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REVIEW ARTICLE OPEN ACCESS

Significance of *In-Vitro* and *In-Vivo* Correlation in Drug Delivery System

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Abstract

The main purpose of development pharmaceutical dosage form is to find out the in vivo and in vitro behavior of dosage form. This challenge is overcome by implementation of in-vivo and in-vitro correlation. Application of this technique is economical and time saving in dosage form development. It shortens the period of development dosage form as well as improves product quality. IVIVC reduce the experimental study on human because IVIVC involves the in vivo relevant media utilization in vitro specifications. The key goal of IVIVC is to serve as alternate for in vivo bioavailability studies and serve as justification for bio waivers. IVIVC follows the specifications and relevant quality control parameters that lead to improvement in pharmaceutical dosage form development in short period of time.

Recently in-vivo in-vitro correlation (IVIVC) has found application to predict the pharmacokinetic behaviour of pharmaceutical preparations. It has emerged as a reliable tool to find the mode of absorption of several dosage forms. It is used to correlate the in-vitro dissolution with in vivo pharmacokinetic profile. IVIVC made use to predict the bioavailability of the drug of particular dosage form. IVIVC is satisfactory for the therapeutic release profile specifications of the formulation. IVIVC model has capability to predict plasma drug concentration from in vitro dissolution media.

Keywords: Bioavailability, convolution, drug dissolution, Bio waivers.

INTRODUCTION

Correlation is a statistical technique that is used in pharmaceutical development and the purpose is to optimize the formulation and to reduce the product development time correlation estimate. The in vivo result should be based on the in vitro data, it should be used as surrogates in bio- availability studies and reduce the number of bio-equivalence study that require post approval changes [1].

IVIVC is define by FDA and USP and its tell the relationship between in vitro property of dosage form and in vivo response of drug; in vitro measure the extent of dissolution and release of drug and in vivo response tell the amount of drug in plasma and amount of drug absorbed [2].

IVIVC is relationship describe that properties of the products and tell about in vitro property of dosage form and in vivo response of dosage form in vitro. Active pharmaceutical moiety is characteristic of products and in vivo response is time of release of active pharmaceutical moiety and its concentration in plasma [3].

United State Pharmacopoeia (USP) Definition

IVIVC is an establishment of relationship between biological property and parameters that derived from biological property of dosage form produced and physicochemical property of same dosage form and parameters derived from biological property are AUC and C_{max} [2].

Food and Drug Administration (FDA) Definition

IVIVC is predictive mathematical method describe relationship between in vitro property of dosage form in relevant to in vivo response [4]. Mostly two dosage forms compared by IVIVC are coated pellets filled in a gelatin capsule and hydrophilic matrix tablet. IVIVC measure the extent of absorption but prediction error related to AUC is 10% and error related to C_{max} is 20%. The absorption of solid dosage form mostly depends upon dissolution in which drug release and is available in solution that should be absorbed [2].

IVIVC has many important tools used as surrogate in vivo and in bioavailability studies also used surrogates for human studies. Its reduces the number of bio-equivalence study but not used in dosage form that have different release mechanism [2]. IVIVC also provision the use of dissolution methods and specifications and Provide help in quality control during manufacturing and selection in of formulations [3].

IN VIVO STUDY

To develop the IVIVC, in vivo absorption data is required thus also the pharmacokinetic and bioavailability studies. Pharmacokinetic study tells that what the effects of drug on the body are. It includes absorption, distribution, metabolism and excretion. On the other hand the bioavailability demonstrates the extent of a drug which reaches the systemic circulation and observed by evaluating AUC (area under plasma drug concentration-time curve), Cmax (maximum plasma drug concentration) and Tmax (time required to achieve Cmax [9].

