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IVIVC using *in silico* and PBPK methods for inhaled drug product development

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Summary

Background: The physiologically based model of the lung included in GastroPlus™ was used to simulate the absorption, distribution, and pharmacokinetics of two APIs from an inhaled combination product. The goal of the study was to evaluate the possibility of developing an *in vitro-in vivo* correlation (IVIVC) to aid in the development of generic inhaled drug products.

Methods: Physiologically based pharmacokinetic (PBPK) models for both APIs were developed using the PBPKPlus™ and PCAT™ modules in GastroPlus based on literature data after intravenous (*iv*), oral (*po*), and inhaled administration. The baseline models were refined by fitting total lung deposition and dissolution rate against Cp-time profiles for APIs from inhaled administration of the reference product. The *in vitro* and *in vivo* dissolution rates from the reference product were used to create an IVIVC, which was used to predict the systemic exposure for test products with the same combination of APIs. The effect of dissolution rate and lung deposition on the predicted exposure was explored.

Results: The PCAT/PBPK models accurately described the systemic exposure of both APIs from the reference product. The dissolution-based IVIVC underpredicted the systemic exposure of APIs from test products. This misprediction appeared to be caused by variability in the lung deposition between formulations rather than by an inaccurate dissolution rate.

Conclusion: This study showed the potential of using an IVIVC to evaluate the *in vivo* dissolution for inhaled products. However, a sensitive method for predicting the differences in lung deposition is required for accurate prediction of overall performance of formulations.

Introduction

Physiologically based pharmacokinetic models and IVIVCs are commonly utilized tools in the formulation development of orally administered drug products. Although these approaches have the potential to help in the formulation development of products administered via other dosage routes as well, in the area of inhaled drug delivery they are often focused only on effect drug deposition [1-2]. The applications accounting for additional processes affecting the drug disposition after inhaled administration (i.e. dissolution, absorption, mucociliary clearance) are more limited [3-4]. The Office of Generic Drugs at the US FDA also expressed interest in these approaches through several funded projects for the development of PBPK models with the focus on generic product development for different administration routes [5].

Several years ago, a mechanistic absorption model for pulmonary administration was developed and included in the GastroPlus software and its utility in first-in-human predictions [6-7], dose evaluation [8], and pediatric predictions [9] was shown in number of poster presentations.

Here we present a recent study where this model was used to explore the possibility of creating an IVIVC for inhaled products using an example of a fixed-dose combination product containing two active pharmaceutical ingredients (API). One of the APIs (API1) is a low-solubility compound (< 10 ug/mL) where the dissolution rate will affect the rate and extent of drug absorption into systemic circulation. The second API (AP2) has sufficiently high solubility that the dissolution rate is not expected to be a rate-limiting factor. Therefore, API1 was the focus of the IVIVC development and evaluation while API2 served as general validation of the pulmonary model.

Methods

All simulations were performed using GastroPlus v9.0. The systemic tissue distribution and clearance were simulated with a full-body PBPK model. All physiologies were generated using the built-in Population Estimates for Age-Related Physiology (PEAR Physiology™) module to match the subjects (gender, age and body weight) from clinical studies. Pulmonary absorption was modeled using the GastroPlus PCAT module with default built-in lung physiologies.

Physicochemical and biopharmaceutical properties for each API were obtained from literature, predicted from structure using ADMET Predictor™ v7.2 (Simulations Plus, Inc.), or fitted against *in vivo* data.

Schematic representation of PCAT module in GastroPlus

First, a model accounting for intestinal absorption, first pass metabolism, and systemic tissue distribution and clearance was developed for each API using plasma concentration-time (Cp-time) profiles following *iv* and/or *po* administration reported in literature. The lung deposition, dissolution rate, and lung permeability were subsequently fitted using Cp-time profiles after inhaled administration of each API (different dose levels, single and multiple doses) from literature. The baseline models based on the literature data were subsequently refined by fitting the total lung deposition and *in vivo* dissolution rate for each API against Cp-time profiles from inhalation of the reference formulation. The refined models were used to explore possibility of creating an IVIVC for these inhaled products.

The *in vitro* and *in vivo* dissolution of each API from different formulations was modeled using a z-factor dissolution model (Eq. 1) [10].

$$DisolutionRate = Z(C_s - C_l)M_{u,t} \qquad \text{Equation 1}$$

Z represents z-factor (fitted to *in vivo* or *in vitro* dissolution data); C_s is compound solubility, C_l is local dissolved compound concentration, $M_{u,t}$ is remaining undissolved compound amount at time t.

The IVIVC was created as a ratio of fitted *in vivo* and *in vitro* z-factor for the reference formulation. The *in vivo* z-factor values for test formulations were predicted using the IVIVC and corresponding *in vitro* z-factor values (Eq. 2)

$$z^T_{InVivo} = \frac{z^R_{InVivo}}{z^R_{InVitro}} z^T_{InVitro} \qquad \text{Equation 2}$$

Z_{InVivo} and $Z_{InVitro}$ represent fitted *in vivo* or *in vitro* Z-factor in the dissolution model, respectively; superscripts R and T denote Reference and Test formulations, respectively.

Results

The PBPK models developed using Cp-time profiles from literature were able to describe the PK of each API after inhaled administration of the reference formulation from the current clinical study with only the expected changes in the lung deposition and dissolution rates. Despite similar particle sizes of the two APIs (as measured in cascade impactor), API2 required 40% higher total lung deposition to accurately match the observed exposure after inhalation of the reference formulation (Table 1).

