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Review Article

In Vitro - In Vivo Correlation: A Review

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ABSTRACT

Correlation between *in vitro* and *in vivo* data have long been sought in biopharmaceutical as a mean of modeling the human organism and thereby monitor and optimize the dosage form with the fewest possible trial in man. One of the challenge of biopharmaceutics research is correlating *in vitro* drug release (dissolution) information of various types of drug formulations to the *in vivo* drug profile and to provide a regulatory perspective on its utility in product development and optimization. A successful correlation can assist in selection of appropriate dissolution acceptance and can be used as a surrogate for in vivo bioavailability and to support biowaivers. It can also assist in quality control for certain scale-up and post approval changes (SUPAC). With the proliferation of modified-release products, it becomes necessary to examine the concept of I*n vitro-In vivo* Correlation (IVIVC) in greater depth. Investigations of IVIVC are increasingly becoming an integral part of extended release drug development. In addition, the Biopharmaceutical Classification System provides a science-based guidance on solubility and permeability drug issues, which are indicators of predictive IVIVC. The aim of this review article is to represents the various notions of IVIVC and its applications, Biopharmaceutical classification systems (BCS) & application of BCS in IVIVC development, Various type of dissolution media and their importance and methodology of dissolution have been highlighted.

Keywords: IVIVC, BCS, Biowaivers, Dissolution, Permeability etc

INTRODUCTION

Rapid drug development necessities the research to find out link between the dissolution testing and the bioavailability, which result as concept of *in vitro- in vivo* correlation.[1] In recent years, the concept and application of the *in vitro-in vivo* correlation for pharmaceutical dosage forms have been a main focus of attention of pharmaceutical industry, academia, and regulatory sectors.[2] Formulation development and optimization is an ongoing process. Development and optimization of formulation is an integral part of manufacturing and marketing of any therapeutic agent which is indeed a time consuming and costly process.[3] The rational development of a delivery system is sensible and expensive procedure. Formulation development and optimization involves varying excipient levels, processing methods, identifying discriminating dissolution methods, and subsequent scale-up of the final product. Because quantitative and qualitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bioavailability studies is always desirable. In this regard, use of *in vitro* data to predict *in vivo* bio-performance can be considered as the rational development of controlled-release formulations.[2, 3]

Definitions

From biopharmaceutical standpoint, correlation could be referred to as the relationship between appropriate *in vitro* release characteristics and *in vivo* bioavailability parameters. Two definitions of IVIVC have been proposed by the USP and FDA. [1,4] According USP IVIVC is "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".

Typically, the parameter derived from the biological property is AUC or Cmax, while the physicochemical property is the *in vitro* dissolution profile.[1]

In other words FDA defined the IVIVC as "Predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and a relevant *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.[4]

Levels of correlation

Form the definition, five correlation levels of IVIVC have been defined in IVIVC FDA guidance.[4]

- Level A Correlation
- Level B Correlation
- Level C Correlation
- Multiple-level C correlation
- Level D correlation

Level A Correlation

This correlation represents a point-to-point relationship between *in vitro* dissolution and *in vivo* dissolution (input/absorption rate) and is consider as the highest category of correlation. 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.[5] In general, correlations are linear at this level. **(Fig. 1)** Although a concern of acceptable non-linear correlation has been addressed, no formal guidance on the non-linear IVIVC has been established.[6]

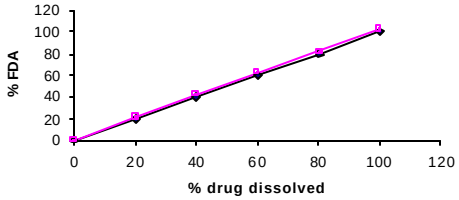

Fig 1: Level A *In vitro-In vivo* Correlation between % Fraction drug absorb (FDA) and % drug dissolved.

