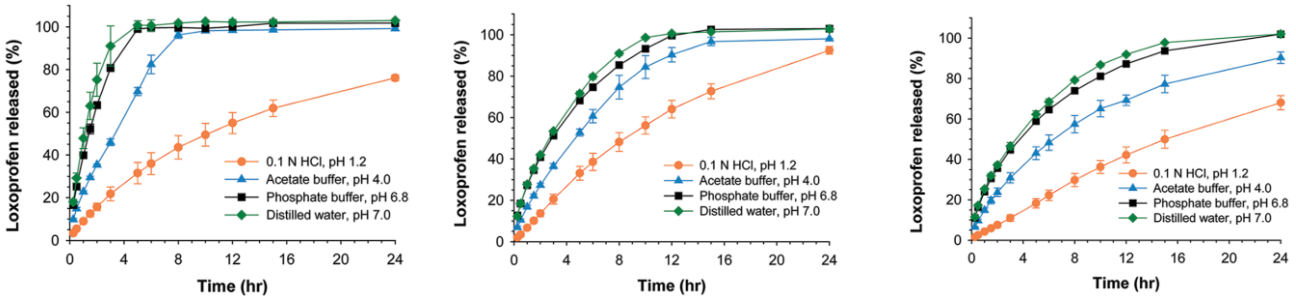
- NSAID used for the treatment of pain or inflammation
- Orally administered three times a day
- The extended release, once a day formulation is not available

Composition of Loxoprofen ER tablet Formulations

substances	ER-A	ER-B	ER-C
loxoprofen	37.5 (180 mg)	37.5 (180 mg)	37.5 (180 mg)
microcrystalline cellulose	53.1	20.25	20.25
polyvinylpyrrolidone K90	3.75	3.75	3.75
HPMC−100 cps	4.65	32.5	
HPMC−4000 cps		5.0	5.0
HPMC−15000 cps			32.5
Mg stearate	1.0	1.0	1.0
total	100.0	100.0	100.0

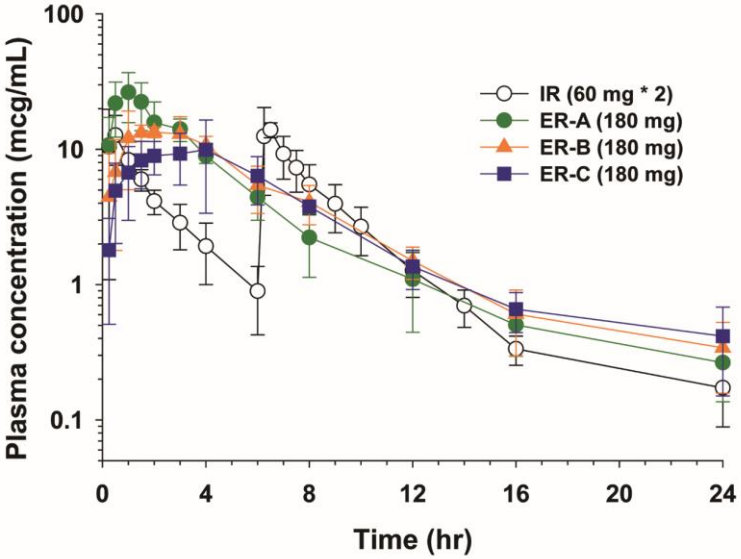
pH-dependent in vivo dissolution

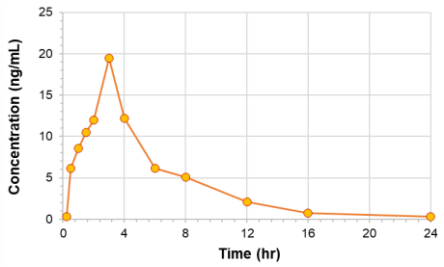
The dissolution rate was significantly altered depending on the dissolution medium pH

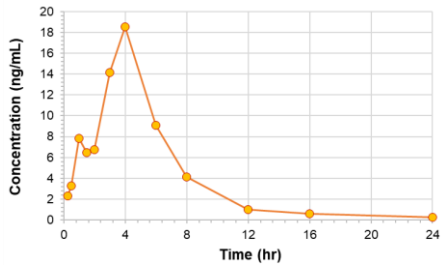


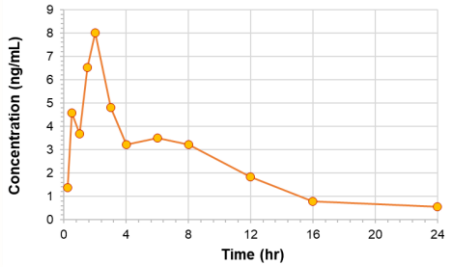
Development of novel physiologically relevant IVIVC model

Characteristics of in vivo pharmacokinetics









- *Double peak was observed*
- *Relative oral bioavailability was reduced by the extend of dissolution rate*

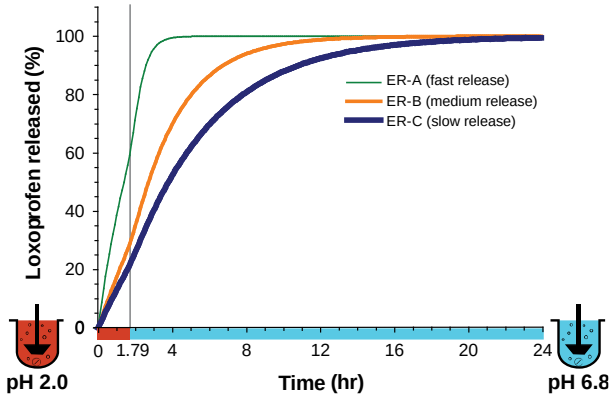
→ *indicating the presence of regional absorption windows*

Parameters	IR (n =6)	ER-A, fast (n = 4)	ER-B, medium (n = 4)	ER-C, slow (n = 4)
Dose (mg)	60 mg × 2 (BID)	180	180	180
$t_{1/2}$ (h)	4.1 ± 1.0	5.5 ± 1.3	5.5 ± 3.0	5.6 ± 1.2
T_{max} (h)	0.4 ± 0.1	0.9 ± 0.4	1.7 ± 0.9	2.6 ± 1.3
C_{max} (μg/mL)	18.1 ± 4.1	29.8 ± 6.5	17.2 ± 3.3	12.1 ± 4.4
$AUC_{infinity}$ (μg·h/mL)	72.2 ± 17.5	99.1 ± 20.9	92.8 ± 7.9	81.9 ± 20.1
V_z/F (L)	9.8 ± 4.6	14.4 ± 5.4	15.5 ± 7.9	17.7 ± 7.5
CL/F (mL/min)	27.7 ± 7.3	30.3 ± 6.6	32.3 ± 2.8	36.6 ± 9.8
Relative BA (%)	-	99.2 ± 21.0	92.9 ± 7.9	82.0 ± 20.2

