In Silico Prediction of Optimal *in Vivo* Delivery Properties Using Convolution-Based Model and Clinical Trial Simulation

Roberto Gomeni[1,2], Carla D'Angeli[1], and Alan Bye[1]

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Purpose. To develop a new strategy for the *in silico* evaluation of the optimal *in vivo* delivery properties of a drug, minimizing a cost function defined by the brain receptor occupancy obtained in positron-emission tomography experiments.

Methods. A convolution-based model was formulated to link *in vivo* delivery rate to plasma concentrations whereas a second-stage model was used to link plasma concentrations to the pharmacodynamic effect. A feedback control approach was applied to identify the optimal *in vivo* delivery rate given an appropriate optimality criterion. Finally, clinical trial simulation was used as a supportive tool for decision-making by evaluating different scenarios accounting for pharmacokinetic/pharmacodynamic parameter uncertainty, inter-subject variability, and drug potency.

Results. The results revealed that the mean *in vivo* delivery time significantly affects brain receptor occupancy whereas the fraction of the dose available for the systemic circulation shows the highest influence on brain receptor occupancy for a given *in vivo* delivery rate. Finally, variability on receptor occupancy seems to be more affected by the inter-individual variability on the disposition PK parameters.

Conclusion. The integration of convolution-based model, feedback control approach, and clinical trial simulation offers a unique tool for *in ilico* improvement of the drug development process by identifying critical issues on drug properties, optimal *in vivo* delivery rate, and potential problems related to the inter-individual variability.

KEY WORDS: computer-assisted drug development; convolution-based model; feedback control; optimal *in vivo* delivery rate; PET imaging; trial simulation.

INTRODUCTION

The development, validation, and acceptance of appropriate biomarkers are seen as crucial in improving the drug discovery and development process. One of the most promising biomarkers being investigated in the development of central nervous system drugs is the measurement of drug binding to specific cerebral receptors (RO) by positron emission tomography (PET) imaging technology (1). PET studies can supply accurate information for a rational definition of a dosage regimen likely to achieve expected therapeutic outcomes, assuming that RO is a surrogate marker of a pharmacologic drug activity (2, 3). Preclinical studies have been conducted on a new compound for neurologic and psychiatric disorders, and an integrated model has been developed linking drug pharmacokinetics (PKs) to RO evaluated in PET experiments. Using this information, "first-time-in-man" and "proof-of-concept" experiments have been designed in humans (4). Moreover, to evaluate the potential of this new chemical entity for clinical development, it appeared essential not only to estimate the appropriate effective dose in man (5) but also to assess the expected optimal *in vivo* delivery rate, which has been identified as an important determinant of therapeutic outcome (6, 7). It was thus decided to investigate the properties that are required for an extended release formulation to prolong the duration of drug activity using an *in silico* approach. The development of *in silico* methods is today greatly enhanced by the availability of the computer-assisted drug development (CADD) technology (5). CADD is a knowledge-based iterative process by which newly collected information is integrated in the existing drug and disease-specific knowledge frame and used to refine and update the overall knowledge on the drug properties. The proposed *in silico* methodology is organized according to the CADD approach in three steps: 1) definition of a mechanistic model linking *In vivo* drug delivery to pharmacodynamic effect, as measured by RO; 2) development of a feedback control approach to estimate the optimal *In vivo* delivery rate; 3) evaluation of the impact of different sources of uncertainty [PK/pharmacodyamic (PD) parameter, inter-subject variability and drug potency] on the predicted pharmacodynamic response using clinical trial simulation.

MATERIALS AND METHODS

Convolution-Based PK Model

For drugs showing linear and time invariant disposition with respect to the input, the plasma concentration (C_p), resulting from an arbitrary dose, can be obtained by convolution:

$$C_p(t) = f(t)*UIR(t) = \int_0^t f(t-\tau)\cdot UIR(\tau)\cdot d\tau \qquad (1)$$

Where τ is the integrating variable (time), $f(t)$ is the rate of *in vivo* delivery, and $UIR(t)$ is the unit impulse response (e.g., the drug disposition and elimination time course estimated from intravenous bolus or infusion). In the example presented below, $f(t)$ will be described by a Weibull model whereas $UIR(t)$ will be described by a two-compartment linear model. The Weibull model (Eq. 2) was because it represents a general function that is currently used to describe *in vitro* dissolution data and *in vivo* input rate (8).

$$f(t) = F_d \cdot Dose \cdot \left(1 - e^{-\left(\frac{t}{t_d}\right)^{\beta}}\right) \qquad (2)$$

Where t_d is the time necessary to deliver 63.2% of the dose, F_d is the fraction of the dose available for the systemic circulation, and β is a unitless number defining the sigmoidal shape of the curve. Numerical convolution was performed using the point-area approach (9), and plasma concentrations after repeated doses were computed using the convolution model prediction based on a unitary dose and the superposition principle (10). A proportional variance error model was assumed to affect plasma concentrations.