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Level A correlation is the most informative and very useful from a regulatory perspective.[7]

The purpose of Level A correlation is to define a direct relationship between *in vivo* data such that measurement of *in vitro* dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. In the case of a level A correlation, an *in vitro* dissolution curve can serve as a surrogate for *in vivo* performance. It is an excellent quality control procedure since it is predictive of the dosage form's *in vivo* performance.[1]

Level B Correlation:

Level B IVIVC uses the principles of statistical moment analysis. In this level of correlation, the mean *in vitro* dissolution time (MDT *vitro)* is compared to either mean *in vivo* residence time (MRT) or the mean *in vivo* dissolution time (MDT *vivo*).[8] **(Fig 2).** Even though it utilizes all of the *in vitro* and *in vivo* data, but it is not considered as point-to-point correlation, because a number of different *in vivo* curves that will produce similar mean residence time values.[4] A level B correlation does not uniquely reflect the actual *in vivo* plasma level curves. Therefore, one can not rely upon a level B correlation alone to justify formulation modification, manufacturing site change, excipient source change, etc. In addition *in vitro* data from such a correlation could not be used to justify

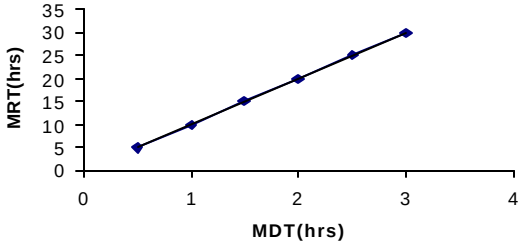

Fig 2: Level B *In Vitro- In Vivo* Correlation between Mean Dissolution Time (MDT) and Mean Resident Time (MRT).

the extremes of quality control standards and as well as least useful for regulatory purposes.[1, 4]

Level C Correlation

A Level C IVIVC establishes a single point relationship between a dissolution parameter (e.g., $t_{50\%}$ or % dissolved in 4hrs) and a pharmacokinetics parameter (e.g., AUC or Cmax) **(Fig 3)**. A Level C correlation does not reflect the complete shape of the plasma concentration-time curve, which is the critical factor that defines the performance of Extended Release (ER) products. Therefore, this is the weakest level of correlation as partial relationship between absorption and dissolution is established. Due to its obvious limitations, the usefulness of a Level C correlation is limited in predicting *in vivo* drug performance. Level C correlations can be useful in early formulation development, including selecting the appropriate excipients, to optimize manufacturing processes, for quality

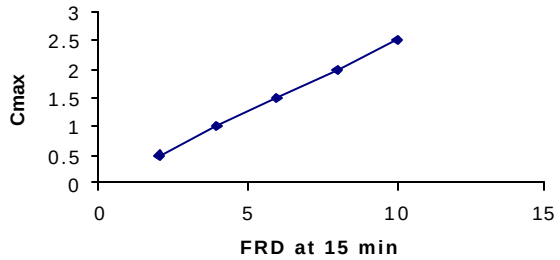

Fig 3: Level C in Vitro- in Vivo Correlation between Cmax and percent dissolved at 15 minutes.

control purposes and to characterize the release patterns of newly formulated immediate-release and modified-release products[2].

Multiple level C Correlation

Multiple Level C correlation reflects the relationship between one or several pharmacokinetic parameters of interest and amount of drug dissolved at several time points of the dissolution profile.[9] A multiple Level C correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution profile.[8] If such a multiple level C correlation is achievable, then the development of a level A correlation is also likely.[4] Multiple point level C correlation may be used to justify a biowaivers, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest.[1, 9]

Level D correlation

It is a rank order and semi quantitative correlation and it is not considered useful for regulatory purpose.[4]

IVIVC AND BIOPHARMACEUTICAL CLASSIFICATION SYSTEMS

The BCS is defined in the FDA guidelines as" The scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability".[10] When combined with the dissolution of drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from Immediate Release (IR) Solid Oral dosage forms such as dissolution, solubility and intestinal permeability which are defined as follow [9, 10]

Solubility: A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less than 250 ml aqueous media over the pH range 1- 7.5.

Permeability: A drug substance is considered highly permeable if the extent of drug absorption is 90 % or greater than 90% of an administered dose based on mass balance determination or in comparison to an intravenous reference dose.

