Review Article
ISSN: 0974-6943

Amitava Ghosh et al. / Journal of Pharmacy Research 2009, 2(8),1255-1260
Available online through
www.jpronline.info

In vitro-In vivo Correlation (IVIVC): A Review

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ABSTRACT

Rapidity in Drug development can be achieved by researchers on finding a mathematical link between bioavailability and dissolution testing which leads to the concept of *in vitro - in vivo correlation* (IVIVC). 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. Several factors such as first pass effect, stereochemistry, should be considered while developing IVIVC. In the present scenario, research is focussed in oral novel dosage forms where knowledge of IVIVC is of paramount importance. Applications of IVIVC ranges from drug and product development, their scale up and post approval changes. Hence, IVIVC should be considered as an important tool in drug development.

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

INTRODUCTION

Pharmaceutical companies are hungry for the rapid drug development and approval, while Regulatory agencies need assurance of the product quality and performances. During the last 25 years, there has been a considerable interest within the pharmaceutical industry, academia, and regulatory sectors in *in vivo* and *in vitro* correlation[1] of oral dosage form. In 1971, Wagner[2] stated that "future research in dissolution rates should be directed mainly towards establishing correlation between *in vitro* and *in vivo* data. An accurate correlation between *in vivo* and *in vitro* data can predict the *in vivo* performances indicating the usefulness of the method which can be used as a major tool for development and production control. To reach a valid correlation, it is necessary to have a valid method to yield measurements both *in vitro* and *in vivo* correlation. The completion of these criteria led to the publication[3] of "Stimuli" by U.S. Pharmacopoeial convention's subcommittee on Biopharmaceutics in Pharmacopoeial Forum in 1988. *In vitro* specifications such as physical and chemical properties, stability, water content, disintegration, solubility, and rate and extent of dissolution used as quality and process control in dosage form manufacturing. The merits of establishing such a relationship are to be measured in terms of cost, time and safety.

In general *in vivo - in vitro* correlation (IVIVC) is defined[2,4] as a mathematical model which describes the relationship between *in vitro* and *in vivo* properties of a drug product, so that *in vivo* properties can be predicted from its *in vitro* behaviour. However, two definitions have been forwarded by USP and FDA. These are as follows:

USP defines IVIVC as the establishment of relationship between a

biological property, or a parameter derived from a biological property produced by a dosage form while FDA defines IVIVC as a predictive mathematical model[2,3,4] which describes relationship between *in vitro* properties of a dosage form and a relevant *in vivo* response.

OBJECTIVES OF *IN VITRO- IN VIVO* CORRELATION[1-4]

In vitro dissolution is one of the vital tools for characterisation 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.

FUNDAMENTALS OF IVIVC[1,2,6,7,8]

USP defined five levels of correlation each of which denotes the ability to predict *in vivo* response of a dosage form from its *in vitro* property. Higher the level better is the correlation. The level of correlation is categorised as:

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

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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 (tmax, Cmax 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.

Predictability of correlation[5,9]

It can be calculated by Prediction error that is the error in prediction of *in vivo* property from *in vitro* property of drug product. Based on therapeutic index of the drug and application of IVIVC, evaluation of prediction error internally or externally may be appropriate. Internal error provides a basis for acceptability of model while external validation is superior and affords greater confidence in model. The % prediction error can be calculated by the following equation:

% Prediction error (P.E) = (Cmax observed – Cmax predicted) × 100/ Cmax observed

Internal predictability

The bioavailability (Cmax, tmax/AUC) of formulation that is used in development of IVIVC is predicted from its *in vitro* property using IVIVC. Comparison between predicted bioavailability and observed bioavailability is done and % P.E is calculated. According to FDA guidelines, the average absolute %P.E should be below 10% and %P.E for individual formulation should be below 15% for establishment of IVIVC.

External predictability

The predicted bioavailability is compared with known bioavailability and % P.E is calculated. The prediction error for external validation should be below 10% whereas prediction error between 10-20% indicates inconclusive predictability and need of further study using additional data set. Drugs with narrow therapeutic index, external validation is required.

REASONS FOR POOR *IN VITRO-IN VIVO* CORRELATION[10]

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 e.g, 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.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)[2,3,11-13]

Biopharmaceutics classification system is based on solubility, intestinal permeability and dissolution rate, all of which governs the rate and extent of oral absorption from immediate release solid oral dosage form. Based on solubility and permeability, there are four classes of BCS as shown in table 1. Solubility criteria defined in present regulatory guidance for classifying an Active Pharmaceutical Ingredients (API) as "highly soluble" requires the highest strength to be soluble in 250ml of water over the pH range of 1-7.5 at 37^0C, otherwise it is considered as poorly soluble. The FDA and also EMEA Guidance define "highly permeable" as having a fraction dose absorbed of not less than 90%. The recently adopted WHO guidelines set a limit of not less than 85% of the fraction dose absorbed, otherwise it is considered to be poorly permeable.

