

Background and objective

Advanced compartmental absorption and transit (ACAT) model can estimate the fraction of dose absorbed and the rate of drug absorption based on the transit model. This model used for small molecule but need various physicochemical properties of drug.

The purpose of this study was to establish a simplified-ACAT model for estimating specific drug kinetics.

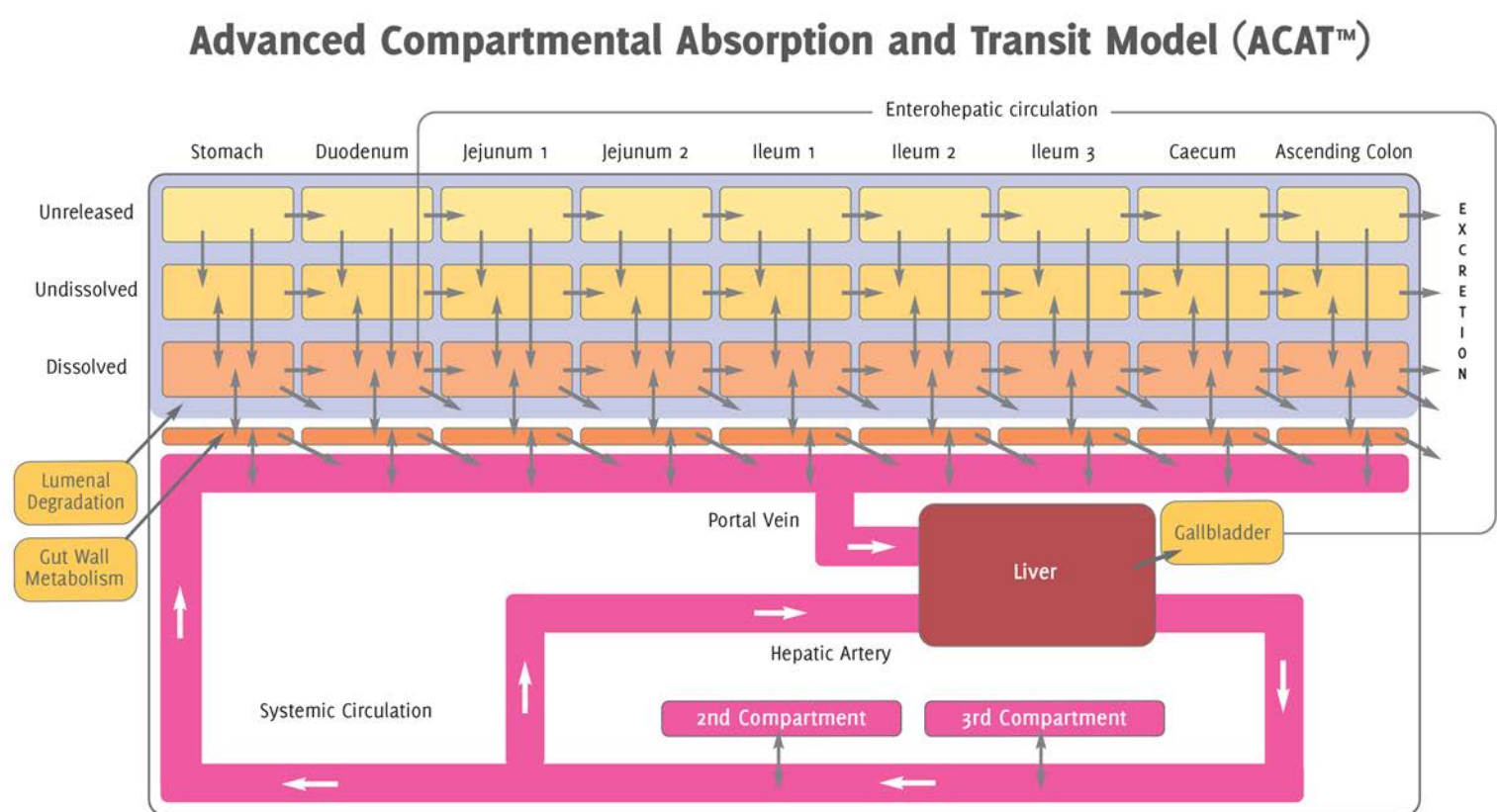


Figure 1. Advanced compartmental absorption and transit model (ACAT™). Figure from "PBPK modeling & simulation Workshop in Chungnam National University 2014"

