# Inhalation model user guide

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## 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. It has been evaluated with salbutamol and is currently being evaluated with seven other drugs.

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.

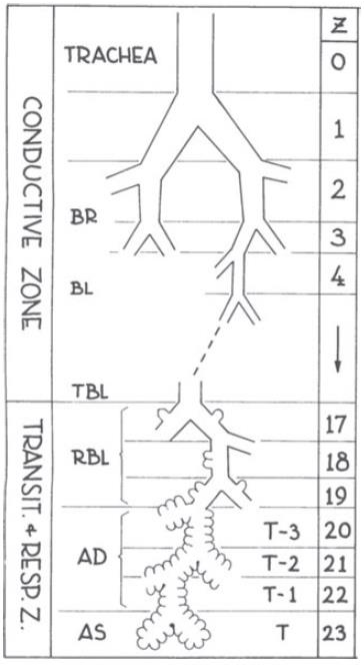



Fig. 82

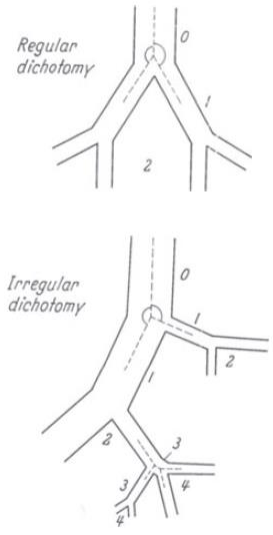



Fig. 83

*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.

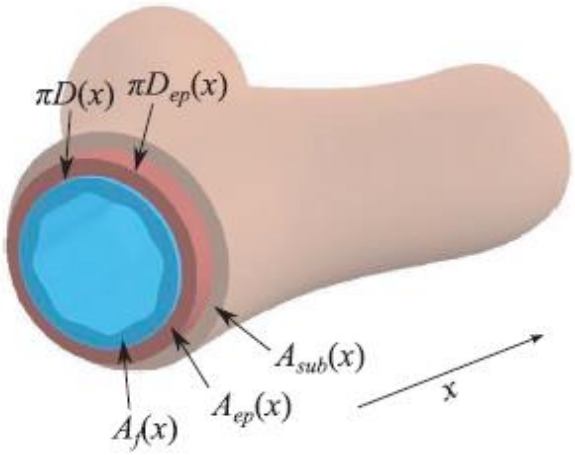



*Figure 2: Diagram demonstrating the three main compartments of the lung. Figure 1 from Boger & Wigstrom (2018).*

## Particle deposition

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.

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 empirical equations (Yu & Diu, 1982) for the probabilities of molecule being deposited at each generation of the lung are too complex to be implemented efficiently in MoBi. Thus, these probabilities are calculated in R. These scripts assume a normal distribution of the particles and take in the mean and the standard deviation of the particle distribution as input. It then calculates the distribution of particles across the lung generations and the extrathoracic region so that all the drug is accounted for. It also calculates the proportion of particles of a given particle radius per volume of drug. These values are then used as initial conditions for the lung model in MoBi.

### 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.*

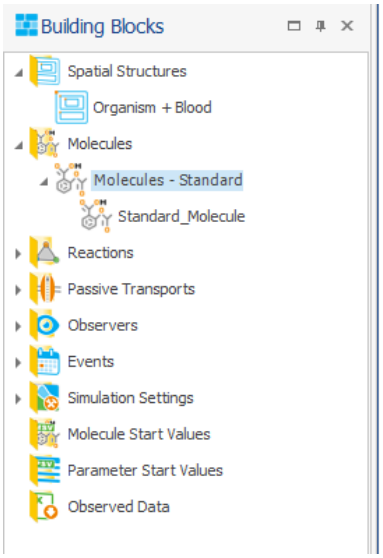
| Parameter name | Default value | Reference |
|---|---|---|
| **Spatial structure** | | |
| Fraction unbound in the ELF | 1 | Boger & Wigstrom, 2018 |
| Unbound tissue-plasma partition coefficient for the lung | 6.5 | Boger & Wigstrom, 2018 |
| Maximum mucociliary clearance rate | 0.36 cm/min | Boger & 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 | |

