Inhalation model user guide

Moriah Pellowe, Andrea Edginton

1 Introduction

Drug absorption in the lungs is a complex biological process that is critical in accurately predicting drug concentration levels within the body after pulmonary drug administration.

This work presents a mechanistic physiologically-based pharmacokinetic (PBPK) model that brings together lung anatomy, particle deposition, particle dissolution, and mucociliary clearance from previous work and connects it to a two-compartment model. The following model has been implemented in MoBi to allow for easy integration with PK-Sim. The model structure is capable of capturing the observed behaviour of molecules of varying solubilities (see the PowerPoint in the GitHub repository for more details).

The model takes in parameters describing the inhaled molecule and the lung. Then, it returns the amount of molecule in each of the compartments of lung (epithelial lining fluid, epithelium, and subepithelium), the extrathoracic region, the central compartment, and the peripheral compartment.

In the following sections, this document will present the theoretical model, the implementation of this model in MoBi, and a tutorial walking the user through the setup and simulation of this model.

2 Theoretical model

Lung anatomy

The lung structure is based on the Weibel lung model (Weibel, 1963), which assumes that the lung consisted of 24 generations with regular dichotomy, i.e. symmetric branching of the airways at each generation. The first 16 generations correspond to the tracheobronchial region of the lung, and the final 8 generations correspond to the alveolar region.

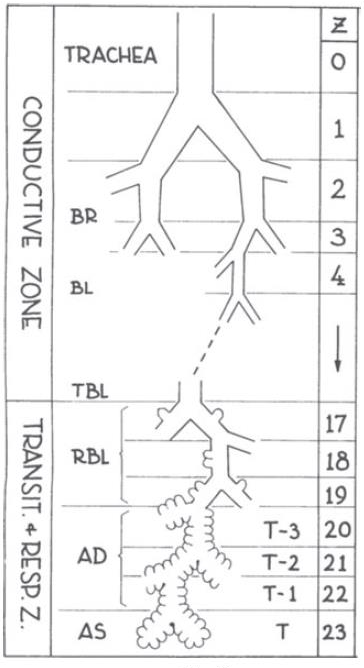


Fig. 82

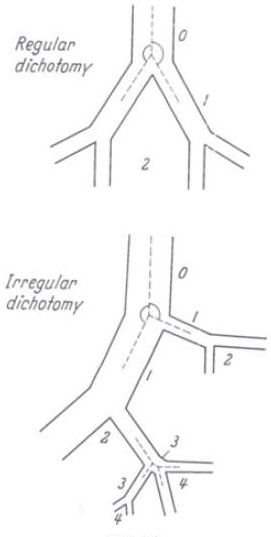


Fig. 83

Figure 1: Weibel model for lung anatomy. Figure 82 from Weibel (1963).

The compartmentalization of each of the lung generations is based on previous work (Boger & Wigstrom, 2018). In each generation of the lung, it is assumed that there are three main compartments: the epithelial lining fluid (ELF), the epithelium, and the subepithelium, each in concentric circles around the lung airway. The subepithelium is then connected to the central compartment.

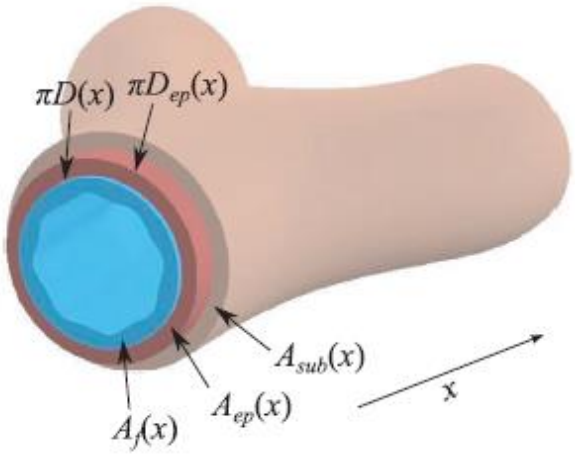


Figure 2: Diagram demonstrating the three main compartments of the lung. Figure 1 from Boger & Wigstrom (2018).

Particle deposition

In the absence of particle deposition information, the particle deposition framework follows the implementation of Boger & Wigstrom (2018), which is based on empirical equations from previous work (Yu & Diu, 1982). In this implementation of particle deposition, four mechanisms are considered: extrathoracic deposition, inertial impaction, gravitational sedimentation, and diffusion. These mechanisms occur with different probabilities during the inhale, breath hold, and exhale phases of the breath, and each of these probabilities is calculated based on empirical equations. One assumption of this implementation is that all the drug is deposited in a single breath cycle, and it is deposited in the extrathoracic region and the epithelial lining fluid of (potentially) all the lung generations

Particle dissolution

Particle dissolution was based on the particle dissolution that has previously been implemented in PK-Sim and MoBi for oral absorption of particles (Willmann et al., 2010). Additional simplifying assumptions were made: 1) particles do not precipitate, and 2) the solubility of the drug is constant across the generations of the lung, 3) the unbound tissue-plasma partition coefficient for the lung is equal to the unbound tissue-ELF partition coefficient, 4) the solubility in the epithelial lining fluid is equal to the solubility at reference pH.

All drug that is deposited in the extrathoracic region is immediately dissolved as we did not make any assumptions about the oral absorption model. The model can be configured to allow for drug in both solid and liquid forms within the extrathoracic region. Then, an oral absorption model can be connected to the inhalation model to handle the particle dissolution and absorption of the drug in the extrathoracic region.

For the drug that is deposited in the epithelial lining fluid of the lung, unbound drug is subject to passive diffusion between the epithelial lining fluid and the epithelium. There is also passive diffusion between the epithelium and the subepithelium as well as between the subepithelium and the central compartment. The molecule's permeability is calculated exactly as in the gut model for the passive diffusion between the three main compartments of the lung (ELF, epithelium, subepithelium). For the passive diffusion between the subepithelium and the central compartment, the rate of mass transfer is assumed to be proportional to the cardiac output. These assumptions of mass transfer between compartments are based on a previous PDE model (Boger & Wigstrom, 2018) but with averaging over the length of each generation due to the discretization of the model.

Mucociliary clearance

The model assumptions for mucociliary clearance are based on previous work (Boger & Wigstrom, 2018). It is assumed that solid drug particles (and not liquid drug) move upwards across the tracheobronchial region where it is then swallowed and deposited into the extrathoracic region. It is assumed that the mucociliary clearance rate is proportional to the ratio of cross-sectional areas between the current lung generation and the uppermost generation, corresponding to the trachea.

3 Implementation of model in MoBi

Particle deposition

The inhalation model includes two R scripts that are used to populate particle deposition, i.e. the initial conditions for the solid drug particles. These two scripts are **populate_model.R** and **custom_deposition.R**.

populate_model.R is used in the absence of deposition information as this script will use empirical equations (Yu & Diu, 1982) to calculate the proportion of drug deposited in each of the lung generations as well as the extrathoracic region based on the particle size distribution and the oral, lung, and device bioavailabilities. The script assumes a normal distribution for the particles and thus takes in the mean and the standard deviation of the particle distribution as input. It also calculates the proportion of particles of a given particle radius per volume of drug, which is used to calculate the number of particles to be considered.

The user may have information about the proportion of drug deposited in the extrathoracic region, the lung, and/or the specific regions of the lung. In this case, the **custom_deposition.R** script can be used to directly specify the amount of drug to be deposited into the lung. Bioavailabilities (oral, lung, and device) can still be defined in this case.

Two things to note: in both cases, the oral bioavailability defined in the R scripts is set in the updated MoBi file as oral bioavailability is involved in mucociliary clearance. On the other hand, the lung and device bioavailabilities are only used in the R script to adjust the amount of drug that is deposited into the lung. Secondly, these particle deposition fractions are independent of dose as the dose is set within the MoBi file.

Mucociliary clearance

In this discrete model, mucociliary clearance is implemented as a recurring shift of solid drug particles from a slice of lung to the slice above it. These slices are set to have equal residence time, and in this model, the solid drug is shifted every 15 minutes.

Table 1: Discrete approximation of MCC.