Development of novel physiologically relevant IVIVC model

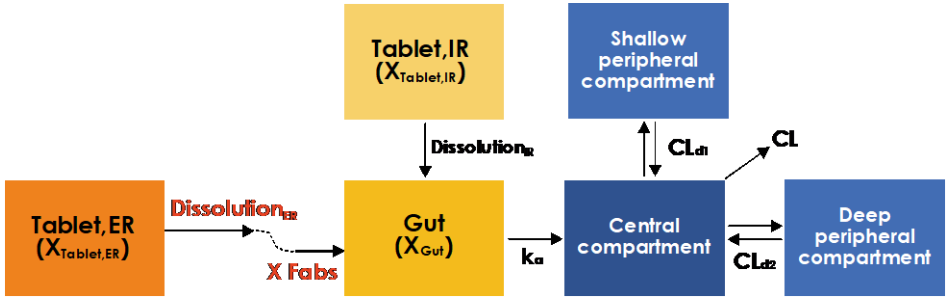
IVIVC model structure

pH dependent dissolution

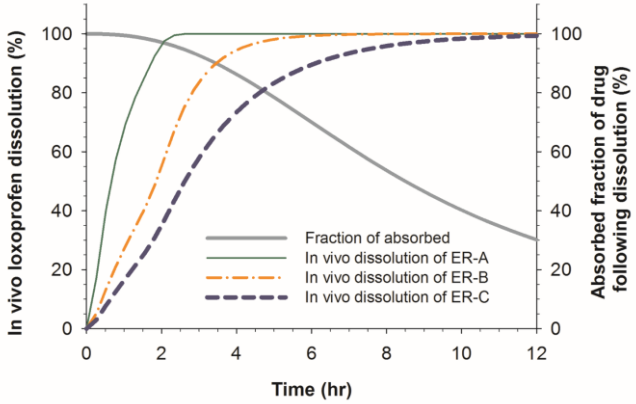


$$V_{max}(t) = V_{max}(0)^{[1+E_{max}\cdot time^{10}/(T_{change50}^{10}+time^{10})}$$

$$\frac{dX_{solid}}{dt} = -\frac{V_{max}(t)}{AM_{50} + X_{solid}} \cdot X_{solid}$$



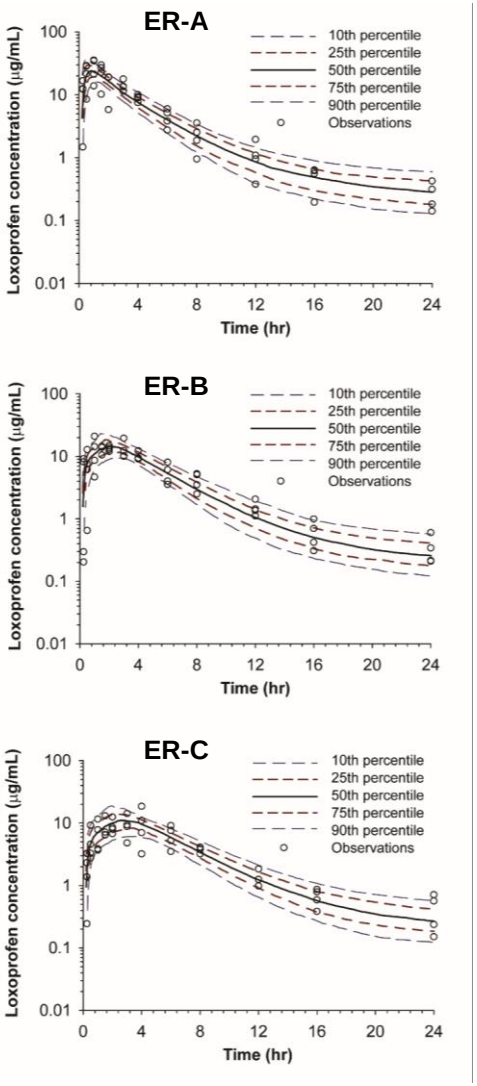
Site dependent absorption

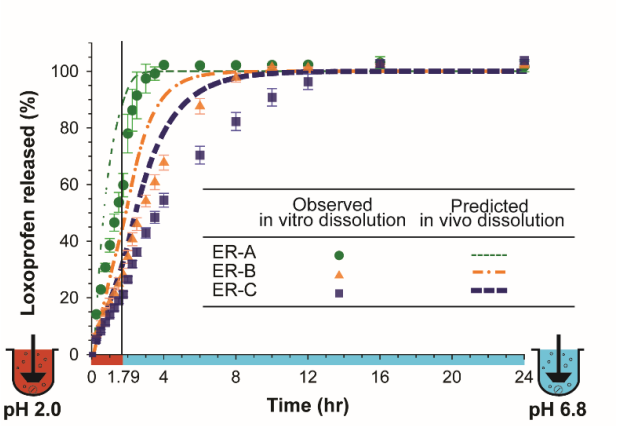


$$F_{abs} = 1 - \frac{Time^{\gamma}}{TW_{50}^{\gamma} + Time^{\gamma}}$$

Development of novel physiologically relevant IVIVC model

Extraction of in vivo dissolution





SR-Tablet	$V_{max}(0)$, in vitro	$V_{max}(0)$, in vivo
ER-A tablet (fast)	6.1839	30.2112
ER-B tablet (medium)	2.4110	8.7297
ER-C tablet (slow)	1.8277	4.9057

