INVITRO – INVIVO CORRELATION

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Invitro and Invivo considerations/correlation

- Need for correlation
- What is in IVIVC
- Types of correlation
- Levels of correlation
- Bio-pharmaceutical classification of drug
- Approaches to seek correlation
- Determination of correlation and related calculations
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Need for correlation ??

The invitro and invivo correlations are performed in order to accomplish their need for..

- Acts as a tool to distinguish Acceptable an Unacceptable drug products.
- Asses the lot-to-lot quality of drug product.
- Guide the development of new formulations.
- Ensures the continuing product quality and performance.
- Achieves the batch-to-batch bioequivalence of the product.

- It also predicts accuracy and precisely along with expected bioavailability characteristics of product.
- Serves as validated quality control check.
- Minimize the use of extensive, expensive and time consuming bioequivalence studies.
- The dissolution test as a quality control test is significantly enhanced if correlation established.
- Ensures the proper release of the drug which is crucial(especially for MR,SR,ER products).

What is in Invitro ~Invivo correlation[IVIVC] ??

- IVIVC is a predictive mathematical model describing the relationship between an invitro property of a dosage form [usually rate on extent of drug dissolution or release] and a relevant invivo response
  - [Eg: plasma drug concentration amount of drug absorbed.

- To obtain IVIVC at least 3batches of the same drug should be available which differ in their invivo as well as performance.

- In case of difference in invivo performance of these batches , invitro test conditions can be suitably modified to correlate with the invivo data of the batches.

- On the other hand if the invitro behavior is different, modification of test conditions are done to achieve similar dissolution profiles showing similar invivo behavior and establish an invitro -invivo correlation.

TYPES OF CORRELATION

- In general approach to the IVIVC they are of 2 types….
  - Quantitative IVIV Correlation
  - Rank order IVIV Correlation

1.Quantitative IVIV correlation

- In general the commonly used quantitative IVIV correlations are:
  - Correlation based on pharmacological response
  - Correlation based on plasma level data.
  - Correlation based on urinary excretion data.

A.Correlation based on plasma level data.

- The linear relationships between dissolution parameters (such as % drug dissolved, rate of dissolution) rate constant for dissolution and parameters from plasma level data (such as % drug absorbed rate of absorption, C_{max} , t_{max} K_a etc.) are developed.

  i.e., % drug dissolved vs. % drug absorbed etc. plots are obtained.

- B.Correlation based on urinary excretion data.
  - The dissolution parameters are correlated to amount of drug excreted (unchanged in urine cumulative amount of drug excreted in a function of time etc.)
- C.Correlation based on pharmacological response
  - An acute pharmacological effect (like LD_{50}) is related to the dissolution parameters.

2.Rank order IVIV correlations

- In general, the correlating data obtained from both the invitro and invivo studies are generally arranged in ascending and descending order of their information.

BIO-PHARMACEUTICAL CLASSIFICATION OF DRUGS

Class	Solubility	Permeability	IVIVC-Expectations
I.	High	High	IVIVC-If dissolution rate is slower than gastric emptying rate, otherwise limited (or) no correlation.
II.	Low	High	IVIVC-Expected if invitro dissolution rate is similar to invivo dissolution rate, unless dose is very high.
III.	High	Low	Absorption is rate determining and limited or no correlation with dissolution rate.
IV.	Low	Low	Limited or no IVIVC expected.

LEVELS OF CORRELATION

- Levels include…
  - (a)Correlation levels A
  - (b) Correlation level B
  - (c) Correlation Level C
  - (d) Multiple Level C Correlation

(a) Correlation levels A

- This correlation is the highest level of correlations in which a 1.1 relationship between an invitro dissolution and invivo bioavailability is seen.
- It is a point-to-point relationship between invivo and invitro data.
- The data treatment involves Wagner-Nelson (or) Loo-Riegelman procedures or by direct mathematical deconvolution followed by comparison of the fraction of drug absorbed and fraction of dissolved invitro to obtain a linear correlation.
  - Advantage: This is the quality control procedure of invitro dissolution test is predictive of the drug product performance invitro.