Methods

1. Study design

Study design	
Animal study	
	Whole body autoradiography (WBA)
	Determination of plasma concentration
Species	Long-Evans (male=5, female=5)
	Sprague-Dawley rat (male=27, female=27)
Sacrifice per time point	1 animal/sex
Sampling time	0.25, 1, 2, 8, 24 hour
	0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24 hour
Sample matrix	esophagus, stomach, small intestine, large intestine, liver, ...
	Plasma
Phase I clinical trial	
Volunteers	30 healthy human
Dose	20, 60, 120, 240, 480 mg
Sampling time	0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 hour
Sample matrix	Plasma

2. Simplified-ACAT model development.

We assumed that the drug, fimasartan (FMS) disintegrated progressively at each compartments of GI tracts while passing through. Then, disintegrated portion is absorbed across the GI membrane, and reach liver first and distribute to other parts of body through systemic circulation.

Our simplified-ACAT model consists of 4 compartments for GI tract's contents, 4 compartments for GI tract which act as an absorption membrane, and 3 compartments for liver, plasma and the rest of the body. For explaining enterohepatic recirculation, a gall bladder compartment was

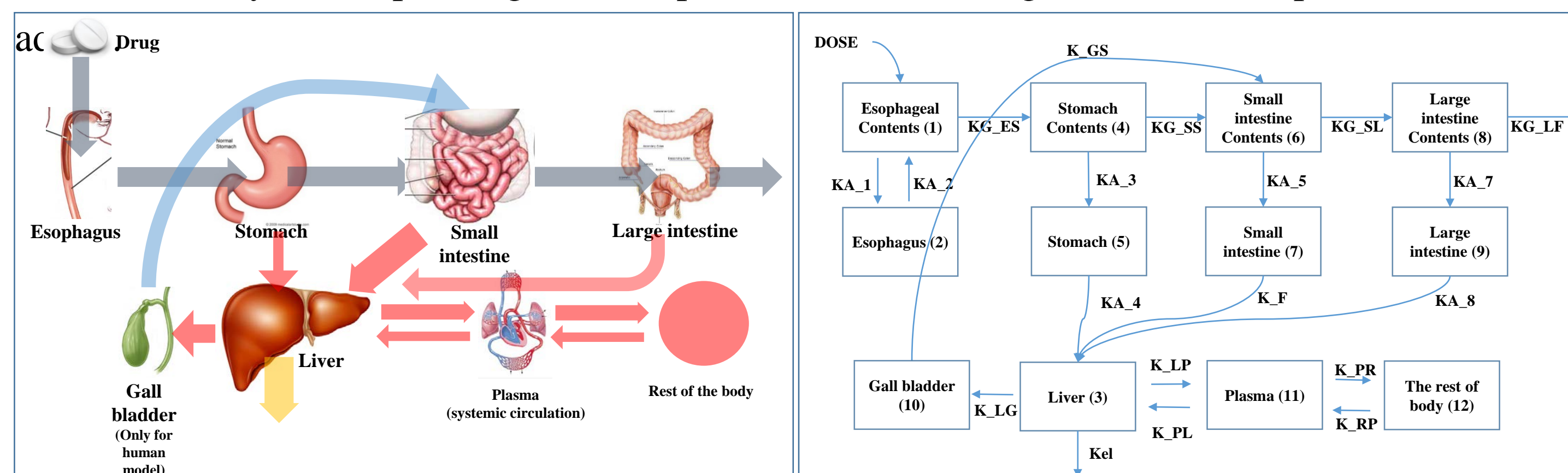


Figure 3. Simplified-ACAT model concepts with major organ in rat. Dark blue arrow means movement of drug. Light red arrow means movement of drug in the blood. Light blue arrow means movement of drug in the bile acid. Yellow arrow means elimination route

Figure 4. Scheme of simplified-ACAT model scheme.