$$V_{max}(0)\text{in vivo} = 5.77 \cdot V_{max}(0)\text{in vitro} - 5.42$$

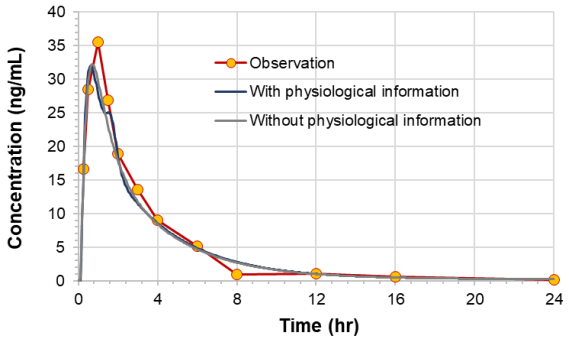
parameter	symbol	unit	population mean (BSV)
volume of distribution of the central compartment	V_1	L	0.87 (0.457)
volume of distribution of the shallow peripheral compartment	V_2	L	21.5 (0.286)
volume of distribution of the deep peripheral compartment	V_3	L	3.49 (0.161)
systemic clearance	CL	L/h	1.69 (0.15)
distribution clearance to the shallow peripheral compartment	CLd	L/h	0.459 (0.439)
distribution clearance to the deep peripheral compartment	CLd2	L/h	3.84 (0.183)
rate constant for absorption from gut	k_a	1/h	10.9 (1.38)
rate constant for absorption from gut for the 2nd dose	k_{a2}	1/h	7.77 (0.61)
time for half maximal bioavailability	$T_{window50}$	h	8.5 (0.242)
Hill coefficient	γ		2.44 (0.281)
time point at which $V_{max\ in\ vivo}$ changed by 50%	$T_{change50\ in\ vivo}$	h	1.79 (0.53)
maximum fold change in V_{max}			
amount of loxoprofen in the s			
initial $V_{max\ in\ vivo}$ for IR tablets			
initial $V_{max\ in\ vivo}$ for ER-A tablets	$V_{max}(0)_{ER\text{-}A\ in\ vivo}$/dose	1/h	30.2 (0.435)
initial $V_{max\ in\ vivo}$ for ER-B tablets	$V_{max}(0)_{ER\text{-}B\ in\ vivo}$/dose	1/h	8.73 (0.276)
initial $V_{max\ in\ vivo}$ for ER-C tablets	$V_{max}(0)_{ER\text{-}C\ in\ vivo}$/dose	1/h	4.91 (0.387)
lag time for ER dissolution	T_{lag}	h	0.11 (0.455)
SD of additive residual error	SD_{in}	ng/mL	0.00216 (0)
proportional residual error	SD_{sl}		0.239 (0)

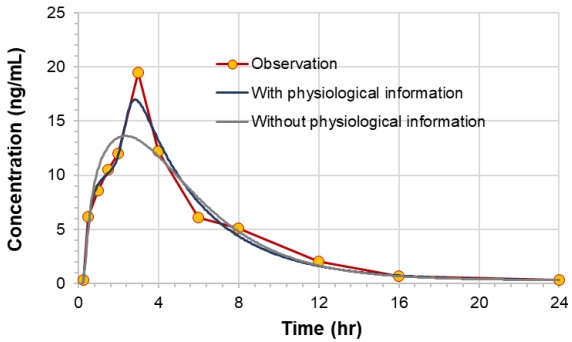
$$V_{max}(t) = V_{max}(0)^{[1+E_{max}\cdot time^{10}/(T_{change50}^{10}+time^{10})}$$

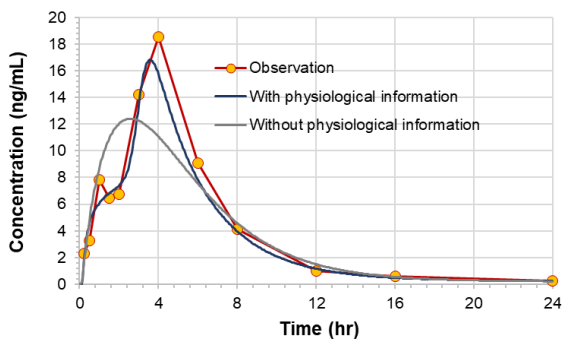
Development of novel physiologically relevant IVIVC model

Interval validation

Model	Formulation	C_{max}			AUC_{0-24h}		
		Obs. (μg/mL)	Pred. (μg/mL)	PE (%)	Obs. (μg/mL)	Pred. (μg/mL)	PE (%)
Model 1 (Conventional IVIVC model)	ER-A	29.82	22.92	23.1	96.95	84.39	12.9
	ER-B	17.17	15.07	12.2	89.35	83.80	6.2
	ER-C	12.06	9.32	22.7	78.07	82.72	6.0
Model 2 (pH dependent dissolution)	ER-A	29.82	25.16	15.6	96.95	84.17	13.2
	ER-B	17.17	16.29	5.1	89.35	86.38	3.3
	ER-C	12.06	13.85	14.8	78.07	84.07	7.7
Model 3 (pH-dependent dissolution, site-dependent absorption)	ER-A	29.82	27.95	6.3	96.95	88.86	8.3
	ER-B	17.17	17.32	0.9	89.35	83.56	6.5
	ER-C	12.06	12.66	4.9	78.07	75.14	3.8