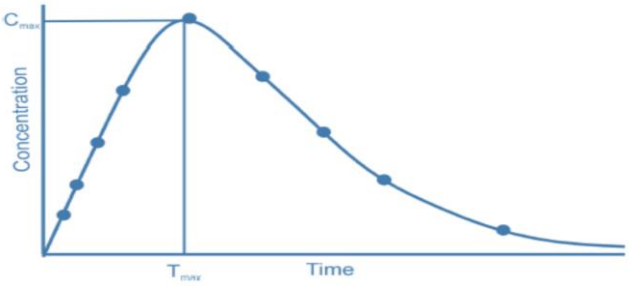


Fig 1: A typical drug concentration (in blood) – time profile Reflecting the fate of a drug in the human body following an oral Dose (tablet/capsule). This figure is taken by the permission of Qureshi, S. A. (2010) [7].

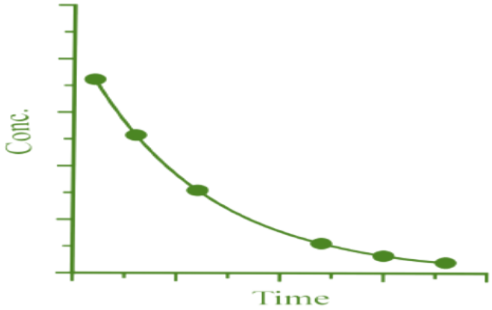


Fig 2: A typical drug concentration (in blood) – time profile reflecting the fate of a drug in human body following an instantaneous absorption, i.e. negligible absorption phase or effect, following administration of a drug through oral route in solution form. This figure is taken by the permission of Qureshi, S. A. (2010) [7].

In Vivo Absorption

In vivo bioavailability studies should be conducted for the New Drug Application (NDA) according to the requirements of FDA. Bioavailability studies are normally performed in young healthy male adult volunteers under controlled conditions such as fasting, non-smoking, and no intake of other medications. The drug is usually given at different time intervals with a washout period of at least five half-lives [14].

The bioavailability study can be accessed via plasma or urine data using the following parameters:

1. Area under the plasma time curve (AUC), or the cumulative amount of drug excreted in urine (Du)
2. Maximum concentration (Cmax), or rate of drug excretion in urine (du/dt)
3. A time of maximum concentration (Tmax).
4. Despite the knowledge of these parameters, cumulative amount absorbed or the in vivo absorption rate is required as the in vivo data for the IVIVC development. Although, flip flop phenomena (in which the rate of absorption is slower than the rate of elimination) can occur the terminal phase of plasma profile may misconceive [13].

There are many different tactics for the setting up in vivo performance of a drug includes convolution and deconvolution methods. Now a day these methods are mostly used as they are easy to compare with in vitro dissolution profile and estimation in vivo performance. Convolution and deconvolution has been extensively applied to delineate the various rate processes in bio pharmaceutics and pharmacokinetics, such as in vivo dissolution, absorption, metabolism, elimination, and pharmacodynamics [12].

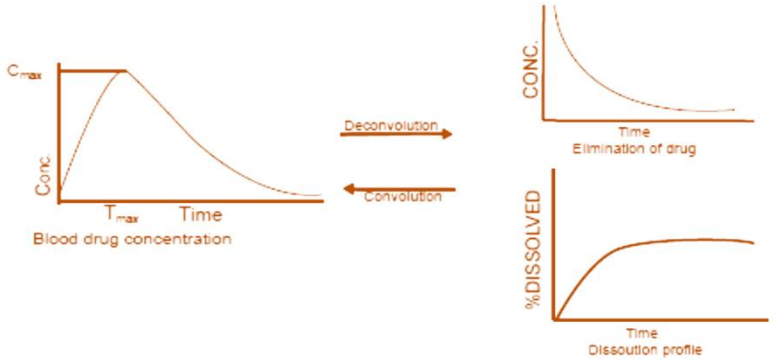


Fig 3: Comparison between convolution and deconvolution. (This picture is taken by the permission of Sakore, S., & Chakraborty, B. (2013) [10].