Generation Number	Residence time [min] (Boger & Wigstrom, 2018)	Approximation [min]
1	28.5	30
2	24.62	30
3	21.2	15
4	18.64	15
5	48.2	45
6	67.34	60
7	88.57	90
8	110.19	105
9	140.35	135
10	174.45	180
11	209.86	210
12	253.31	255
13	282.78	285
14	310.16	315
15	326.56	330
16	358.75	360
SUM	2463.48	2460

The mean residence time of each generation was calculated based on assumptions from previous work (Boger & Wigstrom, 2018). The residence time within each generation was calculated as the time for drug to traverse the full length of the generation, i.e. generation length divided by mucociliary clearance rate. This time was then rounded to the nearest increment of 15 minutes.

Application stop condition

The lung model mechanisms of particle dissolution and mucociliary clearance end once the total amount of drug summed over all particle bins is negligible, i.e. less than 1e-16 umol.

Default parameter values

Lung generation characteristics (length, diameter, and number of airways per generation) followed the Weibel lung model, which was based on lung airway casts (Weibel, 1963).

i	N_i	D_i [cm]	L_i [cm]
1	1	1.539	10.26
2	2	1.043	4.07
3	4	0.71	1.624
4	8	0.479	0.65
5	16	0.385	1.086
6	32	0.299	0.915
7	64	0.239	0.769
8	128	0.197	0.65
9	256	0.159	0.547
10	512	0.132	0.462
11	1024	0.111	0.393
12	2048	0.093	0.333
13	4096	0.081	0.282
14	8192	0.070	0.231
15	16384	0.063	0.197
16	32768	0.056	0.171
17	65536	0.051	0.141
18	131072	0.046	0.121
19	262144	0.043	0.10
20	524288	0.040	0.085
21	1048576	0.038	0.071
22	2097152	0.037	0.060
23	4194304	0.035	0.050
24	8388608	0.035	0.043

Figure 3: Table showing the lung generation characteristics of the Weibel model (1963). Here, i refers to the generation number, Ni refers to the number of airways, Di refers to the airway diameter, and Li refers to the length of the lung generation. Note that these values have been scaled to match a functional residual capacity of 3000 mL for the lung. Table S3 from Boger & Wigstrom (2018).

Table 2: Default parameter values for "Spatial Structure" and "Events" building blocks in MoBi implementation.

Parameter name	Default value	Reference
Spatial structure		
Fraction unbound in the ELF	1	Boger & Wigstrom, 2018
Unbound tissue-plasma partition coefficient for the lung	6.5	Boger & Wigstrom, 2018
Maximum mucociliary clearance rate	0.36 cm/min	Boger & Wigstrom, 2018
Blood-plasma ratio	1	Boger & Wigstrom, 2018
Events		
Thickness of unstirred water layer	20 µm	Willmann et al, 2010
Dose	0 mg	
Start time	0 hr	

Inhalation model with two compartment model

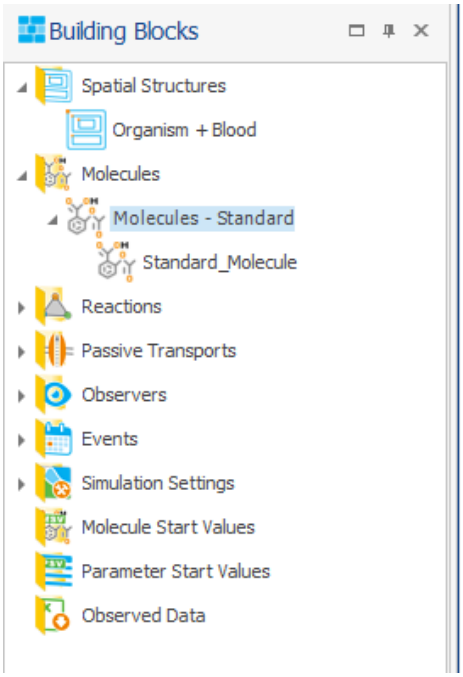
The file **inhalation_model_two_compt_1_Bin_v1.2.mbp3** includes the inhalation model connected to a two-compartment model (as shown in the model diagram). Additional configuration is required if the inhalation model is to be connected to the full body model in PK-Sim or to another MoBi/PK-Sim model.

Model diagram

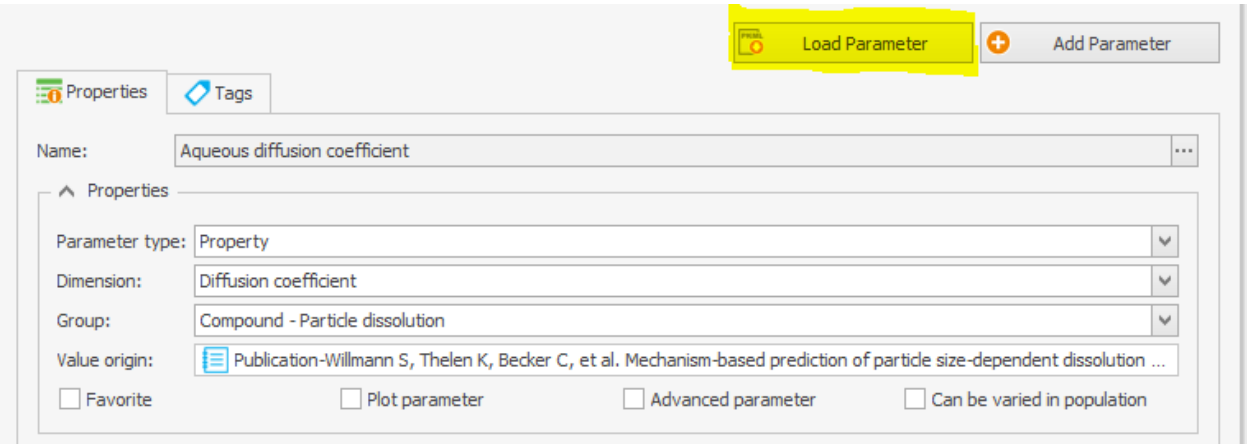
4 Tutorial: Setup and simulation of model

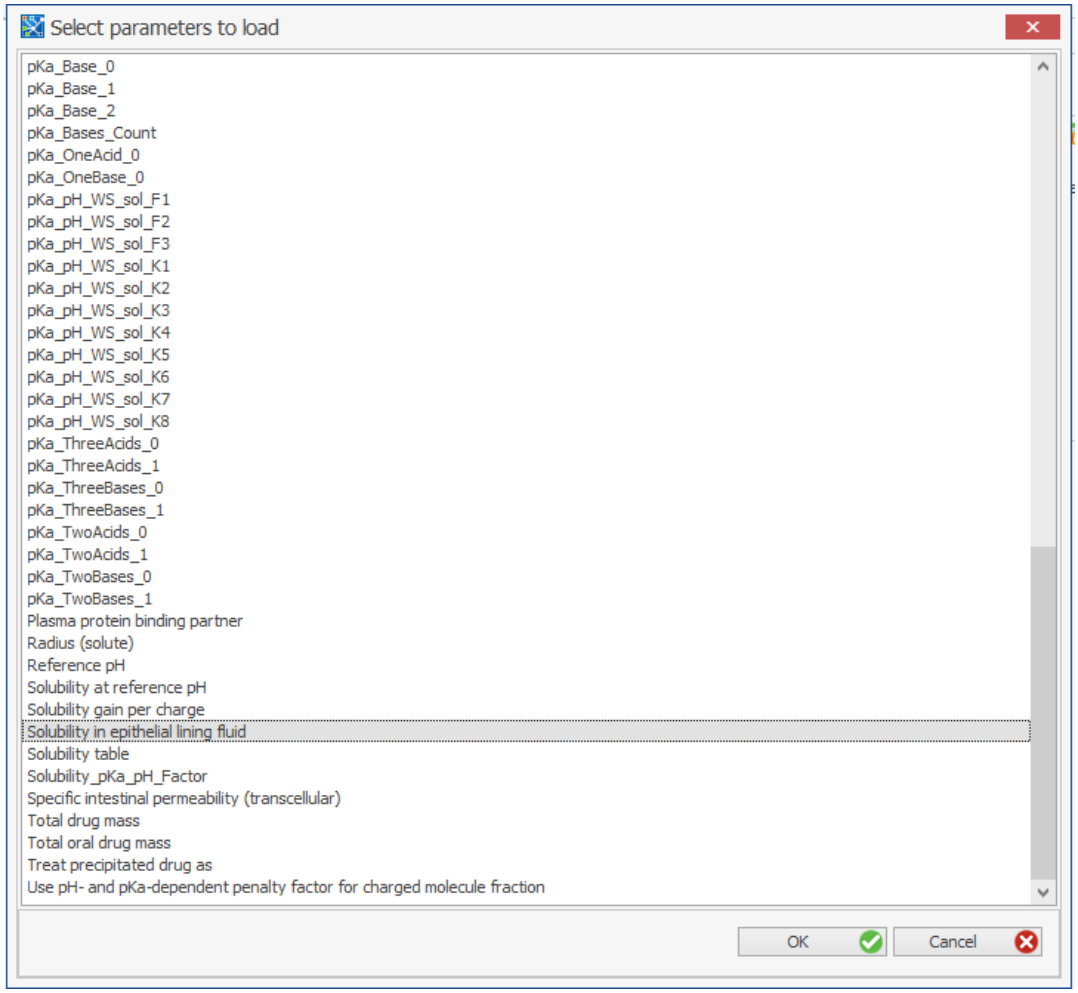
This tutorial will outline a step-by-step implementation of a ciprofloxacin inhaled simulation using the inhalation model connected to a two-compartment model. This inhalation model will require both MoBi and R with the ospsuite R package installed. Note that files mentioned below may be referenced without their version number as these files may be updated in the future.

