

Physiologically-based Pharmacokinetics/Pharmacodynamics model of dapagliflozin, an oral SGLT2 inhibitor



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Introduction

Physiologically-based (PB) systems pharmacology models of glucose homeostasis provide insight into diseases such as diabetes mellitus (DM). Combined with PB pharmacokinetics (PBPK) models of anti-diabetic drugs, they allow hypothesis testing, treatment personalization, or disease-progression studies.

Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors, such as dapagliflozin, belong to a novel and promising medications in the treatment of type 2 DM (T2DM). As the mode of action is common for various SGLT2 inhibitors, modeling the pharmacodynamic (PD) effects of dapagliflozin is of interest for the whole drug class and can significantly increase the value of a glucose homeostasis model.

Objectives

1. Develop a PBPK model of dapagliflozin.
2. Couple the PBPK model with a model of glucose homeostasis based on [1] to predict the observed PD effects.

Methods

The PBPK model of dapagliflozin was developed with PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (OSPS), version 7.0 [2], and coupled with a glucose-insulin homeostasis model based on [1]. The standard representation of the kidney was extended to enable mechanistic modeling of renal glucose filtration.

PK and physico-chemical parameters of dapagliflozin as well as mean concentration-time profiles were extracted from literature for model development and validation. The data include concentration profiles gathered in a 80 µg intravenous (iv) micro-tracer [3], oral single ascending dose (SAD) (range 2.5 – 500 mg) [4, 5], or multiple ascending dose (MAD) (14 days once daily, range 2.5 – 100 mg) [4] studies with healthy subjects.

The PD effect on urinary glucose excretion was evaluated by simulating the stepped hyperglycemic clamp with a single 10 mg dapagliflozin dose reported in [6] and cumulative urinary glucose excretion data from the SAD study [4].

Results I: Dapagliflozin PBPK model

The dapagliflozin PBPK model includes metabolism by the enzymes CYP3A4 and UGT1A9 and renal glomerular filtration. Distribution into tissues is calculated by the OSPS software including P-gp transport as an active process. Relative expression of CYP3A4, UGT1A9, and P-gp is given by the PK-Sim® database (RT-PCR). Physico-chemical properties of the drug extracted from literature and fitted parameter values are listed in Table 1.

The model is able to reproduce observed dapagliflozin PK data from the 12 datasets gathered in healthy subjects with maximal 20% AUC deviation. Comparisons of simulation results with experimental data from SAD and MAD studies are presented in Figures 1(A) and 1(B), respectively.

Table 1: Parameter values of the PBPK model. Parameter values were extracted from literature or estimated by fitting the model to the iv and 2.5, 5, and 50 mg SAD datasets [3,4]. fu: fraction unbound, metab: metabolism

Parameter	Value	Additional information	Source
Mol. weight [g/mol]	408.87	-	[7]
fu in plasma [%]	9	-	[8]
Water solubility [mg/ml]	1.6	-	[9]
Lipophilicity [logP]	2.56	Reference value 2.52	Fit ([10])
P-gp transport	$K_m = 70 \mu\text{M}$	Assumed based on non-saturability	[9]
P-gp transport	$k_{cat} = 180 \text{ min}^{-1}$	-	Fit
UGT1A9 metab.	Linear, $k_{cat} = 25 \text{ l}/\mu\text{mol}/\text{min}$	-	Fit
CYP3A4 metab.	Linear, $k_{cat} = 0.3 \text{ l}/\mu\text{mol}/\text{min}$	< 10% of 50 mg dose	Fit ([5])