Dissolution: A drug product is considered rapidly dissolving when no less than 85 % of the labelled amount of the drug substance dissolves within the 30 minutes using USP dissolution apparatus I at 100 rpm or USP dissolution apparatus II at 50 rpm in 900 ml in 0.1N HCl or SGF USP without enzymes / pH 6.5 buffers or SIF USP without enzymes.BCS is a fundamental guideline for determining the conditions under which *in-vitro in-vivo* correlations are expected. It is also used as a tool for developing the *in-vitro* dissolution specification.[10]

The classification is associated with 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. [6, 7, 11]

Dissolution number

The Absorption number is the ratio of the mean residence time to the absorption time. **The Dissolution number** is a ratio of mean residence time to mean dissolution time.

The Dose number is the mass divided by an uptake volume of 250 ml and the drug's solubility.

Characteristics of Drugs of Various BCS classes

Class I drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step.[10, 11] Bioavailability and dissolution is very rapid. So bioavailability and bioequivalency studies are unnecessary for such product. IVIVC can not be expected. These compounds are highly suitable for design the SR and CR formulations.[13, 14, 15]

Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number.[15] Thes drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability.[14] Thes compounds are suitable for design the SR and CR formulations. IVIVC is usually accepted for class II drugs.[15]

For Class III drugs permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability.[15, 16]

Class IV drugs exhibit poor and variable bioavailability. Sevaral factors such as

Table1: BCS and Expected IVIVC for Immediate Release Drug Products [5, 18, 46]

Class	P	S	IVIVC Expectation for IR product	Possibility of predicting IVIVC form dissolution data
Class I	High	High	IVIVC expected, if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation	Yes
Class II	High	Low	IVIVC expected, if dissolution rate, dose is very high	Yes
Class III	Low	High	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution	No
Class IV	Low	Low	Limited or no IVIVC is expected.	No

S = Solubility, P = Permeability

Table2: BCS for Extended Release Drug Products. [5, 18, 46]

Class	P	S	IVIVC
I A	High & Site Independent	High & Site Independent	Level A expected
IB	Dependent on site & Narrow Absorption Window	High & Site Independent rate is similar to *in vivo* dissolution	Level C expected
IIa	High & Site Independent	Low & Site Independent	Level A expected
IIb	Dependent on site & Narrow Absorption Window	Low & Site Independent	Little or no IVIVC
Va Acidic	Variable	Variable	Little or no IVIVC
Vb Basic	Variable	Variable	IVIVC Level A expected

S = Solubility, P = Permeability

disssolution rate, permeabbility and gastric emptying form the rate limiting steps for the drug absorption. These are unsuitable for controlled release.[13, 19,]

Class V drugs are those ones that do not come under the purview of BCS classification but includes the drugs whose absorption is limited owing to their poor stability in the GI milieu[18]-

- Gastric instability
- Complication in GI lumen
- High first pass metabolisms etc

IN VITRO DISSOLUTION

Drug absorption from a solid dosage form following oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilisation of the drug under physiological conditions, and the permeability across the gastrointestinal tract. The *in vitro* dissolution may be relevant to the prediction of *in vivo* performance due to the critical nature of the first two of these steps.[23, 24, 25]

The objectives of *in vitro* dissolution studies in drug development process is to assess the lot-to-lot quality of a drug product, guide development of new formulations and ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture and the scale-up of the manufacturing process. However, from the IVIVC standpoint, dissolution serves as a surrogate for drug bioavailability. Thus more rigorous dissolution standards may be necessary for the *in vivo* waiver .[21,23] Generally, a dissolution methodology, which is able to discriminate between the study formulations with different release patterns and best, reflects the *in vivo* behaviour should be used to establish an IVIVC.

Dissolution Apparatus: USP-32-NF-27 described seven types of dissolution apparatus to detect the dissolution performance of several dosage forms. These are rotating basket (Apparatus 1), rotating paddle (Apparatus 2), Reciprocating cylinder (Apparatus 3), Flow through cell (Apparatus 4), Paddle over disc (Apparatus 5), Cylinder (Apparatus 6), and Reciprocating Holder (Apparatus 7). However the first two methods are preferred and it is recommended to start with the basket or paddle method prior to using the others unless shown unsatisfactory.[21, 23] Reciprocating cylinder has been found to be especially for bead type modified-release dosage forms. Apparatus 4 may offer advantages for modified release dosage forms that contain active ingredients with very limited solubility. Apparatus 5 and apparatus 7 have been shown to be useful for evaluating and testing transdermal dosage forms.[4]

