IVIVC

IMPORTANCE OF IVIVC AND METHODS OF ESTABLISHING IVIVC

1. INTRODUCTION

The therapeutic efficacy of pharmaceutical formulations is governed by factors related to both the in vitro dissolution characteristics of the drug and its in vivo bioavailability. This inherent interdependency within the drug - patient biosystem is the major concern that underlines the importance of in vitro/in vivo correlation studies. The dissolution rate of a specific dosage form is an arbitrary parameter that is very dependant on the methodology utilized in generating the data. Changes in

- Type of apparatus,
- Dissolution medium,
- Agitation speed,

etc can modify dramatically the dissolution pattern. Therefore, unless it is demonstrated experimentally that the in vitro dissolution behavior reflects the in vivo performance in humans, the data can be of no relevant value in predicting or passing any judgment on the clinical effectiveness of the drug product.

Thus in other words the bioavailability implications of dissolution should never be accepted on faith; rather it has to be proved through carefully designed in vitro-in vivo correlation studies.

Long back, Wagner had stated that**, "Future research in dissolution rate should be directed mainly towards establishing correlation of in-vitro data with in-vivo data."**

A) DEFINITION OF IVIVC

In vitro and *in vivo* correlation (IVIVC) for drug products, especially for solid oral dosage forms, has been developed to predict product bioavailability from *in vitro* dissolution. Biological properties such as *C*max, or AUC have been used to correlate with *in vitro* dissolution behavior such as percent drug release in order to establish IVIVC. IVIVC can be used to set product dissolution specifications; and as a surrogate for *in vivo* bioequivalence in the case of any changes with respect
to formulation, process, or manufacturing site.

- IVIVC has been defined by the Food and Drug Administration (**FDA**) as "**A predictive mathematical model describing relationship between in-vitro property of a dosage form and in-vivo response.**

B) CRITERIA FOR IVIVC

- Successful IVIVC can be developed when in-vitro dissolution is rate limiting step in absorption and appearance of drug in in-vivo circulation following oral or other routes of administration.
- These studies are to be conducted during the early stages of drug product development in order to select the most effective formulation and to establish appropriate dosage regimen.

- The release-controlling excipient in the formulations should either be identical or very similar.

C) OBJECTIVE OF IVIVC

- To reduce the number of human studies during the formulation development
- To serve as a surrogate for in vivo bioavailability
- To support biowaivers.
- To validates the use of dissolution methods and specification settings (This is because the IVIVC includes in vivo relevance to in vitro dissolution specifications).
- To assist quality control for certain scale-up and post-approval changes (SUPAC).

Due to all above objective, such IVIVC leads to

1. Shortens the drug development period,
2. Economizes the resources and
3. Leads to improved product quality.

D) NEED FOR IVIVC

- Theoretically, correlation of in-vivo absorption rate with clinical response will be the most worthwhile approach. But, clinical approach is a poor tool for accurate measurement of bioavailability.
- Determination of drug level at the site of administration would be next logical approach. But again, with some exceptions, it's impossible.
- Urinary excretion analysis of drug is meaningful for establishing IVIVC but due to complicated pharmacokinetic considerations, such as drug metabolism and urine collection problems.thus it is generally assumed that blood(serum/plasma) level measurements give a better assessment of bioavailability and bioequivalence.
- This relationship is an important item of research in the development of drug delivery systems.
- A good IVIVC model can explore the relationship between in vitro dissolution or release and in vivo absorption profiles.
- The IVIVC model relationship facilities the rational development and evaluation of immediate or extended release dosage form as a tool for formulation screening ,in setting dissolution specifications and as a surrogate for bioequivalence testing.

✓ Factors to Consider for Meaningful IVIVC

Strategies to develop meaningful IVIVC for MR products are summarized below. It is important first to obtain *in vivo* data, and then identify the *in vivo* drug release mechanism. The *in vitro* release method can then be designed with consideration to the *in vivo* release profile and mechanism.

E) FACTORS AFFECTING DEVELOPMENT OF A PREDICTABLE IVIVC:-

The following factors play a vital role in development of a predictable IVIVC

1. Complexity of the delivery system.
2. Composition of formulation
3. Method of manufacture
4. Physicochemical properties.
5. Dissolution method.

Some compound properties will prohibit the successful application of IVIVC, such as

- Those with a narrow therapeutic window,
- Those with a variable first-pass effect,
- Endogenous compounds,
- Prodrugs or those with multiple response populations.

✓ Current uses of *in vitro* release testing method

- Formulation development
- Quality assurance and process control
- Evaluation of the changes in the manufacturing process
- Substantiation of label claims
- Compendial testing

2. SOME COMMON TERMS

A) MEAN ABSORPTION TIME: The mean time required for drug to reach systemic circulation from the time of drug administration.

