

Building and evaluation of a PBPK model for dapagliflozin in adults

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1 Introduction

The presented model building and evaluation report evaluates the performance of PBPK model for dapagliflozin in adults.

Dapagliflozin,

The dapagliflozin model is a whole-body PBPK model, allowing for dynamic translation

...reliable predictions of dapagliflozin PBPK adults during model-informed drug development. The presented dapagliflozin PBPK model as well as the respective evaluation plan and PBPK report are provided open-source and transparently documented (<https://github.com/sfrechen/Dapagliflozin-Model>).

2 Methods

2.1 Modeling strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. ([Kuepfer 2016](# 5 References)) Regarding the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published ([PK-Sim Ontogeny Database Version 7.3](# References)). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3 ([Schlender 2016](# 5 References)) or otherwise referenced for the specific process.

First, a base mean model was built using data from the single dose escalation study to find an appropriate structure describing the PK of dapagliflozin plasma. The mean PK model was developed using a typical European individual. Unknown parameters were identified using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility.

Once the appropriate structural model was identified, additional parameters for different formulations were identified.

A final PBPK model was established and simulations were compared to the reported data to evaluate model appropriateness and to assess model qualification, by means of diagnostics plots and predicted versus observed concentration-time profiles, of which the results support an adequate prediction of the PK in adults.

During model building, uncertainties in data-quality, as well as study differences may cause not being able to adequately describe the PK of all reported clinical study data.

2.2 Data used

2.2.1 In vitro / physico-chemical data

A literature search was performed to collect available information on physical chemical properties of dapagliflozin. The obtained information from literature is summarized in the table below, and is used for model building.

| Parameter | Unit | Dapagliflozin literature | Description |
|-----------------|-------------|--------------------------|---|
| MW | g/mol | | Molecular weight |
| pKa | | | Acid dissociation constant |
| Solubility (pH) | mg/L | | Solubility |
| logP | | | Partition coefficient between octanol and water |
| fu | | | Fraction unbound |
| | µM | | Michaelis-Menten constant (Km) |
| | nmol/min/mg | | Vmax |
| | | | |
| | | | |

2.2.2 Clinical data

A literature search was performed to collect available clinical data on dapagliflozin in adults.

The following publications were found in adults for model building and evaluation:

| Publication | Study description |
|-------------------------|-------------------|
| [Dummy](# 5 References) | ... |
| | |
| | |
| | |
| | |
| | |

2.3 Model parameters and assumptions

2.3.1 Absorption

2.3.2 Distribution

2.3.3 Metabolism and Elimination

3 Results and Discussion

The PBPK model **dapagliflozin** was developed with clinical pharmacokinetic data covering ...

3.1 Dapagliflozin final input parameters

The compound parameter values of the final dapagliflozin PBPK model are illustrated below.

Compound: Dapagliflozin

Parameters

| Name | Value | Value Origin | Alternative | Default |
|--|-------------------------|---|------------------|---------|
| Solubility at reference pH | 0.2100844168 mg/ml | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 | Water solubility | True |
| Reference pH | 7 | Database-DrugBank DB06292 | Water solubility | True |
| Lipophilicity | 2.6495139838 Log Units | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 | Optimized | True |
| Fraction unbound (plasma, reference value) | 0.09 | Publication-Kasichayanula et al. 2014 | Human | True |
| Permeability | 0.00041657167125 cm/min | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 | Optimized | False |
| Specific intestinal permeability (transcellular) | 3.8347545732E-05 cm/min | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 | Optimized | False |
| Cl | 1 | | | |
| Is small molecule | Yes | | | |
| Molecular weight | 408.873 g/mol | | | |
| Plasma protein binding partner | Albumin | | | |

Calculation methods

| Name | Value |
|-------------------------|---------------------|
| Partition coefficients | Rodgers and Rowland |
| Cellular permeabilities | PK-Sim Standard |

Processes

Metabolizing Enzyme: UGT1A9-Optimized

Molecule: UGT1A9

Metabolite: Dapagliflozin-3-O-glucuronide

Parameters

| Name | Value | Value Origin |
|----------------------|----------------------------|---|
| Enzyme concentration | 1 µmol/l | |
| Specific clearance | 0.1/min | |
| CLspec/[Enzyme] | 0.402175146 l/ µmol/min | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 |

Metabolizing Enzyme: UGT2B7-Optimized

Molecule: UGT2B7

Metabolite: Dapagliflozin-2-O-glucuronide

Parameters

| Name | Value | Value Origin |
|----------------------|--------------------------------|---|
| Enzyme concentration | 1 µmol/l | |
| Specific clearance | 0.1/min | |
| CLspec/[Enzyme] | 0.0072288071857 l/ µmol/min | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 |

Systemic Process: Glomerular Filtration-assumed

Species: Human

Parameters

| Name | Value | Value Origin |
|--------------|--------------|---|
| GFR fraction | 0.8944188606 | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 |

Metabolizing Enzyme: Hepatic-CYP-Optimized

Molecule: Hepatic-CYP

Parameters

| Name | Value | Value Origin |
|----------------------|-----------------------------|---|
| Enzyme concentration | 1 µmol/l | |
| Specific clearance | 0.1/min | |
| CLspec/[Enzyme] | 0.1397810065 l/ µmol/min | Parameter Identification-Parameter Identification-Value updated from 'PI full (perm)' on 2019-08-06 14:46 |

Formulation: IR tablet

Type: Weibull

Parameters

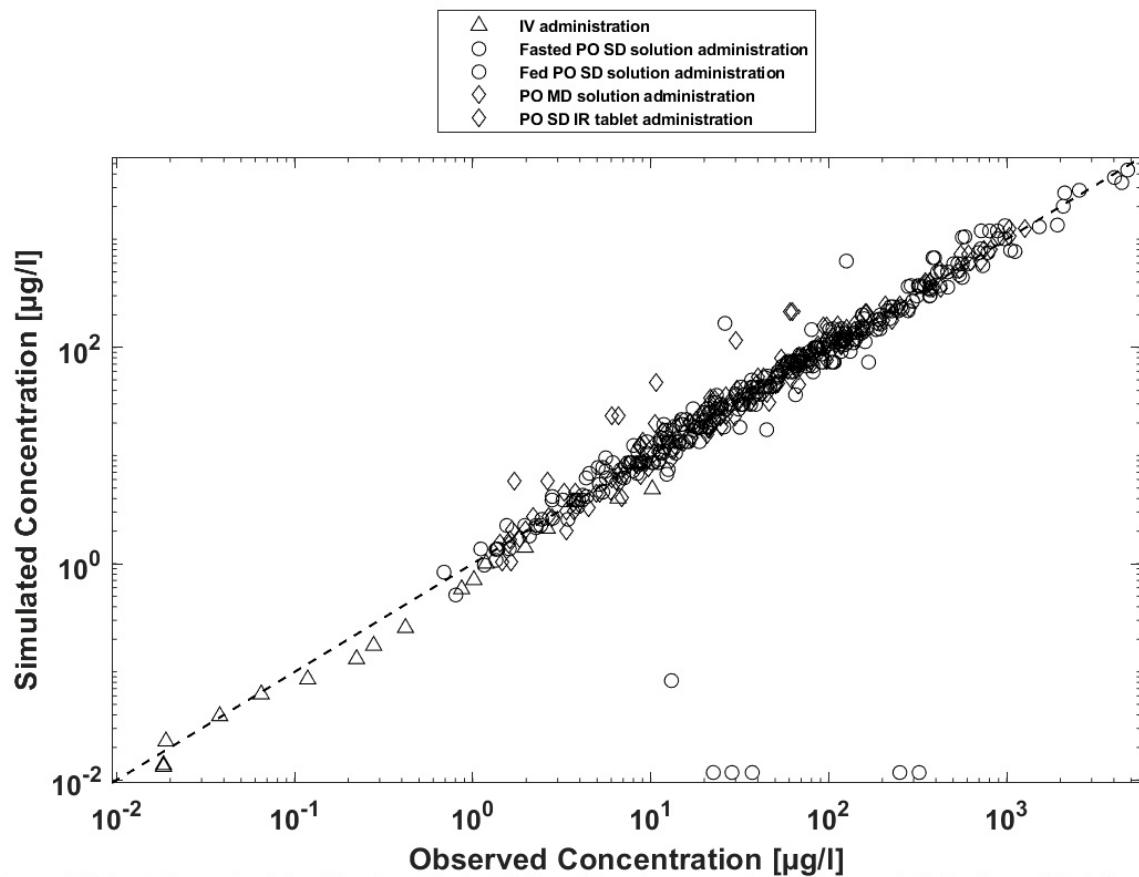
| Name | Value | Value Origin |
|----------------------------------|--------|--------------|
| Dissolution time (50% dissolved) | 30 min | |
| Lag time | 0 min | |
| Dissolution shape | 0.6 | |
| Use as suspension | Yes | |

Formulation: Solution

Type: Dissolved

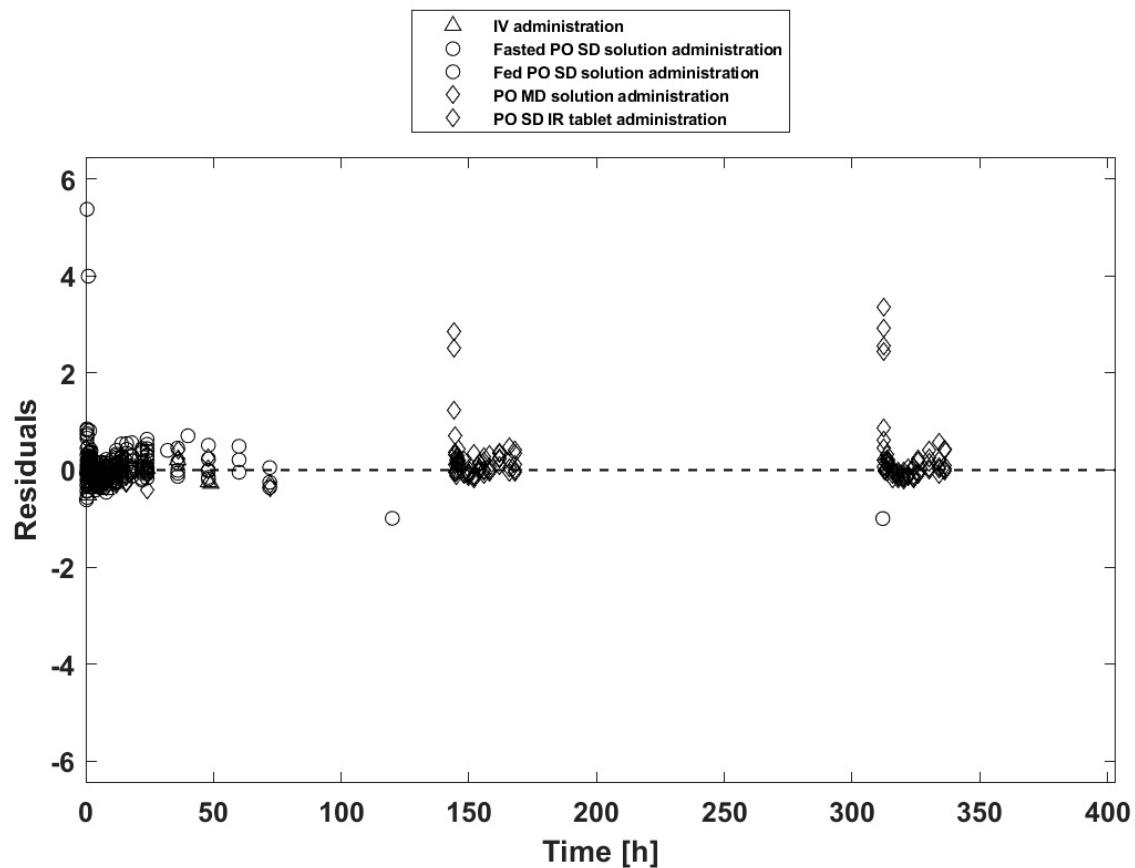
3.2 Dapagliflozin Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for dapagliflozin PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time) of all data used for model building.



Goodness-of-fit visual diagnostic plots of the dapagliflozin PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.339394



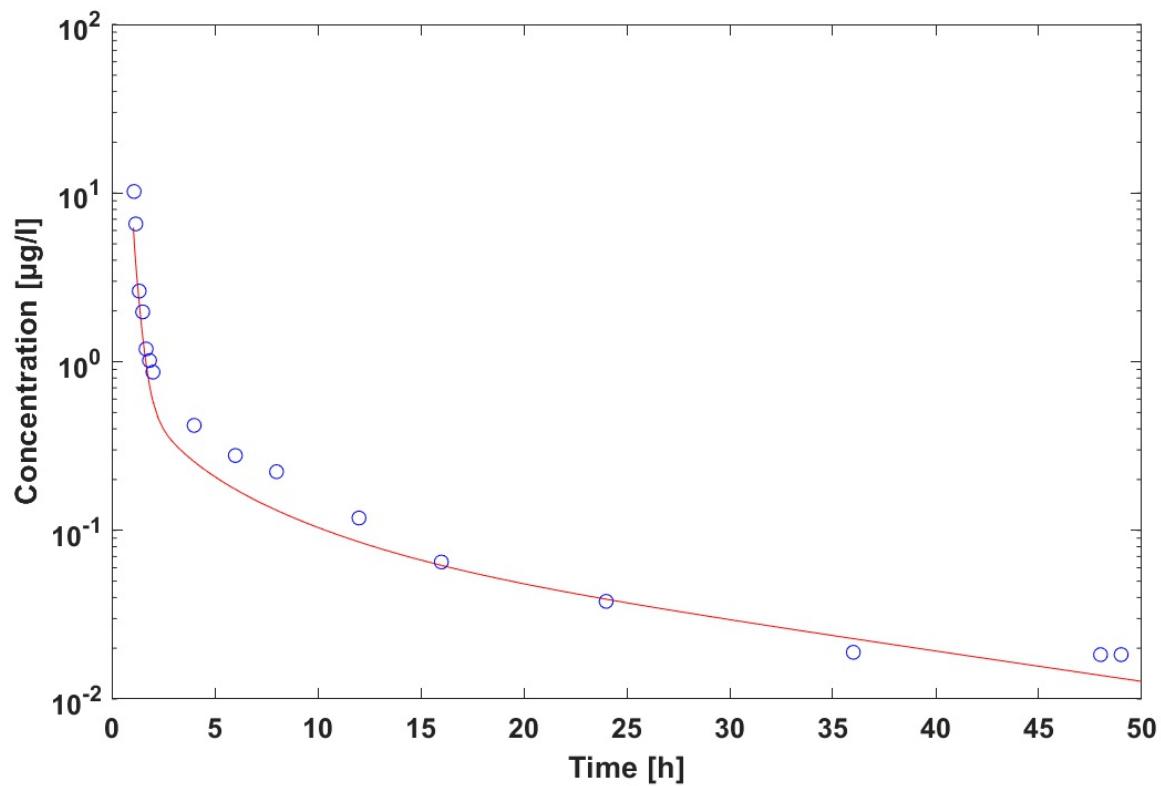
Goodness-of-fit visual diagnostic plots of the Dapagliflozin PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.339394