1. Download the MoBi project file **inhalation_model_two_compt_1_bin.mbp3** and rename it **ciprofloxacin.mbp3**. Open the MoBi project file.
2. Set up the molecule of interest, i.e. Ciprofloxacin.
    a. Right-click the current Molecules building block "Molecules – Standard" and **Delete…** this building block.



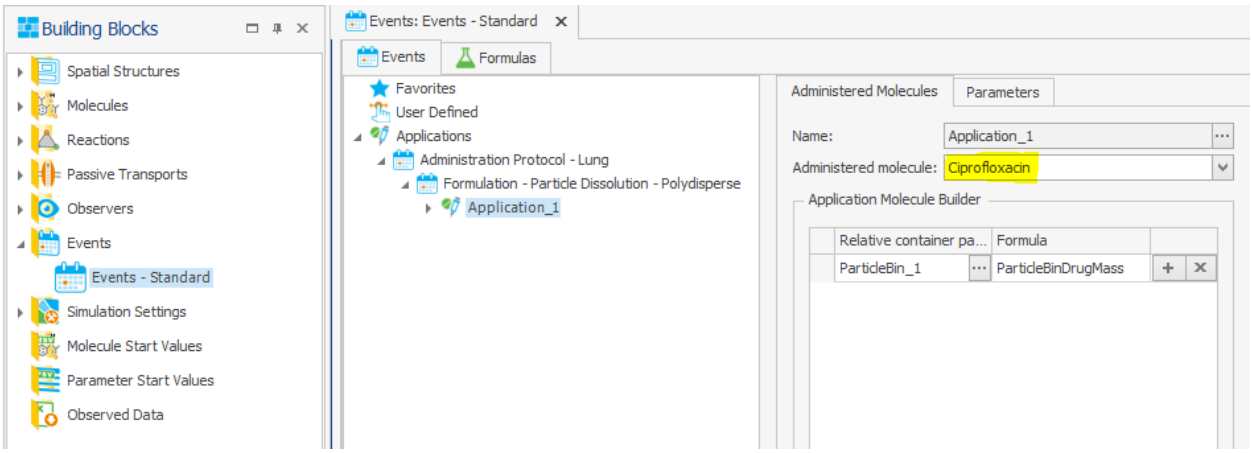
    b. Right-click the "Molecules" building block folder and **Create Molecule Building Block…** and call the new molecule building block "Molecules".
    c. In the white space below **Favorites** and **User Defined**, right-click then **Add PK-Sim Molecule…** and call the new PK-Sim Molecule "Ciprofloxacin". Fill in the physicochemical properties of salbutamol as given below. These physicochemical properties will be used to set up the other molecule parameters.
        i. **Molecular weight**: 331.34 g/mol
        ii. **Lipophilicity**: 0.95 Log units
        iii. **Fraction unbound (plasma, reference value)**: 0.67
        iv. **Solubility at reference pH**: 38.4 mg/mL
    d. Next, we need to add a parameter to the molecule building block that is specific to the inhalation model. Open the **Ciprofloxacin** molecule building block and navigate to **Parameters**. Download the **Standard_Molecule.pkml** file, which contains the parameter that we need. Click **Load Parameter** and navigate to where you have downloaded the **Standard_Molecule.pkml** file and select this file. Then navigate down to "Solubility in epithelial lining fluid" and click OK.





e. Next, we will set up the Events building block to work with the Ciprofloxacin molecule that has just been created.

- **i.** Open the **Events – Standard** building block under the “Events” building block folder.
- **ii.** Open up the tree and navigate to **Application_1** .
- **iii.** Change the **Administered molecule** to Ciprofloxacin.



3. Fill in the parameters for the two compartment model and oral absorption. These parameter values are the result of fitting the two compartment model to ciprofloxacin IV and oral data (not reported).
    a. Right-click the "Parameter Start Values" building blocks folder and **Create Parameter Start Values Building Block…**, and name this parameter start values building block "Ciprofloxacin Parameters" with the following configuration:
        i. **Molecule building block**: Molecules
        ii. **Spatial structure**: Organism + Blood
    b. Update the following parameter values within this parameter start values building block:
        i. **Absorption rate – k_a:** 1.58 1/h
            - Note that this refers to oral absorption.
        ii. **Oral bioavailability – F_oral**: 0.7
        iii. **Time lag of absorption:** 0.39 h
        iv. **Volume [Path Element 1: CentralCompartment]**: 91.7 L
        v. **Elimination rate**: 0.38 1/h
        vi. **k_CP – First-order constant for transfer from central to peripheral compartments**: 0.88 1/h
        vii. **Volume [Path Element 1: PeripheralCompartment]**: 123.28 L
        viii. **k_PC – First-order constant for transfer from peripheral to central compartments**: 0.66 1/h

Parameter Name	Path Element 0	Path Element 1	Path Element 2	Path Element 3	Path Element 4	Start Value
Use pH- and pKa-dependent ...	Ciprofloxacin					0
Kp_u_lung - Unbound tissue-...	Organism	Lung				6.50
Fraction unbound in the epit...	Organism	Lung				1.00
OralApplicationsEnabled	Organism	Lung				1.00
Volume	Organism	ExtrathoracicRegion				1.00 l
Absorption rate - k_a	Organism	ExtrathoracicRegion				1.58 1/h
Oral bioavailability - F_oral	Organism	ExtrathoracicRegion				0.70
Time lag of absorption	Organism	ExtrathoracicRegion				0.39 h
Volume	Organism	CentralCompartment				91.70 l
Blood-plasma ratio	Organism	CentralCompartment				1.00
Cardiac output	Organism	CentralCompartment				5.20 l/min
Elimination rate	Organism	CentralCompartment				0.38 1/h
k_CP - First-order constant f...	Organism	CentralCompartment				0.88 1/h
Volume	Organism	PeripheralCompartment				123.28 l
k_PC - First-order constant f...	Organism	PeripheralCompartment				0.66 1/h
Volume	Organism	ClearedDrug				1.00 l

