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Research Article

BIOSCIENTIFIC PERSPECTIVES ON IVIVC: LINKING PHYSICOCHEMICAL PROPERTIES TO BIOLOGICAL PERFORMANCE

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ABSTRACT

Drug development increasingly uses mathematical models linking bioavailability (BA) and bioequivalence (BE) via *in vitro–in vivo* correlation (*IVIVC*). *IVIVC* helps predict *in vivo* drug behavior from *in vitro* data, reduces clinical testing, and supports biowaivers, aiding tools like the Biopharmaceutical Classification System (BCS). Key factors include drug and dosage form properties, with data gathered from *in vitro* dissolution tests and *in vivo* bioavailability studies. Correlation is established using convolution and deconvolution methods connecting dissolution and pharmacokinetic data. *IVIVC* development involves model building, validation, and assessing internal and external predictability to ensure regulatory reliability. It mainly targets extended-release and oral forms like enteric-coated and multiple-unit systems but also apply to parenteral and nasal delivery. Computational tools such as IDEA and Gastro Plus use statistical and mechanistic models to simulate oral drug absorption, improving the efficiency and accuracy of *IVIVC*-driven drug development.

Keywords: Biowaivers, Convolution, Deconvolution, Validation, Novel dosage forms, *In silico* model Gastro plus.

INTRODUCTION

The U.S. FDA defines in vitro–in vivo correlation (IVIVC) as a predictive mathematical model linking in vitro drug dissolution or release to in vivo responses like plasma concentration or absorption for oral dosage forms. The in vitro data represent drug dissolution rate and extent, while the in vivo data reflect absorption profiles. IVIVC covers its applications, study design, and development and validation processes (U.S.FDA, CDER.,1997). The study aims to identify key factors in developing IVIVC, which primarily uses in vitro dissolution profiles as surrogates for in vivo bioequivalence. IVIVC is applicable when dissolution and drug absorption are rate-limiting steps. It is classified into levels A, B, C, D, and multiple level C based on how well it predicts the in vivo concentration–time profile after oral administration. The FDA guidance outlines three IVIVC correlation methods to be developed early, considering dosage form biopharmaceutical properties. In vivo bioavailability studies, required for NDAs, characterize plasma concentration–time profiles, while in vitro dissolution tests compare these with absorption profiles despite differing conditions. Factors like particle size, molecular size, and GI tract physiology affect dissolution. IVIVC development includes model creation, validation, and application to predict in vivo performance. In vivo absorption is estimated from plasma data using Wagner–Nelson or Loo–Riegelman methods. Correlation techniques include single point, statistical moment, convolution, and deconvolution. Model validation uses internal and external percent predictability errors with defined acceptance criteria. Consider IVIVC development by considering physicochemical, biopharmaceutical, and physiological factors. Key elements include drug solubility, pKa, permeability, salt formation, partition coefficient, environmental pH, particle size, and polymorphism. Biopharmaceutical factors involve ionization, partition coefficient, and surface area. The FDA guideline on IVIVC emphasizes the importance of selecting appropriate development, evaluation, and application strategies based on the Biopharmaceutical Classification System. Absorption prediction software tools are categorized into statistical and mechanistic in-silico models.

MATERIALS AND METHODS

IVIVC is a mathematical model describing the relationship between in vitro and in vivo properties of drugs. Arising

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from absorption kinetics and calculation of in vivo dissolution rate and absorption rate constants, *in vitro* –in vivo correlation can be achieved using, Pharmacological correlation, based on clinical observations, Semi-quantitative correlation, Based on the drug blood levels or urinary excretion data, Quantitative correlation. IVIVC shortens drug development time, economizes resources, and improves product quality. It serves as a surrogate for in vivo bioavailability, supports biowaivers, validates dissolution methods, and reduces bioequivalence required for approval. It also supports biowaivers and validates dissolution methods, reducing SUPAC requirements. (Welling *et al*.,2006). Formulation optimization requires modifications to composition, manufacturing system, and batch sizes to ensure bioequivalence with target methods. In vitro dissolution profiles (IVIVC) serve as a surrogate for in vivo bioequivalence and aid bio-waivers. IVIVC reduces regulatory burden, can justify therapeutically meaningful product specifications, and saves time and value for product improvement. Validated IVIVC serves as justification for biowaivers in level 3 variation filings during scale-up or approval. (IVIVC of dosage forms.,2002).