(b) Correlation level B

- This is based on the principle of statistical moment analysis.
- The mean residence time of the drug in the body and mean dissolution time invitro are determined & correlated.
- In this level there is no point-to-point relationship.
- This type of correlation does not uniquely reflect actual invitro behavior of the formulation because a member of different invivo profiles will provide similar MRT values.
- This has a very limited use in formulation development.
- This level of correlation is less than a level A 1:1 correlation.
- In this mean invitro dissolution time ($MDT_{invitro}$) or mean in vivo dissolution time (MDT_{invivo}).

(c) Correlation Level C

- This uses a single point in the dissolution curve to correlation to plasma drug conc. time data.
- This is the weakest level of correlation because only partial relation between absorption & dissolution is evident.
- It does not utilize all the data & hence, cannot reflect the complete plasma conc. time curve.
- It can only serve as single as guide in formulation development or as a production quantity control procedure.

(d) Multiple Level C Correlation

- The correlation relates more than one pharmacokinetic parameters of Int to the amount of drug dissolution at time points of dissolution profile.

- Indirectly if a multiple level C correlation exists there is a possible of level A correlation.

APPROACHES TO SEEK CORRELATION

- Various approaches have been adopted to establish the invitro-invivo correlation.
- Use of various mathematical statistical models, optimization techniques has been reported.
- Different methods for evaluation & correlation invitro dissolution parameters with some invivo parameters have been published.

Various methods to establish invitro-invivo correlation are as follows:

- Comparison of cumulative adsorption profile & cumulative invitro dissolution profile.
- Correlation of corresponding times to dissolve & respectively adsorbs the same fraction of the dose.
- Correlation between first order dissolution rates & respective bioavailability data by plotting invitro dissolution rate constant vs relative AUC.($r = 0.994$).
- Correlation of cumulative percent dissolved vs $time^2$
- Correlation between invitro mean dissolution time & invivo mean dissolution time ($r = 0.91$)

- The most commonly used methods include:~

- Wagner – Nelson method / deconvolution method.
  - [comparison of fraction adsorbed invivo & fraction released invitro at given times].

- Statistical moment analysis
  - Note: Statistical moment approach can facilitate correlation between invitro dissolution parameters & inturn help to predict bioavailability of formulation by monitoring its dissolution profile.

- Accuracy of the results & meaningful conclusions using statistical moment analysis are dependent on the design of study from which the data is generated.

- Expansion of sampling schedule to longer times can help to minimize the impact of error in the determination of elimination rate constant inherent due to biological and analytical variability.

- There was satisfactory improvement in the correlation between MRT invitro MRT invivo after transformation of the data using statistical moments with correlation coefficient 0.99 and 0.98 at $P<0.05$.

DETERMINATION OF CORRELATION AND RELATED CALCULATIONS

- The data obtained from the invivo studies is used to calculate the amount of drug absorbed into systemic circulation using the methods like :~

WAGNER~NELSON METHOD:~

- The cumulative relative fraction absorbed is calculated by this method.
- The equation involved is:~

$$CRFA = (C_t + K_{el} .AUC_{o\sim t}) / (Kel\sim AUC_{o\sim\infty})$$

- Significance of terms in equation:~

C_t = plasma drug concentration at time t

K_{el} = elimination rate constant

$AUC_{o\sim t}$ =area under curve from time zero to time t

$AUC_{o\sim\infty}$= area under curve from time zero to time infinity

Convolution method:~

- It predicts plasma drug concentration using a mathematical model based on the convolution integral.

- Representation of equation:~

$$C_t = {}_{abs}(U)du$$

- Representation of terms:~

C_t=the plasma drug concentration

γ_{abs} =absorption rate constant

C_δ=concentration time course

Other equations and definitions

Mean residence time(MRT):

- It is the mean time for which the drug resides in the body.
- Representation of equation:

$$MRT = AUMC / AUC$$

- WHERE…
  - AUC= Area under the plasma concentration time curve
  - AUMC = area under moment curve

MEAN ABSORPTION TIME(MAT)

- It is the mean time required for the drug to reach the systemic circulation from the time of drug administration.

