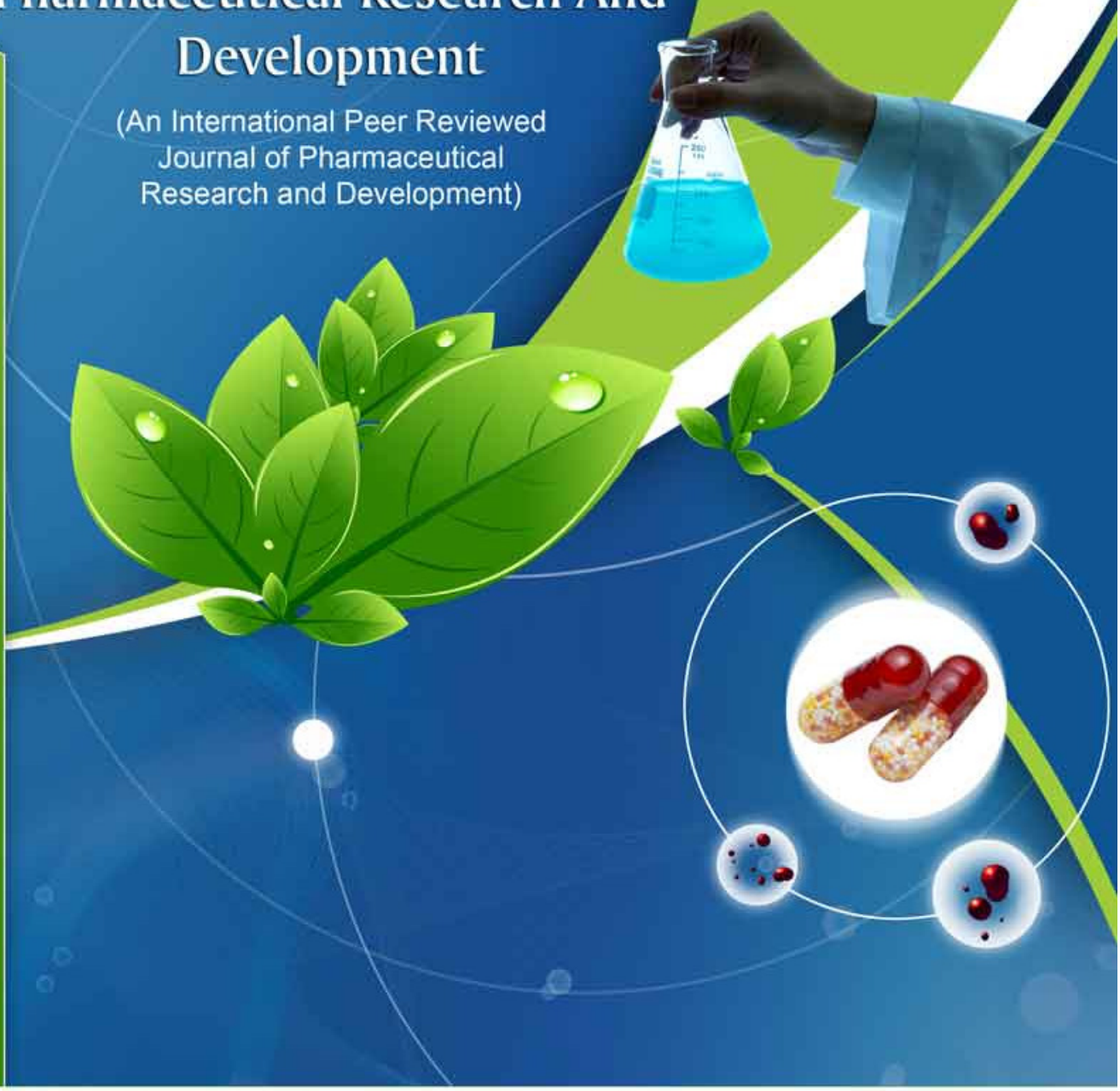
ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD



Volume - 01 Issue - 04 JULY-AUG 2013

website: www.ajprd.com
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Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