$MAT = MRT_{oral} - MRT_{i.v.}$

B) MEAN IN-VIVO DISSOLUTION TIME: It reflects the mean time for drug to dissolve in-vivo. For solid dosage form:

$MDT_{solid} = MRT_{solid} - MRT_{solution}$.

C) MEAN RESIDENCE TIME: The mean time that the drug resides in the body. Also known as mean transit time.

MRT = AUMC / AUC.

Where, AUMC = Area under first moment Curve (Concentration*time Vs time)

AUC = Area under curve (Concentration Vs time)

D) PERCENT PREDICTION ERROR:

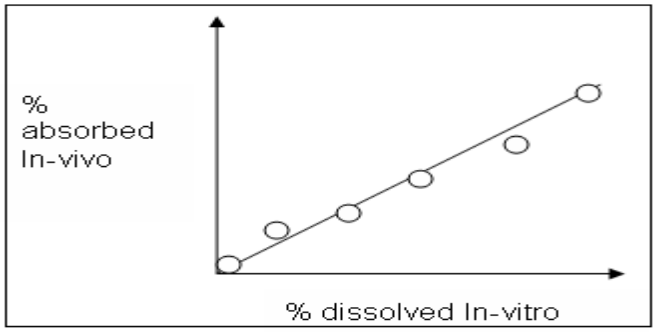
% PE = [(observed value – Predicted value) / observed value] x 100

3. LEVELS OF CORRELATION

There are five levels of IVIVC, which include levels A, B, C, multiple C and D.

A) LEVEL A CORRELATION

- This correlation represents a point-to-point relationship between in vitro dissolution and in vivo dissolution (input/absorption rate). Level A IVIVC is also viewed as a predictive model for the relationship between the entire in vitro release time course and entire in vivo response time course.
- In general, correlations are linear at this level. Although a concern of acceptable non-linear correlation has been addressed, no formal guidance on the non-linear IVIVC has been established.
- The data treatment involves Wagner-Nelson method (which considers body as a single compartment) or Loo-Reigleman or Deconvolution (which needs plasma concentration – time data for a fast releasing formulation i.e. intravenous (i.v.) or fast release oral formulation like solution or suspension or tablet for comparison) method followed by comparison of fraction of drug absorbed and fraction of drug dissolved in-vitro to obtain a linear correlation.
- Formulations showing Level A correlation require no additional human studies to justify change in manufacturing site, raw material supplier or minor formulation changes.



- Level A correlation is the most informative and very useful from a regulatory perspective since it is predictive of the dosage form's in vivo performance.

Significance of Level A Correlation

A Level A correlation defines a linear relationship between in vitro and in vivo data so that measurement of the in vitro dissolution rate alone is sufficient to determine the pharmacokinetic profile in vivo. After a proper validation, IVIVC predicts the in vivo bioavailability results from in
vitro dissolution data,and this simulation reflects the in vivo behavior of the various formulations (*8*). In the presence of an IVIVC,the FDA states (*2*),

In vitro dissolution testing is important for (1) providing process control and quality assurance, (2) determining stable release characteristics of
the product over time; and (3) facilitating certain regulatory determinations (e.g.,absence of effect of minor formulation changes or of change in manufacturing site on performance). In certain
cases, especially for ER formulations, the dissolution test can serve not only as a quality control for the manufacturing process but also as an indicator of how the formulation will performin vivo.
Thus,a main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies…

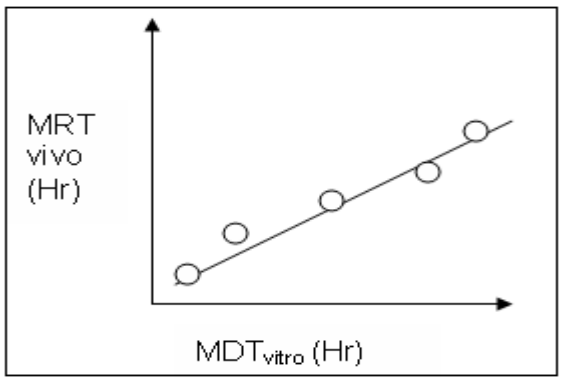
That highlights the significance of IVIVC and dissolution studies both during development and throughout the life of the product. For example,the establishment of dissolution limits could be based on IVIVC, as stated by FDA. IVIVC can also be used to support biowaivers in two cases over the five categories described in the SUPAC guidance (*2*,*3*).

Conclusion

Level A IVIVCs define the relationship between an in vitro dissolution curve and an in vivo input (absorption) profile. A Level A correlation should always be tried a priori in order to have a tool that allows a complete in vivo prediction from an in vitro dissolution curve and thus accelerates the development and assists in some regulatory aspects
(SUPAC). The correlation quality depends solely on the quality of the data. As in vivo data are now well standardized, the main effort must be directed to the in vitro data. Various apparatus and media should be tested and assessed in terms of their in vivo predictability. The user
should always be aware of the limits of the method and of
the confidence of its prediction.

