

# Influence of Circulation System on Estimation of Absorption and Elimination Constant after *per oral* Drug Administration: A Reanalysis

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Rausova, *et al.*: Influence of Circulatory System on Rate Constants

This study aimed to identify the cause of atypical shape of measured concentration-time profile in the peak area by one compartment open model with a lag time (Bateman function with a lag) after single dose oral administration of drug published in “Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Application” by Gabrielsson and Weiner (1997) and two concentration profiles after frequent sampling oral glucose tolerance test. Following the oral administration of 100 µg of substance A to human volunteer, frequent sampling was carried out and concentration-time profiles were obtained. Our hemodynamic circulatory structural model capable of parameters estimation of circulation and gastrointestinal subsystem to explain the plateau within the interval 40-100 min (substance A) and 15-30 min (glucose) of the measured concentration-time profile was developed. The mean residence time, the rate constants of absorption and elimination parameters of our model were calculated. Comparing to the Bateman function, our results demonstrate better approximation of the substance A and glucose concentration-time profile and estimation of absorption rate constant by our structural model. Obtained model results indicate that the atypical shape of measured concentration-time profile of single dose oral administration of drug was probably caused by the gastrointestinal and circulation system with deep compartment. This applies to the substances with high coefficient of absorption.

**Key words:** Absorption rate constant, elimination rate constant, gastric emptying, hemodynamic circulatory model, plateau

The main inspiration for creation of this work was from the book by Gabrielsson and Weiner<sup>[1]</sup>. Authors of chapter “PK 2 - One compartment oral data” (pages 333-340) aimed at the modeling of oral administered substance A using one compartment model presented first order input model known as Bateman function with a lag time<sup>[2-6]</sup>. Parameter estimation by WinNonlin version 1.1 (Scientific Consulting Inc., Apex, NC) were performed.

Bateman function in fig. 1 presents a concave function on the interval 0-100 min, but it does not satisfactorily describe the measured points on the interval 40-100 min (dashed line in fig. 1). Our working hypothesis for the explanation of the pseudolinear phenomena - plateau was that the atypical shape of the measured profile on the interval

40-100 min is caused by the gastrointestinal (GI) and the circulation system. Glucose is used as second example with the atypical shape of the measured concentration profile on the interval 15-30 min. There are also other examples of the atypical shape of the concentration-time profile of oral administered drug, such as L-arginine<sup>[7]</sup>, vitamin C<sup>[8]</sup>, ibuprofen<sup>[9]</sup>, fenobam<sup>[10]</sup>, paracetamol<sup>[11]</sup> and anthocyanins<sup>[12]</sup>.

## MATERIALS AND METHODS

A human volunteer was given a single oral dose comprising 100 µg of substance A. Consequently, the frequent sampling to obtain the concentration-time data was done at 10, 15, 20, 30, 40, 60, 90, 120, 180, 210, 240, 300, and 360 min after substance A administration<sup>[1]</sup>. Two other human volunteers (one male and one female) were given 75 g of anhydrous glucose<sup>[13]</sup> in 250 ml water solution within 1-2 min at time zero. Approval of the study protocol

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was obtained from the Ethic Committee of the Institute of Experimental Endocrinology of Slovak Academy of Sciences<sup>[13]</sup>. Frequent sampling oral glucose tolerance test was performed by the criteria of Expert Committee on Diagnosis and Classification of Diabetes Mellitus<sup>[14]</sup>. The blood samples were collected at 15 min before the glucose was administered and at 8, 15, 22, 30, 45, 60, 90, 120, 140, 160, and 180 min after the glucose was administered. Determination of glucose plasma concentrations was carried out by using the glucose oxidize method (Boehringer Mannheim, Germany)<sup>[13]</sup>.

### Structural model construction:

Inclusion of the GI system to the hemodynamic circulatory model (fig. 2) gives the option to analyze the plateau phenomena on the measured concentration-time profile shown in fig. 1. The scheme of the proposed structural model, with the oral substance dose  $D$  as input and the substance blood concentration in the sampling subsystem  $C_S$  as output, includes the cardiopulmonary subsystem CP, the portal subsystem P, the liver subsystem L, the GI subsystem, the other subsystems O and the sampling subsystem S. Assuming that all of the significant subsystems shown in fig. 2 within the range of measured concentrations formalized behave as linear dynamic systems, then  $i^{\text{th}}$  subsystem can be described by the transfer function  $H_i$  presented the general mathematical model of the subsystem as well-stirred model with time delay:

$$H_i(s) = \frac{g_i}{T_i s + 1} e^{-\tau_i s}$$

where  $s$  is Laplace operator,  $T$  is time constant of the subsystem and  $\tau$  is time delay of the subsystem. The constant  $g_i$  represented the attenuation of the subsystem and quantified the uptake of substance A in specific subsystem is expressed by the form:

$$g_i = \lim_{s \rightarrow 0} H_i(s)$$

The definition and the transfer function of the GI subsystem comprising absorption part A and gastric emptying (GE) (fig. 3) and respecting the mass balance is defined as

$$H_{GI}(s) = \frac{M_A(s)}{D(s)} = \frac{1}{T_A s + 1} (F_1 e^{-\tau_1 s} + F_2 e^{-\tau_2 s})$$

where  $D(t) = \text{Dose} \cdot \delta(t)$ ,  $\delta(t)$  is Dirac function,  $M_A$  is

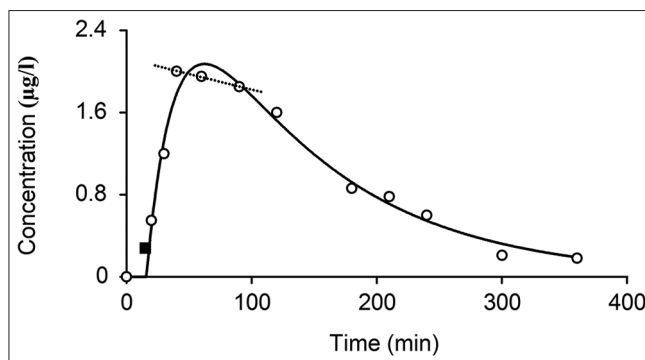


Fig. 1: Observed data and model-predicted concentration-time profile after oral administration of 100 µg of substance A to one human volunteer.

Circles represent measured values, full squares represent omitted measured value in 15<sup>th</sup> min, solid line represents one compartment model with a time delay approximation, dotted line represents atypical, hypothetical linear shape of measured concentration-time profile of substance A on the time interval 40-100 min. Observed data adapted from J. Gabrielsson, and D. Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Application, 2<sup>nd</sup> edition, pp. 333-340, copyright 1997, with permission of Swedish Pharmaceutical Press.

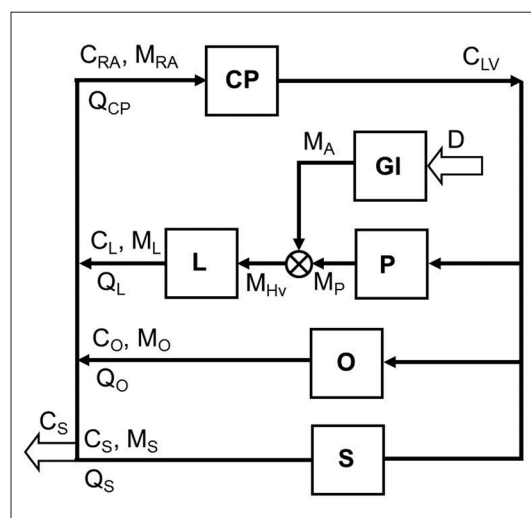


Fig. 2: The scheme of the hemodynamic circulatory model included gastrointestinal subsystem.

$D$  is substance dose, CP is cardiopulmonary subsystem, GI is gastrointestinal subsystem, L is liver subsystem, P is portal subsystem, O is other organ subsystem, S is sampling subsystem,  $M$  is amount of the substance per unit of time,  $A$  is absorption,  $Q$  is plasmatic blood flow,  $C$  is substance blood concentration,  $Hv$  is hepatic vein, RA is right atrium, LV is left ventricle.

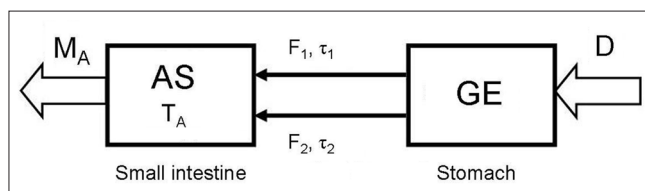


Fig. 3: Gastrointestinal subsystem.

$M_A$  is absorbed amount per unit of time,  $D$  is the dose, AS is absorption site,  $T_A$  is mean residence time of the absorption subsystem, GE is gastric emptying,  $F$  is fraction,  $\tau$  is time delay.

absorbed amount per unit of time in GI subsystem in the first-pass metabolism of the drug,  $T_A$  is mean residence time of the absorption subsystem,  $F$  is fraction and  $\tau$  is time delay of the subsystem.

