In Vitro–In Vivo Correlation Strategy Applied to an Immediate-Release Solid Oral Dosage Form with a Biopharmaceutical Classification System IV Compound Case Study

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ABSTRACT: The ability to predict *in vivo* response of an oral dosage form based on an *in vitro* technique has been a sought after goal of the pharmaceutical scientist. Dissolution testing that demonstrates discrimination to various critical formulations or process attributes provides a sensitive quality check that may be representative or may be overpredictive of potential *in vivo* changes. Dissolution methodology with an established *in vitro–in vivo* relationship or correlation may provide the desired *in vivo* predictability. To establish this *in vitro–in vivo* link, a clinical study must be performed. In this article, recommendations are given in the selection of batches for the clinical study followed by potential outcome scenarios. The investigation of a Level C *in vitro–in vivo* correlation (IVIVC), which is the most common correlation for immediate-release oral dosage forms, is presented. Lastly, an IVIVC case study involving a biopharmaceutical classification system class IV compound is presented encompassing this strategy and techniques. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2125–2130, 2014

Keywords: dissolution; *in vitro*/*in vivo* correlations (IVIVC); *in vitro* models; oral drug delivery; mathematical models

INTRODUCTION

Dissolution testing is an important examination tool in the development of a dosage form as well as subsequent monitoring of its batch-to-batch performance. Potential strategies for developing and validating dissolution tests have been previously described.[1–3] Linking the *in vitro* dissolution results to potential *in vivo* absorption results is an optimum predictability goal for each test.[4] Developing an *in vitro–in vivo* relationship (IVIVR) or correlation (IVIVC) is a specialized section of this dissolution test development. An IVIVR is achieved when there is a similarity in results between *in vitro* and *in vivo*, for example, dissolution rank ordering batches coinciding with *in vivo* pharmacokinetic (PK) ranking. An IVIVC has a mathematical description that provides accurate predictive *in vivo* results across the range of dissolution profiles investigated.

An IVIVC is a key parameter in aiding the formulation optimization with respect to human PK response. IVIVCs have been developed in the past mostly for controlled-release products, and the US FDA has a guidance on developing an IVIVC for extended-release (ER) oral dosage forms.[5] The FDA guidance on dissolution testing of immediate-release (IR) forms provides generalities about IVIVC development, but not with as much detail as outlined in the ER guidance.[6] Other researchers have issued articles on how to investigate potential IVIVCs.[7,8]

The development of an IVIVC for an IR oral dosage can be challenging to achieve because the physiological digestive processes (gastric emptying, hydrodynamic, and pH variations along the GI tract, etc.) have a significant effect on the IR dosage form dissolution rate, in addition to absorption parameters. IVIVCs for IR dosage forms may be achieved if the drug's dissolution process *in vivo* is the rate-limiting step in the overall absorption process.[9] Various dissolution testing strategies for poorly soluble IR products are explained in an article by Brown.[10] Presented here is a potential decision process with recommendations leading into an IVIVC clinical study and the potential outcome scenarios. A biopharmaceutical classification system (BCS) IV compound IR case study describing the investigation and evaluation of a multipoint Level C correlation is demonstrated.

MATERIALS AND METHODS

Formulations

Four capsule batches with varying dissolution profiles were utilized in this study. A wet granulation formulation was used. The fast, typical, slow, and very slow batches were manufactured by varying processing parameters. The capsules are 200-mg strength of compound XYZ.

In Vitro Dissolution

The *in vitro* dissolution analysis was performed using a USP II (Paddle Method) Apparatus. The spindle speed was 50 rpm and the volume used was 900 mL. The optimized media selected was 50 mM phosphate pH 6.8 containing 0.1% sodium lauryl sulfate (SLS) at 37°C. Dissolution samples were analyzed via HPLC. Six capsules per batch were evaluated for the dissolution media

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selection process and 12 capsules from each batch were used for the dissolution experiments in the IVIVC study.

