



Metformin Transport Rates Between Plasma and Red Blood Cells in Humans

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Abstract

Background Metformin has been used for the treatment of type 2 diabetes for over 60 years; however, its mechanism of pharmacological action is not fully clear. Different hypotheses exist regarding metformin distribution and redistribution mechanisms between plasma and erythrocytes/red blood cells (RBCs).

Objective We aimed to test the hypothesis that the metformin distribution between plasma and RBC occurs via concentration difference-driven passive transport and estimated transport rate coefficient values based on metformin concentration time series in plasma and RBCs from *in vivo* studies.

Methods An ordinary differential equation (ODE) system with two compartments was used to describe diffusion-based passive transport between plasma and RBCs. Metformin concentration time series in plasma and RBCs of 35 individuals were used for metformin transport parametrization. Plasma concentration has been approximated by biexponential decline.

Results A single passive transport coefficient, $k = 0.044 \pm 0.014$ (h^{-1}), can be applied, describing the uptake and release transport rate versus the linear equation $v = k \times (M_{\text{pl}} - M_{\text{RBC}})$, where M_{pl} is the metformin concentration in plasma and M_{RBC} is the metformin concentration in RBCs.

Conclusions Our research suggests that passive transport can explain metformin distribution dynamics between plasma and RBCs because transport speed is proportional to the metformin concentration difference and independent of the transport direction. Concentration difference-driven passive transport can explain the mechanism of faster metformin distribution to RBCs the first few hours after administration, and faster release and domination of the redistribution transport rate after metformin concentration in plasma becomes smaller than in RBCs.

Key Points

The objective was to evaluate the metformin distribution mechanisms between plasma and RBC by mathematical modeling and estimate transport rate coefficient based on *in vivo* metformin concentration time-series in human plasma and RBC.

The partitioning and repartitioning between RBC and plasma is modelled as passive transport with the same transport rate coefficient describing influx and outflux, supporting the assumption of diffusion being the main process ensuring metformin transportation between these compartments.

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1 Introduction

Metformin is a first-line oral antidiabetic medication that has been widely used to treat type 2 diabetes for over 60 years. Despite the long clinical experience, its pharmacological mechanisms of action are not fully understood. The mechanisms underlying metformin action appear to be complex and involve both insulin-sensitive and noninsulin-sensitive tissues. While the most classical effect of metformin is the reduction of hyperglycemia by inhibition of hepatic gluconeogenesis, the contribution of mechanisms in other tissues, such as an increase in glucose uptake in skeletal muscle, increase in insulin sensitivity in adipose tissue, and glucose utilization in gut enterocytes, have been demonstrated [1].

Metformin is a small molecule (molecular weight 165 Da) that is not metabolized and is highly hydrophilic. It is of a basic nature and, under physiological pH, is almost fully ionized. Metformin also has negligible protein binding [2]; however, it has a comparably high volume of distribution, i.e. above 200 L after a single oral dose [3]. Metformin is known to be transported across cellular membranes by using active transporters, i.e. PMAT, OCT1, OCT2, OCT3, and MATE1 [4], that explain the observed distribution volume. It is rapidly excreted in urine, with plasma elimination ranging from 2 to 6 h. Nonetheless, terminal elimination of the drug is slow, with a fraction of < 5% being eliminated and with a half-life of between 9 and 17 h [5], suggesting the existence of a deep compartment [6]. The published data suggest that metformin accumulates in a deep compartment formed of red blood cells (RBCs) [7, 8] and a deep tissue compartment, most likely gastrointestinal tissues [9, 10].

Given the hydrophilic nature of metformin, it has been assumed that it cannot cross the phospholipid bilayer via diffusion [4]. At the same time, metformin enters the RBC where relevant transporters are not expressed, suggesting a marginal transport via diffusion [7, 8, 11, 12]. The maximal metformin concentration in RBCs is reached later than in plasma and is considerably lower [8], confirming that the transport to RBCs is not intensive. The measurement of metformin concentrations in major deep compartments of metformin action is clinically unavailable and is currently predicted by some mathematical models [13–15].

RBCs could be used to gain insight into metformin distribution and accumulation in the rest of the body in cases of chronic metformin therapy, as the terminal half-life of metformin in plasma and urine is very similar to the terminal half-life in RBCs [7, 8]. Metformin has a direct pharmacodynamic effect on RBCs in patients with type 2 diabetes as it increases noninsulin-dependent glucose uptake and storage of glycogen under conditions of hyperglycemia [16].

An interesting pharmacokinetic-related peculiarity of RBCs is that plasma is the only metformin carrier interacting with

RBCs, both in uptake and release, and the concentrations in both plasma and RBCs are experimentally determined *in vivo*. The absence of transport proteins in RBC membranes enables assessment of the transport without proteins *in vivo*. This also allows estimation of the membrane transport impact in other tissues. Various authors have described the pharmacokinetic parameters of metformin distribution in RBCs [7, 8, 12]. A few *in vitro* and *in vivo* studies have aimed to describe the metformin distribution between plasma and RBCs [7, 8, 12, 17, 18]; however, based on our knowledge, a mechanistic model-based [19] estimation of the metformin transport mechanism and its parameters based on *in vivo* data has not been carried out.