For substance blood concentration in the right atrium  $C_{RA}$  is valid

$$C_{RA}(t) = \frac{C_L(t)Q_L + C_O(t)Q_O + C_S(t)Q_S}{Q_{CP}} \\ = \frac{M_L(t) + M_O(t) + M_S(t)}{Q_{CP}}$$

where  $Q_{CP}$  is plasmatic blood flow through CP system expressed as follows:

$$Q_{CP} = Q_L + Q_O + Q_S$$

and  $M_L$ ,  $M_O$ ,  $M_S$  are mass quantities that flow from the liver, the other organs and the sampling subsystems into right atrium RA per unit of time.  $Q_L$ ,  $Q_O$ ,  $Q_S$  are plasmatic blood flow via the liver, the other organs and the sampling subsystems.

The definitions and transfer functions of the elementary subsystems, respecting the mass balance, are considered as follows equations:

Regarding the CP subsystem is valid

$$H_{CP}(s) = \frac{C_{LV}(s)}{M_{RA}(s)} = \frac{1}{Q_{CP}}$$

where  $C_{LV}$  is the substance concentration in the left ventricle,  $M_{RA}$  is the substance amount per unit of time in the right atrium and  $Q_{CP}$  is plasmatic blood flow via CP subsystem.

Regarding the portal subsystem  $P$  is valid

$$H_P(s) = \frac{M_P(s)}{C_{LV}(s)} = \frac{g_P Q_P}{T_P s + 1} = \frac{G_P}{T_P s + 1}$$

where  $M_P$ ,  $g_P$ ,  $Q_P$ ,  $G_P$  and  $T_P$  are the substance amount per unit of time, the attenuation, the plasmatic blood flow, the gain and the time constant, respectively, related to the portal subsystem.

Regarding the liver subsystem  $L$  is valid

$$H_L(s) = \frac{M_L(s)}{M_{HV}(s)} = \frac{g_L}{T_L s + 1}$$

where  $M_{HV}$  is the substance amount per unit of time

in the hepatic vein.  $M_L$ ,  $g_L$  and  $T_L$  are the substance amount per unit of time, the attenuation and the time constant, respectively, related to the liver subsystem, where  $g_L$  is dimensionless value.

Regarding the other organ subsystem  $O$  is valid

$$H_O(s) = \frac{M_O(s)}{C_{LV}(s)} = \frac{g_O Q_O}{T_O s + 1} \cdot e^{-s\tau_O} = \frac{G_O}{T_O s + 1} \cdot e^{-s\tau_O}$$

where  $M_O$ ,  $g_O$ ,  $Q_O$ ,  $G_O$ ,  $\tau_O$  and  $T_O$  are the substance amount per unit of time, the attenuation, the plasmatic blood flow, the gain, the time delay and the time constant, respectively, related to the other organ subsystem.

The model of peripheral sampling subsystem  $S$  was considered as ideal subsystem for which is valid

$$H_S(s) = 1$$

For the mean residence time of the drug in the whole body ( $MRT_W$ ) after the oral administration is valid following equation:

$$MRT_W = MRT_{GI} + MRT_{CIRC} \quad (1)$$

and for the mean residence time of the GI subsystem ( $MRT_{GI}$ ) is valid

$$MRT_{GI} = T_A + \sum_{i=1}^n F_i \tau_i$$

where  $T_A$  is mean residence time of the absorption subsystem,  $F$  is absorbed fraction and  $\tau$  is a time delay of the subsystem.

Mean residence time of the substance of the circulation system ( $MRT_{CIRC}$ ) is calculated according to:

$$MRT_{CIRC} = MRT_W - MRT_{GI}$$

Numerical calculation of mean residence time of the whole system  $MRT_W$  from zero to infinity is expressed as

$$MRT_W = \frac{\int_0^{\infty} t \cdot C(t) dt}{\int_0^{\infty} C(t) dt}$$

The absorption rate constant  $k_a$  is expressed as

$$k_a = \frac{1}{T_A}$$

where  $T_A$  is mean residence time of the absorption subsystem.

The elimination rate constant  $k_{el}$  is expressed as

$$k_{el} = -\lim_{t \rightarrow \infty} \frac{\frac{d}{dt} C_s(t)}{C_s(t)} \quad (2)$$

where  $C_s$  is the concentration of the substance in the sampling subsystem S.