3. Fractal kinetics concepts

Fimasartan was highly disposed in liver. The mean tissue:plasma concentration ratio was 658 (range 45.3 – 2340). To describe high disposition of drug in liver, fractal kinetics concept are introduced

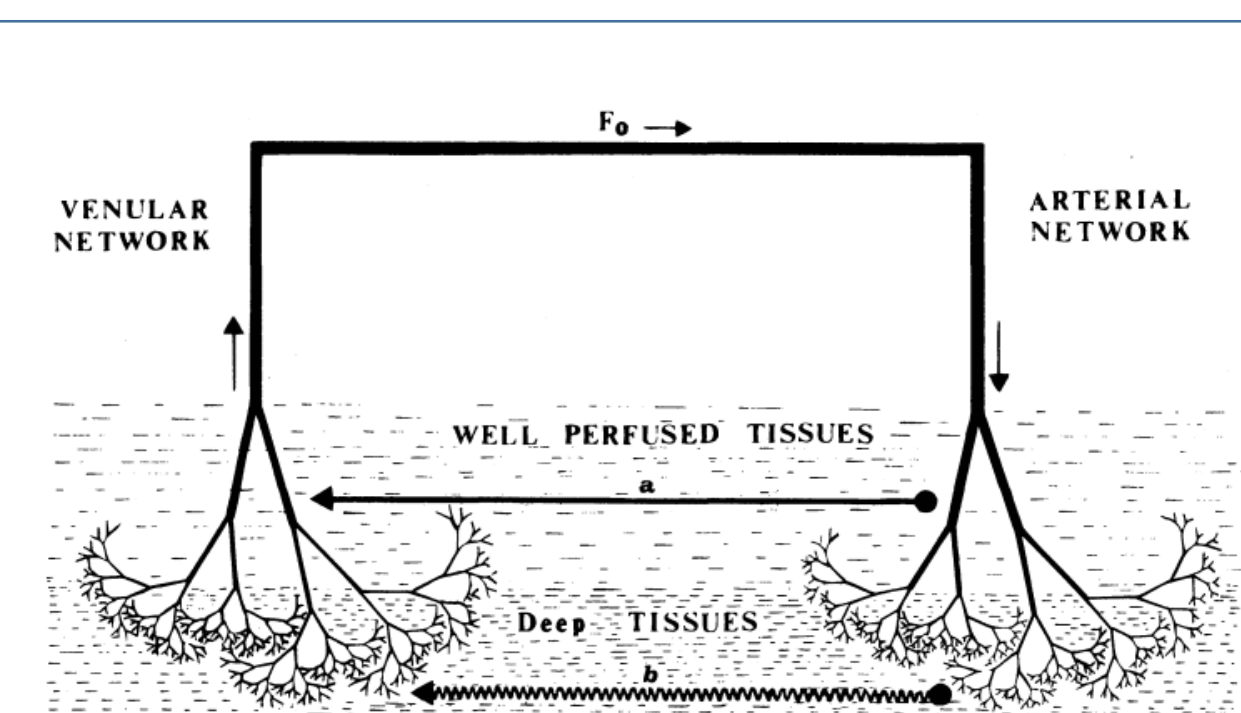


Figure 4. A complete vascular dichotomous network used to describe the distribution of drug in the body. F0 is the total blood flow. The black circle represents the drug. (a) The distribution of drug in well perfused tissues takes place under homogeneous (well stirred) condition. (b) The distribution of drug in deep tissues takes place under heterogeneous (understirred) conditions.[3]