Deconvolution Method

Deconvolution is a model independent method that is used for either one or multiple compartment models. While developing IVIVC the important point is to establish a dissolution testing method which is predictive of the in vivo performance of the testing compound [11]. Deconvolution is a numerical method used to assess the time course of drug input using a mathematical model based on the convolution integral [6]. .The function cδ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and it is typically estimated from intravenous injection bolus data or reference oral solution data. c(t) is the plasma concentration vs. time level of the extended release formulation. rabs is drug input rate of the oral solid dosage form and u is variable of integration [12].The assessment of in vivo absorption profile from the concentration time data can be achieved through the three steps deconvolution methods involving Wagner-Nelson (WN), Loo-Riegelman (LR) methods or model independent methods. (Showed in figure 4) Wagner-Nelson method which is model dependent method is derived by one compartment model, this method have advantage that it requires oral administration only for developing plasma profile of the drug. However, the Loo-Riegelman method requires intravenous data for developing plasma profile of drug and is derived by following two compartment models. The in vivo plasma data obtained from either oral or intravenous administration is required for the application of model independent numerical deconvolution [8].

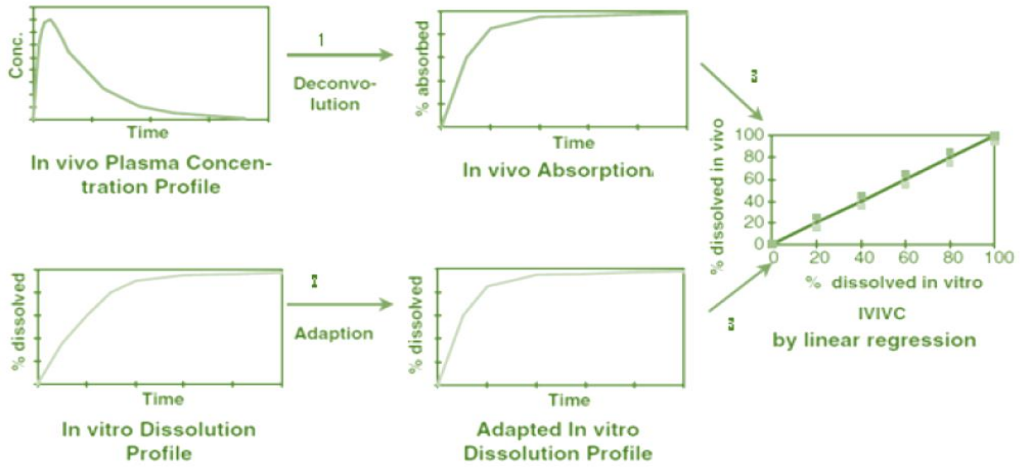


Fig 4: Classical Three Steps of Deconvolution (this figure is taken by the permission of Hardikar, S., Bhosale, A. V., & Budhawant, R. N. (2014) [5].

Convolution Methods

Convolution method which converts input to output i.e. the dissolution profile converts to the plasma concentration profile by this method. Recently, convolution method developed which convolutes the dissolution profile without correlation of the absorption/in vivo dissolution profile with the dissolution profile in vitro (i.e., physiology based model and simulation soft-ware).The model uses multiple differential equations representing various physiological events and convolution-based methods. This convolution method unless the deconvolution method not involved several stages for conversion dissolution profile to plasma profile rather involves single stage (showed in figure 5). Biggest advantage of this method that it not needs any oral/ intravenous administration. 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 PK or physiological models. A critical assessment of the calculated parameters is absolutely

necessary. Further, the fitting procedure should be performed several times with different starting values, in order to avoid reaching a local minimum. Last but not the least, these methods should be optimized to as few variables as possible, as the fitting procedure becomes more complex and error-prone with more variables [6]. Without the sufficient knowledge of in vivo studies the purpose of in vitro studies cannot be fulfilled that can be achieved by IVIVC [8].

