An Automated Process for Building Reliable and Optimal In Vitro/In Vivo Correlation Models Based on Monte Carlo Simulations

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ABSTRACT

Many mathematical models have been proposed for establishing an in vitro/in vivo correlation (IVIVC). The traditional IVIVC model building process consists of 5 steps: deconvolution, model fitting, convolution, prediction error evaluation, and cross-validation. This is a time-consuming process and typically a few models at most are tested for any given data set. The objectives of this work were to (1) propose a statistical tool to screen models for further development of an IVIVC, (2) evaluate the performance of each model under different circumstances, and (3) investigate the effectiveness of common statistical model selection criteria for choosing IVIVC models. A computer program was developed to explore which model(s) would be most likely to work well with a random variation from the original formulation. The process used Monte Carlo simulation techniques to build IVIVC models. Data-based model selection criteria (Akaike Information Criteria [AIC], R^2) and the probability of passing the Food and Drug Administration "prediction error" requirement was calculated. To illustrate this approach, several real data sets representing a broad range of release profiles are used to illustrate the process and to demonstrate the advantages of this automated process over the traditional approach. The Hixson-Crowell and Weibull models were often preferred over the linear. When evaluating whether a Level A IVIVC model was possible, the model selection criteria AIC generally selected the best model. We believe that the approach we proposed may be a rapid tool to determine which IVIVC model (if any) is the most applicable.

KEYWORDS: Monte Carlo simulations, IVIVC models, sigmoid, Hixson-Crowell, Gompertz, Mitcherlich, logistic, Weibull, linear, Higuchi

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INTRODUCTION

An in vitro/in vivo correlation (IVIVC) model uses in vitro dissolution data to predict in vivo concentration outcomes.¹⁻⁴ The Food and Drug Administration (FDA) guidance generally accepts an IVIVC model when the predicted metrics (usually area under the plasma concentration curve [AUC] and maximum concentration [$C_{\max}$]) have prediction errors of less than 10%, compared with the observed metrics⁵:

$$PE = \frac{(Metric_{obs} - Metric_{pred})}{Metric_{obs}} * 100 \quad (1)$$

where PE indicates prediction errors; $Metric_{pred}$, geometric mean of the $C_{\max}$ or AUC predicted by convolution; and $Metric_{obs}$, geometric mean of the $C_{\max}$ or AUC observed in the study. For the simplicity of description, models satisfying this requirement are called "predictive IVIVC models" in this article. A predictive IVIVC model helps reduce the number of bioequivalency studies (BE) during scale-up and postapproval changes by biowaivers. BE studies are FDA regulated and mandated to demonstrate that two formulations have similar pharmacokinetics. For example, when a formulation or manufacturing condition is changed, the resulting in vitro dissolution can be used, through a validated IVIVC, to predict whether the changed formulation is likely to be "bioequivalent" to the original formulation. Under such conditions, the requirement for a clinical study may be waived by the FDA. Another potential benefit of developing an IVIVC model is to provide information on the likelihood of success for a BE study under consideration; this utility is important for internal decision making in the pharmaceutical industry.

The procedure of developing an IVIVC consists of the following 4 steps: (1) collection of cumulative in vitro dissolution data $D(t)$ (in percentages), where $D(t)$ is an increasing function of time; (2) collection of in vivo concentration data $C(t)$ at time t ; (3) calculation of cumulative in vivo absorption rate $A(t)$ from $C(t)$ (eg, via a deconvolution method); and (4) modeling of the relationship between $A(t)$ and $D(t)$.

The direct functional relationship between $C(t)$ and $D(t)$ is often complicated, and few mathematical functions are available to capture this relationship. This is why it is much less common to directly model the relationship between $C(t)$ and $D(t)$, although some authors have explored this strategy.^{6,7} Since both $A(t)$ and $D(t)$ increase from 0% to

100% over time, it is reasonable in many cases to assume that the 2 may have a linear relationship. The linear model is the most commonly used function, particularly when the in vivo absorption profile is almost superimposable on the in vitro dissolution profile. This model may be predictive if the measured ingredient's solubility and permeability characteristics do not confound the controlled-release formulation's rate-controlling characteristics. In some cases, modifications in the model may be made to accommodate such physiological factors as gastric emptying. For an enteric-coated controlled-release dosage form for example, the "clock" for the absorption profile does not start until the formulation is emptied from the stomach. The result often can be a longer lag in vivo than observed in vitro. By instituting a physiologically reasonable "time-shift" to account for gastric emptying, the linear IVIVC might be improved.^{4,8,9} Another variation on the linear model is to incorporate a scaling factor.¹⁰ The scaling factor may accommodate differences in agitation, gut content effects on release and/or dissolution, permeability, and so forth.