Considering that no active transporters are expressed in RBCs, and plasma membrane permeability should be equal in both directions, we hypothesized that concentration difference-driven passive transport can explain the distribution of metformin between plasma and RBCs. Mechanistic mathematical models with diffusion-based passive transport kinetic equations have been built and parametrized using metformin concentration time series in plasma and RBCs from *in vivo* studies.

2 Materials and Methods

2.1 Experimental Data

Metformin concentration-time courses in plasma and RBCs were used [20–22] following a single peroral 500 mg dose of metformin, administered under fed conditions. Thirty-five nondiabetic volunteers were included in this study (Table 1). All participants signed informed consent and the study was approved by the institutional Ethics Committee (PSCUH, Nr. 3000610-18L). To be eligible for this study, subjects confirmed they were not using any medications other than vitamins. The liver enzyme levels of participants (alanine aminotransferase, g-glutamyltransferase) were less than double the respective normal value, and no participants had renal failure (mean serum creatinine 75.6 ± 13.8 mmol/L). Before inclusion in this study, women were asked to provide a urine sample to confirm a negative pregnancy test. Venous blood samples were taken just prior to administration and

Table 1 Characteristics of study participants

Male [<i>n</i> (%)]	15 (42.8)
Female [<i>n</i> (%)]	20 (57.2)
Mean age \pm SD, years	26.71 ± 5.97
Mean BMI \pm SD, kg/m ²	23.61 ± 3.64
Mean serum creatinine \pm SD, mmol/L	75.65 ± 13.81

BMI body mass index, SD standard deviation

at 1, 2, 3, 6, 10, and 24 h postdose. Metformin concentration time series in plasma, and RBCs of the 35 nondiabetic individuals (Online Resource 1) were used for metformin transport parametrization.

2.2 Mathematical Model

A mathematical model was built to test the hypothesis regarding passive transport determining the distribution and redistribution of metformin between plasma and RBCs. Diffusion-based passive transport occurs by random processes through the lipid bilayer membrane from the side with the larger concentration to the side with the lower concentration, and can switch when the concentration proportion changes to the opposite [23]. The driving force of diffusion (simple or facilitated) is the concentration difference (transmembrane concentration gradient), tending to equalize the concentration of molecules on both sides of the membrane [24]. It is essential that the rate of diffusion is directly and linearly proportional to the concentration difference.

The proposed model is based on Fick's Law of diffusion, which describes the time course of the transfer of a solute between two compartments that are separated by a membrane [25]. The rate of diffusion-based passive transport from plasma to RBCs (v_{in}) and the rate from RBCs to plasma (v_{out}) can be calculated as shown in Eqs. 1 and 2 [24]:

$$v_{in} = \frac{D \times a \times P \times M_{pl}}{m}, \quad (1)$$

and

$$v_{out} = \frac{D \times a \times P \times M_{RBC}}{m}, \quad (2)$$

where D is the diffusion coefficient, a is the membrane area, P is the lipid/water partition coefficient of metformin, M is the membrane thickness, M_{pl} is the metformin concentration in plasma, and M_{RBC} is the metformin concentration in RBCs.

In the proposed model, the constants in Eqs. 1 and 2, i.e. diffusion coefficient (D), membrane area (a), lipid/water partition coefficient (P), and membrane thickness (m), are expressed by the diffusion transport rate coefficient k :

$$k = \frac{D \times a \times P}{m}. \quad (3)$$

In the model, we assume that independent transport rate coefficients may be needed to describe uptake (k_{in}) and release (k_{out}) of metformin, and we therefore implemented transport rate equations in the model as follows (Eqs. 4 and 5):

$$v_{in} = k_{in} \times M_{pl}, \quad (4)$$

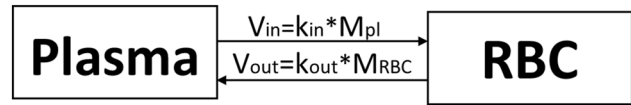


Fig. 1 Two-compartment model of metformin transport between plasma and RBCs with absorption (v_{in}) and release (v_{out}) fluxes. k_{in} transport rate coefficient to RBCs from plasma (h^{-1}), k_{out} transport rate coefficient from RBCs to plasma (h^{-1}), M_{pl} metformin concentration in plasma (ng/mL), M_{RBC} metformin concentration in RBCs (ng/mL), RBC red blood cells

and

$$v_{out} = k_{out} \times M_{RBC}. \quad (5)$$

A special case where $k = k_{in} = k_{out}$ was applied in the modeling experiments to test whether a single diffusion transport rate coefficient can explain experimental results. The summary transport rate, versus including transport in both directions, can then be expressed as follows (Eq. 6):

$$v = k \times (M_{pl} - M_{RBC}). \quad (6)$$

The mathematical model utilizes the fact that RBCs can exchange metformin with plasma only and that metformin concentrations in both compartments are measured. The transport between plasma and RBCs is described as a two-compartment model (Fig. 1) [26].

