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"Review on IVIVC (In Vitro In Vivo Correlation)"

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Content

Abstract

This review article aimed to assess papers published in the last two decades regarding the use of the IVIVC in the development of oral formulations, to demonstrate the scenario in this area, as well as to describe the main characteristics of the assessed studies. IVIVC is a mathematical model that can be used to estimate in vivo behaviour from its in vitro performance. Among all the five levels of correlation, Level A correlation is widely accepted by the regulatory agencies. Biopharmaceutical Classification System (BCS) explains the suitability of IVIVC. Dissolution method design plays a pivotal role in the estimation of correlations. Apparatus qualification and guidelines is other essential parameters in the study of IVIVC.

Keywords:

Fundamentals of IVIVC, Biopharmaceutical Classification System, Biowaiver, Dissolution Methodologies, IVIVC of Novel Dosage Forms, Applications of IVIVC.

Introduction:

USP (United State Pharmacopoeia) Definition: "The establishment of rational relationship between a biological property or a parameter derived from a biological property produced by a dosage from and physicochemical property of same dosage form".

Conceptually, IVIVC describes a relationship between the in-vitro dissolution/release versus the in-vivo absorption.

FDA (Food and Drug Administration) Definition: "A predictive mathematical relationship between in-vitro property of a dosage form and in-vivo response."

IVIVC plays a critical role in drug development and in optimization of formulation which is certainly a time consuming and expensive process.

In IVIVC, "C" denotes Correlation" which means "The degree of relationship" between Two variables.

"The term IVIVC. could also be employed to establish dissolution specification and to support and/ or validate the use of dissolution methods."

Objective:

- 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.

Need of 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.

Why Conduct IVIVC:

An IVIVC model is recommended by regulatory authorities for most modified release dosage forms. The main advantage of IVIVC is that it provides a mechanism for evaluating the change in in vivo absorption based on in vitro dissolution changes when there are small changes in a formulation. Once a validated IVIVC model has been established, it can be used to predict bioavailability and bioequivalence (BA/BE) based on in vitro data that are already available. In such cases, dissolution test results can be used to provide the desired information without the need for any clinical BE studies with human subjects. Another advantage of IVIVC is that it conveys a better understanding of the drug product itself. This can help establish a wider drug product acceptance criteria and formulation stability. IVIVC can also be especially useful for predicting the in vivo effects of changes to the formulation components, manufacturing site, or process. This is extremely important during initial product development however, the value of IVIVC does not end there. Establishing an IVIVC model can be even more valuable after the product has been approved by determining the impact of post-approval manufacturing changes, site of manufacture changes, and any issues with individual lots of manufactured products. All of this can be determined without having to repeat costly in vivo BE studies.

Fundamentals Of IVIVC:

Level A correlation

Among all the level of correlation defined, level A is of prime importance. It is defined as a hypothetical model describing the relationship between a fraction of drug absorbed and fraction of drug dissolved. In order to develop a correlation between two parameters one variable should be common between them. The data available is in vitro dissolution profile and in vivo plasma drug concentration profile whose direct comparison is not possible. To have a comparison between these two data, data transformation is required. The in vivo properties like percent drug dissolved or fraction of drug dissolved can be used while in vivo properties like percent drug absorbed or fraction of drug absorbed can be used respectively. It is considered as a predictive model for relationship between the entire in vitro release time courses. Most commonly a linear correlation exists but sometimes non-linear In vitro- in vivo correlation may prove appropriate. However, no formal guidance for non-linear IVIVC has been established. When in vitro curve and in vivo curve are super imposable, it is said to be 1:1 relationship, while if scaling factor is required to make the curve super imposable, then the relationship is called point-to-point relationship. Level A correlation is the highest level of correlation and most preferred to achieve; since it allows bio waiver for changes in manufacturing site, raw material suppliers, and minor changes in formulation.

Level B correlation

Here the mean in vitro dissolution time (MDT) is compared with either the mean in vivo residence time (MRT) or mean in vivo dissolution time derived by using principle of statistical moment analysis. Though it utilizes all in vitro and in vivo data, it is not considered as point-to-point correlation since number of in vivo curves can produce similar residence time value. Hence, it becomes least useful for regulatory purposes.