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.

Approaches for Development of Correlation[5,14-16]

Basically, two methods are available for the development of correlations

1) Two stage deconvolution approach: This involve estimation of *in vivo* absorption profile from plasma drug concentration - time profile using Wagner Nelson or Looe-Riegelman method, subsequently the relationship with *in vitro* data is evaluated.

2) One stage convolution approach: It computes the *in vivo* absorption and simultaneously models the *in vitro – in vivo* data.

Two stage methods allows for systematic model development while one stage obviates the need for administration of an intravenous, oral solution or IV bolus dose. Mostly IVIVC models developed are simple linear equation between *in vitro* drug released and *in vivo* drug absorbed. But sometimes these data can be better fitted by using non-linear models like Sigmoid, Weibull, Higuchi or Hixon-crowell.

DISSOLUTION METHODOLOGIES, APPARATUS AND CLASSIFICATION[3]

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. Small but persistent differences between the two have their origin in the fact that the American metal processing industry, unlike the European, uses the imperial rather than the metric system. In the European Pharmacopoeia, official dissolution testing apparatus for special dosage forms (medicated chewing gum, transdermal patches) have also been incorporated. Fig. 2 shows the different dissolution apparatus.

DISSOLUTION MEDIUM

The most important parameters which are considered for simulating *in vivo* conditions are pH, buffer composition, buffer capacity, temperature, volume, hydrodynamics etc. Non-compendial media have shown better IVIVC as compared to Compendial media which is listed in the official monographs. Hence non-compendial media have been proved to have discriminating power and are widely used.

Basically, pH increases from small intestine to large intestine (pH 6.7-

8) due to which dissolution testing of extended release drug product should be carried out throughout entire physiological pH range (6.7-8). Ionic strength of dissolution media also plays a vital role in dissolution testing. Ions present in the food and food induced secretions in G.I.T causes changes in ionic strength of G.I. fluid. Buffer capacity has importance in dissolution testing of formulation that contains acidic or basic excipients. Studies[3,5,8] have shown that buffer capacity of a medium is an important criterion in design of dissolution media for *IVIVC*.

QUALIFICATION OF APPARATUS[3]

Due to the nature of the test method, "quality by design" is an important qualification aspect for *in vitro* dissolution test equipment. The suitability of the apparatus for the dissolution/drug-release testing depends on both the physical and chemical calibrations which qualify the equipment for further analysis. Besides the geometrical and dimensional accuracy and precision, as described in USP 27 and European Pharmacopoeia, any irregularities such as vibration or undesired agitation by mechanical imperfection are to be avoided. Temperature of the test medium, rotation speed/flow rate, volume sampling probes and procedures need to be monitored periodically. Another vital aspect of qualification and validation is the "apparatus suitability test." The use of USP calibrator tablets (for apparatus 1 and 2 disintegrating as well as non-disintegrating calibrator tablets) is the only standardized approach to establish apparatus suitability for conducting dissolution tests and has been able to identify or operator failures. Suitability tests have also been developed for Apparatus 3, using specific calibrators and the aim is to generate a set of calibrators for each and every compendia dissolution test apparatus.

PARAMETERS TO BE CONSIDERED WHILE DEVELOPING IVIVC[4,16,17]

1. 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.

2. 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.

3. 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

Table 1: Biopharmaceutical Classification System

BCS Class	Permeability
BCS Class I	High
BCS Class II	High
BCS Class III	Low
BCS Class IV	Low

Table 2: Development of correlation

TWO STEP APPROACH	Step 1: Estimate the in vivo absorption or dissolution time course using an appropriate technique for each formulation and subjects.
	Step 2: Establish link model between in vivo Predict plasma concentration from in vitro using link model.
ONE STEP APPROACH	Predict plasma concentration from an in vitro profile using a link model whose parameters are fitted in one step i. Do not involve deconvolution ii. Link model is not determined separately iii. Can be done without reference like IV bolus.