The metformin concentration in plasma (M_{pl}) is approximated by a biexponential decline (Eq. 7) [27]:

$$M_{pl} = A \times e^{-c \times t} - B \times e^{-d \times t}, \quad (7)$$

where A is the y-intercept of the distribution curve, c is the first-order distribution rate constant, B is the y-intercept of the elimination curve, d is the first-order elimination rate constant, and t represents time.

In the model, we introduced $A = B$ to ensure that the plasma concentration approximation function has 0 value when the metformin dose has been received at $t = 0$. The metformin concentration in RBCs (M_{RBC}) is a dependent variable determined by reactions. The values of diffusion coefficients and biexponential decline parameters are identified by parameter estimation fitting model simulations to the experimental data.

An ordinary differential equation (ODE) system was used to describe the diffusion-based passive transport rate between plasma and RBCs using the two rate equations (4) and (5). Two models for each of the 35 patients have been developed and parametrized during parameter estimation: (1) independent transport coefficients (k_{in} and k_{out}) for uptake and release; and (2) single coefficient k used for transport in both directions (uptake and release coefficients are equal).

The volume of the RBC compartments was fixed in the model for all 35 individuals, at a value corresponding to a body weight of 70 kg for humans, with 2198 mL of RBCs [28]. The size of the plasma compartment was not defined because the plasma concentration was fixed by biexponential decline (Eq. 7) and approximation of experimental data. Time to reach maximum concentration (T_{\max}) and maximum concentration (C_{\max}) values were determined from model simulations.

COPASI software [29] was used for mathematical modeling and parameter estimation. The fitness of experimental data with model simulations was measured using the mean square error (MSE) value calculated by *COPASI*. *ConvAn* [30] was used to select the most appropriate optimization method, and a modification of the *COPASI* wrapper *SpaceScanner* [31] was applied for parallel optimization runs. Sample models describing the average experimental curve with a single (Biomodels ID: MODEL2103170001) and independent (Biomodels ID: MODEL2103170002) diffusion transport rate coefficient in *COPASI* format (Online Resource 2) and SBML format (Online Resource 3) were deposited in the *BioModels* database [32].

3 Results

3.1 Single Diffusion Transport Rate Coefficient k -Value versus the Independent k_{in} and k_{out}

Parameter estimations to match the model simulations with experimental results were performed using (1) independent k_{in} and k_{out} values, and (2) a single coefficient k

(corresponds to $k = k_{\text{in}} = k_{\text{out}}$). Both cases were applied to the metformin concentration-time courses, and on the average time course, of 35 individuals.

The single transport rate coefficient of the average concentration-time course data from 35 experimental measurements was $k_{\text{ave}} = 0.044 \text{ h}^{-1}$ (Fig. 2a), which is equal to the average value of all individual single coefficients ($k = 0.044 \pm 0.014 \text{ h}^{-1}$). Furthermore, the estimated independent transport rate coefficients for the average curve were $k_{\text{in/ave}} = 0.044 \text{ h}^{-1}$ and $k_{\text{out/ave}} = 0.039 \text{ h}^{-1}$ (Fig. 2b). At the same time, the average values of the estimated transport rate coefficients for individuals were $k_{\text{in}} = 0.044 \pm 0.012 \text{ h}^{-1}$ and $k_{\text{out}} = 0.043 \pm 0.013 \text{ h}^{-1}$ (Online Resource 4). Figure 2 demonstrates that a single coefficient can describe experimental results equally well compared with two independent coefficients.

The estimated coefficients for individual curves are highly variable between individuals (Fig. 3), reflecting the known high variability of metformin pharmacokinetics among individuals. In our experimental data (see Online Resource 1), there are big differences in individual concentration-time course data for the metformin concentrations in plasma and RBCs. The coefficients of individuals have a wide $k_{\text{in}}/k_{\text{out}}$ ratio (ranging from 0.45 to 2.56). In 14 cases, k_{out} is larger than k_{in} , and, in 21 cases, it is the opposite, while their average values are very similar (0.044 and 0.043). Remarkably, individuals' k -values (Fig. 3) were larger than k_{in} if $k_{\text{in}} > k_{\text{out}}$, and smaller than k_{in} if $k_{\text{in}} < k_{\text{out}}$. In other words, k_{in} values were between k_{out} and k -values in all cases except for one individual (No. 19 in Fig. 3). There was a very high correlation (0.99) between k and k_{in} , while the k correlation with k_{out} was smaller and negative

