Research Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Venkatesh Murukutla, IJPRBS, 2016; Volume 5(3): 1-9 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

RATIONAL APPROACH TO THE ANALYSIS OF *INVITRO-INVIVO* CORRELATION

VENKATESH MURUKUTLA, KONKIPUDI VENKATA SHIVAIAH

Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, India.

Accepted Date: 10/04/2016; Published Date: 27/06/2016

Abstract: *In vitro–in vivo* correlation (*IVIVC*) allows prediction of the *in vivo* performance of a drug based on the *in vitro* drug release profiles. To develop an effective *IVIVC*, the physicochemical and biopharmaceutical properties of the drug as well as the physiological environment in the body must be taken into consideration. A more informative way to examine the predictability of the *in vitro* parameters is to examine whether processing and storage conditions associated with loss or improvement *in vivo* viability are also associated with corresponding changes to the *in vitro* parameters. An important objective of pharmaceutical product development is to gain better understanding of the *in vitro* and *in vivo* drug performances. Through the successful development and application of an *IVIVC*, *in vivo* drug performance can be predicted from its *in vitro* behaviour.

Keywords: *IVIVC-in vitro in vivo* correlation , Extended release, Modified release, Food and drug administration,__BCS-Biopharmaceutical classification system, FDA-Food and drug administration, ER-Extended release, MR-Modified release, GI-Gastro intestine.

PAPER-QR CODE

Corresponding Author: MR. VENKATESH MURUKUTLA

Access Online On:

www.ijprbs.com

How to Cite This Article:

Venkatesh Murukutla, IJPRBS, 2016; Volume 5(3): 1-9

1. INTRODUCTION

An *in vitro in vivo* correlation (*IVIVC*) is defined by the U.S. Food and Drug Administration (FDA) as a predictive mathematical model describing the relationship between the *in vivo* property of an oral dosage form and 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 absorbed[(1)]. Correlations between *in vitro* and *in vivo* data (*IVIVC*) are often used during pharmaceutical development in order to reduce development time and optimize the formulation. The main focus of this paper is to point out that poor correlations do not necessarily mean that the specific *in vitro* parameters are poor predictors of *in vivo* viability, but may be related to the fact that *in vivo* measurements, as absolute values, do not accurately reflect the *in vitro* data. A more informative approach with regard to the predictability of *in vitro* tests is to investigate whether specific conditions where there is a change *in vivo* viability are also associated with corresponding *in vitro* changes.

2. Considerations in *IVIVC* development

While it is widely recognized that correlations exist between *in vitro* drug dissolution and *in vivo* drug absorption, limited progress has been made towards the development of a comprehensive model capable of predicting *in vivo* drug absorption based on dissolution. This is due to the existence of a complex array of factors that contribute to the process of drug dissolution and absorption. In general, these factors can be classified into threegroups; physicochemical factors, biopharmaceutical factors, and physiological factors. In order to develop a model that can demonstrate good correlation between *in vitro* drug dissolution and *in vivo* drug absorption, these factors have to be taken into consideration.

1. Physiochemical properties.

2. Biopharmaceutical properties

3. Physiological properties

A more informative way of looking at the predictability of various *in vitro* parameters

Another approach to investigate the predictability of various *in vitro* assays is to examine whether conditions with loss of platelet *in vivo* viability are also associated with corresponding expected changes in the *vitro* parameters, and vice versa.[(2)]

1. Physicochemical properties:

Physicochemical properties play a major role in predicting the *in vivo* absorption of drug candidates. For almost all drugs administered orally, dissolution is a prerequisite to drug

absorption and clinical efficacy. Dissolution is dependent on several physicochemical properties, including solubility, pH dependency, salt forms, and particle size.

2. Biopharmaceutical properties:

Drug permeability plays a major role in drug absorption, particularly in orally administered dosage forms. The trans cellular permeability (Pm) of a compound is defined as:

$$P_m=k_pd_m/l_m$$

Where Kp is the membrane-water partition coefficient, Dm is the membrane diffusivity, and Lm is the membrane thickness. Another parameter that may be useful in model development is the oil–water partition coefficient. In particular, octanol–water partition coefficient (P or log P) of neutral or unionized species is often used to provide insight into the ability of compounds to pass through membranes for absorption.