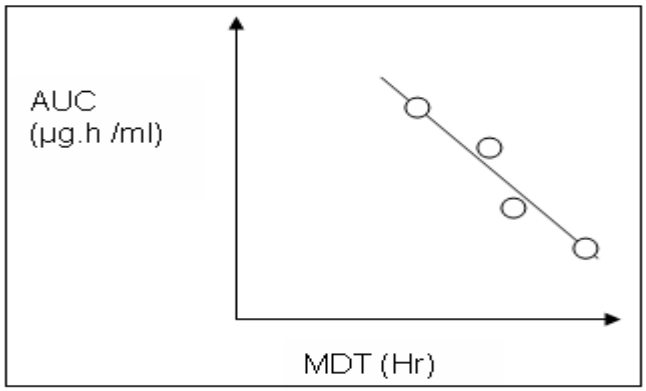
B) LEVEL B CORRELATION

- A predictive mathematical model for relationship between summery parameters that characterize the in-vitro and in-vivo time course i.e. it compares the Mean In-vitro Dissolution Time (MDT_{vitro}) to the Mean In-vivo Dissolution Time (MDT_{vivo}), Mean in vitro dissolution time (MDT_{vitro} to the Mean Residence Time In-vivo (MRT), or In-vitro Dissolution Rate Constant (k_d) to Absorption Rate Constant(k_a).
- In Level B correlation, the mean in vivo dissolution or mean residence time is compared to the mean in vitro dissolution time by using statistical moment analytical methods.
- This type of correlation uses all of the in vitro and in vivo data; thus, it is not considered as a point-to-point correlation.
- This is of limited interest and use because more than one kind of plasma curve produces similar mean residence time.



C) LEVEL C CORRELATION

- A predictive mathematical model of relationship between the amounts dissolved in-vitro at a particular time (e.g., % of drug dissolved in 1 hour) or time required for in-vitro dissolution of a fixed percent of dose (e.g., T50%,T90%) and a summery pharmacokinetic parameter that characterizes in-vivo time course. e.g., Cmax, Tmax, T1/2 or AUC.
- It's considered as lowest correlation level as it does not reflect a complete shape of plasma concentration time curve.



D) MULTIPLE LEVEL C CORRELATIONS

- It relates one or more pharmacokinetic parameters to the percent drug dissolved at several time points of dissolution profile. Thus be more useful
- If a multiple level C correlation exists, there's a possibility of Level A correlation.

Level	In vitro	In vivo
A	Dissolution curve	Input (absorption) curves
B	Statistical Moments: MDT	Statistical Moments: MRT, MAT, etc
C	Disintegration time, Time to have 10, 50, 90% Dissolved, Dissolution rate, Dissolution efficiency	C_{max}, T_{max}, K_a, Time to have 10, 50, 90% absorbed, AUC (total or cumulative),

NOTE:-

Level B and C correlations can be useful in early formulation development, including selecting the appropriate excipients, to optimize manufacturing processes, for quality control purposes, and to characterize the release patterns of newly formulated immediate-release and modified-release products relative to the reference.

E) LEVEL D CORRELATION

1. Level D correlation is a rank order and qualitative analysis and is not considered useful for regulatory purposes. It is not a formal correlation but serves as an aid in the development of a formulation or processing procedure

4. CORRELATION METHODS

A) SIMPLE POINT TYPE

The percentage of drug dissolved in a given time or the time taken for a certain percentage of drug to be dissolved, is correlated with certain parameter of the bioavailability

B) COMPARISON OF PROFILES

- The entire in vivo response time profile can be correlated to the entire dissolution rate time curve.
- Some of the in vivo and in vitro parameters employed for correlation are as follows.

In vivo data	In vitro data
1. Plasma conc. time profile ○ Plasma concentration at time t, ○ C max, ○ tmax, ○ AUC_o^t AUC_o^∞ ○ t30% t50% t90%	**1. Percent drug dissolution profile** ○ Percent drug dissolved at time t, ○ tmax, ○ 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%
2. Pharmacokinetic parameters ○ Absorption &elimination rate constant & half life	**2. Kinetic parameter** ○ Dissolution rate constant. ○ Dissolution half life
3. Percent drug absorbed time profile	**3. Percent drug dissolved time profile** ○ Percent drug dissolved at time t
4. Statistical moment analysis ○ MRT , MAT	**4. Statistical moment analysis** ○ MDT

C) DIRECT,DIFFERENTIAL-EQUATION-BASED

in-vitro-in-vivo correlation (IVIVC) method = a novel method

A new, differential equation-based in-vitro-in-vivo correlation (IVIVC) method is proposed that directly relates the time-profiles of in-vitro dissolution rates and in-vivo plasma concentrations by using one- or multi-compartment pharmacokinetic models and a corresponding system of differential equations.

