In Silico Modelling for Orally Inhaled and Nasal Drug Product Development

Q&A with Will Ganley, Senior Specialist, Nanopharm

Can you Explain '*in Silico* Modeling' and What a PBPK Model is?

In silico modeling involves using computer simulations to predict how drugs behave in the human body. An example is physiologically based pharmacokinetic (PBPK) modelling, which uses drug property, physiology, and biochemical data to predict absorption, distribution and excretion (ADME) processes using pharmacokinetic models.

The outcome is a system of equations employing a 'bottom-up' strategy that begins with modeling each specific process that moves the drug throughout the body. Starting from these foundational elements and progressing to a comprehensive model that integrates data from various sources, such as *in vitro* tests and clinical trials, we can replicate observed clinical outcomes. By developing a model that assigns significance to input data based on physiological relevance, we create solutions that accurately predict clinical outcomes, resulting in a trustworthy PBPK model.

How is the PBPK Model Applied Specifically to Inhaled Drug Products?

A typical whole-body PBPK model can be regarded as a large flow diagram, which maps mass transport processes across different types of tissue and blood vessels. If all the drug mass starts in the lung after a subject has inhaled, the model shows that the drug mass moves through the rest of the body and is exposed to the different tissues and blood compartments before it is ultimately metabolised and eliminated. For orally inhaled products, we are particularly interested instead in the details of what happens in the lungs.

The lung can be divided into two broad regions: the central region, which encompasses the upper airways where the blood flow goes from the arterial blood through to the venous blood, and the lower peripheral airways where the blood flow

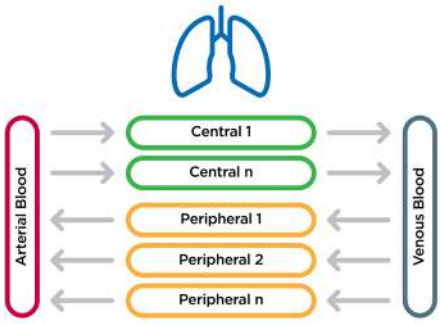

Figure 1: High Level Lung Structure

is reversed. We can further segment both regions into more granular compartments.

Within each compartment, the mucus layer is where the drug will typically start its journey as either a completely dissolved system, for example from a nebuliser, or as undissolved particles. For the latter, we directly simulate the particles' dissolution in the mucus layer before they permeate down into the lung tissue.

In the mucus layer, dissolved drug will passively diffuse into the epithelium, then subepithelium, before entering the blood vessels and being carried away to the rest of the body. Knowing this, it is important that we consider the inputs to the model when developing and designing studies that allow us to generate the model's input parameters.

There are two key types of input parameters for orally inhaled PBPK models. Deposition data that is obtained through deposition models or imaging data. Commonly used deposition models include computational fluid dynamics (CFD) or semi-empirical methods (such as the National Council on Radiation Protection and Measurements model). The advantage of CFD models is that computed tomography (CT) scans of healthy volunteers and patient airways can be used in the simulations to generate realistic and subject specific deposition predictions in the lungs.

The other form of input data is dissolution data, typically through *in vitro* studies. At Nanopharm, we have developed a dose collection system called Dissohale™ that allows us to deposit the lung dose uniformly and measure its dissolution. We then use a modelling approach that allows us to determine the dissolution of deposited particles that are irregular in shape and agglomerated. We take the fitted equivalent spherical representation of these particles and scale down the dissolution medium volume, matching the mucus volume in each region of the lung, which can be input into our PBPK model.

How Do You Use This Information to Generate Data?

Once we have the input parameters for the PBPK model, the next step is to address the questions posed by clinical product development.

To start, we define the problem – whether it be as simple as observing the interplay between two competing processes, through

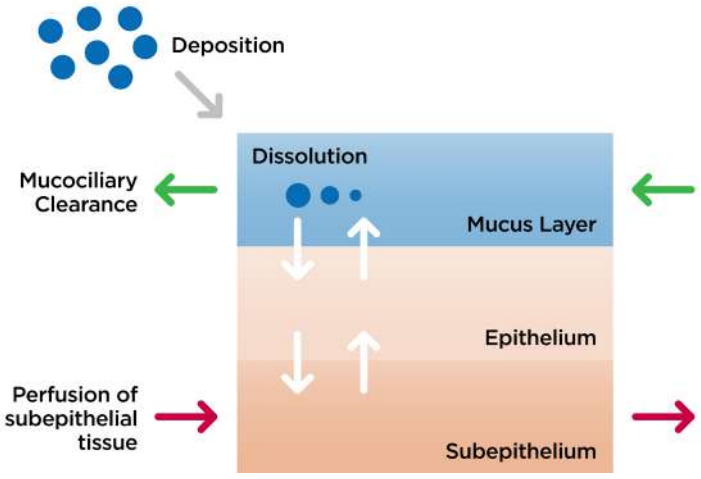

Figure 2: Detailed Lung Region Structure

to a complex scenario of simulating a clinical trial. This information allows us to determine the number of lung compartments required, the dissolution model, and whether we will obtain the input parameters from pre-clinical data or literature.