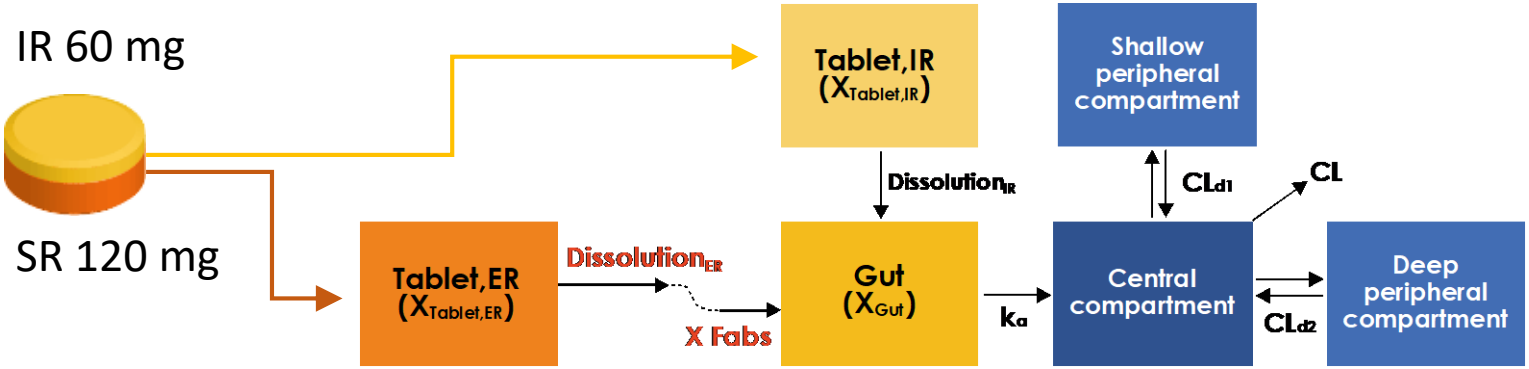


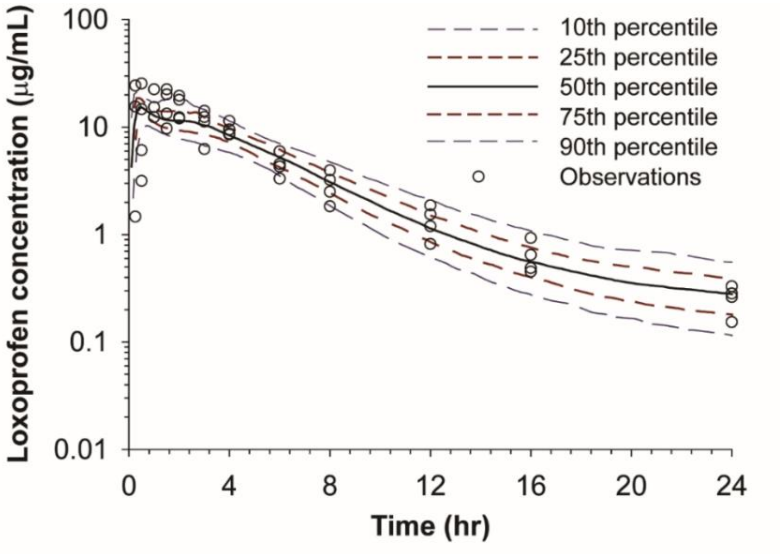


Kim TH, Shin S et al. Mol Pharm, 2017, 14(1): 53-65

Development of novel physiologically relevant IVIVC model

External validation and application





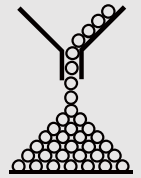
Parameter	Observed	Predicted	PE (%)
C_{max} (μg/mL)	18.79	17.29	8.0%
$AUC_{0\text{-}24h}$(μg·h/mL)	87.93	81.87	6.9%

Novel extended IVIVC combined with DoE

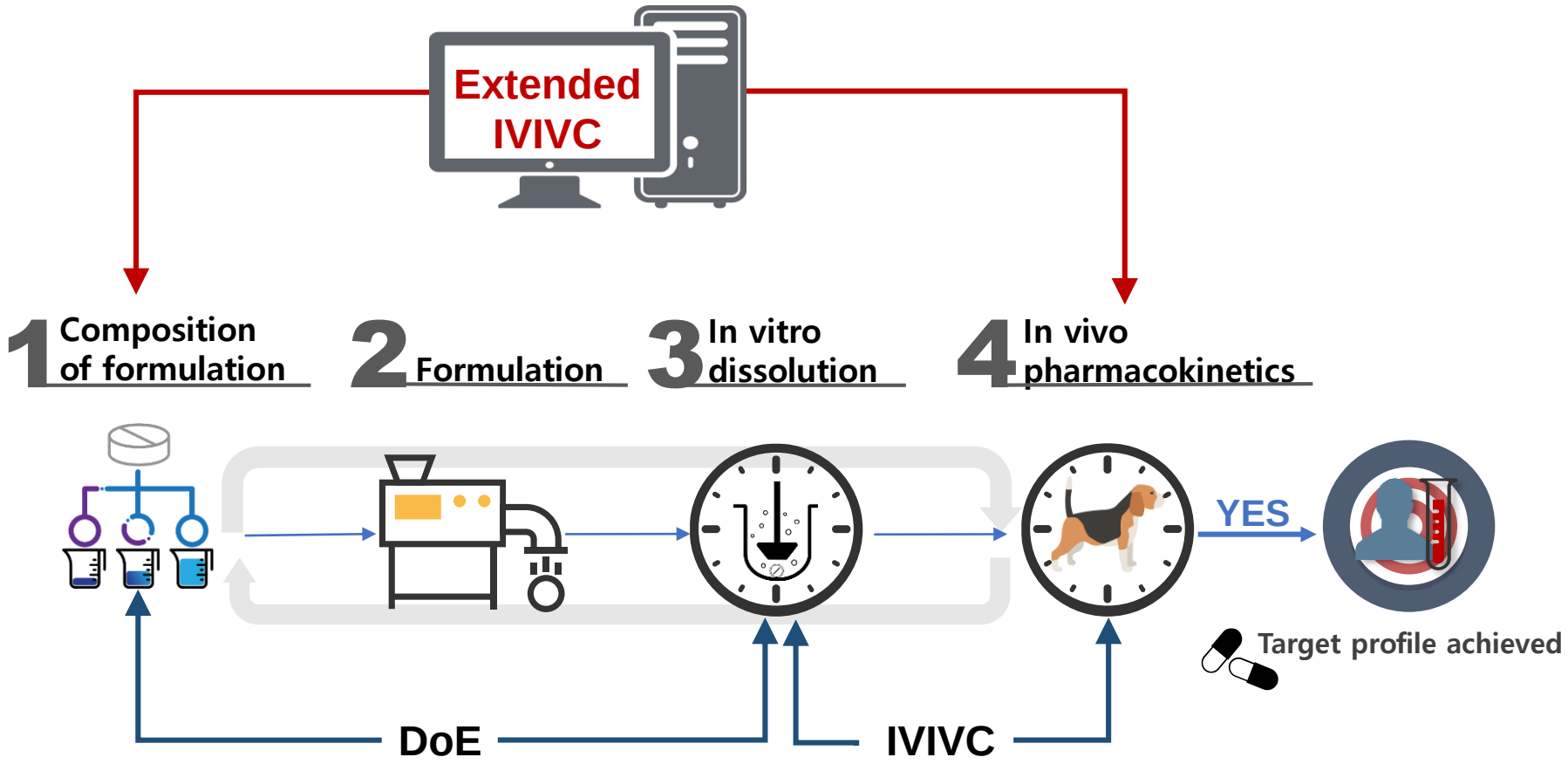
> **Design of experiments (DoE)**
> Design of experiments (DOE) is a systematic method to determine the relationship between **factors affecting a process** and **the responses** of that process.

Optimization of formulation composition using DoE

Type of excipient	Factor	Level	Response
Diluent	Lactose	and/or (5~20%) and/or (10~40%) (15~30%)	Flowability Dissolution Stability…
	MCC		
	Starch		
Disintegrant	Croscarmellose	and/or	
	Crospovidone		
Binder	HPMC	or (5~20%) or (10~20%) (5~15%)	
	HPC		
	Povidone		
Lubricant	Mg stearate	or	
	Talc		



Novel extended IVIVC combined with DoE



Novel extended IVIVC combined with DoE

Case study 2 (ketoprofen)

- Nonsteroidal anti-inflammatory drug (NSAID).
- Dosage: 25 mg orally 3 times a day
- BCS Ⅱ – Suitable for IVIVC
- Highly permeable at upper intestine

Formulation of ketoprofen ER tablets

Components	Percentage (wt%)
Dexketoprofen trometamol	40.55%
Lactose (X_1)	**8.5~48.5%**
HPMC2208-100 cps (X_2)	**0~30%**
HPMC2208-4000 cps (X_3)	**0~30%**
Mg stearate	0.95%
Total	100%

X_1 : Lactose
X_2 : HPMC2208 100cps
X_3 : HPMC2208 4000cps

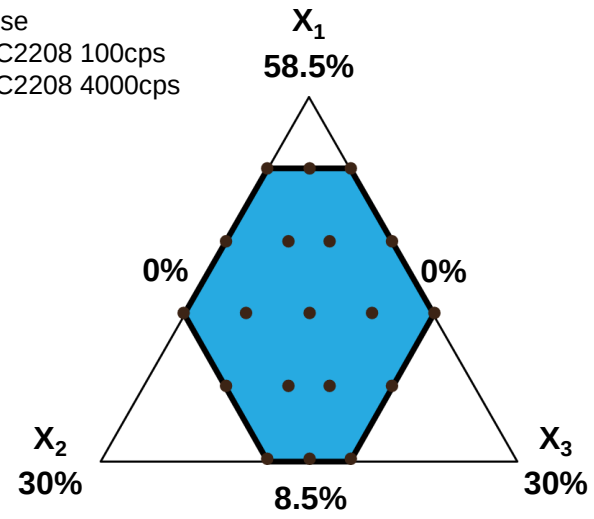


Figure. Nineteen runs in simplex mixture design.

