WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 11, 764-778 Review Article ISSN 2278 – 4357

THE COMPARITIVE STUDY OF IVIVC CORRELATION AND ITS INTERPRETATION

Bogadi Subhasri, Prof. K. Thyagaraju and Vothini Sarath Babu*

S.V.U. College of Pharmaceutical Sciences, S.V. University, 517502, A.P.

Article Received on
05 Sept. 2018,

Revised on 25 Sept. 2018,
Accepted on 15 October 2018

DOI: 10.20959/wjpps201811-12645

***Corresponding Author**
Vothini Sarath Babu
S.V.U. College of Pharmaceutical Sciences, S.V. University, 517502, A.P.

ABSTRACT

The in vitro- in vivo correlation is important for development of dosage form. In vitro dissolution studies are not sufficient for explain therapeutic activity of drug. So IVIVC is one of mathematical model which is used to explain a relation between in vitro dissolution and in vivo bioavailability. In vitro dissolution means process of release of drug from dosage form which reflect a bioavailability where as in vivo, release of drug from gastrointestinal tract must reflect the profile of dosage form in order to assure a biological response. The main purpose of studying IVIVC is product development and surrogate for in vivo studies to support biowaivers also allow the setting dissolution specification and methods. The pharmaceutical industries are in search of way that can save a cost and resources of drug development. The IVIVC fixes dissolution acceptance criteria and also used in bioequivalence study. The different levels of IVIVC was proposed for oral dosage forms and later adopted globally. Currently the four levels are categorised by FDA depending upon type of data used to establish relationship and predict the complete plasma profile of dosage form.

KEYWORDS: IVIVC correlation, dissolution, Interpretation.

ABBREVATION: IVIVC means in vitro –in vivo correlation, MRT-mean residence time, MDT –mean in vitro dissolution time.

In Vitro In Vivo Correlation (IVIVC)

In vitro dissolution refers to the process of dissolution (release) of drug from a dosage form as measured in an in vitro dissolution apparatus.[6]

In vivo dissolution refers to the process of dissolution of drug in gastrointestinal tract.[1]

- In vitro in vivo correlation is a predictive mathematical model describing the relationship between in vitro property and release form of dosage form and a relevant in vivo response.[6]
- Dissolution method (in vitro) must reflect the bioavailability (in vivo) profile of the dosage form in order to assure biologic response.[6]
- In IVIVC, 'C' denotes "CORRELATION'' which means the degree of relationship between two variables. This term does not limit a relationship to only the linear type but allows for non linear relationship as well.[4]
- For drug products intended for systemic activity the biological property produced by the dosage form is usually assumed to be related to the presence of the drug in the systemic circulation i,e., the pharmacokinetic profile. As the elimination process is generally not affected by the dosage form. the process of the drug into the general circulation is likely to govern the degree to which the biological property is produced by the dosage form.[4]
- On the in vitro side, the dissolution of this process is the most frequently in vitro variables used to generate an IVIVC.[4]
- In vitro properties are rate (or) extent of drug released under a given set of conditions.[15]
- In vitro properties are plasma drug concentration expressed in terms of c_{max}, AUC.[4,15]

Apporoches for the Correlating In vitro Dissolution Data with Plasma Data

The basic approaches by which the correlation between dissolution testing and bioavailability are.[6]

1. Predicting the mathematical models (linear relationship) between the in vitro dissolution testing and existing bioavailability data.
2. Modifying the dissolution methodology the basis of existing bioavailability and clinical data.[1,6]

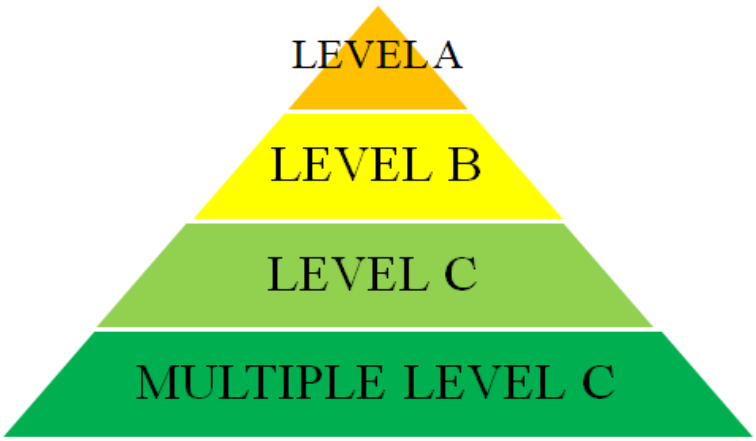
Though the former approaches is widely used. The later is under investigation. Since no single dissolution test methodology can be applied to all the drugs. A proper dissolution method is chosen. So that the rate of dissolution of the product may be corrected to the rate of absorption of the drug in the body. For certain drug products, bioavailability may be demonstrated by evidence obtained in vitro in levels of in vivo.[6]

