Received: 29 March 2023 | Revised: 12 August 2023 | Accepted: 2 October 2023

DOI: 10.1002/psp4.13067

ARTICLE

A convolution-based in vitro-in vivo correlation model for methylphenidate hydrochloride delayed-release and extended-release capsule

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Abstract

Delayed-release and extended-release methylphenidate hydrochloride (JORNAY PM®) is a novel capsule formulation of methylphenidate hydrochloride, used to treat attention deficit hyperactivity disorder in patients 6 years and older. In this paper, we develop a Level A in vitro-in vivo correlation (IVIVC) model for extended-release methylphenidate hydrochloride to support post-approval manufacturing changes by evaluating a point-to-point correlation between the fraction of drug dissolved in vitro and the fraction of drug absorbed in vivo. Dissolution data from an in vitro study of three different release formulations: fast, medium, and slow, and pharmacokinetic data from two in vivo studies were used to develop an IVIVC model using a convolution-based approach. The time-course of the drug concentration resulting from an arbitrary dose was considered as a function of the in vivo drug absorption and the disposition and elimination processes defined by the unit impulse response function using the convolution integral. An IVIVC was incorporated in the model due to the temporal difference seen in the scatterplots of the estimated fraction of drug absorbed in vivo and the fraction of drug dissolved in vitro and Levy plots. Finally, the IVIVC model was subjected to evaluation of internal predictability. This IVIVC model can be used to predict in vivo profiles for different in vitro profiles of extended-release methylphenidate hydrochloride.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Modeling by translating the convolution integral into a system of differential equations is one of the most efficient implementations of convolution-based approach. This single-stage approach utilizes the observed data without deconvolution and it can directly predict the plasma concentration time course resulting from a given in vivo input function.

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WHAT QUESTION DID THIS STUDY ADDRESS?

How a model-informed drug development strategy based on convolution-based approach can be prospectively developed and applied to support the drug development process by identifying the in vitro drug properties.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study adds a Level A in vitro-in vivo correlation (IVIVC) model development procedure to our knowledge for the delayed-release/extended release-methylphenidate hydrochloride (JORNAY PM®; formerly known as HLD200) utilizing Ironshore Pharmaceuticals & Development, Inc.'s proprietary drug delivery platform, DELEXIS® which is a novel and proprietary drug delivery technology that contains two functional film coatings that act synergistically to achieve a unique pharmacokinetic profile.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The proposed IVIVC analysis provides the pharmaceutical companies with a methodological framework to develop Level A IVIVC model support post-approval manufacturing changes.

INTRODUCTION

Methylphenidate hydrochloride is a central nervous system stimulant and is used as a first line of treatment for attention deficit hyperactivity disorder (ADHD).[1–3] Delayed-release and extended-release (DR/ER) methylphenidate hydrochloride (JORNAY PM®; formerly known as HLD200) with methylphenidate hydrochloride as the active moiety is the first drug utilizing Ironshore Pharmaceuticals & Development, Inc.'s proprietary drug delivery platform, DELEXIS® which is a novel drug delivery technology that contains two functional film coatings that act synergistically to achieve a unique pharmacokinetic (PK) profile. The first layer delays the initial release of drug for up to 10 h while the second layer helps to control the rate of release of the active pharmaceutical ingredient throughout the day.[4] DR/ER-methylphenidate hydrochloride is indicated for the treatment of ADHD in patients 6 years and older with recommended starting dose of 20 mg once daily taken orally in the evening and has demonstrated improvement in the severity of ADHD symptoms in the early morning and throughout the day.[5]

To support the approval of manufacturing scale-up changes for extended-release formulations, a bioequivalence study is one option which takes a considerable amount of time, effort, and monetary investment. In this context, in vitro-in vivo correlation (IVIVC) modeling plays a critical role in the pharmaceutical development of dosage forms as it has the potential to serve as a surrogate for in vivo bioavailability studies and to support biowaivers. IVIVC can also be applied to (a) predict human absorption and the in vivo plasma concentration profiles based on in vitro data, (b) optimize dosage forms, (c) set dissolution acceptance criteria, and (d) establish bioequivalence based on in vitro data.[6] Thus, the applications of IVIVC attract the attention of the pharmaceutical industry.

Several modeling approaches have been proposed in the past for the development and evaluation of IVIVC. These approaches can be classified into two categories: (a) requiring deconvolution and (b) based on the implementation of a convolution-based approach. In the traditional deconvolution-based approaches, modeling is conducted on deconvoluted data rather than on raw PK data, often leading to unstable and unreliable results.[7] In contrast, convolution-based approaches lead to more consistent and reliable results. One of the most efficient implementations of convolution-based approach is modeling by translating the convolution integral into a system of differential equations.[8] This method is a single-stage approach in which the model utilizes the observed data directly without transformation (i.e., through deconvolution). One of the important advantages of this modeling approach includes the ability to directly predict the plasma concentration time course resulting from a given in vivo input function.