Mixture design for ketoprofen ER tablet dissolution control

DoE for ketoprofen ER tablet

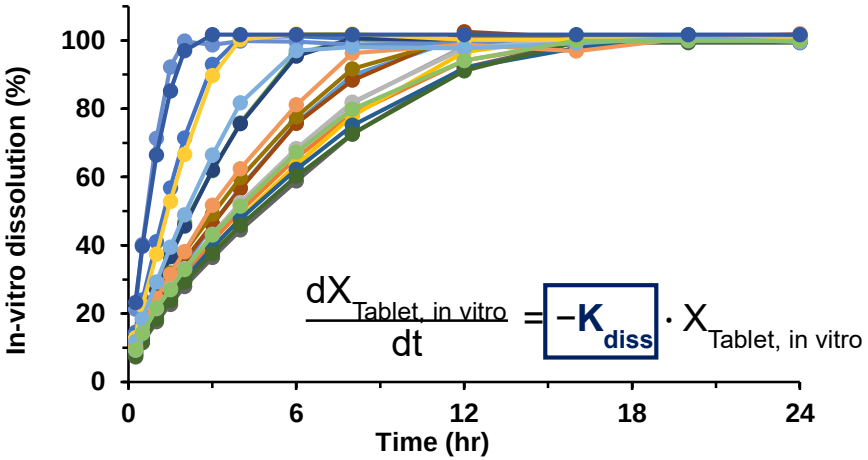
	Factor and level			Response
Run	X_1 (%)	X_2 (%)	X_3 (%)	Y (hr)
1	48.5	0	10	1.57
2	18.5	17.5	22.5	5.04
3	18.5	22.5	17.5	4.75
4	8.5	30	20	5.28
5	18.5	30	10	4.18
6	38.5	7.5	12.5	2.85
7	28.5	30	0	2.88
8	28.5	15	15	4.17
9	8.5	25	25	5.86
10	38.5	0	20	3.85
11	18.5	10	30	5.49
12	8.5	20	30	5.79
13	48.5	10	0	0.84
14	28.5	22.5	7.5	3.70
15	28.5	0	30	4.76
16	38.5	20	0	1.75
17	38.5	12.5	7.5	2.62
18	28.5	7.5	22.5	4.772
19	48.5	5	5	0.88

- **Critical Material Attribute (CMA)**

  X_1 : Lactose
  X_2 : HPMC2208 100cps
  X_3 : HPMC2208 4000cps

- **Critical Quality Attributes (CQA)**

  Y : Rate of dissolution ($1/K_{diss}$)

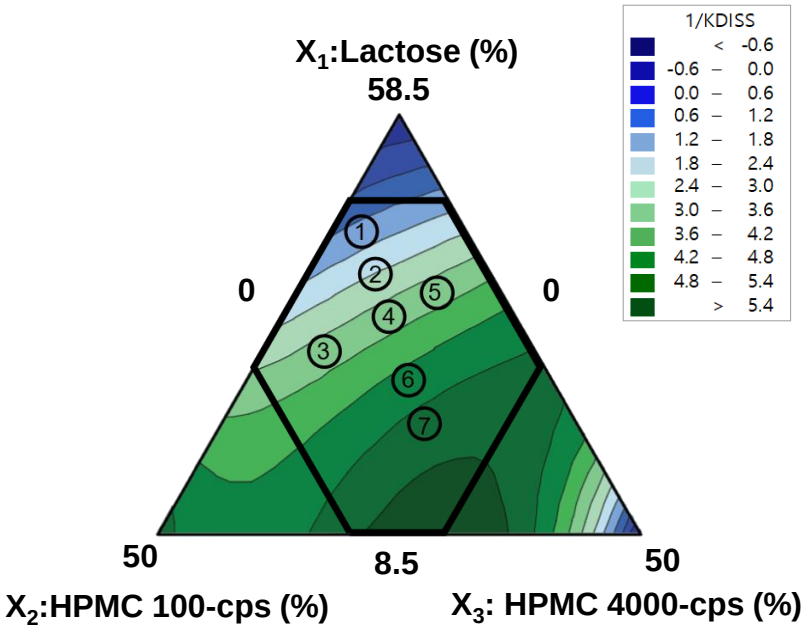


- **Best fit mathematical model**

$$1/K_{diss} = -0.007201X_1 + 0.104230X_2 - 0.147401X_3 + 0.010989X_1X_3 + 0.009113X_1X_3 - 0.000108X_1X_3(X_1-X_3) - 0.000205X_2X_3(X_2-X_3) - 0.000012X_1X_2X_3$$

Mixture design for ketoprofen ER tablet dissolution control

External validation for DoE



Contour plot for $1/K_{diss}$ presenting the effect of formulation composition. ①~⑦ indicate point of external validation

Experimentally observed

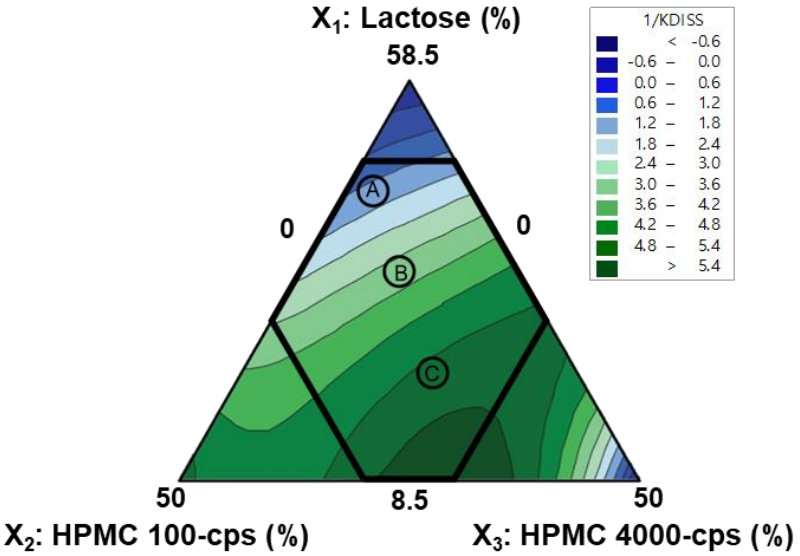
Validation	Observed $1/K_{diss}$	Predicted $1/K_{diss}$	PE (%)
Point 1	1.47	1.44	2.08 %
Point 2	2.07	2.05	1.34 %
Point 3	3.22	3.28	1.84 %
Point 4	3.42	3.24	5.42 %
Point 5	3.28	3.10	5.53 %
Point 6	4.96	4.85	2.16 %
Point 7	5.55	5.26	5.62 %