All model calculation and parameter estimation using the Clinical Trials DataBase software<sup>[15]</sup> were performed. Employing the parameters of the developed structural mathematical model (figs. 2 and 3), the vector  $\lambda$  of estimated parameters was determined as follows:

$$\lambda = (T_A, F_1, F_2, \tau_1, \tau_2, g_L, T_L, Q_{CP}, G_O, G_P, T_O, T_P, \tau_O)$$

The point estimate the model parameters by the Monte Carlo method<sup>[16]</sup> implemented in Computer Controlled Sequential Simulation method<sup>[17,18]</sup>.

## RESULTS AND DISCUSSION

The final outcome of the processed data obtained from the human volunteer is presented in fig. 4 (substance A), 5-6 (glucose) and Tables 1-3.

Figs. 4 and 5 show the measured and modeled concentration-time profile C of substance A and glucose 1 and the influence of the first absorbed fraction  $F_1$  and the second absorbed fraction  $F_2$ . The absorbed fractions  $F_1$  and  $F_2$  expressed by partial concentration-time profiles  $C_1$  (dashed line) and  $C_2$  (dotted line), respectively, are responsible for the

**TABLE 1: MODEL ESTIMATED PARAMETERS OF THE GASTROINTESTINAL SUBSYSTEM**

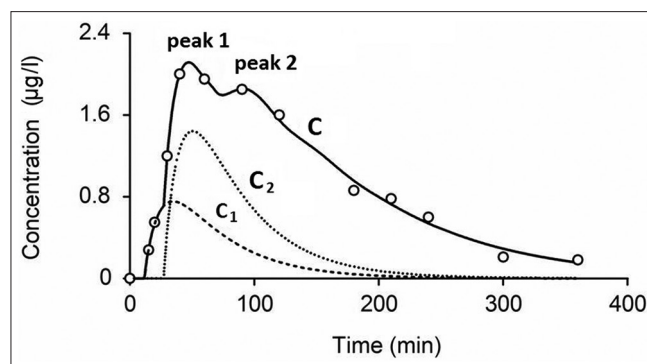
Substance	$F_1$ (%)	$F_2$ (%)	$T_a$ (min)	$\tau_1$ (min)	$\tau_2$ (min)	$MRT_{GI}$ (min)
Substance A	34.348	65.652	44.717	11.503	27.227	68.354
Glucose 1	33.000	66.000	2.852	1.731	13.398	12.271
Glucose2	100	0	1.085	7.751	0	8.836

$F_{1,2}$ =Absorbed fractions of the substance dose,  $\tau_{1,2}$ =Time delays of the subsystem,  $T_a$ =Mean residence time of the absorption subsystem,  $MRT_{GI}$ =Mean residence time of the gastrointestinal subsystem

main peak 1 of the final concentration-time profile C and presents the result of the effect of gastric emptying. The final shape of the concentration-time profile C for  $t \leq 60$  min is expressed as:

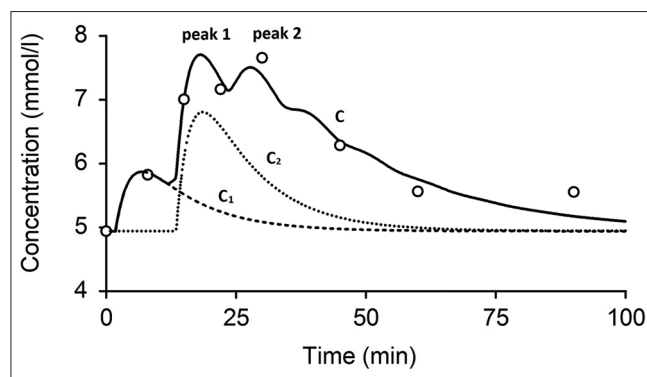
$$C(t) = C_1(t) + C_2(t)$$

where  $C_1$  and  $C_2$  are the partial concentration-time profiles developed by fraction  $F_1$  and  $F_2$ , respectively. Consequently, the secondary peak 2 is the time transformed peak 1 probably influenced by the deep compartment and the circulation system. Fig. 6 shows the measured and modeled concentration-time profile of glucose 2. In comparison with concentration-time profile of glucose 1 and substance A, concentration-time profile glucose 2 comprises only one absorbed fraction.