Alternatively, when these variations fail to improve the linear relationship, several nonlinear models have been proposed for this purpose. When there is a longer absorption lag than dissolution lag, one of the models that demonstrates a "step" (eg, the sigmoid model) may predict better than the linear model. On the other hand, if the permeability or dissolution of a compound decreases as the formulation travels from the small intestine into the colon, the absorption may lag behind the dissolution; in this case, the Higuchi model may be preferred.

Mendell-Harary found that, according to Akaike Information Criteria (AIC, equation 2), the sigmoid, Hixson-Crowell, Gompertz, and Mitcherlich models best fit their modified release beaded capsule formulation; the logistic and Weibull models—while worse than the first 4—were better than the linear model; and the Higuchi model had the worst fit of their IVIVC.¹¹ However, this generalization might not be the case for other IVIVC. A large-scale survey may be needed to either find out if there is any model that universally works well or provide some guidance on what model works well under what circumstance(s).

In the authors' computer program, the linear model and the 7 nonlinear models are simultaneously evaluated.¹¹ The automated IVIVC modeling process included deconvolution, fitting the 8 different functions for each data set, convolution, computation of prediction error, and cross-validation. While the shape of these functions may greatly vary (depending on the parameter values), one such family of curves is shown in Figure 1.

The objectives of this simulation study are to evaluate the performance of each model under different circumstances and to investigate the effectiveness of common statistical model selection criteria for choosing IVIVC models.

Figure 1. Eight IVIVC Models for Formulation C.

MATERIALS AND METHODS

The following materials were used in this study: compound A, compound B (Pfizer Inc, Groton, CT) and pseudoephedrine HCl (BASF, Florham Park, NJ). Some salient biopharmaceutical properties of these compounds are listed in Table 1.

Formulation and Dissolution Studies

Five formulations were initially examined using the programs. One formulation with very short duration controlled release (CR) sampling and one formulation with an incomplete (ie, truncated) plasma sampling profile were not summarized in this report. The results of 3 formulations are summarized, and one example (formulation A) is detailed here for illustrative purposes. The formulations "A" (containing compound "A") and "C" (containing pseudoephedrine HCl) were made using the osmotically-driven "pump," asymmetric membrane technology (AMT).¹² Compounds with good solubility were candidates for this technology. In brief, the core consisted of a tablet containing active drug, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, and water. The core was compressed into a tablet and coated with a membrane consisting of ethylcellulose or cellulose acetate, polyethylene glycol, acetone, and water. The asymmetric coating controlled the release of the active drug. Dissolution testing of the controlled-release formulations was performed using *United States Pharmacopeia (USP)* apparatus 2 with paddles rotating at 50 rpm. The dissolution medium was 900 mL of pH 1.2 simulated gastric fluid without enzymes (SGF), which was maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The 1-L dissolution vessels were covered to minimize evaporation. Sample aliquots of 5 mL were withdrawn from each vessel at 1, 2, 4, 8, 12, 20, and 24 hours and filtered prior to analysis by reversed-phase high-performance liquid chromatography (HPLC). Typically, a 20- μL volume was injected into a mobile phase consisting of 77/18/5: 0.2% trifluoroacetic acid, acetonitrile, 2-propanol, at a 0.5 mL/min flow rate, and detected at 264 nm with a retention time of 2.6 minutes.

Table 1. Selected Biopharmaceutical Properties of Compounds in Formulations A, B, and C*

Compound/ Formulation	MW* (dalton)	Solubility (mg/mL) [†]	Log P [‡]	pK _a	Permeability [§]
A/A	490	<0.1	2.9	7.3	HP/LP
B/B	428	>30	4.7	2.9	HP
Pseudoephedrine HCl/C	165	>100	0.9	9.4	HP

*MW indicates molecular weight; [†]solubility measured at pH 6.5 and higher; [‡]octanol/pH 7 water; [§]HP (high permeability) indicates F_a (fraction of the compound is absorbed after oral administration) > 90%, LP (low permeability) indicates F_a < 90%.

^{||}Compound A is a substrate for saturable intestinal efflux: at low doses it shows characteristics of LP, at high doses it shows characteristics of HP (According to the manufacturer, written personal communication; Rob Polzer, Pfizer Inc, Ann Arbor, MI).