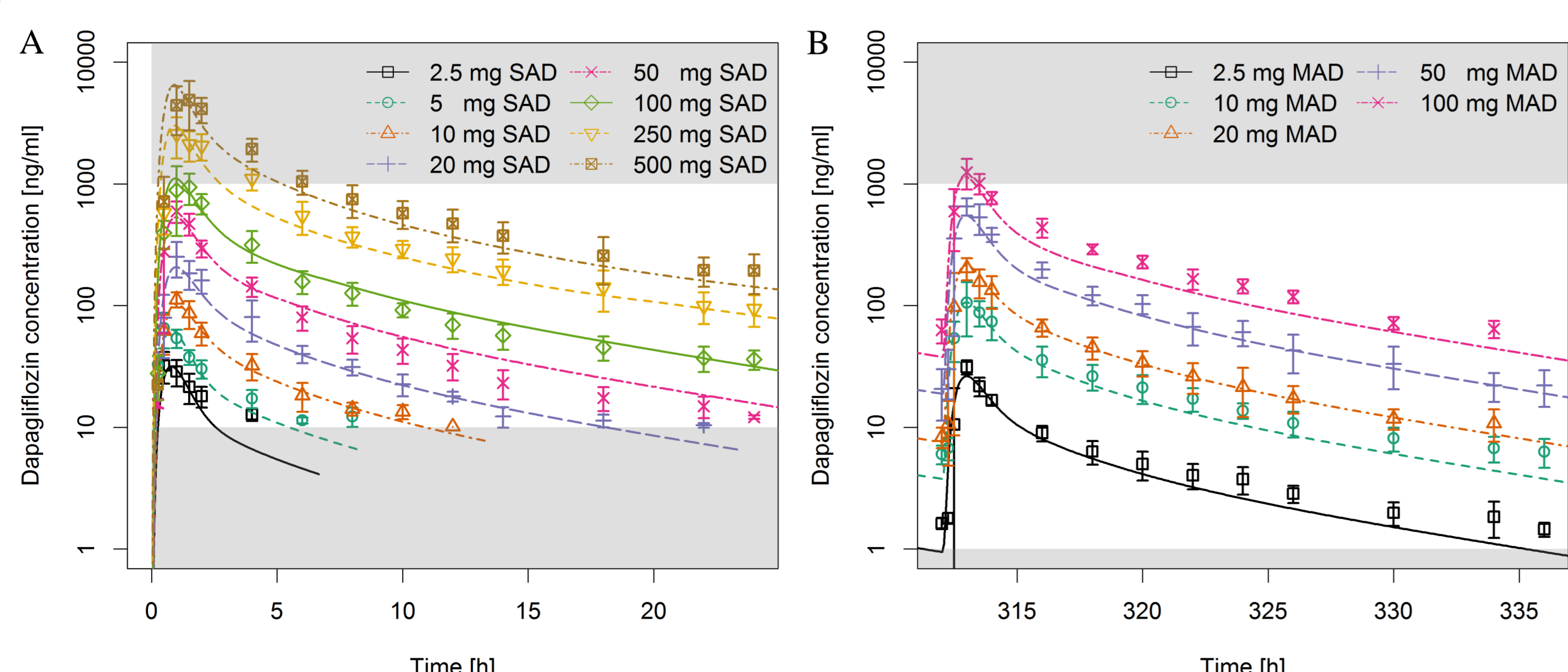


Figure 1: PK profiles of dapagliflozin after oral administration. Panel A: Mean (SD) plasma concentration-time profiles after single doses of dapagliflozin. Panel B: Mean (SD) plasma concentration-time profiles of dapagliflozin on day 14 of once-daily MAD study. Grey shaded areas indicate values below or above the limits of quantification. Data from [4].

Results II: Modeling of SGLT2 inhibition

A mechanistic model of renal glucose filtration and reabsorption was developed as depicted in Figure 2. The PD effect of dapagliflozin is modeled as reversible binding of the drug to SGLT2 in the proximal convoluted tubuli (PCT). The rate of dapagliflozin-SGLT2 complex formation is given by the equation

$$C_{dapa} \times C_{SGLT2} \times \frac{k_{off}}{K_d} - C_{complex} \times k_{off}$$

with C_{dapa} , C_{SGLT2} , and $C_{complex}$ the concentrations of dapagliflozin, SGLT2, and the complex, respectively, k_{off} the dissociation rate constant, and K_d the dissociation constant for complex formation. With *in vitro* values for $K_d = 6 \text{ nM}$ and $k_{off} = 0.12 \text{ min}^{-1}$ [10], the model successfully predicted increased urinary glucose excretion (UGE) observed over a wide range of plasma glucose concentrations (5.5-30.5 mM, Figure 3(A)) [6] and the cumulative glucose excretion over 120 hours for various dapagliflozin doses (Figure 3(B)) [4]. Predicted effect on plasma glucose concentrations and renal glucose reabsorption rates are presented in Figure 4 for a simulation of three days of a standard healthy individual.

