आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

**IFTM University, Moradabad, Uttar Pradesh**

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# E-Content

# IFTM University, Moradabad

# Bioavailability and Bioequivalence:

## In vitro In vivo Correlation

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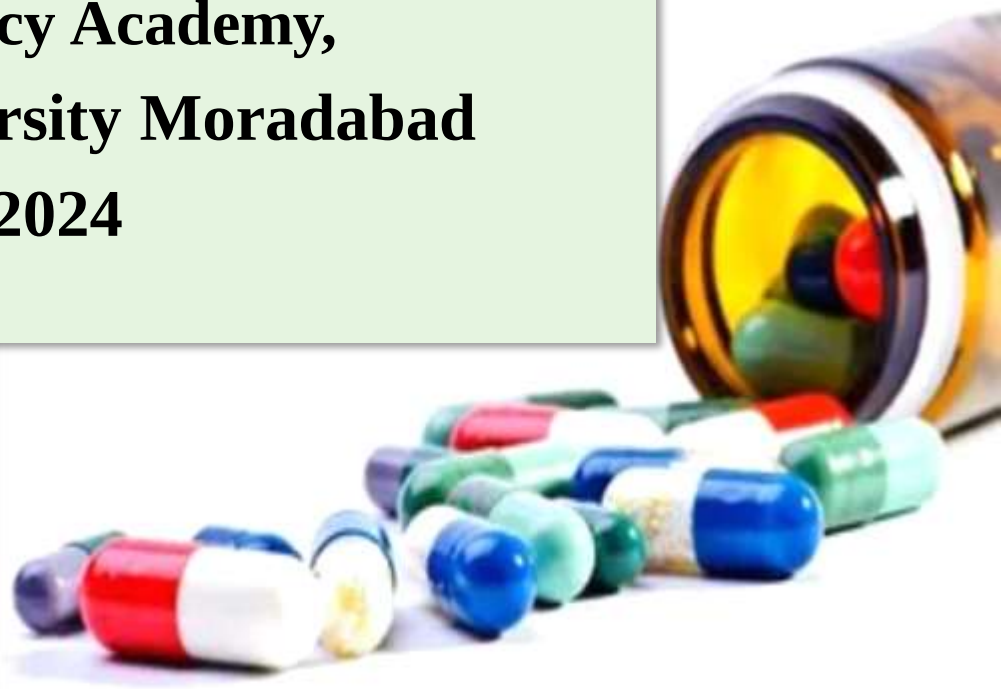
**2024**



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# INTRODUCTION

## Definition

- USP- Establishment of a rational relationship between a biological parameter, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of same dosage form.
- FDA- Predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and a relevant *in vivo* response.

# Important role of IVIVC

- It serves as a surrogate of in vivo and assists in supporting biowaivers.
- Supports the use of dissolution methods and specifications.
- Assists in quality control during manufacture and selecting appropriate formulations.

# Bio pharmaceutical classification system

- Bio pharmaceutical classification system (BCS) is a fundamental guideline for determining the conditions under which IVIVC's are expected.
- It is also used as a tool for developing the *in vitro* dissolution specification.
- BCS is associated with dissolution and absorption model which considers the key parameters controlling drug dissolution and absorption as a set of dimensionless numbers:

  a) The absorption number

  b) The dissolution number

  c) The dose number

# The Absorption Number

- It is the ratio of the mean residence time ($T_{res}$) to the mean absorption time ($T_{abs}$).
- It can be calculated by:

$$A_n = T_{res} / T_{abs}$$
$$= (\Pi R^2 L/Q)/ R/P_{eff}$$

where,

L= Tube length

R= tube radius

Q= fluid flow rate

$P_{eff}$ = effective permeability

# The Dissolution Number

- It is the ratio of the mean residence time to mean dissolution time.

$$D_n = T_{res} / T_{diss}$$

$$= \frac{\Pi R^2 L/Q}{\rho r_o^2 / 3DC_s^{min}}$$

where

P= Partial density

$r_o$= Initial particle radius

D= Particle acceleration

$C_s^{min}$ =Minimum aqueous solubility in the physiological pH range of 1 to 8.

# The Dose Number

- It is the ratio of dose to the product of volume of 250 ml and drug's solubility.

$$D_0 = \text{Dose} / V_0 * C_s^{min}$$

Where,

$V_o$ = Initial gastric volume equal to 250 ml derived from typical bioequivalence study protocols.

# Table 1: BCS and expected IVIVC

| Class | Solubility | Permeability | Absorption rate control step | IVIVC |
|---|---|---|---|---|
| I | High | High | Gastric emptying time | Correlation (if dissolution is slower than GET) |
| II | Low | High | Dissolution | Correlation |
| III | High | Low | Permeability | Little or no correlation |
| IV | Low | Low | Case by case | Little or no correlation |

# CORRELATION

1) IN VITRO STUDIES

Dissolution rate testing

- Dissolution testing has emerged as a highly valuable test to characterize the drug product performance.
- It is possible to predict accurately and precisely absorption or *in vivo* release profile and expected bioavailability for a drug based on its *in vitro* dissolution profile parameters.
- A validated dissolution test can minimize the use of extensive, expensive and time consuming bioequivalence studies involving humans as subjects.