4. Set up the molecule start values building block for the simulation.
    a. Right-click the "Molecule Start Values" building block and **Create Molecule Start Values Building Block…** , and name this molecule start values building block "Ciprofloxacin MSV" with the following configuration:
        i. **Molecule building block**: Molecules
        ii. **Spatial structure**: Organism + Blood
    b. The inhaled dose will not be configured here but in the **Events** building block at a later step. However, a molecule start values building block is required to create a simulation. Thus, we will use this empty one.
5. This tutorial considers the monodisperse case, i.e. all particle sizes are of the same size. At this step in the simulation setup process, the user can optionally add particle bins if considering a polydisperse case, i.e. having particles of different sizes. See optional step A below on how to set up a polydisperse simulation. Note that the remainder of this tutorial sets up a monodisperse simulation.
6. Set up the inhalation simulation and export the simulation.
    a. Right-click the "Simulations" folder and **Create Simulation…** , and name the simulation "Inhaled ciprofloxacin" with the following configuration. Note that this should already be the configuration since these are the only building blocks available:
        i. **Spatial Structure:** Organism + Blood
        ii. **Molecules:** Molecules
        iii. **Reactions:** Reaction
        iv. **Passive Transports:** Passive Transports
        v. **Observers:** Observer
        vi. **Events:** Events - Standard
        vii. **Simulation Settings:** Simulation Settings 1
        viii. **Molecule Start Values:** Ciprofloxacin MSV
        ix. **Parameter Start Values:** Ciprofloxacin Parameters
    b. Note that we can try to run the simulation, but we will not produce any results. This is because the administration of inhaled drug has not been configured yet. This will be done outside of MoBi in R. To do this, we will need to export the pkml file.
        i. Right-click the simulation and **Save Simulation to MoBi pkml file Format…** and save as **inhaled_ciprofloxacin.pkml** .
7. In R, use the **populate_model.R** and **configure_inhalation_parameters.R** scripts included with the inhalation model to populate the initial conditions of the simulation. You may do this with any code editor or IDE (integrated development environment), but for instructional purposes, the instructions and screenshots are from using RStudio.
    a. Download the files **populate_model.R** , **custom_deposition.R** , and **configure_inhalation_parameters.R** into the same directory.
    b. Open RStudio and navigate to the folder where you have saved **inhaled_ciprofloxacin.pkml** .
    c. The following arguments will need to be configured in order to run the **populate_model.R** script. Note that these values have already been configured in the **configure_inhalation_parameters.R** script.
        i. Pkml file name : **inhaled_ciprofloxacin.pkml**

ii. Molecule name : Ciprofloxacin
iii. Particle diameters of each bin (in dm) : 2.6e-5
iv. Geometric mean of particle radius (in dm) : 2.6e-5 / 2
v. Geometric standard deviation of particle radii (in dm) : 1.8e-5 / 2
vi. Oral bioavailability : 0.7
vii. Lung bioavailability : 0.2509824
viii. Log-normal distribution : TRUE
ix. Note that there are additional parameters that can be configured using the **populate_model.R** script including breathing frequency, fraction of breath that is inspiratory, breath hold time, delay volume, tidal volume, and bolus volume.

d. Run the first 20 lines of the **configure_inhalation_parameters.R** script by highlighting the code and clicking **Run**. Alternatively, you can run each individual line of code by pressing **Ctrl + Enter** while your cursor is on each line of code.

configure_inhalation_parameters.R

Source on Save | Run | Source

```
# Reset environment
rm(list=ls())

# Load scripts
source("populate_model.R")
source("custom_deposition.R")

molecule_name <- "Ciprofloxacin"
particle_diameters_dm <- 2.6e-5
geomean_particle_radius_dm <- 2.6e-5/2
gsd_particle_radius_dm <- 1.8e-5/2

########## Empirical equations ##########
# Inhaled
pkml_file <- "inhaled_ciprofloxacin.pkml"
oral_bioavailability <- 0.7
lung_bioavailability <- 0.2509824

populate_model(pkml_file, molecule_name, particle_diameters_dm, geomean_particle_radius_dm, gsd_particle_radius_dm,
               oral_bioavailability, lung_bioavailability, logScale = TRUE)

########## Stass et al (2017) deposition ##########
# Inhaled
pkml_file <- "inhaled_ciprofloxacin.pkml"
deposition_fractions <- matrix(c(0.394, rep(0.015875, 24)), nrow=25, ncol=1)
oral_bioavailability <- 0.7
# Lung and device bioavailabilities are already taken into account in deposition_fractions, so the values are left at 1

custom_deposition(pkml_file, molecule_name, particle_diameters_dm, geomean_particle_radius_dm, gsd_particle_radius_dm,
                  deposition_fractions, oral_bioavailability, logScale = TRUE)
```

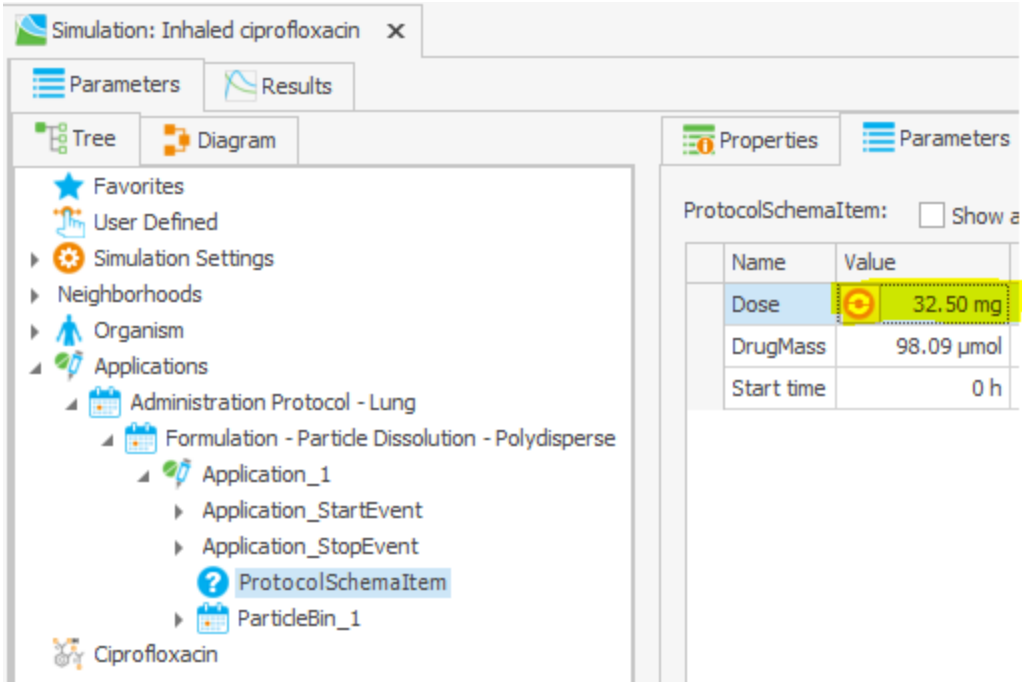
e. Note that in the output, there are 25 generations shown. This is because the extrathoracic region is included here as the first generation. Additionally, you should find that a pkml file has been generated called **populated_inhaled_ciprofloxacin.pkml .** This is the updated simulation file.

f. Note that this process will need to be repeated and a different file generated for every particle size distribution under consideration.

