IN VITRO IN VIVO CORRELATIONS

Presented By

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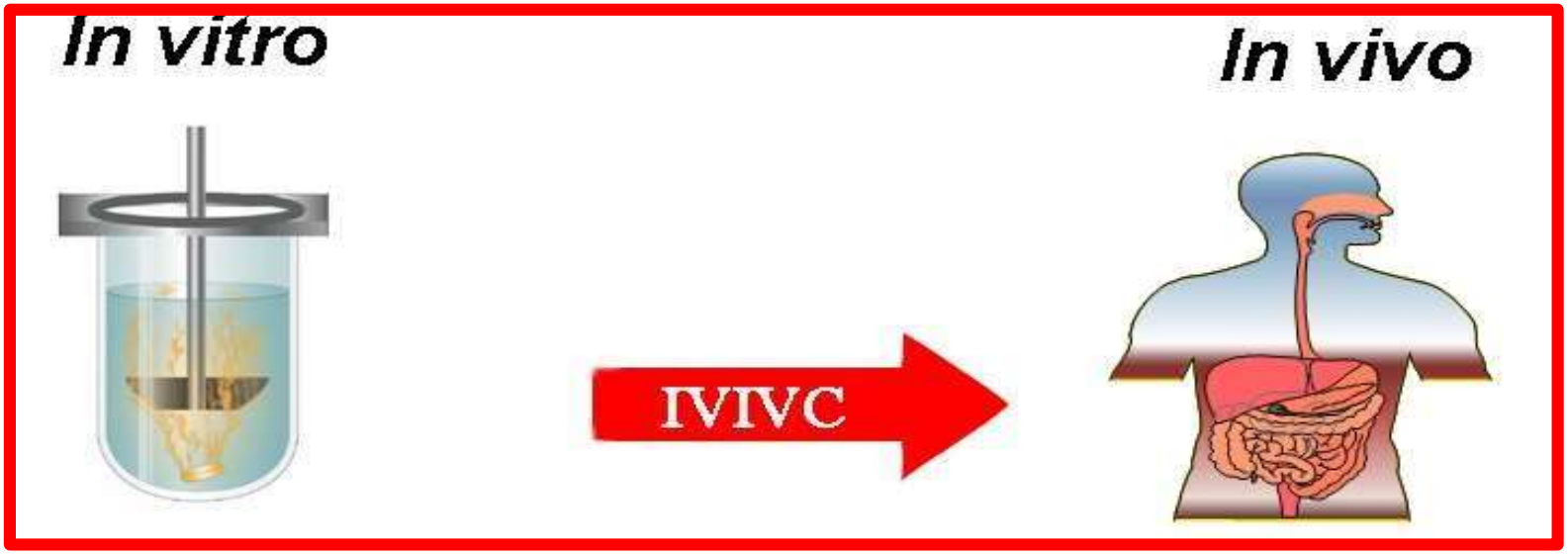
IN VITRO - IN VIVO CORRELATION (IVIVC)



Definitions

- ***In vitro*** dissolution: It's a process of release of drug from dosage form as measured in an ***in vitro*** dissolution apparatus
- ***In vivo*** dissolution: process of dissolution of drug in the GI tract.
- **Correlation:** relationship between *in vitro* dissolution rate and *in vivo* absorption rate as used in bio-equivalence guidance
- ***IVIVC*** has been defined as "a predictive mathematical model describing the relationship between an *in-vitro* property of a dosage form and an *in-vivo* response"

DEFINITION:

- 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 relationships as well.

- Conceptually, *IVIVC* describes a relationship between the *in vitro* dissolution / release versus the *in vivo* absorption.

- FDA had defined *IVIVC* as “A predictive mathematical model describing relationship between *in-vitro* property of a dosage form and *in-vivo* response.”

- *In-vitro* properties are rate or extent of drug released under a given set of conditions. *In-vivo* properties are plasma drug conc. expressed in terms of Cmax, AUC.

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APPLICATIONS

1. To ensure batch to batch consistency in the physiological performance of a drug product by use of such in vitro values.
2. To serve as a tool in the development of a new dosage form with desired in vivo performance.
3. To assist in validating or setting dissolution specification (i.e. the dissolution specifications are based on the performance of product in vivo).
4. IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development.

APPROACHES FOR DEVELOPING CORRRELATIONS:

The basic approaches by which correlations between dissolution testing and bioavailability are:

- Predicting the mathematical model(linear relationship) between the *in vitro* dissolution testing and existing bioavailability data.
- Modifying the dissolution methodology on the basis of existing bioavailability and clinical data.