Clinical Studies

The Institutional Human Experimentation committee, in accordance with all applicable regulations, approved the study, and informed consent was obtained after the nature and possible consequences of the studies were explained. Although these studies were completed over a period of 10 years, and therefore no 2 studies were completely alike, there were some similarities in their protocols. Pharmacokinetic studies were performed with separate cohorts, as part of respective candidate development programs. The studies used a crossover design, which evaluated the pharmacokinetics of the CR and the immediate release (IR) formulation. The cohorts consisted of 6 to 12 normal, healthy, male subjects between the ages of 18 and 45, who weighed between 61 and 91 kg. Formulations were administered to fasted subjects with a total volume of 240 mL water. Meals were provided to all subjects at 4.25 and 10 hours following formulation administration. A suitable wash-out period of at least 1 week was observed between crossover dosing. Analysis of compound A in plasma or serum was completed using a published assay.¹³

Pharmacokinetic Calculations

The preliminary calculations used the software Kinetica (Version 2.2, Thermo/Innaphase, Philadelphia, PA). C_{max} was determined by inspection of the data. T_{max} was defined as the time of first occurrence of C_{max}. Area under the plasma concentration vs time curve (AUC_{last}) was calculated for the interval of predose to the time of last quantifiable concentration (T_{last}). Terminal phase rate constants in plasma (kel) were estimated as the slope of the least-squares regression of log plasma concentration against time for the linear terminal portion of the curves. AUC_{last} was extrapolated to infinity (AUC_∞): AUC_∞ = AUC_{last} + C_{last}*/kel, where C_{last}* is the concentration estimated at T_{last} from the aforementioned regression. Geometric mean values of C_{max} and AUC_∞ were reported. Arithmetic mean values of other parameters were reported.

Some software programs (eg, Kinetica 2.0) compute derivation, integration, AUC, convolution, and deconvolution based on observed time points via piece-wise approximation. Any sharp curve will lead to statistically significant errors. An alternative method is to fit the curve first, and then compute the parameters based on the estimated curves. If the type of the curve can be determined with reasonable precision, this approach should be more accurate than the piece-wise approach. The Levenberg-Maquart algorithm¹⁴ was used for fitting the nonlinear models in the author's program to increase convergence rate.

A thorough analysis of 9 types of data sets (2 bolus, 5 oral, 2 infusion) with numerous methods (eg, trapezoidal, log-linear) concluded that the parabolic fitting approach was preferred.¹⁵ The parabola method was implemented in this program.

Model Selection Procedure

The Akaike Information Criteria (AIC) is shown in Equation 2¹⁶:

$$AIC = n \log \left(\frac{1}{n} \sum_{t=1}^n [A_{obs}(t) - A_{pre}(t)]^2 \right) + 2(P + 1) + n \quad (2)$$

where P is the number of parameters in the model, and n is the number of sample points. The adjustment (P + 1) is used because the variance of error distribution σ² is unknown, which adds one more parameter to the P regression coefficients. AIC is derived for small P/n and large sample size n. For moderate P/n or small sample size, the term 2P does not penalize over-parameterization enough. AIC is a negatively biased estimate of true Kullback-Leibler information,¹⁷ while the corrected AIC (AIC_c) is an unbiased estimate of the true information when the model is linear, and approximately unbiased when the model is nonlinear¹⁸:

$$AIC_c = AIC + \frac{2(P + 1)(P + 2)}{(n - P - 2)} \quad (3)$$

Since different models may perform well for different data, most of the proposed models are worth consideration.

In practice, a necessary step is to use corrected AIC to scan all the models and select the best fit for a specific data. In addition, R^2 and adjusted R^2 (R_a^2) were calculated according to Equations 4 and 5:

$$R^2 = 1 - \left(\frac{SSE}{SST} \right) \quad (4)$$

$$R_a^2 = 1 - \left(\frac{SSE}{SST} \right) * \frac{(n-1)}{(n-3)} \quad (5)$$

where SSE is the sum of squares of errors; SST is the total sum of squares; and n is the number of time points.

Simulation Study

Model selection criteria were R^2 , adjusted R^2 , AIC, and AIC_c , as described above. The effectiveness of a model selection criterion was measured by its ability to select the model that had the best chance to pass the FDA requirement on PE in AUC and C_{max} . Prediction error in AUC and prediction error in C_{max} are denoted by “AUC-PE” and “ C_{max} -PE.” The criteria to “pass the FDA requirements” are met if both AUC-PE and C_{max} -PE are within 10%.