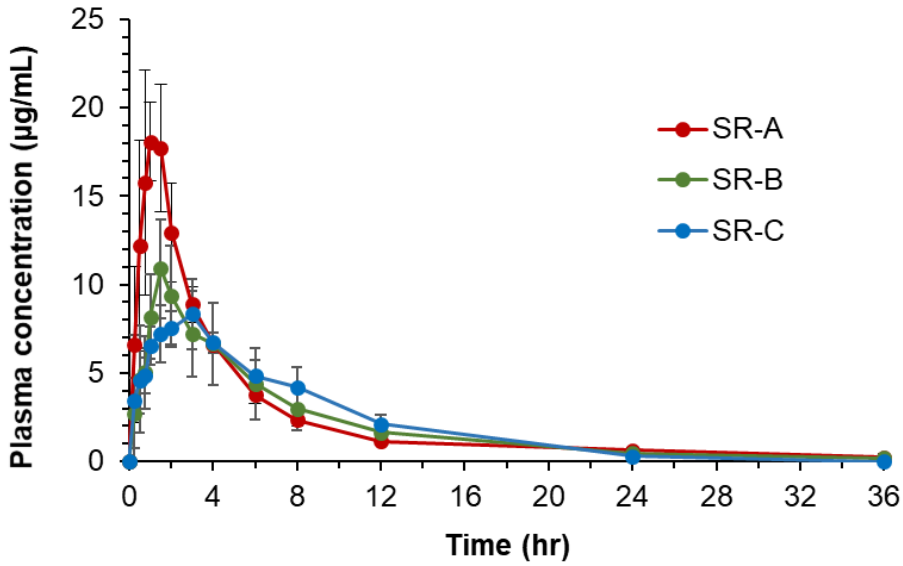
Model predicted

$$1/K_{diss} = -0.007201X_1 + 0.104230X_2 - 0.147401X_3 + 0.010989X_1X_3 + 0.009113X_1X_3 - 0.000108X_1X_3(X_1-X_3) - 0.000205X_2X_3(X_2-X_3) - 0.000012X_1X_2X_3$$

Novel extended IVIVC combined with DoE

Characteristics of in vivo pharmacokinetics



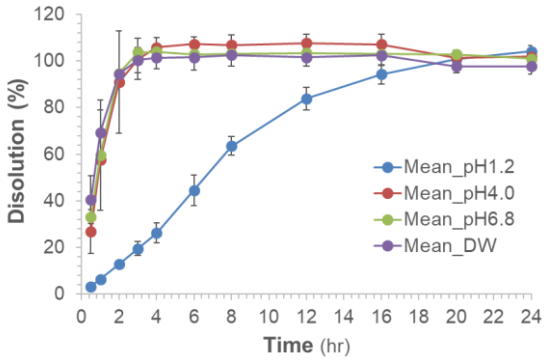


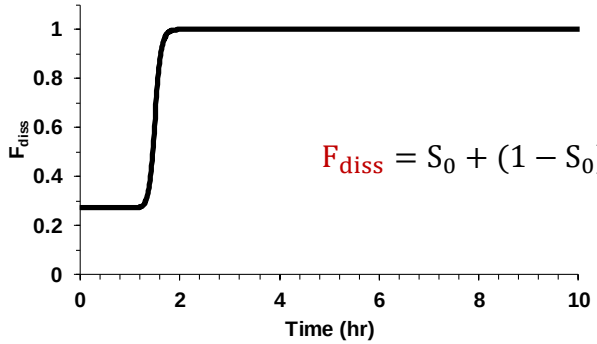
Group	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{all} (μg·hr/mL)
SR-A ①	8.66 ± 4.44	1.13 ± 0.43	20.00 ± 2.20	84.24 ± 6.89
SR-B ④	7.74 ± 3.26	2.13 ± 1.25	11.44 ± 1.92	73.68 ± 19.31
SR-C ⑦	4.27 ± 0.78	2.75 ± 0.5	8.79 ± 1.09	74.27 ± 8.06

Novel extended IVIVC combined with DoE

IVIVC model structure

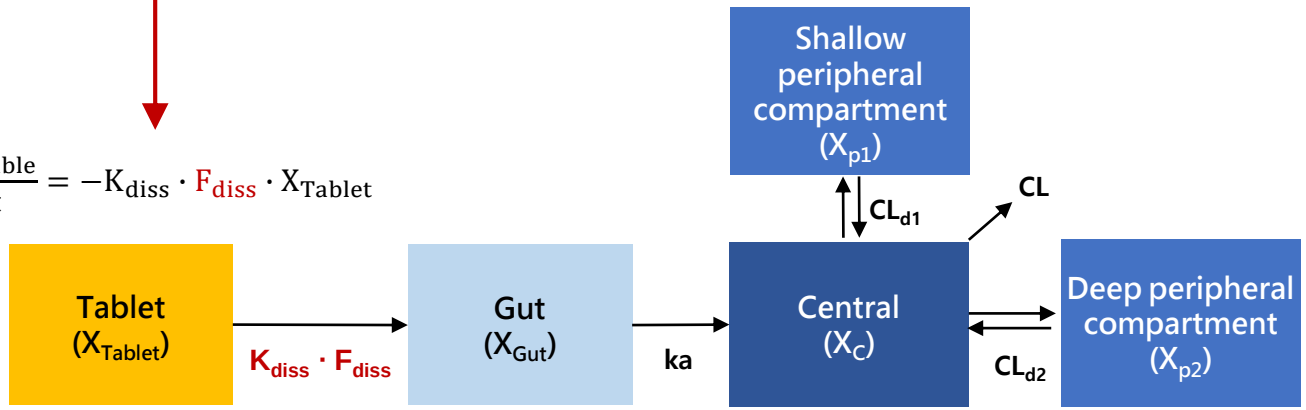
pH dependent dissolution





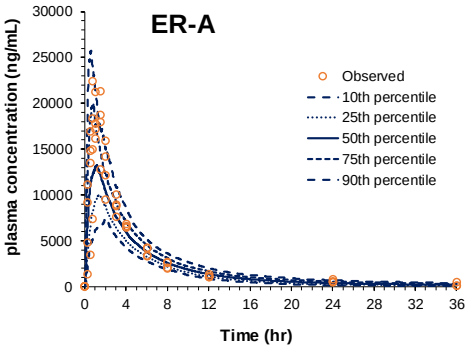
$$F_{diss} = S_0 + (1 - S_0) \times \frac{Time^{HILL}}{TC_{50}^{HILL} + Time^{HILL}}$$