## Model diagram

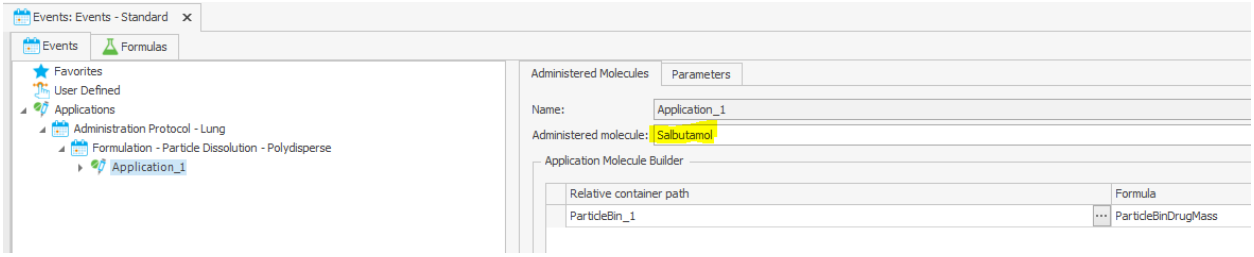
# 4 Tutorial: Setup and simulation of model

This tutorial will outline a step-by-step implementation of a salbutamol model (specifically for the (R)-enantiomer) using the inhalation model. This inhalation model will require both MoBi and R with the ospsuite R package installed. Note that this tutorial will walk through the setup for a single simulation and there are many places for customization in this process that are not covered here.

1. Download and open the MoBi model file **inhalation_model_two_compt_1_bin.mbp3** .
2. Set up the molecule of interest, i.e. Salbutamol.
    a. Delete the current Molecules building block “Molecules – Standard” .




    b. **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 “Salbutamol”. 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**: 239.31 g/mol
        ii. **Lipophilicity**: 0.06 Log units
        iii. **Fraction unbound (plasma, reference value)**: 0.77
        iv. **Solubility at reference pH**: 14100 mg/L
    d. Next, we will set up the Events building block to work with the Salbutamol molecule that has just been created.
        i. Open **Events – Standard** building block under **Events**.
        ii. Open up the tree and navigate to **Application_1** .
        iii. Change the **Administered molecule** to Salbutamol.