Parameters used for correlating in vitro dissolution with plasma data.[3]

INVITRO parameters	INVIVO parameters
Time for specific amount dissolved (eg.50% of the dose dissolved)	Area under the concentration in blood stream Vs time curve. Maximum concentration in blood stream.
Amount dissolved at specific time point.	Fraction absorbed, absorption rate constant.
Mean dissolution time	Mean residence time, mean dissolution time, mean absorption time.
Parameters estimated after modaling the dissolution process.	Concentration at time t Amount absorbed at time t

Levels of IVIVC[1]

There are four levels of IVIVC that have been described in the FDA guidance, which include levels A,B,C and Multiple c.



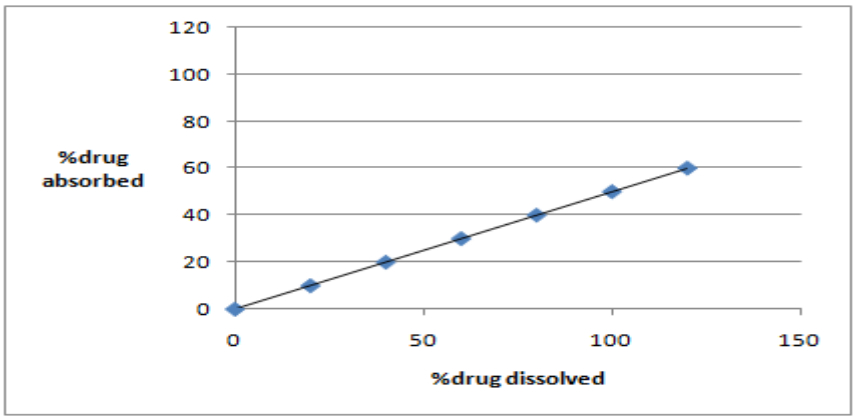
The concept correlation level is based upon the ability of the correlation to reflect the complete plasma drug level time profile which will result from administration of the given dosage form.[1]

Level A Correlation

a. In level A, it correlates the entire in vitro and in vivo profile has regulatory relevance.
b. It gives a point - point variation. So it gives a super impossible curve.[3]
c. Usually correlation is linear and no formal guideline on the non linear IVIVC.
d. Estimation of in vitro absorption (Fa) and fraction of drug dissolved (fd) in vitro obtain a linear correlation.

Purpose; Define Direct Relationship

- In Formulation, level A correlation require no additional human studies to justify change in manufacturing site raw material supplier (or) minor formulation changes.
- Most informative and very useful from a regulatory perspective.



Importance of Level A Correlation

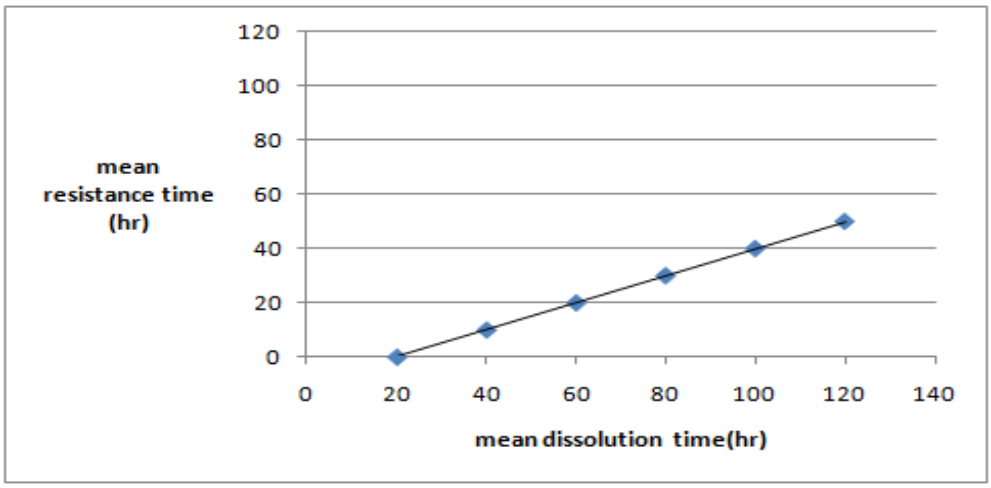
- It serves as indicating quality control procedures for predicting dosage form performance.[5]
- Determining a stable release characteristics of the product over time
- It developes a point to point correlation.[5]
- Because a super impossible curves, the in vitro data is alternative to in vivo data.[11]