Dissolution medium: In general an aqueous test medium is preferred. The pH of dissolution medium, however, differs slightly by various guidance. Water which is allowed by some guidance [5, 20] or buffered solution preferably not exceeding pH 6.8 is recommended by FDA as the initial medium for development of an IVIVC [5, 17]. As recommended by USP, deaerated water, a buffered solution (typically pH 4 to 8) or a dilute acid (0.001 to 0.1 N) may preferably be used as dissolution medium for modified-release dosage forms[4]. To simulate intestinal fluid or gastric fluid a dissolution medium of pH 6.8 or pH 1.2 should be employed respectively[1]. Since the drug solubility depends on the composition of the dissolution medium, surfactants, pH, and buffer capacity play a major role in drug solubility in the GI tract[19]. For poorly soluble drugs, therefore, addition of surfactant (e.g., 1% SLS) may be appropriate. In general, non-aqueous and hydro-alcoholic systems are discouraged unless supported by a documented IVIVC.[2, 17] More extreme testing conditions (e.g. pH>8) should be justified [5, 26, 27] Strict simulation of physiologic gastrointestinal environment is not recommended and addition of enzyme, salts and surfactants need to be justified [17, 22]

Agitation speed and temperature: The common agitation speed is 75-100 rpm for apparatus I (basket type) and with apparatus II (Paddle type) is 50-75 rpm. The temperature should be 37± 0.5 ^{0} C is described by the most of the pharmacopoeias (as the human body temp is 37 ^{0}C) [5].

Sample point: The normal test duration for immediate release is 15 to 60 minutes with a single time point. For example, BCS class I recommend 15 minutes. Additionally, two time points may be required for the BCS class II at 15 minutes and the other time at which 85% of the drug is dissolved. [23] In contrast, *in vitro* dissolution tests for a modified release dosage form require at least three time points to characterize the drug release. The first sampling time (1-2 hours or 20- 30% drug release) is chosen to check dose-dumping potential. The intermediate time point has to be around 50% drug release in order to define the *in vitro* release profile. The last time point is to define essentially complete drug release.[4, 9] The dissolution limit should be at least 80% drug release. Further justification as well as 24-hours test duration are required if the percent drug release is less than 80. [4, 13]

IN VIVO ABSORPTION

The FDA requires *in vivo* bioavailability studies to be conducted for a New Drug Application (NDA). Bioavailability studies are normally performed in young healthy male adult volunteers under some restrictive conditions such as fasting, non-smoking, and no intake of other medications. The drug is usually given in a crossover fashion with a washout period of at least five half-lives. The bioavailability study can be assessed via plasma or urine data.[28]

Several approaches can be employed for determining the *in vivo* absorption.Wagner-Nelson, Loo-Riegelman, and numerical deconvolution are such methods. Wagner Nelson and Loo-Riegelman are both model dependent methods in which the former is used for a one-compartment model and the latter is for multi-compartment system.[16, 29]Convolution

and deconvolution methods are numerical methods used to develop the IVIVC Model.Deconvolution is used to estimate the time course of drug input using a mathematical model based on the convolution integral. Convolution method computes the *in vivo* absorption and simultaneously models the *in vitro-in vivo* data. [28]

FACTORS AFFECTING IVIVC

Before developing IVIVC some properties of the drug should be taken in to consideration. These properties are-

Stereochemistry: Due to the stereoselectivity, one enantiomer may have more affinity towards receptor than other. This results in difference in pharmacokinetics and pharmacodynamics behaviour of two enantiomers of same drug. In such conditions dissolution data of the recemate will not be usefull for development of IVIVC. So, consideration of stereoisomerism in development of IVIVC may provide more meaningfull relationship. Sirisuth et al., 2000 have studied influence of stereoselectivity on development and predictability of IVIVC using Metoprolol Tartrate ER tablet. The study concluded that Metoprolol recemate data can not be used to accurately predict R enantiomer drug concentrations. However, the recemate data was predictive of active stereoisomer. [24]

First pass effect: First pass effect decreases the systemic availability of parent drug. Therefore the amount of drug reaching to systemic circulation will not match with amount of drug release in GIT. Hence use of plasma concentration data of parent drug will not be appropriate to calculate *in-vivo* drug release. In such condition the dissolution data of such drug will not be useful for the development of IVIVC[25].