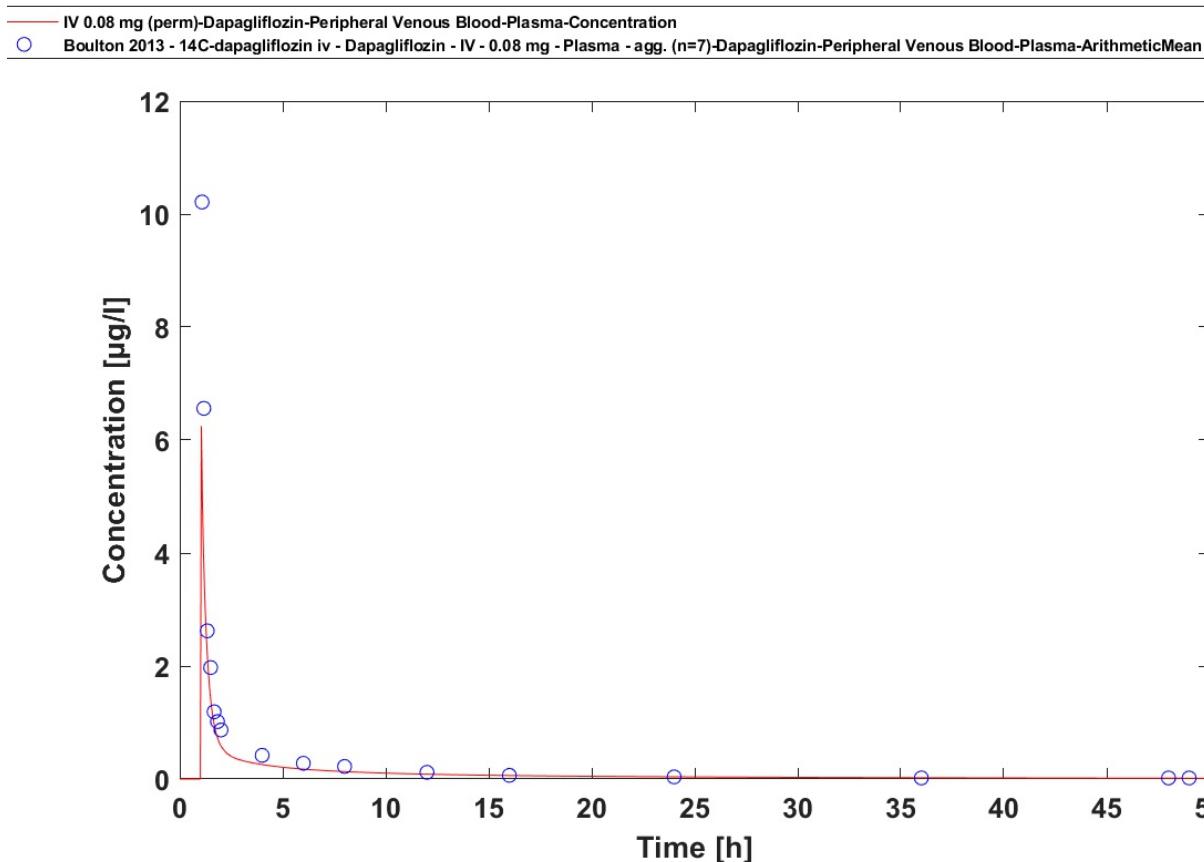
3.3: Dapagliflozin Concentration-Time profiles

Simulated versus observed plasma concentration-time profiles of all data are listed below.

IV 0.08 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Boulton 2013 - 14C-dapagliflozin iv - Dapagliflozin - IV - 0.08 mg - Plasma - agg. (n=7)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

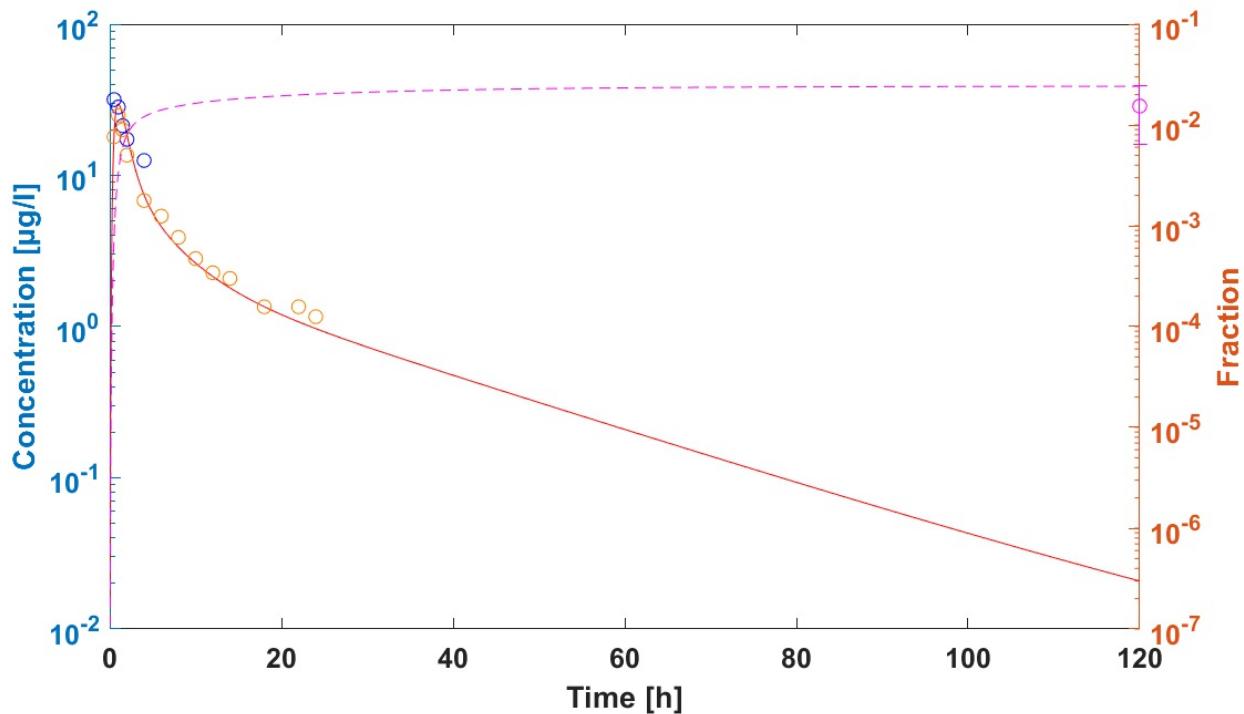


IV 0.08 mg (perm)



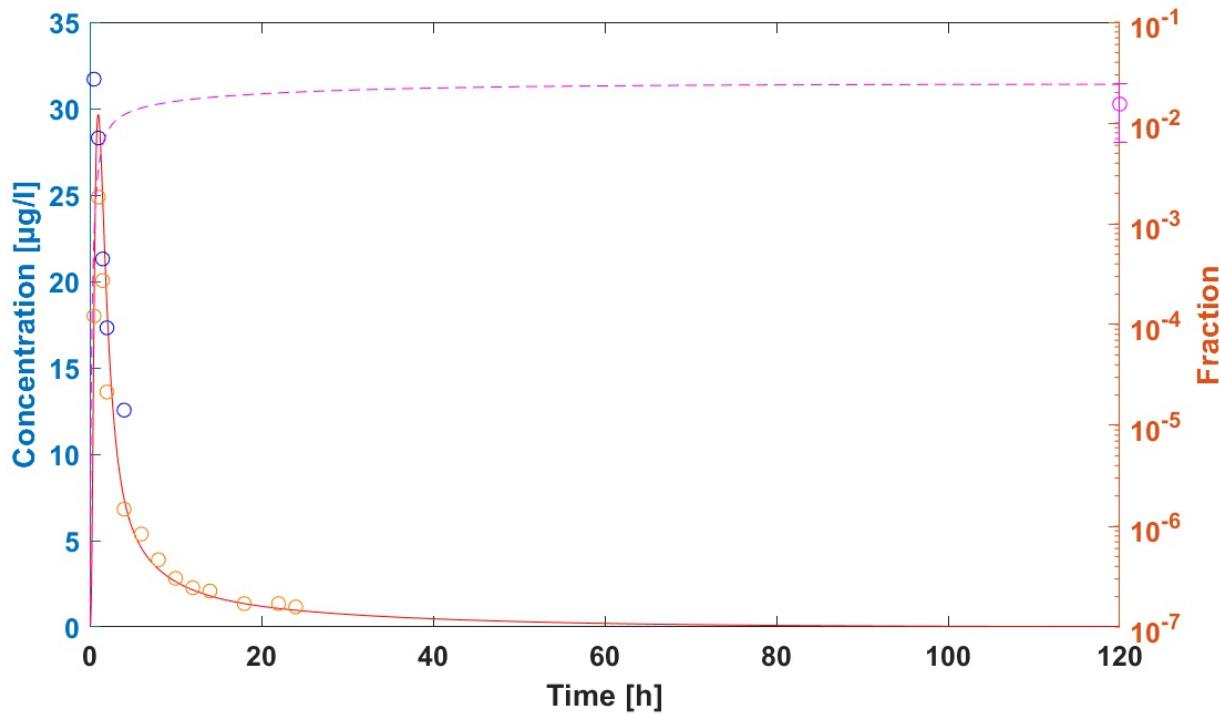
Time Profile Analysis 1

— PO SD 2.5 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
○ Komoroski 2009 - SAD 2.5 mg (Urine) - Dapagliflozin - PO - 2.5 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
— PO SD 2.5 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine
— Komoroski 2009 - SAD 2.5 mg - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
— Komoroski 2009 - MAD 2.5 mg (day 1) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

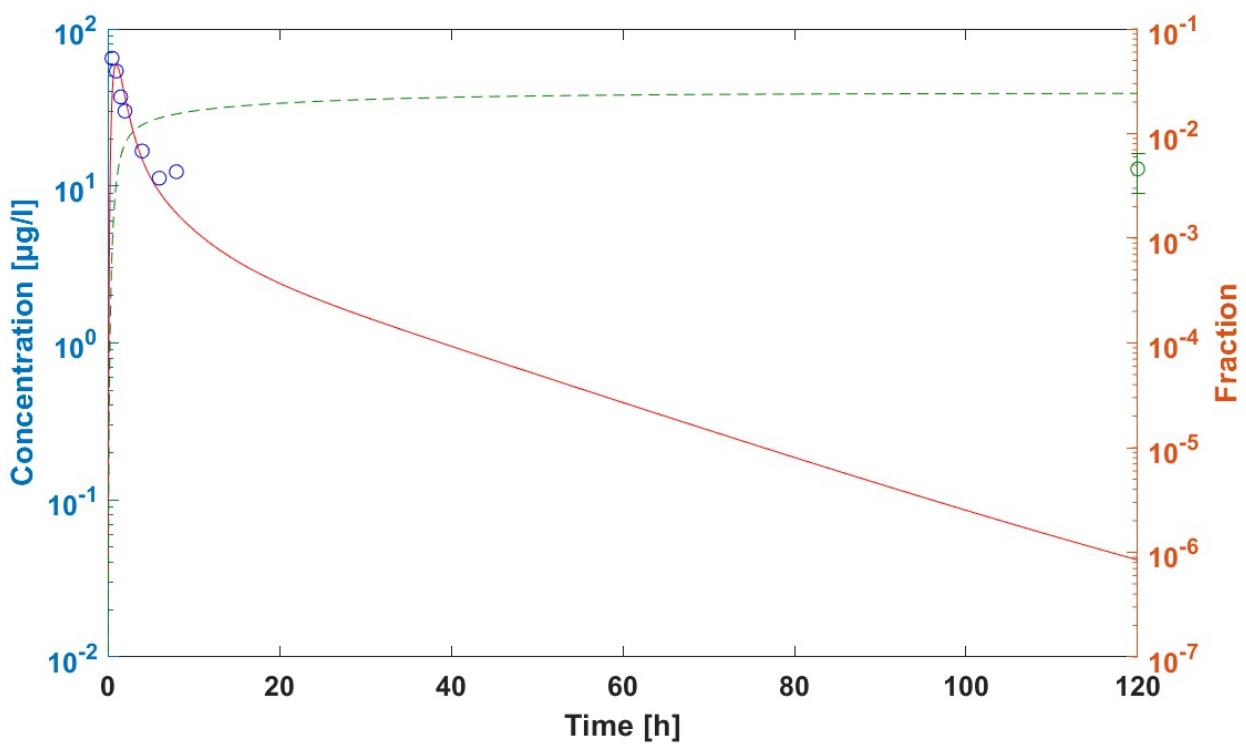
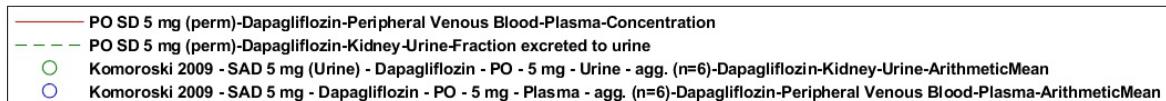


PO SD 2.5 mg (perm)

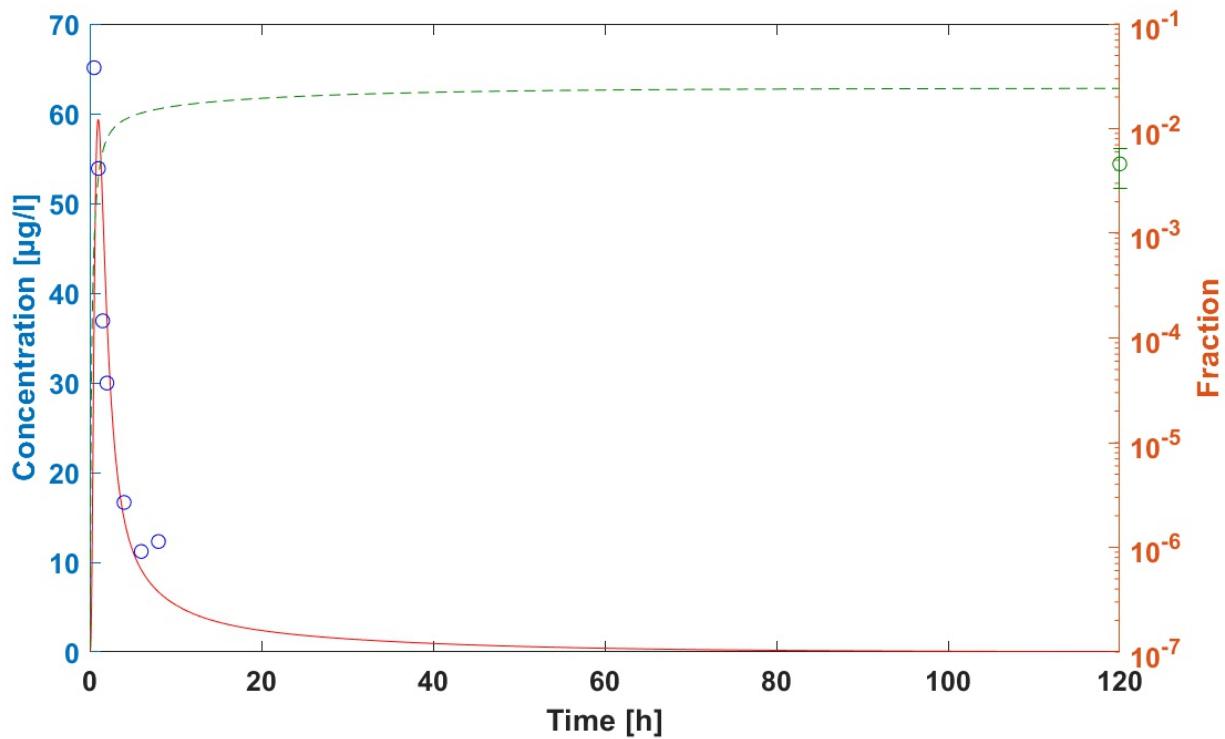
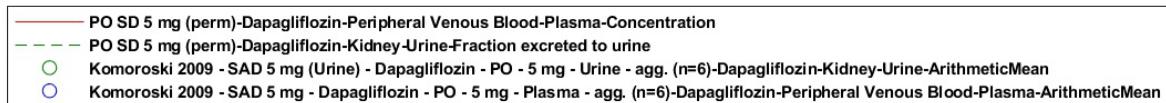
| | |
|--|---|
| | PO SD 2.5 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration |
| | Komoroski 2009 - SAD 2.5 mg (Urine) - Dapagliflozin - PO - 2.5 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean |
| | PO SD 2.5 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine |
| | Komoroski 2009 - SAD 2.5 mg - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean |
| | Komoroski 2009 - MAD 2.5 mg (day 1) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean |



PO SD 2.5 mg (perm) 1

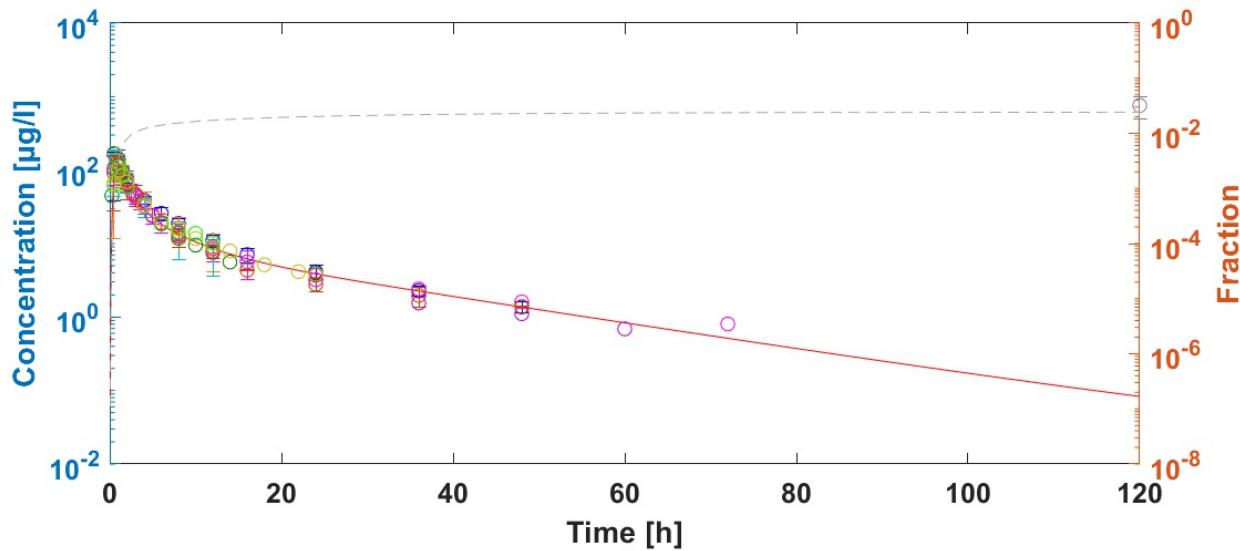


PO SD 5 mg (perm)



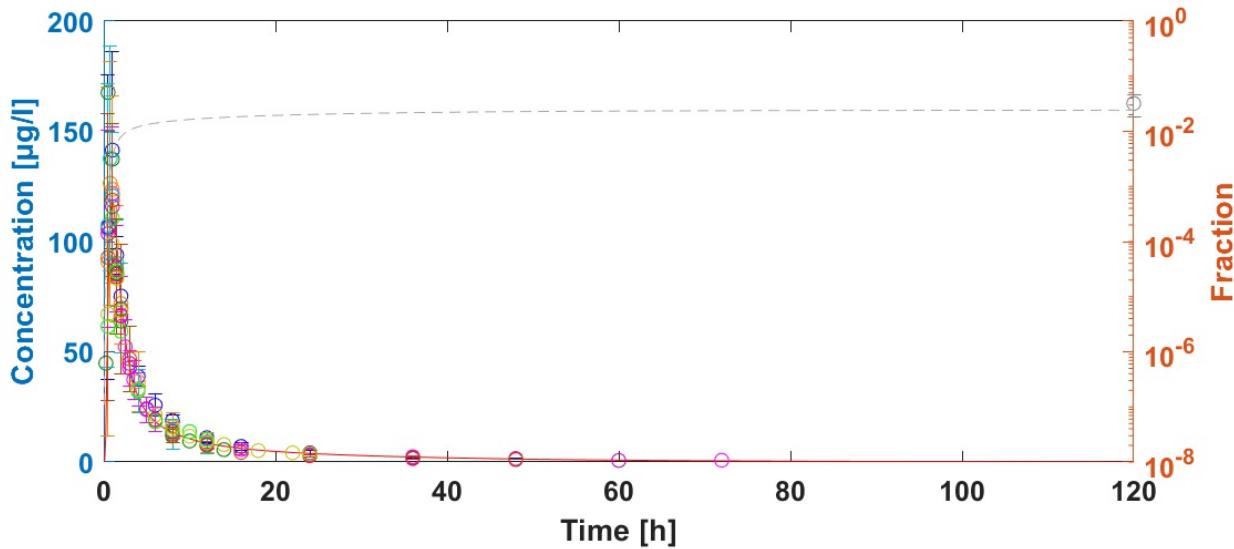
PO SD 5 mg (perm) 1

)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
 -Dapagliflozin po - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=7)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 itrol (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=22)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - fasted - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - Study 2: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=16)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 - Dapagliflozin - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=42)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 lc - Healthy Volunteers - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 AD 10 mg - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 AD 10 mg (Urine) - Dapagliflozin - PO - 10 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
 IAD 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine



PO SD 10 mg (perm)

)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
 agiliflozin po - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=7)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 itrol (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=22)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - fasted - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=14)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 la - Study 2: Control (Perpetrator Placebo) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=16)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 - Dapagliflozin - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=42)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 lc - Healthy Volunteers - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 AD 10 mg - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 AD 10 mg (Urine) - Dapagliflozin - PO - 10 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
 IAD 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine



Time Profile Analysis 1

n)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration

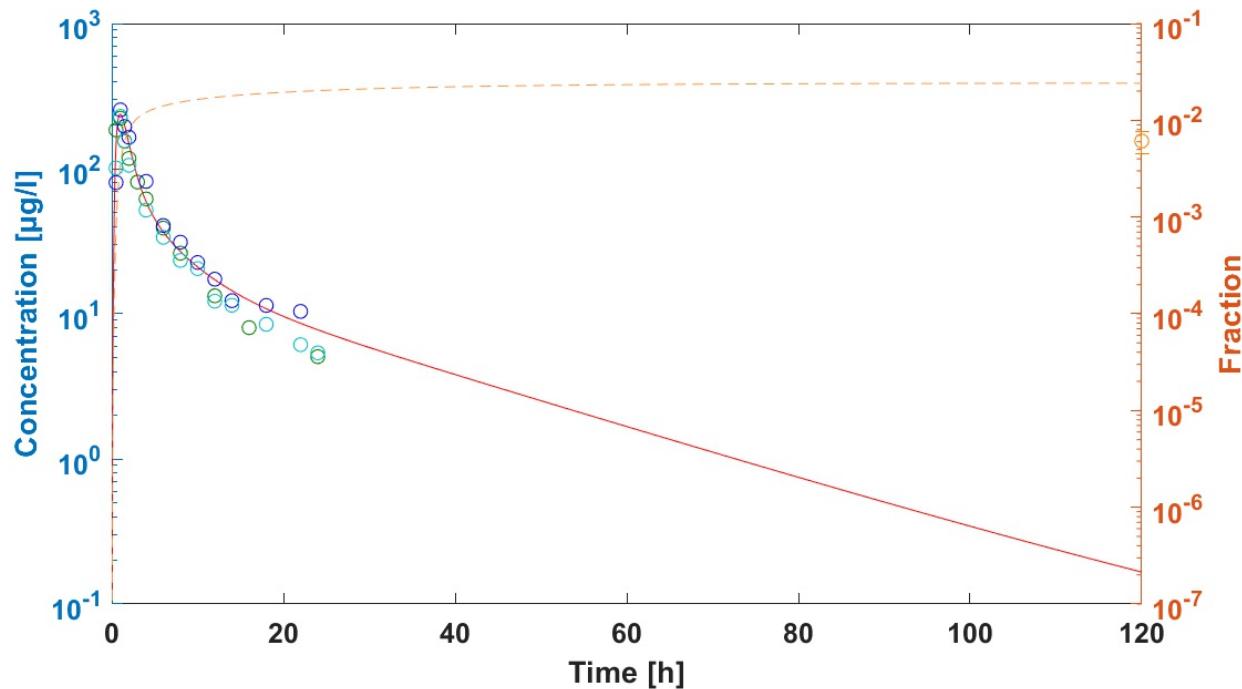
SAD 20 mg (Urine) - Dapagliflozin - PO - 20 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean

n)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine

I2 - Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=24)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

SAD 20 mg - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

MAD 20 mg (day 1) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO SD 20 mg (perm)

n)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration

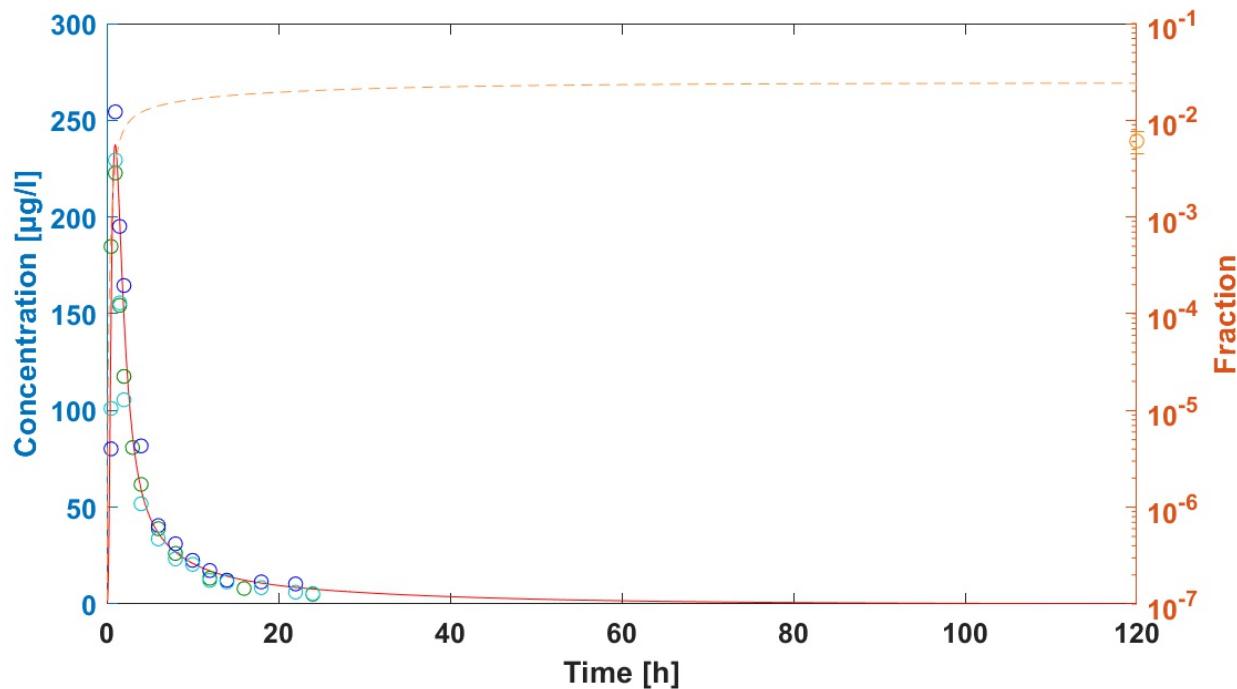
SAD 20 mg (Urine) - Dapagliflozin - PO - 20 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean

n)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine

I2 - Study 1: Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=24)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

SAD 20 mg - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

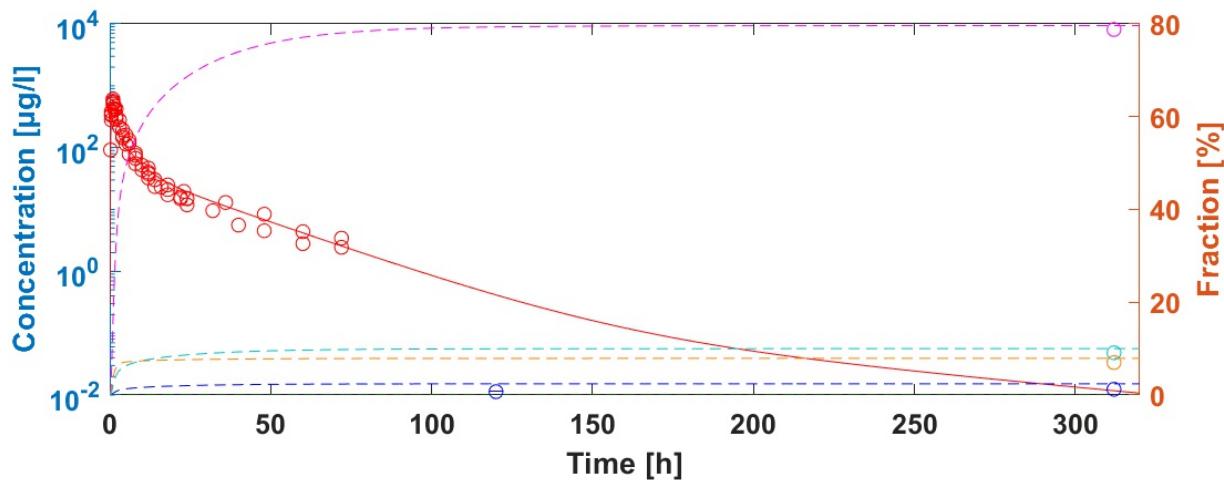
MAD 20 mg (day 1) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO SD 20 mg (perm) 1

ration

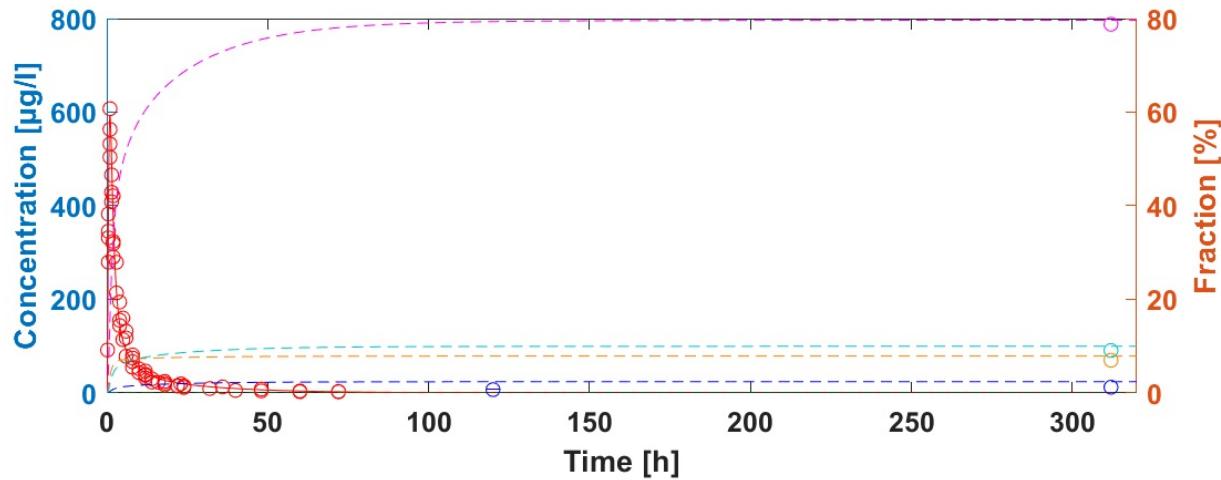
Total fraction of dose-Dapagliflozin
Total fraction of dose-Dapagliflozin
iflozin - PO - 50 mg - Plasma - agg. (n=24)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
iflozin - PO - 50 mg - Plasma - agg. (n=8)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
i - PO - 50 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
3)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
nanged feces excret.) - Dapagliflozin-2-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-2-O-glucuronide-Undefined-Undefined-ArithmeticMean
i, (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
sm-Total fraction of dose-Dapagliflozin
iflozin oxidative metabolites - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin oxidative metabolites-Undefined-Undefined-ArithmeticMean
nanged feces exret.) - Dapagliflozin-3-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-3-O-glucuronide-Undefined-Undefined-ArithmeticMean
gg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO SD 50 mg (perm)