The objective of this paper is to develop a Level A IVIVC model to support DR/ER-methylphenidate hydrochloride post-approval manufacturing changes. Dissolution data from an in vitro study and PK data from two in vivo studies of three different release formulations: fast, medium, and slow, were used to develop and validate the IVIVC model using a novel convolution-based approach.

METHODS

Data

Dissolution data for the fast, medium, and slow-release formulations of methylphenidate hydrochloride from an in vitro study and the PK data from two in vivo studies were used for the entire IVIVC modeling and internal model evaluation. The details of the studies are as follows.

Study 1: In vivo PK study of the immediate release formulation of DR/ER-methylphenidate hydrochloride

Study 1 was a phase I, single-center, single-dose, open-label, randomized, crossover, comparative bioavailability study of DR/ER-methylphenidate hydrochloride, to an immediate-release (IR) formulation of methylphenidate hydrochloride in healthy adult volunteers under fasted condition.[9] In this study, a total of 12 subjects were randomly assigned to two treatment sequence cohorts (DR/ER-methylphenidate hydrochloride, 100 mg and IR methylphenidate hydrochloride, 20 mg) of 12 subjects each in a crossover fashion. The PK data from the IR methylphenidate hydrochloride 20 mg group were used for IR PK model development.

Study 2: In vitro dissolution study of fast, medium, and slow-release formulations of DR/ER-methylphenidate hydrochloride

Study 2 was an in vitro study of three different release formulations of DR/ER-methylphenidate hydrochloride.[10] The dissolution testing for the first 2 h took place in 0.1 N hydrochloride, and then for the next 4 h in pH 6.0 phosphate buffer, and finally in pH 7.2 phosphate buffer for the remaining time (6–24 h).

Study 3: In vivo PK study of fast, medium, and slow-release formulations of DR/ER-methylphenidate hydrochloride

Study 3 was a phase I, single-center, single-dose, open-label, randomized, crossover, comparative bioavailability study of three formulations of DR/ER-methylphenidate hydrochloride in healthy adults.[10] A total of 18 subjects were randomly assigned to six treatment sequence cohorts of three subjects each in a crossover fashion (as described in Table S1) to receive the three different formulations of DR/ER-methylphenidate hydrochloride 100 mg described in study 2: fast, medium (DR/ER-methylphenidate hydrochloride formulation and reference treatment), and slow. All subjects were dosed under fasted conditions.

The data analyses comprised five steps: (i) estimation of fraction dissolved in vitro, (ii) estimation of unit impulse response, (iii) estimation of fraction absorbed, (iv) development of IVIVC model, and (v) evaluation of internal predictability of the IVIVC model (Figure S1). Each step is described below.

Estimation of fraction dissolved in vitro

Three different models were evaluated for describing the mean in vitro dissolution data of each DR/ER-methylphenidate hydrochloride formulation: sigmoid-E_{max}, single-Weibull, and double-Weibull type models described in Equations 1, 2, and 3, respectively.

$$f_{\text{diss}}(t) = \frac{t^{\gamma}}{\text{td}_{50}^{\gamma} + t^{\gamma}} \tag{1}$$

$$f_{\text{diss}}(t) = \left[1 - \exp\left\{-\left(\frac{t}{\text{td}}\right)^{\text{ss}}\right\}\right] \tag{2}$$

$$f_{\text{diss}}(t) = \left[1 - \left(ff \cdot \exp\left\{-\left(\frac{t}{\text{td}}\right)^{\text{ss}}\right\} + (1 - ff) \cdot \exp\left\{-\left(\frac{t}{\text{td}_1}\right)^{\text{ss}_1}\right\}\right)\right] \tag{3}$$

Here, t denotes time and $f_{\text{diss}}(t)$denotes the cumulative fraction of drug dissolved in vitro. For the sigmoid-E_{max} model, td_{50} is the time needed for the formulation to dissolve 50% of the total amount, and γ is a shape parameter. For the single-Weibull model, td denotes the time to dissolve 63.2% of the drug amount and ss is the sigmoidicity factor. For the double-Weibull model, ff and (1 − ff) are the fractions of the amount dissolved in the first process and the second process respectively, td and td_1 are the times to dissolve 63.2% of the drug amount in the first and the second process respectively, and ss and ss_1 are the sigmoidicity factors for the first and the second process, respectively.

The final in vitro dissolution model was selected by comparing the Akaike information criterion (AIC) as these were non-nested models and by visual inspection of individual dissolution model fits. The AIC criterion was computed as: $AIC = -2\text{Loglikelihood} + 2n$ where n is the total number of parameters in the model.

Estimation of unit impulse response

The individual PK data for the IR formulation from study 1 were utilized to characterize the disposition and elimination of methylphenidate hydrochloride.