Criteria for *IVIVC*S

IVIVC is developed during early drug product development stages to select effective formulations and dosage regimens, with release-controlling excipients either identical or very similar, to limit absorption and appearance of drugs.

Need for *IVIVC*

The *IVIVC* model is a valuable tool for improving drug delivery systems by examining the relationship between *in vitro* dissolution or release and *in vivo* absorption profiles. It aids in developing and accessing dosage shapes, aiding in system screening, inputting dissolution, and bioequivalence testing. Urinary excretion analysis is not suitable for accurate bioavailability measurements.

Factors affecting development of a predictable *IVIVC*

Complexity of the delivery system. Composition of the formulation. Method of manufacture. Physicochemical properties. Dissolution method.

***IVIVC* LEVELS**

Correlation levels

According to the FDA and USP guidelines, the *in vitro* and *in vivo* correlation is categorized into five levels i.e. A, B, C, D, and multiple level C based on the guidelines the predictive capability to reflect the concentration & time *in vivo* profile after administration of an oral dosage form. The correlation levels are useful in formulation development.

Level A

Level A correlation is the highest "point to point" or highest level of correlation between *in vitro* dissolution profile and *in vivo* plasma drug concentration profile input rate and time of drug release. These methods are mostly used for data obtained from the dissolution profile and plasma concentration-time data level to develop a correlation.

Level B

Level B correlation is based upon the principles of statistical moment analysis; the mean in vitro dissolution time (MDT vitro) of the product is correlated with the mean in vivo dissolution time (MDT Vivo) or means residence time (MRT) is compare based on curves. Although level B can be used for all in vivo and in vitro data, it's not considered as the point-to-point correlation but different curves produce a similar means of residence time. It does not justify the exact plasma concentration curve. It cannot be justifying the quality control of the standard and regulatory processes (Lu, Ying *et al*.,2011).

Level C

Level C IVIVC is a single-point relationship between a dissolution rate (in vitro) and AUC, C max, T max, Ka, or time to have 10, 25, 50, and 90 sorbed (in vivo) the schematic representation of level C curve shown in Figure.4[9]. A Level C correlation does not give a clear idea about the plasma concentration-time profile, which is the critical factor that defines the performance of any controlled-release product hence not so much reliable but has a good impact in the early stage of formulation development (Cardot JM *et al*.,2006).

Level multiple C

A multiple Level C correlation relates one or several in vivo pharmacokinetic parameters of interest as described in Level C to the amount of drug dissolution rate/efficiency. =It can be used to endorse biowaiver if dissolution is commenced with at least three times a point. Level A correlation is likely to develop when multiple correlations are established at each time point for the same Point

Level D

Level D correlation is a nonparametric correlation between the in vivo pharmacokinetic parameter and the in vitro dissolution parameter. It is usually based on ordinal data but not quantitative, thus considered to be the weakest correlation. Level D correlation serves as a formulation development or processing procedure

Correlation methods

There are three methods of IVIVC that have been described in the FDA guidance, The IVIVCs must be established as early as possible in the development and biopharmaceutical properties of the dosage form. For a given drug, a correlation is related to the dosage form or type of dosage form. Modification of the excipients, product design, and release mechanism is evaluating by using three methods which included.

Simple point type

The percentage of drug dissolved in a given time or the time is taken for a certain percent of the drug to be dissolved is correlated with the parameter of the bioavailability. The selection of those correlative points is commonly is biased with the translation of the effects may be deceptive.

Comparison of profile

The complete *in vivo* reaction time profile can be correlated to the entire dissolution rate time curve. The exceptional technique to increase dissolution assessments that assume reliably the time direction of the *in vivo* behavior of the drug. A number of the *in vivo* and *in vitro* parameters employed for correlation are given in Table.1.

Table 1. Some of the in vivo and in vitro parameters employed for correlation.