Food effect: Presence of food make may alter dissolution behavior of drug and hence it becomes an important factor that should be considered in IVIVC development. Presence of food in stomach alters the pH, ionic strengh, enzymes level, gastric emptying time etc. Al-Behaisi et al 2002 studied the *in vitro* dissolution profile of Deramciclane containing film coated tablets under simulated *in vivo* conditions in both fasting and fed state. The relevence of food effect on dissolution profile studied and a correlation between *in vitro* dissolution data and certain pharmacokinetic parameter was investigated[30].

APPLICATIONS OF IVIVC IN DRUG DELIVERY

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). Modified-release dosage forms often rely on rate-controlling technologies based on osmosis, diffusion-dissolution, matrix-retardation, etc, to retard, control, and extend the release of drugs, which are administered orally or parenterally[31]. Throughout the years, novel delivery systems, such as OROS systems, microspheres, implants, liposomes, nanoparticles and in situ gels have been investigated for their ability to deliver drugs as a substitute for conventional dosage forms, such as solutions, suspensions, or immediate-release dosage forms or viscous topical preparations[32]. The primary objective of these dosage forms is to achieve zero-order, pulsatile, or "on demand" delivery. Thus, a main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post-approval changes.[33] The applications of IVIVC in oral drug delivery have been discussed extensively in the literature, [32, 33] whereas not much has been addressed with respect to parenteral drug 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 further on in this paper.[34]

IVIVC - Parenteral Drug Delivery

IVIVC can be developed and applied to parenteral dosage forms, such as controlled-release particulate systems, implants, liposomes, niosomes etc, that are either injected or implanted [19, 35]. The current release research is focused on shortening the time span of *in vitro* release experiment with aim of providing quick reliable methods for assessing and predicting drug release.[35] However, there are relatively fewer successes in the development of IVIVC for such dosage forms, which could be due to several reasons like-

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[19]. 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[36]**.**

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).[36] 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.[37, 38] In addition, establishing the relationship between plasma drug concentrations to the *in vitro* drug release for these systems would be difficult due to the limited volume of tissue fluids and area of absorption at the site of administration, unlike following the oral route of administration.[39] 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.[38, 39]

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. [10, 20]

Dissolution Specifications

Modified-release dosage forms typically require dissolution testing over multiple time points, and IVIVC plays an important role in setting these specifications [5, 12]. 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.[41, 42]

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.[41, 43] 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 [5, 12].

Early Stages of Drug Delivery Technology Development

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.[11]

Concept of Mapping

Mapping is a process which relates Critical Manufacturing Variables (CMV), including formulation, processes, and equipment variables that can significantly affect drug release from the product, to a response surface derived from an in vitro dissolution curve and an in vivo bioavailability data [39, 44]. The mapping process defines boundaries of in vitro dissolution profiles on the basis of acceptable bioequivalence criteria. The goal is to develop product specifications that will ensure bioequivalence of future batches prepared within the limits of acceptable dissolution specifications.[45] Dissolution specifications based on mapping would increase the credibility of dissolution as a bioequivalence surrogate marker and will provide continuous assurance and predictability of the product performance. The mapping provides for the employment of a dissolution method correlated to the rate and extent of drug bioavailability, which has also been optimized to be sensitive to CMV.

FUTURE PROSPECTS

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).

CONCLUSION

IVIVC is the link between *in vitro* and *in vivo* performance of the drug product. It has wide application in drug delivery at various stages of development to setting dissolution specifications. The most critical application of IVIVC with respect to cost savings due to the avoidance of expensive clinical trials.IVIVC includes *in vivo* relevance to *in vitro* dissolution specifications and can serve as surrogate for *in vivo* bioavailability and to support biowaivers. It can also assist in quality control for certain scale-up and post-approval changes. Therefore, the activity in the area of IVIVC for oral extended release dosage forms has increased. The FDA Guidance on IVIVC provides general methods and guidelines for the establishment of IVIVC. The number of studies reported in the area of establishing IVIVC for non-oral dosage forms are very scarce and further research is necessary in the development of more meaningful dissolution and permeation methods.

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