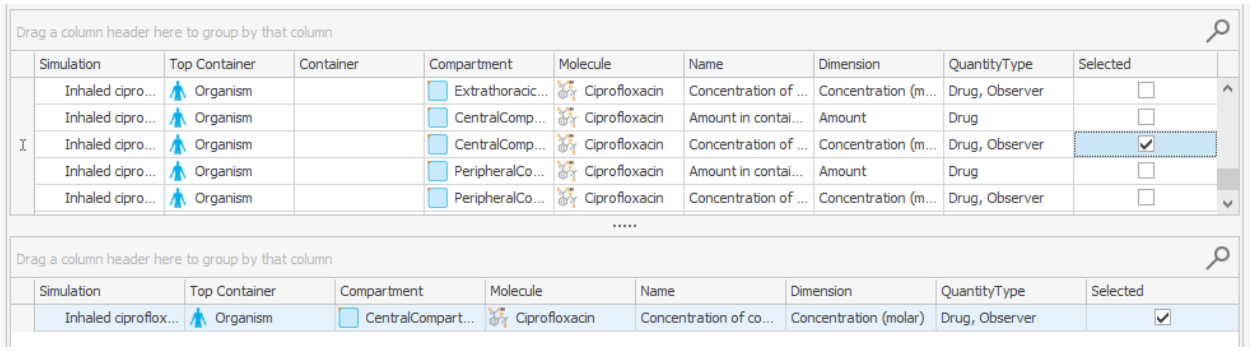
Output

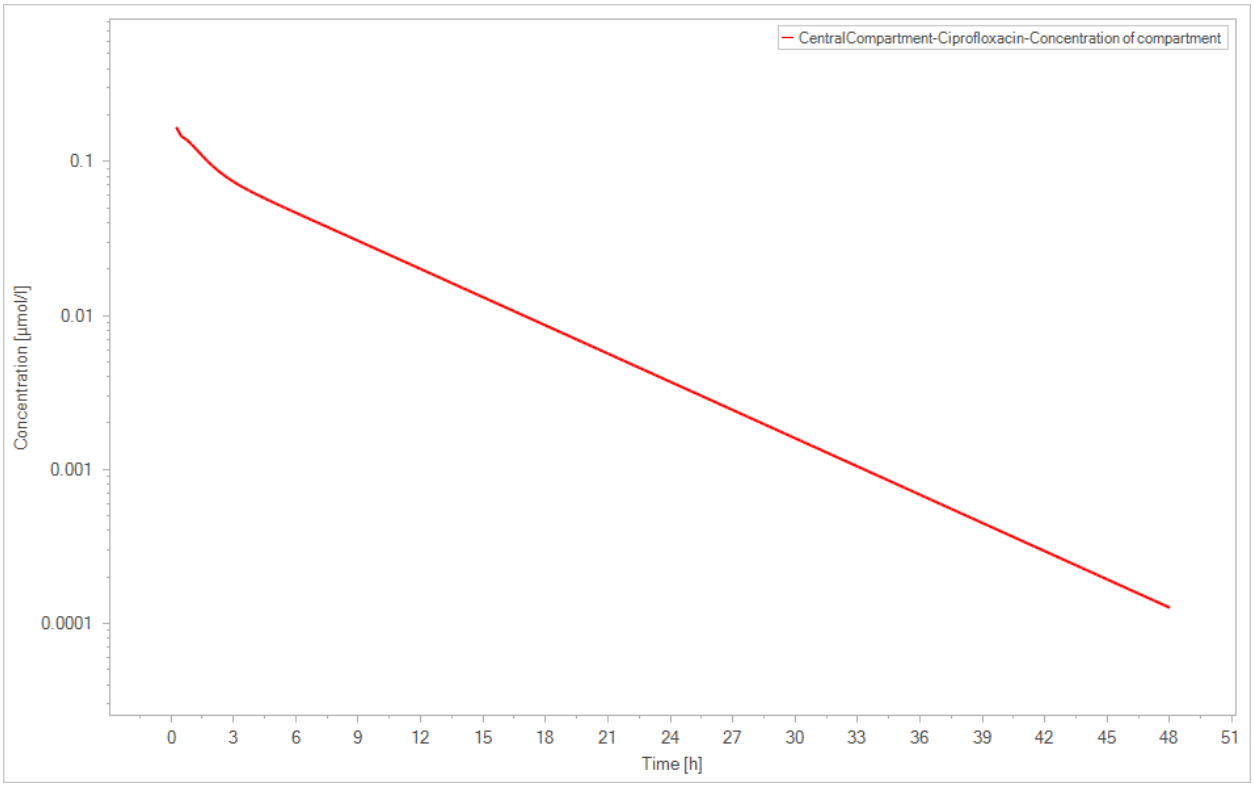
```
> # Reset environment
> rm(list=ls())
>
> # Load scripts
> source("populate_model.R")
> source("custom_deposition.R")
>
> molecule_name <- "Ciprofloxacin"
> particle_diameters_dm <- 2.6e-5
> geomean_particle_radius_dm <- 2.6e-5/2
> gsd_particle_radius_dm <- 1.8e-5/2
>
> ########## Empirical equations ##########
> # Inhaled
> pkml_file <- "inhaled_ciprofloxacin.pkml"
> oral_bioavailability <- 0.7
> lung_bioavailability <- 0.2509824
>
> populate_model(pkml_file, molecule_name, particle_diameters_dm, geomean_particle_radius_dm, gsd_particle_radius_dm,
+                          oral_bioavailability, lung_bioavailability, logScale = TRUE)
Loading required package: rClr
Loading the dynamic library for Microsoft .NET runtime...
Loaded Common Language Runtime version 4.0.30319.42000

[1] "Note: Since logScale==TRUE, the mean is interpreted as the geometric mean and the sd as the geometric standard deviation."
$number_of_particles_factor
[1] 1.086629e+14

$distribution_across_gens
             [,1]
 [1,] 0.115475964
 [2,] 0.004304984
 [3,] 0.003764628
 [4,] 0.003402754
 [5,] 0.003235231
 [6,] 0.006477385
 [7,] 0.007449715
 [8,] 0.007632506
 [9,] 0.006996685
[10,] 0.006956297
[11,] 0.006287771
[12,] 0.005558908
[13,] 0.005095836
[14,] 0.004390305
[15,] 0.004103594
[16,] 0.004285539
[17,] 0.005292981
[18,] 0.006847163
[19,] 0.010908029
[20,] 0.017771878
[21,] 0.029457945
[22,] 0.048623937
[23,] 0.023155895
[24,] 0.000000000
[25,] 0.000000000
```

8. Load the newly generated file **populated_inhaled_ciprofloxacin.pkml** into MoBi.
    a. Double-click the newly generated file **populated_inhaled_ciprofloxacin.pkml** and MoBi will open with your new simulation already loaded.
    b. **Important note:** Only the simulation parameters have been updated. Thus, do NOT update the simulation building blocks from the individual building blocks as they will over-write the parameters that have been updated by the R script.
9. Update the dose within the simulation, run the simulation, and compare to observed data.
    a. Open the simulation **Inhaled ciprofloxacin** and click the **Parameters** tab and the **Tree** view.
    b. Navigate to the dose by expanding the following hierarchy: **Applications → Administration Protocol – Lung → Formulation – Particle Dissolution – Polydisperse → Application_1 → ProtocolSchemaItem** .
    c. Click the **Parameters** tab in the adjacent window to the right. For the parameter **Dose**, update the value to 32.5 mg. Note that this change has only been made in the simulation and not to the original building block.