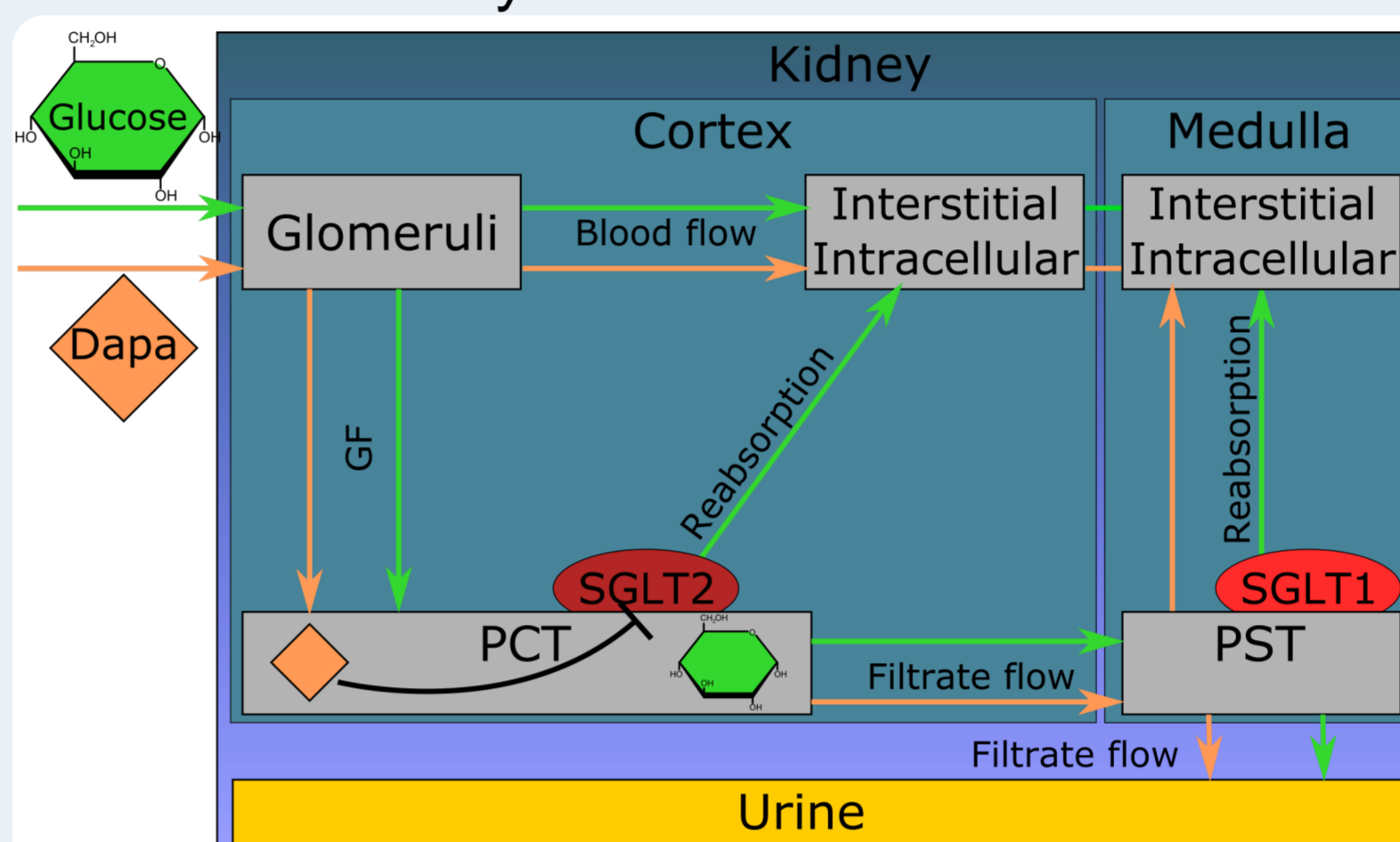


Figure 2: Structure of the glucose filtration model. Green and orange arrows represent glucose and dapagliflozin flows, respectively. Dapa: dapagliflozin, GF: glomerular filtration, PCT: proximal convoluted tubuli, PST: proximal straight tubuli.