Level B Correlation

- It is based on the principle of statistical moment analysis.[5]
- In this level of correlation, the mean in vitro dissolution time (MDT vitro) of the product is compared either mean residence time (MRT) or the mean in vivo dissolution time (MDTvivo0.[1]
- It compares.[4]

1) MDT vitro to MDT in vivo
2) MDT vivo to MRT
3) In vitro dissolution rate constant (Kd) to absorption rate constant (ka)

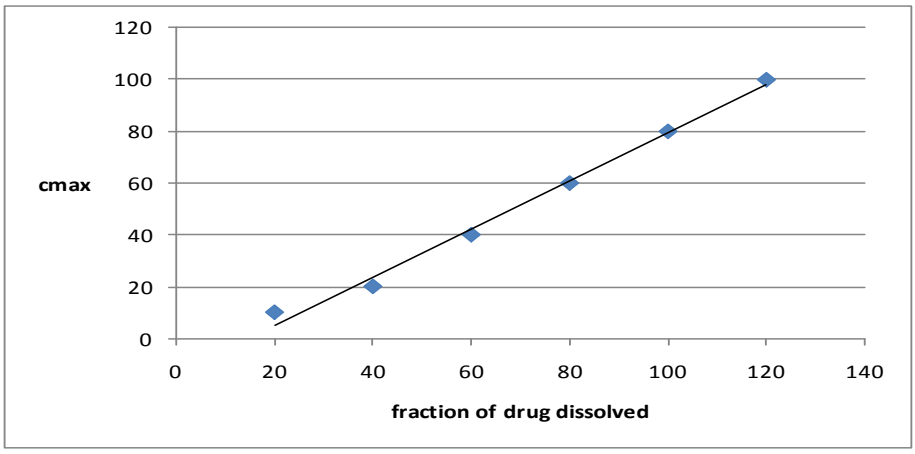
This type of correlation uses all of the in vitro and in vivo data. But least useful for regulatory purposes because more than one kind of plasma curve produces similar MRT.[6]



Limitations

- Level B correlation is not unique. Because MRT remains same though, the shape of in vitro curves is different. Therefore, to justify the formulation modifications.[7]
- It is not suitable for the quality control studies.[4]
- This type of correlation alone fails to justify a formulation, modification, manufacturing site etc.[5]

Level C Correlation



- Predictive mathematical model which relates one dissolution time point to one pharmacokinetic parameters that characterizes in vivo time course (eg,. Cmax AUC, tmax).
- It can be useful in the early stages of formulation development when piolet formulations are being selected.
- It does not reflect a complete a shape of plasma concentration time curve. It is lowest correlation level.[9]

Multiple Level Correlations

- This type of correlation should be based on at least three dissolution time points covering the early, middle, and late stages of the dissolution time profile.[1,2]
- It relates one (or) more pharmacokinetic parameters to the percent drug dissolved at several time points of dissolution profile thus may be more useful.[1]
- When this correlation is achieved at time point at the same parameter such that the effect on the in vivo performance of any change in dissolution can be assessed.[19]

Level D Correlation

- It is semi quantitative (qualitative analysis) and rank order correlation and it is not considered useful for regulatory purpose.[9]
- It serves as aid in the development of formulation.[20]

TABLE:

LEVEL	INVITRO	INVIVO
A	Dissolution curve	Input (absorption curve)
B	Statistical moments: mean dissolution time(MDT)	Statistical moments: Mean residence time (MRT), mean absorption time(MAT)
C	Disintegration time, time to have 10%, 50%, 90% dissolved, dissolution rate, dissolution efficiency (DE)	Maximum observed concentration (c_{max}), observed at time (t_{max}), absorption constant ($k_{a)}$ time to have 10,50,90% absorbed, AUC(total (or)cumulative)

A: one to one relationship between invitro and in vivo data.[1]

eg; Invitro dissolution v_s invivo absorption

B: correlation based on statistical moments

eg; Invitro MDT v_s invivo MRT

C: point to point relationship between a dissolutionand pharmacokinetic parameters (2)

eg; Invitro 150% v_s invivo T_{max}

Multiple C: Relationship between one (or) several Pk parameters and amount dissolved at several time points.