Pharmacodynamic Response Model

The pharmacologic effect can be generally linked to plasma concentration using the following two methods: the effect compartment approach and the indirect effect model-

[1] GlaxoSmithKline, Via A. Fleming 2, 37135 Verona, Italy.

[2] To whom correspondence should be addressed. (e-mail: rog31390@gsk.com)

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ing approach. Sometimes drug concentration in the effect compartment (C_e) is a better predictor of the pharmacodynamic response. In this case, C_e may be estimated from the convolution of plasma concentration with the function $T(t)$:

$$C_e = C_p(t) * T(t) = \int_0^t C_p(t-\tau) \cdot k_{e0} e^{-k_{e0}\tau}\, d\tau \qquad (3)$$

Where k_{e_0} is the effect compartment equilibration rate constant. PD response can be modeled by the classic drug-receptor theory using the drug concentration (C) in the plasma compartment or in the effect site compartment. In the example presented below, C was assumed to be equal to C_p, and the sigmoidal $E_{\max}$ model was used with $E_{\max}$ fixed to 100:

$$PD(C) = \frac{E_{\max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \qquad (4)$$

An alternative modeling strategy is to use the indirect effect model approach. This approach assumes that the pharmacodynamic response is described by the differential equation:

$$\frac{dPD}{dt} = k_{in} \cdot (1 + H_1(t)) - k_{out} \cdot (1 + H_2(t)) \qquad (5)$$

Where k_{in} is a zero-order constant for production, k_{out} is the first-order rate constant for loss of response, and $H1(t)$ and $H2(t)$ are functions defining the stimulation or inhibition of the response (11). The proposed algorithm can use any of the two pharmacodynamic modelling approaches described above.

Adaptive Feedback Control Procedure

A feedback control process has been developed to estimate the properties of an extended release formulation by minimizing a cost function (CF), as defined by RO. The rationale for the use of RO as a surrogate marker of clinical efficacy was based on studies conducted on drugs of the same class, which suggest that the therapeutic effect occurs when RO is maintained above 70% over 24 h during chronic treatment of a few weeks' duration. CF was defined in relation to the therapeutic window (i.e., the minimal and maximal clinical effect value over a given time interval) within which the pharmacodynamic response is expected to lie (12).

$$CF = \frac{1}{T_e - T_s} \int_{T_s}^{T_e} (PD(t) - PD^*)^2 \cdot r \cdot dt \qquad (6)$$

Where T_e and T_s define the beginning and the end time of the evaluation period, $PD(t)$ is the estimated pharmacodynamic response, $PD^* = (PD_{\max} + PD_{\min})^*0.5$, $PD_{\min}$ and $PD_{\max}$ are the lower and upper bound of the therapeutic window, and r is a weighting factor that penalises the predicted $PD(t)$ effect when $PD(t)$ falls outside the therapeutic window. r is set to 1 for $PD(t)$ values inside the therapeutic window and to a large value otherwise. CF is a function of dose, frequency of administration and drug delivery rate, but for the purpose of the present analysis, CF was considered as only dependent on the delivery rate. The dosage regimen was fixed to the one presenting appealing properties for the new compound: once a day dose at the maximal safe dose. A direct search algorithm, based on the Hooke and Jeeves's method, has been implemented to minimise CF using of an iterative process starting from predefined initial parameter values (13).