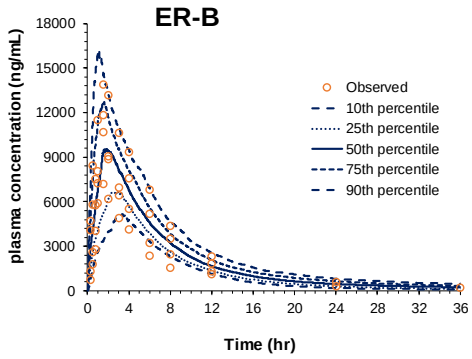
$$\frac{dX_{Table}}{dt} = -K_{diss} \cdot F_{diss} \cdot X_{Tablet}$$

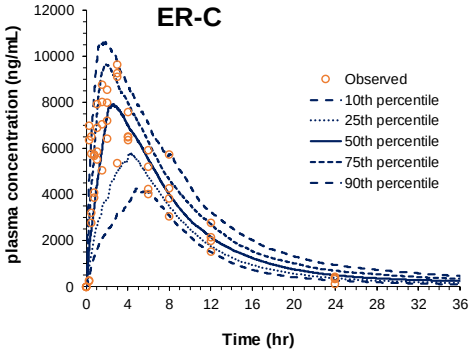


Novel extended IVIVC combined with DoE

Extraction of in vivo dissolution

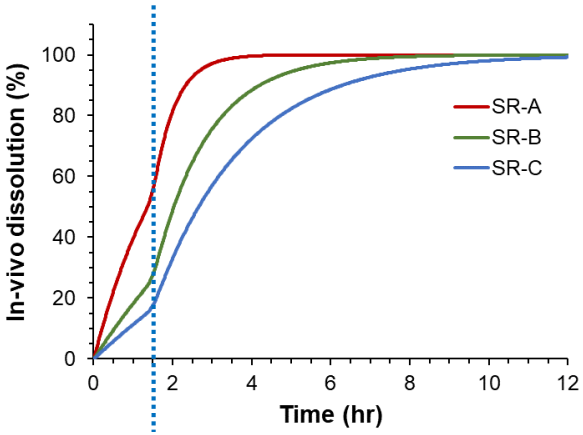




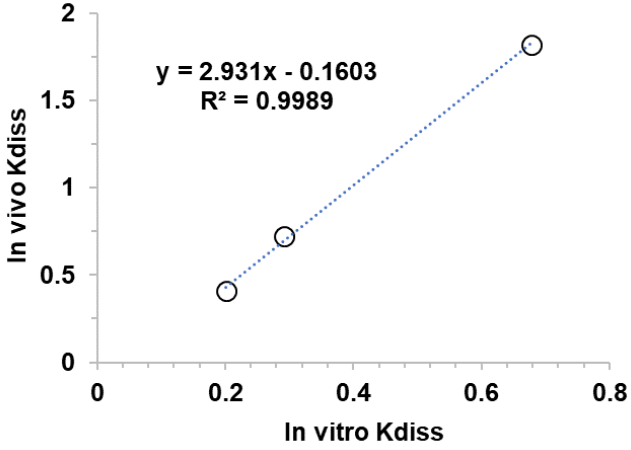


SR-Tablet	K_{diss}, in vitro	K_{diss}, in vivo
SR-A tablet (fast)	0.67735	1.820
SR-B tablet (medium)	0.29192	0.722
SR-C tablet (slow)	0.20159	0.409

TC_{50}=1.5 hr



K_{diss} in vivo = 2.931·K_{diss} in vitro − 0.1603

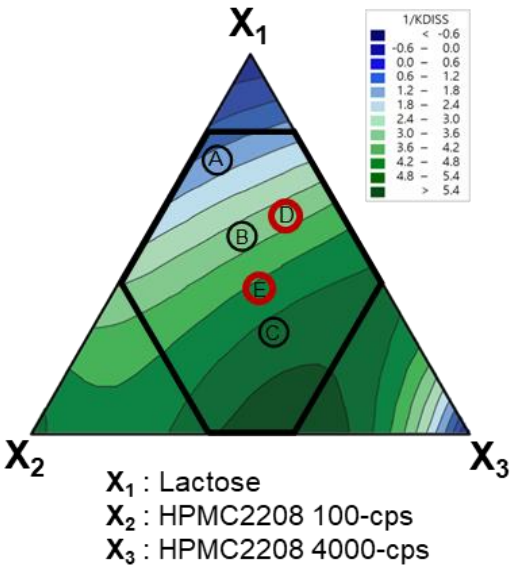


$$F_{diss} = S_0 + (1 - S_0) \times \frac{Time^{HILL}}{TC_{50}^{HILL} + Time^{HILL}}$$

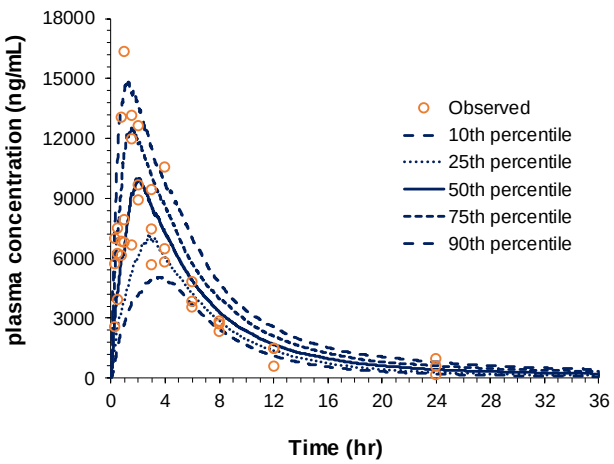
Novel extended IVIVC combined with DoE

Model validation

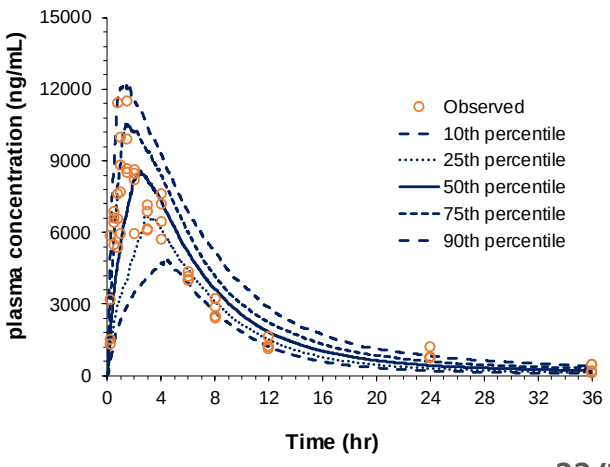
Validation	Formulation	C_{max}			$AUC_{0\text{-}36h}$		
		Obs. (µg/mL)	Pred. (µg/mL)	PE (%)	Obs. (µg/mL)	Pred. (µg/mL)	PE (%)
Internal validation	SR-A	20.00	18.54	7.28%	84.24	76.93	8.69%
	SR-B	11.44	11.98	4.67%	73.68	75.34	2.26%
	SR-C	8.79	8.86	0.78%	74.27	76.08	2.44%
External validation	SR-D	12.40	12.12	2.28%	73.24	76.78	4.83%
	SR-E	10.35	10.11	2.30%	73.98	75.12	1.53%