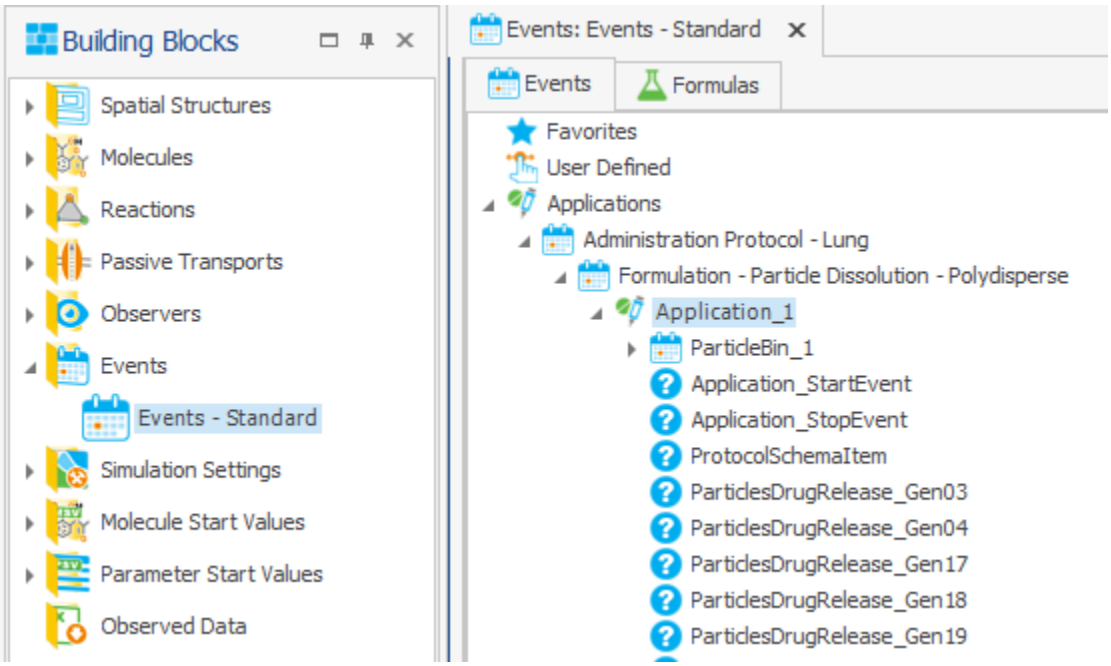



3. Fill in the parameters for the two compartment model and oral absorption. These parameter values are a result of fitting the two compartment model to salbutamol IV data.
    a. Right-click **Parameter Start Values**, click **Create Parameter Start Values Building Block…**, and name this parameter start values building block "Salbutamol 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:** 0.47 1/h
            - Note that this refers to oral absorption.
        ii. **Oral bioavailability – F_oral**: 0.09
        iii. **Volume [Path Element 1: CentralCompartment]**: 28355.24 mL
        iv. **Elimination rate**: 1.67 1/h
        v. **k_CP – First-order constant for transfer from central to peripheral compartments**: 3.13 1/h
        vi. **Volume [Path Element 1: PeripheralCompartment]**: 58896.32 mL
        vii. **k_PC – First-order constant for transfer from peripheral to central compartments**: 1.51 1/h