Trial Simulation

Information gathered from drugs of the same class suggests that the therapeutic effect of the new compound is expected when the RO is maintained above 70% over 24 h during chronic treatment of a week's duration. Therefore, the therapeutic window was defined by $PD_{\max} = 100\%$, $PD_{\min} = 70\%$, $T_s = 162$ h, and $T_e = 192$ h. Five simulations, including several scenarios, were performed. The aim of the first simulation was to evaluate the *in vivo* average delivery rate (t_d* and β*) required to meet the therapeutic objective. Despite the information gathered from interspecies scaling, uncertainty persists on the expected fraction of the dose available for the systemic circulation in human (F_d) and on the *in vivo* drug potency (EC_{50}). Therefore, a second simulation was performed to evaluate the influence of alternative F_d and EC_{50} values on the expected clinical outcome. Finally, the objective of the third simulation was to evaluate the impact of inter-individual variability (IIV) on the absorption parameters, on disposition parameters, and on drug potency. One-hundred subjects receiving an oral dose of 30 mg once a day for a week were enrolled in each simulation scenario. In the first simulation, F_d was fixed to 0.6, EC_{50} was estimated from *in vitro* binding studies (0.467 ng/mL), and an IIV of 20% was used for each parameter.

The optimal t_d and β values were estimated for each subject using $t_d = 1.5$ h and $\beta = 0.5$ (the values describing the oral solution absorption rate) as initial parameters in the search algorithm. The estimated average t_d and β values (t_d* and β*) were, therefore, considered as typical delivery values for the optimal formulation and used in the subsequent simulations. Sensitivity analysis was performed to investigate the influence of potential changes and errors in model parameters on conclusions drawn from this simulation. The normalised sensitivity index (SI), quantifying the percentage change in pharmacodynamic response at a percentage change of the parameter p, was computed for the median PD (PD*) and p (p*) reference and optimal values (14) as:

$$SI = \frac{\partial PD}{\partial p} \cdot \frac{p^*}{PD^*} \qquad (7)$$

The highest SI values are associated to the most relevant parameters. In the second simulation, t_d and β were fixed to t_d* and β* while the clinical outcome was evaluated for three values of F_d (0.4, 0.6, and 0.8) and EC_{50} (0.367, 0.467 and 0.567 ng/ml) assuming an IIV of 20% for each parameter. A total of nine simulation scenarios were investigated.

In the third, fourth, and fifth simulations t_d and β were fixed to t_d* and β*, F_d to 0.6, and EC_{50} to.467 ng/mL, whereas the influence on the clinical outcome of low and high IIV values were investigated as follows. Simulation 3: IIV on PK absorption parameters (t_d, β, and F_d) of 10%, 20%, or 30%, and 20% for all other parameters; simulation 4: IIV on PK disposition parameters (clearance and V) of 10%, 20%, or 30%, and 20% for all other parameters; and simulation 5: IIV on drug potency (EC_{50}) of 10%, 20%, or 30%, and 20% for all other parameters

The PK parameters [clearance = 109.5 L/h, $k_{12} = 0.1$ h^{-1}, $k_{21} = 0.12$ h^{-1}, volume of the central compartment = 498

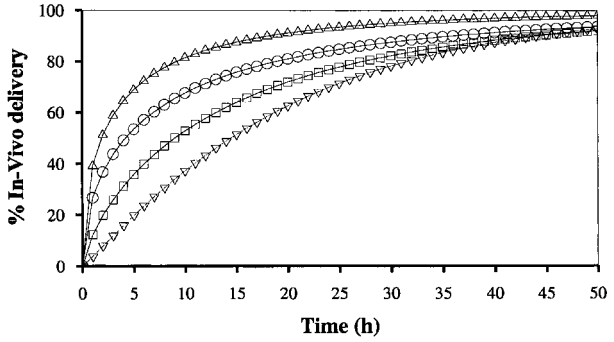

Fig. 1. Weibull model predicted *in vivo* delivery curves estimated by the adaptive feedback control algorithm as a function of the targeted therapeutic window: RO = 50–100%, t_d = 3.75, β = 0.53 (△); RO = 60–100%, t_d = 8.08, β = 0.56 (○); RO = 70–100%, t_d = 14.6, β = 0.76 (□) and RO = 80%-100%, t_d = 20.3, β = 1.08 (▽).