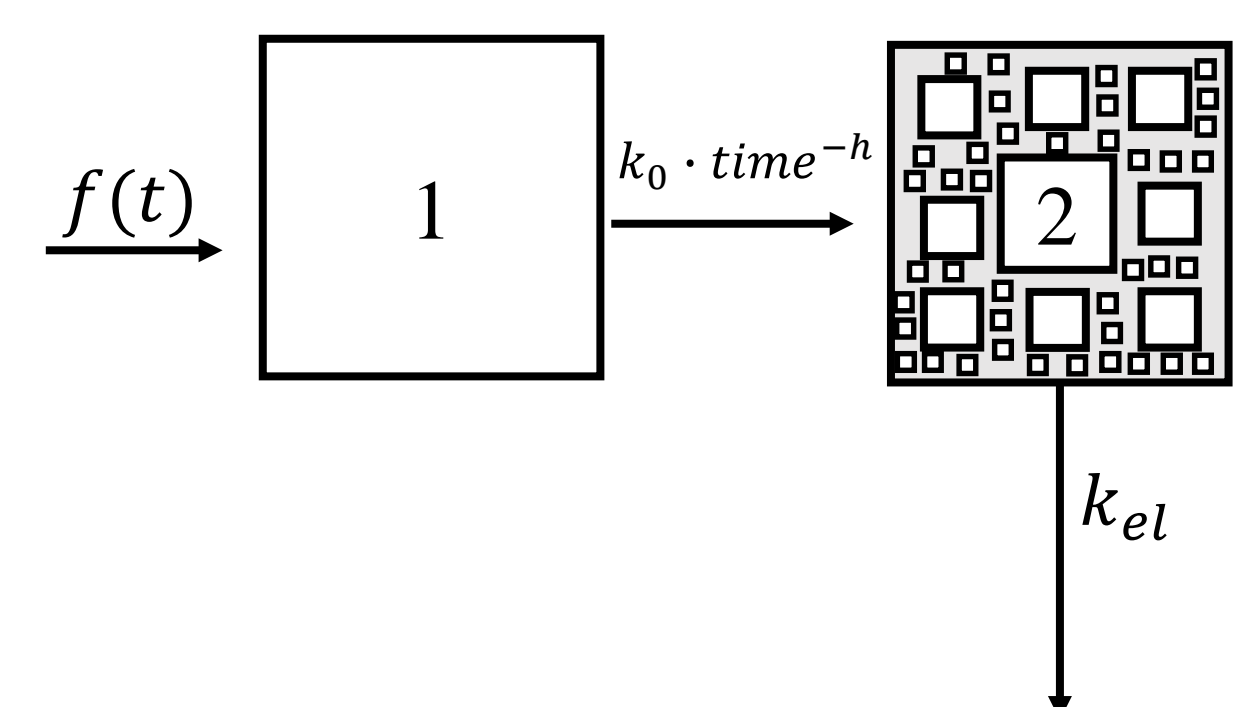


Figure 5. Model scheme of fractal kinetics used in simplified-ACAT model.

Standard kinetics on homogenous tissue was explained by following equations.

$$\frac{dC}{dt} = -k \cdot C \quad k: \text{Rate constant}$$

Rate constant (k) in kinetics equation was changed in heterogeneous condition by time and fractal dimension factor.

$$k = k_0 \cdot \text{time}^{-h} \quad k_0: \text{Correlation coefficient}$$

$$h = 1 - \frac{d_s}{2} \quad h: \text{Fractal dimension factor}$$

$$d_s: \text{Length of random walk}$$

Differential equations for explanation about 1-compartment PK model concerned fractal kinetics was following.

$$\frac{dA(1)}{dt} = -k_{el} \cdot t^{-h} \cdot A(1)$$

Above equation was transformed by inverse logit function for avoidance zero approximation of rate constant when time was zero.