**Fig. 4:** Concentration-time profile of substance A and influence of its absorbed fractions.

Circles represent measured values, solid line C represents model approximation,  $C_1$  and  $C_2$  represent partial concentration-time profile developed by fraction  $F_1$  and  $F_2$ , respectively, peak 1 is the effect of the sum of the partial profiles  $C_1$  and  $C_2$ , peak 2 is the response of the deep compartment and the circulation system effect on peak 1.



**Fig. 5:** Concentration-time profile of glucose 1 and influence of its absorbed fractions.

Circles represent measured values, solid line C represents model approximation,  $C_1$  and  $C_2$  represent partial concentration-time profile developed by fraction  $F_1$  and  $F_2$ , respectively, peak 1 is the effect of the sum of the partial profiles  $C_1$  and  $C_2$ , peak 2 is the response of the deep compartment and the circulation system effect on peak 1.

**TABLE 2: MODEL ESTIMATED PARAMETERS OF THE CIRCULATION SUBSYSTEM**

Substance	$Q_{CP}$ (l/min)	$g_L$ (min/l)	$G_P$ (min/l)	$G_O$ (min/l)	$\tau_o$ (min)	$T_L$ (min)	$T_P$ (min)	$T_O$ (min)	$MRT_{CIRC}$ (min)
Substance A	1.600	0.969	1.023	0.323	43.575	4.239	1.623	6.733	62.292
Glucose 1	2.000	0.229	0.453	1.032	9.704	10.636	3.877	1.498	26.485
Glucose 2	2.48	1.022	0.445	0.872	13.568	15.072	4.689	1.274	34.231

$Q_{CP}$ =Plasmatic blood flow via cardiopulmonary subsystem,  $g$  is attenuation of the subsystem,  $G$ =Gain of the subsystem,  $\tau$ =Time delay of the subsystem,  $T$ =Mean residence time of the subsystem, L=Liver subsystem, P=Portal subsystem, O=Other organ subsystem,  $MRT_{CIRC}$ =Mean residence time of the circulation subsystem

**TABLE 3: MODEL DERIVED PARAMETERS AND COMPARED PARAMETERS BY HEMODYNAMIC CIRCULATORY MODEL AND ESTIMATED USING BATEMAN FUNCTION**

	$k_a$ (1/min)	$k_a^*$ (1/min)	$k_{el}$ (1/min)	$k_{el}^*$ (1/min)	$MRT_w$ (min)
Substance A	0.022	0.043	0.008	0.009	130.646
Glucose 1	0.35	0.047	0.041	0.045	38.756
Glucose 2	0.922	0.365	0.039	0.048	43.067

$k_a$ =Absorption rate constant,  $k_{el}$ =Elimination rate constant,  $MRT_w$ =Mean residence time of the whole system, \*Derived or estimated parameters by using Bateman function

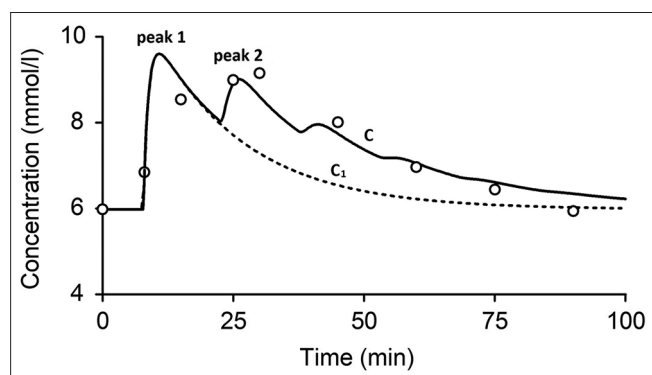


Fig. 6: Concentration-time profile of glucose 2 and influence of its absorbed fractions.

Circles represent measured values, solid line C represents model approximation,  $C_1$  represents partial concentration-time profile developed by fraction  $F_1$ , peak 1 is the effect of the partial profile  $C_1$ , peak 2 is the response of the deep compartment and the circulation system effect on peak 1.

The model estimated parameters of the GI and the circulation subsystems are listed in Tables 1 and 2, respectively. The model parameters of the GI subsystem include absorbed fractions  $F_1$  and  $F_2$ , time delays  $\tau_1$  and  $\tau_2$ , mean residence time of the absorption subsystem  $T_A$  and  $MRT_{GI}$ . Obtained results of the model approximation show approximately twice more value of the second fraction contrary to the first fraction (Table 1).