IN VITRO–IN VIVO CORRELATION (IVIVC): A BIOPHARMACEUTICAL TOOL TO SHORTEN DEVELOPMENT DURATION

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Received: 31 July 2013, ***Revised and Accepted: 5 August 2013***

ABSTRACT

United States Food and Drug Administration (FDA) have given guidelines for both immediate and modified release dosage so as to minimize bioavailability studies during formulation design and optimization. An in vitro–in vivo correlation (IVIVC) may be defined as a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response. When a meaningful IVIVC has been established, it can be used as a surrogate for bioequivalence potentially minimizing the number of bioequivalence studies to be performed during drug product development. An IVIVC can be used to request biowaivers from regulatory agencies for certain formulation or production changes within the lifecycle of a product. This reduces the need for expensive bioequivalence testing in humans. This review article presents a comprehensive overview of systematic procedure for establishing and validating an in vitro in vivo correlation level A, B and C. It encompasses all mathematical concepts of IVIVC development such as GastroPlus™, TIM1, Drug Dissolution/Absorption Simulating System (DDASS) and other methods.

KEYWORDS: *IVIVC, GastroPlus, TIM1, DDASS, Wagner-nelson method, Loo-Reigelman method*

INTRODUCTION

Time is an important factor in successful drug development and all strategies to shorten development duration while supporting safety and overall quality of the product are encouraged. In vitro–in vivo correlation (IVIVC) is a biopharmaceutical tool recommended to be used in development of formulations [1]. An in vitro–in vivo correlation (IVIVC) for an oral product may be defined as a predictive mathematical model describing the relationship between an in vitro property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g. plasma drug concentration or amount of drug absorbed) [2]. When correlation is established and validated, prediction of in vivo profile can be done based on in vitro dissolution profile. Those predictions can be used in a wide range of applications such as to be a surrogate of in vivo study for formulation variation and also, for example, to validate scale up with a factor more than 10, to justify widening of dissolution limits, to validate production transfers, to modify the manufacturing process as the predictions allow to guaranty the in vivo performance and the bioavailability or bioequivalence of the formulations [1, 3].

More recently the concept of Quality by Design (QbD) has been implemented in formulation development. A goal of QbD is to identify the critical quality attributes (CQAs) required to provide safety and efficacy to the

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patient. These critical quality attributes are then controlled to assure product performance. Thus rather than assuring product quality by performing a test after manufacturing, such as dissolution, QbD has the goal of assuring product quality by controlling the manufacturing process. A hurdle in implementation of QbD is in the establishment of the relation between the CQAs and safety and efficacy. The CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. Given the multiple number of attributes, it is not financially feasible to establish relationships to safety and efficacy during clinical trials [1, 2]. In recent years, a number of drugs are being developed. Thus there is a growing need of pharmacokinetic studies; subsequently it has become a very tedious, expensive and time consuming task to collect and handle huge pharmacokinetic data. It is therefore, useful to develop pharmacokinetic simulation models for the prediction of pharmacokinetic parameters. Pharmacokinetic simulation model is defined as a computational and/or mathematical tool that interprets drug kinetics in living environment under specific conditions [4]. An IVIVC can be used to request biowaivers from regulatory agencies for certain formulation or production changes within the lifecycle of a product. This reduces the need for expensive bioequivalence testing in humans [5].

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

The biopharmaceutical classification system (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [6].

Characteristics of drugs in BCS

Class I drugs exhibit a high absorption number and a high dissolution number.

Class II drugs have a high absorption number but a low dissolution number.

Class III drugs exhibit a high variation in the rate and extent of drug absorption. Permeability is rate limiting step for drug absorption.

Class IV drugs exhibit poor and variable bioavailability.

Biopharmaceutics Classification System can be used to assess whether or not dissolution is likely to control absorption [2]. In vitro-in vivo correlation is normally expected for highly permeable drugs or drugs under dissolution rate-limiting conditions as shown in Table I and II [7, 8].