$$\frac{dA(1)}{dt} = \frac{-k_{el}}{\text{Time}^h} \cdot A(1)$$

Results and discussion

1. Comparing conventional PK model and Fractal kinetic PK model

After applying fractal kinetics, robustness is improved and prediction range of the model was narrow. Figures below are comparing predictability and robustness of each method

1) Simulation data of liver disposition (simplified-ACAT model for rat)

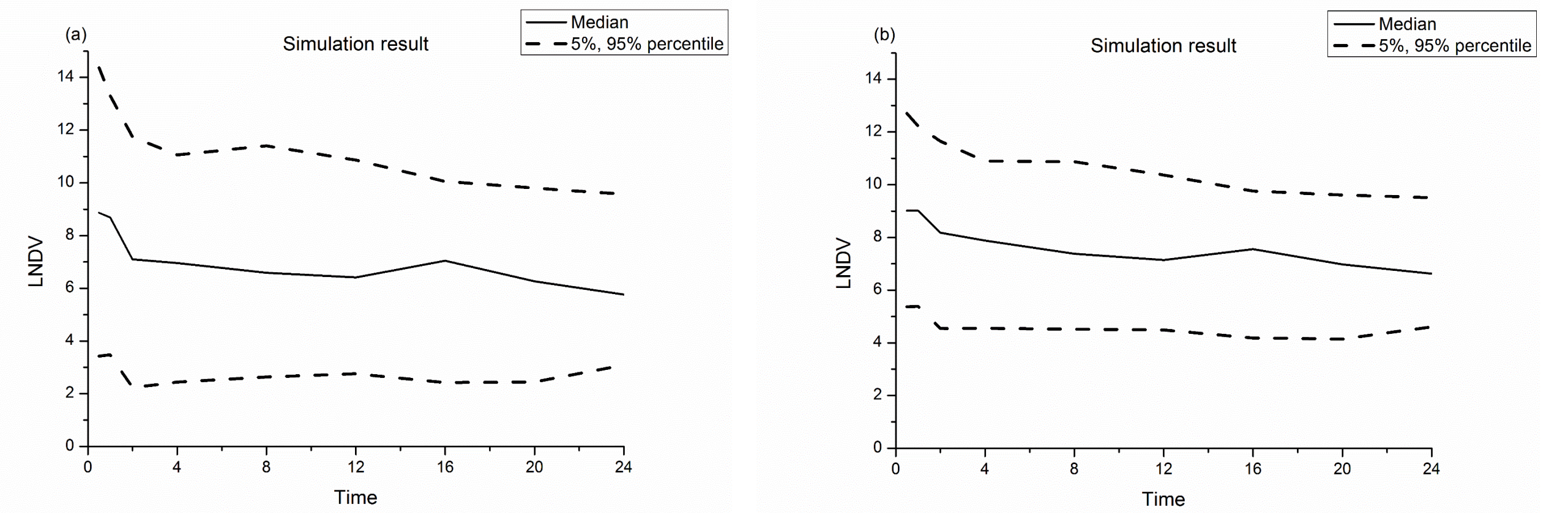


Figure 7. Comparison of two simulation results. (a) Simulation results using conventional rate constant to describe distribution from small intestine to liver. (b) Simulation results using fractal kinetics to describe distribution from small intestine to liver. After applying fractal kinetics, prediction range was narrow.

