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In-Vitro In-Vivo Correlation Studies - An overview

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ABSTRACT

In vitro-invivo correlation plays a key role in pharmaceutical development of dosage form, optimization of formulation. This articles describes about the regulatory criteria and the factors associated with developing an In-vitro and in-vivo correlation. This factors plays an important role in optimizing the design and protocol required fort development of any dosage form and to identify the bioavailability pattern of the dosage forms. This article provide information on the various guidelines, factors in developing the correlations, bio pharmaceutical classification system,and other applications.

Keywords: In Vitro In Vivo correlation, Food and Drug Administrations Factors, Bio pharmaceutical classification system.

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INTRODUCTION

In vitro in vivo correlations (IVIVC) play a key role in the drug development and optimization of formulation which is certainly a time consuming and expensive process. Formulation optimization requires alteration in formulation, composition, equipments, batch sizes and manufacturing process. If such types of one or more changes are applied to the formulation, the in vivo bioequivalence studies in human may required to be done to prove the similarity of the new formulation which will not only increase the burden of carrying out a number of bioequivalence studies but eventually increase the cost of the optimization process and ultimately marketing of the new formulation. To overcome these problems it is desirable to develop in-vitro tests that reflect can bioavailability data. IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development. Thus, the main objective of an IVIVC is to serve as surrogate for in vivo bioavailability .

IVIVC is a mathematical relationship between in-vitro properties of a dosage form with its in vivo performance. The in-vitro release data of a dosage form containing the active substance serve as characteristic in-vitro property, while the In vivo performance is generally represented by the time course of the plasma concentration of the active substance. These in-vitro & In vivo data are then treated scientifically to determine correlations.

For oral dosage forms, the in-vitro release is usually measured and considered as dissolution rate. The relationship between the in-vitro and in vivo characteristics can be expressed mathematically by a linear or nonlinear correlation. However, the plasma concentration cannot be directly correlated to the in-vitro release rate; it has to be converted to the in -vivo release or absorption data, either by pharmacokinetic compartment model

analysis or by linear system analysis[1].

IVIVC definition

Definition of IVIVC

As per the USP, the establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form[2].

Food and drug administration (FDA) definition of IVIVC

An in-vitro in-vivo correlation (IVIVC) has been defined by the Food and Drug Administration (FDA) as “a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response”.

Generally, the in-vitro property is the rate or extent of drug dissolution or release while the In vivo response is the plasma drug concentration or amount of drug absorbed. Practically, the purpose of IVIVC is to use drug dissolution results from two or more products to predict similarity or dissimilarity of expected plasma drug concentration (profiles). Before one considers relating in -vitro results to in vivo, one has to establish as to how one will establish similarity or dissimilarity of in vivo response i.e. plasma drug concentration profiles. The methodology of establishing similarity or dissimilarity of plasma drug concentrations profile is commonly known as bioequivalence testing[3].

Rationale of IVIVC

Reduction of regulatory burden

IVIVC can be used as substitute for additional in vivo experiments, under certain conditions.

Optimization of formulation

The optimization of formulations may require changes in the composition, manufacturing process, equipment, and batch sizes. In order to prove the validity of a new formulation, which is bioequivalent with a target formulation, a considerable amount of efforts is required to study bioequivalence (BE) /bioavailability (BA).

Justification for "therapeutic' product quality

IVIVC is often adequate for justification of therapeutically meaningful release specifications of the formulation.

Scale up post approval changes (Time and cost saving during the product development)

Validated IVIVC is also serves as justification for a bio waivers in filings of a Level 3 (or Type II in Europe) variation, either during scale up or post approval, as well as for line extensions (e.g., different dosage strengths).

IVIVC as surrogate for *in-vivo* bioequivalence and to support biowaivers (Time and cost saving)

The main purpose of an IVIVC model to utilize in-vitro dissolution profiles as a surrogate for *in vivo* bioequivalence and to support bio waivers

Factors in developing a Correlation

Bio pharmaceutics classification system (BCS)

Bio pharmaceutics Classification System (BCS) is a fundamental guideline for determining the conditions under which in-vitro, in-vivo correlations are expected[4]. It is also used as a tool for developing the in-vitro dissolution specification.

The classification is based on the drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers: the Absorption number, the Dissolution number and the Dose number[5,6].

The Absorption number is the ratio of the mean residence time to the absorption time.

The mean residence time is the average of the residence time in the stomach, small intestine and the colon. The fraction of dose absorbed then can be predicted based on these three parameters. For example, Absorption number 10 means that the permeation across the intestinal membrane is 10 times faster than the transit through the small intestine indicating 100% drug absorbed. Small intestine indicating 100% drug absorbed.

In the BCS, a drug is classified in one of four classes based solely on small intestine indicating 100% drug absorbed[7].

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A bio pharmaceutics drug classification scheme for correlating in-vitro drug product dissolution and in vivo bioavailability is proposed based on recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. This classification system, the drugs are divided into high/low-solubility and permeability classes. Currently, BCS guidelines are provided by USFDA, WHO, and

EMEA (European Medicines Academy)

Class I: HIGH solubility / High permeability,

Class II: LOW solubility / High permeability,

Class III: HIGH solubility / LOW permeability,

Class IV: LOW solubility / LOW permeability.

