In the US, each year around 400,000 people succumb to ailments related to the lung, making these the third most frequent cause of death in the country.¹ In Canada, 16% of deaths are a result of respiratory illnesses,³ whereas in the UK, one out of seven people suffer from chronic lung diseases.² These statistics have catalysed an increased interest in improving our understanding of the pharmaceutical and pharmacological aspects of delivering drugs to the lungs. Traditionally, therapeutic ingredients have been delivered to the body (including the lungs) through oral and intravenous (IV) administration. There are many challenging factors in the oral administration of drugs that may preclude this possibility for a given compound. These factors include poor solubility and/or degradation as a result of physicochemical instability in the gastro-intestinal (GI) tract, poor permeability (and absorption), high carrier-mediated efflux, extensive gut and hepatic first-pass metabolism, or significant drug-drug interactions.⁴ Similarly, for IV administration, the factors that may limit usage include high (possibly toxic) concentrations in non-relevant healthy organs (also relevant for oral doses), patient preferences (frequency of administration, needle phobia) and self-administration compliance issues.⁵ The possibility of avoiding some or all of these disadvantages, coupled with a very large absorptive surface area (approximately 140 m² in an adult human), make the lungs an attractive platform for aerosolised administration of a large variety of drugs, such as bronchodilators, anti-inflammatory agents, mucolytics, antiviral agents, anticancer agents and phospholipid-protein mixtures for surfactant replacement therapy.⁶

One of the major challenges in the development of a new molecular entity (NME) is the characterisation of its absorption, distribution, metabolism and excretion (ADME) properties. An understanding of these properties helps us to predict the human pharmacokinetic (PK) behavior of the drug (concentration-time profiles in the plasma, lungs and other organs of the body). It may also help in choosing the optimal dosage form and dosing range for clinical trials and for predicting potential drug-drug interactions (DDIs) and population variabilities,⁷ thereby speeding up the (Phase I) clinical studies by 1-6 months.⁸ The traditional method for predicting human PK has been through allometric scaling of preclinical (animal) data.¹⁰¹¹ However, this involves the use of compartmental pharmacokinetics, where the body is arbitrarily represented by one, two or three theoretical compartments with no relationship to anatomy and physiology. In addition, compartmental PK models require in vivo data to be collected first, which makes true prediction impossible. Mechanistic physiologically based PK

A key challenge in the development of a new therapeutic product is the characterisation of its ADME to help predict the human pharmacokinetics (PK). In this article, Siladitya Ray Chaudhuri, PhD, Senior Scientist, and Viera Lukacova, PhD, Team Leader, Simulation Technologies, both of Simulations Plus, Inc, outline the advantages of physiologically based PK (PBPK) models over traditional compartmental pharmacokinetics-based approaches, and describe how a mechanistic physiologically based pulmonary drug delivery model using the GastroPlus software can be of benefit in the development of novel inhalable formulations.

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(PBPK) models can be predictive when parameterised with \textit{in vitro} or \textit{in silico} properties because the introduction of physiological and anatomical properties allows for the prediction of volume of distribution from molecular structure.\textsuperscript{13} PBPK models can be used for early prediction of concentration-time profiles in the plasma and organs of the body. Thus, PBPK modeling has become a powerful tool for predicting concentration-time profiles for NMEs and other drugs of interest.\textsuperscript{6,14}

Unlike its compartmental counterpart, the complexity of the PBPK methodology (hundreds of differential equations and biopharmaceutical parameters) prevents its expression in a simple analytical form. As a result, variations of whole-body PBPK models have been incorporated in several commercially available software products such as ChloePK,\textsuperscript{20} PKSim,\textsuperscript{17} Simcyp,\textsuperscript{16} and GastroPlus\textsuperscript{18}. In a two-year prospective study to predict human exposure of 21 NMEs using \textit{in vitro} and \textit{in vivo} data from preclinical species, GastroPlus was shown to be more accurate than its commercial counterparts and more accurate than the method used previously at Pfizer.\textsuperscript{21} As a result, GastroPlus has been adopted by Pfizer for all First In Human (FIH) predictions.\textsuperscript{22}