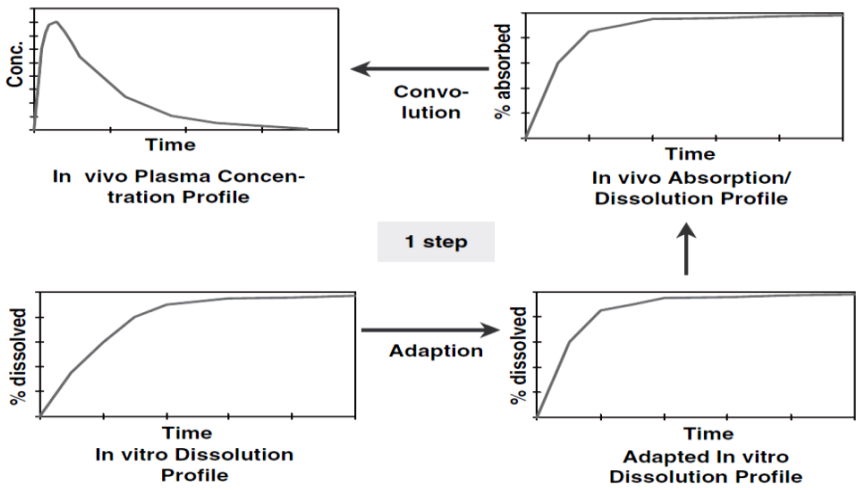
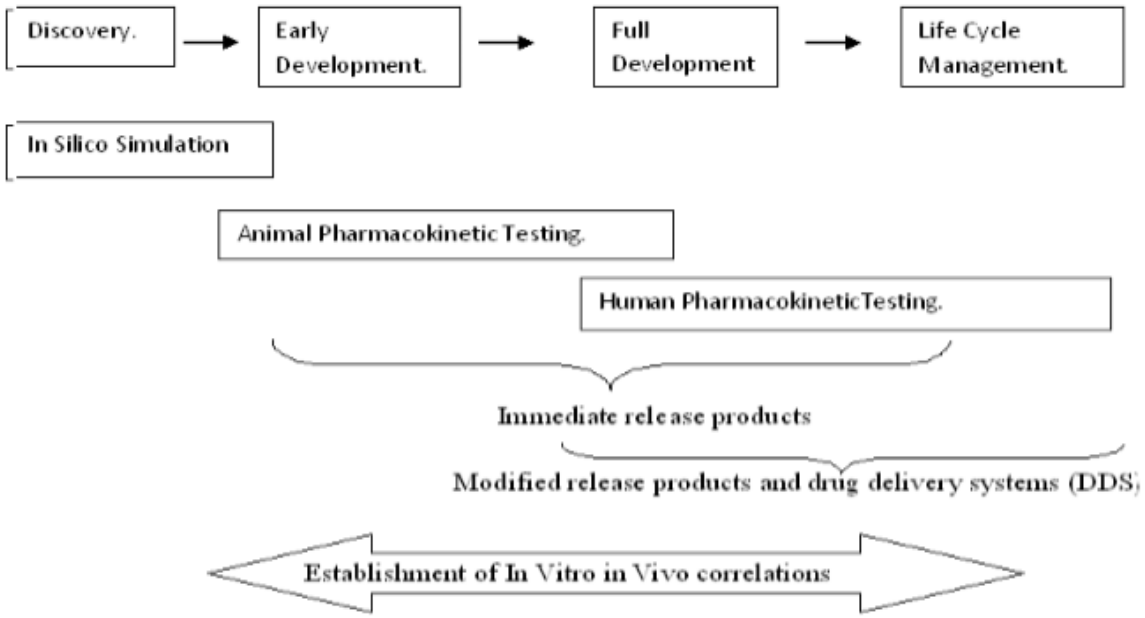


Fig 5: The One Step Procedure of a convolution (this figure is taken by the permission of Hardikar, S., Bhosale, A. V., & Budhawant, R. N. (2014) [5].

OBJECTIVES OF IN VITRO – IN VIVO CORRELATION

In vitro dissolution is one of the vital tools for characterization of biopharmaceutical quality of a dosage form at different stages of drug development. In vitro dissolution data helps in the evaluation and interpretation of possible risks, especially in the modified release dosage form and the food effects on bioavailability that influence the gastrointestinal conditions. It also plays a great role while assessing changes in the manufacturing process. However, none of these purposes will be fulfilled by in vitro dissolution testing without sufficient knowledge of its in vivo relevance. IVIVC have been defined in many ways and have been a subject to much controversy. A meaningful correlation must be quantitative [5] so as to allow interpolation between data, thus making the in vitro model predictive. IVIVC also ensures batch to batch consistency in the physiologic performance of a drug product [4].