Semi-log plot of mean IR methylphenidate hydrochloride concentration showed a constant slope for the concentration decline. Hence, the one-compartment disposition model with first-order absorption with or without lag-time and first-order elimination were evaluated to describe the IR methylphenidate hydrochloride PK. Different absorption models were then evaluated to refine the fit of the absorption phase, including a zero-order absorption model with and without lag-time. The between-subject variability (BSV) in PK parameters were incorporated as exponential random error models, assuming a log-normal distribution of the PK parameters. Proportional and combined (proportional + additive) residual unexplained variability (RUV) models were compared to describe the methylphenidate hydrochloride concentrations. The final model was selected based on model diagnostic plots (individual and population predicted vs. observed concentration plots, and conditional weighted residuals vs. time plots), individual goodness of fit plots, −2Loglikelihood (−2LL) and precision of parameter estimates. An alternative model was considered as a significantly better descriptor of data when the reduction in the −2LL associated with the model was greater than or equal to 3.84, for 1 degree of freedom (df).

Estimation of fraction absorbed

To estimate fraction absorbed for the fast, medium, and slow-release formulations, a convolution-based model, similar to that reported by Gomeni et al.,[11] was developed subsequently after in vitro dissolution model and the methylphenidate hydrochloride IR PK model development. The primary purposes of this step were to generate fraction absorbed in vivo independent of the in vitro dissolution parameters in order to inspect the shape of the time-course, and to provide an estimate of the BSV (variance) for the extended-release formulations.

The time-course of the methylphenidate hydrochloride drug concentration $C_p(t)$ resulting from an arbitrary dose was considered as a function of the in vivo drug absorption and the disposition and elimination processes defined by the unit impulse response (UIR) function using the convolution integral:

$$C_p(t) = f(t) * I(t) = \int_0^t f(\tau) \cdot I(t-\tau)\, d\tau \tag{4}$$

where $C_p(t)$ is the in vivo methylphenidate hydrochloride concentration, $f(t)$ is the rate at which the drug is absorbed from a dosage form, $I(t)$ is the UIR at any time t, and $*$ denotes the convolution operator. Here, $f(t)$ is defined as

$$f(t) = \frac{d}{dt}[\text{Amount to be absorbed at time } t] = \text{relF} \cdot \text{Dose} \cdot \frac{d}{dt}\left[1 - f_{\text{absrem}}(t)\right] \tag{5}$$

where relF is the relative bioavailability of the current formulation with respect to the IR formulation, $f_{\text{absrem}}(t)$ is the fraction of the drug remaining to be absorbed at any time t, and is estimated by numerical approximation using a finite difference approach as

$$\frac{d}{dt}\left[1 - f_{\text{absrem}}(t)\right] \cong \frac{f_{\text{absrem}}(t) - f_{\text{absrem}}(t+\Delta)}{\Delta} \tag{6}$$

where Δ is fixed as 0.001 h, sufficiently small.

In the present analysis, the convolution integral model described in Equation 4 is translated into a system of differential equations as:

$$\frac{dA}{dt} = \text{relF} \cdot \text{Dose} \cdot \frac{d}{dt}\left[1 - f_{\text{absrem}}(t)\right] - k_{\text{el}} \cdot A; Cp = \frac{A}{V} \tag{7}$$

where A is the amount of drug in central compartment, k_{el} is the elimination rate constant, and V is the volume of distribution for central compartment. The mean parameters for the disposition model were fixed to the estimates from the UIR function. The BSV of PK parameters were estimated as exponential random error models, assuming a log-normal distribution of the PK parameters. Proportional and combined (proportional + additive) residual error models were compared to describe the RUV in methylphenidate hydrochloride concentrations.

Development of IVIVC

The present analysis is focused on the development of a Level A IVIVC by evaluating a point-to-point correlation between $f_{\text{abs}}(t)$, the fraction of drug absorbed, and $f_{\text{diss}}(t)$, the fraction of drug dissolved in vitro. The scatterplots of $f_{\text{diss}}(t)$ vs. $f_{\text{abs}}(t)$ and Levy plots (in vitro dissolution time vs. in vivo absorption time for a given percentage) were used to assess potential temporal differences in the in vitro and the in vivo processes (for example, when the dissolution is faster than the in vivo absorption). In case of temporal differences, a time scaling function was included in the model to establish IVIVC.[12]

A general time-scaling model considered in the assessment of the IVIVC includes a linear component describing the intercept (a_1) and the slope (a_2) and a nonlinear component describing the time-shifting (b_1), time-scaling (b_2), and time-shaping factor (b_3) as

$$f_{\text{abs}}(t) = a_1 + a_2 \cdot f_{\text{diss}}\left(b_1 + b_2 \cdot t^{b_3}\right). \tag{8}$$

In the absence of temporal differences among $f_{\text{abs}}(t)$ and $f_{\text{diss}}(t)$: $a_1 = 0$, $a_2 = 1$, $b_1 = 0$, $b_2 = 1$, and $b_3 = 1$. Otherwise, the IVIVC can be established by estimating the appropriate values of the parameters a_1, a_2, b_1, b_2, and b_3.