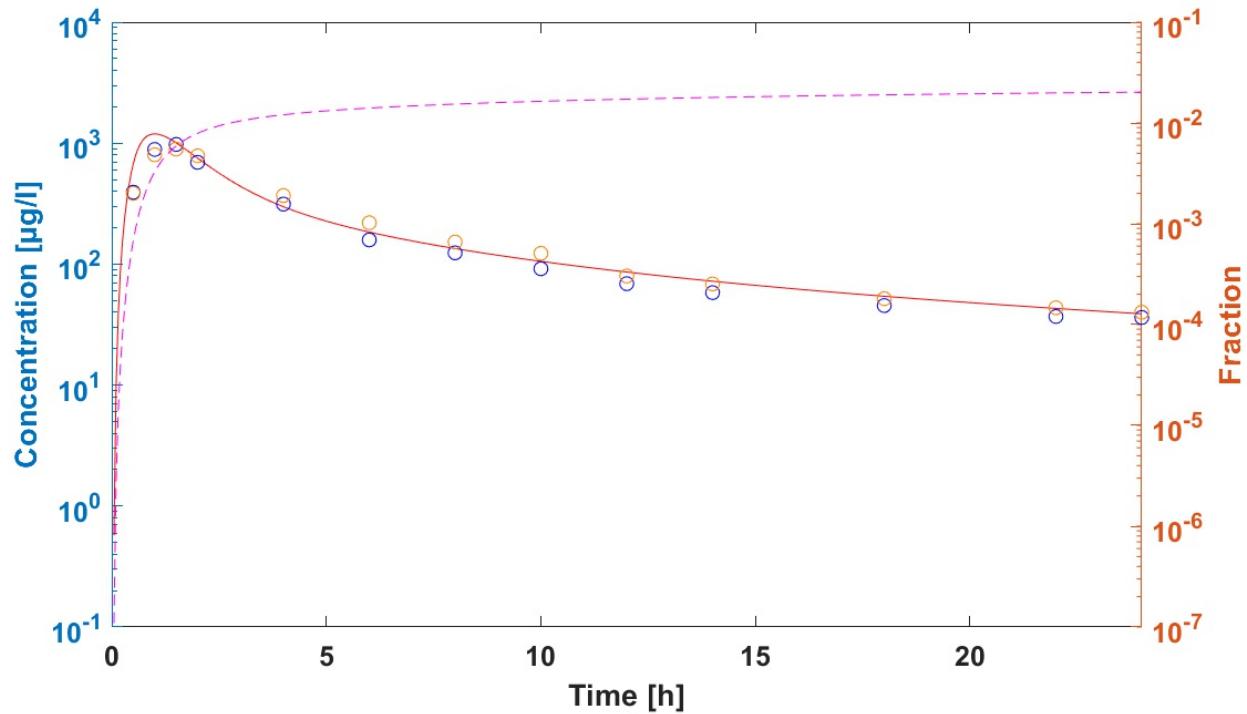
ration

Total fraction of dose-Dapagliflozin
Total fraction of dose-Dapagliflozin
iflozin - PO - 50 mg - Plasma - agg. (n=24)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
iflozin - PO - 50 mg - Plasma - agg. (n=8)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
i - PO - 50 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
3)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
nanged feces excret.) - Dapagliflozin-2-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-2-O-glucuronide-Undefined-Undefined-ArithmeticMean
i, (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
sm-Total fraction of dose-Dapagliflozin
iflozin oxidative metabolites - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin oxidative metabolites-Undefined-Undefined-ArithmeticMean
nanged feces exret.) - Dapagliflozin-3-O-glucuronide - PO - 50 mg - Fraction - agg. (n=6)-Dapagliflozin-3-O-glucuronide-Undefined-Undefined-ArithmeticMean
gg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



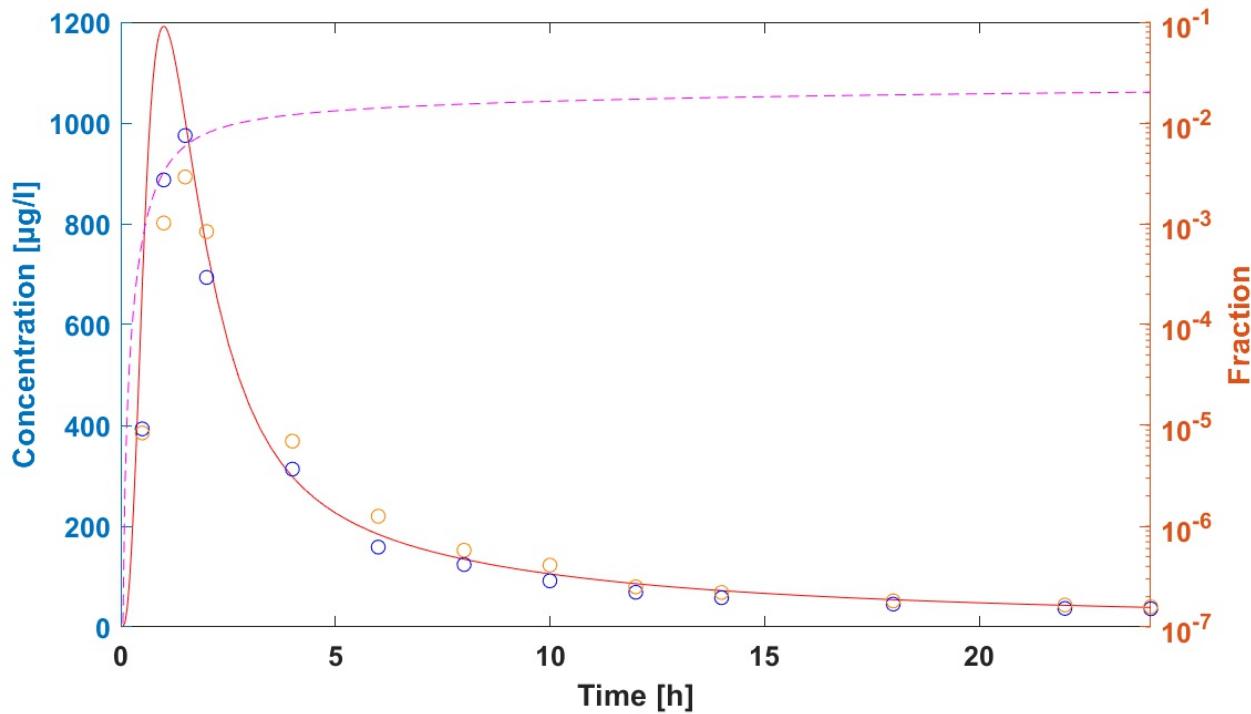
PO SD 50 mg (perm) 1

— PO SD 100 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
 Komoroski 2009 - SAD 100 mg (Urine) - Dapagliflozin - PO - 100 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
— PO SD 100 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine
 Komoroski 2009 - SAD 100 mg - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 Komoroski 2009 - MAD 100 mg (day 1) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



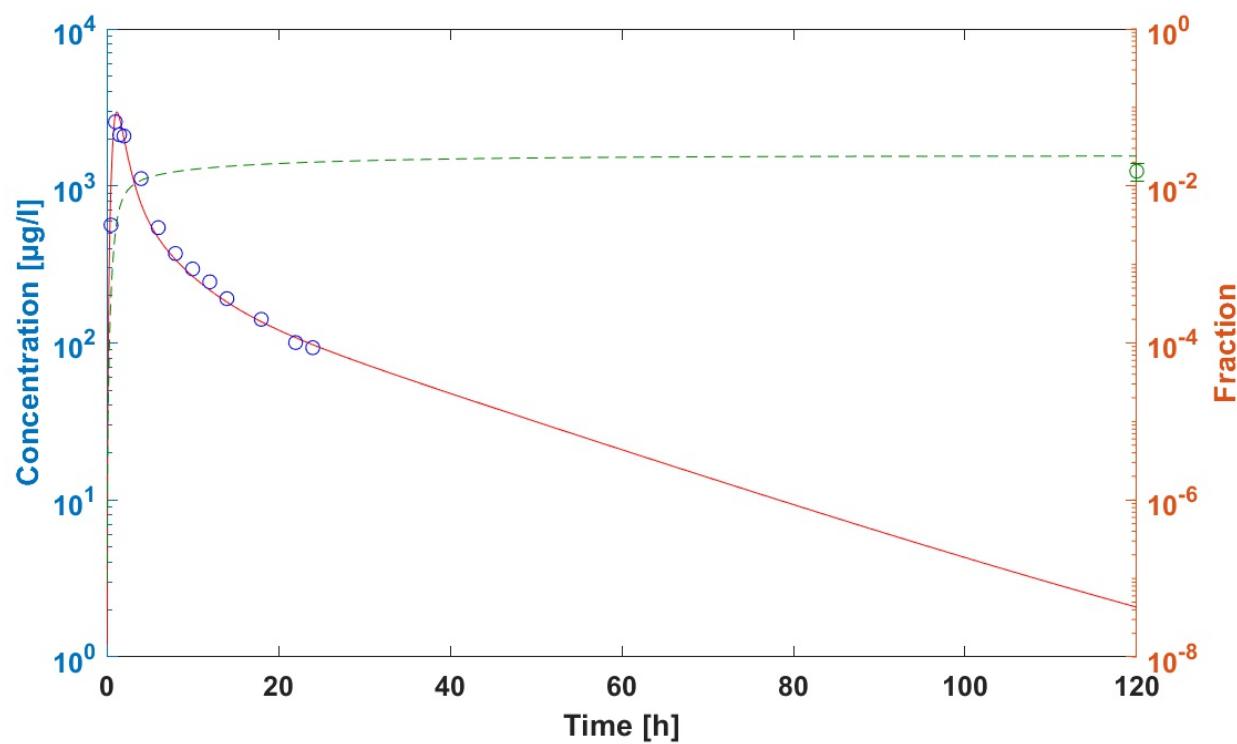
PO SD 100 mg (perm)

— PO SD 100 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
 Komoroski 2009 - SAD 100 mg (Urine) - Dapagliflozin - PO - 100 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
— PO SD 100 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine
 Komoroski 2009 - SAD 100 mg - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
 Komoroski 2009 - MAD 100 mg (day 1) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



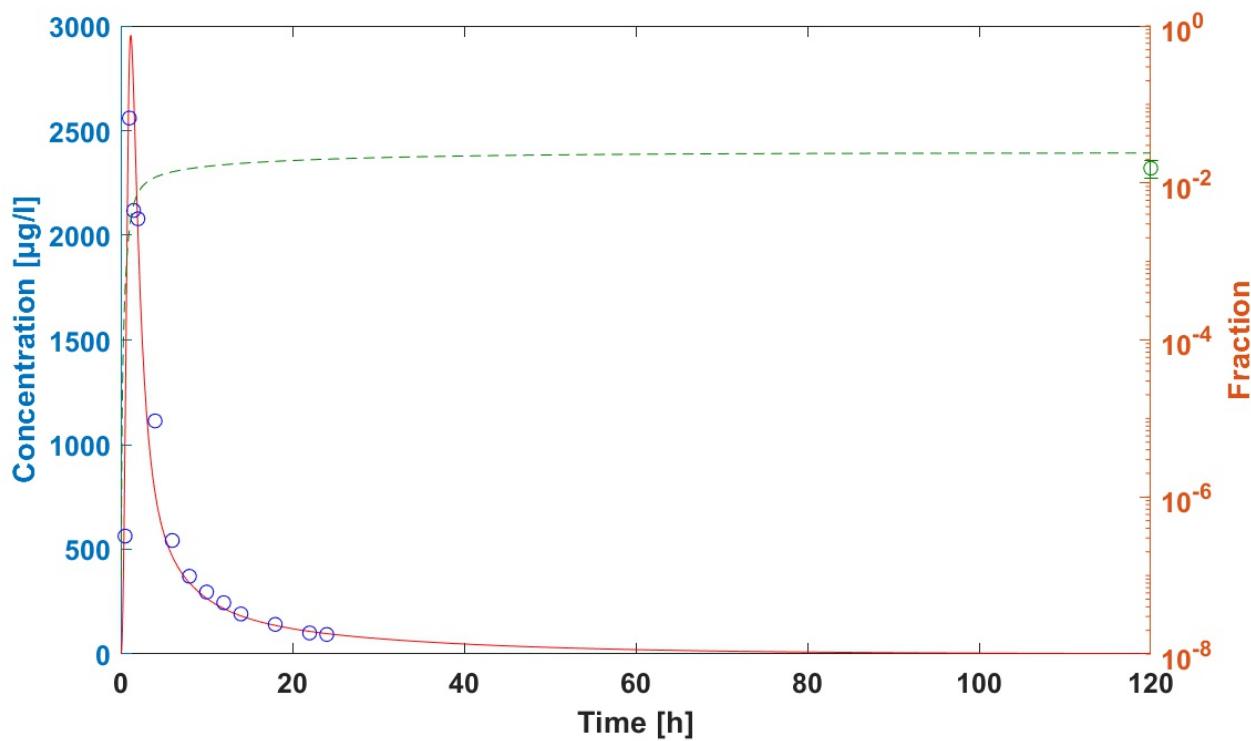
PO SD 100 mg (perm) 1

— PO SD 250 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
) Komoroski 2009 - SAD 250 mg fasted - Dapagliflozin - PO - 250 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
) Komoroski 2009 - SAD 250 mg fasted (Urine) - Dapagliflozin - PO - 250 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
 - - PO SD 250 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine



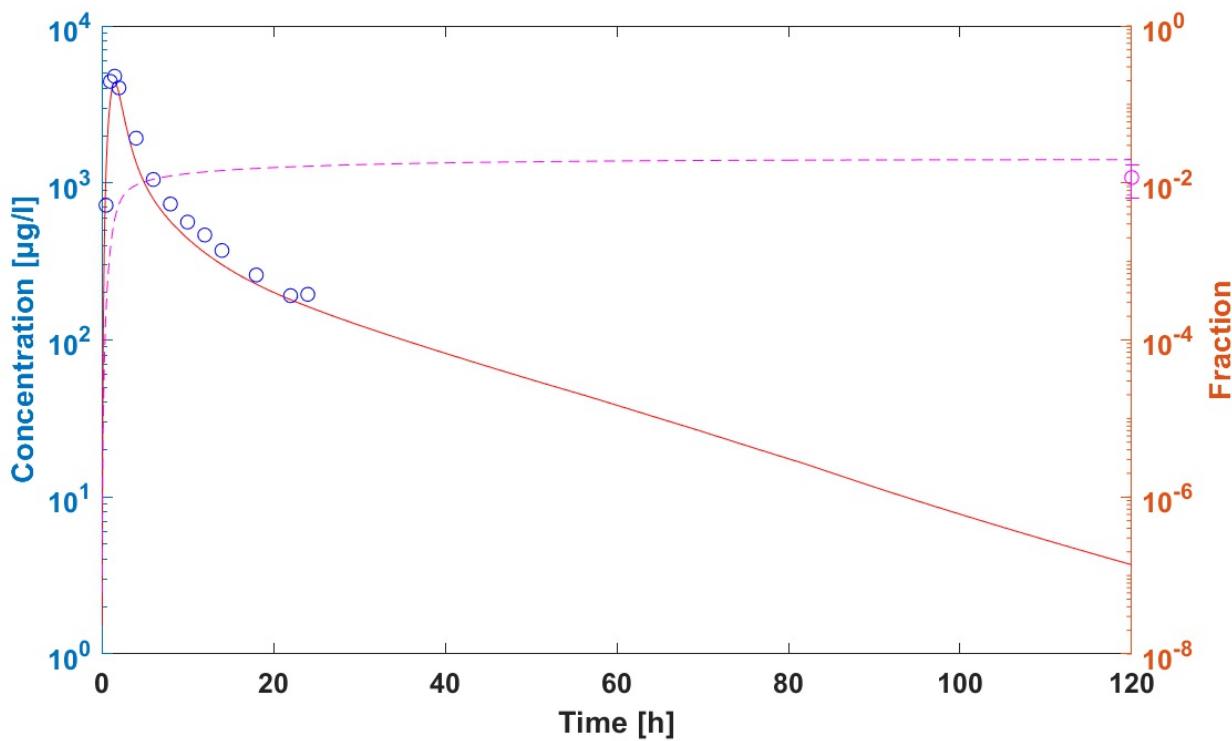
PO SD 250 mg (perm)