IVIVC in Drug Development Process [5]



FUNDAMENTALS OF CORRELATION

The purpose of establishing the in vitro in vivo correlation to know or to get the vast knowledge about the drug release study from a drug delivery system by oral route. This is important to study the in vitro availability to produce the correlation in vitro/ in vivo for suitable drugs. The purpose of identifying the various parameters like pharmacokinetics and pharmacodynamics and various biopharmaceutical parameters also in presence of the food is to prepare the efficacious and validate [2].

Levels of Co-Relation

According to the FDA guidelines the levels of correlation divided into four levels [16].

Level A Correlation

Level A correlation it is the highest point to point correlation between in vitro dissolution profile and in vivo input rate concentration time of drug release [16].

The percent of absorbed drug can be calculated by the model independent techniques such as model dependent numerical deconvolution. These are the mostly use all data obtain from dissolution profile and plasma level to develop a correlation. The purpose of this correlation is define the in vivo direct relationship such as in vitro dissolution rate single is enough to determine the biopharmaceutical rate of the dosage form.in the level A correlation dissolution curve show surrogate for in vivo performance [17]. Therefore changing in raw material, method of manufacture, change in manufacture site, minor modification in formulation, and strength of product can b use without additional justification of human studies. It's an excellent quality control which predicts the dosage form in vivo performance [16].

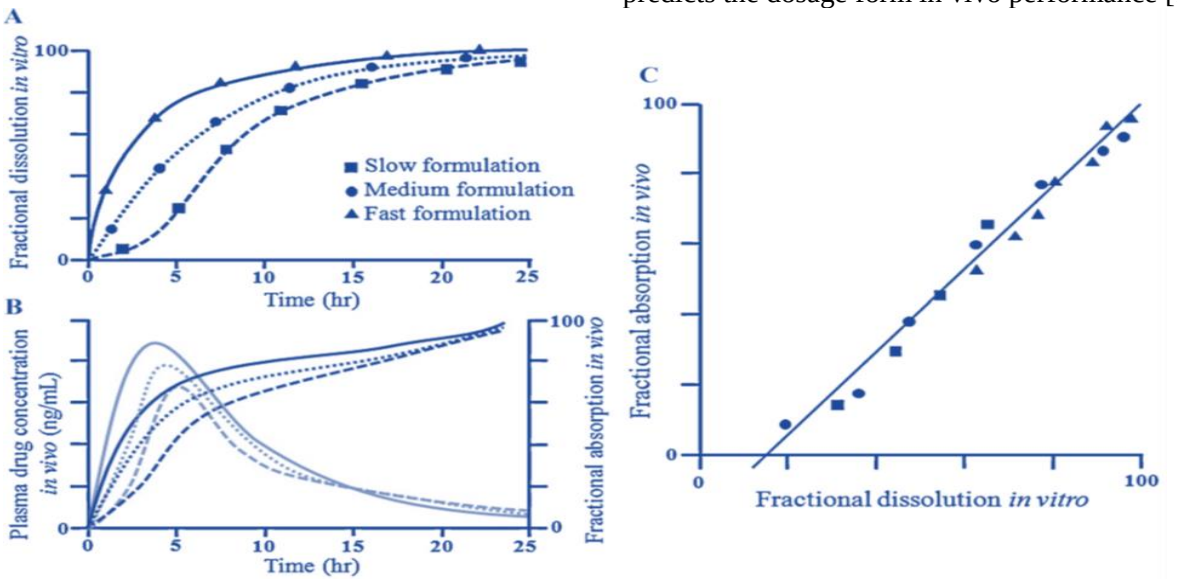


Fig 6: Example of Level A IVIVC. (A) In vitro dissolution profiles of slow (square), medium (circle), or fast drug formulations (triangle). (B) In vivo studies provide plasma drug concentration of each formulation (gray lines), which can be converted to factional absorption profile (black lines) by deconvolution. (C) Level A IVIVC can be derived from the fractional dissolution in vitro and the fractional absorption in vivo. Figure shows a linear correlation, but FDA accepts non-linear correlation as well [16].