The rate of in-vivo input is connected to the rate of in-vitro dissolution through a general functional dependency that allows for time scaling and time shifting. A multiplying factor that accounts for the variability of absorption conditions as the drug moves along is also incorporated.

Two data sets incorporating slow-, medium-, and fast-release formulations were used to test the applicability of the method, and predictive powers were assessed with a leave-one-formulation-out approach. All fitted parameters had realistic values, and good or acceptable fits and predictions were obtained as measured by plasma concentration mean squared errors and percent AUC errors. Introduction of step-down functions that account for the transit of the dosage form past the intestinal sites of absorption proved useful.

By avoiding the integral transforms used in the existing deconvolution- or convolution-based IVIVC models, the present method can provide increased transparency, improved performance, and greater modelling flexibility

IMPORTANT CONSIDERATIONS IN DEVELOPING A CORRELATION

- When the dissolution is not influenced by factors such as pH, surfactants, osmotic pressure, mixing intensity, enzyme, ionic strength, and a set of dissolution data obtained from one formulation is correlated with a deconvoluted plasma concentration-time data set.
- In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of appropriate scaling factor (time corrections).
- If one or more of the formulations may not illustrate the same relationship between in vitro performance and in vivo profiles compared with the other formulations, the correlation is still valid
- The in vitro dissolution methodology should be able to adequately discriminate between the study formulations.
- During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a one-to-one correlation between the in vitro dissolution profile and the in vivo dissolution profile
- An established correlation is valid only for a specific type of pharmaceutical dosage form (tablets, gelatin capsules, etc.) with a particular release mechanism (matrix, osmotic system, etc.) and particular main excipient and additives
- Extrapolation of IVIVC established in healthy subjects to patients has to be taken into account.
- The release rates, as measured by percent dissolved, for each formulation studied, should differ adequately (e.g., by 10%).

5. ESTABLISHING IN VITRO/IN VIVO CORRELATION

It can be achieved using

1. Pharmacological correlations based on clinical observations.
2. Semi quantitative correlations based on the drug blood levels or urinary excretion data.

3. Quantitative correlations arising from absorption kinetics and calculation of in vivo dissolution rate and absorption rate constants.

TWO BASIC TYPE OF CORRELATION

1. **Quantitative correlation:**-In vivo parameter-y ,in vitro-x, y= mx +c
   - Pearson product moment correlation coefficient, r (-1 to +1) quantify strength of relationship between x & y.
   - If r is close to 1 (strong correlation) If r is close to zero (weak correlation)

2. **Rank order correlation** :-(spearman rank correlation, rs) Values of the two variables are ranked in ascending or descending order.

6. STAGES OF IVIVC MODEL DEVELOPMENT

Model development involves two stages:

1. Model development
2. Model validation

A) MODEL DEVELOPMENT

- The principles of IVIVC model development have been successfully applied to oral dosage forms. However, the ground rules for developing and validating IVIVC models for novel and non-oral dosage forms/delivery systems (microspheres, implants, liposome, etc) are still unclear today.
- For orally administered drugs, IVIVC is expected for highly permeable drugs or drugs under dissolution rate-limiting conditions, which is supported by the Biopharmaceutical Classification System (BCS).
- For extended-release formulations following oral administration, modified BCS containing the three classes (high aqueous solubility, low aqueous solubility, and variable solubility) is proposed.

Class	Solubility	Permeability	IVIVC expectation
I.	High	High	IVIVC: if dissolution rate is slower than gastric emptying rate. Otherwise limited or no correlation required.
II.	Low	High	IVIVC is expected if in-vitro dissolution rate is similar to in-vivo dissolution rate, unless dose is very high.
III.	High	Low	Absorption/permeability is rate determining and limited or no correlation with dissolution rate.
IV.	Low	Low	Limited or no IVIVC expected.

A number of methods are available to probe the in vitro-in vivo relationships. Among the earliest methods are the two-stage Deconvolution methods that involve estimation of the in vivo absorption profile from the concentration-time data using the Wagner-Nelson methods (Stage 1). Subsequent to the estimation of the in vivo absorption profile, the relationship with in vitro dissolution is evaluated (Stage 2). More recently, one-stage convolution-based approaches for IVIVC have been investigated.

The **one-stage convolution methods** compute the in vivo absorption and simultaneously model the in vitro-in vivo data.

While the **two-stage method** allows for systematic model development, the one-stage method obviates the need for the administration of an intravenous, oral solution or immediate-release bolus dose.