Table 3: Apparatus classification in the European Pharmacopoeia for different dosage forms

For solid dosage form	Paddle apparatus, basket apparatus, flow –through apparatus
For transdermal patches	Disk assembly method, cell method, rotating cylinder method
For special dosage forms	Chewing apparatus (medicated chewing gums)
	Flow-through apparatus

Table 4: Investigations of In vitro Dissolution and In vivo Bioavailability Relationship

Drug	Test Formulation	Comments
Steroids and Hormones		
Prednisolone	5mg tablets	Products were bioequivalent despite difference in in vitro dissolution. Dissolution test modified to agree with in vivo data.
Prednisone	5mg and 50mg tablets	In vitro dissolution rate not predictive of overall bioavailability.
Anti-inflammatory and analgesic agents		
Aspirin	Four 300mg tablets	No IVIVC correlation
Ketoprofen	50mg conventional capsules and two 200mg sustained release capsules	Slower absorption and reduced systemic bioavailability from slower dissolving SR capsule.
Indomethacin	Four Indomethacin preparations	All preparations were bioequivalent despite different dissolution rate of one preparation.
Respiratory Tract		
Theophylline	Four experimental controlled release formulations	Correlations obtained between in vitro and in vivo data
Central Nervous system Drugs		
Promethazine	Two 50mg tablets, one 25mg tablet and a solution	No discrimination. No significant differences among products in in vitro or in vivo data
Antibacterial and antifungal		
Griseofulvin	Four 100mg capsules compared in dog and humans	Good in vitro-in vivo correlation using specific sink condition dissolution method.
Doxycycline	Three 100mg capsules compared with a suspension and a solution	Rank order correlation between dissolution rates and absorption rate constants, but no statistical significant difference in bioavailability of the three capsules products
Nitrofurantoin	Nineteen 100mg products	Neither disintegration nor dissolution accurately reflected absorption
Hypoglycaemic Agents		
Glyburide	Four marketed preparations	Two dissolution tests yielded different rank orders of dissolution rates. Neither test correlated with in vivo data
Cardiovascular		
Isosorbide dinitrate	Two experimental 40mg tablets	Products were bioequivalent despite different in vitro release rates
Digoxin	Seven 0.25mg tablets	Close correlation between dissolution rate and bioavailability

hence prediction of *in vivo* availability of active enantiomer. So consideration of stereoisomerism in the development of IVIVC may provide more meaningful relationship.

PARAMETERS STUDIED FOR IVIVC

Earlier disintegration was considered as the most important pertinent *in vitro* parameter but recently, dissolution rate has been used as a manufacturing process standard and is generally considered to be the *in vitro* parameter most likely to correlate with *in vivo* bioavailability.

In vivo bioavailability is described in terms of the rate and extent of drug absorption. Rate of absorption is reflected in peak drug concentrations in plasma (C_{max}) and the terms at which they occur (t_{max}). Other methods may be used to describe absorption rate profile, for example, deconvolution and statistical moment theory. However use of these approaches does not detract from the basic relationships between absorption rate, C_{max} and t_{max}. Extent of absorption is re-

Comments

Products were bioequivalent despite difference in in vitro dissolution.
 Dissolution test modified to agree with in vivo data.
In vitro dissolution rate not predictive of overall bioavailability.
No IVIVC correlation
Slower absorption and reduced systemic bioavailability from slower dissolving SR capsule.
All preparations were bioequivalent despite different dissolution rate of one preparation.
Correlations obtained between in vitro and in vivo data
No discrimination. No significant differences among products in in vitro or in vivo data
Good in vitro-in vivo correlation using specific sink condition dissolution method.
Rank order correlation between dissolution rates and absorption rate constants, but no
 statistical significant difference in bioavailability of the three capsules products
Neither disintegration nor dissolution accurately reflected absorption
Two dissolution tests yielded different rank orders of dissolution rates.
Neither test correlated with in vivo data
Products were bioequivalent despite different in vitro release rates
Close correlation between dissolution rate and bioavailability

flected in C_{max} and also the area under the plasma drug curve (AUC).

ATTEMPTS TO ESTABLISH *IN VITRO – IN VIVO* CORRELATION[1,4,5,18]

Many attempts have been made to establish *IVIVC* for a variety of drugs. Some of these are summarized in the Table 3 which describes studies on a variety of dosage forms for a broad spectrum of therapeutic indications, and provides a brief comment on the results obtained.

IVIVC OF NOVEL DOSAGE FORMS [1,2,19-21]

1. ENTERIC COATED MULTIPLE UNIT 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 emptying 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.

2. PARENTERAL CONTROLLED OR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Three methods for *in vitro* drug release study of microparticles system for parenteral administration have been established by far. These include sample and separate, flow through cell and dialysis technique.

3. BUCCAL TABLETS

Spiegeleer et al have developed a useful correlation between *in vivo* residence time of mucoadhesive tablets in mouth and *in vitro* bending point of the same. Linear regression models permits optimization of buccal tablets to enhance the adhesion time using *in vitro* bending point as selection criteria.

4. TRANSDERMAL DRUG DELIVERY SYSTEM

USP 29 gives methods for *in vitro* drug release testing of transdermal patches like paddle over disk, cylinder method and reciprocating disk method. But Franz diffusion cell are highly used.