In Vivo Studies in Healthy Human Volunteers

A randomized, four-way crossover clinical study was conducted with 12 healthy volunteers. The subjects were dosed 800 mg, four 200-mg strength capsules, of compound XYZ. The capsules were dosed with 240 mL of water 30 min after a standard breakfast. Dosing was followed by a 4-h fast. Each treatment period is followed by at least a 2-day washout period. The plasma concentrations are sampled predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h postdose.

Considerations for an IVIVC Study Design

There are many benefits of having an IVIVC. With an IVIVC, a true understanding of how the dissolution results relate to *in vivo* PK parameters is achieved. Having this correlation potentially allows the use of the *in vitro* dissolution test in lieu of clinical PK studies that may normally be needed during formulation optimization, scale-up, process change, and site transfer. This approach minimizes the need for clinical resources and may accelerate the program. Lastly, an IVIVC helps in the justification of clinically relevant dissolution specifications.

An IVIVC investigation may be an integrated part of Quality by Design (QbD).[11] A main driver of QbD is ensuring the safety and efficacy of the dosage form by developing a control strategy based on product understanding. Performing a risk assessment and determining the critical quality attributes that may potentially affect the dosage form performance are part of the QbD process. The relationship, if any, of these critical attributes to *in vivo* response may involve the performance of an IVIVC clinical study to clearly define their effect.[12]

The dissolution method evolves as the method is continually optimized based on its discriminatory ability to critical formulation/process characterization changes or any clinical study with varied similar formulations.[11,13] During development, formulation modifications or new formulations may be tested in the clinic based on risk assessment. The clinical PK results should always be examined with regard to the potential of optimizing the dissolution test. Optimizing a dissolution test is modifying the test to better replicate the *in vivo* outcome.

A human IVIVC PK study could be carried out as (1) part of a relative PK study to bridge from early formulations to the commercial formulation, (2) a stand-alone exploratory biopharmaceutics IVIVC study, or (3) included in other clinical plans.[13] Simulations or modeling could be used to predict the sensitivity of PK parameters to the *in vitro* dissolution rate.[14] This will help to determine the need for a study and the appropriate test articles.

A single PK study with three to four arms would typically be used to address active pharmaceutical ingredient (API) particle quality attributes, formulation variations, and process variations. This would be a relative bioavailability (BA) study, not a bioequivalency study, and would normally be viewed as a scientific study to characterize the relationship between *in vitro* dissolution and *in vivo* performance. BA studies are specified for IVIVC studies in FDA guidance on dissolution testing of IR solid oral dosage forms and ER IVIVCs.[5,6] The BA studies should be sufficiently powered to adequately characterize the *in vivo* performance of the dosage.

It is recommended that a minimum of three batches with distinct (e.g., differing by 10%)[5] dissolution profiles be used. The dose used in the IVIVC study should be within the expected commercial dose range. Variants of the potential commercial formulation should be developed for use in an IVIVC exploratory biopharmaceutics study. These may typically include some or all of the following: A drug substance particle size variant, a formulation variant (such as low disintegrant) and a process variant (such as over granulation). It is recommended that all of the variants represent extreme differences, beyond those expected within the normal operating space or from future anticipated changes. Normal operating space is the anticipated operating space that will be validated for commercial manufacture. This recommendation reduces the risk of clinical variation potentially leading to *in vivo* differences (or lack of differences) that are not representative of the actual relative performance of the dosage forms within the normal operating space.

It is recommended to modify the expected formulation/processing rather than using a different formulation or adding a different excipient; this would raise questions regarding the possible impact on the release mechanism. The modifications would be characterized using the *in vitro* dissolution method, with adequate *in vitro* discrimination demonstrated. This is generally interpreted as at least a 10% difference at the specified time point between the dissolution profiles. With this strategy, the PK results would be representative of what could be encountered from variations outside the normal operating space. This three to four arms clinical study assesses the impact of dissolution differences on *in vivo* performance. The more variables examined, the stronger or more encompassing the outcome can be applied to explain the potential *in vivo* significance of future changes.