L] were based on scaling from preclinical studies and previously reported data (4). The median and the 5th and 95th percentiles of the pharmacodynamic effect (RO) were estimated at 24 h after the seventh dose to evaluate and compare the different simulation scenarios. Each parameter was assumed to be lognormally distributed, and the coefficient of variation associated to the distribution was used as a measure of the IIV. The computer simulations were performed using the NONMEM (Version V) software (15). Through repeated Monte Carlo simulations, the distribution of possible outcomes for each of many variations on experimental design

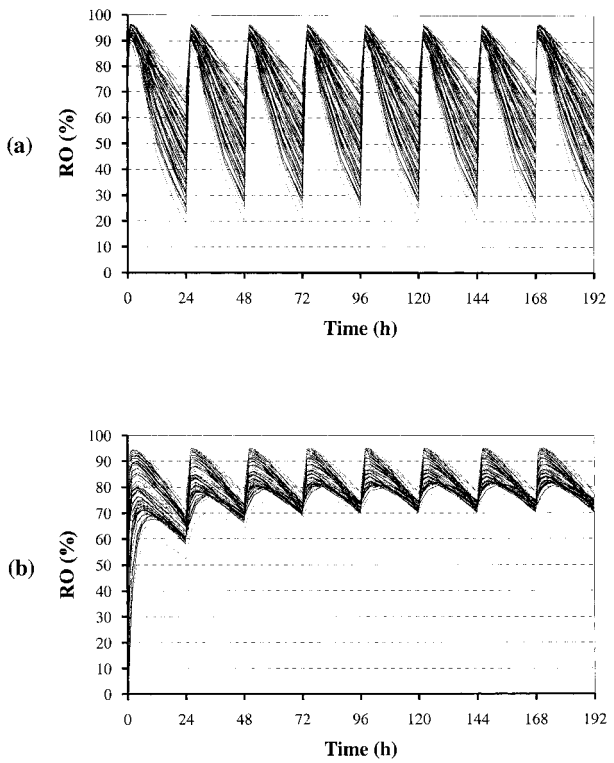

Fig. 2. Simulation 1. Time–course of the individual predicted RO values after the administration of an oral dose of 30 mg once a day for a week. (a) RO values estimated with the initial *in vivo* delivery parameters (t_d = 1.5 h and β = 0.5). (b) RO values estimated with the adjusted *in vivo* delivery parameters (t_d = 14.6 h and β = 0.76) and a therapeutic window defined by RO ranging from 70% to 100%.

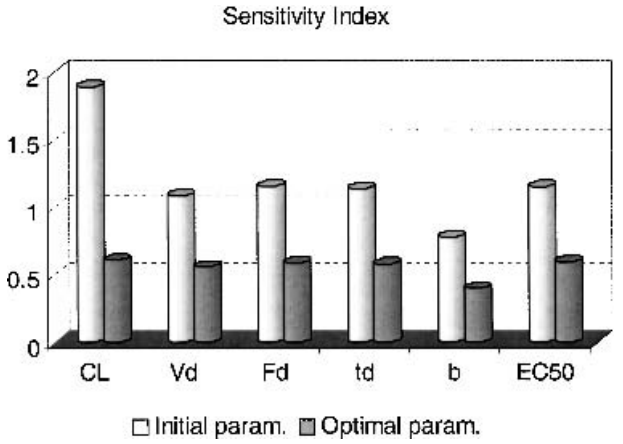

Fig. 3. RO sensitivity to model parameters computed for the initial and optimal t_b and β values.

was estimated. The simulations were based on a stochastic model describing drug disposition and effects in a single subject over time as a function of subject characteristics, study design, and random factors. Statistical analyses of the simulated parameters were performed using SAS system (Version 8) (16).

RESULTS

Simulation 1

Fixing the upper RO value to 100%, four different minimal RO values (50%, 60%, 70%, and 80%) were used to explore the influence of different settings in the therapeutic window on the expected *in vivo* delivery properties. The estimated mean Weibull model parameters for the 4 RO values are: t_d = 3.75 h, β = 0.53; t_d = 8.08 h , β = 0.56; t_d = 14.6 h , β = 0.76, and t_d = 20.3 h , β = 1.08. Figure 1 displays the predicted *in vivo* delivery curves estimated by the adaptive feedback control algorithm as a function of the targeted therapeutic window. Figure 2 displays the time-course of the predicted individual RO values after an oral dose of 30 mg once a day for a week. The optimal *in vivo* delivery parameters for a therapeutic window defined by 70% < RO < 100%, were t_d = 14.6 h and β = 0.76. Figure 3 displays the RO