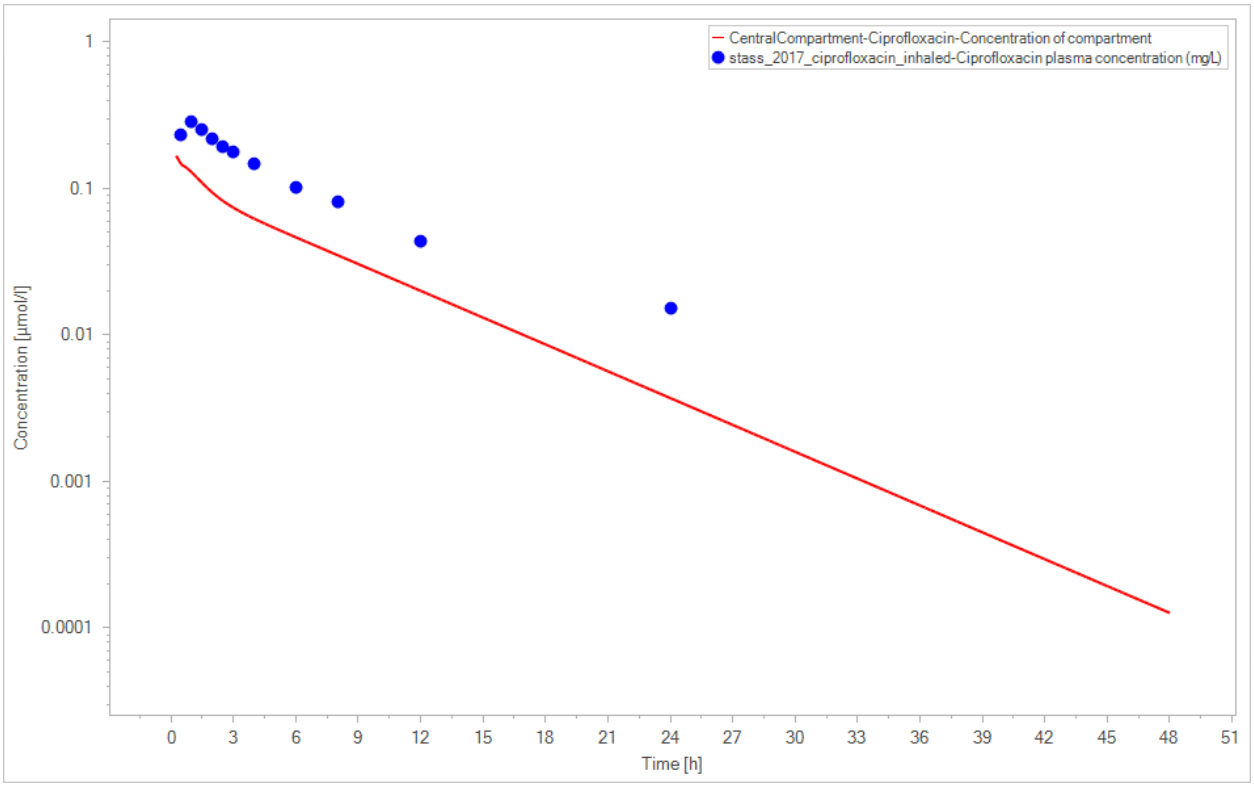


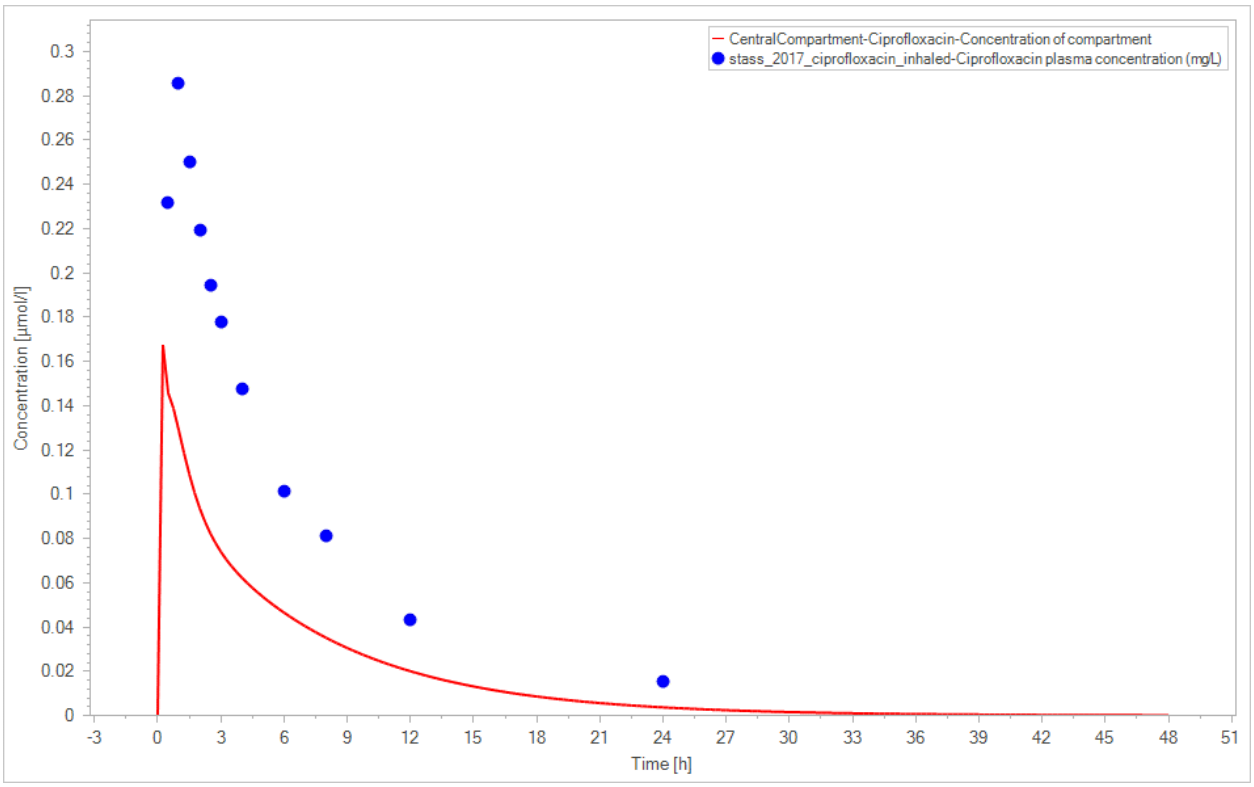
d. Navigate to the **Results** tab, and click **Define Settings and Run**. Scroll down to the central compartment concentration (see screenshot below) and check the corresponding box. Click OK. The simulation will then run and produce a plot of the concentration in the central compartment following an inhaled dose.





e. We will now add observed data for comparison. Download the file **stass_2017_ciprofloxacin_inhaled.pkml** from the GitHub repository. Right-click the "Observed Data" building block folder and **Load Observed Data…** . Select the downloaded pkml file.
    i. Drag the observed data building block **stass_2017_ciprofloxacin_inhaled** onto the simulation plot to add the observed data for comparison. You will find that the inhalation simulation underestimates the observed data. Below are plots on logarithmic and linear scales.





ii. You can now close this MoBi file and save it if you wish.

10. To improve this simulation, we will now make use of additional deposition information that we have and use the **custom_deposition.R** script to use that information instead of the empirical equations used in the **populate_model.R** script.

a. Again, the following arguments will need to be configured in order to run the **populate_model.R** script. Note that these values have already been configured in the **configure_inhalation_parameters.R** script.
   i. Pkml file name : **inhaled_ciprofloxacin.pkml**
   ii. Molecule name : Ciprofloxacin
   iii. Particle diameters of each bin (in dm) : 2.6e-5
   iv. Mean particle radius (in dm) : 2.6e-5 / 2
   v. Standard deviation of particle radii (in dm) : 1.8e-5 / 2
   vi. Oral bioavailability : 0.7
   vii. Deposition fractions (note that this is configured as a matrix of values as in the **configure_inhalation_parameters.R** script):
      - Extrathoracic proportion : 0.394
      - Proportion in each of 24 lung generations : 0.015875
         a. Total lung proportion: 0.381

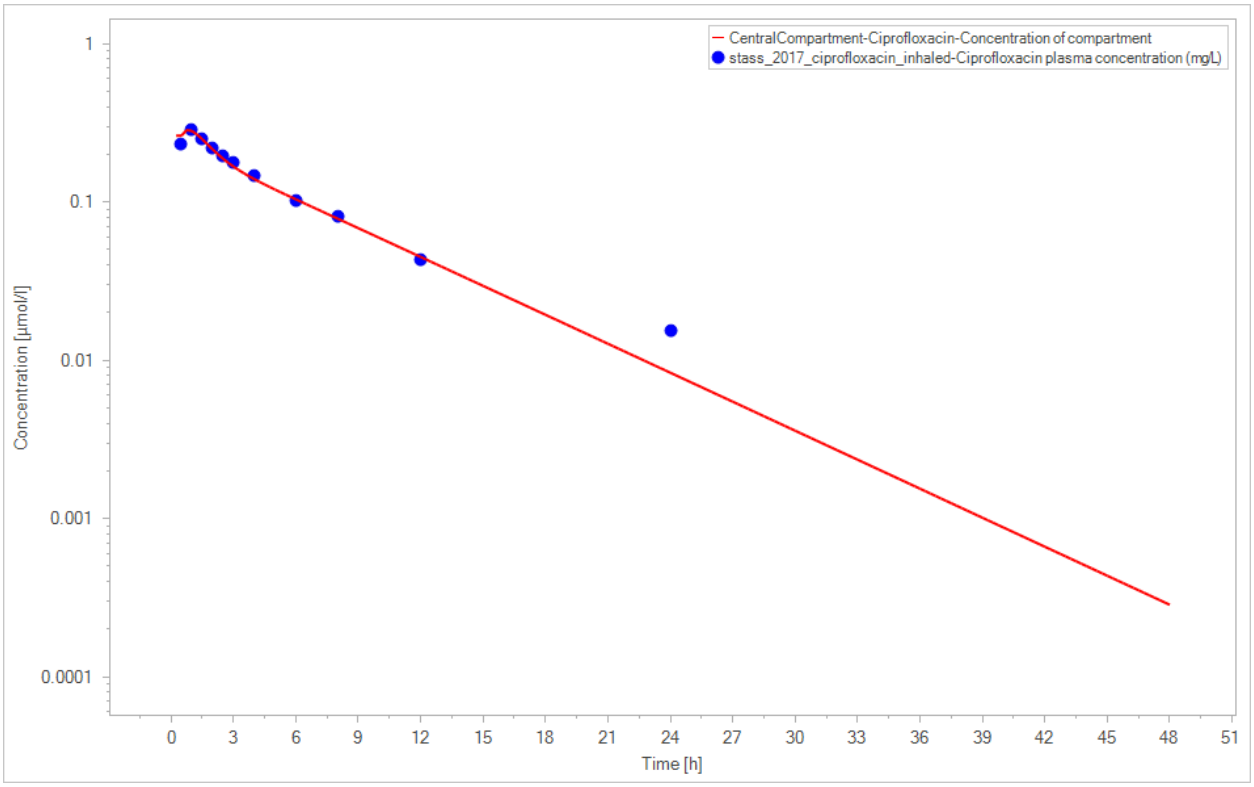
b. Run lines 1-11 and lines 24-31 of the **configure_inhalation_parameters.R** script by highlighting the sections of the code and clicking Run. Alternatively, you can run each individual line of code by pressing Ctrl + Enter while your cursor is on each line of code.