TABLE 1 Mean parameter estimates for final methylphenidate hydrochloride in vitro dissolution model – fast, medium, and slow-release.

Parameter	Description	Estimate (mean)		
		Fast	Medium	Slow
td_{50}	Time to 50% dissolution, h	8.86	13.7	21.0
gamma	Shape parameter	9.20	6.65	6.62
Additive error		0.653	1.38	0.291

TABLE 2 Mean parameter estimates for methylphenidate hydrochloride IR PK model in fasted subjects.

Parameter	Description	Estimate	
		Mean	95% CI
tlag	Lag time, h	0.448	[0.418, 0.476]
K_a	Absorption rate constant, h^{-1}	2.88	[2.14, 4.10]
V	Central volume of distribution, L	2480	[2080, 3050]
k_{el}	Elimination rate constant, h^{-1}	0.270	[0.252, 0.294]
ω^2_{tlag}	BSV on tlag (variance)	0.00700	[0.00100, 0.0156]
ω^2_{Ka}	BSV on K_a (variance)	0.165	[0.00749, 0.364]
ω^2_{V}	BSV on V (variance)	0.107	[0.0353, 0.182]
$\omega^2_{k_{el}}$	BSV on k_{el} (variance)	0.0146	[0.00154, 0.0262]
Proportional residual error (%)		10.6%	[6.11, 14.8]
Additive residual error, ng/mL		0.00400	[0.00159, 0.00670]

Abbreviations: BSV, between subject variability; CI, confidence interval; IR, immediate release; PK, pharmacokinetic.

The mean PK data of the fraction absorbed for the three extended-release formulations were used to develop the IVIVC model. In addition to the parameters in Equation 8, the relative bioavailability fractions for medium and slow formulations ($relF_{medium}$, and $relF_{slow}$) compared to fast formulation ($relF_{fast} = 1$), and the additive residual errors were also estimated. The bioavailability parameters $relF_{medium}$ and $relF_{slow}$ were included in the model to account for differences in bioavailability among the formulations. The BSV of V and k_{el} were fixed to the estimates from IR PK analysis.

Internal predictability evaluation of IVIVC

The internal predictability evaluation of IVIVC model was accomplished using data from the three formulations used to develop the model.

The internal predictability evaluation of IVIVC model was performed in accordance with the US Food and Drug Administration (FDA) recommendations.[6] The relevant exposure metrics (peak plasma concentration [C_{max}] and area under the curve to infinity [$AUC_{0-\infty}$]) were estimated using noncompartmental analysis (NCA) from the model-predicted PK data for each formulation and compared with the observed values. The prediction error (%PE) was calculated for each PK metrics using the equation

$$\%\,PE = \frac{1}{n}\sum \frac{|\text{Predicted value} - \text{Observed value}|}{\text{Observed value}} \times 100 \tag{9}$$

where n is the number of formulations. The criteria for assessing the level of predictability for each PK metric average were %PE less than or equal to 10% with no individual values greater than 15%. If criteria were not met, the evaluation of external predictability would be required.

All modeling, simulations, and NCA were performed using Pumas version 2.3.1 and NONMEM version 7.5.1.[13] A first-order conditional estimation with interaction method was used for the PK model parameter estimation. The dissolution model estimation was performed using the Naïve Averaged approach.

RESULTS

Estimation of fraction dissolved in vitro

Mean in vitro dissolution data for the fast, medium, and slow-release formulations from study 2 were used to develop the dissolution model (Figure S2, Table 1). The AIC values for the sigmoid-E_{max}, single-Weibull, and double-Weibull type models defined in the Equations 1, 2, and 3 were 23.9, 47.1, and 30.3 units, respectively, for the fast

formulation. A similar trend in AIC values was obtained for the medium (47.8, 72.0, and 48.8) and slow-release formulations (12.0, 81.7, and 31.3). Therefore, the sigmoid-E_{max} type model was selected as the final model due to lowest AIC value.

Estimation of UIR

The individual PK data of 12 subjects enrolled in study 1 were utilized to characterize the disposition and elimination of the IR formulation of methylphenidate hydrochloride. The IR-methylphenidate hydrochloride PK was best described by a one-compartment model with a first-order absorption process, with a lag-time, and linear elimination (Figure S3, Table 2). A combined proportional and additive residual error model had lower -2LL compared to proportional error model and adequately described the residual variability for the IR formulation of methylphenidate hydrochloride as shown in Figures S3 and S4. The estimated mean apparent volume of the central compartment, V was 2480 L and elimination rate constant, k_{el} was 0.270 h^{-1}. The BSV was in the range of ~3.0% to 50.0%.