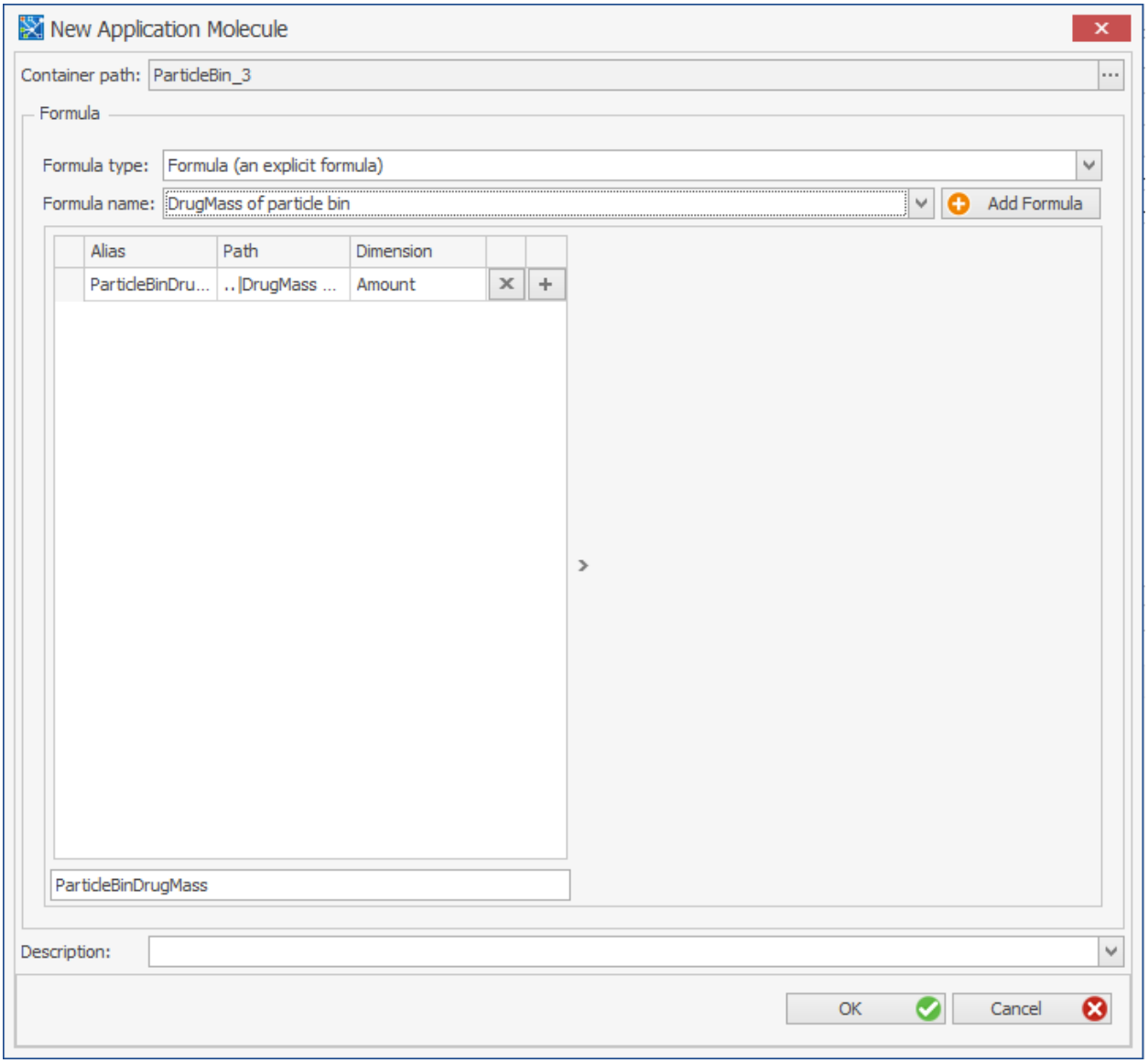
| Parameter Name | Path Element 0 | Path Element 1 | Path Element 2 | Path Element 3 | Path Element 4 | Start Value |
|---|---|---|---|---|---|---|
| OralApplicationsEnabled | Organism | Lung | | | | 1.00 |
| Fraction of drug clearing device | Organism | Lung | | | | 1.00 |
| Volume | Organism | ExtrathoracicRegion | | | | 1.00 l |
| Absorption rate - k_a | Organism | ExtrathoracicRegion | | | | 0.47 1/h |
| Oral bioavailability - F_oral | Organism | ExtrathoracicRegion | | | | 0.09 |
| Volume | Organism | CentralCompartment | | | | 28355.24 ml |
| Blood-plasma ratio | Organism | CentralCompartment | | | | 1.00 |
| Cardiac output | Organism | CentralCompartment | | | | 5.20 l/min |
| Elimination rate | Organism | CentralCompartment | | | | 1.67 1/h |
| k_CP - First-order constant for transfer from central to peripheral compartments | Organism | CentralCompartment | | | | 3.13 1/h |
| Volume | Organism | PeripheralCompart… | | | | 58896.32 ml |
| k_PC - First-order constant for transfer from peripheral to central compartments | Organism | PeripheralCompart… | | | | 1.51 1/h |
| Volume | Organism | ClearedDrug | | | | 1.00 l |

4. Set up the initial conditions for the simulation.
    a. Right-click **Molecule Start Values**, click **Create Molecule Start Values Building Block…** , and name this molecule start values building block "Salbutamol Initial Conditions" 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.

5. (optional, note that the rest of the tutorial corresponds to the monodisperse case) 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. 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".




    b. 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.




6. Set up the inhalation simulation and export the simulation.
    a. Right-click **Simulations**, click **Create Simulation…** , and name the simulation “Salbutamol Simulation” 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:** Salbutamol Initial Conditions
        ix. **Parameter Start Values:** Salbutamol 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 **salbutamol_simulation.pkml** .