Class I: High solubility- high permeability drugs

In case of class I , drugs (such as metoprolol) is well absorbed (though its systemic availability may be low due to first pass extraction/ metabolism) and the rate limiting step to drug absorption is drug dissolution or gastric emptying if dissolution is very rapid. The dissolution specification immediate release (IR) dosage forms of perhaps 85% dissolved in less than 15 min. May insure bioequivalence. To insure bioavailability for this case, the dissolution profile must be well defined and reproducible[7,8,9,10].

Class II: Low solubility- high permeability drugs

This is the class of drugs (such as phenytoin) for which the dissolution profile must be most clearly defined and reproducible. More precisely this is the case where absorption number, (An) is high and Dissolution number (Dn) is low. Drug dissolution in vivo is then the rate controlling step in drug absorption and absorption is usually slower than for class I[3].

Class III: High solubility-low permeability drugs

For this class of drugs (such as cimetidine) Permeability is the rate controlling step in drug absorption. While the dissolution profile must be well defined, the simplification in dissolution specification as in Class I is applicable for immediate release dosage forms where drug input to the intestine is gastric emptying rate controlled.. Both rate and extent of drug absorption may be highly variable for this class of drugs, but id dissolution is fast i.e. 85% dissolved in less than 15 min, this variation will be due to the variable gastrointestinal transit, luminal contents , and membrane permeability rather than dosage form factors [3].

Class IV: Low solubility-low permeability drugs

This class of drugs present significant problems for effective oral delivery. The number of drugs that fall in this class will depend on the precise limits used from the permeability and solubility classification.

General application of an IVIVC

1. Providing process control and quality assurance.
2. Determining stable release characteristics of the product over time.
3. Facilitating certain regulatory determination e.g absence of effect of minor formulation change or of change in manufacturing site on performance. In certain cases mainly for extent release tablets, the dissolution test can serve not only as a quality control for the manufacturing process but also an indicator of how he formulation will perform invivo thus an main objective of developing and evaluating an IVIVC is to establish the dissolution test as a tool for human bioequivalence studies.
4. Comparing changed and unchanged drug products for both strength as recommended in SUPAC-MR.
5. Bioequivalence has been demonstrated on the highest strength (comparing changed and unchanged drugs products)
6. Documentation of dose proportionality may not be necessary if bioequivalence has been demonstrated on the highest and lowest strength of drug products.

7. Dose proportionality has been demonstrated for the extent release dosage form. In the last circumstance.

This concept underlying the BCS published finally led to introducing the possibility of waiving *in vivo* bioequivalence (BE) studies in favor of specific comparative *in vitro* testing to conclude BE of oral immediate release (IR) products with systemic actions.(11) In terms of BE, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate BE of two drug products. The BCS thus enables manufacturers to reduce the cost of approving scale-up and post approval changes to certain oral drug products without compromising public safety interests.[(12)] It is a drug-development tool that allows estimation of the contributions of three major factors, dissolution, solubility and Intestinal permeability that affect oral drug absorption from IR solid oral dosage forms. It was first introduced into regulatory decision making process in the guidance document on immediate release solid oral dosage forms: Scale-up and post approval changes. BCS system is an indicator of developing a predictive IVIVC and also examined the importance of drug dissolution and permeability on IVIVC validity.

Role of IVIVC in drug delivery

Various rate controlling technologies are used as the basis for Modified release dosage forms e.g. Diffusion-dissolution, matrix retardation, osmosis, etc. to control, and prolong the release of drugs, for the administration by oral or parenteral route (). The novel drug delivery systems have been developed such as OROS, liposomes, niosomes, microspheres, nanoparticles, implants, in-situ gelling system, organogels, transdermal

drug delivery systems, parenteral depots, etc. as a substitute for conventional dosage forms. The obvious objective of these dosage forms is to achieve zero-order, long term, pulsatile, or "on demand" delivery. Major applications of IVIVC related to oral drug delivery and

a few issues related to the development of IVIVC models for parenteral drug delivery are addressed herewith [12.]

Role of IVIVC in Technology Transfer

The most crucial stage in the drug development is drug candidate selection. Such selection is primarily based on the drug "developmental" criteria, which include physicochemical properties of the drug and the results obtained from preformulation, preliminary studies involving several in-vitro systems and *in vivo* animal models, which address efficacy and toxicity issues. During

this stage, IVIVC (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 candidates. In such correlations, study designs including study of more than one formulation of the modified-release

Limitations in the IVIVC versus In Vivo Data

The absorption of the drug should be LINEAR, the pharmacokinetic process depend up on the dose administered, rate of absorption, comparison between formulation and simulation cannot be made. This non linearity can be overcome by active absorption, which by inducing or inhibiting first pass metabolism. The release may be depend on the formulation and must be slower phenomenon between dissolution and absorption. Absorption should be the limiting factor in comparison to the drug release and correlation may be attempted. More than one dosage form is needed and if possible intravenous or solution is essential to calculate de convolution.

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