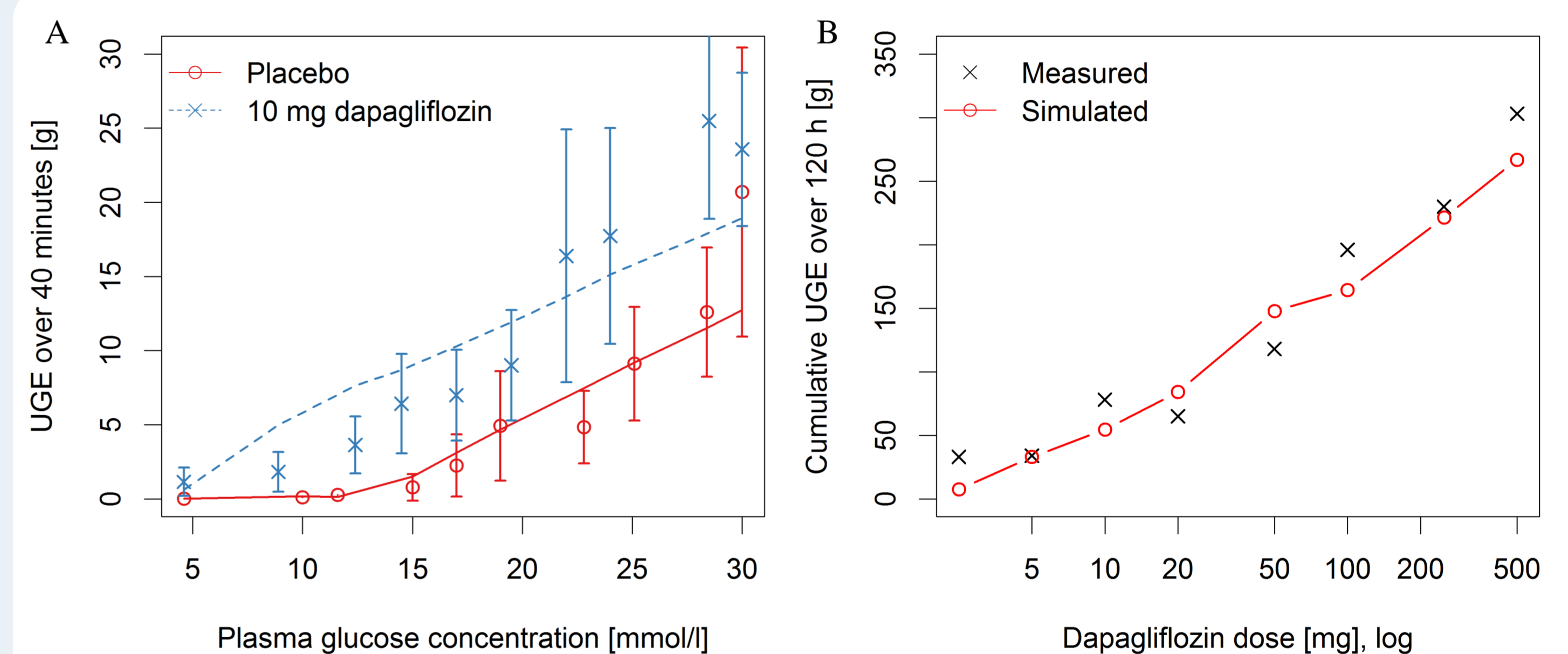


Figure 3: Prediction of effect of dapagliflozin on glucose excretion. Panel A: Amount of glucose excreted in urine over 40 minutes during a stepped hyperglycemic clamp with 10 mg dapagliflozin or placebo. Glucose levels were increased stepwise, and each clamp level was maintained for 40 minutes [6]. Panel B: Amount of glucose excreted over 120 hours in the SAD study reported in [4]. UGE: urinary glucose excretion.