3. Physiological properties:

Besides physicochemical and biopharmaceutical considerations, physiological conditions are also important factors to consider for successful establishment of *IVIVC*, since physiological

Conditions can affect both drug dissolution as well as the rate and extent of drug absorption. In the previous sections, we have demonstrated the influence of pH on solubility, dissolution and membrane permeation. The effect of pH becomes particularly important in the human body, where there is an inherent pH gradient. The most well-known and commonly studied pH gradient is located throughout the GI tract, where it can range from values of 1–2 in the

Stomach to 7–8 in the colon. In the small intestine, where the vast majority of orally ingested substances are absorbed, the pH value ranges broadly from 5 to 8. These changes in GI pH profile can alter drug solubility, dissolution, stability and permeability. To further complicate the situation, the physiological environment is constantly adjusting and changing according to normal human activity such as food intake. Another important physiological property for

oral dosage forms is the GI transit time, which affects the extent of drug release in the body. Typically, the gastric emptying time for liquids is 1 h, while for solid materials it is approximately 2–3 h. Consequently, the administration of drugs with liquid or with solid food will result in different drug transit times, leading to variations in extent of drug release. Additionally, food intake stimulates the release of enzymes and digestive fluids, and these may enhance or hinder drug absorption. As we can see, in order to accurately quantitative the relationship between *in vitro* data and *in vivo* response, the mathematical model must account for such changes.

3. Approaches to developing *IVIVC* models

There are four levels of *IVIVC*:

Level A correlation is the point-to-point correlation between *in vitro* and *in vivo* profiles. This is generally considered as the highest level of correlation and allows prediction of the entire *in vivo* concentration time course from the *in vitro* dissolution profile (Fig. 1A).

Level B correlation compares a summary parameter from the mean *in vitro* profile with a summary parameter from the mean *in vivo* profile (Fig. 1B).This type of correlation is not considered useful.

Level C correlation establishes a single time point correlation between a dissolution parameter and an *in vivo* parameter. An extension of this type of correlation is the multiple Level C correlation, which relates several in vitro parameters to *in vivo* parameters at multiple time point (Fig. 1C).

Multiple Level C correlation are regarded as more useful than Level C correlations. Many case studies on different levels of *IVIVC* have been reported in the literature[4] for example, *IVIVC* for fenofibrate immediate release tablets was investigated.

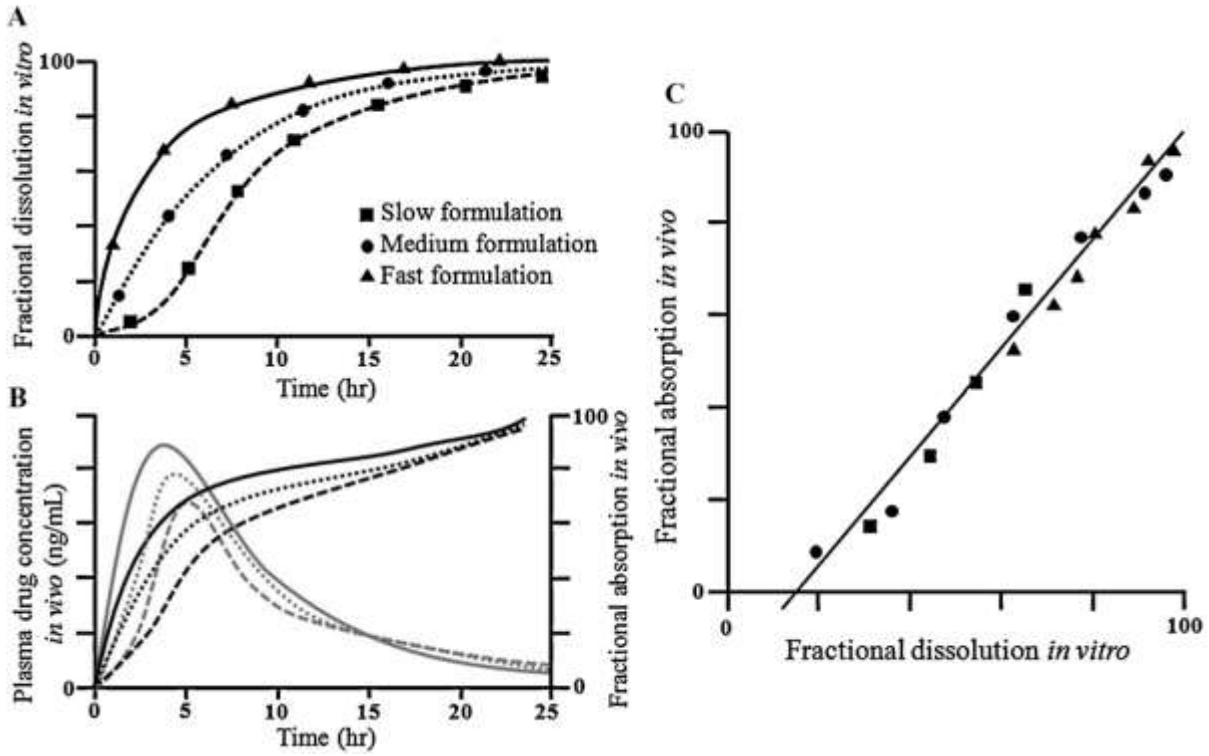

Fig. 1. Example of Level A IVIVC. (A) In vitro dissolution profiles of slow (square), medium (circle), or fast drug formulations (triangle). (B) In vivo studies provide plasma drug

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.