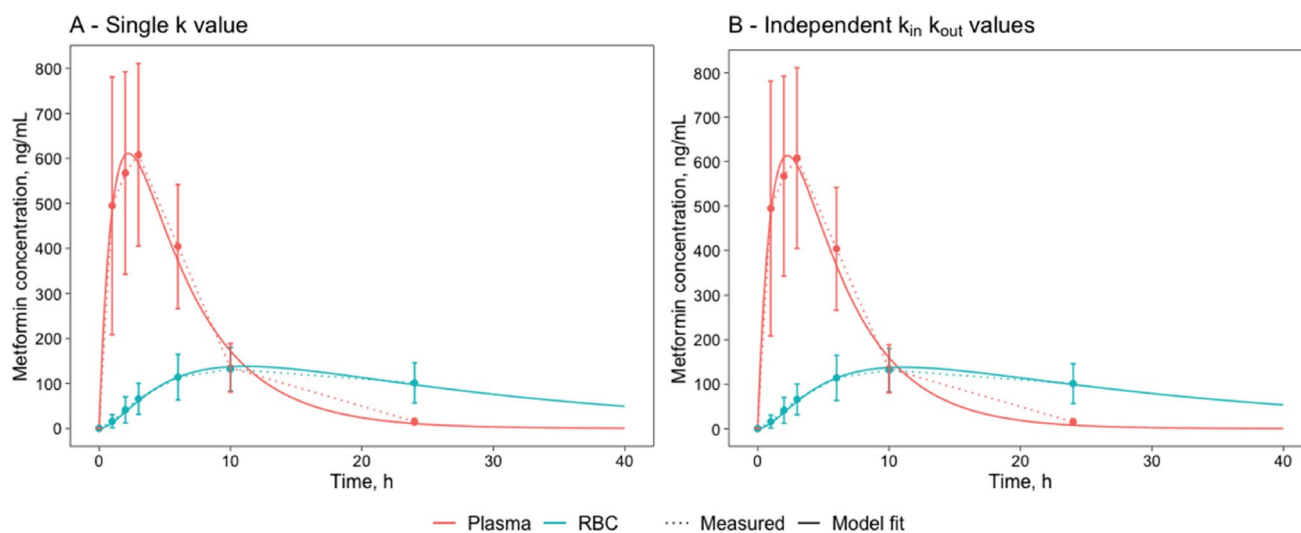


Fig. 2 Parameter estimation results of the average curve. Dots show experimental values while lines represent the model simulation. **a** Single k -value ($k_{\text{ave}} = 0.044 \text{ h}^{-1}$, mean square error = 286); and **b**

independent k_{in} and k_{out} values ($k_{\text{in/ave}} = 0.044$ and $k_{\text{out/ave}} = 0.039 \text{ h}^{-1}$, mean square error = 273). *RBCs* red blood cells

Fig. 3 Diffusion coefficient k , k_{in} and k_{out} values per individual (average values are represented by lines). The average values of k and k_{in} were identical.

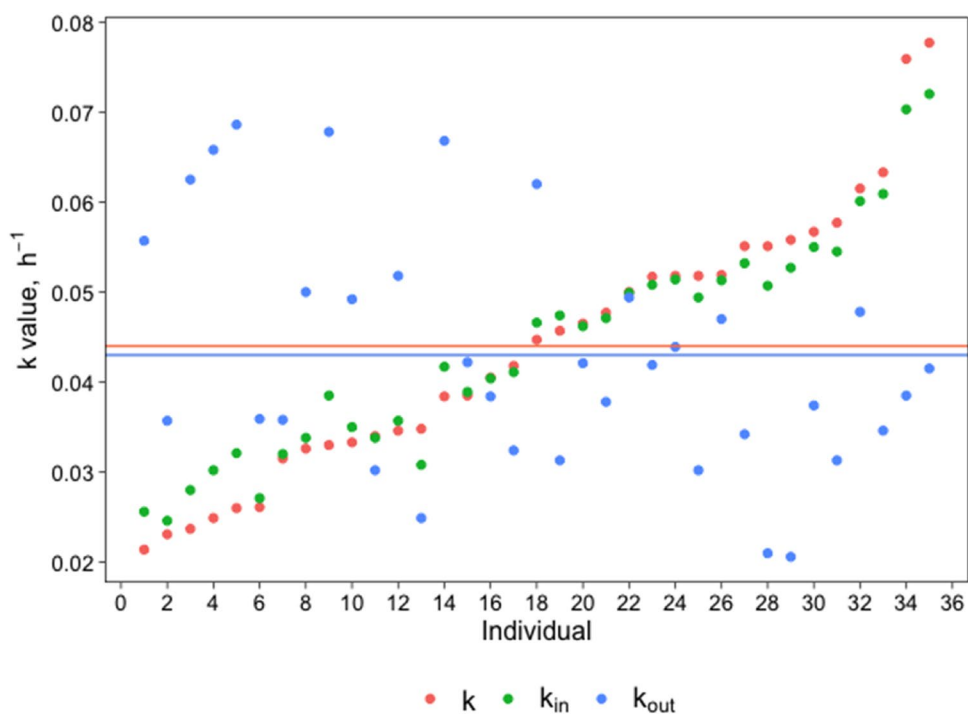
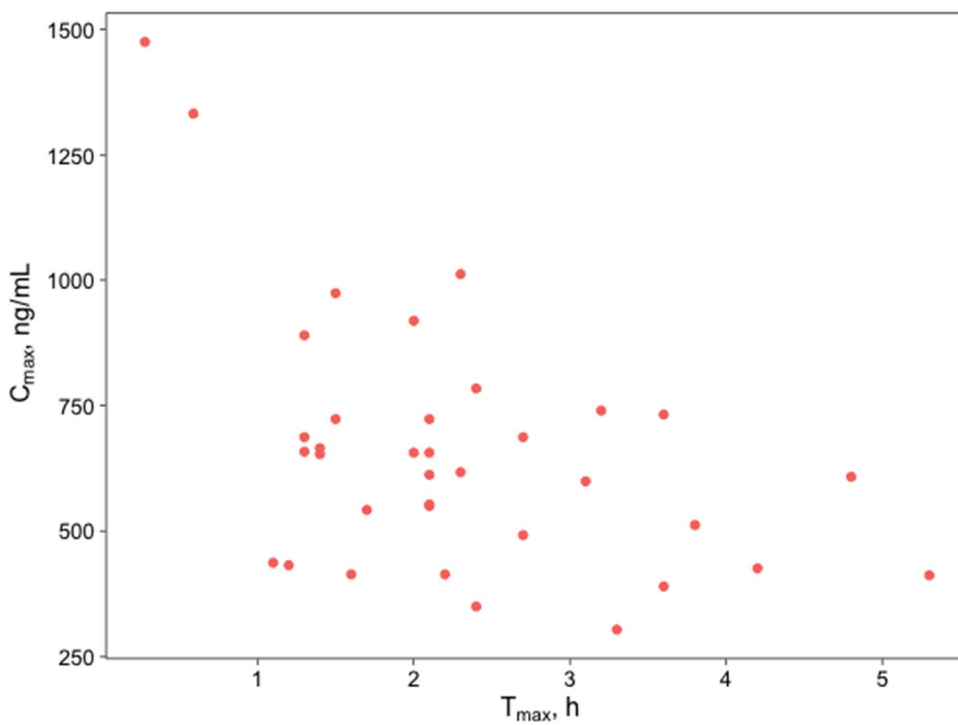