The simulation study consisted of each data set being fitted using the 8 IVIVC models, followed by (1) model selection

based on PE criteria and the model selection criteria R^2 , R_a^2 , AIC, and AIC_c using the original data set ($n = 1$); (2) model selection based on PE criteria using a “cross-validation” data set simulated by adding a $\pm 10\%$ random variation to the original data set ($n = 1$); (3) a $\pm 10\%$ random variation added to the original concentration data to create 4999 additional data sets for each formulation ($n = 4999$); (4) 95% confidence intervals (CI) about the PE were calculated for each model ($n = 4999$); and (5) the percentage of 4999 simulations and original dataset that a specific model selected by the above criteria (PE, R^2 , R_a^2 , AIC, or AIC_c) passed the FDA requirements.

The creation of additional data sets simulated the practical situation of formulation changes. A model built on the first large batch of tablets intended for a large clinical trial (biobatch) may work for the original data set simply by chance. Using the bootstrap method and introducing random variation, a reliably predictable model can be selected based on the biobatch, and the model is likely to be applicable for formulations varying from the biobatch within a certain range.

For each of the formulations, this IVIVC process was completed for each of the 5000 data sets in the simulation. An SAS/IML (SAS for Windows, Release 8, Cary, NC) program

Table 2. Simulation Results for Formulation A: Prediction errors in AUC and C_{max} , AIC, AIC_c , R^2 , R_a^2 , estimated 95% confidence intervals of prediction errors, and percentages of models pass FDA requirements on prediction errors*

	Linear	Gompertz	Sigmoid	Weibull	Logistic	Micherlich	Hixson	Higuchi
Ori-data AUC PE:	8.96	14.63	0.90	0.26	19.51	3.63	4.82	6.58
Model-based	11.52	14.82	1.85	1.34	19.59	4.30	5.38	7.55
Cross-validation								
Ori-data C_{max} PE	21.27	2.88	-4.71	-3.24	9.23	-3.20	-2.17	0.34
Model-based	16.80	-3.08	-12.71	-11.14	3.78	-11.14	-8.44	-7.13
Cross-validation								
Ori-data:								
AIC	92.45	93.14	88.58	88.80	96.50	87.55	86.48	89.08
AIC_c	95.12	98.14	97.15	97.37	101.50	92.55	89.15	90.28
R^2	0.926	0.933	0.960	0.959	0.914	0.957	0.953	0.934
R_a^2	0.920	0.920	0.946	0.945	0.897	0.948	0.949	0.934
95% CI†:	6.37 ~	12.30 ~	-1.04 ~	-1.57 ~	17.25 ~	0.99 ~	2.74 ~	4.41 ~
AUC PE	11.57	16.85	2.93	2.66	21.88	6.21	6.89	8.73
C_{max} PE	15.08 ~	-1.83 ~	-9.20 ~	-8.14 ~	3.21 ~	-8.18 ~	-7.53 ~	-5.72 ~
	29.4	11.23	4.25	5.19	17.41	5.22	6.87	9.62
% Pass‡:								
AUC PE	79.10	0.00	100.00	100.00	0.00	100.00	100.00	99.90
C_{max} PE	0.00	95.50	98.90	99.60	49.50	99.50	99.50	97.90

*Ori-data indicates that the results are based on the original IVIVC data of the compound; AUC, area under the plasma concentration curve; PE, prediction errors; C_{max} , maximum concentration; AIC, Akaike Information Criteria; and AIC_c , corrected AIC; and R_a^2 , adjusted R^2 .

†95% confidence intervals based on 5000 simulation replications

‡ % Pass is the percentage of simulation replications in which the prediction errors by the models are within the Food and Drug Administration requirement of 10%.

was written to carry out this simulation (code is available upon request). This program performed the whole IVIVC process for multiple data sets in a single run. The program took only a few hours to complete all the computations for each formulation with 5000 data sets. The initial values can be any value (estimated from Kinetica or a program available upon request) did not affect the results but affected the convergence speed and thus the computational time.