Estimation of fraction absorbed

The individual PK data of 18 subjects for all the three formulations from study 3 were used to develop the PK model for the fraction absorbed estimation, as described in Equation 7. The mean volume (V) and the mean elimination rate constant (k_{el}) in this analysis were fixed to the corresponding V and k_{el} estimates respectively obtained from the IR-methylphenidate hydrochloride PK analysis. In addition, in this step, the relative bioavailability was assumed to be same for all the formulations. The time course of in vivo absorption of the three formulations was assumed to be characterized by in vitro dissolution (i.e., the sigmoid-E_{max} model). The parameter estimates of the population PK model for fraction absorbed are shown in Table 3. The goodness-of-fit diagnostic plots for the three formulations are shown in Figures S5 and S6 suggesting that the population PK model for fraction absorbed estimation was adequate in describing the methylphenidate hydrochloride concentrations resulting from the administration of the fast, medium, and slow-release formulations of DR/ER-methylphenidate hydrochloride. The results of this analysis provided an updated BSV (variance) estimate of k_{el} and V as 0.352 and 0.331, respectively. These variability estimates together with the mean estimates of k_{el} and V (0.270 h^{-1} and 2480 L) for UIR were used in the assessment of the IVIVC.

Estimation of IVIVC

The temporal difference in the scatterplots of $f_{diss}(t)$ vs. $f_{abs}(t)$ and Levy plots in Figure 1 suggested a potential need for time-scaling and time-shifting. Hence, a basic IVIVC model was developed to evaluate the correlation between the in vitro dissolution and the in vivo absorption resulting with the inclusion of time scaling correction. The mean of the observed methylphenidate hydrochloride concentrations for each of the three formulations from the population PK model for fraction absorbed estimation was used to develop basic IVIVC model. The parameter estimates of the IVIVC model are presented in Table 4. The variance–covariance matrix estimation step failed, and

TABLE 3 Mean parameter estimates for the fraction absorbed model of methylphenidate hydrochloride.

		Estimate	
Parameter	**Description**	**Mean**	**95% CI**
td_{50}	Time to 50% dissolution, h	11.8	[11.3, 12.1]
Gamma	Shape parameter	7.37	[7.03, 7.72]
RELF	Relative bioavailability to IR formulation	0.726	[0.668, 0.791]
k_{el}	Elimination rate constant, h^{-1}	0.270 (Fixed)	–
V	Central volume of distribution, L	2480 (Fixed)	–
$\omega^2_{td_{50}}$	BSV on td_{50} (variance)	0.0508	[0.0323, 0.0700]
ω^2_{gamma}	BSV on gamma (variance)	0.0287	[0.0170, 0.0400]
$\omega^2_{k_{el}}$	BSV on k_{el} (variance)	0.352	[0.282, 0.428]
ω^2_V	BSV on V (variance)	0.331	[0.244, 0.414]
Proportional residual error (%)		10.6	[9.49, 11.76]
Additive residual error, ng/mL		0.160	[0.13, 0.19]

Abbreviations: BSV, between subject variability; CI, confidence interval; IR, immediate release.