Level C correlation

It is referred as single point correlation which is established in between one dissolution parameter (t50%) and one of the pharmacokinetic parameter ($t_{max,}$ C_{max} or AUC). However, it does not reflect the complete shape of plasma drug concentration time curve, which is the critical factor that defines the performance of a drug product. Level C correlation is helpful in early stages of development when pilot formulations are being selected

Multiple Level C correlation

It refers to the relationship between one or several pharmacokinetic parameters of interest and amount of drug dissolved at several time point of dissolution profile. It should be based on at least three dissolution time points that includes early, middle and late stage of dissolution Profile.

Level D correlation

It is a semi quantitative and rank order correlation and is not considered useful for regulatory purpose.

Benefits:

IVIVC can benefit programs in many ways and for a variety of submission types. IVIVC analyses can be used to support:

- Abbreviated New Drug Applications (ANDA)
- New Drug Applications (NDA) for oral drugs with extended release characteristics
- Abbreviated Antibiotic Drug Applications (AADA) as a surrogate for in vivo BE determinations

IVIVC can also be used to support biowaivers, which allows Sponsors to waive in vivo BA and/or BE study requirements. When requesting biowaivers for drug manufacturing changes, IVIVC can be used in lieu of certain otherwise required in vivo studies if sufficient safety and efficacy have been established. Recently, IVIVC has been used in the Quality by Design (QBD) framework to establish clinically meaningful drug product specifications using dissolution as the endpoint.3 IVIVC can be used for setting dissolution specifications such as:

- supporting strength change justification
- small changes in the formulation
- changes to the site of manufacture
- batch-to-batch quality control

FDA Guidelines For IVIVC

The FDA Guidance, "Extended Release oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations," is more than 20 years old but remains the definitive source of regulatory thinking on IVIVC. At the time of its release, the ability to accurately and precisely predict expected BA characteristics for an extended release product from its dissolution profile had been a long sought-after goal. The recommendations within the guidance cover IVIVC for oral, extended release drug products that are being developed for regulatory review as part of an NDA, ANDA, or AADA. The guidance outlines:

- how to develop an IVIVC model
- how to evaluate predictability
- how to use IVIVC to establish specifications for dissolution
- how to apply IVIVC as a surrogate for in vivo BE studies.

Reasons For In IVIVC:

Fundamentals – When in vivo dissolution is not the rate limiting pharmacokinetic stage, and when no in vitro test can simulate the drug dissolution along the gastrointestinal tract.

Study design – With inappropriate in vitro test conditions.

Dosage form – When the drug release is not controlled by the dosage form or is strongly affected by the stirring of synthetic liquid.

Drug substance – With a non- linear pharmacokinetics, for Eg- first - pass hepatic effect, an absorption window, a chemical degradation and a large inter or intra subject variability. All these factors are of vital concern and should be kept in mind, especially the inter variability of patients' response to a drug.

General IVIVC Consideration:

Successful IVIVC relationships demonstrate that different release rates of two or more formulations result in corresponding differences in absorption profiles via the same absorption mechanism.

For each of the formulations studied, the release rates, as measured by percent dissolved, should differ by at least 10%. This should also result in in vivo profiles that show comparable differences in Cmax and AUC between each formulation (i.e., formulations that differ by a given percentage in vitro should show a corresponding difference in vivo).

The predictive performance of an IVIVC model is estimated as prediction error. The evaluation of this prediction error is based on either internal datasets and/or additional external datasets and depends upon the intended application of an IVIVC analysis and the therapeutic area of the drug.

IVIVC development is much more likely to successful for drugs with high solubility, when in vitro and in vivo data are available from a variety of formulations including a solution formulation as a reference.

Biopharmaceutics Classification:

Biowaiver for BCS Class I

On the basis of FDA guidelines, sponsor can request biowaiver for BCS Class I in immediate release solid oral dosage form, if the drug is stable in GIT and having narrow therapeutic index with no excipient interaction affecting absorption of drug in the oral cavity. Once a drug enters in stomach; it gets solubilised in gastric fluid rapidly before gastric emptying and the rate and extent of absorption is independent of drug dissolution as in case of solution. Hence, the goal of biowaiver is achieved

Biowaiver Extension Potential for BCS Class II

The rate and extent of absorption of BCS Class II drug depends on in vivo dissolution behaviour of immediate release products. If in vivo dissolution can be predicted from in vitro dissolution studies, in vivo bioequivalence study can be waived. In vitro dissolution methods can mimic in vivo dissolution behaviour of BCS Class II drug and are appealing but experimental methods can be difficult to design and validate because of number of processes involved.