Fig. 4 T_{max} and C_{max} of individual plasma curves. T_{max} time to reach maximum concentration, C_{max} maximum concentration



(- 0.41), which might be explained by a tendency to satisfy experimental data on the uptake phase of metformin because, in the first 6 h, there were five experimental data points where the MSE was calculated, while there were

only two measurements (at 10 and 24 h) for the elimination phase.

The C_{max} and time to reach C_{max} (T_{max}) (Fig. 4) were also very different among individuals, leading to larger differences between the model simulations and experimental

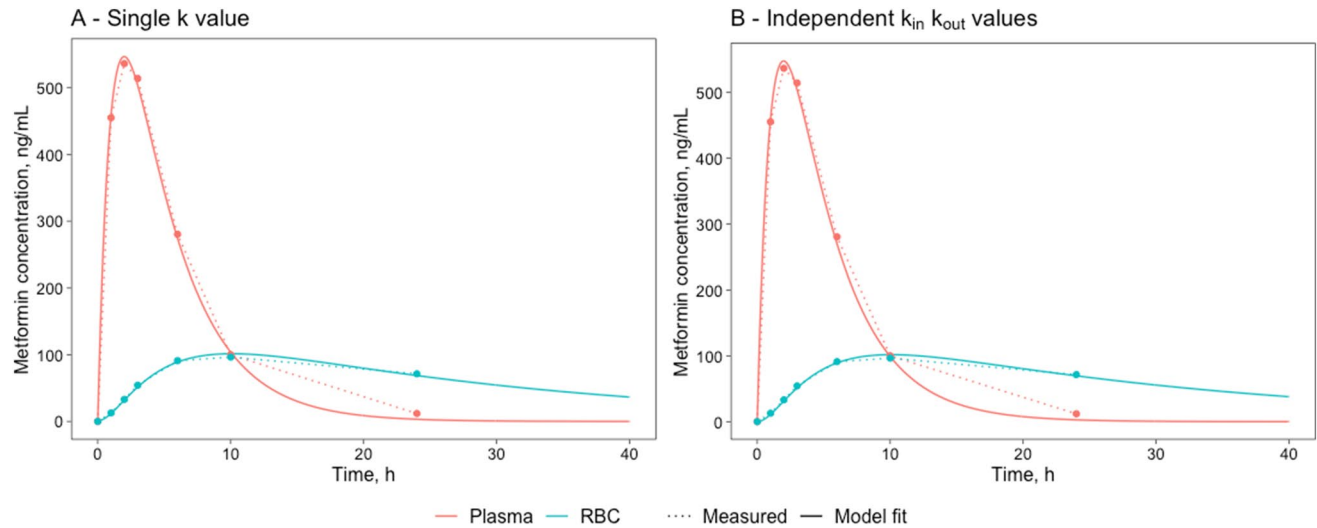


Fig. 5 Parameter estimation results of the best-fit, individual 16. The dots show the experimental values, while the lines represent the model simulation. **a** Single k -value ($k = 0.040$, mean

square error = 67); **b** different k_{in} and k_{out} values ($k_{in} = 0.040$ and $k_{out} = 0.038$, mean square error = 65)