- Table 2: Some parameters required to be controlled during *in vitro* dissolution testing

| S No | Parameters to be controlled | Conditions |
|---|---|---|
| 1 | Apparatus | Rotating basket, paddle type, flow through cell, reciprocating cylinder |
| 2 | Speed of rotation | 100 rpm (capsules), 50 rpm (tablets), 25 rpm (suspensions) |
| 3 | Temperature | 37±0.50 |
| 4 | pH | Varies (1.2 to 7.6) |
| 5 | Samples | 12 |
| 6 | Dissolution media | Buffers or simulated GI fluids |
| 7 | Sampling time | Frequent sampling till NLT 75-80% drug release |

- The following variables derived from such *in vitro* studies can be correlated with the *in vivo* data.

i. Time for some percent of the drug to dissolve *in vitro*.

ii. Concentration of solution at a given time.

iii. Percent dissolved Vs time plots.

iv. Rate of dissolution Vs time plots.

v. First order plot of percent not dissolved Vs time.

- Comparision between dissolution profiles could be achieved using

a) Difference factor (f1)

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t]\} * 100$$

Where,

$R_t$ is dissolution value of reference batch at time t

$T_t$ is dissolution value of test batch at time t

b) Similarity factor (f2)

$$f2 = 50 * \log \{[1+(1/n) \sum (Rt-Tt)^2]^{-0.5}] * 100$$

f1 exists from 0 to 15

f2 exists from 50 to 100

## 2) IN VIVO STUDIES

- FDA requires *in vivo* bioavailability studies to be conducted for a new drug approval (NDA).
- Bioavailability studies are normally performed in young healthy male human volunteers under some restrictive conditions.
- The drug is given in a cross over fashion with a washout period of at least 5 half lives.

- The bioavailability can be assessed via plasma/urine data using

i. AUC
ii. $C_{max}$
iii. Rate of drug excretion in urine (dDu/dt).
iv. $T_{max}$

- Several approaches can be employed for determining in vivo absorption

i. Wagner Nelson method
ii. Loo Riegelman method
iii. Numerical Deconvolution method

- Wagner Nelson method is used for one compartment model, Loo Riegelman method is used for multi compartment model and the numerical Deconvolution method is model independent method.

# i. Wagner Nelson Method

- It is less complicated than Loo Riegelman method
- The cumulative amount of drug absorbed at time t is calculated using

$$F_T = \frac{C_T + K_E \int_0^T C\,dt}{K_E \int_0^\infty C\,dt}$$

Where

$C_T$ is plasma concentration at time T

$K_E$ is elimination rate constant

# ii. Loo Riegelman Method

- This method requires drug concentration time data after both oral and intravenous administration of the drug to the same subject and the fraction of drug absorbed at any time t is given by

$$F_T = \frac{C_T + K_{10} \int_0^T C\,dt + (X_P)T / V_C}{K_{10} \int_0^\infty C\,dt}$$

where

$(X_P)T$ is the amount of drug in peripheral compartment as a function of time

$V_C$ is the apparent volume in central compartment

$K_{10}$ is the apparent first order elimination rate constant

# iii. Deconvolution Method

- It is a numerical method used to estimate the time course of drug input.
- For example., the absorption rate time course ($r_{abs}$) that results in plasma concentration ($c_t$) may be estimated by solving the convolution integral equation for $r_{abs}$

$$C_t = \int_0^t C_\delta (t-u)\, r_{abs} (u)\, du$$

Where

$C_t$ is plasma concentration

$C_\delta$ is concentration time course that would result from instantaneous absorption of a unit amount of drug and it is typically estimated from i.v bolus $C_t$ Vs time

$r_{abs}$ is input rate of oral solid dosage form

u is variable of integration

# Levels of Correlation

- The concept of 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.
- Depending upon usefulness, three correlation levels have been defined and categorized as

i. Level A correlation
ii. Level B correlation
iii. Level C correlation

# Level A correlation

- Highest level of correlation.
- Represents point to point relationship between *in vitro* dissolution rate and *in vivo* input rate of the drug from the dosage form.