In vivo data	In vitro data
Plasma conc. time profile Plasma concentration at time t, Cmax, tmax, AUC_o^t, AUC_o^∞ t30%, t50%, t90%.	**Percent drug dissolution profile** Percent drug dissolved at time t, Time taken for maximum amount of drug to dissolve. Total amt. of drug dissolved. Time for a certain percentage of drug to dissolve such as t30% t50% t90%. Time taken for maximum amount of drug to dissolve.
Pharmacokinetic parameters Absorption & elimination rate constant & half life	**Kinetic parameters** Dissolution rate constant Dissolution half life
Percent drug absorbed time profile	**Percent drug dissolved time profile** Percent drug dissolved at time t
Statistical moment analysis MRT, MAT	**Statistical moment analysis** MDT

Direct differential equation based *IVIVC*

Single and multiple kinds of compartment pharmacokinetic models and a corresponding system of differential equations are used in vitro-in vivo correlation (IVIVC) method is proposed that directly relates the time-profiles between in vitro dissolution rates and in vivo plasma concentrations. The rate of in vivo input is connected to the charge of in vitro dissolution through time-shifting. A multiplying factor which is known as the variability of absorption conditions as the drug moves along is also incorporated. All fitted parameters had realistic values, and good or acceptable fits and predictions are evaluated by using plasma concentration which gives an idea about the mean squared errors and percent AUC errors.

RESULTS AND DISCUSSION

The plasma concentration curve is one of the most common representations of a drug in the body obtained after administration of formulation to healthy volunteer, it depends upon the amount drug into the blood flow which depends on the dissolution rate, dosage form, polymorphism, pKa, solubility, particle size, crystal shape and stability in the gastrointestinal tract (GIT), and its pharmacokinetics input processes. The disposition of the drug depends upon the drug and patient (Hamed M *et al*.). The model-independent parameters such as Plasma concentration-time profile are Plasma concentration at time t, Cmax, Tmax, AUCot, AUCo∞ , and t30%, t50%, t90%. Pharmacokinetic parameters are Absorption & elimination rate constant & half-life, Percent drug absorbed time profile and Statistical moment analysis are MRT, MAT. Several approaches can be used for determining the In vivo absorption. Wagner-Nelson, Loo-Riegelman, and numerical deconvolution methods. Wagner Nelson and LooRiegelman are both model-dependent methods in which the former is used for a one-compartment model and the latter is for a multi compartment system. The Wagner Nelson method is less complex than the Loo Riegelman as there is no requirement for intravenous data. However, misinterpretation of the terminal phase of the plasma profile may be possible in the occurrence of a flip flop phenomenon in which the rate of absorption is slower than the rate of elimination (Veng-Pedersen P *et al*.).

To compare the in vivo absorption profile with in vitro data and in vitro profile must be obtained by dissolution tests that differ in many ways compared to in vivo. Any method which can discriminate between the formulations can be used but certain techniques tend to be preferred, i. e. , paddle, flow-through cell, and basket (USP II, IV, I, respectively). Aqueous media is preferred pH not exceeding 6. 8 or 7. 2 for the use of the poorly soluble drug of surfactant is acceptable. Composition of media to mimic fasted and fed state such as the fasted state simulated intestinal fluid and fed state simulated intestinal fluid media. Parameters such as Kinetic parameters are Dissolution rate constant, Dissolution half-life. Percent drug dissolved time profile is Percent drug dissolved at time t, Statistical moment analysis is MDT and the Percent drug dissolution profile parameters are Percent drug

dissolved at time t, Time taken for the maximum amount of drug to dissolved, Total amount of drug dissolved. Time for a certain percentage of drugs to dissolve such as t30% t50% t90%. These methods are based on area calculations from the amount released at various times. *IVIVC* was accomplished in various stages including the development of the correlation model, validation of the model, and utilization of *in vivo* prediction of the targeted formulation. The rules for developing and validating IVIVC models for novel and non-oral dosage forms or delivery systems • For orally administered drugs, IVIVC is expected for highly permeable drugs under dissolution rate-limiting conditions, which is accepted by BCS. But, the regulations for developing and validating IVIVC fashions for novel and non-oral dosage bureaucracy/delivery systems (Gangadhar Sunkara *et al*.2007).

Biopharmaceutics classification system (BCS) is based on solubility, intestinal permeability, and dissolution rate, which governs the rate and extent of oral absorption from the immediate-release solid oral dosage form. The FDA and also EMEA guidelines define "highly permeable" as having a fraction dose absorbed of not less than 90%. The world health organization (WHO) guidelines set a limit of not less than 85% of the fraction dose absorbed, otherwise it is considered to be poorly permeable. The classification is based on the absorption model and drug dissolution, which serves as key parameters that controlling the drug absorption as a set of the Dissolution number, the Absorption number, dimensionless numbers, and the Dose number (Galia E *et al*.,1998). Step 1: Estimate the *in vivo* dissolution time and absorption by using an appropriate technique for each formulation and subject. Step 2: Establish a link model to predict the *in vivo* plasma concentration from *in vitro* data.