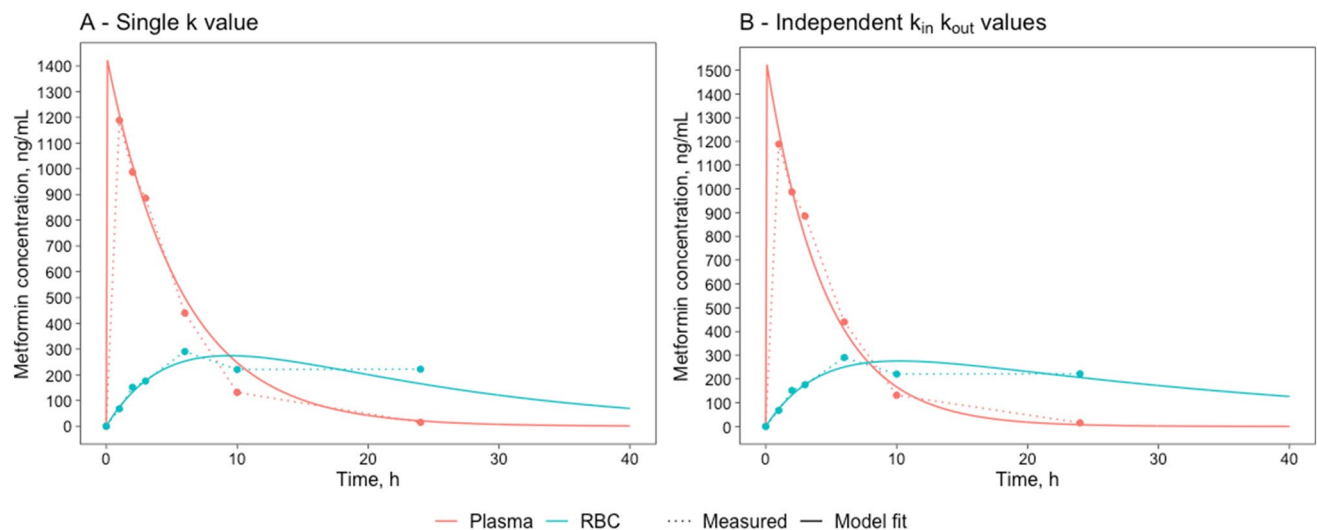


Fig. 6 Parameter estimation results of the worst-fit, individual 31. The dots show the experimental values, while the lines represent model simulation. **a** Single k -value ($k = 0.058 \text{ h}^{-1}$, mean square

error = 9244); **b** different k_{in} and k_{out} values ($k_{in} = 0.055 \text{ h}^{-1}$ and $k_{out} = 0.031 \text{ h}^{-1}$, mean square error = 6271).

data, expressed as the MSE (see Online Resource 4). A faster T_{max} correlates with a higher k -value. The MSE average value for a single diffusion coefficient (1522 ± 1761) was larger than the value of independent diffusion coefficients (1026 ± 1321).

The differences between the best (Fig. 5) and worst (Fig. 6) MSE values for individual experimental data for parameter estimation results were large. The case with the smallest MSE (Fig. 5) demonstrated a very good fit, partly because the experimental results for plasma and RBC data fit the biexponential decline very well; however, it was

different for individual No. 31 (Fig. 6), where plasma and RBC concentrations did not correspond to the expected biexponential curve. In both extreme cases, the model with a single coefficient performed similar (Figs. 5a and 6a) to the model with two independent coefficients (Figs. 5b and 6b).

3.2 Correlation of Model Parameters

The correlation between k , k_{in} , and k_{out} is described in Sect. 3.1. Correlation of the single diffusion transport rate

coefficient (k) of tested individuals using other parameters was tested using experimental and modeling results. There was a weak negative correlation of -0.35 with the T_{\max} of metformin concentration in plasma, indicating that individuals with a smaller T_{\max} in plasma are likely to have a larger k -value, enabling them to reach maximum concentration faster. No correlation (-0.071) of k was found with the C_{\max} of metformin concentration in plasma.

When analyzing individual cases of two transport rate coefficients, k_{in} and k_{out} , several interesting correlations were found. The low correlation between k_{in} and k_{out} of -0.30 agrees with the wide-ranging $k_{\text{in}}/k_{\text{out}}$ ratio. A strong positive correlation (0.67) between k_{out} and T_{\max} suggests that a later maximum point leads to faster discharge of metformin, enabled by a larger k_{out} . A weak negative correlation (-0.29) was found between k_{out} and C_{\max} , while k_{in} had a weaker correlation with both T_{\max} (-0.26) and C_{\max} (-0.12).

The $k_{\text{in}}/k_{\text{out}}$ ratio characterizes the dominance of the k_{in} coefficient over the k_{out} coefficient. The ratio equals one if both coefficients are the same, and is larger than 1 if k_{in} is bigger than k_{out} . The correlation between the $k_{\text{in}}/k_{\text{out}}$ ratio and T_{\max} was -0.51 , indicating that a faster and higher maximum would need larger k_{in} values relative to k_{out} . Surprisingly, a low correlation (0.10) had a $k_{\text{in}}/k_{\text{out}}$ ratio with C_{\max} .