Mathematical Techniquies[15]

Assessment of in vivo drug release or absorption from plasma level time profile.

- **Model Dependendent**

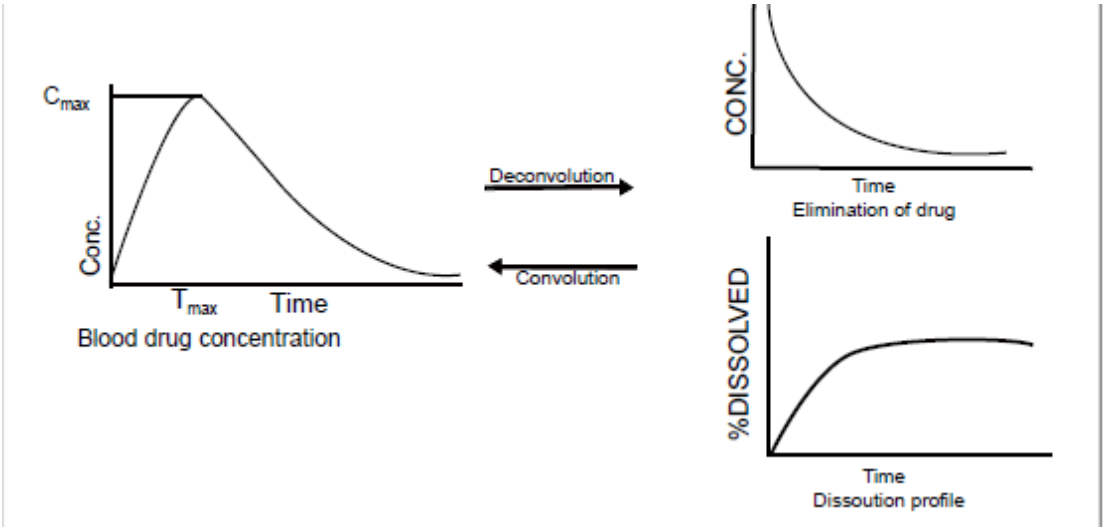
Based on the mass balance among the pharmacokinetic compartments (Wagner- Nelson, loo-Riegelma).

- **Model Independent**

Based on linear system analysis (convolution & Deconvolution).

Models

- It is generally assumed that absorption and dissolution have a linear relationship hence dissolution and absorption characterstics of drug are commonly shown interchangeably.[12]
- It is to be noted that one should be able to establish drug profiles with dissolution profiles combined with the pharmacokinetic characterstics of the drug.[7]
- This process of obtaing a drug profile from dissolution results is known as "**CONVOLUTION ''**[4]
- The opposite of this i.e,. obtaining (or)extracting a dissolution profile is know n as **"DECONVOLUTION"**.[4]



Convolution

- ✓ In the development of convolution model the drug concentration time profiles obtained from dissolution results may be evaluated using for in vivo bioavailability /bioequivalence assessment based on C_{max} and AUC parameters.[9]
- ✓ In mathematical terminology, dissolution results become an input function and plasma concentrations (eg from IV) become a weighing factors (or) the solid oral product.[9]

- ✓ Using the NONMEM package, a non linear mixed effects model can be fitted to the data with time scale model linking the invitro and invivo components.[10]
- ✓ It has been demonstrated that the convolution based and differential equation based models can mathematically equivalent.[2]
- ✓ The results are more readily interpreted in terms of in vitro release on conventional bioequivalence metrics.[12]

Mathematically we can write the convolutions are

$$c(t) = c\infty(t)f(t) = \int_o^t c6(t)F(t - C)dt$$

Where C(t) = plasma drug concentration after oral dose

C(t) = plasma concentration after an iv dose (or) a dose of oral solution

Upon taking the derivative of c(t) with respect time

$$c(t) = c\infty(t)F(t) = c\infty(0)\int_0^t F(₮)dt$$

When $c\infty(0) = 0$

$$c\infty(t) \times f(t)$$

Advantages of this approach relative to deconvolution based IVIVC approaches include the following: the relationship between measured quantities (In vitro release & plasma drug concentration) is modelled directly in a single stage rather than via an indirect two stage approaches.[1]