The most basic IVIVC models are expressed as a simple linear equation (Equation 1) between the in vivo drug absorption and **in vitro** drug dissolved (released).

Y (in vivo absorption) = mX (in vitro drug dissolved) + C

In this equation, m is the slope of the relationship, and C is the intercept.

Ideally, m=1 and C=0, indicating a linear relationship. However, depending on the nature of the modified-release system, some data are better fitted using nonlinear models, such as Sigmoid, Weibull, Higuchi, or Hixson-Crowell.

Equation 1 may be applied to most formulations with comparable in vitro and in vivo duration of release. However, for dosage forms with complicated mechanisms of release, which are of longer duration, in vitro release may not be in the same time scale as the in vivo release. Thus, in order to model such data, it is necessary to incorporate time-shifting and time-scaling parameters within the model (Figure 1). This is the kind of data that is routinely encountered in the development of sustained-release dosage forms.

In vivo release rate (X'vivo) can also be expressed as a function of in vitro release rate (X'rel,vitro) with parameters (a, b), which may be empirically selected and refined using appropriate mathematical processes as shown in Equation 2.An iterative process may be used to compute the time-scaling and time-shifting parameters.

X'vivo (t) = X'rel, vitro (a + bt)

DETERMINING THE FRACTION OF DOSE ABSORBED

- **Model Dependent methods**
  1. Wagner Nelson Equation
  2. Loo-Riegelman Method

- **Model Independent methods**
  1. Deconvolution

B) MODEL VALIDATION

- It can be accomplished using data from the formulations used to build the model (internal validation) or using data obtained from a different (new) formulation (external validation).
- While internal validation serves the purpose of providing basis for the acceptability of the model, external validation is superior and affords greater "confidence" in the model.

1. Internal Validation:

(1) Using the IVIVC model, for each formulation, the relevant exposure parameters (C_{max} and AUC) are predicted and compared to the actual (observed) values. The prediction errors are calculated using Equation.3

$$\text{Prediction Error (\%PE)} = \left(\frac{C_{\text{max observed}} - C_{\text{max predicted}}}{C_{\text{max observed}}}\right) * 100$$

$$= \frac{(AUC_{observed} - AUC_{predicted})}{AUC_{observed}} * 100$$

(2) The criteria set in the FDA guidance on IVIVC are as follows: For C_{max} and AUC, the mean absolute percent prediction error (% PE) should not exceed 10%, and the prediction error for individual formulations should not exceed 15%.

2. External Validation:

(1) For establishing external predictability, the exposure parameters for a new formulation are predicted using its in vitro dissolution profile and the IVIVC model and the predicted parameters are compared to the observed parameters.

(2) The prediction errors are computed as for the internal validation. For Cmax and AUC, the prediction error for the external validation formulation should not exceed 10%. A prediction error of 10% to 20% indicates inconclusive predictability and illustrates the need for further study using additional data sets.

(3) For drugs with narrow therapeutic index, external validation is required despite acceptable internal validation, whereas internal validation is usually sufficient with non-narrow therapeutic index drugs.

7. EVALUATION OF IVIVC

Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of prediction error internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to define the IVIVC model. Evaluation of external predictability is based on additional test data sets.

Internal predictability is applied to IVIVC established using formulations with three or more release rates for non-narrow therapeutic index drugs exhibiting conclusive prediction error. If two formulations with different release rates are used to develop IVIVC, then the application of IVIVC would be limited to specified categories. Under these circumstances, for complete evaluation and subsequent full application of the IVIVC, prediction of error externally is recommended.

External predictability evaluation is not necessary unless the drug is a narrow therapeutic index, or only two release rates were used to develop the IVIVC, or, if the internal predictability criteria are not met i.e. prediction error internally is inconclusive. However, since the IVIVC will potentially be used to predict the in vivo performance for future changes, it is of value to evaluate external predictability when additional data are available.

The objective of IVIVC evaluation is to estimate the magnitude of the error in predicting the in vivo bioavailability results from in vitro dissolution data. This objective should guide the choice and interpretation of evaluation methods. Any appropriate approach related to this objective may be used for evaluation of predictability.

8. APPLICATIONS OF IVIVC IN DRUG DELIVERY

1. EARLY STAGES OF DRUG DELIVERY TECHNOLOGY DEVELOPMENT

Proof-of-Concept the selection of a drug candidate marks the most crucial stage in the life cycle of drug development. Such selection is primarily based on the drug "developability" criteria, which include physicochemical properties of the drug and the results obtained from preliminary studies involving several in vitro systems and in vivo animal models, which address efficacy and toxicity issues. During this stage, exploring the

relationship between in vitro and in vivo properties of the drug in animal models provide an idea about the feasibility of the drug delivery system for a given drug. In such correlations, study designs including study of more than one formulation of the modified-release dosage forms and a rank order of release (fast/slow) of the formulations should be incorporated. Even though the formulations and methods used at this stage are not optimal, they prompt better design and development efforts in the future.