**7.** In R, load the inhalation model using the ospsuite R package and the file **populate_model.R** . You may do this with any IDE, but for instructional purposes, I will describe these steps as they would be found in RStudio.

**a.** Open RStudio and navigate to the folder where you have saved **salbutamol_simulation.pkml** .

**b.** Download the file **populate_model.R** into the same directory and load the script into R using **source("populate_model.R")** .

**c.** The following arguments will need to be configured in order to run the **populate_model.R** script:

**i.** Pkml file : **salbutamol_simulation.pkml**

**ii.** Molecule name : Salbutamol

**iii.** Particle diameters of each bin (in dm) : 2.1e-5

**iv.** Mean particle radius (in dm) : 2.1e-5

**v.** Standard deviation of particle radii (in dm) : 0.75e-5

**vi.** Note that there are additional parameters that can be configured using this script including breathing frequency, fraction of breath that is inspiratory, breath hold time, delay volume, tidal volume, and bolus volume.

**vii.** Note that the scripts can be configured to allow for custom deposition models that take into account inhaled bioavailability or fraction of drug clearing the device.

**d.** The function can then be run as shown below in the R script example.

**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_salbutamol_simulation.pkml**. This file is the updated salbutamol simulation file with the inhalation parameters automatically updated.

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

R script

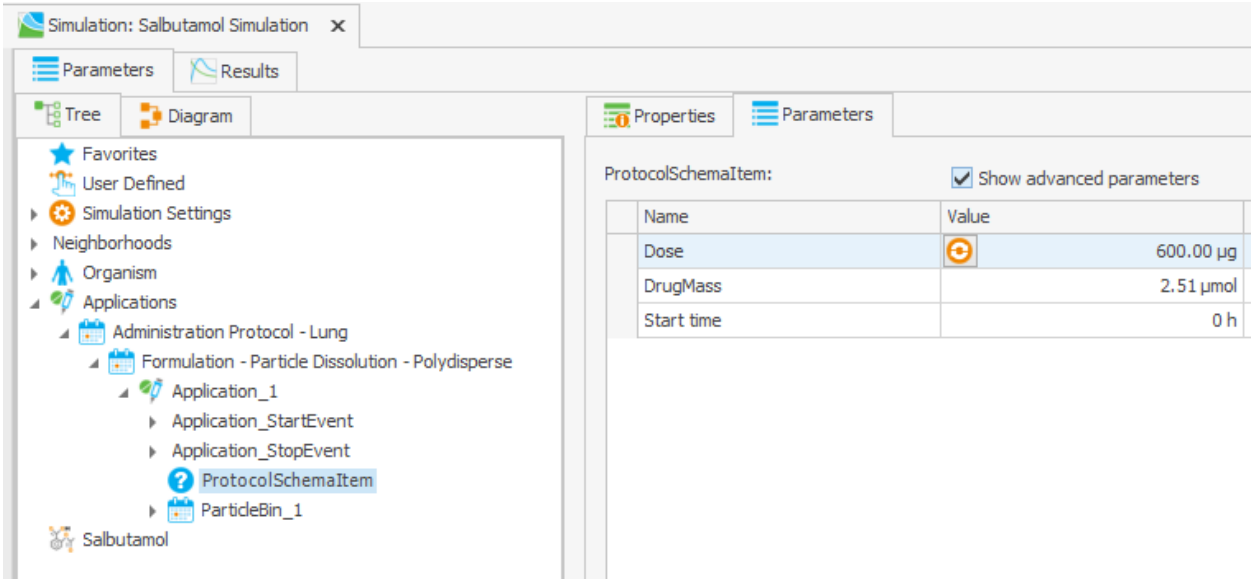
```
source("populate_model.R")

# set inhalation parameters
pkml_file <- "salbutamol_simulation.pkml"
molecule_name <- "Salbutamol"
particle_diameters_dm <- c(2.1e-5)
mean_particle_radius_dm <- 2.1e-5
sd_particle_radius_dm <- 0.75e-5

# populate model
populate_model(pkml_file, molecule_name,
               particle_diameters_dm, mean_particle_radius_dm, sd_particle_radius_dm)
```