Level B Correlation

A level B by using the principle of statically moment analysis we correlate it here we compare the in vitro dissolution time (MDT) of the product with the mean in vivo dissolution time or means residence time. Although level B can use for all in vivo and in vitro data , it's not consider to be the point to point correlation but there are different curves which produce the similar means of residence time. It does not justify the exact plasma curve so that's why a person can't rely upon it, because it's not enough to justify the quality control of standard [16].

Level C Correlation

It also establishes the single point relationship. It's done between dissolution like percent half of drug dissolve in 4 hours and its pharmacokinetics parameters such as AUC,C_{max} ,T_{max} [18].

Multiple Level C Correlation

It relates on several pharmacokinetics time points like amount of drug dissolve at several time points of the dissolution profile cover the 3 dissolution time points early, middle and last stage of the dissolution profile [10].

IN-VITRO CORRELATION

In vitro correlation provides the basic tool for the characterization of Bio-pharmaceutical quality of the Dosage form and the various stages during the Drug development. In vitro correlation also plays an important role in accessing the various risk factor and changes during the manufacturing process of dosage form [6].

Reasons for Poor in-Vitro Correlation [18]

There are the following reasons which cause the poor correlation.

Study design- Inappropriate test condition.

Dosage form-If the dosage form is not correct and the drug release profile is un-controlled and effected by the strong stirring.

Drug substance- Non D linear pharmacokinetic parameters like First pass effect, absorption of drug etc.

Methods use in in-Vitro Correlation Study

Dissolution Test

In vitro correlation, the dissolution test plays a fundamental and the basic role in the designing and drug development [21].

Apparatus

Following are the apparatus which are used in dissolution test they are depended upon the, Nature of the dosage form, Nature of the test, Duration. The dissolution study par usually performed in the Rotatory paddle apparatus by adding the 900ml of media at the paddle and the stirring speed is about 25-50rpm and the temp should be under controlled which is about 37C [23].

Apparatus 1: Rotating Basket

This apparatus consists of a rotating basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing dissolution medium. The entire flask is immersed in a constant temperature bath set at 37°C. Agitation is provided by rotating the basket. The rotating speed and position of basket must meet specific requirements set forth in the current USP. The most common rotating speed for basket is 50-100 rpm. A disadvantage of rotating basket is that the formulation may clog to 40- mesh screen [25].

Rotatory Paddle Apparatus [21]

Disintegration time

The disintegration time also effect during drug development. The disintegration time depend upon the Bio-relevant media. The disintegration time is not affected if we used the same media for the dosage form. The disintegration time is only effected in the case of poor dosage form and by using the different media.

IN VITRO DISSOLUTION

Dissolution is the process in which a solid substance enters the solvent phase to yield a solution [20]. Dissolution is a multi-step process including heterogeneous interactions between phases of solute-solute and solvent-solvent phases and at the solute-solvent interphase [21]. The tests to characterize the dissolution behaviour of the dosage form are conducted using methods and apparatus that have been standardized worldwide [20]. Both disintegration and dissolution are parameters of prime importance in dosage form development. In some cases where disintegration is slow rate of dissolution can affect disintegration. Disintegration usually reflects the formulation variables while dissolution reflects the effect of solubility and particle size [22]. If a direct relationship is present between dissolution and disintegration, waiver of a dissolution testing requirement is thought about. Dissolution tells whether drug can become available for absorption [23].

Conditions for In Vitro Systems

Enzymes used are of physiological amount. PH should be appropriate according to nature of enzymes [25]. Products of digestion should be removed. At each stage of digestion mixing should be proper. Transit time for each stage should be should be physiological. A dynamic peristaltic approach should be used [19]. The volume composition and hydrodynamics of the contents in the gastrointestinal lumen should be accurately simulated [24].

Selection of Dissolution Method

The selection of dissolution method depends on, pH solubility profile and pKa of drug, the drug permeation or partition coefficient [22], apparatus should be geometrically and dimensionally accurate and precise .Any irregulations such as vibrations and undesired agitations by mechanical imperfections must be avoided. Temperature of test medium, rotation speed / flow rate, volume, sampling probe and procedures need to be monitored [24].