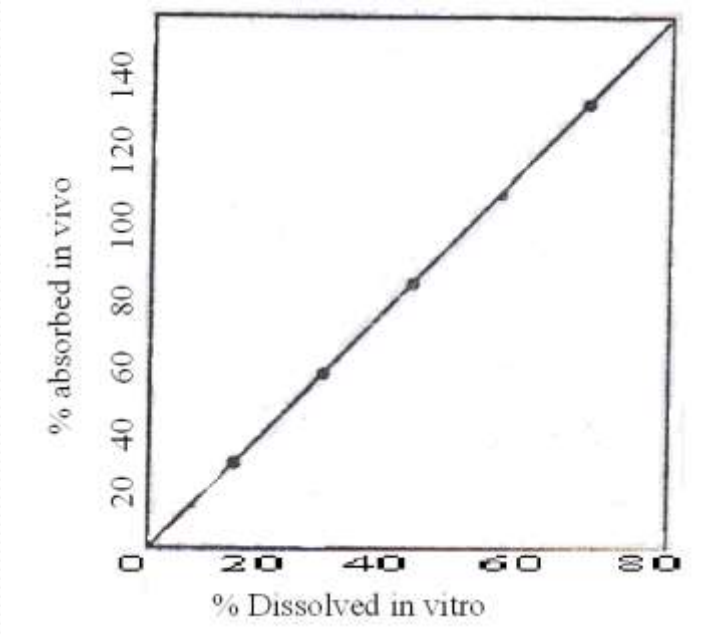


fig 1: correlation between % theophylline dissolved in vitro and % absorbed after administration of theophylline

# Level B Correlation

- In this level of correlation, the mean absorption time is plotted against mean dissolution time for at least three preparations.
- This utilizes the principle of statistical moment analysis.

$$MAT = MRT_{i.v} - MRT_{oral}$$

- But there may not be point to point correlation

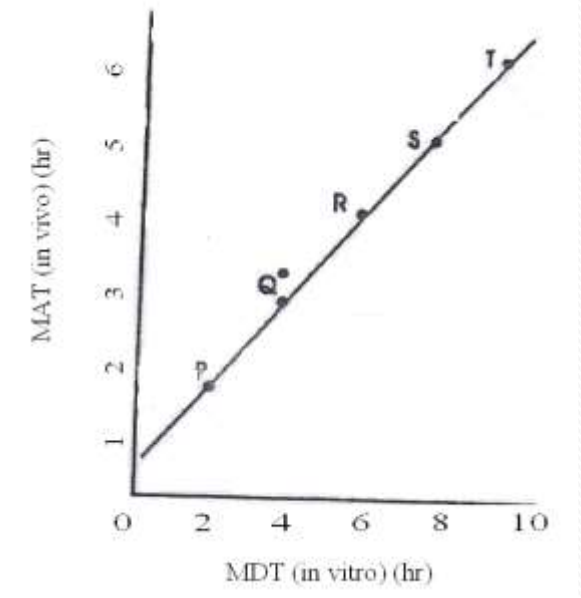


fig 2: schematic representation of correlation of meanin vitro dissolution time(MDT) with mean in vivo absorption time for five formulations

# Level C Correlation

- Single point correlation.
- Selected parameters are correlated for 3 or more preperations
- Ex., $t_{50\%}$ Vs AUC or Cmax or Tmax

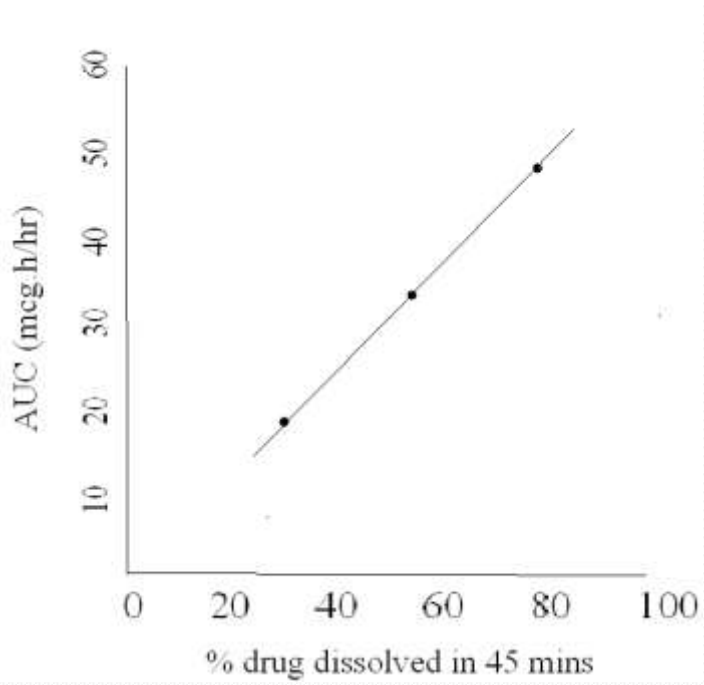


fig 3: schematic representation of correlation between % drug dissolved in 45 min and AUC obtained from plasma concentration

# Applications of an IVIVC

- Biowaivers
- Establishment of dissolution specifications
- Mapping

# Conclusion

- IVIVC includes *in vivo* relevance to *in vitro* dissolution specifications and can serve as surrogate for *in vivo* bioavailability and supports biowaivers.
- Many laboratories are engaged to find better means to estimate *in vivo* behaviour of the drug after oral administration by using simple *in vitro* dissolution tests.
- Efforts are on to modify the dissolution specifications to surrogate the bioavailability and *in vivo* testing.
- Several computer programmes have been developed to simulate *in vivo* release pattern of the dosage forms by using the data obtained from the IVIVC.


thank
you