RESULTS AND DISCUSSION

Table 2 contains PE for AUC (top 2 rows) and $C_{\max}$ (rows 3 and 4) based on the original data and the cross-validation data (top 2 rows). The preferred model had PE < 10% for both $C_{\max}$ and AUC. Four somewhat standard statistical criteria for “goodness of fit,” namely, AIC, AIC_c , R^2 , and R_a^2 are listed in the middle rows. The 95% CI for the AUC-PE and $C_{\max}$ -PE, and percentage of simulation replications probability in which the PE are smaller than 10% are listed in the bottom 2 rows. The 95% CI are computed based on the 5000 simulation replications (ie, the lower end of the interval is

the low 2.5%, while the upper end of the interval is the top 2.5% among all estimated 5000 PE). The preferred model had a range of PE values within $\pm 10\%$. The preferred model also had a higher percentage of the 5000 simulations that “passed” the FDA 10% rule (bottom row).

In Table 3 is listed the percentage of simulations where each model was selected as the best model according to different criteria (given by “% Choice” in the tables) and the percentages of these simulations that passed the FDA requirements (given by “% Pass”). For example, for formulation A, (see discussion below) according to R^2 , the sigmoid model was selected as the best model in 94.6% of 5000 simulations (%Choice, middle row, Table 3). The percentage of times that the PE passed the FDA rule was 94.6% (AUC) and 93.5% ($C_{\max}$).

The Hixson-Crowell model was the better model for formulation A, for the following reasons: (1) The Hixson-Crowell model had the best chance of all the models to pass the FDA requirements for formulation A when changes to the biobatch may be needed. Its 95% confidence intervals demonstrated

Table 3. Simulation Results for Formulation A: The Percentage of Models Selected by Criteria AIC, AIC_c , R^2 , and R_a^2 that have less than 10% error in the predicted AUC and $C_{\max}$ *

	Linear	Gompertz	Sigmoid	Weibull	Logistic	Micherlich	Hixson	Higuchi	Overall
AIC:									
% Choice*					3.84		90.48	5.68	100.00
% Pass: AUC					0.00		90.48	5.68	96.16
$C_{\max}$					0.30		90.10	5.34	95.74
Corrected AIC:									
% Choice					0.58		64.06	35.36	100.00
% Pass: AUC					0.00		64.06	35.34	99.40
$C_{\max}$					0.04		63.72	33.98	97.74
R^2 :									
% Choice			94.56		5.44				100.00
% Pass: AUC			94.56		0.00				94.56
$C_{\max}$			93.52		0.42				93.94
R_a^2 :									
% Choice					5.04	2.92	91.78	0.26	100.00
% Pass: AUC					0.00	2.92	91.78	0.26	94.96
$C_{\max}$					0.38	2.92	91.40	0.26	94.96
AUC PE:									
% Choice			36.58	61.46		1.96			100.00
% Pass: AUC			36.58	61.46		1.96			100.00
$C_{\max}$			36.08	61.32		1.86			99.26
$C_{\max}$ PE:									
% Choice		21.64	16.78	7.22	0.78	6.66	20.02	26.90	100.00
% Pass: AUC		0.00	16.78	7.22	0.00	6.66	20.02	26.90	77.58
$C_{\max}$		21.64	16.78	7.22	0.78	6.64	20.02	26.90	99.98

*AIC indicates Akaike Information Criteria; AIC_c , corrected AIC; R_a^2 , adjusted R^2 . AUC, area under the plasma concentration curve; $C_{\max}$, maximum concentration; and % Choice, the percentage that a specific model is chosen by the criteria;

that this model was most unlikely among all the models to have PE outside the 10% range (95% CI row, Table 2). (2) The Hixson-Crowell model had both AUC-PE and $C_{\max}$ -PE within 10% for both the original data and the cross-validation data (top 2 rows, Table 2). (3) With the Hixson-Crowell model, all 5000 data sets passed the PE requirement in AUC and only 0.5% failed to pass the PE requirement in $C_{\max}$ (bottom row, Table 2).

The Higuchi, sigmoid, and Mitcherlich models were nearly as statistically optimal as the Hixson-Crowell for formulation A. The Higuchi model passed both AUC-PE and $C_{\max}$ -PE requirements for both the original data and the cross-validation data, but it had the upper ends of CI very close to 10%, which made it more likely to fail. The Higuchi model also had slightly higher failure rates than the Hixson-Crowell model. The sigmoid model was better for predicting AUC but failed the cross-validation for $C_{\max}$ -PE. The sigmoid (−9.20) and the Weibull (−8.14) models had lower limits of 95% CI close to −10%, which in some situations made them more likely to fail the $C_{\max}$ -PE requirement than the Hixson-Crowell model (−7.53). The AUC-PE “% Choice” (Table 3) ranked the Mitcherlich model (1.96) lower than sigmoid (36.6) or Weibull (61.5) models.

