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Review Article

In-Vitro In Vivo Corelation

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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. Key factors include drug solubility, pKa, drug permeability, octanol-water partition coefficient and pH of environment. In general, construction of an IVIVC involves three stages of mathematical manipulation: construct a functional relationship between input (in vitro dissolution) and output (in vivo dissolution); establish a structural relationship using data collected; parameterize the unknowns in the structural model. Some key mathematical relationships used in IVIVC development are presented. The establishment of an effective IVIVC has important implications in quality control and regulatory compliance.

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 vitro 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 (FDA, 1997). 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 behavior. The establishment of a meaningful IVIVC can provide a surrogate for bioequivalence studies, improve product quality, and reduce regulatory burden. Since the pioneering works of Edwards (Edwards, 1951) and Nelson (Nelson, 1957) in correlating aspirin and theophylline dissolution rates with their respective in vivo appearances following oral administration, IVIVC has gained increasingly more significance in the pharmaceutical product development field. In

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particular, the emergence of new lipophilic drug candidates with low aqueous solubility demands special considerations during IVIVC model development. The objective of the present review is to examine the various factors that need to be considered in the development of an IVIVC, including physicochemical factors, biopharmaceutical factors, and physiological factors. We will discuss general approaches to developing an IVIVC. In particular, the steps associated with the construction of an IVIVC including modeling and data analysis will be addressed in detail. Lastly, the various applications of a meaningful IVIVC will be briefly described.

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 toward 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 three groups; 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.

Objective:

- To reduce the number of human studies during the formulation development.
- To serve as a surrogate for in vivo bioavailability
- To support biowaivers.
- To validates the use of dissolution methods and specification settings (This is because the IVIVC includes in vivo
- relevance to in vitro dissolution specifications).
- To assist quality control for certain scale-up and post- approval changes (SUPAC).
- Due to all above objective, such IVIVC leads to:

1. Shortens the drug development period.

2. Economizes the resources and

3. Leads to improved product quality

Need of IVIVC:

1) Theoretically, correlation of in-vivo absorption rate with clinical response will be the most worthwhile approach But, clinical approach is a poor tool for accurate measurement of bioavailability.

2) Determination of drug level at the site of administration would be next logical approach. But again, with some exceptions, it's impossible.

3) Urinary excretion analysis of drug is meaningful for establishing IVIVC but due to complicated pharmacokinetic considerations, such as drug metabolism and urine collection problems. Thus it is generally assumed that blood(serum/plasma) level measurements give a better assessment of bioavailability and bioequivalence.

4) This relationship is an important item of research in the development of drug delivery systems.

5) A good IVIVC model can explore the relationship between in vitro dissolution or release and in vivo absorption

profiles.

6) The IVIVC model relationship facilities the rational development and evaluation of immediate or extended release

dosage form as a tool for formulation screening, in setting dissolution specifications and as a surrogate for bioequivalence testing

Fundamentals Of IVIVC:

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 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

FDA Guidelines For IVIVC

The FDA Guidance, "Extended Release oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations," is more than 20 years old but remains the definitive source of regulatory thinking on IVIVC. At the time of its release, the ability to accurately and precisely predict expected BA characteristics for an extended release product from its dissolution profile had been a long sought-after goal. The recommendations within the guidance cover IVIVC for oral, extended release drug products that are being developed for regulatory review as part of an NDA, ANDA, or AADA. The

Guidance outlines:

- how to develop an IVIVC model
- how to evaluate predictability
- how to use IVIVC to establish specifications for dissolution
- how to apply IVIVC as a surrogate for in vivo BE studies.

IVIVC Of Novel 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 emp- tying 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.

Application:

a) IVIVC for transdermal estradiol systems (novel pharmaceuticals)

b) Why IVIVC fail for immediate release dosage form

c) Dissolution simulators:

i. Gronings model

ii. Sartorius dissolution simulator

iii. Sartorius membrane filter solubility simulator

iv. Sartorius membrane filter absorption simulator.

Approaches:

There are mainly of two approaches:

1.By establishing a relationship between the in-vitro dissolution and the in-sive bioavailability parameters.

2.By using the data obtained from previous bioavailability studies to modify the dissolution methodology in order to arrive at meaningful in-vitro in vivo correlation.