Typically, IVIVC studies for BCS class I and III compounds may not be needed because these compound classes have the potential for biowaivers.[15] The *in vivo* dissolution rate of a BCS I must be slower than the gastric emptying for an IVIVC. BCS III and IV compounds have low permeability (potentially rate limiting), which reduces the probability of achieving an IVIVC. The case study presented here is for a BCS IV compound. The highest probability of achieving an IVIVC for an IR product is a BCS II compound with low solubility and high permeability.[9]

If there is no significant change in dissolution profile from target at any pH (based on an f2 calculation), then an IVIVC study may not be needed. If there is no expectation of different PK performance based on dissolution or other physical–chemical properties of the drug substance or drug product, the potential value of an IVIVC study should be weighed against the risks of seeing apparent clinical differences that are simply because of *in vivo* variability. Lastly, an evaluation of the potential IVIVC benefits given the current status of the project should be carefully evaluated as part of risk assessment.

IVIVC Potential Outcomes

In Vitro Differences; No In Vivo Differences

This scenario provides a dissolution range within which formulation and/or process changes that were clinically tested lead to significant changes in dissolution rate without impacting *in vivo* PK performance. This outcome potentially supports latitude in establishing specifications based on the process capability for the critical attributes examined in the clinical study. The

Table 1. Dissolution Comparison Using Dissolution Media Containing 0%, 0.1%, 0.3%, and 0.5% SLS in pH 6.8 Phosphate Buffer

Sample Time (min)	Slower	Faster	Faster Minus Slower
	Percent Dissolved in 0% SLS (RSD)		
10	31(6.0)	35(3.2)	4
20	44(3.7)	51(1.2)	7
30	51(3.3)	59(1.1)	8
45	57(2.8)	66(1.0)	9
60	61(2.8)	71(0.9)	10
	Percent Dissolved in 0.1% SLS (RSD)		
10	49 (3.7)	69(2.2)	20
20	65(2.2)	87(1.2)	22
30	71(6.2)	91(4.1)	20
45	80(2.5)	95(0.8)	15
60	84(2.5)	97(0.9)	13
	Percent Dissolved in 0.3% SLS (RSD)		
10	54(6.9)	77(4.0)	23
20	67(6.2)	89(6.2)	22
30	73(6.0)	93(2.7)	20
45	76(10.4)	92(7.7)	16
60	80(9.5)	92(6.1)	12
	Percent Dissolved in 0.5% SLS (RSD)		
10	58(3.9)	84(4.1)	26
20	72(3.6)	93(2.0)	21
30	78(3.7)	95(1.5)	17
45	84(3.8)	96(1.5)	12
60	87(4.0)	97(1.4)	10

Presented are dissolution averages (n = 6) demonstrating the discriminatory ability of the tested media.

Note: The slower and faster batches are similar to but are not the actual slow and fast batches used in the clinical study.

dissolution rate of the slowest batch would normally be used to strengthen the justification of the desired specification set.

In Vitro Differences; In Vivo Differences

A clinical BA study showing differences that can be explained using scientific reasoning can be used to critique and optimize the dissolution test method. The dissolution results at specific time points should be compared with the C_{max} and AUC values derived for each IR batch. If necessary, the dissolution method should be optimized to mimic the *in vivo* response. At a minimum, a rank-order relationship should be achieved at an appropriately selected time point. Ultimately, a linear relationship is desired when the geometric mean *in vivo* parameter (such as C_{max} or AUC) is plotted against the *in vitro* percent dissolved. Such a linear relationship would ideally support the design space because the variant batches are outside of the normal operating space. Furthermore, the linear relationship would provide a strong justification (dependent on the critical attributes included in the study) for allowing postapproval changes based on the dissolution test results.

No In Vitro Differences; No In Vivo Differences

If a discriminating dissolution method cannot be found despite best efforts, an *in vivo* study on formulation/process variants may still be performed. If no *in vivo* differences are seen among the batches, there is no issue. However, this outcome does not provide support for any variation in dissolution rate that may occur in the future.