Biowaiver Extension for BCS Class III

If excipient used in two pharmaceutically equivalent solid oral immediate release product does not affect the drug absorption and the products dissolves very rapidly (>85% in 15 min.) in all relevant pH ranges, there is no reason to believe that these products would not be bioequivalent.

Dissolution methodologies, apparatus and classification

The principle applied to dissolution has stood the test of time. Basic understanding of these principles and their application are essential for the design and development of sound dissolution methodologies as well as for deriving complementary statistical and mathematical techniques for unbiased dissolution profile comparison. USP 27, NF22 (11) now recognized seven dissolution apparatus specifically and describes with allowable modifications in detail. The choice of dissolution apparatus should be considered during the development of the dissolution methods, since it can affect the results and duration of the test. The type of dosage form under investigation is the primary consideration in apparatus selection. The compendial apparatus for dissolution as per USP are: Apparatus 1 (rotating basket), Apparatus 2 (paddle assembly), Apparatus 3 (reciprocating cylinder), Apparatus 4 (flow-through cell), Apparatus 5 (paddle over disk), Apparatus 6

(cylinder), Apparatus 7 (reciprocating holder). The European Pharmacopoeia has also adopted some of the apparatus designs described in the USP, with some minor modifications in the specifications.

Parameters to be considered while developing

Metabolic factors: A drug must pass sequentially from the gastrointestinal lumen, through the gut wall, and the liver, before entering in the systemic circulation. This sequence is an anatomic requirement because blood perfusion virtually all gastrointestinal tissues drain into the liver via the hepatic portal vein. Drug loss may occur in the GIT due to the instability of the drug in the GIT and/or due to complexation of drug with the components of the GI fluids, food, formulation excipients or other co-administered drugs. In addition, the drug may undergo destruction within the walls of the GIT and/or liver.

Drug loss in GIT: Any reaction that completes with the absorption of a drug may reduce oral bioavailability of a drug. Reaction can be both enzymatic and non-enzymatic. Acid hydrolysis is a common non-enzymatic reaction. Enzymes in the intestinal epithelium and within the intestinal microflora, which normally reside in the large bowel, metabolize some drug. The reaction products are often inactive or less potent than the large molecule.

Stereochemistry: When one enantiomer has higher affinity towards receptors than other, the phenomenon is termed as stereo selectivity which results in pharmacokinetics or pharmacodynamics. If such stereoisomers in the form of racemate are administered orally, one form may have higher bioavailability than the other. Obviously use of in vitro dissolution data of racemate will not be useful in the development of IVIVC and hence prediction of in vivo availability of active enantiomer So consideration of stereoisomerism in the development of IVIVC may provide more meaningful relationship.

Approaches:

There are mainly of two approaches:

1.By establishing a relationship between the in-vitro dissolution and the in-sive bioavailability parameters.

2.By using the data obtained from previous bioavailability studies to modify the dissolution methodology in order to arrive at meaningful in-vitro in vivo correlation.

IVIVC Of Novel Dosage Form:

Individual unit is emptied gradually and separately from the stomach to duodenum. Simulation of these conditions in vitro is troublesome and may be impossible. Takashi et al developed a method to predict dissolution in GIT from in vitro data in consideration of gastric emp- tying process. Direct prediction of in vivo absorption profile from in vitro dissolution data in multiple unit system was difficult but convolution method overcame this problem. Good correlation (level A) was obtained for multiple unit enteric coated granules by using convolution method.

Application:

a) IVIVC for transdermal estradiol systems (novel pharmaceuticals)

b) Why IVIVC fail for immediate release dosage form

c) Dissolution simulators:

i. Gronings model

ii. Sartorius dissolution simulator

iii. Sartorius membrane filter solubility simulator

iv. Sartorius membrane filter absorption simulator.

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