It predicts plasma concentration from an *in vitro* profile using a link model whose parameters are fitted in one step, Does not involve deconvolution, Link model is not determined separately, Can be done without reference like IV bolus (Johnson KC *et al*.,1996). The correlation techniques available in the pharmaceutical sciences are Single point, statistical moment, and convolution and deconvolution techniques with the resulting potential utility as a predictive tool. This technique represents the correlation between the dissolution time point (t 50%, t 90%, etc.) to the pharmacokinetic parameter. It is useful as formulation development and production quality control procedure. Factor such as the plasma level that defines the performance of the dosage form for this correlation approach is not predictive of actual *in vivo* product performance. Level C correlation can be established by this technique (JC Boylan *et al*.,2002).

The Mean Residence Time (MRT) based totally on statistical moment gives one method for correlating *in vivo-in vitro* information data. The statistical moment's theory is based on the preliminary assumption that the movement of the individual drug molecules through the body compartment is assumed by probability. Deconvolution is a numerical method used to assess the time course of drug input using a mathematical model based on the convolution integral(Margolskee, Alison, et al.,2016). These are derived by the one-compartment model, this method has the advantage that it requires oral administration only for developing the plasma profile of the drug (Dunne A *et al*.,2005). This method develops the dissolution profile without correlation of absorption between *in vivo* and *in vitro* dissolution profile based on the physiology model and simulation software. This model uses in various physiological process events and convolution-based methods. However, these methods can only mathematically fit the data by minimizing the squared error, even though the results obtained are mathematically correct it may not be meaningful pharmacokinetic or physiological models. These methods should be optimized to as few variables as possible, as the fitting procedure becomes more complex and errors with more variables. (Uppoor VRS.,2001). The *in vivo* performance is to evaluate the predictability of the *IVIVC*. The *in vivo* properties such as AUC and Cmax are used to calculate the prediction errors. The *in vivo* bioavailability results from *in vitro* dissolution data by predicting the error. Acceptance criteria for internal and external Predictability are given in Table.2.

Table 2. Acceptance.

Internal predictability	External predictability
Average %PE of 10% or less for Cmax and AUC %PE for each formulation should not exceed 15%	Average %PE of 10% or less for Cmax and AUC %PE between 10-20% demands for additional data sets.
If these criteria are not met external predictability should be performed	%PE greater than 20% indicates in adequate predictability

Internal validation states that the purpose of providing a basis for the acceptability of the model. Internal validation results from the evaluation of the prediction errors that are calculated by using the (equation 8 & 9) observed in vivo properties such as AUC and Cmax were estimated, used to develop the IVIVC versus in vivo predicted parameter from the developed IVIVC.

$$\text{Prediction} = \frac{[(\text{Cmax observed} - \text{Cmax predicted}) * 100}{[\text{Cmax observed}]} \quad \text{Equation 1}$$

$$\text{Error (\%PE)} \frac{[(\text{AUC observed} - \text{AUC predicted}) * 100}{[\text{AUC observed}]} \quad \text{Equation 2}$$

Internal Predictability %PE (average) of ≤10% establishes predictability. %PE for any formulation should not be >15%. Non-compliance with these criteria depicts inconclusive internal predictability and external predictability should be performed. External validation must be established that the parameters are predicted using the *in vitro* dissolution profile and the *IVIVC* model is compared to the observed parameters. External Predictability Percent Predictability Error ≤10% for Cmax and AUC sets up the external predictability. Percent predictability error between 10–20% shows inconclusive predictability. In such cases, further study is demanded using additional data sets. Percent predictability error > 20% generally indicates poor predictability and has to be justified (EMA,2012)