No In Vitro Differences; In Vivo Differences

If *in vivo* differences are observed in the BA study that cannot be explained based on knowledge about the formulation and compound, the possibility exists that the differences are because of the variation in the clinical response and not to the formulation modifications.[13] For example, if an overgranulated batch or a batch with a reduced amount of disintegrant produce higher C_{max} values than the target formulation, this would be the opposite of scientific expectations. In such cases, further *in vivo* studies may be considered to understand whether there is any true *in vivo* effect of the tested critical formulation variables. With scientifically sound *in vivo* differences, efforts should be made to achieve a discriminatory dissolution method. If the *in vitro* dissolution method still cannot be made to distinguish between nonsimilar *in vivo* behaving batches (not discriminating), another nondissolution analytical technique should be used and specifications established to monitor and control the appropriate parameter to ensure that the *in vivo* performance of future batches will be acceptable. For example, if the dissolution method cannot be made sensitive to distinguish clinically relevant API changes (salt to free form or amorphous to crystalline changes) in the dosage and then a spectroscopic technique needs to be established. Unfortunately, because of the uniqueness and complexity of the human GI tract, it is not an absolute that all clinically relevant parameters would be distinguished via dissolution testing.

Level C IVIVC Analysis

An IVIVR can refer to any relationship between *in vitro* dissolution data and *in vivo* PK (or potentially pharmacodynamic) data based on a physicochemical understanding of the drug substance, drug product, and absorption, distribution, metabolism, and excretion (ADME) processes. An IVIVC is a subtype of IVIVR in which the *in vitro* dissolution rate can be mathematically correlated with one or more PK parameters.[12,13,15]

When differences are seen in both the *in vitro* dissolution data and the *in vivo* PK data, the geometric mean *in vivo* PK parameters, AUC, and C_{max} are compared graphically with the dissolution average values for the batches used in the clinical study. If a rank-order relationship appears to be present, a linear regression analysis is performed. If a linear relationship is achieved for one or more of the PK responses, an IVIVC may be possible. If the relationship is not linear, a curve-fitting calculation may be performed to correlate *in vitro* to *in vivo* response.

To determine the acceptability of this relationship or correlation, the FDA guidance on ER dosage form IVIVC may be used as a reference. This is the best regulatory reference for IVIVCs in general, with the understanding that although IVIVCs have a higher probability for ER products, they are rare for IR products. Following the ER guidance for IR dosages, the prediction error (PE) is determined for each batch. The PE is the percent difference between the actual mean value of the *in vivo*

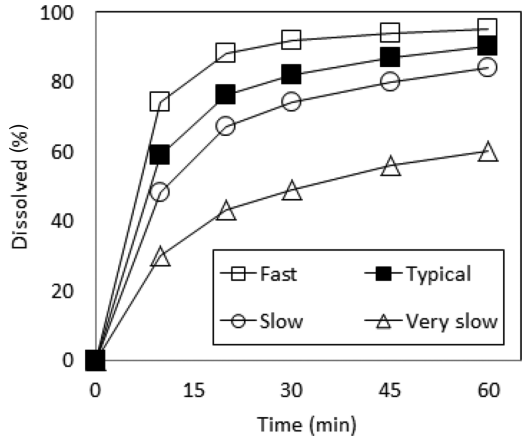

Figure 1. Dissolution profiles of four IVIVC batches tested using pH 6.8 phosphate buffer with 0.1% SLS.

parameter and the value predicted using the average dissolution rate and the correlation equation. The guidance states an acceptable IVIVC is demonstrated when the average absolute percent PE is less than or equal to 10% and individual batch percent PE values are less than or equal to 15%.

RESULTS

This case study pertains to solid oral dosage form of compound XYZ that is a BCS Class IV compound with low aqueous solubility and low permeability. The dissolution media are limited to a neutral pH because of the chemical stability. A surfactant, in this case SLS, is needed in the dissolution medium to dissolve the compound. Other surfactants were investigated and SLS was selected as the preferred one. Studies were conducted to determine whether the discrimination of the dissolution method could be improved by varying the amount of SLS in the dissolution media. Two batches manufactured using different process parameters creating different dissolution rates were tested using the USP Apparatus II (Paddle) at 50 rpm and with a 900-mL dissolution medium of 50 mM phosphate buffer at pH 6.8 containing 0.0%, 0.1%, 0.3%, and 0.5% SLS (Table 1). Utilizing the dissolution medium containing no SLS, both batches dissolved slowly and only 61%–71% of the active was dissolved at 60 min. Using the dissolution medium with different levels of SLS, greater than 80% of active was dissolved at 60 min.