— PO SD 250 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
) Komoroski 2009 - SAD 250 mg fasted - Dapagliflozin - PO - 250 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
) Komoroski 2009 - SAD 250 mg fasted (Urine) - Dapagliflozin - PO - 250 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean
 - - PO SD 250 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine

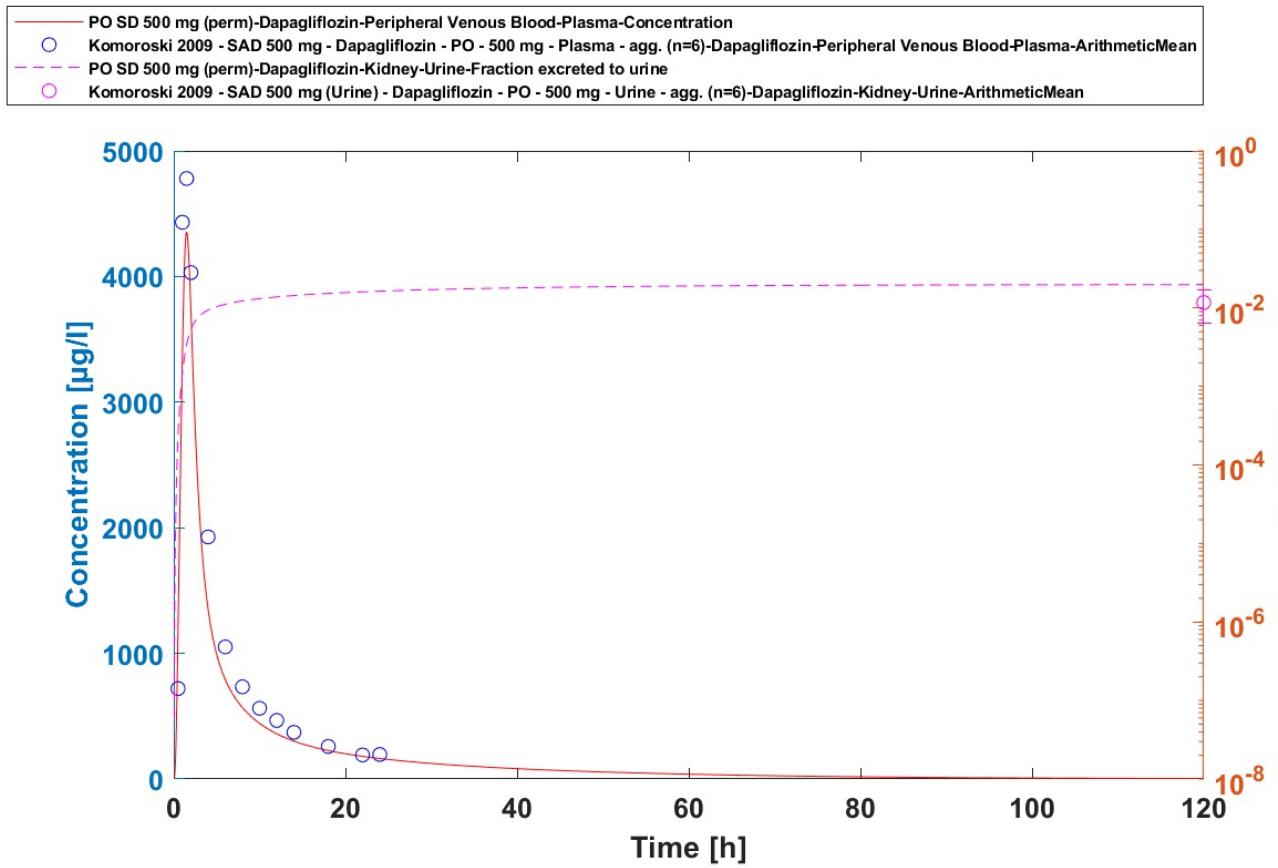


PO SD 250 mg (perm)

| |
|---|
| — PO SD 500 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration |
| ○ Komoroski 2009 - SAD 500 mg - Dapagliflozin - PO - 500 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean |
| — PO SD 500 mg (perm)-Dapagliflozin-Kidney-Urine-Fraction excreted to urine |
| ○ Komoroski 2009 - SAD 500 mg (Urine) - Dapagliflozin - PO - 500 mg - Urine - agg. (n=6)-Dapagliflozin-Kidney-Urine-ArithmeticMean |

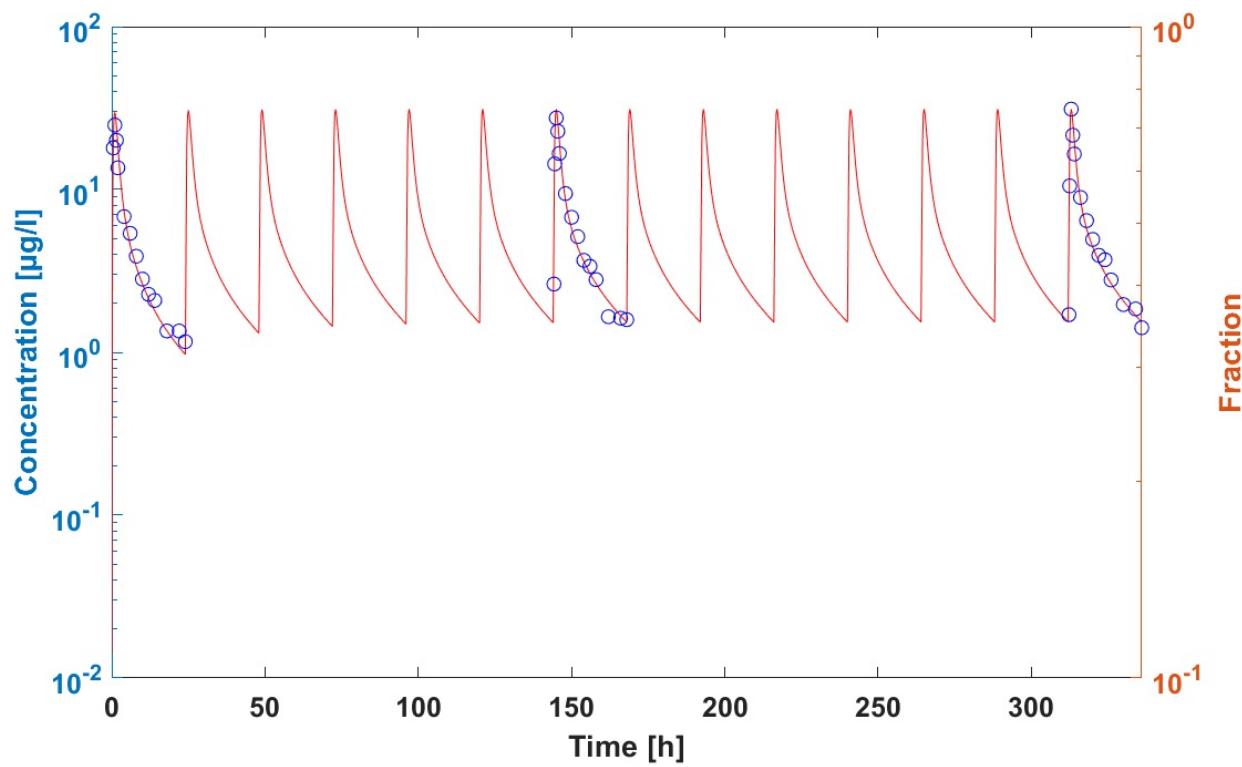


PO SD 500 mg (perm)



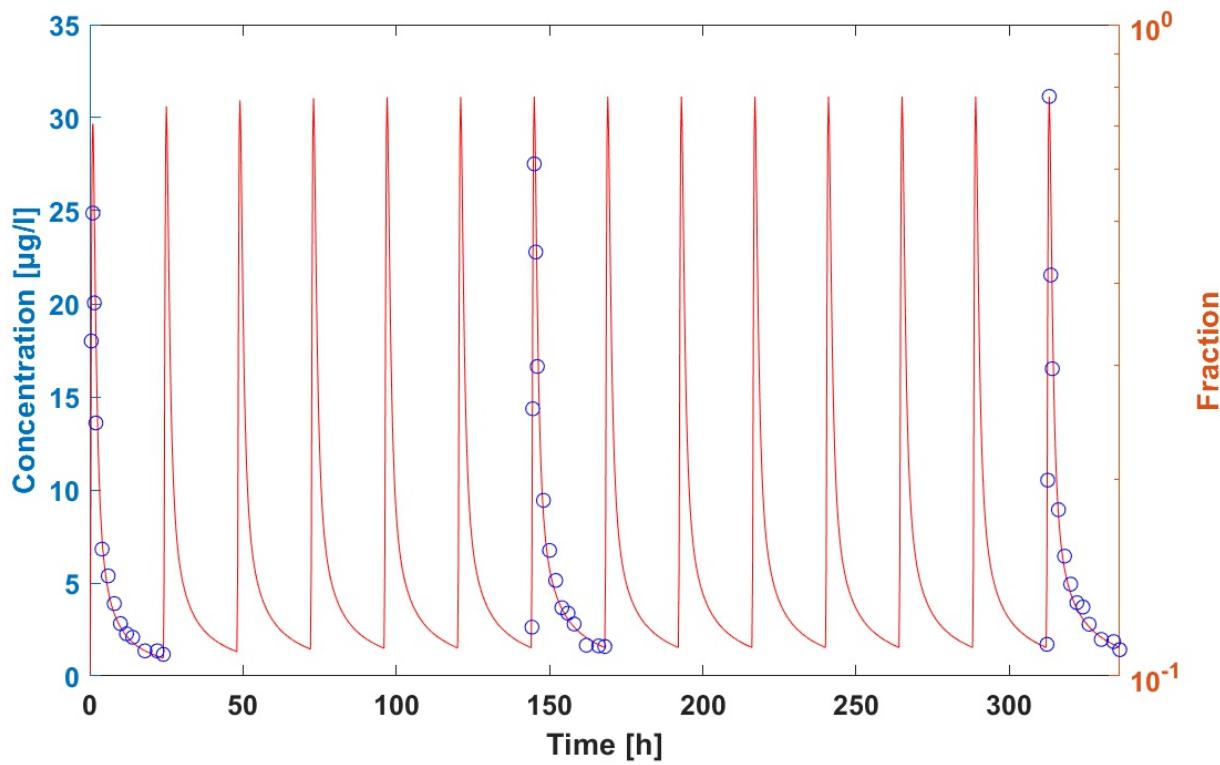
PO SD 500 mg (perm) 1

| 2.5 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
| oski 2009 - MAD 2.5 mg (day 1) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
| oski 2009 - MAD 2.5 mg (day 7 and day 14) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO MD 2.5 mg (perm)

| 2.5 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
oski 2009 - MAD 2.5 mg (day 1) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
oski 2009 - MAD 2.5 mg (day 7 and day 14) - Dapagliflozin - PO - 2.5 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

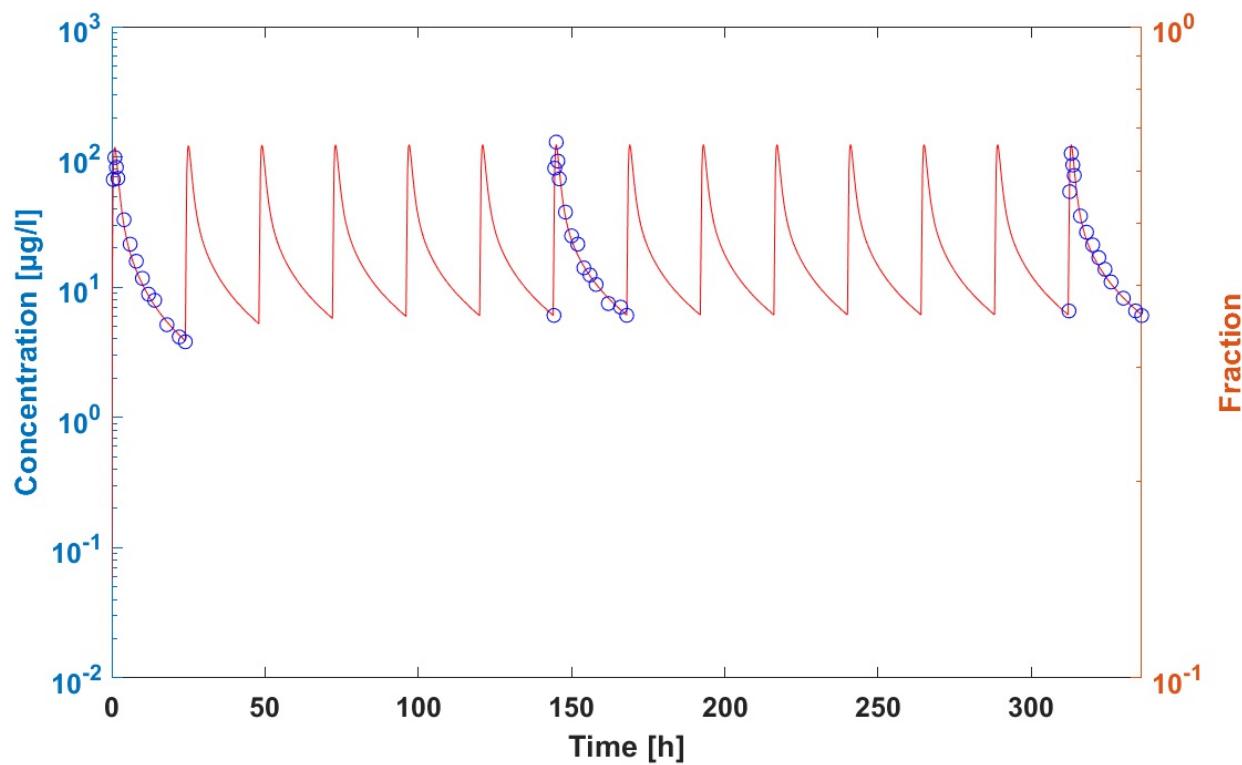


PO MD 2.5 mg (perm) 1

D 10 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration

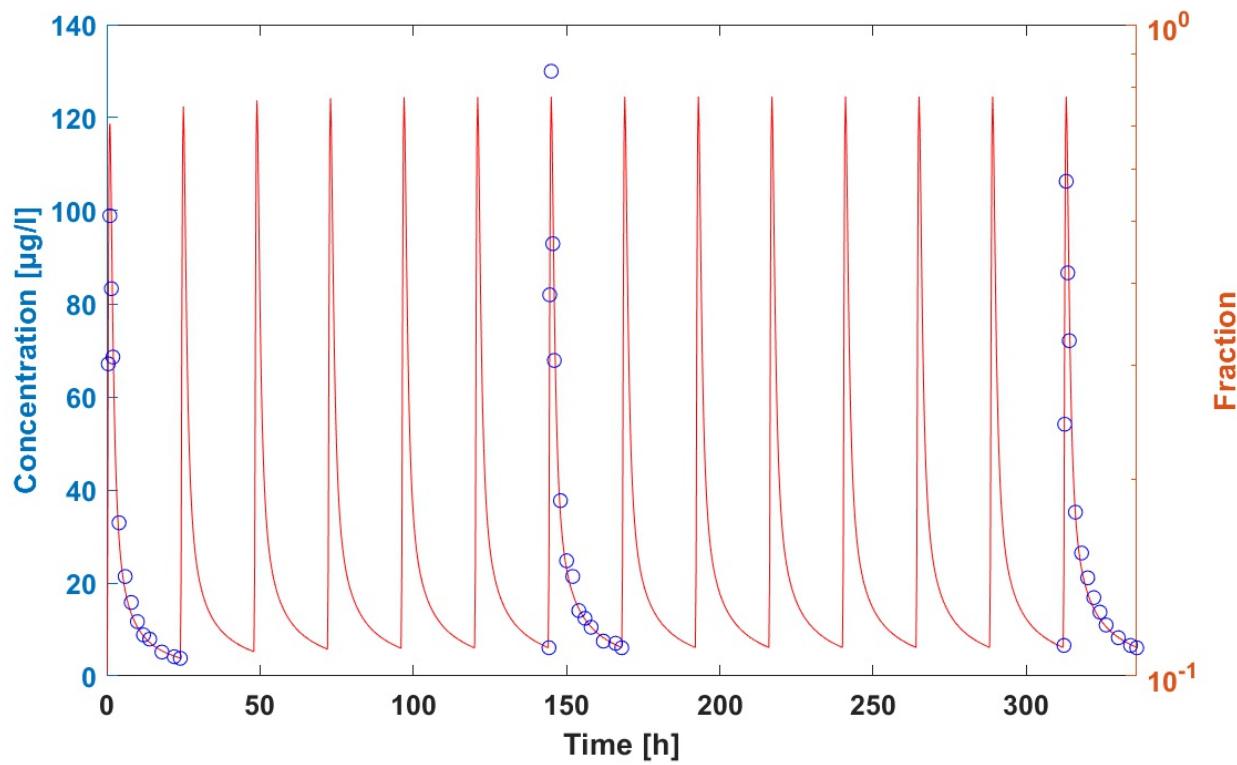
roski 2009 - MAD 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean

roski 2009 - MAD 10 mg (day 7 and day 14) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