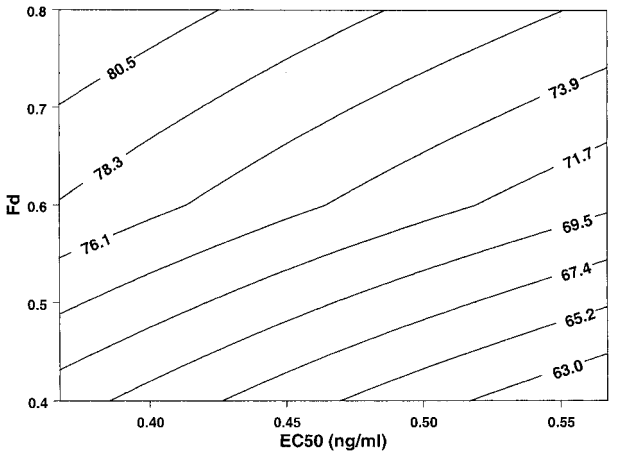

Fig. 4. Simulation 2. Contour plot summarizes the simultaneous influence of F_d and EC_{50} on the expected RO values.

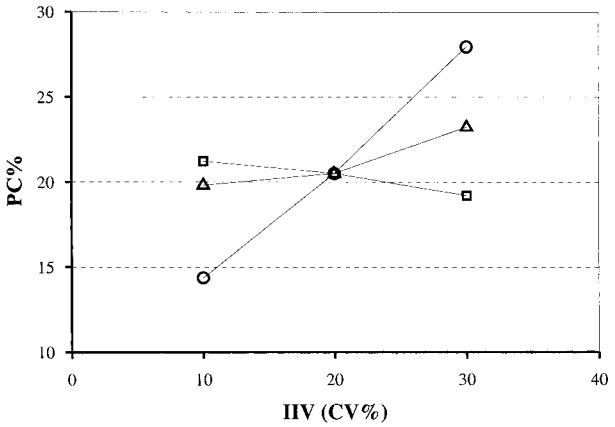

Fig. 5. Simulations 3, 4, and 5. Percentage changes of the difference between median RO and 5th RO percentile as a function of the IIV dispersion on the absorption parameters (△), disposition parameters (○), and drug potency (□).

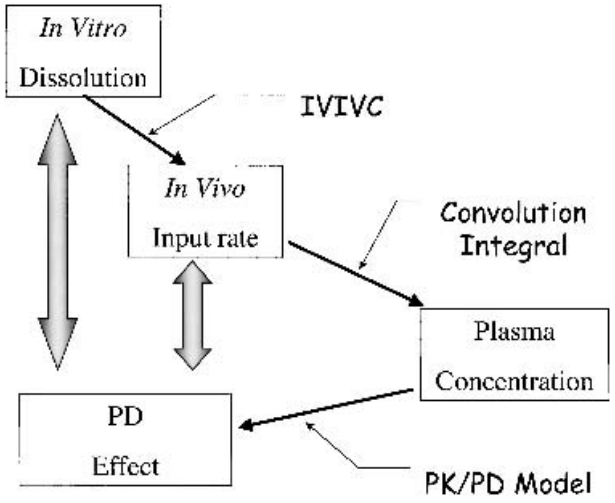

Fig. 6. Flow chart of the integrated model linking *in vitro* dissolution and/or *in vivo* input rate to the pharmacodynamic response.

sensitivity to changes in model parameters computed at the initial and optimal t_b and β values.

Simulation 2

The predicted median RO values estimated 24 h after the seventh dose as a function of different values of F_d and EC_{50} are displayed in the contour plot shown in Figure 4.

Simulations 3, 4, and 5

The median RO values and the 5th and 95th percentiles have been estimated 24 h after the seventh dose at increasing IIV dispersion values. The 5th RO percentile represents the most sensitive parameter to predict lack of drug efficacy in a target population: the lower this value, the higher the likelihood of lack of efficacy.

$$PC\% = 100 \cdot \frac{Median - 5^{th}\ percentile}{Median} \tag{8}$$

The percentage change relative to the difference between median RO and 5th RO percentile is displayed in Figure 5. This parameter shows how IIV on absorption PK, disposition PK, and drug potency affects the likelihood of lack of efficacy.

DISCUSSION

This article illustrates an integrated approach for the *in silico* design of an extended release formulation using feedback control theory, a convolution-based model, and trial simulation technology jointly with PET imaging data. The availability of validated biomarkers significantly increases the interest for the use of *in silico* methods for the prediction of the expected properties of new compounds. This approach enables a discriminating criterion among drug candidates. It also allows one to differentiate products by investigating competitors' weakness and strengths, to design experiments, to predict optimal dosage regimens, and finally to define the required formulation properties.