- Given by equation:

$$MAT = MRT_{oral} \sim MRT_{iv}$$

Mean invitro dissolution time($MDT_{invitro}$):

- It indicates the mean time for the drug to dissolve under invitro dissolution conditions.

- Representation of equation

$$MDT_{invitro} = \{ M \sim (b).\, dt \} / M$$

- Mean invivo dissolution time reflects mean time for drug to dissolve invivo. It is calculated by using equation:

$$MDT_{solid} = MRT_{solid} \sim MRT_{solution}$$

ie., $$MDT_{invivo} = MRT_{solid} \sim MRT_{solution}$$

GRAPHICAL REPRESENTATION

Level A method:

- These methods utilize all the invivo and invitro data available is essential for development.

Level B correlation:

- Some parameters like MRT or MDT invivo and MDT invitro are compared.
- All the invivo and invitro data is being used in this kind of correlation it can not be a point-point correlation.

Level C correlation:

- In particular, invivo parameter(C_{max}/T_{max}/AUC/$T_{1/2}$) for formulation with different invitro dissolution behaviour are correlated with specific invitro dissolution parameter.

FAILURE OF CORRELATION

- The drugs with dissolution data that correlate with drug absorption in the body indicates the poor correlation of dissolution to drug absorption.
- These are also instances where a drug has failed the dissolution test and yet is well absorbed.
- The pb of no correlation between bioavailability & dissolution may be due to complexity of drug absorption & the weakness of dissolution design.
- It is important, the any new dissolution test be carefully researched before being adopted as a method for predicting the drug absorption.

COMPARISON STUDY PROFILES

IN VITRO STUDIES	IN VIVO STUDIES
I. Percent drug dissolution profile	I. Plasma concentration time profile
a) Percent drug dissolved at time t	a) Plasma concentration at time t
b) Maximum drug dissolved at time t	b) Peak plasma conc. C_{max}
c) Time taken for maximum amount of drug to dissolved (t_{max})	c) Time taken for C_{max}
d) Total amount of drug dissolved	d) AUC at a interval (AUC_{∞_0})
e) Time for certain % of drug to dissolve such as t30%,t50%,t90%	e) Time for certain % of drug to reach the blood such as $t_{30\%}, t_{50\%}, t_{90\%}$.....
Pharmacokinetic parameter:	Pharmacokinetic parameter:
(a) Dissolution rate constant	(a) Absorption rate constant (k_a)
(b) Dissolution half life	(b) Elimination constant (k_e)
	(C) Absorption half life ($t_{a1/2}$)
	(d) Elimination half life ($t_{e1/2}$)
3.Percent drug dissolved time profile Percent drug dissolved at time 't'	3. Percent drug absorbed tome profile Percent drug absorbed at time 't'
4.Statical movement analysis	4. Statical movement analysis
MDT- Mean dissolution time	MRT- Mean residence time
	MAI- Mean Absorption time

Limitations

- 1.It has been observed that in vitro test does not necessarily mean that the formulations will be have similarly in vivo.
- 2.In contrast some of the reports also indicate good bioavailability of the formulations having poor in in vitro dissolution profiles.
- 3. Invitro dissolution data can be utilized for prediction of in vivo performance of the dosage form if there exists a meaningful method for transformation of data .
- 4. Invitro data can not be directly compared with in vivo data since the measurement of in vivo release /absorption is not straight forward .
- 5.Use of classical single point pharmacokinetic parameters such as C_{max} and T_{max} to assess bioavailability /bioequivalency of dosage forms is contra versions

FUTURE TRENDS

- To estimate invivo behavior of the drug after oral administration by using simple invitro dissolution tests .
- Efforts are on to modify the dissolution specifications to surrogate the bioavailability and the in vivo testing.