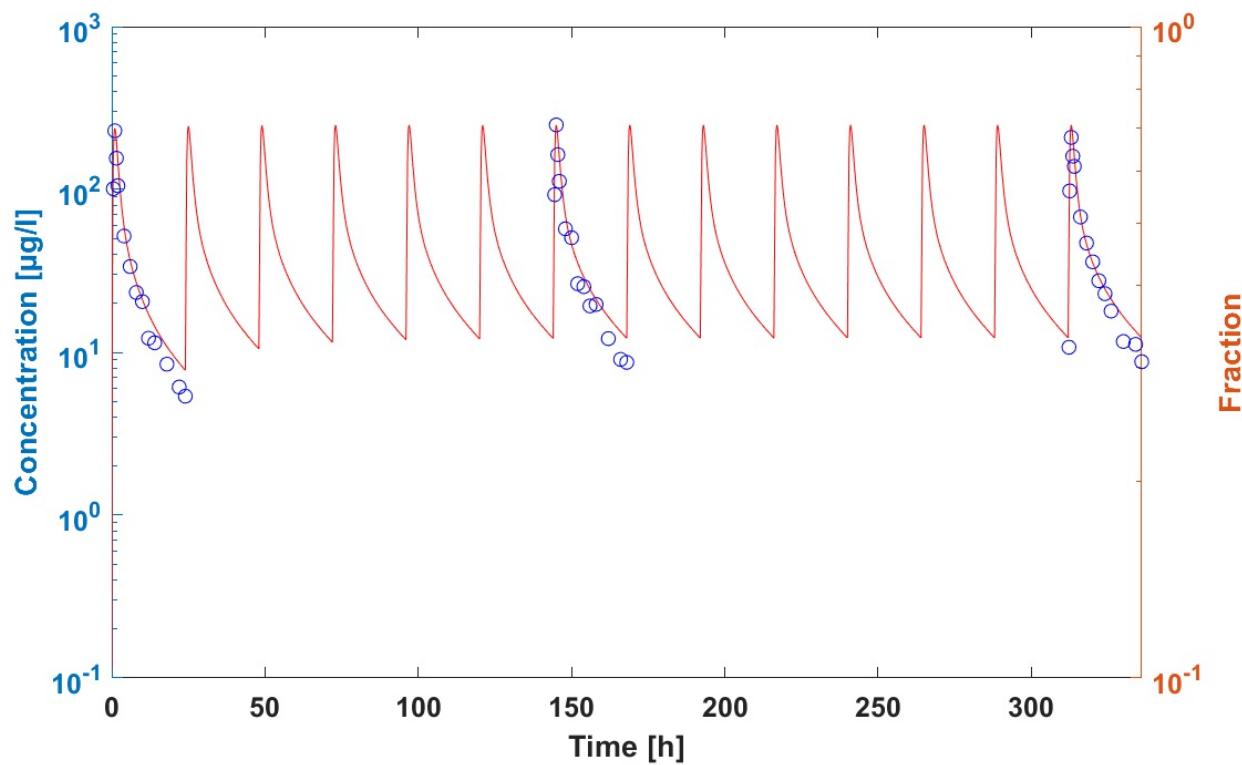
PO MD 10 mg (perm)

D 10 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Iroski 2009 - MAD 10 mg (day 1) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Iroski 2009 - MAD 10 mg (day 7 and day 14) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



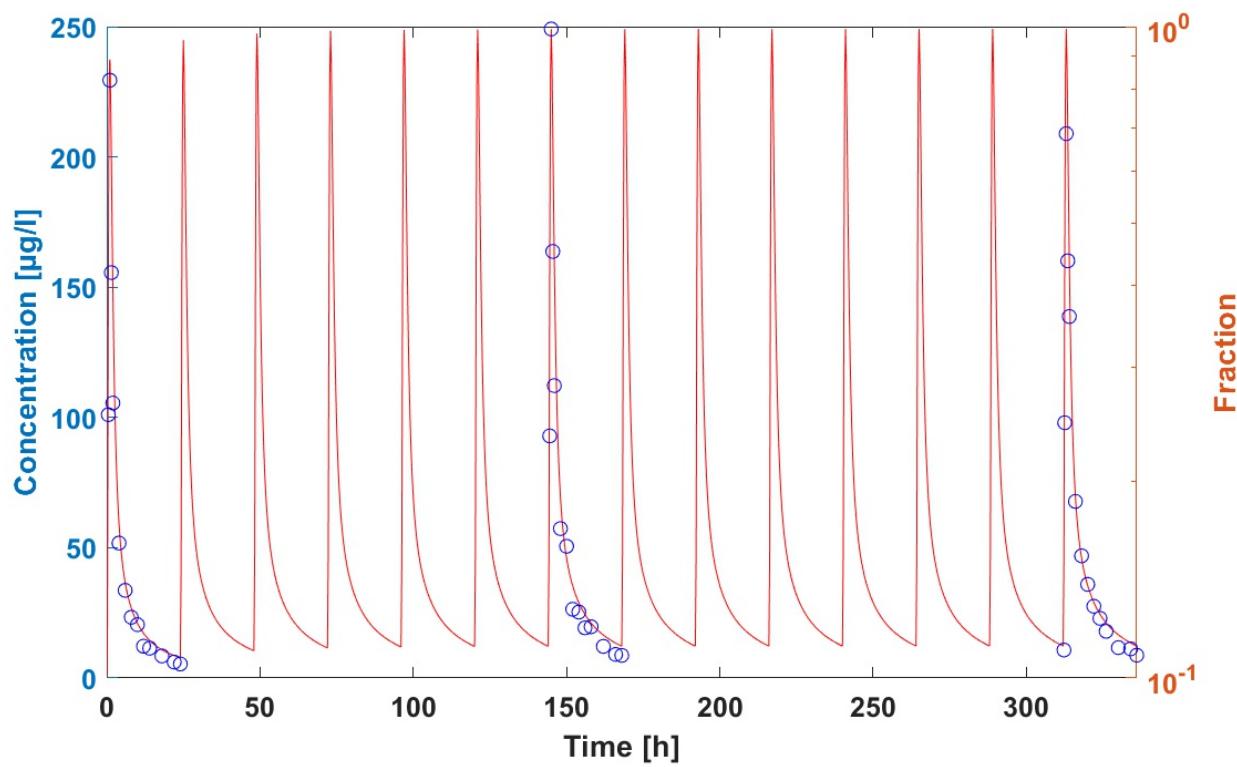
PO MD 10 mg (perm) 1

D 20 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Iroski 2009 - MAD 20 mg (day 1) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Iroski 2009 - MAD 20 mg (day 7 and day 14) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



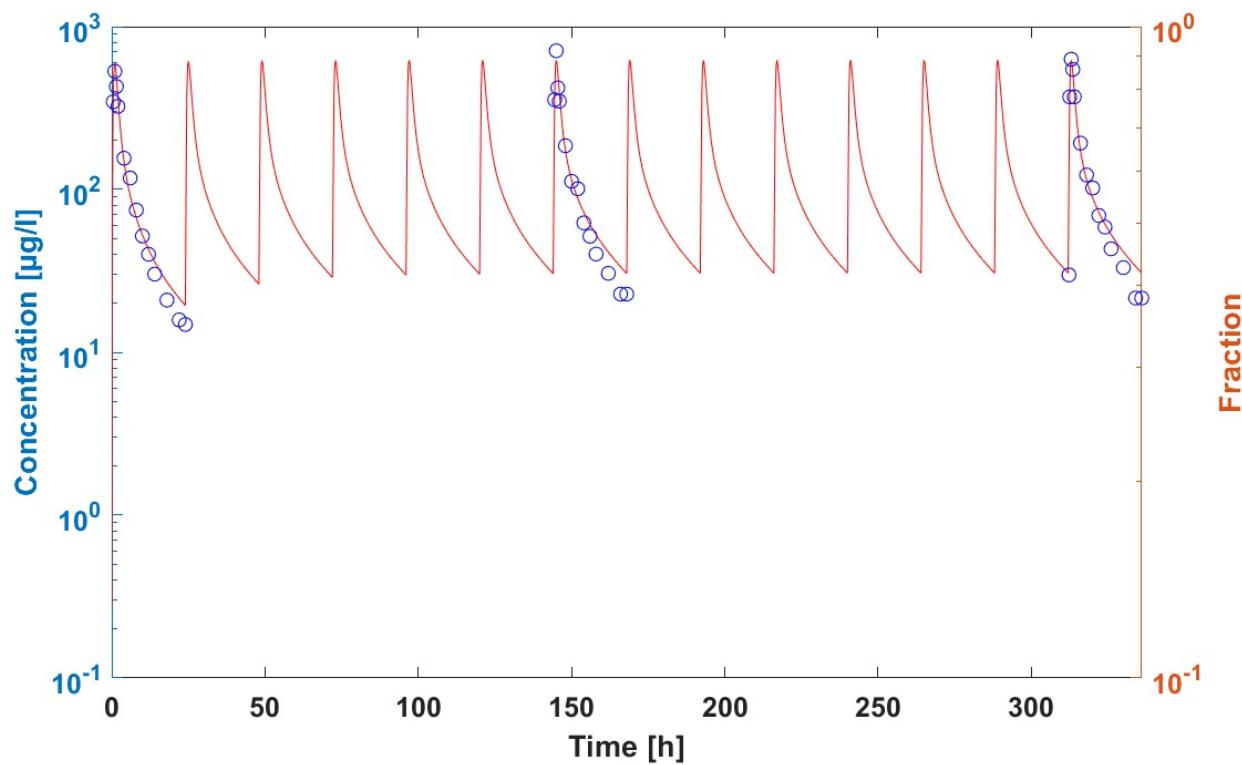
PO MD 20 mg (perm)

D 20 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Iroski 2009 - MAD 20 mg (day 1) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Iroski 2009 - MAD 20 mg (day 7 and day 14) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



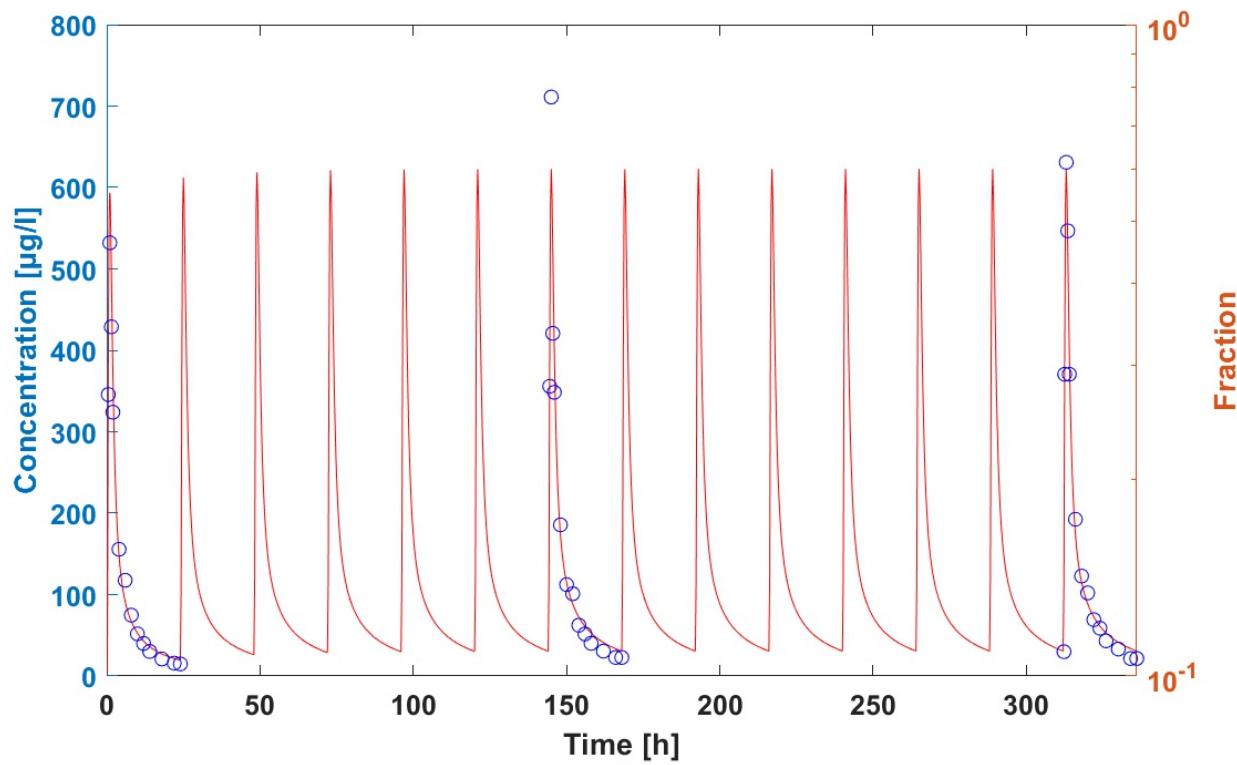
PO MD 20 mg (perm) 1

D 50 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Iroski 2009 - MAD 50 mg (day 1) - Dapagliflozin - PO - 50 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Iroski 2009 - MAD 50 mg (day 7 and day 14) - Dapagliflozin - PO - 50 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