Recently, the PBPK formalism of GastroPlus was extended to include a detailed, mechanistic multi-compartment physiological model of the lung and nose to describe the administration of inhaled and intranasal aerosolised drug molecules.\textsuperscript{22} This model describes the lungs as a collection of up to five compartments: an optional nose (containing the anterior nasal passages; ET1); extra-thoracic (naso- and oropharynx and the larynx; ET2); thoracic (trachea and bronchi; BB); bronchiolar (bronchioles and terminal bronchioles; bb); and alveolar-interstitial (respiratory bronchioles, alveolar ducts and sacs and interstitial connective tissue; AI). The scheme is similar to that adopted in the ICRP 66 model\textsuperscript{23} and is shown in Figure 1.

Immediately after administration, the drug is partly exhaled while the remainder is either swallowed or deposited in the mucus/surfactant layer lining the airways of the various pulmonary compartments in the model. The fractions of the administered drug in each compartment depend on the formulation characteristics (particle size, density, shape factor, etc) and can either be predicted by a built-in ICRP 66 deposition scheme\textsuperscript{23} or specified by the user. The model accounts for various processes that the drug is subject to in the lung, such as mucus/ciliary transit, dissolution/precipitation, absorption into the bloodstream, and the effects of surfactant layers and the cells, metabolism, and transfer into the systemic circulation.

The dissolution rate kinetics in the pulmonary mucus can be described by a variety of methods (including the traditional Noyes-Whitney equation,\textsuperscript{24} taking into account the solubility of the compound at the pH of the mucus (pH = 6.9),\textsuperscript{25} particle size and shape, particle density, and water diffusion coefficient. The passive absorption of drugs is driven by a concentration gradient with rates dependent on physiological (for example, surface area) and drug-dependent physicochemical properties (for example, permeability) for each compartment.

A large portion of the inhaled dose can be swallowed and this has been accounted for by connecting the lung compartments to the advanced compartmental absorption and transit ACAT\textsuperscript{9} (GI) physiological model\textsuperscript{23} within GastroPlus. The lung compartments are also connected to systemic PK models in GastroPlus to simulate drug appearance in plasma after combined absorption from the airways and the GI tract. Human lung physiological parameters (surface area, thickness and volume for the mucus and cell) for each compartment were obtained from the literature\textsuperscript{26,27,28} “The drug-dependent input parameters (including pulmonary cells, non-specific binding in mucus/surfactant layers and the cells, metabolism, and transfer into the systemic circulation.

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is applied to a series of bins, each containing a fraction of API particles with equal particle radius. Equations describing the relevant masses across bins and compartments are shown in the boxed text below.

The relevant masses across bins and compartments are given as:

\[
\text{mass of drug in bin } k = \omega_k \times \text{Dose} \\
\text{mass of drug in bin } k \text{ and compartment } j = f_{\text{comp}}^{j} \times \omega_k \times \text{Dose} \\
\text{mass of drug in compartment } j = \sum_{k=1}^{n_{\text{bin}}} \left( f_{\text{comp}}^{j} \times \omega_k \times \text{Dose} \right) \times f_{\text{comp}}^{j} \times \text{Dose}
\]

where \( \omega \) represents mass fraction of API particles in each bin.

The API is often associated with a drug carrier/excipient (commonly lactose) having a different particle-size distribution. In such cases, the model assumes that the API particles will form a coating on the carrier if they are sufficiently small (less than a pre-defined minimum or cut-off value), otherwise there will be no interaction between the two. Small particles of the API bind onto the surface of the carrier particles (according to the ratio of surface area of particles in each carrier bin), then are distributed amongst the pulmonary compartments based on the composite radius of the API-carrier complex. Larger API particles will be distributed amongst the pulmonary compartments based on their own radius (independent of the carrier particles). Figure 2 is a graphical representation of this scheme for collective distribution.