To evaluate any potential relationship between dissolution rate and human PK and to possibly establish a clinically relevant registration acceptance criterion for the dissolution test of the dosage form, a BA PK study was conducted using four batches with distinctively different dissolution profiles. The fast, typical, slow, and very slow batches were manufactured by varying processing parameters. Ideally, another critical parameter different from processing parameters would be included in the IVIVC study to strengthen the applicability of the correlation but because of other project constraints, this was not performed. The dissolution profiles ($n = 12$ per average) of the batches used in the PK study are presented in Figure 1 with their respective data listed in Table 2. The range of dissolution average values at the 45- and 60-min time points were 56%–94% and 60%–95%, respectively.

The human PK study was conducted following necessary Institutional Review Board approvals. The PK results from the clinical study with 12 subjects under fed conditions are also listed in Table 2 and the *in vivo* profiles are plotted in Figure 2. The fast and the slow batches were compared with the typical batch, and when compared with each other, have clinical ratios that range from 80 to 100 for C_{max}, and AUC, respectively. The very slow batch has lower ratios of 74 and 78 for C_{max} and AUC, respectively, as compared with the typical batch. This is a sufficient range in *in vivo* parameters for the IVIVC determinations.

DISCUSSION

In selecting the appropriate level of SLS in the dissolution media, evaluation results are showed in Table 1; no significant difference in discrimination was found using the 0.1%, 0.3%, or 0.5% SLS dissolution media. The 0.1% SLS level was minimally needed to dissolve at least 80% of the compound by 60 min. Therefore, the dissolution medium containing the least amount of surfactant, 0.1% SLS, was selected. The dissolution method used in the IVIVC modeling involves a USP II Apparatus at 50 rpm with a 900-mL volume of 50 mM phosphate pH 6.8 containing 0.1% SLS medium at 37°C.

Relationships between the *in vitro* dissolution time point averages and human PK geometric mean parameters are demonstrated. Comparisons of the dissolution averages for the 45- and 60-min time points to the human PK data are displayed graphically in Figures 3 and 4 as examples. The potential for linear relationships is achieved indicating the possibility of a multipoint Level C IVIVC. The point scatter and nonrank ordering of the points for the C_{max} plot, which may be because of typical clinical variation, definitely reduces the potential and applicability of any IVIVC that may be calculated. A main utility of pursuing this C_{max} IVIVC is to reinforce the AUC IVIVC, indicating that *in vitro* dissolution is indeed indicative of *in vivo* behavior.

The FDA's guidance on ER IVIVC can be applied to IR dosage form IVIVC investigations. Each linear equation is used to

Table 2. Summary of Clinical BA PK Geometric Means ($n = 12$ Subjects) and Batch Dissolution Averages ($n = 12$ Dosages)

Batch	C_{max} (ng/mL)	C_{max} Ratio[a]	AUC (l) (ng h/mL)	AUC Ratio[a]	Average Percent Label Dissolved				
					10 min	20 min	30 min	45 min	60 min
Fast	2222	96	7778	100	74	88	92	94	95
Typical	2310	—	7777	—	59	76	82	87	90
Slow	1844	80	6882	88	48	67	74	80	84
Very slow	1715	74	6040	78	30	43	49	56	60

[a]Ratio compared with typical.