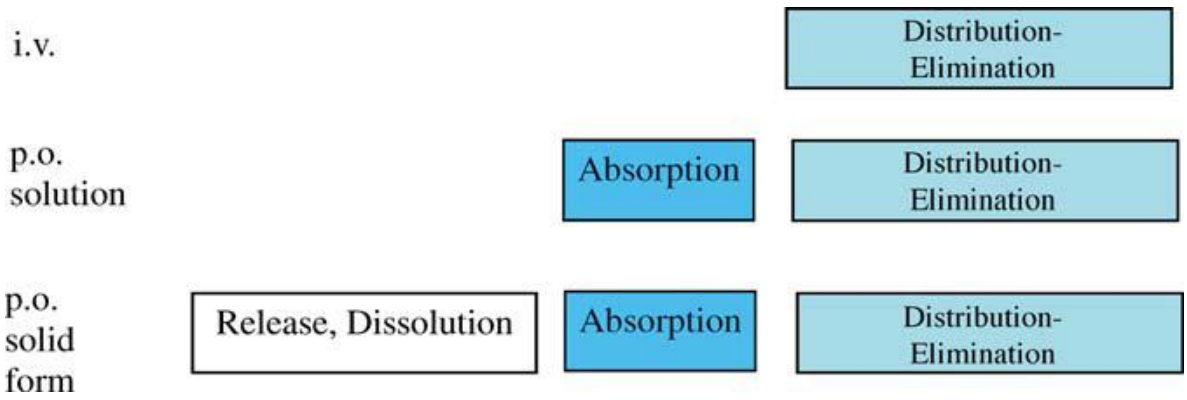
2. FORMULATION ASSESSMENT

In Vitro Dissolution a suitable dissolution method that is capable of distinguishing the performance of formulations with different release rates in vitro and in vivo is an important tool in product development. IVIVC facilitates the process of such method development. Depending on the nature of the correlation, further changes to the dissolution method can be made. When the discriminatory in vitro method is validated, further formulation development can be relied on the in vitro dissolution only.

3. DISSOLUTION SPECIFICATIONS

Modified-release dosage forms typically require dissolution testing over multiple time points, and IVIVC plays an important role in setting these specifications. Specification time points are usually chosen in the early, middle, and late stages of the dissolution profiles. In the absence of an IVIVC, the range of the dissolution specification rarely exceeds ± 10% of the dissolution of the pivotal clinical batch. However, in the presence of IVIVC, wider specifications may be applicable based on the predicted concentration-time profiles of test batches being bioequivalent to the reference batch.

The process of setting dissolution specifications in the presence of an IVIVC starts by obtaining the reference (pivotal clinical batch) dissolution profile. The dissolution of batches with different dissolution properties (slowest and fastest batches included) should be used along with the IVIVC model, and prediction of the concentration time profiles should be made using an appropriate convolution method. Specifications should optimally be established such that all batches with dissolution profiles between the fastest and slowest batches are bioequivalent and less optimally bioequivalent to the reference batch.



Main phenomena after administration of various formulations (8).

4. FUTURE BIOWAIVERS

Frequently, drug development requires changes in formulations due to a variety of reasons, such as unexpected problems in stability, development, availability of better materials, better processing results, etc.

Having an established IVIVC can help avoid bioequivalence studies by using the dissolution profile from the changed formulation, and subsequently predicting the in vivo concentration-time profile. This predicted profile could act as a surrogate of the in vivo bioequivalence study. This has enormous cost-saving benefit in the form of reduced drug development spending and speedy implementation of post-approval changes. The nature of post-approval changes could range from minor (such as a change in non release-controlling excipient) to major (such as site change, equipment change, or change in method of manufacture, etc).

5. IVIVC – PARENTERAL DRUG DELIVERY

IVIVC can be developed and applied to parenteral dosage forms, such as controlled-release particulate systems, implants, etc, that are either injected or implanted. However, there are relatively fewer successes in the development of IVIVC for such dosage forms, which could be due to several reasons, a few of which are discussed further.

1. **Burst Release** - In the case of polymer-based delivery systems, the underlying issue with developing IVIVC is drug release during the initial period called burst release, which results in biphasic plasma profiles. The bi-phasic profile is believed to occur due to the loosely associated drug particles with the surface of the (polymer) particles. Because the burst release is unpredictable and unavoidable, sophisticated modeling techniques are needed to correlate the in vitro and in vivo data.

2. **Potent Drugs & Chronic Therapy** - In general, several parenteral drug delivery systems are developed for potent drugs (e.g., hormones, growth factors, antibiotics, etc) and for long-term delivery (anywhere from a day to a few weeks to months). The design of such systems is very complex, and changing the composition or method of manufacture of these systems would affect their in vivo performance drastically.