THE IVIVC CAN BE ACHIEVED

The IVIVC can be achieved using pharmacokinetic simulation models for the prediction of pharmacokinetic parameters. Pharmacokinetic simulation model is defined as a computational and/or mathematical tool that interprets drug kinetics in living environment under specific conditions [9, 10].

Advanced Compartmental Absorption and Transit model (GastroPlusTM)

GastroPlus™ is simulation software that uses the ACAT. In the ACAT model, the small intestine is divided into different compartments and calculates the fraction dose absorbed for each compartment. The program has three input tabs, namely, compound, physiology and pharmacokinetic tab, comprising three sets of factors influencing oral drug absorption. In the compound tab, Log P, solubility, diffusion coefficient and human effective permeability can be predicted using the ADMET predictor module from GastroPlus™. Other data in the compound tab are set at default values. The drug release profile is used by the software to calculate the drug concentration in each compartment. The human Log D absorption model can be used to estimate the changes in permeability as the drug travelled along the gastrointestinal (GI) tract. All other parameters were fixed at default values that represent human fasted physiology [11-13].

Gastroplus™ then calculates the fraction dose absorbed based on the ACAT model using drug concentration, permeability and transit times in each compartment. In pharmacokinetics tab, blood/plasma concentration ratio and percent of drug unbound to plasma proteins can be estimated

by ADMET predictor module, and optimizing process from optimizing module is used to estimate the pharmacokinetic parameters (CLr, Vc, k12, and k21). All other pharmacokinetic parameters are kept fixed at default values.

In establishing the IVIVC using deconvolution approach, in vivo release which calculated from GastroPlus™ was compared to the virtual in vitro dissolution profiles. In the convolution approach, the level A IVIVC was developed by comparing the plasma concentration observed and plasma concentration predicted by GastroPlus™.

Saibi et al employed GastroPlus™ as a tool to investigate the absorption profile of risperidone in the gastrointestinal tract disposition based on its physicochemical and pharmacokinetic parameters and to build its in vitro–in vivo correlation based on the model built. GastroPlus™ (version 7.0.0.01, Simulation Plus, Inc., Lancaster, CA, USA) was used to simulate the in vivo absorption profile. Risperidone is an antipsychotic with extremely potent serotonin-5HT2 and potent dopamine-D2 antagonistic properties. Risperidone belongs to class II of the BCS. A level A IVIVC was successfully developed in all dissolution media with percent prediction error for Cmax and the area under the curve less than 10% for both reference and test drug [14].

TNO Intestinal Model (TIM1)

TNO intestinal model (TIM1) is a multi-compartmental, dynamic, computer-controlled in vitro system developed at TNO Nutrition and Food Research (Zeist, The Netherlands) simulating the GI tract in man. TIM1 is composed of four serial compartments simulating the stomach, the duodenum, the jejunum and the ileum. The absorption phase in TIM1 can be simulated by the use of a dialysis membrane. Therefore, this system could only be used for drugs which are absorbed by passive diffusion and not by active transport because the mucosal cells are not involved in the current configuration. This artificial digestive system (ADS) fulfils all the requirements correspond to the physiological states:

Sequential use of enzymes in physiological amounts,

- Appropriate pH for the enzymes,
- Removal of the products of digestion,
- Appropriate mixing at each stage of digestion,
- Physiological transit times for each step of digestion, and
- A peristaltic dynamic approach.

In addition, this in vitro model can maintain the possibility of introducing a solid meal to investigate all food–drug interactions and food impact on the dosage form behaviour [15].

Souliman and co-workers had used this artificial digestive system to estimate the availability of acetaminophen immediate release tablets for absorption in fasted and fed states. Acetaminophen used as an antipyretic and analgesic belongs to class I of the biopharmaceutical classification system (highly soluble and readily permeate the intestine). A comparison study was carried out between the classical and the novel methods to estimate the efficacy of the new in vitro system to simulate the influence of food on drug release and absorption in vivo. The availability of acetaminophen for absorption was estimated in TIM1 by measuring the drug concentration in the jejunal and ileal dialysis fluids, following its passive diffusion through the hollow fiber membranes which were connected to the two compartments representing the jejunum and the ileum, respectively. A level A in vitro in vivo correlation was established with a correlation coefficient of 0.9128 and 0.9984 in the fasted and fed states, respectively. Despite the “poor” IVIVC established in the fasted state, TIM1 results were closer to those of in vivo than those obtained with the paddle method.