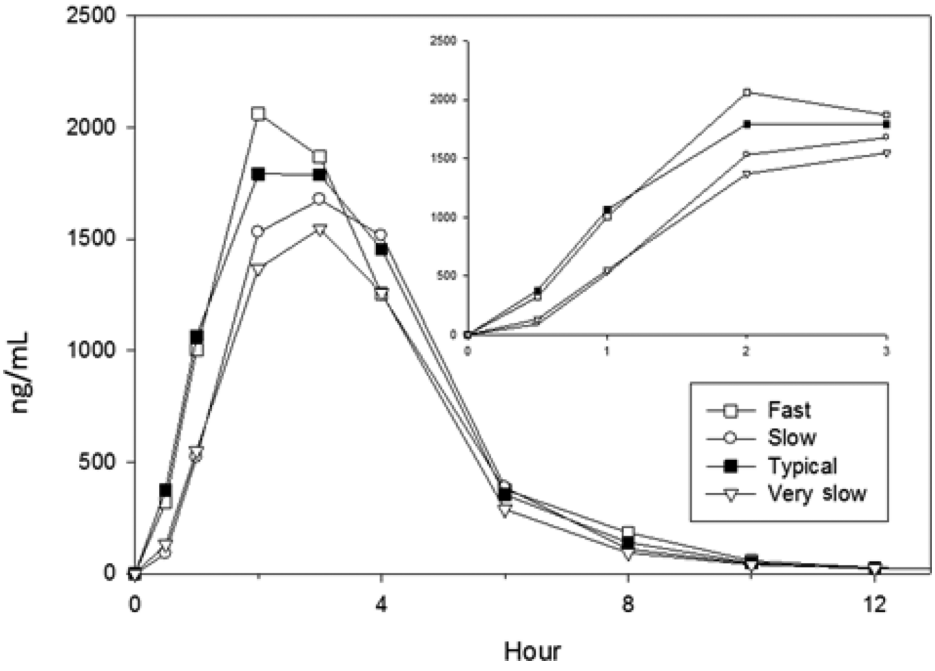

Figure 2. Pharmacokinetic profiles (first 3 h shown in insert) of compound XYZ blood levels versus time.

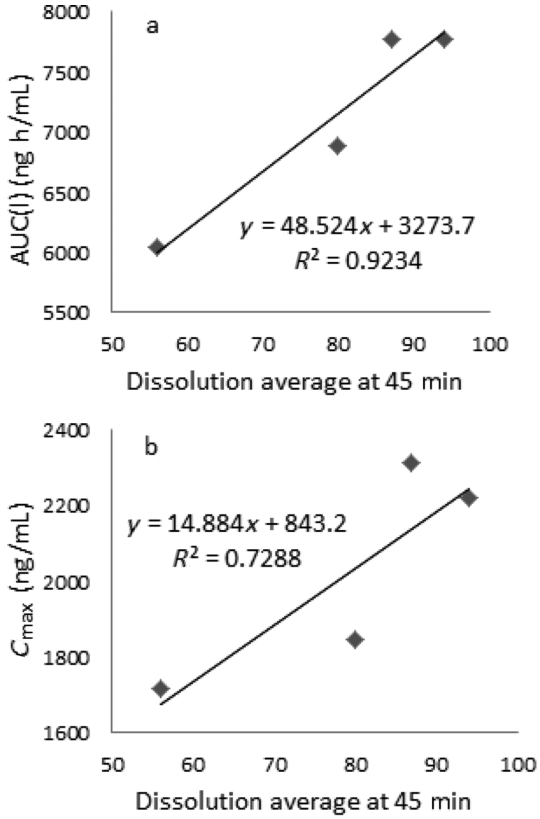

Figure 3. The *in vivo* geometric means versus the 45-min dissolution averages: (a) AUC (l) (ng h/mL) and (b) C_{max} (ng/mL).