3. Limited volume of tissue fluids and Area of absorption at the site of administration, unlike following the oral route of administration. Therefore, it is very difficult to specify the in vitro dissolution conditions that reflect the observed differences in the in vivo plasma profiles corresponding to the in vitro release profiles. In such instances, to establish a good IVIVC model, the drug concentrations should be monitored in the tissue fluids at the site of administration by techniques such as microdialysis, and then the correlation should be established to the in vitro release.

9. NEW IVIVC APPLICATIONS

A) IVIVC FOR TRANSDERMAL ESTRADIOL SYSTEMS (Noven pharmaceuticals)

The data generated in development of Novens Vivelle. Dot^{TM} using human cadaver skin has enabled such an IVIVC. Utilizing this human cadaver model, a ratio of skin permeation of 2.9 to 1.0 was established over five studies for Vivelle.Dot^{TM} vs. Vivelle^{R} .This ratio of skin permeation or Estradiol delivery was subsequently confirmed, in vivo, on human volunteers in a pharmacokinetic study involving 12 patients where bioequivalence was demonstrated.

B) WHY IVIVC FAIL FOR IMMEDIATE RELEASE DOSAGE FORM

For Level A analysis, the fraction drug absorbed (Fa) is plotted against the fraction drug dissolved (Fd). The fraction drug absorbed profile is obtained by deconvoluting the

plasma profile. Deconvolution is essentially a back calculation to answer the question: "What must the drug absorption profile have been, given the plasma profile?"

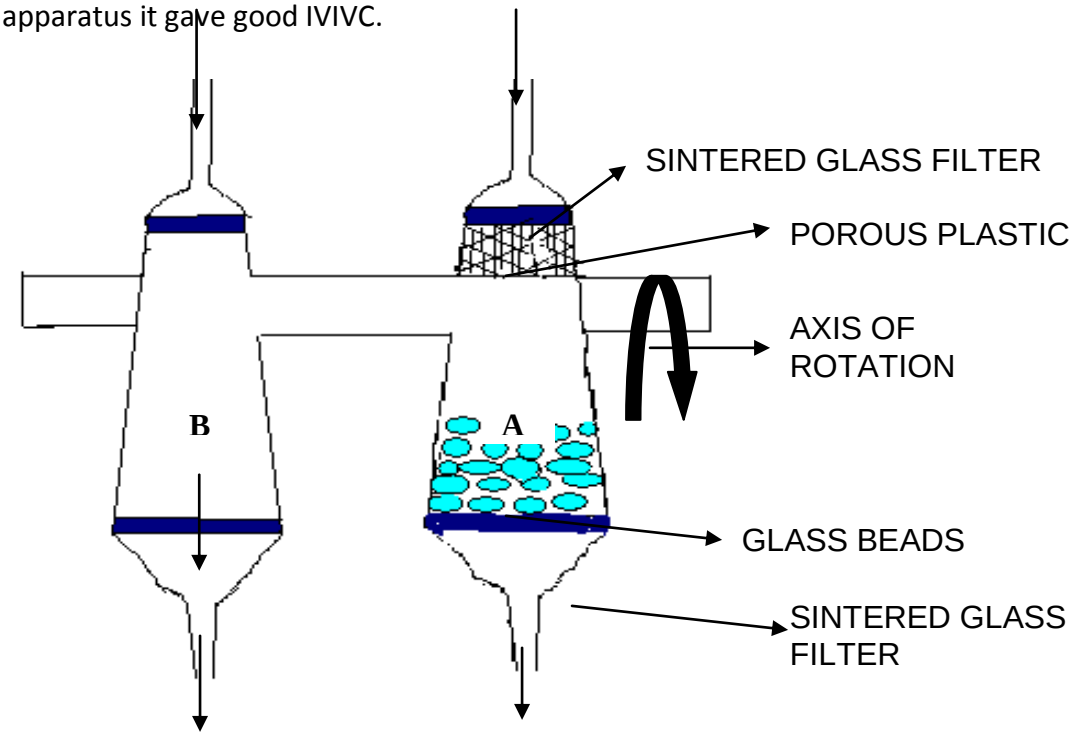
A statistic from Level A analysis is r, the correlation coefficient. Its square r2, ranges from zero to one and is a measure of the strength of relationship between Fa against Fd. Often, results with sufficiently large r2 (e.g. greater than 0.9) yielded "a (successful) correlation." An r2 value that was too low resulted in a "no correlation" conclusion.

Only products with dissolution rate-limited absorption (and with complete absorption) can be expected to exhibit a Level A plot with a slope of one and zero intercept, immediate release products will "fail" the Level A method

C) DISSOLUTION SIMULATORS

In order to enhance the capability of in vitro dissolution as a predictor of the in vivo behavior of dosage forms. But many of these attempts required highly complex and expensive apparatus with questionable advantage over traditional systems.