The initial IVIVC developed for API1 correctly predicted a significant difference in pharmacokinetics between the test formulations and the reference formulation. However, the overall prediction errors for the test formulations were outside of the IVIVC limits established for oral formulations (Table 2). Closer examination of the predicted and observed average Cp-time profiles showed that, even though the overall exposure was underpredicted, the shape of the Cp-time profile, including the initial peak which would depend on the rate of drug dissolution and absorption, were predicted correctly (Figure 1). This suggests that the differences in the *in vivo* dissolution rates of API1 between the formulations were predicted correctly from the IVIVC, but the total bioavailable dose was underpredicted. Considering very low systemic bioavailability of this API after *po* administration, the underprediction of systemic exposure was assumed due to underpredicted lung deposition for the test formulations. The total lung deposition was fitted for each test formulation (results shown in Table 2) and the relationship between the known formulation parameters and the fitted lung deposition was explored.

Table 1: Cmax and AUC prediction errors for API1 and API2 after inhalation of reference formulation.

	API1 % PE	API2 % PE
Cmax	2.8	-4.37
AUC(0-48)	-1.5	-1.73

% PE – percent prediction error

Table 2: Comparison of Cmax and AUC prediction errors for API1 after inhalation of the three test formulations with different total lung deposition fractions. Both sets of simulations used the same *in vivo* dissolution rates as predicted from the IVIVC.

	Assuming the same total lung deposition as for reference			Total lung deposition fitted for each formulation		
	F01 % PE	F05 % PE	F06 % PE	F01 % PE	F05 % PE	F06 % PE
Cmax	-3.34	-12.87	-18.74	10.10	10.73	10.62
AUC(0-48)	-23.05	-29.24	-34.23	-11.73	-8.5	-8.44

% PE – percent prediction error

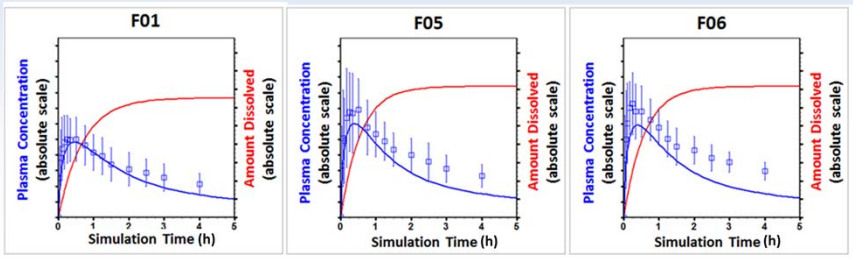

Figure 1 - Predicted *in vivo* dissolution profiles (red) and plasma concentration time profiles (blue) for the three test formulations using the IVIVC built from the reference formulation and assuming the same total lung deposition as fitted for the reference formulation.

The fitted lung deposition for test formulations correlated well with mass mean aerodynamic diameter (MMAD), but not with impactor-sized mass (ISM), or fine particle mass (FPM) as shown in Figure 2.

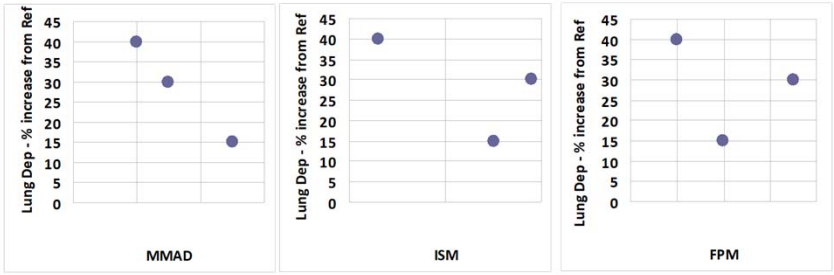

Figure 2 - Fitted total lung deposition of API1 in the test formulations (shown as % increase from total lung deposition of API1 in reference formulation) vs mean mass aerodynamic diameter (MMAD), impactor-sized mass (ISM), and fine particle mass (FPM).

The fitted lung depositions of API1 were used to predict the total lung depositions of API2 from each test formulation. Simulations of both APIs from the reference formulation showed that API2 required 40% higher fraction of the dose to be deposited in the lung than API1. The same ratio of deposition fractions for the two APIs resulted in good prediction of systemic exposure (Cmax and AUC) for API2 after inhalation of all three test formulations (Table 3).

Table 3: Cmax and AUC prediction errors for API2 after inhalation of the three test formulations using the API2 deposition fractions predicted from deposition fractions fitted for both APIs in the reference formulation and the fitted API1 deposition fractions for all test formulations.

	F01 % PE	F05 % PE	F06 % PE
Cmax	-11.56	-10.55	-12.21
AUC(0-48)	-1.18	14.49	5.89

% PE – percent prediction error

Conclusions

This study demonstrated the potential of using an IVIVC to evaluate the *in vivo* dissolution rates for inhaled products. However, a sensitive method for predicting the differences in lung deposition is required for more accurate prediction of overall systemic exposure after inhaled administration. The model showed a good correlation between the fitted total lung deposition and MMAD of the API. Further studies are needed to evaluate the applicability domain of such correlations and possible other manufacturing aspects that might affect the lung deposition of the API.

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