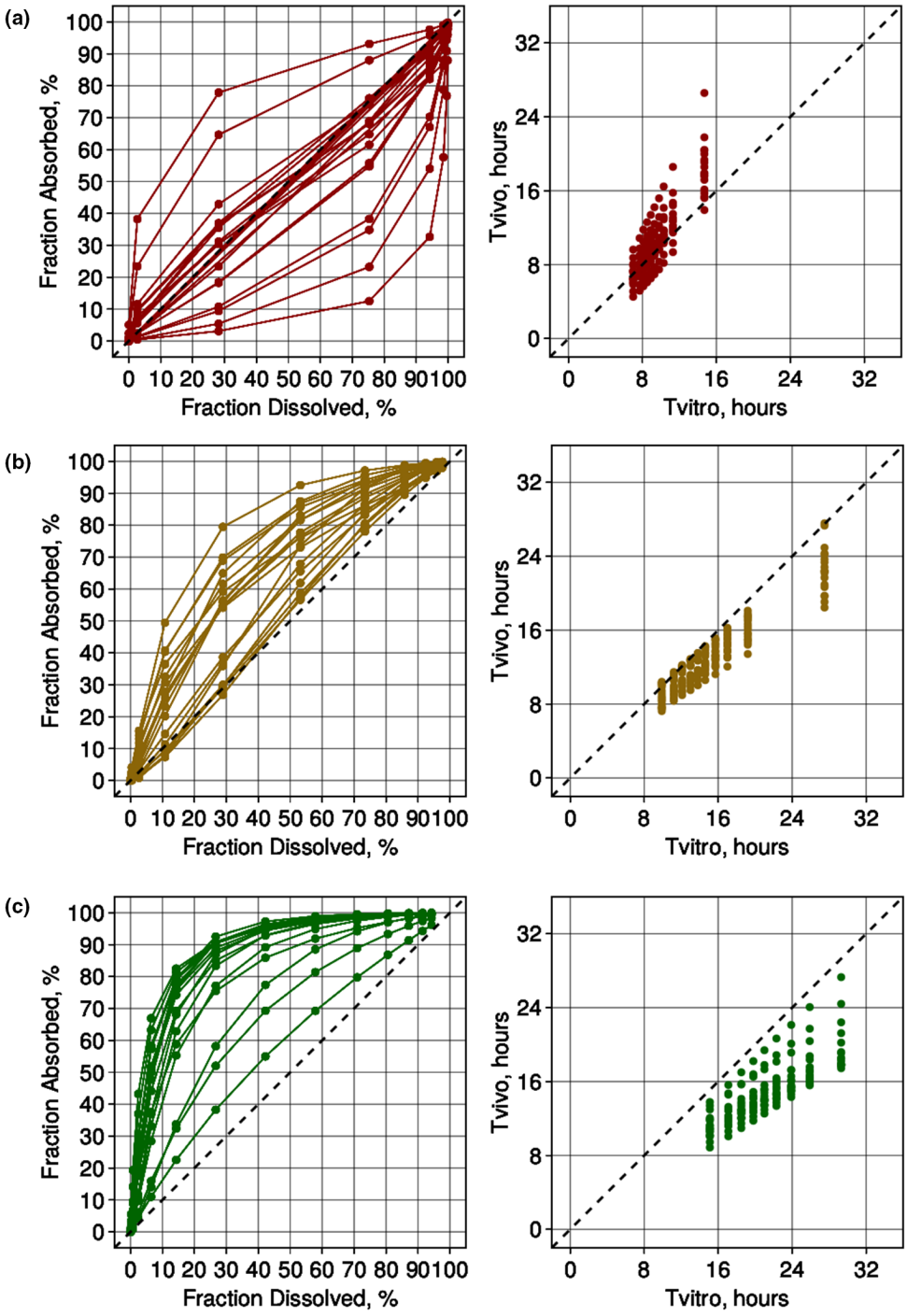

FIGURE 1 Fraction absorbed versus fraction dissolved (left panel) and Levy plot (right panel) for (a) fast, (b) medium, and (c) slow-release formulations.

hence standard error could not be estimated for the model parameters. The IVIVC model predictions for the fast, medium, and slow-release formulations are presented in Figure 2. In addition, the model-predicted relative bioavailability of the medium and slow-release formulations with respect to the fast-release formulation were 80.1% and 32.2%, respectively.

Internal predictability evaluation of IVIVC

To validate the IVIVC model internally, $AUC_{0-\infty}$ and C_{max} were estimated for each of the three formulations using NCA of observed data and of the IVIVC model predictions and then compared. The %PEs estimated using Equation 9 are presented in Table 5. The %PE (1.35%–13.1%) across all

TABLE 4 Mean parameter estimates for the IVIVC model.

Parameter	Description	Estimate (mean)
a_1	Base absorption	0 (Fixed)
a_2	Absorption scale	1 (Fixed)
b_1	Time shift	11.8
b_2	Time scaled for dissolution	0.258×10^{-4}
b_3	Shape parameter for dissolution	4.8
$RELF_{fast}$	RelF for fast formulation compared to IR formulation	1 (Fixed)
$RELF_{medium}$	RelF for medium formulation compared to IR formulation	0.801
$RELF_{slow}$	RelF for slow formulation compared to IR formulation	0.322
k_{el}	Elimination rate constant	0.27 (Fixed)
V_c	Central volume of distribution	2480 (Fixed)
$\omega^2_{k_{el}}$	BSV on k_{el} (variance)	0.352 (Fixed)
ω^2_V	BSV on V (variance)	0.331 (Fixed)
Additive residual error (ng/mL)		0.646

Abbreviations: BSV, between subject variability; IR, immediate release; IVIVC, in vitro-in vivo correlation; RelF, relative bioavailability.