PROBLEMS FOR IVIVC

In-vivo performance of oral formulation is a critical factor affecting the pharmacokinetics of dosage form. Body's physiology and anatomy criticize the ivivc performance. Moreover in vivo drug absorption also affected by food content in GIT. The disease or healthy state, enzymatic reaction, GIT motility and comedication greatly influence the in vivo behaviour of drug release profile and bioavailability. So all such factors cause hindrance in accurate prediction of therapeutic response of drug from in-vivo in-vitro correlation IVIVC [25].

BIOPHARMACUTICLE CLASSIFICATION SYSTEM [21]

The bio pharmaceutical classification system gives guidelines for consideration for determining in vitro and in vivo correlation. Its classification base on the solubility and intestinal permeability. It further divided into following classes

Bio Pharmaceutics Drug Classification and IVIVC outcomes for Immediate release Drug

CLASS	SOLUBILITY	PERMEABILITY	IVIVC
I	High		Correlation
II	Low	High	IVIVC expected
III	High	Low	Little- no IVIVC
IV	Low		Little- no IVIVC

Bio pharmaceutics Drug Classification for extended release drug Products [21]

CLASS	SOLUBILITY	PERMEABILITY	IVIVC
IA	High & site independent	High& independent	level A expected
IB	High & site independent	Dependent on site & Narrow Absorption window	level C expected
II a	Low & site independent	High& site independent	level A expected
II b	Low & site independent	Dependent on site & Narrow Absorption window	little or no IVIVC
Va: Acidic	Variable	Variable	little or no IVIVC
Vb: basic	Variable	Variable	level A expected

IVIVC OF NOVEL DOSAGE FORMS [3]

Enteric-Coated Multiple Unit Dosage Form

Individual unit dosage form is slowly emptied into duodenum from stomach. Direct predication of IV absorption profile from IV dissolution is difficult to handle. This problem is overcome by using convolution method.

Parenteral Controlled Drug Delivery System

Parenteral controlled drug delivery system has been established for micro particles for parenteral administration to evaluate the drug release study. Three methods are reported, dialysis technique, sample and separate and flow through.

Transdermal Drug Delivery System

United States pharmacopoeia (USP) 29 provides approaches for in vitro drug release testing of transdermal patches, such as cylinder method, paddle over disk, reciprocating disk method. Franz diffusion cell method is highly used method for IVIVC for transdermal drug delivery system.

Suppositories

Lipophilic based suppositories are characterized by modified basket or paddle methods. Conventional basket, paddle or flow through cells is highly recommended for hydrophilic based suppositories.

APPLICATION OF IVIVC IN DRUG DELIVERY SYSTEM [11]

Biopharmaceutical Classification System (BCS)

BCS classification is a best approach to categorize the drugs substances based on solubility and permeability. Drugs compounds under this category are classified into four groups. BCS system is a best way to determine whether IVIVC for certain dosage forms can develop or not.

Biowaivers

FDA is also granted exemptions in bioavailability and bioequivalence studies for bio waivers. Some authentic models are using a basis for bio waivers to avoid time and cost during pharmaceutical formulation development process.

Non oral Dosage Forms

Currently FDA mainly focusing on IVIVC studies for oral dosage forms. Different models are also established for non-oral dosage form with modifications in mode and duration of drug delivery system. The outmost critical challenge for developing in vitro studies for non-oral dosage forms are under process.

CONCLUSION AND FURTHER RECOMMENDATIONS

This review attempts to elucidate the different methods for developing IVIVC for manufacturing process. Level A is outmost level which defines the relationship between dissolution (in vitro) and absorption (in-vivo). Correlation is also depending upon the quality of data. Dissolution is the most important tool to ensure the consistency in manufacturing process. FDA guideline for establishment of IVIVC is applicable for oral dosage forms but it is also used in non-oral dosage form.

Authors also recommend further research for developing IVIVC for non-oral dosage forms, inhaled devices and dermatological medicines. Many studies did not highlight the mathematical methods and simulation techniques. Its dare need to develop mathematical calculations for IVIVC studies.

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