4 Discussion

4.1 Single versus Independent Diffusion Coefficients

The current study suggests that a single passive transport rate coefficient is sufficient for the description of metformin exchange between plasma and RBCs, even in the case of large individual variation in the concentration dynamics of metformin in plasma (Fig. 4 and Online Resource 1). The introduction of independent coefficients (k_{in} and k_{out}) does not radically improve the fitness (Figs. 2, 5, and 6). The similarity of the average values of k_{in} and k_{out} (0.044 h^{-1} and 0.043 h^{-1} , respectively) underlines that the transport rate coefficients are the same in both directions despite the wide distribution of k_{out} (Fig. 3) and low correlation with k . In the case of a smaller number of involved individuals, the average values might not be that close. The very high correlation between k and k_{in} , and weak correlation with k_{out} , might be explained by the fact that five experimental data points were measured in the first 3 h, when the impact of k_{in} is dominating, and just two data points were measured after 6 h. This stimulates k_{in} to be similar to k in determining the correctness of the first data points, leaving k_{out} to compensate deviations from the experimental data after 6 h, with low correlation to k .

The fact that the transport rate is proportional to the concentration, and the same coefficient can be used in both directions, supports the hypothesis that passive transport is the dominant mode of metformin exchange between plasma and RBC, and the influence of active transport processes is negligible because, in the case of active transport, the transport rate coefficients should be (1) nonlinear and (2) stronger in one of the directions. Our research cannot determine if passive transport is carried out by simple diffusion or facilitated diffusion. This is in line with earlier published research suggesting that transport between plasma and RBCs occurs exceptionally via passive transport (diffusion) only as the metformin-specific transporters are not expressed on the RBC surface [4, 8], contradicting alternative assumptions that metformin's hydrophilic nature is not suitable for crossing the lipid bilayer via diffusion [4]. It could be speculated that the unique properties of metformin as a small molecule (165 Da), and the high ionization level at physiological pH, favors its entry and release from the RBCs through concentration-driven mechanisms such as diffusion mechanisms relayed on aqueous channels [33], therefore the permeability of metformin should be equal in both directions [34, 35]. Based on these theoretical assumptions, we could conclude that our results do not contradict the previously established physicochemical properties of metformin and are in line with mentioned theoretical assumptions.

It has been previously observed that the metformin repartitioning rate (we assume that the metformin transport rate is meant here) from RBCs into plasma was two- to even fivefold faster than distribution from plasma into the RBCs [17, 18], however the mechanistic process behind this phenomenon has not been provided. In other research, it has been presumed that the pH difference between plasma and RBCs could cause the slower repartitioning from RBCs due to the electronegative membrane potential and ion-trapping effect of metformin into the RBC due to its basic properties [36–38], thus challenging the observations described by Xie et al. [18]. In the current study, the use of independent coefficients to describe uptake (k_{in}) and release (k_{out}) allowed faster uptake or release of metformin but did not improve the fit to experimental data. Therefore, it could be assumed that the *in vivo* ion-trapping effect has no or negligible effect on metformin repartitioning from the RBCs. According to the model simulations, the proportions between incoming and outgoing metformin transport rates constantly change (Fig. 7). A single transport rate coefficient ($k = k_{\text{in}} = k_{\text{out}}$) does not mean the same incoming and outgoing flux of metformin because the influx and outflux (formulas 1 and 2) are proportional to the metformin concentration. As a consequence, the resulting flux is proportional to the concentration difference on both sides of the RBC membrane. The concentration in plasma is greatest immediately after administration of the dose, leading to a much faster influx