Deconvolution

- ✓ It is a numerical method used to estimate the time course of drug input using a mathematical model based on the convolution integral.[10]
- ✓ Based on the IVIVC model, the predicted fraction of the drug dissolved. it is most commonely used method the literature.
- ✓ This technique requires a comparision between in vivo dissolution data with in vitro dissolution profiles
- ✓ Based on this model the prediction fraction drug is calculated from observed fraction drug dissolved.[11]
- ✓ A major limitations of this approach is that it often multiple products having potentially different in vivo release.[12]

- ✓ These products are then used to define experimental conditions (Medium apparatus etc,.) for a appropriate dissolution test to reflect their behaviour.[11]

Interpretation of In vitro Dissolution Studies /Data

The performed in vitro dissolution studies either pass (or) fail is determined depends up on "Q" value which defines as the drug dissolved at specific time interval. according to USFDA the invitro dissolution studies should performed in 3 phages.

Phage 1

In vitro dissolution studies should be performed with 6 dosage units.

- In which average of 6 dosage units should be Q+5
- Not more than 2 dosage units cont Q-5

Phage 2

- If phage 1 is failed, the invitro dissolution studies are continued with additional 6 dosage forms.
- The average of 12 dosage units (phage-1 + phage -2)should be not less than (or) equal to (≤)Q.
- Not more than 2 dosage forms contain Q-15.
- None of one dosage units contain Q+25.

Phage 3

- If phage2 is failed then dissolution studies are continued with additional 12 dosage units.
- Average of 24 dosage units (phage -1+2+3) should be (≤ Q).
- Not more than 2 dosage units contain Q-25.
- None of one dosage unite contain Q+15

Comparitive Dissolution Studies

The dissolution testing requires multiple time points in case of modified release dosage forms, in this case IVIVC plays a very important role in setting these specification.[21] IVIVC starts by obtaining a reference dissolution profile.[21] The dissolution batches with different properties (fastest to slowest) should be used along with the IVIVC model, prediction of concentration time profiles should be made using a appropriate convolution method .Specifications should established to all batches with dissolution time profiles between the fastest and slowest batches are bioequivalent and less in reference batch[15] the above

specifications should allow the majority of batches to pass and is possible only if valid level A model.[15]

The in vitro dissolution studies of reference (branded) and test ((generic) dosage units are compared by using Q value.

Conditions for Comparitive Dissolution

- Minimum 12 dosage units should be considered.[22]
- For test and reference dosage units maintain same dissolution time intervals.
- Minimum 3 dissoluion points should be considered.[17]

Calculation

The in vitro dissolution studies of test and reference products can be calculating by using 2 factors f_1 and f_2.

F_1(dissimilarity factor)

It explains the difference between test and reference dosage units.

It obtained by using Q value.

It is calculated by using an equation

$$f1 = \frac{£(Rt-Tt)^2}{\sum Rt} \times 100$$

F2 (similarity factors)

It explain similarity between test and reference dosage units.

It obtained by using a Q value

It is calculated by using an equation

$$f2 = 50 \log\left(\frac{1}{\sqrt{1+\frac{£Rt-Tt}{n}}}\right)100$$

R_t = percentage drug dissolved from reference at time t.

n= number of dissolution points

T_t= percentage drug dissolved from test at time t

Interpretation of Data

If f_1 value is between 1-15, indicates a similarity between test and reference dosage units.

If $f_2$vvalue is between 50-100 indicates a similarity between test and reference dosage units.

If f_2 value is 100 indicates ideal with reference.

If test and reference products release more than 85% of drug release after 15% then there is no need to compare the dissolution studies.

Need for IVIVC

- Determination of drug level at the site of administration.[21]
- Urinary excretion analysis of drug is meaningful for establishing IVIVC but complicated pharmacokinetic considerations.[18]
- Thus it generally assumed that blood (serum /plasma)level measurements which gives a better assessment of bioavailability and bioequivalence.[13]
- Theoretically worthwhile, but clinical approach is a poor tool for accurate measurement of bioavailability.[16]

Some of the Often Used Quantitative Linear Invitro and Invivo Correlation Are

- **Correlation based on plasma level data**

Here linear relationships between dissolution parameters and plasma level data containing percentage absorption, rate of absorption and absorption constant.