5. SUPPOSITORIES

Modified basket or paddle methods are recommended for lipophillic suppositories while conventional basket, paddle or flow-through cells are recommended to be suitable for hydrophilic suppositories.

6. NASAL DRUG DELIVERY SYSTEM

Variety of methods on *in vitro* testing of nasal drug delivery system like emitted dose, droplet or particle size distribution, spray pattern and plume geometry are available. FDA guidance recommends these methods as a means of documenting bioavailability and bioinequivalence for topically acting solution formulations, because they can be performed reproducibly and are more discriminating among products.

7. COLONIC DRUG DELIVERY SYSTEM

Crohn's disease or chronic inflammatory colitis may be more effectively treated by direct drug delivery to the colon. Mesalamine (5-aminosalicylic acid, Asacol) is available in a delayed-release tablet coated with an acrylic based resin that delays the release of the drug until it reaches the distal ileum and beyond.

8. RECTAL AND VAGINAL DRUG DELIVERY

Rectal drug administration can be either for local or systemic drug delivery. Rectal drug delivery for systemic absorption is preferred to drugs that cannot be tolerated orally or in situations where the drug cannot be given orally. A sustained-release preparation may be prepared for rectal administration.

Vaginal drug delivery is generally for local drug delivery but some systemic drug absorption can occur. Progesterone Vaginal suppositories have been evaluated for the treatment of Pre- menstrual syndrome of Anxiety and irritability. Antifungal agents are often formulated into suppositories for treating vaginal infections. Fluconazole, a triazole antifungal agent has been formulated to treat vulvovaginal candidiasis.

APPLICATIONS[2,4,8,22]

The most vital application of IVIVC is to use *in vitro* dissolution study in lieu of human bioequivalence studies which will reduce the number of human bioequivalence studies during initial approval process as well as certain scale up and post approval changes.

1. Manufacturing Control

The extended release products are distinguished through their input rate to the absorption site. Therefore, the rate of drug release from these products is an important feature and should be carefully controlled and evaluated. The *in vitro* dissolution/release test is meaningful only when the test results are correlated to the products' *in vivo* performances.

2. Process Change Assurance

 The manufacturing processes of approved products are regulated by the regulatory agencies. The manufacturers are required to demonstrate that kind of change, even an engineering improvement, does not cause changes in the finished product's *in vivo* performance. Consequently, many changes have to be supported by a

bioequivalence study. With the availability of an *in vitro* test with one-to-one correlation to the product's *in vivo* performance, a bioequivalence study should no longer be necessary. In such cases, the scientists and regulatory agencies may consider a pilot pharmacokinetic study as an assurance that the new excipient does not inadvertently affect the absorption.

3. Dissolution/Release Rate Specifications

Without a correlation, the specifications of an *in vitro* test can be established only empirically. This approach is data driven but is valid only if all the batches have been extensively evaluated in clinical trials; furthermore, it probably can detect only relatively large differences between different batches. It is therefore more precise to set up the specification using the correlation to evaluate the *in vivo* consequences of the range. Clearly, the pharmacokinetic consequences alone are not sufficient to set up the specifications. The pharmacodynamic knowledge is the key to make the specification clinically meaningful. In the absence of the information, some scientists may be willing to rely on the empirical bioequivalence range of ±20% as the first guidance. In case of a one-to-one correlation, this automatically translates in a dissolution rate change of ±20%. It is empirically derived dissolution range is much wider than ±20%, and then the companies invariably believe that the products have been punished by the presence of one-to-one correlation.

4. Early development of Drug Product and Optimization

In the early stages of drug product development drug products are characterised by some *in vitro* systems and some *in vivo* studies in animal models to find out toxicity and efficacy issues.

5. Biowaiver for Minor Formulation and Process Changes

After the evaluation of critical manufacturing variables and *in vitro* dissolution rate for controlled release formulation an IVIVC has been established. *In vitro* dissolution data is used to justify minor formulation and process changes. The changes may include minor change in shape, size, amount and composition of materials, colours, flavours, procedure, and coating, source of inactive and active ingredients, equipment or site of manufacturing.

Conclusion

It is clear that a complex relationship exists between *in vitro* dissolution and *in vivo* bioavailability. While it is desirable to use product dissolution to predict *in vivo* behaviour, many years of investigation have shown that this goal cannot be achieved with our current knowledge. Indeed, the assumption of such a relationship could be potentially dangerous.

Dissolution testing is essential as a quality control to ensure process and batch consistency in the manufacturing process. It has failed, however to predict differences among products that are poorly available *in vivo* or those that are super bioavailable relative to existing standards.

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Source of support: Nil, Conflict of interest: None Declared