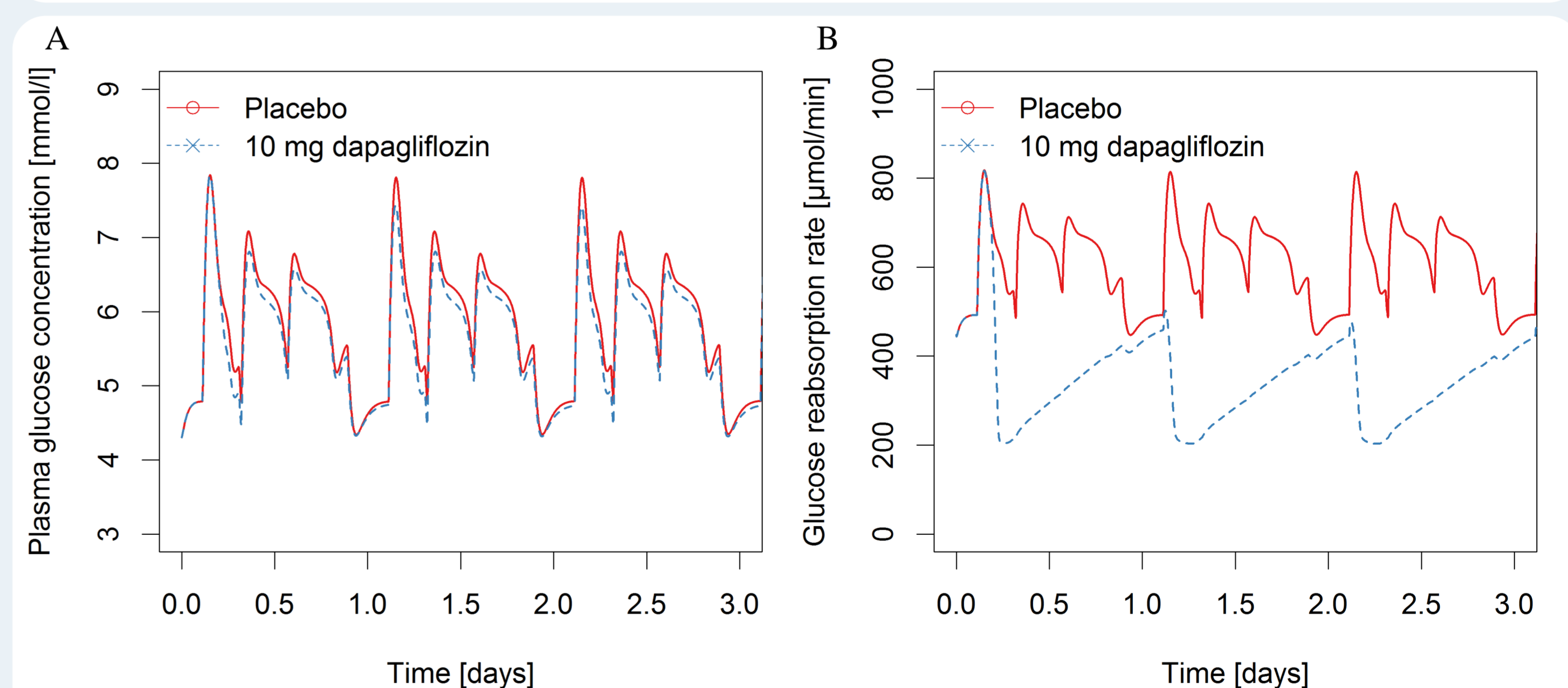


Figure 4: Simulation of three days with the coupled glucose and dapagliflozin models. Three days with three standard meals were simulated with the glucose homeostasis model for a healthy virtual patient without (red solid lines) or with (blue dashed lines) administration of 10 mg dapagliflozin once daily. Panel A: Glucose concentrations in plasma. Panel B: Rates of renal glucose reabsorption.

Conclusions

A PBPK model incorporating all relevant processes involved in PK of dapagliflozin was developed. Its mechanistic coupling with the glucose homeostasis model extends the area of application of the latter from insulin treatment to oral antidiabetic therapies.

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