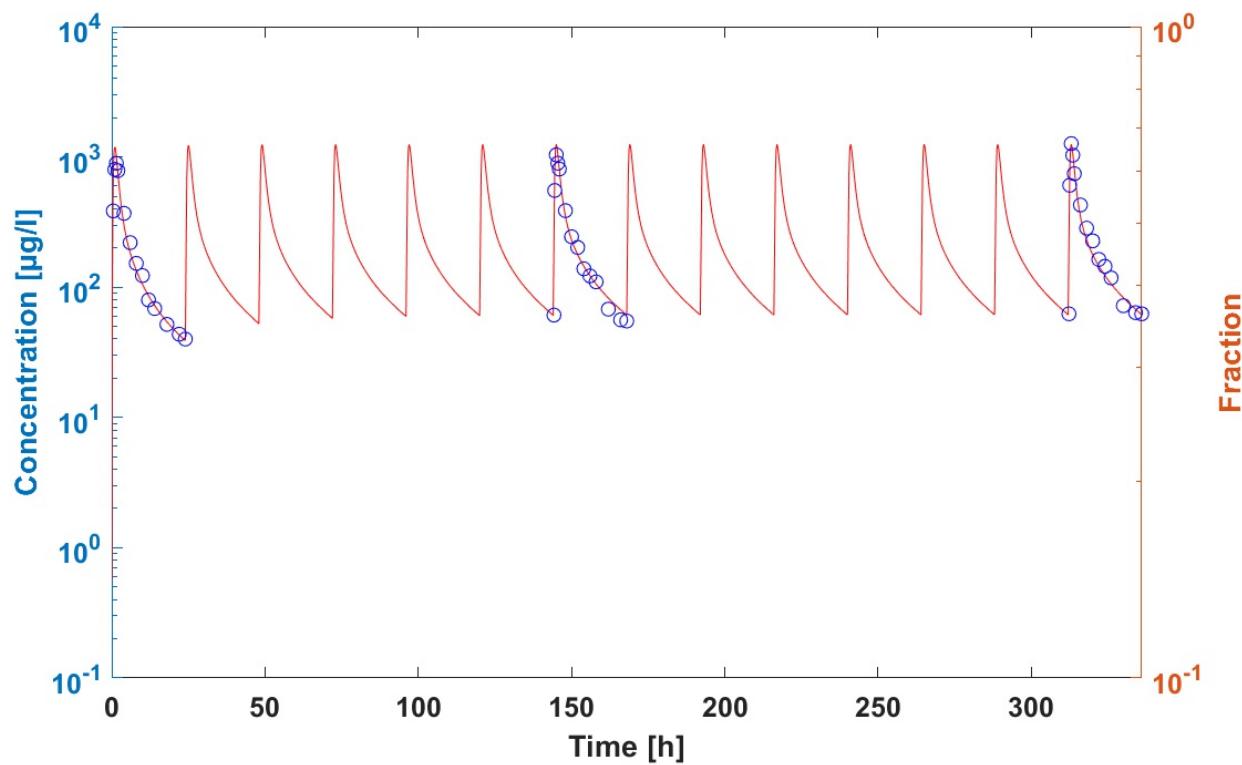
PO MD 50 mg (perm)

D 50 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Iroski 2009 - MAD 50 mg (day 1) - Dapagliflozin - PO - 50 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Iroski 2009 - MAD 50 mg (day 7 and day 14) - Dapagliflozin - PO - 50 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



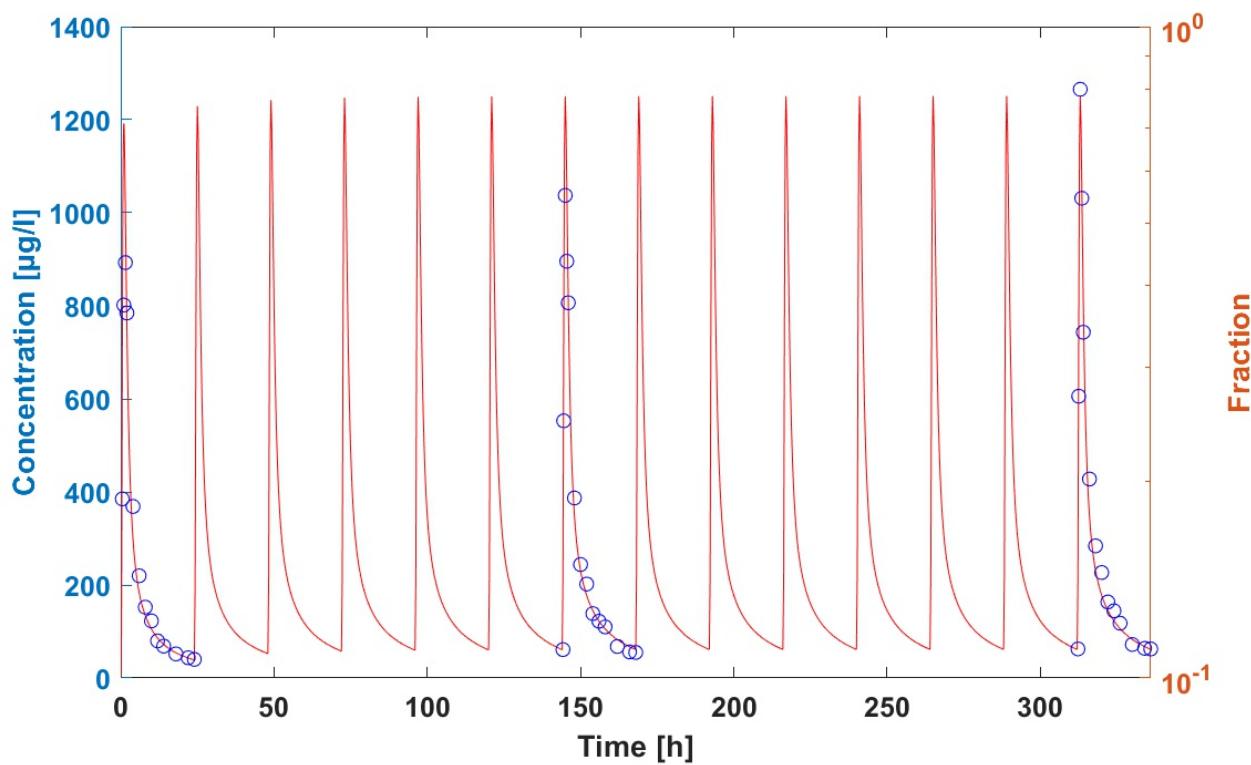
PO MD 50 mg (perm) 1

100 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Isaki 2009 - MAD 100 mg (day 1) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
Isaki 2009 - MAD 100 mg (day 7 and day 14) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



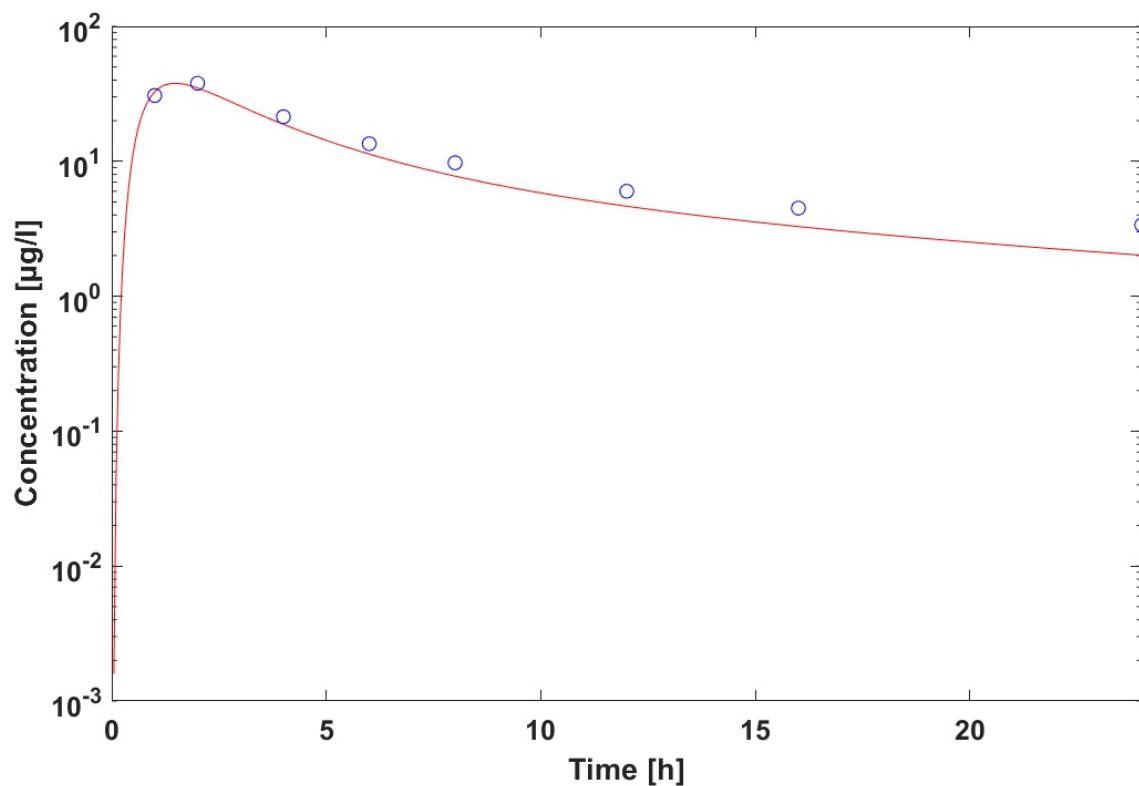
PO MD 100 mg (perm)

100 mg (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
iski 2009 - MAD 100 mg (day 1) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
iski 2009 - MAD 100 mg (day 7 and day 14) - Dapagliflozin - PO - 100 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



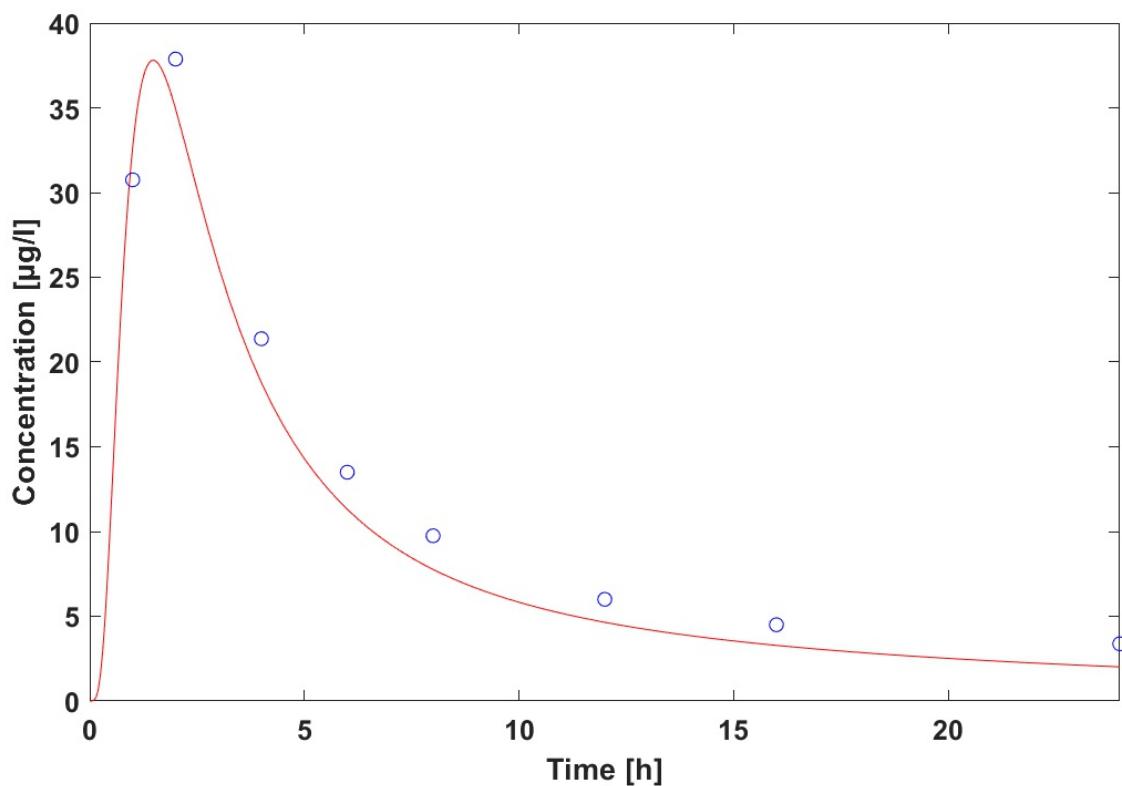
PO MD 100 mg (perm) 1

5g IR tablet (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
5 - Study 1 Treatment A (single oral doses) - Dapagliflozin - PO - 5 mg - Plasma - agg. (n=36)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



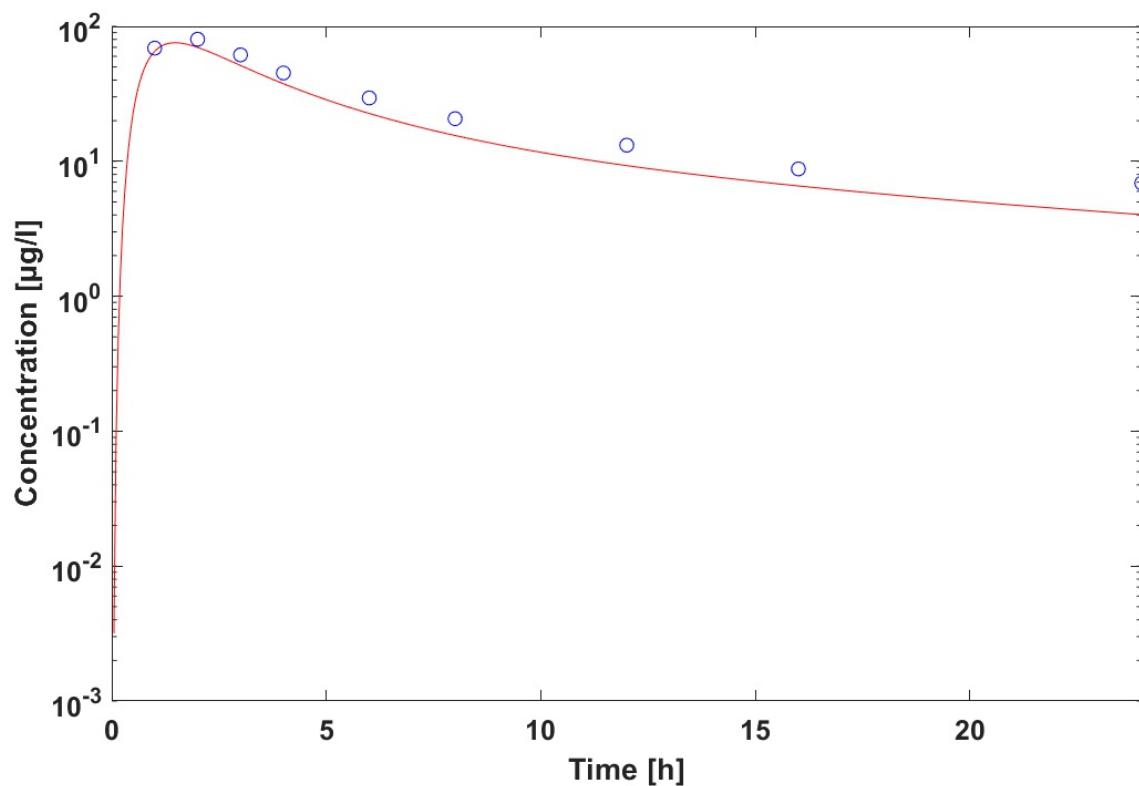
PO SD 5 mg IR tablet (perm)

1g IR tablet (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
5 - Study 1 Treatment A (single oral doses) - Dapagliflozin - PO - 5 mg - Plasma - agg. (n=36)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