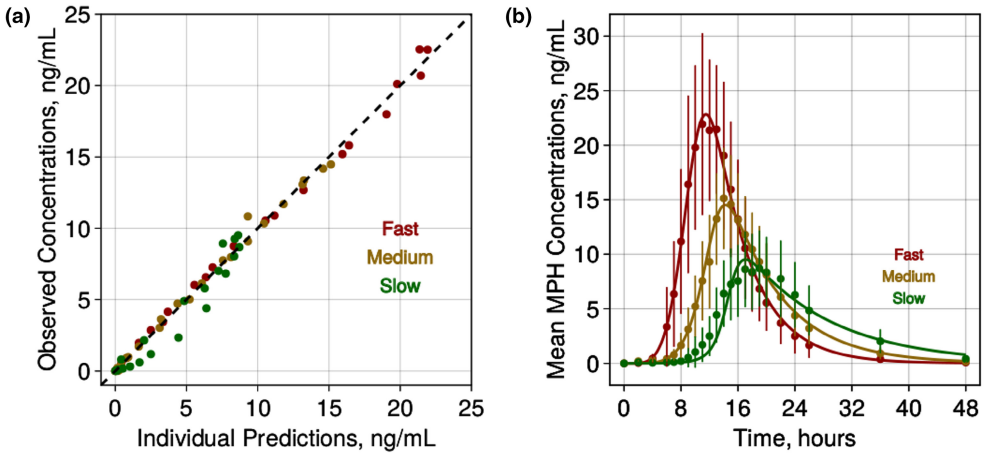

FIGURE 2 Mean MPH PK observed concentrations (dots) with the predicted values by the IVIVC model for the fast, medium, and slow-release formulations. (a) Observed vs. individual predicted concentration plot, (b) individual formulation fits (vertical lines at the observations represent 95% confidence intervals). IVIVC, in vitro-in vivo correlation; MPH, methylphenidate hydrochloride; PK, pharmacokinetic.

TABLE 5 Evaluation for internal predictability of the IVIVC model.

	Observed values		Predicted values		% Prediction error	
Formulations	C_{max}, ng/mL	$AUC_{0-\infty}$, ng h/mL	C_{max}, ng/mL	$AUC_{0-\infty}$, ng h/mL	C_{max}	$AUC_{0-\infty}$
Fast	25.2	231	21.9	234	13.1%	1.35%
Medium	15.6	177	15.1	181	3.23%	2.42%
Slow	9.57	151	8.71	156	9.01%	3.51%
Average					8.45%	2.43%

Abbreviations: $AUC_{0-\infty}$, area under the curve to infinity; C_{max}, peak plasma concentration; IVIVC, in vitro-in vivo correlation.

the three formulations was below 15%. The average %PE across the three formulations was 2.43% and 8.45% for $AUC_{0-\infty}$ and C_{max}, respectively. Hence, the IVIVC model passes the criterion for internal predictability according to the FDA Guidance.[6]

The results from NONMEM and Pumas were identical for all models and across all parameter estimates and hence the results from NONMEM are not presented in this paper. Owing to the sequential nature of the model building, estimates from previous steps had to be manually typed into the subsequent step in NONMEM. Whereas in Pumas, all model estimates and outputs could be called as internal objects eradicating repetitive tasks and the potential for typographical errors. In addition, Pumas offers greater flexibility compared to NONMEM because it provides a comprehensive data management system that simplifies the handling and manipulation of the datasets. Hence, Pumas results were chosen to be included in the manuscript.

DISCUSSION

The convolution-based method for assessing IVIVC has been shown to present several benefits with respect to the conventional assessment of IVIVC using convolution and deconvolution methodologies.[8,14] The main interest of the convolution-based method is that the overall IVIVC assessment can be implemented using a set of differential equations that are directly integrated without the need of applying convolution or deconvolution procedures. In this framework, various functional dependencies (e.g., time scaling) can be easily introduced to describe or to connect in vitro dissolution and in vivo absorption profiles. This can provide improved performance and increased modeling flexibility as no special software tools are required other than standard software for modeling (such as Pumas or NONMEM). Furthermore, the traditional methods based on the deconvolution and convolution approach require the assumption of linearity of the system being studied and are, therefore, unsuitable for use with compounds exhibiting dose disproportional kinetics. At variance of this limitation, the convolution-based approach can easily accommodate potential dose disproportionality in the PK processes by integrating the description of the potential nonlinearity in the differential equation used to define the IVIVC model.[14]

The mean apparent volume of the central compartment was estimated to be 2480 L in IR PK analysis of methylphenidate hydrochloride. There is quite a bit of variability in reported apparent V of methylphenidate hydrochloride. After a systematic review of the reported V, it is found that the volume estimate reported in this paper seems to be reasonably close to the volume estimate reported by Gomeni et al. and the FDA summary basis of approval for Ritalin LA.[15–18]

The IVIVC model was developed using the in vitro dissolution and the in vivo PK data of three ER formulations (fast, medium, and slow). The in vitro dissolution data were able to describe the in vivo PK time course adequately for each formulation evaluated.

The potential need for time-scaling and time-shift components in the IVIVC model was evaluated by inspecting the scatterplots of $f_{diss}(t)$ versus $f_{abs}(t)$ and Levy plots, as shown in Figure 1, which suggested a temporal difference between the rates of dissolution and absorption. Mechanistically, this is expected given that the commercial formulation of DR/ER-methylphenidate hydrochloride was designed to release the drug at a certain rate, taking into account the retention and absorption location(s) through the gastrointestinal (GI) tract. The fast and slow formulations were developed for the purpose of developing the IVIVC, perturbing the original optimized final formulation (which is close to the medium formulation). Hence, deviations in the time scale between in vivo and in vitro profiles is understandable.