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Some of the often used quantitative linear *in vitro-in vivo* correlation are:

- **Correlations based on the plasma level data:** Here linear relationships between dissolution parameters and plasma level data are established.
- **Correlations based on the urinary excretion data:** Here, dissolution parameters are correlated to the amount of drug excreted unchanged in the urine, cumulative amount of drug excreted as a function of time, etc.
- **Correlations based on the pharmacological Response:** An acute pharmacological effect such as LD50 in animals is related to any of the dissolution parameters.

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- **Statistical moments theory** can also be used to determine the relationships such as mean dissolution time *(in vitro)* versus mean residence time *(in vivo).*
- Though examples of good correlations are many, there are instances when positive correlation is difficult or impossible.
- E.g., in case of corticosteroids, the systemic availability may not depend upon the dissolution characteristics of the drug.
- Several factors that limit such a correlation include dissolution methodology, physicochemical properties of the drug, physiological variables.

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Parameters for correlations

SL. No.	*IN VITRO*	*INVIVO*
1.	Dissolution rate	Absorption rate (or absorption time)
2.	Percent drug dissolved	Percent of drug absorbed
3.	Percent drug dissolved	Maximum plasma concentration, C_{max}
4.	Percent drug dissolved	Serum drug concentration, C_p

Dissolution rate versus absorption rate

If dissolution of drug is rate limiting step, the faster the dissolution rate, the faster is the rate of appearance of drug in the plasma. Therefore, absorption time and dissolution time may be considered for correlation

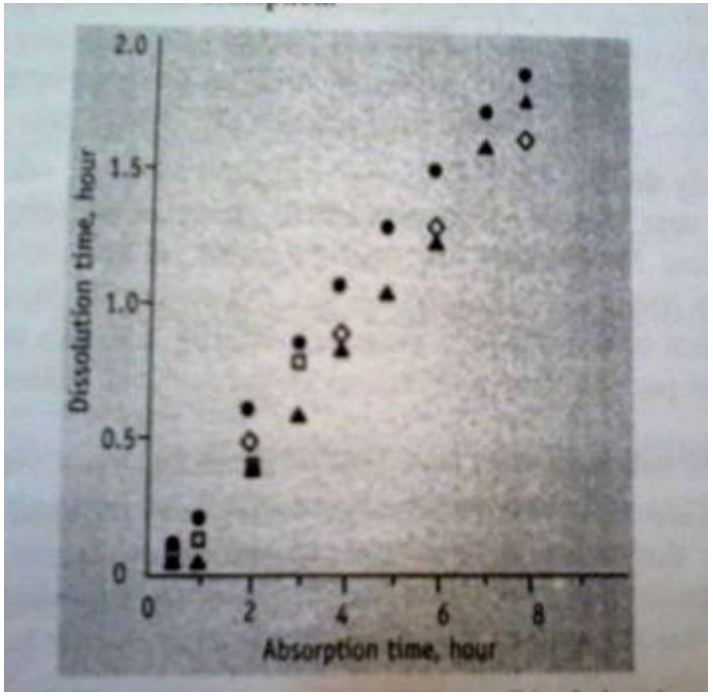

Figure 1: *In vitro-in vivo* correlations- Dissolution time Vs absorption time of three sustained release products

Percent of drug dissolved versus percent of drug absorbed:

. Appropriate dissolution medium and a slow stirring rate during dissolution should be considered to mimic *in vivo* dissolution.

. If the drug is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent drug absorbed to the percent drug dissolved.