Based on the original IVIVC data of formulation A, criteria AIC, AIC_c , and R_a^2 , all selected the Hixson-Crowell model

as the preferred model; only R^2 selected the sigmoid model as the preferred model (middle rows, Table 2). Based on the 5000 simulations with formulation A, the program selected the Hixson-Crowell model as the preferred model by criteria AIC and R_a^2 , in over 90% of the formulation A simulations. Almost all (99.4%) of the models selected by AIC_c criteria passed the AUC-PE requirement, while 97.7% of these models passed the $C_{\max}$ -PE requirement. These percentages were similar to those selected by AIC (96.2% and 95.7%), which were in turn slightly better than those by R^2 and R_a^2 (Overall column, Table 3) This observation suggests that for the formulation A data set, the criteria AIC_c or AIC were best for selecting models that would result in PE that would pass the FDA rules, and as we have seen, these criteria selected the Hixson-Crowell model.

CONCLUSION

As summarized in Table 4, in the examples used for illustration, no single model was clearly the “best” for all data sets, when “best” was defined as the model having the best chance to pass the FDA requirements. Of these data sets, the formulation B had 95% CI outside the 10% range (ie, a model could not be found that would pass the FDA requirements for 95% of the cases simulated). Also as summarized in Table 4, AUC-PE and $C_{\max}$ -PE were in disagreement for this formulation.

Table 4. Summary of Simulation Results: Model Performance, Performance of Model Selection Criteria, and Agreement Between AUC-PE and $C_{\max}$ -PE*

Formulation	Formulation Characteristics	Best Models [†]	Models That Should Not Be Used [‡]	Performance of Model Selection Criteria	AUC-PE and $C_{\max}$ - PE Agreement
A	AMT Good solubility Intermediate release (T80 = 12 hour)	Hixson-Crowell, Weibull Mitcherlich, Sigmoid Higuchi	Logistic Linear Gompertz	Work OK Although the best model Hixson-Crowell was never selected by R^2	Somewhat agree Less than 23% of models with best $C_{\max}$ -PE did not pass AUC-PE
B	Matrix Tablet Intermediate Solubility Intermediate Release (T80 = 10 hour)	Weibull Sigmoid	Linear, Logistic, Gompertz, Higuchi, Mitcherlich, Hixson-Crowell	Do not work The best model Weibull was never selected by any of the 4 criteria	Strongly disagree Over 85% of models with best AUC-PE did not pass $C_{\max}$ -PE and vice versa
C	AMT Good solubility Intermediate release (T80 = 12 hour)	Hixson-Crowell, Weibull Mitcherlich, Sigmoid Higuchi	Logistic Linear Gompertz	Work OK Although the best model Hixson-Crowell was never selected by R^2	Somewhat agree Less than 23% of models with best $C_{\max}$ -PE did not pass AUC-PE

*AUC indicates area under the plasma concentration curve; PE, prediction errors; $C_{\max}$, maximum concentration; and AMT, asymmetric membrane technology. Results for Formulation A were described in the text. Results for Formulations B and C are available upon request.

[†]These models have the best chance to pass the FDA requirements and are ranked in order. Models in the same order have similar performance; eg, Hixson-Crowell and Weibull are the best models for Formulation A with similar performance.

[‡]These models have either no chance or substantially less chance than the “Best Models” to pass the FDA requirements.

The apparent inability of the program to select an optimal IVIVC model for the matrix formulation B may be related to the difficulty in developing any IVIVC with formulations not likely to be pH-independent or stirring rate-independent. For such formulations, the FDA Guidance recommends that several differing formulations are evaluated during the IVIVC development process.⁵ For example, 3 different matrix formulations might need to be evaluated for the development of the IVIVC for formulation B. Although this specific example was not discussed, it would be easy to modify the program to accomplish such an analysis.

Whenever possible, an attempt should be made to interpret the chosen IVIVC model with consistent physicochemical, pharmacokinetic, and physiological observations. However, the authors' program may be a useful tool in screening the most commonly employed models for further consideration. Finally, when no model is selected as "preferred," a "Level A" IVIVC may not be likely. In this case, either additional formulations need to be considered in the "Level A" model development, or an alternate relationship (eg, "multiple level C") should be pursued. The authors will provide additional examples upon request.

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