The relevance of the time-scaling component in the convolution-based model was formally evaluated by comparing the model performance in the presence and absence of time-scaling. The comparison of alternative models (test model: the one with time-scaling and reference model: the one without time-scaling) was conducted using the likelihood ratio test.[19] The assumption of this method is that the change in the objective function values which -2LL in case of Pumas (i.e., Δ-2LL = [(−2LL of test model) – (−2LL of reference model)] is chi-squared (χ^2) distributed with df equal to the difference in the number of parameters between the test and the reference model. The -2LL values in Pumas were: 524 units and 194 units for the reference and or the test model, respectively. Therefore, Δ-2LL was −329 with 3 df indicating that the inclusion of time-scaling component in the convolution-based model significantly improved the ability of the model to describe the data.

The NCA indicated that the relative bioavailability of the fast formulation relative to IR was 1.33. In our opinion, the extended-release formulation is unlikely to have higher bioavailability than IR. Particularly given the relative bioavailabilities of medium and slow-release formulations are lower than the fast formulation. Most likely, the value of the relative bioavailability to be higher than one is a result of two different studies in different sets of subjects. Hence, the bioavailability of fast formulation was assumed to be one. The relative bioavailabilities of medium and slow formulations were estimated in the IVIVC estimation step. For the same mechanistic reasons with respect to the absorption process, the bioavailability varied with the rate of drug

release. Hence, relative to the fast formulation, the medium and slow formulations have lower bioavailabilities. The key for developing a reliable IVIVC model is to be able to quantify the change in bioavailability. Having a different bioavailability is not an issue, as long it is quantifiable and justified. Mechanistically the bioavailability is a function of the time to dissolve 50% of the drug (td_{50}). The td_{50} estimates for fast, medium, and slow formulations are 8.86 h, 13.7 h, and 21.0 h, respectively. The slower the formulation traverses through the GI tract the lower the bioavailability, presumably due to where the absorption occurs. The main purpose of quantifying the change in bioavailability is to allow the IVIVC model to be able to interpolate for dissolution rates that are within the fast and slow formulation release rates.

Overall, the time-course of mean methylphenidate concentrations for fast, medium, and slow formulations are well-predicted by the IVIVC model (Figure 2). For the slow formulation, the model slightly underestimates the concentrations during 10–16 h. The reasons for this slight deviation could range from dissolution conditions to natural unexplained variability in the PK data. Nevertheless, the IVIVC model performed well and the largest %PE associated with C_{max} for the fast formulation was 13.1% (within 15% per FDA Guidance), with the average %PE across all formulations within 10%. Hence, the IVIVC model passes the evaluation for internal predictability according to the FDA Guidance and does not warrant evaluation for external predictability.[6]

The existing IVIVC model requires additional enhancement to be effectively applied to a future formulation scenario, wherein only in vitro dissolution data are available and relative bioavailability remains unknown. As the relative bioavailability of a formulation corresponds directly to its dissolution rate, further refinement of the IVIVC model is necessary. This refinement would involve incorporating a bioavailability submodel, which is likely to be nonlinear in nature. This submodel would serve the purpose of predicting the relative bioavailability of a novel formulation based on td_{50}, time to dissolve 50% of the drug in vitro. Subsequently, the refined IVIVC model would facilitate the identification of safe zones of the dissolution profiles for new formulations, enabling them to satisfy the criteria for bioequivalence.

Overall, a successful IVIVC model was developed and validated according to the internal predictability criteria, as recommended by the FDA Guidance.[6] These results provide Level A IVIVC model support for DR/ER-methylphenidate hydrochloride post-approval manufacturing changes.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. B.I. and J.G. designed the research. R.G., J.G., and P.G. performed the research. B.I., R.G., and J.G. analyzed the data.

ACKNOWLEDGMENTS

The authors thank Cassandra Uchida and Michelle Po for proofreading.

FUNDING INFORMATION

This research work was supported by Ironshore Pharmaceuticals & Development, Inc.

CONFLICT OF INTEREST STATEMENT

J.G. is a co-founder of Pumas-AI that commercializes Pumas software and also a co-founder of Vivpro Corporation. J.G. and R.G. are paid consultants to Ironshore Pharmaceuticals & Development, Inc. B.I. is an employee of Ironshore Pharmaceuticals & Development, Inc. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gupta PK, Incledon B, Gobburu JVS, Gomeni R. A convolution-based in vitro-in vivo correlation model for methylphenidate hydrochloride delayed-release and extended-release capsule. *CPT Pharmacometrics Syst Pharmacol*. 2024;13:132-142. doi:10.1002/psp4.13067