CONCLUSIONS

The establishment of in vitro / in vivo correlation (IVIVC) offers several significant advantages in pharmaceutical development. IVIVC enhances our

comprehension of dosage forms and serves as a predictive tool capable of reducing the necessity for specific clinical bioequivalence studies.

REFERENCES

1. D. M. Brahmankar, S. B. Jaiswal. Biopharmaceutics and Pharmacokinetics – A Treatise. Vallabh Prakashan, 2006, 138-160.
2. Amann LC, Gandal MJ, Lin R, Liang YL, Siegel SJ. In Vitro-In Vivo Correlations of Scalable PLGA-Risperidone Implants for the Treatment of Schizophrenia. Pharm. Res. 2010;27:1730–1737. doi: 10.1007/s11095-010-0152-4. [DOI] [PubMed] [Google Scholar]
3. Balan G, Timmins P, Greene DS, Marathe PH. In vitro-in vivo correlation models for metformin after administration of modified release oral dosage forms to healthy human volunteers. J. Pharm. 2001;90:1176–1185. doi: 10.1002/jps.1071. [DOI] [PubMed] [Google Scholar]
4. Bigora S, Piscitelli D, Dowell J. Use of nonlinear mixed effects modelling in the development of in vitro - in vivo correlations. In: Young D, Devane JG, Butler J, editors. Advances in Experimental Medicine and Biology. Plenum Press; New York: 1997. pp. 207–215. [DOI] [PubMed] [Google Scholar]
5. Buch P, Holm P, Thomassen JQ, Scherer D, Branscheid R, Kolb U, Langguth P. IVIVC for Fenofibrate Immediate Release Tablets Using Solubility and Permeability as In Vitro Predictors for Pharmacokinetics. J. Pharm. Sci. 2010;99:4427–4436. doi: 10.1002/jps.22148. [DOI] [PubMed] [Google Scholar]
6. Buchwald P. Direct, differential equation based in vitro - in vitro correlation method. J. Pharm. Pharmacol. 2003;55:495–504. doi: 10.1211/002235702847. [DOI] [PubMed] [Google Scholar]
7. Carlson JA, Mann HJ, Canafax DM. Effect of pH on disintegration and dissolution of ketoconazole tablets. Am. J. Hosp. Pharm. 1983;40:1334–1336. [PubMed] [Google Scholar]
8. Dokoumetzidis A, Papadopoulou V, Macheras P. Analysis of dissolution data using modified versions of Noyes-Whitney equation and the Weibull function. Pharm. Res. 2006;23:256–261. doi: 10.1007/s11095-006-9093-3. [DOI] [PubMed] [Google Scholar]
9. Dressman JB, Amidon GL, Fleisher D. Absorption potential: estimating the fraction absorbed for orally administered compounds. J. Pharm. Sci. 1985;74:588–589. doi: 10.1002/jps.2600740523. [DOI] [PubMed] [Google Scholar]
10. Dunne A. Approaches to developing in vitro-in vivo correlation models. In: Chilukuri DM, S G, Young D, editors. Pharmaceutical Product Development. Informa Healthcare USA; New York: 2007. pp. 47–70. [Google Scholar]
11. Eddington ND, Marroum P, Uppoor R, Hussain A, Augsburger L. Development and internal validation of an in vitro-in vivo correlation for a hydrophilic metoprolol tartrate extended release tablet formulation. Pharm. Res. 1998;15:466–473. doi: 10.1023/a:1011988601696. [DOI] [PubMed] [Google Scholar]
12. Edwards LJ. The dissolution and diffusion of aspirin in aqueous media. Trans. Faraday Soc. 1951;47:1191–1210. [Google Scholar]
13. The Food and Drug Administration, U.S. Extended release solid dosage forms: development, evaluation and application of in vitro/in vivo correlations. 1997 doi: 10.1007/978-1-4684-6036-0_25. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf. [DOI] [PubMed]