Following on from that, we verify the prediction feasibility to check whether the predictions follow the right time course, or the right curve shape and ensure they are not producing wildly unexpected results. To do this, we recommend gathering clinical data either generated as part of the drug development programme or from literature. For any uncertainty with initial data, we recommend that parameters be refined until the model is producing the data that is expected within the model.

Can You Introduce Simhalation™, and Discuss How it is Being Used in Drug Development?

Simhalation™ is an in-house PBPK model, developed at Nanopharm. Our software will generate a set of equations representing the system and build executable computer code.

The model will ask us for two things: physiological specifications (for example, the lung surface areas of the subjects we are interested in) and the molecular specification (such as log pKa and the rate of hepatic clearance). This allows us to input parameters for a range of patients and a range of formulations or molecules, run our simulations and finally generate the output we are looking for.

The Simhalation PBPK model can be used across the entire product development life cycle for orally inhaled drug products, but first it is important to understand how different 'levers' in the model will affect the exposure of a drug at the site of action.

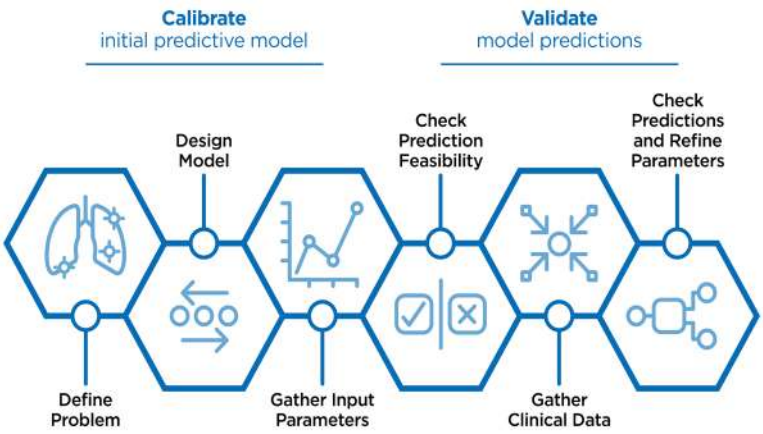

Figure 3: PBPK Model Building Process

Factors such as how the angle of insertion from different device variants impacts the deposition within the nose, dissolution rates and mucociliary clearance (MCC) which can be propagated through to the local or systemic exposure in the PBPK model to understand the effect on the exposure of your target drug at the site of exposure. Using this information, we can run multiple simulations for repeated dosing and assess things like inter- and intra-subject variability as well.

How Can You Ensure The PBPK Model is Credible Enough to Provide the Answers You Need?

There are two key concerns I see with PBPK models:

The first concern is that PBPK models are so highly parameterised that users think it is possible to achieve any answer by tuning the parameters accordingly, and secondly, are we able to justify using the model if we are going to have to perform a clinical study anyway?

Before starting any work, it makes sense to address both concerns by revisiting how the model is going to be used. Are we using it to answer some simple drug product development questions, or are we trying to replace a clinical study or use the predicted data to aid regulatory decision making?

Because these two things require different levels of credibility to be established, it can be useful to understand the model constraints, and the data available.

Even if we do not know the exact value of parameters for a given model – such as the lung epithelial permeability – for the types of molecules we are looking at, we might know their values to within a few orders of magnitude. Applying all the known or estimated model parameter ranges constrains the prediction space, meaning that the scope of possible predictions is quite limited.

Secondly, look at the data available or consider how it could be generated. Can we access data from available literature, or do we need to generate this for ourselves? Once a model is verified for a particular type of molecule, say a lowly soluble and highly soluble molecule, the model validation data should be applicable to other molecules and products of the same type. The regulatory landscape surrounding this is evolving rapidly now and should allow the use of validated modelling "platforms" in submissions soon using frameworks such as the Model Master File, which is current being developed by the United States Food and Drug Agency.