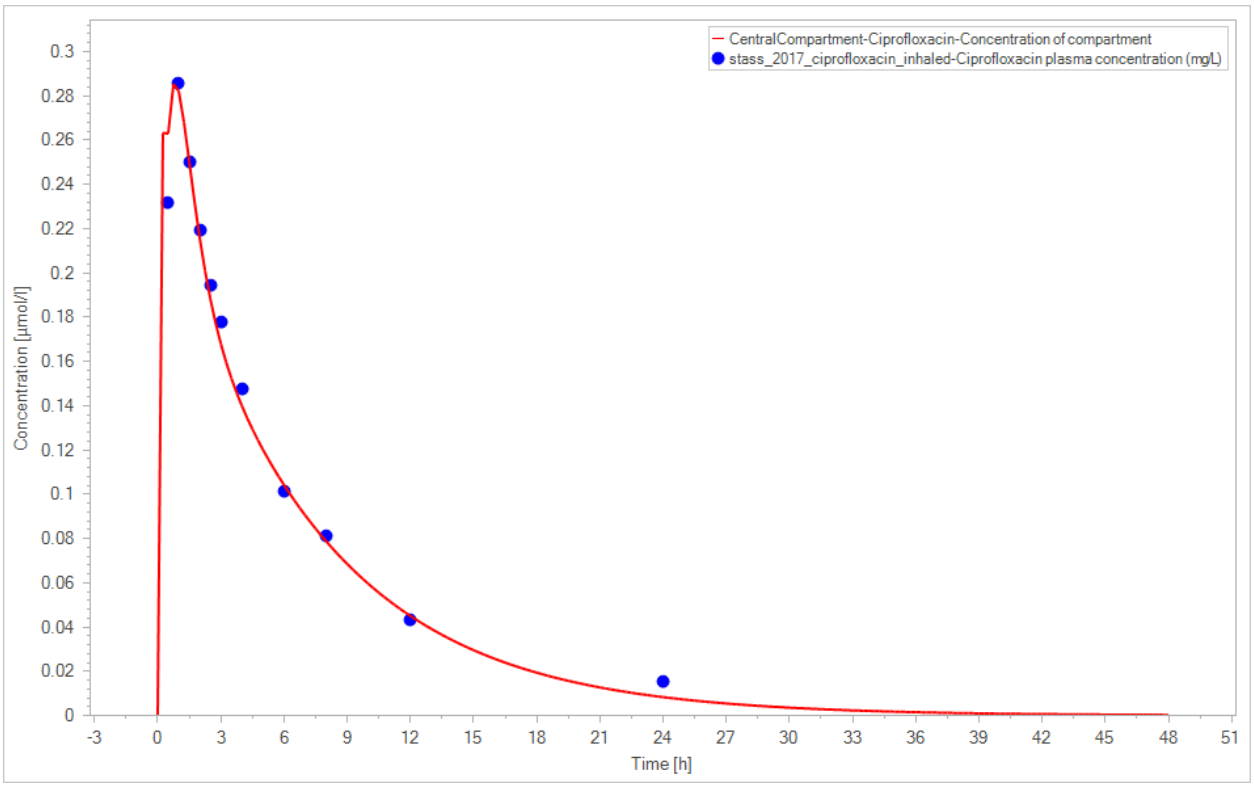
c. As with the **populate_model.R** script, there are 25 generations shown. This is because the extrathoracic region is included here as the first generation. Additionally, you should find that a pkml file has been generated called **custom_inhaled_ciprofloxacin.pkml .** This is the updated simulation file.

Output

```
> # Reset environment
> rm(list=ls())
>
> # Load scripts
> source("populate_model.R")
> source("custom_deposition.R")
>
> molecule_name <- "Ciprofloxacin"
> particle_diameters_dm <- 2.6e-5
> geomean_particle_radius_dm <- 2.6e-5/2
> gsd_particle_radius_dm <- 1.8e-5/2
> pkml_file <- "inhaled_ciprofloxacin.pkml"
> deposition_fractions <- matrix(c(0.394, rep(0.015875, 24)), nrow=25, ncol=1)
> oral_bioavailability <- 0.7
> # Lung and device bioavailabilities are already taken into account in deposition_fractions, so the values are left at 1
>
> custom_deposition(pkml_file, molecule_name, particle_diameters_dm, geomean_particle_radius_dm, gsd_particle_radius_dm,
+                               deposition_fractions, oral_bioavailability, logScale = TRUE)
[1] "Note: Since logScale==TRUE, the mean is interpreted as the geometric mean and the sd as the geometric standard deviation."
$number_of_particles_factor
[1] 1.086629e+14

$distribution_across_gens
          [,1]
 [1,] 0.394000
 [2,] 0.015875
 [3,] 0.015875
 [4,] 0.015875
 [5,] 0.015875
 [6,] 0.015875
 [7,] 0.015875
 [8,] 0.015875
 [9,] 0.015875
[10,] 0.015875
[11,] 0.015875
[12,] 0.015875
[13,] 0.015875
[14,] 0.015875
[15,] 0.015875
[16,] 0.015875
[17,] 0.015875
[18,] 0.015875
[19,] 0.015875
[20,] 0.015875
[21,] 0.015875
[22,] 0.015875
[23,] 0.015875
[24,] 0.015875
[25,] 0.015875
```

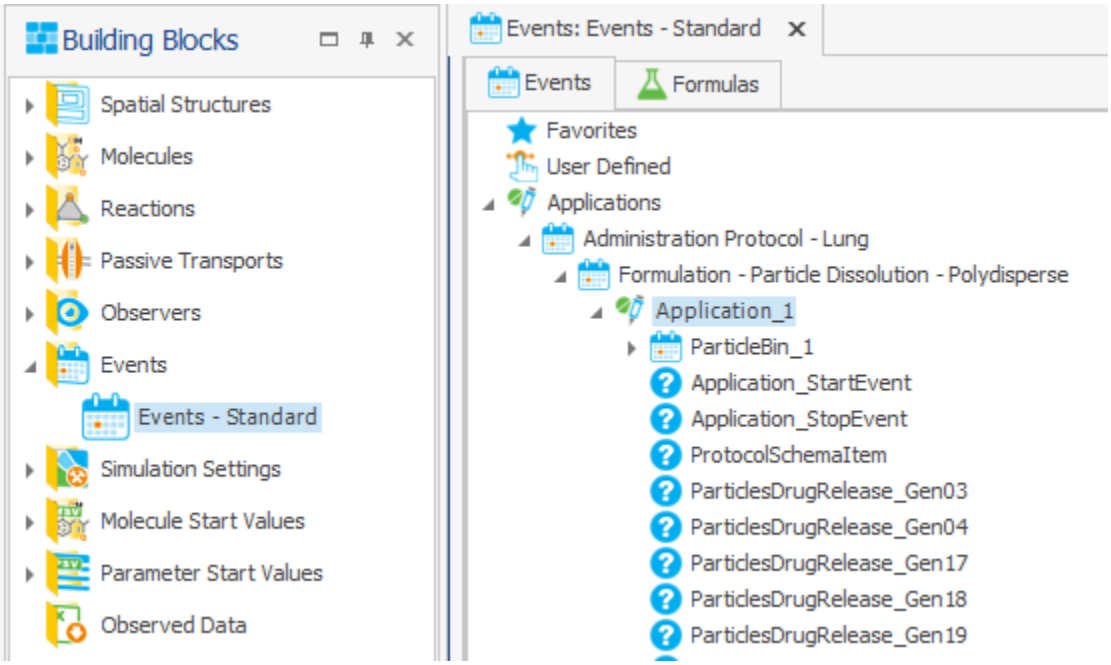
11. Repeat steps 8 and 9 with the newly generated file **custom_inhaled_ciprofloxacin.mbp3** . Below, we show the simulation results (logarithmic and linear scales) from this file.