2) Visual predictive check plot of plasma concentration of FMS in rat

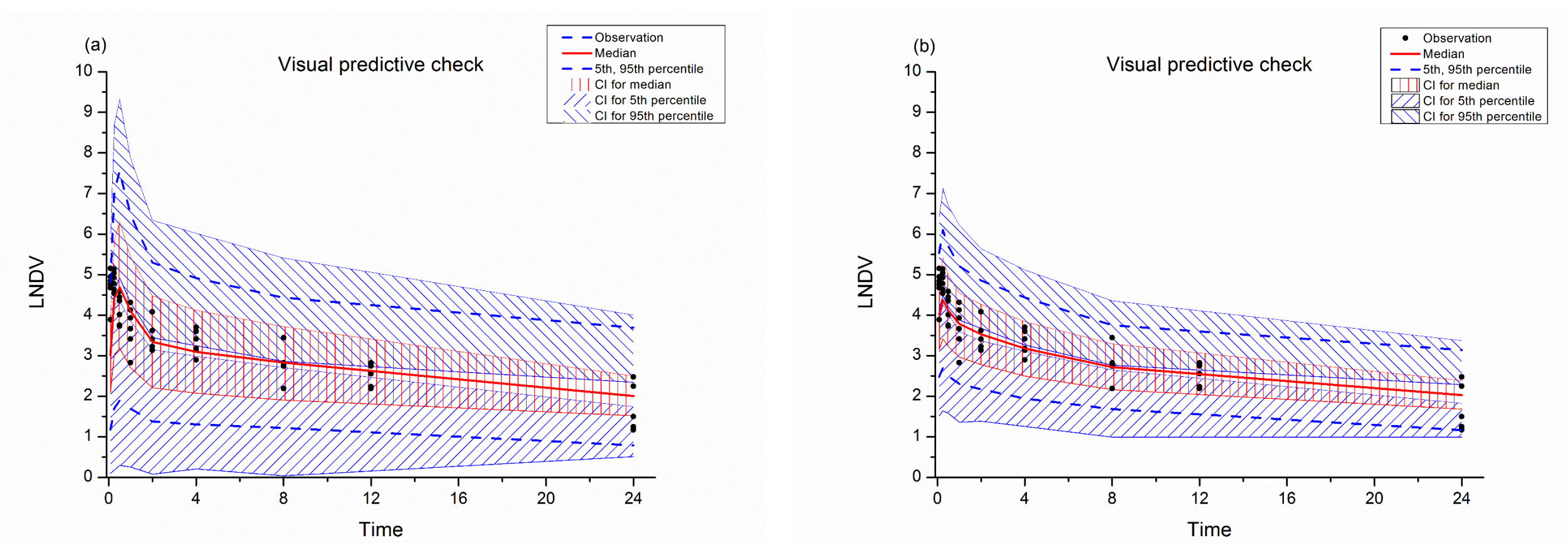


Figure 8. Comparison of two visual predictive check plot. Closed black circle represent observed plasma concentration of FMS. The red solid line represents the median of the simulated concentrations. The blue dashed line represent the 5th and 95th percentile of the simulated concentrations. The lower blue, red, upper blue shaded area represent the 95% confidence intervals for the 5th percentile, median, 95th percentile, respectively. (a) Visual predictive check for model using conventional rate constant. (b) Visual predictive check for model using fractal kinetics.

3. Application to Human

Simplified-ACAT model of FMS for human is developed using rat WBA and plasma data.