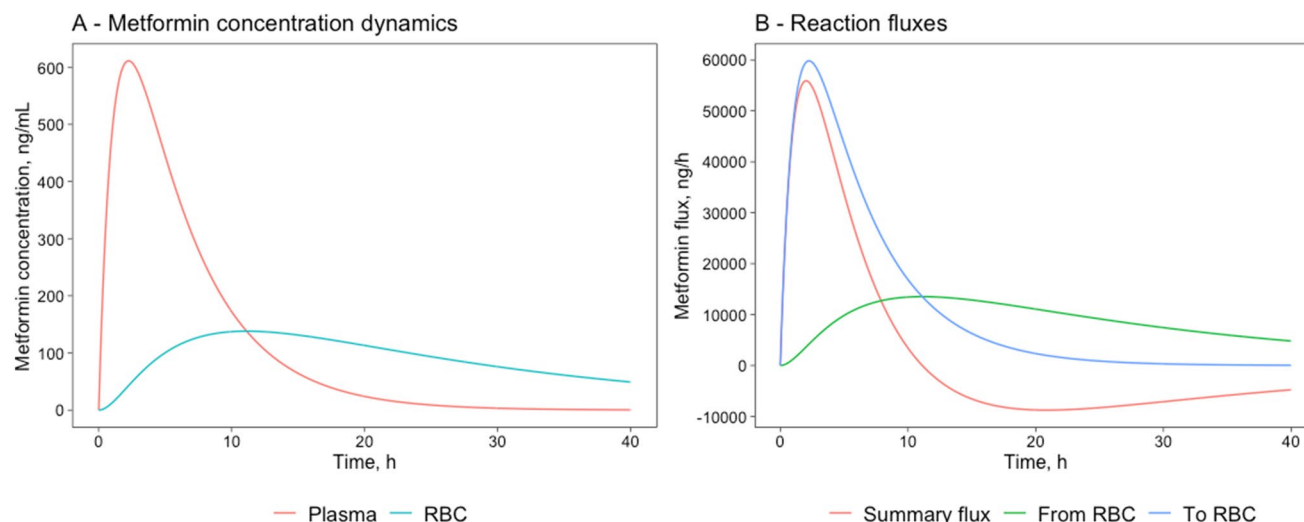


Fig. 7 Dynamics of concentrations in **a** plasma and RBCs, and **b** influx (blue), outflux (red), and summary flux (green) to RBCs in the case of the average curve with a single coefficient. *RBCs* red blood cells

than outflux at the uptake phase and the opposite at the elimination phase, where plasma concentration is smaller than in RBCs (Fig. 7). Therefore, the statement mentioned earlier regarding the repartitioning rate being two- to fivefold faster [18] is true, starting from about the 12th hour (Fig. 7), and wrong before that time. However, the difference in transport flux rates is due to the difference in concentrations, while the diffusion transport rate coefficient stays the same.

Another interesting aspect of metformin exchange between plasma and RBCs is the contradiction between the involvement of concentrations equalizing passive transport and the fact that in long-term use, the mean concentration values in plasma and RBCs do not become equal as determined experimentally [12] and by mathematical modeling [13]. This contradiction can be explained by the heavy time-dependence of the concentration in plasma, leading to very fast metformin transport to RBCs during the first hours after dose administration, followed by long and slow transport from RBCs, both following the concentration gradient. The effects of both processes are not equal, causing differences in the mean values of metformin concentrations in plasma and RBCs.

4.2 Passive Transport Coefficient Values

Both the measurement accuracy and approximation accuracy can influence the estimated diffusion coefficient values. The proposed single diffusion transport rate coefficient $k = 0.044 \pm 0.014 \text{ h}^{-1}$ can differ between studies to some extent. We have applied our model to published data from other studies.

The dynamics of metformin concentrations in plasma in model simulations are in line with the study by Robert

and colleagues, where a single peroral dose of metformin 850 mg was administered, which is similar to that reported in the current study. The concentration ratio switches over in favor of RBCs in a time-dependent manner approximately 8–16 h after administration [7, 8], while in our experimental data and simulations of the average curve, this occurs at 11.5 h. It has been found that the C_{\max} and elimination half-life ($t_{1/2}$) differ between RBCs and plasma (300 vs. 1700 ng/mL and 23.4 vs. 2.7 h, respectively) [8], and correspond with our results, where the C_{\max} and $t_{1/2}$ in RBCs and plasma for the average curve (Fig. 2) were 140 and 617 ng/mL and 33 and 7.5 h, respectively. The transport rate coefficient estimated for an average concentration-time curve of a single peroral dose of metformin 850 mg according to Fig. 1 in the study by Robert and colleagues was 0.039 h^{-1} , which is close to the k -value reported in this current study.

Lalau et al. [39] reported on the lactic acidosis and extremal metformin accumulation in a patient treated with metformin. Metformin concentrations in the blood reached 130-fold concentrations (80,000 ng/mL) after administration of 850 mg twice daily [12, 39], compared with those observed in this current study. The transport rate coefficient estimated in our model was 0.025 h^{-1} , which is within the range of coefficients estimated from individual patients (Fig. 3).

The calculated transport rate coefficient values of $0.044 \pm 0.014 \text{ h}^{-1}$ from our study data, 0.039 h^{-1} from the data reported by Robert and colleagues [8], and 0.025 h^{-1} reported by Lalau and Lacroix [12] fall within the values observed among the individuals involved in the current study (Fig. 3).

5 Conclusions

It is possible to describe the partitioning and repartitioning between RBCs and plasma using a single transport rate coefficient, supporting the assumption that diffusion was the main process ensuring metformin transportation between RBCs and plasma. A single transport rate coefficient for both transport directions does not contradict the different metformin transport rates to and from RBCs because the transport rate is proportional to the concentration difference. After dose administration, the metformin concentration in plasma is larger than in RBCs, thus ensuring faster partitioning into RBCs, while, after concentration equilibrium, the concentration in RBCs is higher and repartitioning becomes faster.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40262-021-01058-2>.

Declarations

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Conflicts of interest Janis Kurlovics, Darta Maija Zake, Linda Zaharenko, Kristaps Berzins, Janis Klovinš, and Egils Stalidzans have no conflicts of interest that are directly relevant to the contents of this article.

Author contributions JKu, DMZ, KB and ES participated in the data analysis and interpretation and were involved in the preparation review and approval of this article. JKu, KB and ES developed the structure of the model. LZ and JKI were involved in the acquisition of data and review and approval of this article.

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