The model parameters of the circulation subsystem include plasmatic blood flow in the CP subsystem  $Q_{CP}$ , gain of the liver, portal, and the other organ subsystems as  $G_L$ ,  $G_P$ , and  $G_O$ , respectively, time delay of the other subsystem  $\tau_o$ , mean residence time of the liver, portal, and the other organ subsystems as

$T_L$ ,  $T_P$ , and  $T_O$ , respectively, and  $MRT_{CIRC}$  are listed in Table 2.

The comparison between derived or estimated parameters by our developed hemodynamic circulatory model and parameters estimated by using the Bateman function is listed in Table 3.

Our work as a reanalysis of the study of Gabrielsson and Weiner<sup>[1]</sup>, was focused on the identification of the system defined by the oral administered substance A and frequent sampling oral glucose tolerance test data as the input and the measured concentration-time profile as the output by hemodynamic circulatory structural model included GI subsystem. This is for the substances with high coefficient of absorption.

While one compartment open model (Bateman function) was not capable of fitting the measured data within the time interval 40-100 min (fig. 1) in case of substance A and the time interval 15-30 min in case of glucose, our model approximation presents a good fitting of the measured values within this interval (figs. 4-6). The shape of final concentration-time profile C as the result of the parameters estimation by our structural model is characterized by the individual peaks 1 and 2. Regarding obtained results of our modeling, the peak 1 is expressed by the sum of the partial concentration-time profiles  $C_1$  and  $C_2$  related to the individual absorbed fractions  $F_1$  and  $F_2$ , respectively, which suggest the effect of the GI system. The second peak 2 presents the influence mainly of the circulation system included the deep compartment to the final concentration-time profile of substance A in the observed human subject. In Table 1, the first fraction  $F_1$  (34.425% - substance A) and (33% - glucose 1) was absorbed in the small intestine with the time delay of 11.579 min (substance A) and 1.731 min (glucose 1) compared to the second absorbed fraction  $F_2$  (65.575% - substance A) and (66% - glucose 1) with the time delay of 27.262 min (substance A) and 13.398 min (glucose 1).

Glucose 2 had only one fraction with time delay of 7.751 min.

The mean residence time of the substance A in the GI system  $MRT_{GI}$  (68.354 min) is almost similar to the  $MRT_{CIRC}$  (62.292 min). As for the glucose 1 and glucose 2,  $MRT_{GI}$  is (12.271 min) and (8.836 min) and  $MRT_{CIRC}$  (26.485 min) and (34.231 min), respectively (Table 2).

The attenuation of the liver subsystem  $g_L$  expressed in the steady state SS as  $g_L = \frac{C_{outSS}}{C_{inSS}}$ , where  $C_{in}$  is

the input substance concentration to the system and  $C_{out}$  is the output substance concentration from the system, characterizes the substance uptake in the liver subsystem. In the case of  $C_{out} < C_{in}$  is  $g_L < 1$  else  $g_L = 1$ . Observed  $g_L = 0.969$  (Table 2) then indicates the uptake of the substance A in the liver. The uptake of the glucose in the liver is 0.229 (glucose 1) and 1.022 (glucose 2).

Table 3 shows to the comparison between the individual absorption  $k_a$  and elimination  $k_{el}$  rate constants. Absorption rate constant  $k_a^*$  according to study<sup>[1]</sup> of 0.043 l/min appears 2 times higher values in comparison with our estimated value  $k_a$  of 0.022 l/min. The elimination rate constant  $k_{el}^*$  (0.009 l/min) according to study<sup>[1]</sup> presents similar values compared to calculations (Eq. 2) related to our developed structural model (0.008 l/min and 0.295 l/min, respectively). The value of mean residence time  $MRT_w$  of the whole body calculated by our structural model was 130.646 min (substance A), 38.756 min (glucose 1) and 43.067 (glucose 2). Model estimated value of  $k_a$  for glucose 1 is 0.35, which is similar to the value estimated by Bateman function (0.47) and for glucose 2 is 0.922 is 3 times higher as compared to the value estimated by using Bateman function (0.365). Model estimated values  $k_c$  for glucose 1 and 2 are 0.41 and 0.39, respectively and they are very similar to the values estimated by using Bateman function (Table 2).

In summary, obtained model results show a good approximation of the final concentration-time profile of substance A and glucose by our hemodynamic circulatory structural model compared to the Bateman function. Our work presents the validation of the hypothesis that the atypical shape of measured concentration-time profile of oral administered

substance A and glucose single dose was due to the effect of the GI subsystem and the circulation system included the deep compartment.

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