SR-D: External validation set for DoE



SR-E: External validation set for IVIVC model



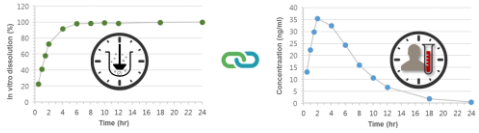
Summary

What is "In Vitro-in Vivo Correlation (IVIVC)"?

US FDA definition of IVIVC

A predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response

Application 1: Prediction of PK profile from dissolution pattern

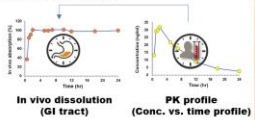


In vitro property: Dissolution — In vivo response: PK profile

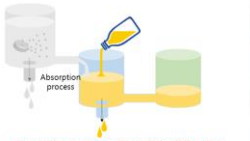
Application 2: Design the optimal dissolution pattern for the desired PK profile

Limitation of the conventional IVIVC approach

Step 1. (The most critical step)
Prediction of in vivo dissolution profile in the GI tract from plasma concentration-time profile



In vivo dissolution (GI tract) — PK profile (Conc. vs. time profile)



Assuming complete absorption of the drug after dissolution without absorption process

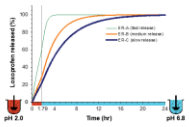
- Conventional IVIVC method cannot describe complex systemic drug disposition such as nonlinear PK or EHC which are frequent cases.
- Conventional methods assume all dissolved drug is completely absorbed without any limitation.
  → thus only can be applied for BCS I and II drugs.
  → cannot describe complex physiological absorption process.

Novel IVIVC approach may be necessary to improve predictability of in vivo drug performance and to expand application of IVIVC

Development of novel physiologically relevant IVIVC model

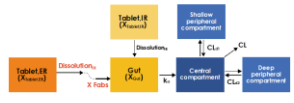
IVIVC Model structure

pH dependent dissolution

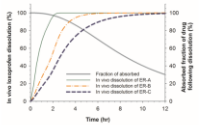


$$V_{max}(t) = V_{max}(0)^{[1+E_{max}\cdot time^{10}/(C^{10}_{change50}+time^{10})}$$

$$\frac{dX_{solid}}{dt} = -\frac{V_{max}(t)}{AM_{50}+X_{solid}}\cdot X_{solid}$$



Site dependent absorption



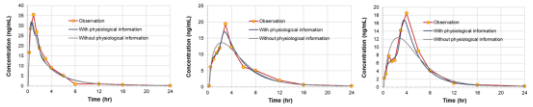
$$F_{abs} = 1 - \frac{Time^{\gamma}}{TW_{50}^{\gamma} + Time^{\gamma}}$$

11/25

Development of novel physiologically relevant IVIVC model

Interval validation

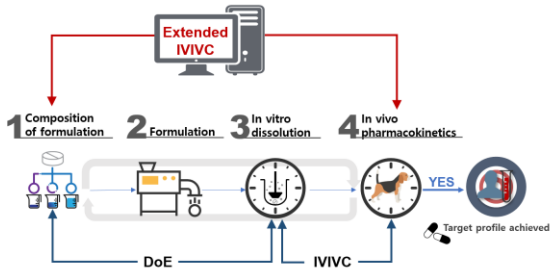
Model	Formulation	C_{max} Obs. (μg/mL)	C_{max} Pred. (μg/mL)	C_{max} PE (%)	$AUC_{0\text{-}24h}$ Obs. (μg/mL)	$AUC_{0\text{-}24h}$ Pred. (μg/mL)	$AUC_{0\text{-}24h}$ PE (%)
Model 1 (Conventional IVIVC model)	ER-A	29.82	22.92	23.1	96.95	84.39	12.9
	ER-B	17.17	15.07	12.2	89.35	83.80	6.2
	ER-C	12.06	9.32	22.7	78.07	82.72	6.0
Model 2 (pH dependent dissolution)	ER-A	29.82	25.16	15.6	96.95	84.17	13.2
	ER-B	17.17	16.29	5.1	89.35	86.38	3.3
	ER-C	12.06	13.85	14.8	78.07	84.07	7.7
Model 3 (pH-dependent dissolution, site-dependent absorption)	ER-A	29.82	27.95	6.3	96.95	88.86	8.3
	ER-B	17.17	17.32	0.9	89.35	83.56	6.5
	ER-C	12.06	12.66	4.9	78.07	75.14	3.8



Kim TH, Shin S et al. Mol Pharm, 2017, 14(1): 53-65

13/25

Novel extended IVIVC combined with DoE



16/25

Novel extended IVIVC combined with DoE

Model validation

Validation	Formulation	C_{max} Obs. (μg/mL)	C_{max} Pred. (μg/mL)	C_{max} PE (%)	$AUC_{0\text{-}36h}$ Obs. (μg/mL)	$AUC_{0\text{-}36h}$ Pred. (μg/mL)	$AUC_{0\text{-}36h}$ PE (%)
Internal validation	SR-A	20.00	18.54	7.28%	84.24	76.93	8.69%
	SR-B	11.44	11.98	4.67%	73.68	75.34	2.26%
	SR-C	8.79	8.86	0.78%	74.27	76.08	2.44%
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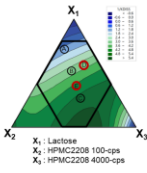
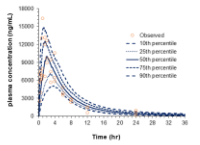
	SR-E	10.35	10.11	2.30%	73.98	75.12	1.53%

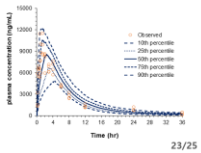


X_1 : Lactose
X_2 : HPMC2208 100-cps
X_3 : HPMC2208 4000-cps

SR-D: External validation set for DoE



SR-E: External validation set for IVIVC model



23/25