Output

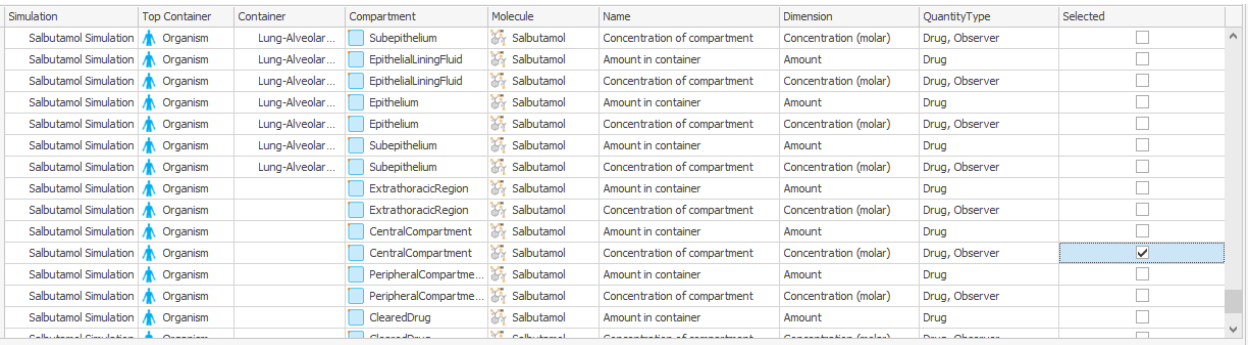
```
> populate_model(pkml_file, molecule_name,
+                particle_diameters_dm, mean_particle_radius_dm, sd_particle_radius_dm)
$number_of_particles_factor
[1] 2.06226e+14

$distribution_across_gens
             [,1]
 [1,] 0.10479601
 [2,] 0.01608296
 [3,] 0.01394766
 [4,] 0.01263815
 [5,] 0.01203795
 [6,] 0.02413790
 [7,] 0.02785634
 [8,] 0.02865701
 [9,] 0.02639065
[10,] 0.02635184
[11,] 0.02394091
[12,] 0.02128962
[13,] 0.01964552
[14,] 0.01708535
[15,] 0.01613777
[16,] 0.01704462
[17,] 0.02122703
[18,] 0.02763934
[19,] 0.04410625
[20,] 0.07217967
[21,] 0.12111101
[22,] 0.20438204
[23,] 0.10131444
[24,] 0.00000000
[25,] 0.00000000
```

8. Load the newly generated file **populate_salbutamol_simulation.pkml** into MoBi.
    a. Open MoBi, and create a new project by clicking **File → New → Amount Based Reactions** . Name this file **salbutamol_inhalation.mbp3** .
    b. Delete the existing building blocks. These building blocks will be imported when the new pkml file is imported. Note that we cannot use the previous salbutamol MoBi file as both simulations have variables with the same name, causing issues in importing.
    c. Load the simulation by right-clicking **Simulations** and clicking **Load simulation…** . Select **populated_salbutamol_simulation.pkml** . All of the building blocks should load into the MoBi project.
    d. **Important note:** Only the simulation parameters have been updated. Thus, do NOT update the simulation building blocks from the individual building blocks.
9. Update the dose within the simulation and run the simulation.
    a. Open the simulation **Salbutamol Simulation** 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 a positive value, e.g. 600 µg.