14. The Food and Drug Administration, U.S. FDA Guidance for Industry. - Waiver on in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics classification systems. 2005 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf.
15. Finkelstein A, McClean D, Kar S. Local drug delivery via coronary stent with programmable release pharmacokinetics. Circulation. 2003;107:777–784. doi: 10.1161/01.cir.0000050367.65079.71. [DOI] [PubMed] [Google Scholar]
16. Finkelstein L, Carson ER. Mathematical modelling of dynamic biological systems. 2nd ed John Wiley & Sons; New York: 1985. [Google Scholar]
17. Hansch C, Fugita T. Rho-sigma-pi analysis. A method for the correlation of biological activity and chemical structure. J. Am. Chem. Soc. 1964;86:1616–1626. [Google Scholar]
18. Johnson KC, Swindell AC. Guidance in the setting of drug particle size specification to minimize variability in absorption. Pharm. Res. 1996;13:1795–1798. doi: 10.1023/a:1016068705255. [DOI] [PubMed] [Google Scholar]
19. Kramer SD. Absorption prediction from physicochemical parameters. Pharm. Sci. Technol. 1999;2:373–380. doi: 10.1016/s1461-5347(99)00188-1. Today. [DOI] [PubMed] [Google Scholar]
20. Kutner M, Nachtsheim C, Neter J, Li W. Applied linear statistical models. 5th ed McGraw-Hill; New York: 2004. [Google Scholar]
21. Langenbucher F. Handling of computational in vitro/in vivo correlation problems by Microsoft Excel II. Distribution of functions and moments. Eur. J. Pharm. Biopharm. 2003;55:77–84. doi: 10.1016/s0939-6411(02)00115-7. [DOI] [PubMed] [Google Scholar]
22. Li SF, He HD, Parthiban LJ, Yin HQ, Serajuddin ATM. IVIVC considerations in the development of immediate-release oral dosage form. J. Pharm. Sci. 2005;94:1396–1417. doi: 10.1002/jps.20378. [DOI] [PubMed] [Google Scholar]
23. Lincoff AM, Furst JG, Ellis SG, Tuch RJ, Topol EJ. Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. J. Am. Coll. Cardiol. 1997;29:808–816. doi: 10.1016/s0735-1097(96)00584-0. [DOI] [PubMed] [Google Scholar]
24. Mendell-Harary J, Dowell J, Bigora S. Nonlinear in vitro - in vivo correlations. In: Young D, Devane JG, Butler J, editors. Advances in Experimental Medicine and Biology. Plenum Press; New York: 1997. pp. 199–206. [DOI] [PubMed] [Google Scholar]
25. Modi NB. In vitro-in vivo correlation. In: Chilukuri DM, S G, Young D, editors. Pharmaceutical Product Development. Informa Healthcare USA; New York: 2007. pp. 107–123. [Google Scholar]
26. Nelson E. Solution rate of theophylline salts and effects from oral administration. J. Am. Pharm. Assoc. Sci. 1957;46:608–614. doi: 10.1002/jps.3030461012. [DOI] [PubMed] [Google Scholar]
27. Ochoa L, Igartua M, Hernandez RM, Solinis MA, Gascon AR, Pedraz JL. In vivo evaluation of two new sustained release formulations elaborated by one-step melt granulation: Level A in vitro-in vivo correlation. Eur. J. Pharm. Biopharm. 2010;75:232–237. doi: 10.1016/j.ejpb.2010.02.008. [DOI] [PubMed] [Google Scholar]

28. Polli JE, Crison JR, Amidon GL. Novel approach to the analysis of in vitro-in vivo relationships. J. Pharm. Sci. 1996;85:753–760. doi: 10.1021/js9503587. [DOI] [PubMed] [Google Scholar]
29. Serajuddin ATM, Jarowski CI. Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical bases and their hydrochloride salts. J. Pharm. Sci. 1985;82 doi: 10.1002/jps.2600740208. [DOI] [PubMed] [Google Scholar]
30. Shabbits JA, Chiu GNC, Mayer LD. Development of an in vitro drug release assay that accurately predicts in vivo drug retention for liposome-based delivery systems. J. Control. 2002;84:161–170. doi: 10.1016/s0168-3659(02)00294-8. Release. [DOI] [PubMed] [Google Scholar]
31. Shore PA, Brodie BB, Hogben CAM. The gastric secretion of drugs: a pH partition hypothesis. J. Pharmaco.l Exp. Ther. 1957;119:361–369. [PubMed] [Google Scholar]
32. Sirisuth N, Augsburger LL, Eddington ND. Development and validation of a nonlinear IVIVC model for a diltiazem extended release formulation. Biopharm. Drug Dispos. 2002;23:1–8. doi: 10.1002/bdd.270. [DOI] [PubMed] [Google Scholar]
33. Winne D. Shift of pH-absorption curves. J. Pharmacok. Biopharm. 1976;5:53–94. doi: 10.1007/BF01064809. [DOI] [PubMed] [Google Scholar].

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