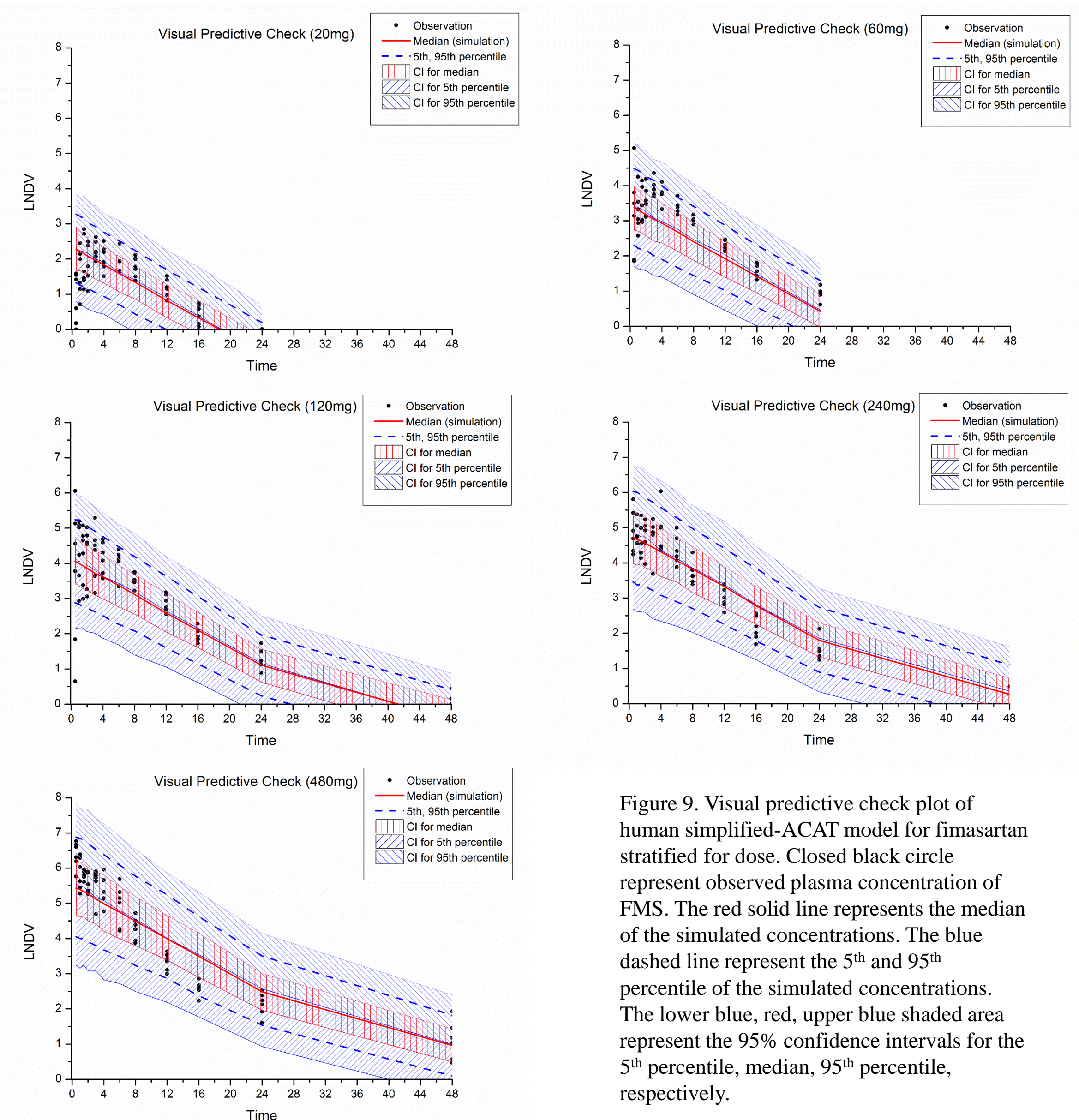


Figure 9. Visual predictive check plot of human simplified-ACAT model for fimasartan stratified for dose. Closed black circle represent observed plasma concentration of FMS. The red solid line represents the median of the simulated concentrations. The blue dashed line represent the 5th and 95th percentile of the simulated concentrations. The lower blue, red, upper blue shaded area represent the 95% confidence intervals for the 5th percentile, median, 95th percentile, respectively.

We developed a simplified-ACAT model to describe human plasma concentration of fimasartan, angiotensin receptor blocker. This model is based on the rat simplified-ACAT model built from WBA and plasma concentration data.

Using fractal kinetics, we could not explain the extensive disposition of drug in liver perfectly, but objective function value decreased 83.9 and the prediction range was narrow.

Our simplified-ACAT has limitations because rat data is not enough to explain variability. Nevertheless, this model appears to be promising and should be further evaluated

References

- [1] Grant, L. *et al.* Eur J Clin Pharmacol 63, 485-498 (2007)
- [2] Benjamin, G *et al.*, PAGE 2014
- [3] Macheras, P. *et al.* Pharm. Res. 13, 663~70 (1996)

Acknowledgement

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