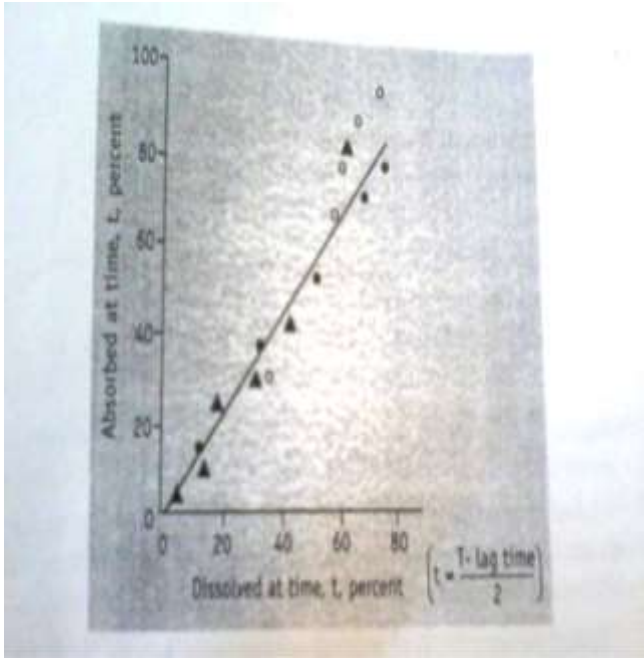

Figure 2: *In vitro-in vivo* correlations- Percent of drug dissolved Vs percent of drug absorbed of three sustained release aspirin products

Percent of drug dissolved versus maximum plasma concentration:

A poorly formulated drug may not be completely dissolved and released, resulting in lower plasma drug concentration.

The percentage of drug released at any time interval will be greater for more bioavailable drug product, the peak serum concentration will be higher for the drug that shows highest percent of drug dissolved.

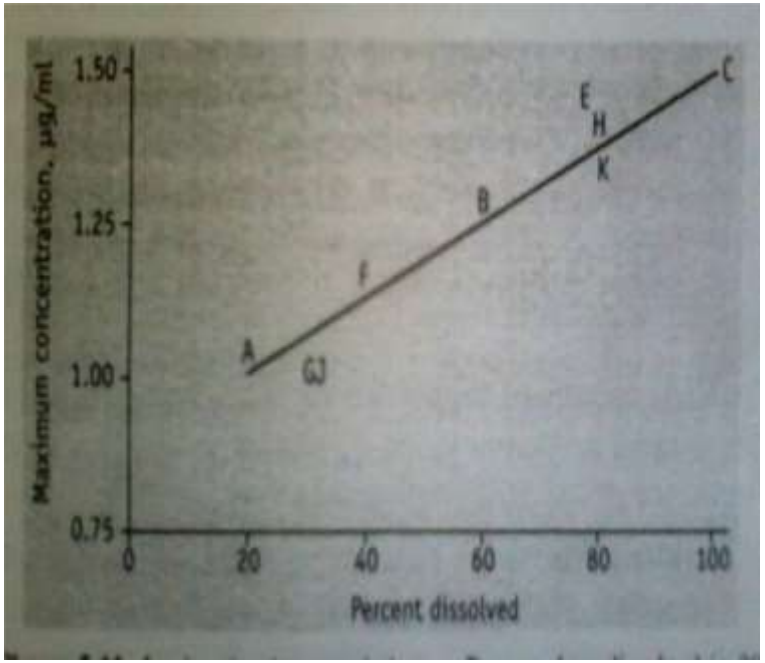

Figure 3: percent drug dissolved in 30 minutes Vs C_{max} of drug for nine products of phenytoin (100 mg).

Serum drug concentration versus percent of drug dissolved

- In a study on aspirin absorption, serum concentration of aspirin was correlated to percent of drug dissolved using an in vitro dissolution method
- Dissolution of drug is rate limiting step, and various formulations with different dissolution rates has difference in serum concentration of aspirin