INVITRO parameters	INVIVO parameters
1. % dissolution	% Absorption
2. Dissolution rate (or) rate of dissolution	Rate of absorption
3. Dissolution rate constant	Absorption rate constant

- **Correlation based on urinary excretion data**

Here, dissolution parameters are correlate the amount of drug excreted unchanged in the urine, cumulative amount of drug excreted as a function of time etc.

INVITRO parameters	INVIVO parameters
1. %dissolution	% Excretion
2. Rate of dissolution	Rate of excretion
3. Dissolution rate constant	Excretion rate constant

- **Correlation based on the pharmacological response**

An accurate pharmacological effect such as CD_{50} in animals relates to any of the dissolution parameters.

Several factors that limit such a correlation include dissolution methodology physicochemical properties of drug, physiological variables.[6]

Application of An IVIVC(2,3)

1. Application in drug delivery system

- Various rate controlling technologies are used as basis for modified release dosage forms.[15]

  eg, diffusion –dissolution, matrix retardation, osmosis etc,. to control and prolong the release of drug.
- The obvious objectives of these dosage forms is to achieve zero order long term, pulsatile delivery.[16]
- Novel drug delivery systems have been developed such as OROS, liposomes, niosomes, pharmacosomes microspheres nanoparticles, implants etc,. as substitute for conventional dosage forms.

2. In a early stages of drug delivery technology development

- During this stage, IVIVC(exploring the relationship between incitro and invivo properties) of the drug in animals models provide an idea about the flexibility of the drug delivery system for a given drug caandiates.
- The most crucial stage in drug development in drug candidate selection. Such selection is primarily based on the drug " developability" criteria which includes physico-chemical properties of drug and finally results obtained from preformulation
- The preliminary studies involving several in vitro systems and in vivo animal models which serves as efficacy and toxicity issues.[15,22]

3. Formulation assessment: In vitro dissolution[17]

- **A** suitable dissolution method that is capable of distinguish the performance of formulation with different releas rates invitro and invivo is an important tool in product development.
- on further changes, dissolution method can be made. Depending on the nature of the correlation

4. Dissolution specification[10,23]

- Modified release dosage forms typically requires a dissolution testing over multiple time points, IVIVC plays an important role in setting these specifications.
- Specification time profiles are usually chosen in the early, middle, late stages of dissolution profiles.

- In presence of IVIVC, wider specifications may be appilicable based on predictive concentration –time profiles of test batches being bioequivalent to the reference batch.

5. IVIVC parentral drug delivery

- IVIVC can be applied and developed to parentral dosage forms, such as controlled release particulate systems, depot systems, implants etc,. that are either injectiond (or) implanted.[8]
- However, therare relative; y fewer successes in the development of IVIVC for such dosage forms, which could be due to several reason.[14]
- Sophisticated modeling techniquies are needed to correlate the invitro invivo data, incase of burst release which is unpredectible and un avoidable.[8]
- In certain cases, deviations should acceptable up to maximum range of 25%, beyond this range, the specifications should support by bioequivalence studies.[10]

6. Future biowaivers

Frequently drug development requires changes in formulations due to variety of reasons such as unexpected problems in stability, development etc,. The established IVIVC can help to avoid bioequivalence studies by using dissolution time profile from changed formulation, predicting the in vivo concentration time profile.[15,23] The surrogate of the in vivo bioequivalence study has one of the cost saving benefit in the form of reduced drug development and speed implementation of post approval changes.[24]

Limitations of IVIVC

1. Complexibility of the drug absorption

A number of biological factors influence the drug absorption. these factors can not be mimicked in invitro.[6]

2. Weakness of the dissolution designs

Being in vitro model, it is natural to have certain limitations. The physics of tablating as well as nature of mechanical and hydrodynamic forces that are operate during dissolution are not well understood.[6]

More than one dosage form is needed and if possible intravenous or solution is essential to calculate deconvolution.