4. Development of *in vitro* release tests

For modified release dosage forms, it is often necessary to use an *in vitro* method of release testing that exceeds the *in vivo* rate of drug release. Since these dosage forms are typically designed to release their contents over periods of weeks, months or even years, it becomes impractical to wait for a real-time test for batch release of product. Therefore, accelerated methods are often developed to assist in batch release of product. Accelerated tests, by their nature, (e.g. elevated temperature or use of solvents) can change not only the rate of drug release but also the mechanism of release. Therefore, it is very important to understand the accelerated method and how it may affect the drug release mechanism. In some cases there may be a good correlation between accelerated release profiles of different formulation sand their real-time profiles, however this may not always be the case. That detail studies of the effect of accelerated temperature and pH on the release profiles of different modified release microsphere formulations[5-6]. It is possible that the mechanism of release can change such that even the rank order of the release profiles of different formulations change. Consequently care needs to be taken in selecting an accelerated release method. The purpose of the test should also be considered. For example, for tests intended to support an *IVIVC*, the release profile from an accelerated test should correlate with the *in vivo* release profile. Where it is not possible to achieve such a correlation with an accelerated release test, such a test may still be useful for batch release of the product. However, the development of an additional real-time test will still be needed if the intent is to develop an *in vitro* test that is predictive of *in vivo* product performance. Accordingly, the purpose for developing an *in vitro* drug release test needs to be considered.

Examples of potential purposes include:

• The quality control for batch release;

• An assessment of the impact of manufacturing process changes;

• The substantiation of label claims;

• An evaluation of the potential for dose dumping;

• An assessment of *in vivo* stability;

• The prediction of *in vivo* performance and

• The establishment of an *IVIVC*.

A more informative way of looking at the predictability of various *in vitro* parameters:

Another approach to investigate the predictability of various *in vitro* assays is to examine whether conditions with loss of platelet *in vivo* viability are also associated with corresponding expected changes *in vitro* parameters, and vice versa.[11].

5. Applications of *IVIVC*:

1. Biopharmaceutical classification system:

The biopharmaceutical classification system (BCS) is a way to categorize drug compounds based on their solubility and permeability properties. Under the BCS, drug substances can be grouped into four classes:

Class 1 compounds are highly soluble and highly permeable;

Class 2 substances have high permeability but relatively low solubility;

Class 3 compounds are highly soluble but not very permeable;

Class 4 drug substances have both low solubility and low permeability.

In general, it is recognized that the successful development and application of an *IVIVC* require dissolution to be the rate-limiting step in the process of drug administration and absorption. For Class 1 compounds, there are no rate-limiting steps for drug absorption, with the possible exception of immediate release dosage forms, for which gastric emptying could potentially become the rate-limiting step [7]. For Class 2 compounds dissolution is the rate-limiting step in absorption, therefore the establishment of *IVIVC* is expected. For Class 3 compounds, *IVIVC* is generally regarded as unlikely but may be possible depending on the relative rates of dissolution and intestinal transit. For Class

4 compounds *IVIVC* is highly unlikely. Classification according to the BCS will enable early determination of whether *IVIVC* can be developed for a certain drug candidate.

2. Bio-waivers:

A bio-waiver is an exemption granted by the FDA that allows *in vivo* bioavailability and/or bioequivalent studies to be avoided. A predictive and reliable *IVIVC* model can serve as a basis for bio-waivers, allowing reductions in time and costs during pharmaceutical product

development. For immediate release dosage forms, the successful development of *IVIVC* models may be limited to Class 2 and Class 3 compounds classified under the BCS. There by restricting the application of bio-waivers to these classes of drug compounds. However, according to FDA guidelines bio-waivers can also be requested for Class 1 compounds provided the drugs are solubilised in the gastric fluid sufficiently rapidly that gastric emptying does not become the rate-limiting step. The situation for extended release (ER) dosage forms is more complex, since the factors considered in the BCS (i.e., solubility and intestinal permeability) are insufficient to predict the rate and extent of dissolution for extended release drugs. Despite these limitations, the FDA has published important guidelines for establishing *in vitro in vivo* correlation for extended release dosage forms. Readers should refer to the document "FDA Guidance for Industry–extended release oral dosage forms: development, evaluation, and application of *in vitro in vivo* correlation" [(2)]and "FDA Guidance for Industry−Waiver on *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Bio pharmaceutics classification systems"[(1)] for more detailed information.