CentralCompartment-Ciprofloxacin-Concentration of compartment
stass_2017_ciprofloxacin_inhaled-Ciprofloxacin plasma concentration (mg/L)
Concentration [µmol/l]
1
0.1
0.01
0.001
0.0001
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time [h]

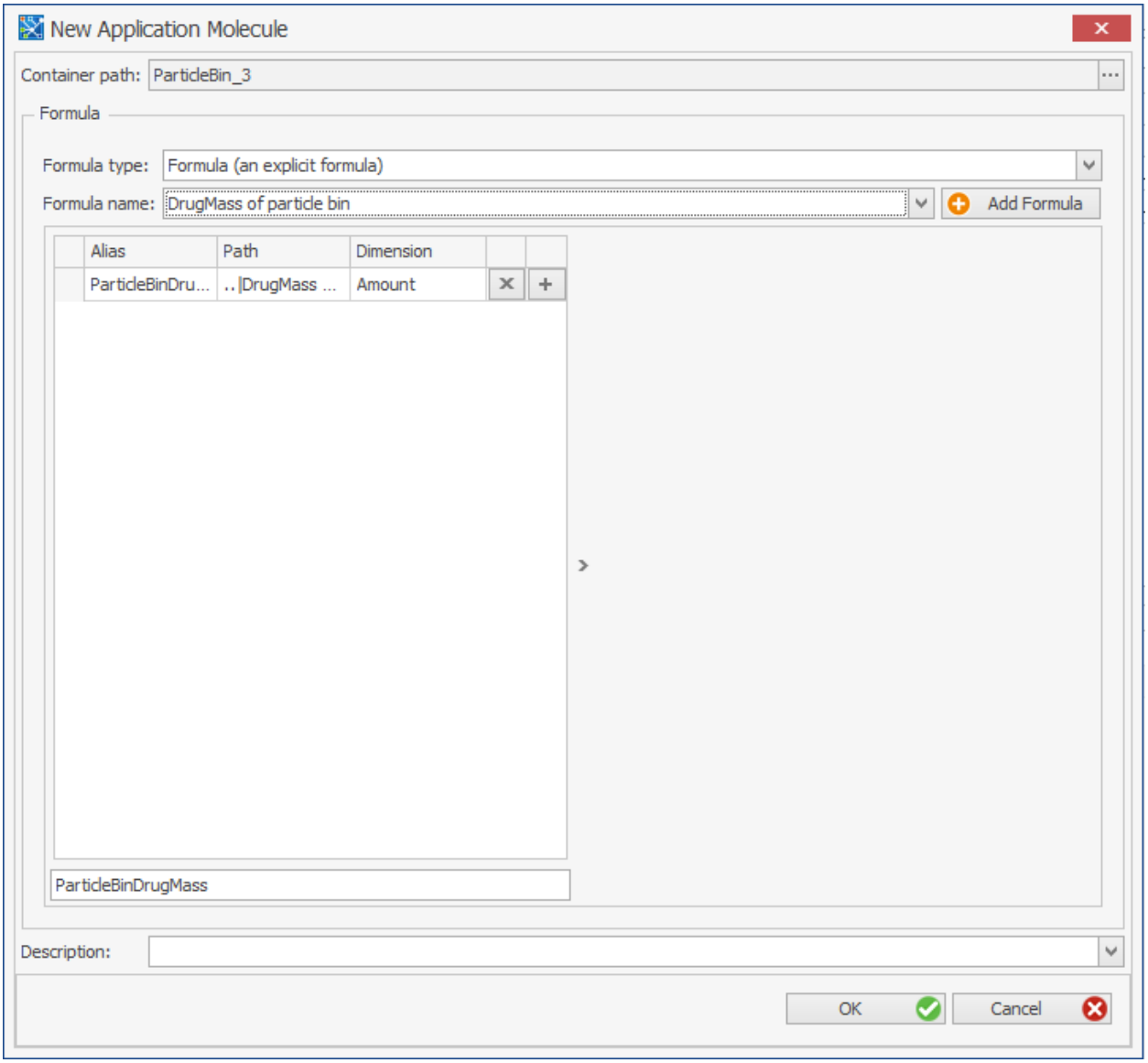

CentralCompartment-Ciprofloxacin-Concentration of compartment
stass_2017_ciprofloxacin_inhaled-Ciprofloxacin plasma concentration (mg/L)
Concentration [µmol/l]
0.3
0.28
0.26
0.24
0.22
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
-3 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time [h]

Optional step A: Setting up a polydisperse simulation

1. Set up the number of particle bins. By default, the lung template **inhalation_model_two_compt_1_bin.mbp3** only contains 1 particle bin, simulating a monodisperse powder formulation. To set up a polydisperse powder formulation, additional bins are needed.
    a. Download the file **ParticleBin_1.pkml**, the template for a particle bin.
    b. Open the **Events – Standard** building block and navigate to **Applications → Administration Protocol – Lung → Formulation – Particle Dissolution – Polydisperse → Application_1** . Right-click **Application_1** and **Load Event Group…** . Load **ParticleBin_1.pkml** and rename it to "ParticleBin_2". Repeat this process for the number of bins that you would like to simulate. Be sure to follow the naming convention so that the nth particle bin is named "ParticleBin_n".



    c. Navigate to **Application_1**, right-click the empty space under **Application Molecule Builder** and **Create Application Molecule…** . Click **…** next to the bar for the **Container path**. Set the path to **Relative path** and navigate to the new bin, e.g. **Applications → Administration Protocol – Lung → Formulation – Particle Dissolution – Polydisperse → Application_1 → ParticleBin_2**, then click **OK**. Change the **Formula type** to **Formula (an explicit formula)** and click **DrugMass of particle bin** . Then, click OK. Repeat this process for the number of bins that you had previously created.


New Application Molecule
Container path:
ParticleBin_3
Formula
Formula type:
Formula (an explicit formula)
Formula name:
DrugMass of particle bin
Add Formula
Alias
Path
Dimension
ParticleBinDru...
..|DrugMass ...
Amount
ParticleBinDrugMass
Description:
OK
Cancel

5 References

Boger, Elin, and Markus Fridén. 2018. “Physiologically Based Pharmacokinetic/Pharmacodynamic Modeling Accurately Predicts the Better Bronchodilatory Effect of Inhaled Versus Oral Salbutamol Dosage Forms.” Journal of Aerosol Medicine and Pulmonary Drug Delivery 32(1): 1–12.

Boger, Elin, and Oskar Wigström. 2018. “A Partial Differential Equation Approach to Inhalation Physiologically Based Pharmacokinetic Modeling.” CPT: Pharmacometrics & Systems Pharmacology 7(10): 638–46.

Stass, Heino et al. 2017. “Ciprofloxacin Dry Powder for Inhalation in Patients with Non-Cystic Fibrosis Bronchiectasis or Chronic Obstructive Pulmonary Disease, and in Healthy Volunteers.” Journal of Aerosol Medicine and Pulmonary Drug Delivery. http://www.liebertpub.com/doi/abs/10.1089/jamp.2015.1282 (March 17, 2021).

Weibel, Ewald R., Andre Cournand, and Dickinson Richards. 1963. Morphometry of the Human Lung. Berlin: Springer.

Willmann, Stefan et al. 2010. “Mechanism-Based Prediction of Particle Size-Dependent Dissolution and Absorption: Cilostazol Pharmacokinetics in Dogs.” European Journal of Pharmaceutics and Biopharmaceutics 76(1): 83–94.

Yu, C.p., and C.k. Diu. 1982. “A Comparative Study of Aerosol Deposition in Different Lung Models.” American Industrial Hygiene Association Journal 43(1): 54–65.