What is useful about this framework is that we can do it as a paper-based exercise before modelling commences to understand what

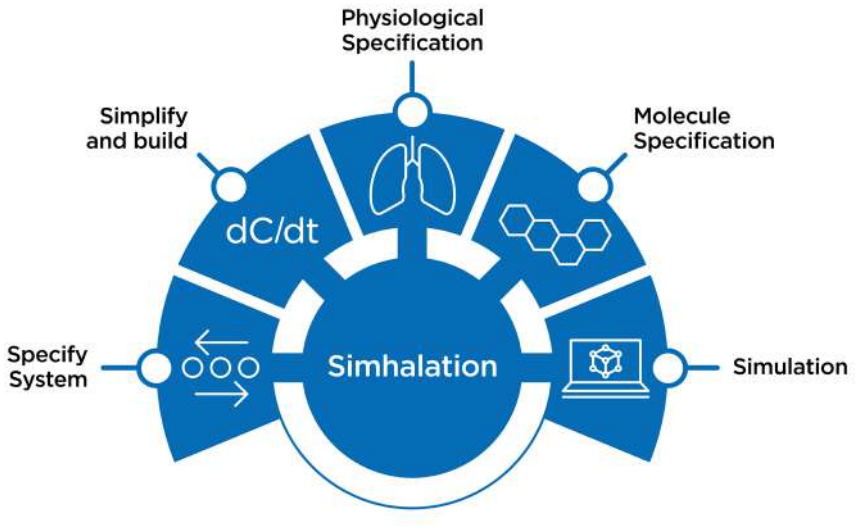

Figure 4: Simhalation Modeling Process

we can and can't use the model for, whether we need to perform any lab work or if we can already answer our questions of interest.

Can You Share Some Examples Where You Have Used PBPK Modeling For OINDPs at Nanopharm?

There are a few examples of how we've used PBPK modeling for orally inhaled drug product development here at Nanopharm.

The Influence of Dry Powder Inhaler Dissolution on Systemic Pharmacokinetics

We wanted to look at the dissolution of dry powder inhalers (DPIs) to understand what the influence of the dissolution of fluticasone propionate is on the systemic exposure of these drug products.

We were able to parameterise the model for fluticasone propionate using data from a literature study to reproduce three different doses by tweaking the dose in the model but keeping all other parameters the same.

Within the study data, three different dry powder formulations of fluticasone propionate had been developed with different aerodynamic and dissolution rates. Using this, we refined our model parameters against one of them and then using the in vitro data that was generated in that study, we extracted the dissolution rates and input that in the model for the other two formulations.

We found that with the PBPK model, we were able to reproduce the shapes of the systemic pharmacokinetic curves by tuning the dissolution parameters and show that dissolution was the driving factor and make credible predictions by using the data. Also, we predicted the systemic exposure of different parameters as if we were developing a product.

The model ended up concluding that you can deliver different doses fluticasone propionate to the lung with different dissolution rates, and if the total dose is fixed, then the total exposure that the subject received will be the same across different formulations but the maximum concentration will be different. This is an important consideration for drug product safety and would be useful information at the start of a new development program.

How Disease State Attribute Influences Local Drug Exposure for Cystic Fibrosis Patients

In another example, we were looking specifically at the delivery of spray dried amikacin sulphate powder to cystic fibrosis patients using a spray dried powder characterised using the anatomical mouth-throat models and realistic breathing profiles. We were very interested in the difference in exposure for both cystic fibrosis patients and healthy volunteers.

We parameterised the model using literature data and then worked to generate CFD deposition data using two lung geometries from our database. When we ran these simulations comparing a cystic fibrosis patient and a healthy volunteer, we found that when the same dose was delivered to these two subjects, the healthy volunteer would receive a lot more of it to their peripheral lung whereas the cystic fibrosis patient would receive a lot more to their central lung. Inputting this data into our PBPK model and running a sensitivity analysis similar, we were interested in disease state differences rather than differences in performance parameters.

When we input some other aspects of cystic fibrosis into the model – such as mucus thickness – we're able to see what effect that might have on systemic exposure. In this case, it effectively dilutes the mucus layer and means less of the drug can get through to the tissue as quickly. But due to the thick and sticky mucus of cystic fibrosis patients, the cilia beating is inhibited resulting in mucus clearance that isn't particularly effective. So, in the model, we can represent this by effectively turning mucus clearance off.

What we found is that this gave us a negligible change compared to having mucus clearance on, and our hypothesis is to this might be the case is that the spray dried amikacin sulphate actually dissolves very quickly and permeates through the lung, before the mucociliary clearance would have been able to have an effect.

How Do Regulators View These Models?

It depends on the regulators that we work with, but in our experience at Nanopharm, we've had a lot of interaction with the US FDA at various points over the past couple of years.

They have been interested in how simulation approaches might be used to form part of alternative bioequivalence approaches for orally inhaled and nasal drug products. The feedback we have gotten during our interactions has been very positive because they are really interested to see how this technology could be used to reduce the burden on clinical testing and complexity required to get drugs to market.

The FDA are currently working on the concept of a model master file which would allow technology providers like ourselves to keep validation data on file at the FDA for drug developers to reference. This has the potential to reduce duplication of effort and broaden access to modeling and simulation for drug submissions.