3. Non-oral dosage forms:

Currently, regulatory guidance for *IVIVC* is mainly focused on oral dosage forms. However, similar principles of developing *IVIVC*s can be applied to non-oral dosage forms, with certain modifications to adjust for different modes and durations of drug delivery.

Perhaps one of the most challenging aspects of developing *IVIVC*s non-oral drug delivery systems is how to design *in vitro* studies such that the *in vivo* behavior is reflected as much as possible. For example, it is difficult to apply classical *IVIVC* to drug-eluting stents because it is a local delivery system, not a systemic delivery system like oral dosage forms. Several publications have attempted to correlate *in vitro* pharmacokinetics of paclitaxel[(9)] and dexamethasone [(10)] loaded stents with *in vitro* delivery into the artery wall with limited success.

Another difficulty that may hinder the design of appropriate *in vitro* studies is the lack of suitable dissolution media that reflect the *in vivo* environment non-oral delivery systems are subjected to. This is particularly the case for implanted drug delivery devices and liposomal products. Liposomal formulations have traditionally demonstrated poor correlation between *in vitro* and *in vivo* performance, possibly due to the physiological presence of a lipid membrane 'sink' to which released drugs may bind[(12)]. To circumvent this problem, a novel drug release assay has been developed using excess multi-lamellar vesicles[(12)]. This method demonstrated improved correlation between *in vitro* data and *in vivo* release of doxorubicin, verapamil and cetramide.

6. Conclusions

The development of a predictive and reliable *IVIVC* model is a complex process. Prof. Taken Higuchi, a pioneer in this field, developed one of the most important controlled release equations, known as the Higuchi's equation. Since then this well-known and widely used equation has influenced drug delivery development and provided groundwork for subsequent *IVIVC* modelling. This review attempts to elucidate some of the general principles involved in the construction of *IVIVC*. Before the commencement of model building, it is important to consider the factors that may contribute to the *in vitro* and *in vivo* performance of the drug compound .Since by definition the *IVIVC* is a mathematical model, various algebraic, calculi and statistical methods are employed in its development. Once a reliable *IVIVC* model has been developed, it can serve as regulatory guidance for pharmaceutical industry. With justified modifications, its applications can be expanded to include more dosage forms beside oral dosage forms. Currently numerous studies have been conducted that demonstrate the existence of relationships between *in vitro* dissolution and *in vivo* release data. However, most of these studies fail to provide mathematical models that describe these relationships. What is needed is not only more extensive research into *IVIVC*, but also better mathematical methods and simulation techniques.

7. References

1. The Food and Drug Administration, U.S., 2005. FDA Guidance for Industry –Waiver In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms based on a Bio-pharmaceutics Classification Systems. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf.

2. Holme S. Storage and quality assessment of platelets. Vox Sang 1998;74(Suppl. 2):207 16.

3. The Food and Drug Administration, U.S., 1997. Extended Release Solid Dosage Forms: Development, evaluation and Application of In vitro/In vivo correlations.http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/ucm070239.pdf.

4. Buch, P., Holm, P., Thomassen, J.Q., Scherer, D., Branscheid, R., Kolb, U., Langguth, P., 2010. IVIVC for fenofibrate immediate release tablets using solubility and permeability as in vitro predictors for pharmacokinetics. J. Pharm. Sci. 99, 4427–4436.

5. B.S. Zolnik, D.J. Burgess, Effect of acidic pH on PLGA microsphere degradation and release, J. Control. Release 122 (3) (2007) 338–344.

6. B.S. Zolnik, P.E. Leary, D.J. Burgess, Elevated temperature accelerated release testing of PLGA microspheres, J. Control. Release 112 (3) (2006) 293–300.

7. Modi, N.B., 2007. In vitro–in vivo correlation. In: Chilukuri, D.M., Sunkara, G., Young, S. G. (Eds.), Pharmaceutical Product Development. Informa Healthcare USA, New York, pp. 107–123.

8. The Food and Drug Administration, U.S., 1997. Extended Release Solid Dosage Forms: Development, Evaluation and Application of In vitro/In vivo correlations. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf.

9. Finkelstein, A., McClean, D., Kar, S., 2003. Local drug delivery via coronary stent with programmable release pharmacokinetics. Circulation 107, 777–784.

10. Lincoff, A.M., Furst, J.G., Ellis, S.G., Tuch, R.J., Topol, E.J., 1997. Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. J. Am. Coll. Cardiol. 29, 808–816.

11. Shabbits, J.A., Chiu, G.N.C., Mayer, L.D., 2002. Development of an in vitro drug release assay that accurately predicts *in vivo* drug retention for liposome-based delivery systems. J. Control. Release 84, 161–170.