Student’s t-test was carried out to investigate if the ratio between in vitro results using the ADS and in vivo ones is significantly (S) or non-significantly (NS) different from one. The ratio between in vitro and in vivo results is non-significantly different in fasted and fed

states which confirm the predictability of the novel in vitro model.

Wagner–Nelson and Loo–Riegelman method

The Wagner–Nelson procedure and the Loo–Riegelman method with the linear trapezoidal rule can be used to obtain an in vivo cumulative release profiles. For a rapid absorption process of drug, it is appropriate to use the Wagner–Nelson procedure or the Loo–Riegelman method for obtaining an absorption profile, because the difference between the cumulative amount released and the cumulative amount absorbed could be negligible. The Loo–Riegelman method is used usually in the calculation of the cumulative absorption of the drug which is fitted to a two-compartment model. Though the Wagner–Nelson method is mainly applied to the pharmacokinetic study of the drug fitted to a one-compartment model, due to its simplicity, this method is also used for the drugs fitted to a two-compartment model. When these procedures are used to acquire the IVIVC, pharmacokinetic parameters from drug immediate release formulation is necessary.

The relationship between percent in vitro dissolution in PBS at 37ºC and the fraction of drug absorbed in vivo (Fa) can be determined using the Wagner–Nelson method by the following equation:

$$Fa = (Ct/Ke + AUC0–t)/AUC0–\infty$$

Loo–Riegelman method:

$$Fa = [Ct/K10 + AUC0–t + (Xp)t/(Vc \times K10)]/AUC0–\infty$$

Linear regression analysis was applied to the IVIVC plots.

D.F Chu et al used three formulations with different release rates to establish the IVIVC of huperzine A loaded sustained release microspheres in dogs. Huperzine A, a lycopodium alkaloid isolated from the herb Huperzia serrata, is a reversible and selective inhibitor of acetylcholinesterase. The data generated in the pharmacokinetic study after the i.v. administration of the huperzine A solution and after the i.m. and s.c. administrations of the microsphere formulations to dogs were used to develop the IVIVC (Level A). Since huperzine A was diffusion-controlled released from the polymeric matrix and was absorbed in vivo rapidly, a good linear regression relationship was observed between the percent in vitro dissolution in PBS at 37ºC and the percent absorption or percent AUC ($R2 = 0.974–0.990$, $P < 0.001$ for the Wagner–Nelson method; $R2 = 0.959–0.993$, $P < 0.001$ for the Loo–Riegelman method) and percentAUC0–∞ ($R2 = 0.98–0.992$, $P < 0.001$). After i.m. administration the linear relationship between the in vitro and the in vivo releases was better than that after s.c. administration [16].

A.R Patel et al explored the potential in vitro–in vivo correlation (IVIVC) of novel methylene-substituted 3,3'-diindolylmethane (DIM) between the in vitro permeability and the oral absorption. DIM is an active metabolite of indole-3-carbinol derived from cruciferous vegetables and this compound exhibits a broad spectrum of anticancer activities. DIM has poor oral bioavailability due to its low solubility. They employed deconvolution of i.v. and oral data using a three compartment Loo–Riegelman method to determine the fraction absorbed with time in vivo and compared this to their fraction absorbed in Caco-2 cells. Pharmacokinetic properties in rats were determined using non-compartmental and compartmental techniques with WinNonlin® 5.0 software following i.v. and oral administration. There was no correlation found between in vitro permeability values and the oral absorption pharmacokinetics. They observed an initial phase of reduced DIM absorption rates over 50 min following oral administration, which may have led to a lack of correlation with in vitro permeability assays [17].