I think we're getting there, and over the next few years I expect to see more drug products approved using simulations like CFD and PBPK as a key part of the data package.

Is The Model Able to Make Predictions About Repeated Dosing?

Repeated dosing can refer to multiple doses during a day, or multiple doses over a predetermined time. But with the PBPK model, we can inject doses at any time point during the simulation (Figure 5). If a drug is to be delivered once daily, we can simulate how it might build up in the body over time.

This is particularly useful when considering repurposing a drug that is taken via a different route – intramuscular injection or intravenous infusion, for example – and how that builds up in the body over time. Using the PBPK model, we can try to replicate this with our orally inhaled product before proceeding with clinical development.

How Do You Validate Your Model? Do You Have to Validate Every Molecule?

We need to make sure that the data we produce using these models is robust and valid. The US FDA are quite public about their expectations, and this is making the process of validation easier.

At Nanopharm, we perform validation typically through a risk-based framework called the ASME V&V 40, that has been provided to us by the US FDA. We identify how a model is going to be used and the credibility level is required, so that we can design a validation package based on that.

The validation framework is used to verify that your model solves the numerical problem to an appropriate degree of accuracy, and that your model outputs can be compared to clinical data. Currently we perform this to validate each individual molecule that we investigate.

Recently, the term 'platform validation' has been used a lot – this is where you take a simulation methodology, such as PBPK or CFD, and demonstrate that it is valid for typical use cases. This could be where the model works for varying solubilities and permeabilities, and a combination of the two. Provided that we can show that the model predicts well for the extremes of these cases, we can claim validity for the cases in between too.

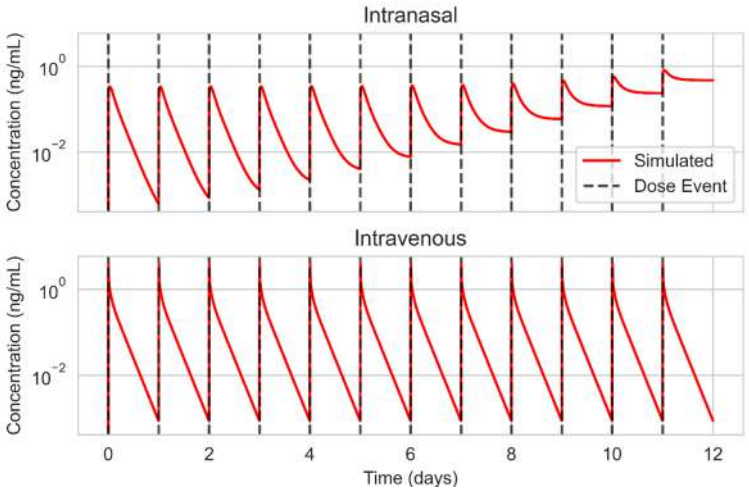

Figure 5: Simulated Repeated Intranasal and Intravenous Dosing

Could Simulation Replace Certain Clinical Studies for Orally Inhaled Products?

We can say that PBPK model structures for orally inhaled and nasal drug products are very well established. The main challenge in making them work is generating the required parameters and input data from your pre-clinical and formulation development work.

There are many different applications for PBPK models in the product development for OINDPs – spanning from early development where you're interested in identifying your critical parameters, all the way through to clinical validation where you're trying to either derisk or replace clinical studies.

Understanding what it is that you are using your model for means that you can establish what validation data are required and what the possibilities for using that model are. It is worth noting that most of the applications that we have seen fall somewhere in between those requiring that robust clinical validation, such as the granting of biowaivers, and those requiring only inputs literature studies, such as addressing low risk product development decisions.

Will Ganley

Will Ganley, Senior Specialist at Nanopharm, an Aptar Pharma company, is a Physical Chemist with a PhD from the University of Bristol, UK. He started his career as a postdoc in Pharmaceutical Surface Science Lab at the University of Bath, UK. His focus was on advancing physical characterisation and simulation techniques for dry powder inhaler formulations, aiming to better understand the connection between physical attributes and delivery to patients. In 2019 Will joined Nanopharm as Head of Computational Pharmaceutics where he led the development of a number of statistical and mechanistic modelling methodologies, notably Nanopharm's Simhalation PBPK platform. Will is now a senior member of the Science & Technology department at Nanopharm where he supports Nanopharm's customers in product development and regulatory strategy and manages a portfolio of internal research and development projects aimed at advancing Nanopharm and Aptar Pharma's scientific excellence in the use of advanced physical characterisation and digital technologies in inhaled and nasal drug product development. Will has authored a number of peer reviewed publications on pharmaceutics, statistics and physical chemistry, has presented his work at a range of international conferences and is a Scientific Advisor for the Drug Delivery to the Lungs conference.