**EXAMPLE 1: Budesonide**

We employed the pulmonary drug delivery component of the ADRM within GastroPlus to simulate absorption and PK of inhaled budesonide in healthy human subjects, as reported by Miller et al.\(^\text{22}\) The PKPlus\(^\text{19}\) module of GastroPlus was used to fit systemic PK parameters for budesonide from observed Cp–time profiles after IV administration of a 0.4 mg dose in healthy human subjects, as reported by Miller et al.\(^\text{22}\) The PKPlus\(^\text{19}\) module of GastroPlus was used to fit systemic PK parameters for budesonide from observed Cp–time profiles after IV administration of a 0.4 mg

There may be several reasons for these deviations, among them the input value for particle size. In the above simulation, we assumed the aerosol particles were 1.25 \( \mu \text{m} \) in radius, which is within the usual range for these formulations.

Nonetheless, to assess the effect of particle size of an inhaled formulation on the bioavailability of the drug, a parameter sensitivity analysis (PSA) was carried out. In this automated GastroPlus mode, multiple simulations were carried out by gradually varying particle size, while keeping all other parameters fixed, as shown in Figure 4.

Varying particle size affects the deposition fractions in the lungs as well as the rate of dissolution in the epithelial lining fluid. Variations in the deposition pattern (% drug deposited in each lung compartment) and bioavailability (reflecting the changes in both deposition pattern and dissolution rate) with varying particle size are shown in Figure 5.

Figure 5 indicates that variation in bioavailability follows a pattern very similar to the variation in fraction inhaled in the alveolar-interstitial compartment. A possible explanation is that any drug that is deposited in compartments other than alveolar-interstitial can be cleared by mucociliary transit and ultimately swallowed. Swallowed drug is subject to dissolution limitations in the stomach and GI tract as well as high (~ 85%) first-pass extraction in the liver; hence, it may not contribute significantly to the net bioavailability, in this case. In order to further differentiate between the effects of varying particle size on the deposition pattern and the dissolution rate, simulations were run with varying particle size but using a fixed deposition fraction (via the “User-Defined” option), pre-calculated for particles with radius 1.25 \( \mu \text{m} \) according to the ICRP 66 method (% of dose deposited: ET2 = 4.16, BB = 2.52.

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**Figure 3:** Predicted (line) and observed (circle) plasma concentration-time profiles for inhaled administration of 0.4 mg aerosolised suspension of budesonide with no fitted parameters.

**Figure 4:** Variation of plasma concentration-time profile with changing particle size (0.75–2 \( \mu \text{m} \)). Deposition fractions were calculated for each particle size using the built-in ICRP 66 method.
The results of this analysis are shown in Figure 6. Figure 6 indicates that, in this case, changing particle size has no effect on bioavailability. Thus, the changes to the predicted bioavailability in Figure 5 are mainly due to changing deposition fractions in the lung.

EXAMPLE 2: TOBRAMYCIN

The case of Tobramycin further highlights the predictive ability of the pulmonary model as well as its scalability across dose levels and dosage forms. We also simulated the absorption and PK of inhaled aerosolised tobramycin in healthy human subjects as reported by Newhouse et al. Two dose levels and formulations were considered: an aerosolised suspension (Pulmosphere, 80 mg) and a solution (TOBI, 300 mg). We used a similar methodology as described previously: systemic PK was obtained from an independent source of IV data and was used unchanged; GI physiology was the default “fasted” state human ACAT model. In this case, however, reported experimental values of deposition fractions were used in place of the ICRP 66 model. Also, none of the physicochemical or physiological parameters were altered from their pre-calculated default values. Figure 7 shows that there is good agreement between the observed plasma concentration-time points and the simulated profile.

CONCLUSION

Our mechanistic physiologically based pulmonary drug delivery model provides quite good agreement between observed and simulated plasma concentration-time profiles for both budesonide and tobramycin even with no ex post facto calibration of the model (that is, no input parameters were fitted). We believe this new capability offers a valuable tool for scientists in the development and understanding of inhaled and intranasal drug candidates.

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