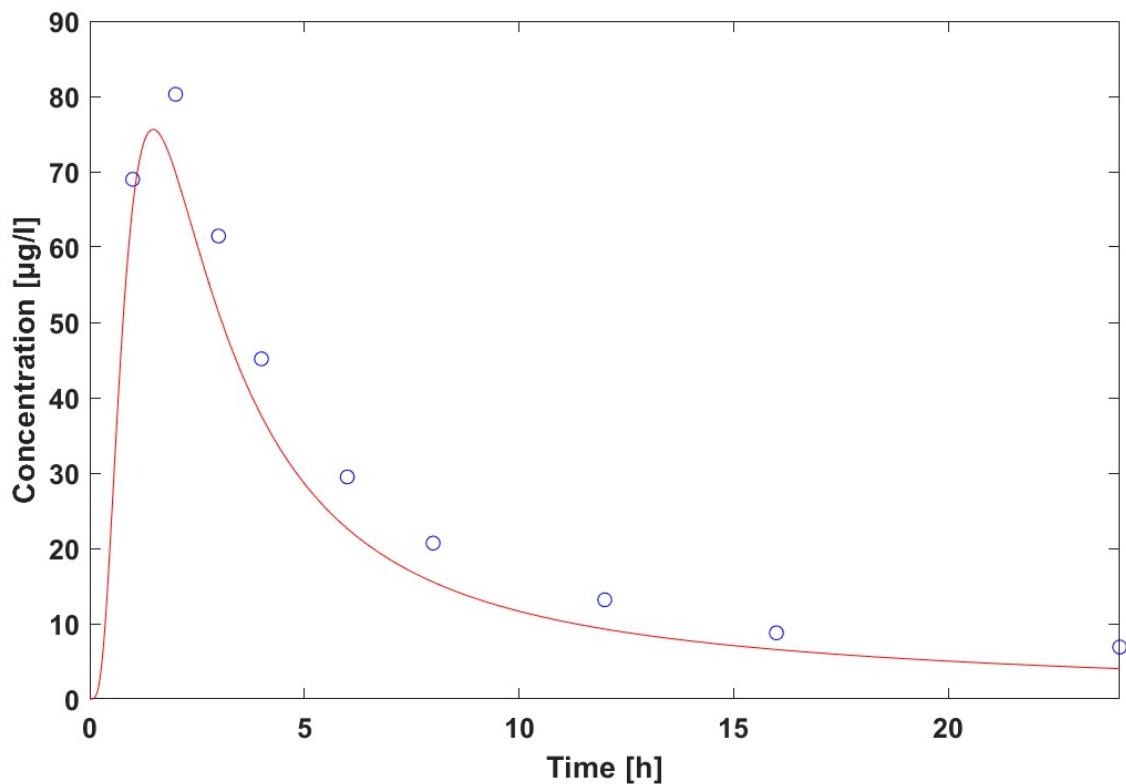
PO SD 5 mg IR tablet (perm) 1

IR tablet (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
i - Study 2 Treatment A (single oral doses) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=36)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



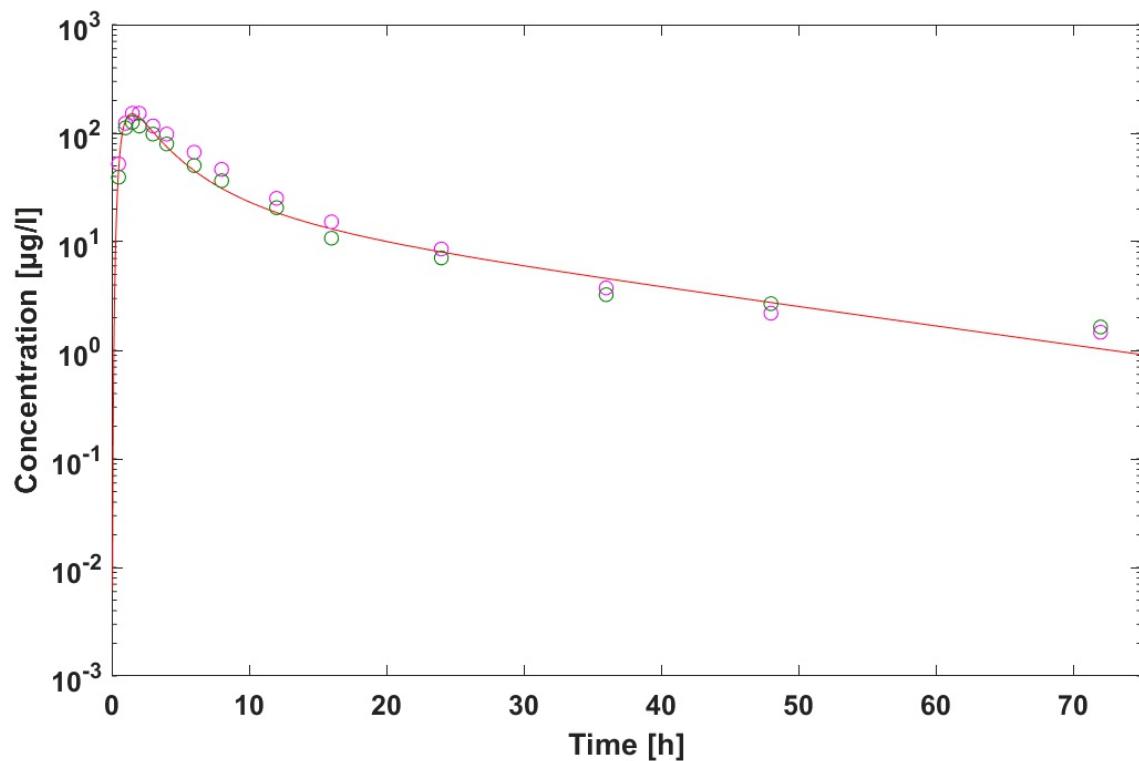
PO SD 10 mg IR tablet (perm)

1g IR tablet (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
i - Study 2 Treatment A (single oral doses) - Dapagliflozin - PO - 10 mg - Plasma - agg. (n=36)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



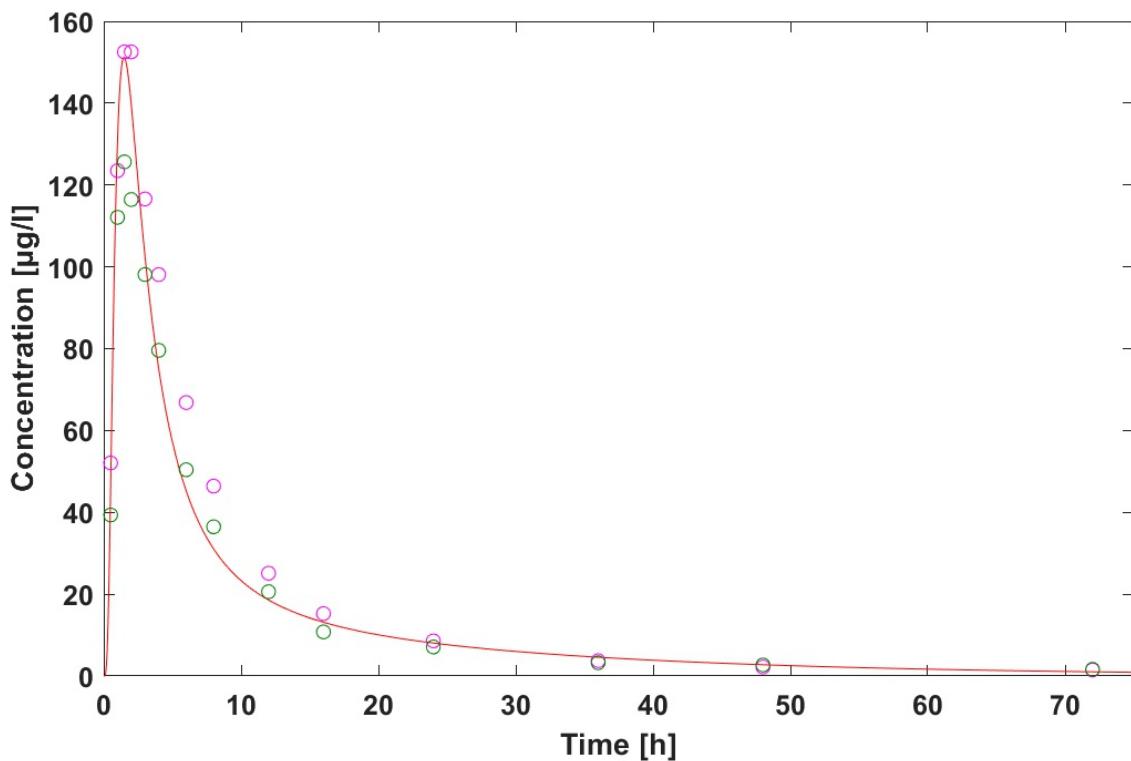
PO SD 10 mg IR tablet (perm) 1

m)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
idy 3: 20 mg Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=18)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
idy 2: 20 mg Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=18)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



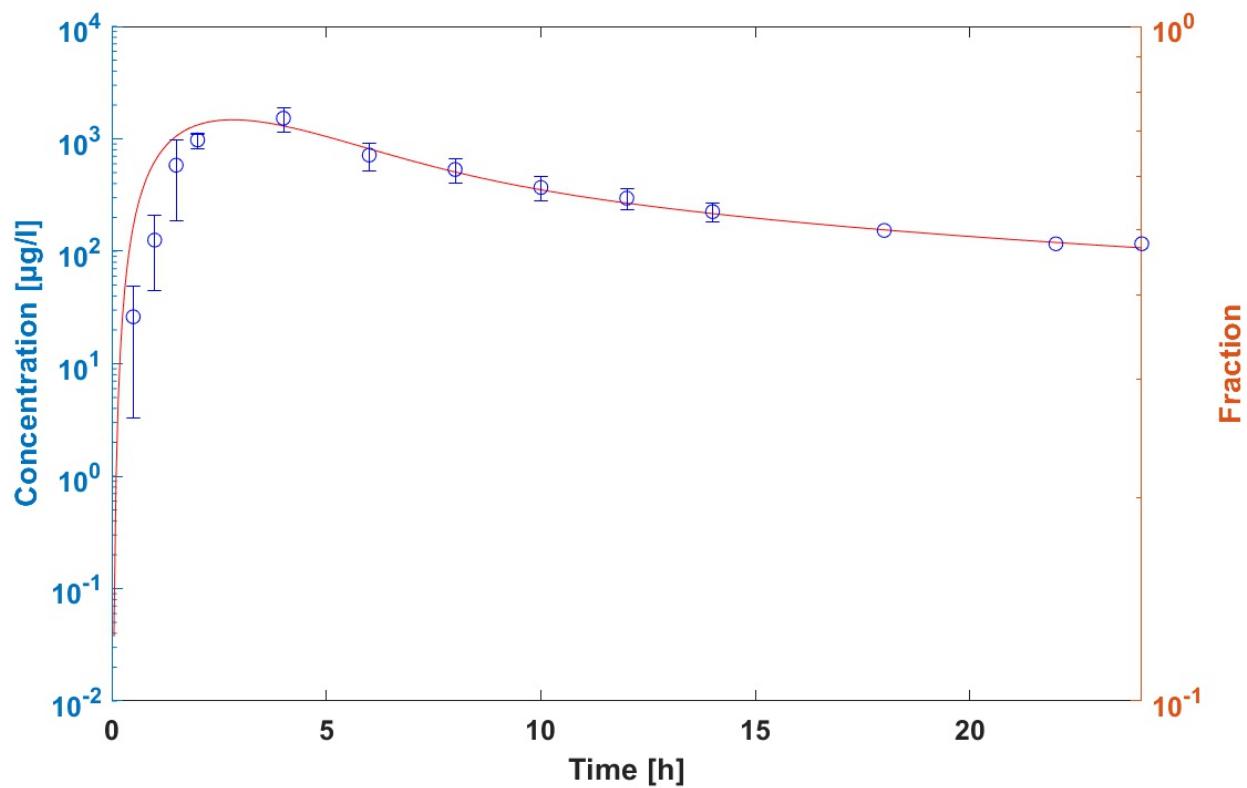
PO SD 20 mg IR tablet (perm)

m)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
idy 3: 20 mg Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=18)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean
idy 2: 20 mg Control (Perpetrator Placebo) - Dapagliflozin - PO - 20 mg - Plasma - agg. (n=18)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



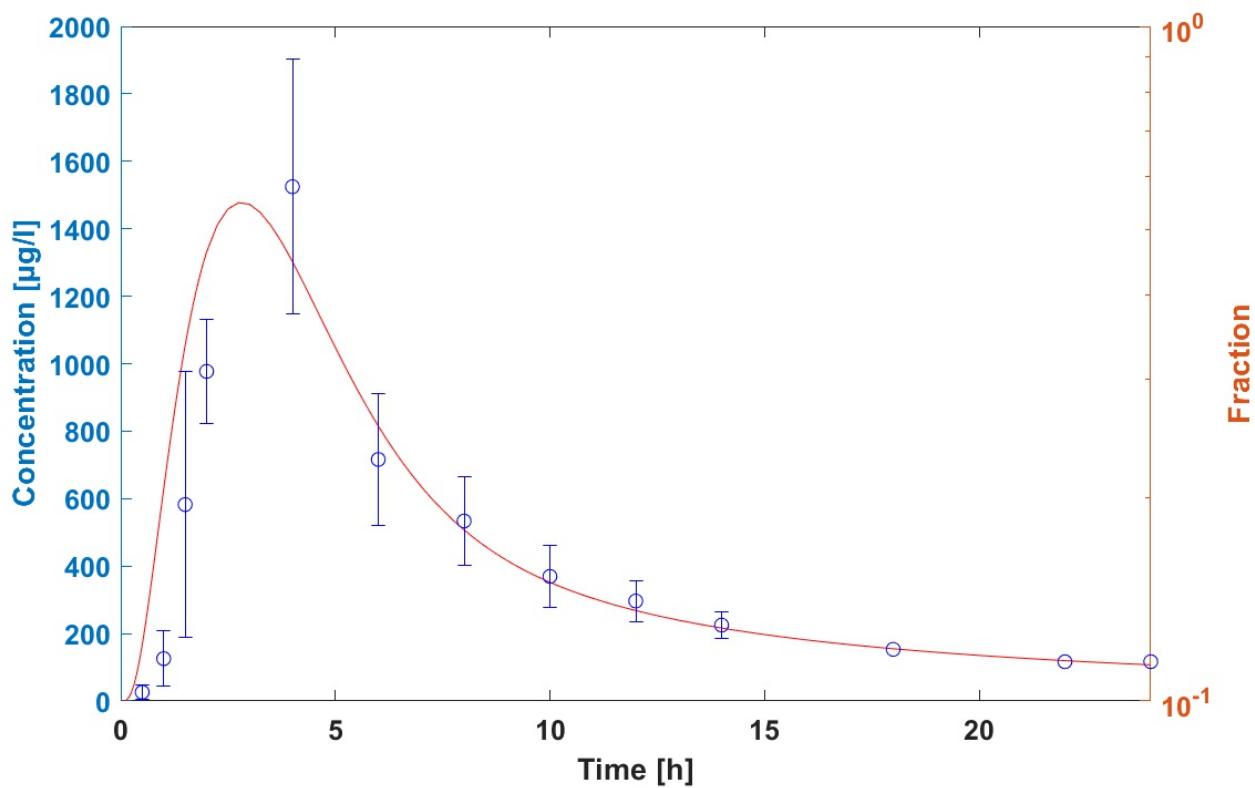
PO SD 20 mg IR tablet (perm) 1

PO SD 250 mg fed (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Komoroski 2009 - SAD 250 mg fed - Dapagliflozin - PO - 250 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO SD 250 mg fed (perm)

PO SD 250 mg fed (perm)-Dapagliflozin-Peripheral Venous Blood-Plasma-Concentration
Komoroski 2009 - SAD 250 mg fed - Dapagliflozin - PO - 250 mg - Plasma - agg. (n=6)-Dapagliflozin-Peripheral Venous Blood-Plasma-ArithmeticMean



PO SD 250 mg fed (perm) 1

4 Conclusion

The final dapagliflozin PBPK model applies metabolism by and adequately describes the pharmacokinetics of dapagliflozin in adults receiving SD, MD of dapagliflozin ranging from ...mg, includingdifferent oral formulations.

This model could be applied for the investigation of DDI, and translation to special populations such as pediatrics with regard to ... metabolism.

5 References

dummy 2019 Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Merschman SA, Strohmaier KM, Ramael S, Lasseter KC, Stone JA, Gottesdiener KM, Wagner JA. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008 Feb;83(2):293-9. Epub 2007 Aug 22.