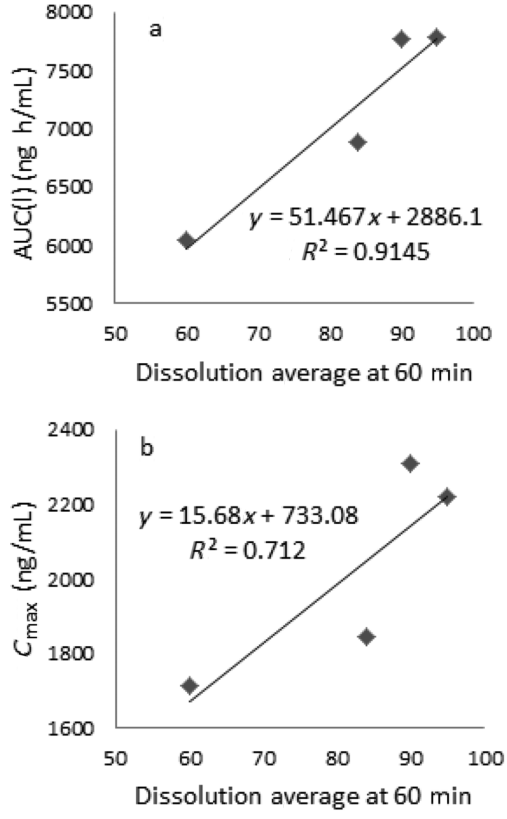

Figure 4. The *in vivo* geometric means versus the 60-min dissolution averages: (a) AUC (l) (ng h/mL) and (b) C_{max} (ng/mL).

calculate from the dissolution averages the predicted human PK parameter, either C_{max} or AUC. The PE percent between predicted and measured is then determined. The PE percentages for the 45- and 60-min linear relationships are listed in Tables 3 and 4. The IVIVC acceptance criteria from the ER guidance are that each batch percent PE $\leq$ 15% and that the average absolute percent PE $\leq$ 10%. This set of criteria is met for both of these time points and for all four batches. This IVIVR

Table 3. Prediction Error Examination Based on the Linear Relationship of the PK Parameters Versus the 45-min Dissolution Average

Batch	Predicted AUC (l) (ng h/mL)	Measured AUC (l) (ng h/mL)	PE Percentage
Very slow	5991	6040	−1
Slow	7156	6882	4
Typical	7495	7777	−4
Fast	7835	7778	1
Average Absolute PE			3
Batch	Predicted C_{max} (ng/mL)	Measured C_{max} (ng/mL)	PE Percentage
Very slow	1677	1715	−2
Slow	2034	1844	10
Typical	2138	2310	−7
Fast	2242	2222	1
Average Absolute PE			5

The predicted parameter is the value attained when the dissolution average for that particular batch is entered into the correlation equation.

Table 4. Prediction Error Examination Based on the Linear Relationship of the PK Parameters Versus the 60-min Dissolution Average

Batch	Predicted AUC (l) (ng h/mL)	Measured AUC (l) (ng h/mL)	PE Percentage
Very slow	5974	6040	−1
Slow	7209	6882	5
Typical	7518	7777	−3
Fast	7775	7778	0
Average Absolute PE			2
Batch	Predicted C_{max} (ng/mL)	Measured C_{max} (ng/mL)	PE Percentage
Very slow	1674	1715	−2
Slow	2050	1844	11
Typical	2144	2310	−7
Fast	2223	2222	0
Average Absolute PE			5

The predicted parameter is the value attained when the dissolution average for that particular batch is entered into the correlation equation.

may now be considered a multipoint Level C IVIVC. However, the C_{max} IVIVC may be considered more of a supportive justification to the AUC IVIVC. Looking at the C_{max} plots in Figures 3 and 4, the correlation points are not ideally distributed around the length of the line. So even with an IVIVC that technically meets the acceptance criteria for C_{max}, how the points are distributed could call in question the validity of the IVIVC if this was the best/only IVIVC achieved for this product.

CONCLUSIONS

There have been limited examples in the literature for IVIVC investigations of IR products. A potential IVIVC study design strategy is presented here. The strategy describes selecting potential batches with variants on more than one critical quality attribute outside the normal operating space. The potential clinical study outcomes and follow-up scenarios are detailed. The aspects involved in mathematically correlating an *in vitro* response to an *in vivo* response and determining an IVIVC are described. A specific IR Level C IVIVC case study on a BCS class IV compound was highlighted, demonstrating in a stepwise fashion the calculations.

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