CONCLUSION

IVIVC can serve as the surrogate for in vivo bioavailability and to support biowaivers also setting the dissolution specification and methods. IVIVC is a tool applied in various areas and stages of drug development to find a place in the regulatory bodies around the world. It can serve as surrogate for in vivo bioavailability and to support biowaivers also allows setting the dissolution specification and methods. The substitute of expensive clinical trials with the use of IVIVC is purchase the most important feature of IVIVC. (2)From the regulatory point of view IVIVC can assist certain scale up and post approval changes. Pharmaceutical industry has been striving to find a ways to saving precious resource in relevant to the budgets and increasing the cost of drug development from regulatory point of view IVIVC can assist certain scale-up and post approval changes.

REFERENCES

1. Sakore s. chakraborty B. in vitro-in vivo correlation (IVIVC) a stradegic tool in drug development j.bioequivalent avsilable, 2011.
2. Uppoor VRS(2001)regulatory perspectives on invitro (dissolution) /invivo (bioavailability) correlation, Jcontrol Ref., 72: 127-132.
3. Food and drug administration (1997) guidences for industry: extended release oral dosage form :development, evalution, and application of in vitro-in vivo correlation.
4. Pharmaceutical dissolution testing, author, (dressman & kramen) pg. no 233.
5. Uppoor VRS(2001)regulatory perspectives on invitro (dissolution) /invivo (bioavailability) correlation, Jcontrol Ref., 72: 127-132.
6. Subhramanyam cvs, biopharmaceutics and pharmacokinetics concepts and application. 1st edn. Delhi. vallabh prakashan 2010-164p.
7. Brahmankar DM, Jiswal sb, biopharmaceutics and pharmacokinetics –A treatise 2nd edition. delhi :vallabh prakashan: 2009-329p.
8. Shargel C Andrew Yu-applied biophaarmaceutics and pharmacokinetics 2nd edition, singapoor, the Megraw-Hill companies: 2012222,380-36p.
9. Jaber E (2006) in vitro in vivo correlation: from theory to aplications, J. pharmaceutical sciences, 9: 169-189.
10. Young D chiluker D.becker R, Biogra S, Farrell C(2002) approaches to developing level A.IVIVC for injectable dosage forms, AAPS pharmascciences, 4: M1357.
11. Gaunor C, donne A, davis (2004)a differential equatios approaches to invitro –invivo correlation modeling, international conference dobulin.

12. Gaynor C.dunne A, davis J (2008).a differential equations approach to invitro –invivo correlation modelling. international biometric conference Dublin.
13. Food and drug administration, Rockville, MU. Abdou, HM(1998)dissolution bioavailability and bioequivalemce. easton pennsylavania. mock printing.
14. Dunne A (2007) approaches developing IVIVC models, ch5. In chilukuri, sunkaraand young (eds) pharmaceutical product development : in vitro-in vivo correlation. Taylor and francis new yorcorrelation. Tak.
15. chilukur DM, sunkara g(2003) IVIVC: an important tooli in the drug delivery systems. drug deliv technol, 3: 4.
16. Young D, devane JG, Butler J(1997) in vitro in vivo correlations. new York;plenum press
17. Young D, chilukuri D, Becker R, Biora s, farrellc, et al.(2002)approaches to developing level –A IVIVC for injectable dosage forms. AAPS pharm sci., M1357.
18. shargel L,YU ABC (1993) applied biopharmaceutics and pharmacokinetics. East Norwark, Connecticut: Appleton & lange. 36 galia E, Nicolaides E.
19. Jaber E (2006) in vitro –in vivo correlation: from theory to applications. J pharm pharmaceuticals sci., 9: 169-189.
20. SirisuthN, Eddington ND(2002) in vitro in vivo correlations, systemic methods for the development and validation of an IVIVC metoprolol and naproxen examples. Int J generic drugs, 3: 250-258.
21. Modi NB, lam A, linddemulder E, Wang B, gupta SK(2000) application of in vitro –in vivo correlation (IVIVC) in setting formulation release specifications. Biopharm drug dispos, 21: 321-326.
22. Venkatesh s, Lipper RA(2000) role of the development scientist in compound lead selection and optimization. J pharm sci., 89: 145-154.
23. Hwang SS, Gorsline JJ, Louie J, dye D, Guinta D, et al. (1995) in vitro in vivo evalution of once daily controlled release pseudoephedrine product. J clin pharmacol, 35: 259-267.42.
24. FDA (1997)Guidence for industry : SUPAC-MR :Modified release solid oral dosage forms :scale-up and post approval changes :chemistry, manufacturing and contros, in vitro dissolution testing, and in vivo bioequivalence testingand in vivo bioequivalence documentation.