After data collection and the development of a structural model, the unknown constants in the model have to be estimated. There are many statistical methods used for parameterization, including the method of a maximum relative, the method of least squares, and Bayesian analysis. The statistical characteristics of the data collected can be used to select the appropriate method for parameterization (Kutner, M *et al*.,2004). The correlations exist between *in vitro* drug dissolution and *in vivo* drug absorption; limited progress has been made toward the development of a comprehensive model capable of predicting *in vivo* drug absorption based on dissolution. This is due to the existence of a complex array of factors that contribute to the process of drug dissolution and absorption. To develop a model that can demonstrate a good correlation between *in vitro* drug dissolution and *in vivo* drug absorption, these factors have to be taken into consideration (Li SF.*et al*.,2005), A) Physicochemical properties, B) Biopharmaceutical properties, C) Physiological properties Physicochemical properties play a major role in predicting the *in vivo* absorption of drug candidates. Dissolution is dependent on several physicochemical properties, including solubility, pH dependency, salt forms, and particle size. A classical mechanistic equation that attempts to model dissolution is the Noyes-Whitney dissolution equation which incorporates in the physicochemical factor (Kramer SD *et al*.,1999). Biopharmaceutical properties include Drug permeability, ionization, partition coefficient, absorption potential. It plays a major role in solubility and permeability of the compound. Drug permeability plays a major role in drug absorption, particularly in orally administered dosage forms. The third important component of the overall process of *IVIVC* is the GI physiology since it could limit both the rate and the extent of drug absorption. Physiological properties include GI content, gastrointestinal ph, and GI transit time (Lindahl A *et al*.,1997).

Linear and non-linear correlation models were examined using the fraction dissolved and absorbed from various combinations of extended-release formulations eg: diltiazem, ketoprofen (Eddington, N.D *et al*.,1998). Plasma drug concentration profiles were predicted by convolution of the *in vivo* dissolution rates and the validity of the correlation was estimated by calculating prediction errors for Cmax and AUC for each formulation. The developed non-linear relationship relates the dissolution data to predict the bioavailability profile, Cmax 12. Simple linear equations between *in vitro* drug released and *in vivo* drug absorbed are developed by *IVIVC* models. The main objective for developing and comparing an *IVIVC* is to establish the dissolution test for human bioequivalence studies, which may additionally reduce the number of bioequivalence studies carried out all the initial approval process and post-approval changes. The *in vitro* dissolution testing is used to implement the process such as (1) providing process control and quality assurance; (2) determining stable release characteristics of the product over time; and (3) facilitating certain regulatory determinations. A predictive and reliable *IVIVC* model can be based on biowaiver, permitting reductions in time and charges at some point in pharmaceutical product improvement. Category 1: Biowaivers without an *IVIVC* For formulations consisting of dosage form, with the only difference between strengths and the number of beads, approval of lower strengths without an *IVIVC* is possible, provided bioavailability data for the highest strength. Category 2: Biowaivers Using an *IVIVC* for Non-Narrow Therapeutic Index Drugs Category 3: Biowaivers Using an *IVIVC* for Narrow Therapeutic Index Drugs If external predictability of an *IVIVC* is established, the waivers will allow for the development of *IVIVC* if at least two formulations/release rates have been studied. The waivers will be granted if dissolution data are submitted in compendial medium (e.8) Category 4: Biowaivers using *In Vitro* Dissolution Is Independent of Dissolution Test Conditions. Category 5: biowaiver conditions for which an *IVIVC* Is Not Recommended.

CONCLUSION

In vivo bioavailability studies should be performed to characterize the plasma concentration and time profile of the formulation. This involves the estimation of *in vivo* absorption profile from plasma drug concentration-time profile using Wagner–Nelson or Loo–Riegelman method. The correlation techniques available in the pharmaceutical methods are Single point, statistical moment, and convolution and deconvolution techniques with the resulting predictive tool. The *in vitro* parameter is used to determine the MDT and MRT using trapezoidal rules. The *in vivo* properties such as AUC and Cmax are used to calculate the prediction errors. In silico, *in Vitro*, and *in vivo* data can be used to predict absorption properties. The *in vivo* performance is to evaluate the predictability of the *IVIVC*. The *in vivo* properties such as AUC and Cmax are used to calculate the prediction errors. The *in vivo* bioavailability results from *in vitro* dissolution data by predicting the errors and acceptance criteria. *In silico*, in Vitor, and *in vivo* data can be used to predict absorption properties. Gastroplus can be utilized to simulate and predict oral drug absorption in different development phases for drug products.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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