Singh and co-workers made attempts to correlate the in vivo plasma level data obtained for both the optimized SNEDDS formulations and pure drug with the corresponding in vitro drug release data and establish various levels of IVIVC. For establishing Level A IVIVC, percent drug absorbed data at various time points were obtained using modified Wagner-Nelson

method and correlated with percent drug release data. Excellent Level A correlations were observed with all the formulations. Since carvedilol is a poorly water-soluble drug exhibiting nearly complete and dissolution-limited absorption, it is anticipated to show good point-to-point correlation between in vitro and in vivo performance (i.e., Level A). Consequent establishment of IVIVC demonstrated that the in vitro dissolution performance correlated well with the in vivo absorption parameters [18].

Kapil and co-workers has recently reported a successful point to point level A correlation for a buccoadhesive film of rivastigmine, an anti-Alzheimer drug. In vitro drug dissolution data derived using Franz diffusion cell was compared against pharmacokinetic parameters obtained from the rabbits used as an animal model. However this study has several limitations and it is questionable whether it is possible to consider this correlation as valid as Kapil and co-workers used three rabbits to derive the pharmacokinetic data which represents a very poor and inadequate sample size [19].

D. Juenemann et al ascertain the ability of in vitro biorelevant dissolution tests to predict the in vivo performance of nanosized fenofibrate and microsized fenofibrate [20]. In vitro–in silico–in vivo correlations were established for both microsized and nanosized fenofibrate in both the fed and fasted state by combining dissolution tests with the STELLA® 9.1.1 software (isee systems, NH, USA).

Drug Dissolution/Absorption Simulating System (DDASS)

Drug dissolution/absorption simulating system (DDASS) is presented schematically in Figure 1. DDASS is expected to imitate the process of dissolution and permeation of solid formulation simultaneously [21].

A basket is installed in the drug-dissolving vessel (DDV; modeled stomach) to carry the complete oral dosage forms. The vertical center line of the basket passes through the axis of the vessel so that drug dosage forms will be in the middle of the DDV. On the one hand, the eccentricity ratio of the magnetic stir bar will not be changed since it does not collide with a dosage form, so the hydrodynamic effects of dissolution medium will not vary. On the other hand, the complete oral dosage forms will stay at the same position and maintain the same solid–liquid interface dynamic effects. Secondly, a wire-steel strainer on the top of the pH-adjustment vessel (PAV; model stomach) as a first filtering system to prevent escape of undissolved particles from the PAV. A Millipore filter is installed between the PAV and side-by-side diffusion chamber as a second filtering system to further purify the drug solution. The flow rate of each solution is controlled by using a peristaltic pump.

Qiang et al studied the correlation between in vitro dissolution and in vivo absorption to evaluate the release characteristics of isosorbide mononitrate dosage forms obtained from the DDASS and basket/paddle methods, and they determined which method more accurately modeled in vivo bioavailability. Isosorbide mononitrate is an organic nitrate used in the prophylaxis of angina pectoris. The dissolution and absorption kinetic parameters of isosorbide mononitrate dosage forms in DDASS and the pharmacokinetic parameters in beagle dogs were determined using Phoenix WinNonlin version 6.1 (Pharsight Co., Ltd., USA), assuming a non-compartmental analysis model. A better IVIVC was established between DDASS permeation and dog absorption for each isosorbide mononitrate dosage form than between in vitro dissolution and dog absorption.

CONCLUSION

In the current regulatory environment, a validated IVIVC is not necessary to justify the setting of product specification. However, if there is an interest in obtaining biowaivers of future in vivo bioequivalence studies, validation of the IVIVC is often essential [2]. Development of in vitro release models for formulation development as well as quality control purposes is a critical activity which, preferably, should be initiated in the early design phase. Optimally, construction of an in vitro release model may lead to establishment

of an in vitro in vivo correlation (IVIVC) [22]. Most often such point-to-point relationships are linear; however, non-linear correlations are also acceptable. Importantly, development of a true IVIVC requires that a mathematical model describes the in vitro in vivo relationship for two or more formulations exhibiting different release characteristics. When a meaningful IVIVC has been established, it can be used as a surrogate for bioequivalence potentially minimizing the number of bioequivalence studies to be performed during drug product development.

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