1. **Gronings model**: - It consists of two interconnecting flow through cells and a reservoir for the dissolution medium, all contained in a constant temperature water bath. The dosage form disintegrates in the gastric part of the model and some of the drug particles are continuously pumped into the intestinal part. During an experiment the cells are rotated by a slow speed electric motor. Unlike conventional dissolution apparatus it gave good IVIVC.



GRONINGS MODEL

2. **Sartorius dissolution simulator: -** This was designed to be used in conjunction with c&d apparatus. The dissolution simulator is composed of two identical plastic cylinders containing dissolution media, the pH of which can be changed to mimic the passage from stomach to intestine. Membrane filters are used with the system and the cylinders rotate around a horizontal axis to provide a gentle agitation .Samples are withdrawn automatically for analysis at a rate that is related to the rate of drug diffusion in the absorption simulator.

3. **Sartorius membrane filter solubility simulator:-**
4. **Sartorius membrane filter absorption simulator:-**This essentially consists of a dialysis cell designed to determine the diffusion rate of the drug.

10. NON-LINEAR CORRELATION

IVIVCs reported in the literature are predominantly based on a linear relationship between the bioavailability parameters and in vitro release data. Non-linear though predictive IVIVCs studies, however, are very scarce in the literature. In the IVIVC study reported by Sirisuth et al, linear and non-linear (quadratic, cubic and sigmoid functions) correlation models were examined using pooled fraction dissolved and absorbed from various combinations of the diltiazem extended release formulations.

Linear and non-linear regressions have also been attempted for in vivo input and in vitro release for the controlled-release ethylcellulose-coated pellets containing adenosine derivative. The relationship between fraction absorbed in vivo and fraction released in vitro for membrane coated pellets was curvilinear indicating that there was a time-scale difference between in vivo and in vitro testing being much shorter for in vivo absorption. The authors, therefore, concluded that an in vitro dissolution test with a shorter time frame and faster release may be required to establish a linear IVIV correlation (34).

IVIVR

One possible substitution for IVIVC is IVIVR, with "R" denoting "relationship." By comparison with Level A IVIVC, IVIVR analysis would concern the elucidation of the in vitro dissolution - in vivo absorption relationship. Hence, IVIVR need not be limited to straight-line relationships, which appear to be generally incorrect for IR products (1,6,7). One intent of IVIVR should be to learn about the relative contribution of dissolution to a product's overall absorption kinetics.
One model for IVIVR is (3):

$$F_a = \frac{1}{f_a}\left(1 - \frac{\alpha}{\alpha - 1}\left(1 - F_d\right) + \frac{1}{\alpha - 1}\left(1 - F_d\right)^{\alpha}\right)$$

where
Fa is the fraction of the total amount of drug absorbed at time t,
fa is the fraction of the dose absorbed at t = #,

K is the ratio of the apparent first-order permeation rate constant (kpaap) to the first-order dissolution rate constant (kd), and
Fd is the fraction of drug dose dissolved at time t.

Of note is that the Level A method is a special (linear) case of eq 1. If fa = 1.0 (i.e. complete absorption) and □>>1# (i.e. strongly dissolution rate-limited absorption), then Fa = Fd, as in Fig 1.

This IVIVR analysis has been applied to several formulations of metoprolol, piroxicam, and ranitidine (6,7). IVIVR analysis indicated that formulation properties and drug substance biopharmaceutic properties influenced the degree to which dissolution controlled overall absorption kinetics. Interestingly, dissolution was not rate-limiting from even the slowest dissolving IR formulations for the high solubility drugs.

Future Directions

The use of the term IVIVR rather than IVIVC is preferred. Immediate release products are amenable to dissolution-absorption analysis. However, the term IVIVR itself is neither new (8), nor fundamental. Rather, what is needed is a better understanding of in vivo dissolution, and its in vitro surrogate, the dissolution test. Additionally, dissolution needs to be considered in the context of other parallel and sequential processes (e.g. permeability, degradation, and transit). Through a better understanding of dissolution, dissolution and IVIVR can facilitate not only SUPAC-type changes, but also facilitate drug product development.

QUESTION BANK

1. What do you mean by IVIVC? Add a brief note on its importance.
2. Add a note on suitability and factors affecting predictable IVIVC?
3. Discuss different levels of correlation given by FDA?
4. Add a note on stages of IVIVC Model development?
5. Describe in brief application of IVIVC?
6. Add a note on future directions of IVIVC?
7. Write short note on
    - IVIVR
    - Dissolution simulators
    - Parenteral IVIVC
    - Causes of failure of Parenteral IVIVC

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