The results of the first simulation reveal that changes in *in vivo* delivery rate can significantly affect the receptor occupancy after a chronic treatment, with a fixed dosage regimen, mainly altering the mean *in vivo* drug delivery time. However, this finding is probably more enhanced by the disposition properties of the drug under evaluation because drugs that show a relatively short half-life are expected to be greatly influenced by changes in delivery profile. In addition, t_d seems to drastically influence the extent of variability on the predictions: with small t_d the relative dispersion is larger at 24 h (trough time) and smaller at 2 h (peak time) whereas with large t_d, we observed an opposite trend in the receptor

Table I. Simulation 3, 4, and 5. Median RO with the 5th and 95th Percentiles Estimated 24 h after the 7th Dose Estimated at Increasing IIV Dispersion Values

Simulation	IIV (CV%)	Median RO%	5th percentiles	95th percentiles	PC%
3 (absorption)	10	73.85	59.21	88.24	19.82
	20	73.83	58.69	87.53	20.51
	30	73.42	56.36	88.88	23.24
4 (disposition)	10	74.29	63.62	86.67	14.36
	20	73.83	58.69	87.53	20.51
	30	74.04	53.33	89.47	27.97
5 (potency)	10	74.64	58.8	86.06	21.22
	20	73.83	58.69	87.53	20.51
	30	72.74	58.76	88.49	19.22

occupancy dispersion, as displayed in Figure 2. This finding indicates how the dispersion on pharmacodynamic response can be controlled and adjusted to meet requirements by tuning the *in vivo* delivery rate. The sensitivity analysis indicates that receptor occupancy is more sensitive to model parameter changes estimated at low (1.5 h) than at high t_d (15.6 h) value. At low t_d, clearance is the most relevant parameter whereas at high t_d value, all the parameters showed similar sensitivity index. This result seems to indicate that the model response is less affected by parameter variability and estimation error at high dissolution time values. The results of the second simulation are summarised in the contour plot (Fig. 4) showing the simultaneous influence of F_d and EC_{50} on the expected receptor occupancy values: RO > 70% is expected with EC_{50}< .55 ng/mL but with $F_d > 0.65$. Obviously, these considerations remain strictly related to the PK/PD properties of each drug. In any case, these findings may constitute a helpful supportive tool for the screening of alternative drug candidates in the drug development process. The aim of the last three simulations was to investigate the influence of IIV on receptor occupancy dispersion at 24 h after the seventh dose. The 5^{th} percentile of the receptor occupancy distribution was considered as a measure of the risk for lack of efficacy. The results reported in Table I show an almost linear increase of the percentage error with the increase of the coefficient of variation of disposition PK parameters, whereas only minor changes are observed on the percentage error with the increase of the coefficient of variation of absorption PK parameters and drug potency. This finding emphasizes the need to identify and control the sources of IIV in the disposition kinetic parameters during the clinical development process, as a key factor for an effective use of this drug. We can finally recall that one of the challenges in biopharmaceutics research is to find the relationship between *in vitro* characteristics of an oral formulation and its *in vivo* performance. Such a relationship is known as "*in vitro/in vivo*" correlation. Three possible correlation levels (A, B, and C) have been defined: level A establishes a direct relationship between the *in vitro* and the *in vivo* dissolution/time profiles whereas levels B and C relate summary statistics for the *in vitro* and *in vivo* profiles. Only type A correlation enables one to use *in vitro* data to predict *in vivo* performance. Using predictive mathematical model, one can assess the relation between the *in vitro* dissolution/release and *in vivo* response time course (17). Therefore, for a formulation that presents correlation of level A, the pharmacodynamic characteristics (such as onset and duration of action, maximum intensity of effect, time of maximum effect, and offset rate) can be directly linked to the *in vitro* dissolution properties. In these circumstances, the proposed convolution-based PK model can be easily extended by replacing the *in vivo* input rate with the *in vitro* dissolution rate after appropriate time-scaling parameters correction has been applied (18). This possibility can significantly enlarge the applicability of an *in silico* evaluation of the drug release properties for formulation development (Fig. 6). In conclusion, the results show that the use of surrogates or direct measurements of clinical endpoints jointly with convolution-based model, feedback control approach and clinical trial simulation offers a unique integrated tool for the *in silico* drug development process by identifying critical issues on drug formulation properties, optimal *in vivo* delivery rate and potential problems related to the inter-individual variability.

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