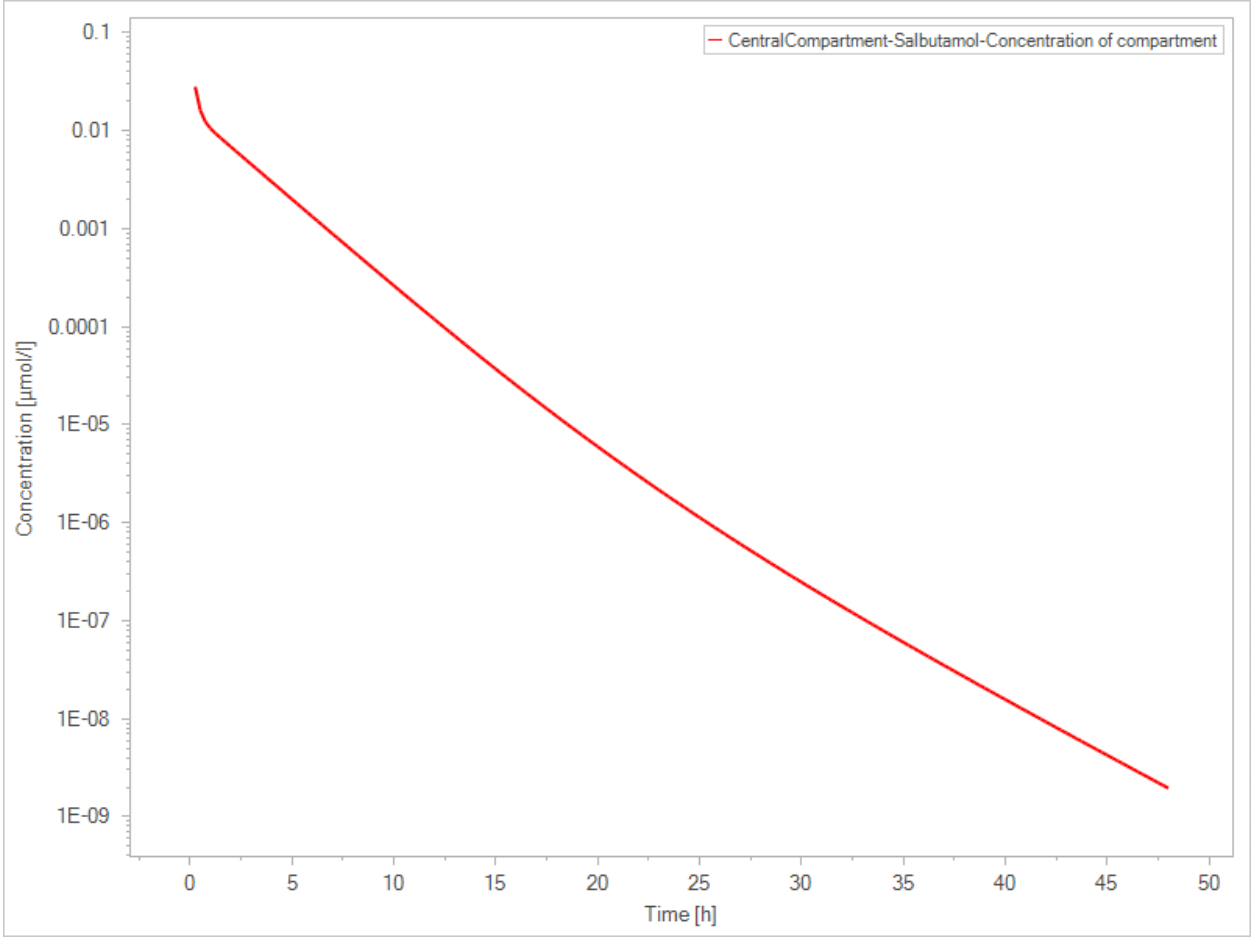
**d.** Right-click the **Salbutamol Parameters** building block within the simulation and **Commit to building block…** .




**e.** Navigate to the **Results** tab, and click **Define Settings and Run**. Scroll down to the **Central Compartment** concentration 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 of 600 ug of salbutamol.



Results




# 5 References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