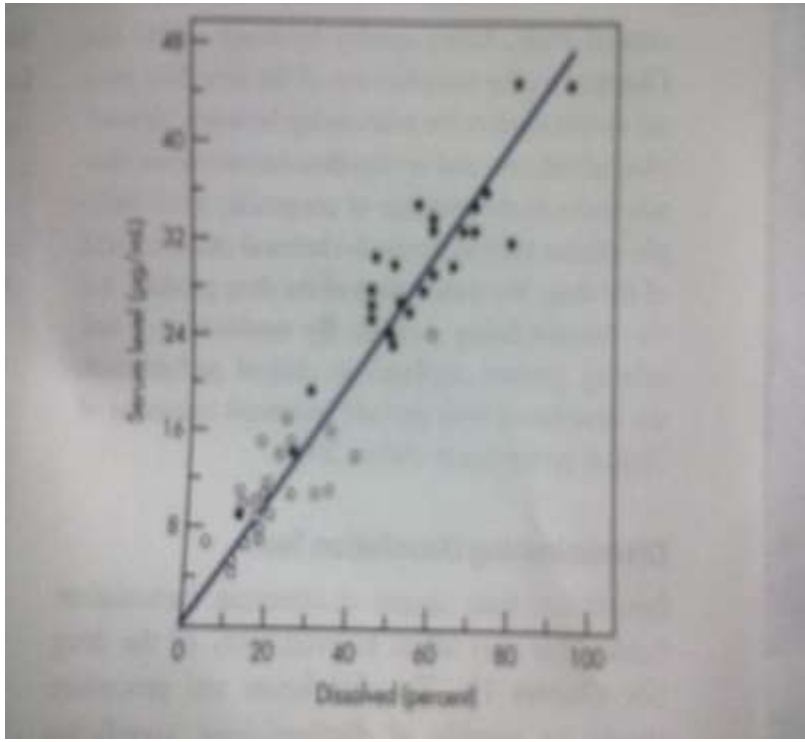

Figure 4:*In vitro-In vivo* correlations-serum drug concentration Vs percent of drug dissolved of aspirin

Levels of correlation

- Level A Correlation
- Level B Correlation
- Level C Correlation
- Multiple Level C Correlation

Level A correlation -

Point-to-Point relationship

It is estimated by two step method, deconvolution followed by comparison of fraction of drug absorbed to the fraction of drug dissolved.

Defines a direct relationship between *in vivo* data such that measurement of *in vitro* dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form.

An *in vitro* dissolution curve can serve as a surrogate for *in vivo* performance

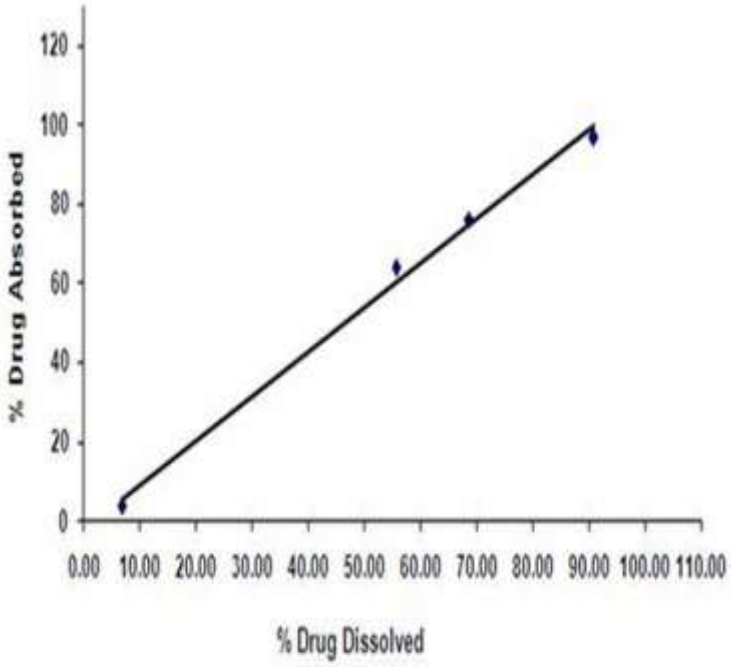

Figure : Correlation between percent theophylline dissolved *in vitro* and percent theophylline absorbed after administration of extended release product

Importance of level A correlation

- The *in vivo* dissolution serves as *in vivo* indicating quality control procedure for predicting dosage form performance.
- Determining stable release characteristics of the product over time.
- A point to point correlation is developed.

Level B correlation:

Level B correlation utilizes the principles of statistical moment analysis.

Mean *in vitro* dissolution time (MDT_{vitro}) of the product is compared to mean *in vivo* residence time (MRT).

MRT may be calculated as the ratio of the area under the first moment curve (AUMC) to the AUC, where AUMC is the area under the curve observed for the product of time and concentration versus time.

- Not a point to point corelation

Limitations

- Level B correlation is not unique, because MRT remains same, though the shape of in vivo curves are different.
- Therefore it fails to justify the formulation modifications.

Level C correlation

Level C correlation represents a single point correlation.

One dissolution time point ($t_{50\%}$, $t_{90\%}$, etc.) is compared to one mean pharmacokinetic parameter such as AUC, t_{max} or C_{max}.

Weakest level of correlation as partial relationship between absorption and dissolution is established.

- Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected.
- Lowest correlation level

Multiple level C correlations

- Multiple Level C correlation relates one or several pharmacokinetic parameters of interest (C_{max}, AUC, or any other suitable parameters) to the amount of drug dissolved at several time points of the dissolution profile.
- Its correlation is more meaningful than that of Level C as several time points are considered.

Table 1: Various parameters used in *IVIVC* depending on the level.

LEVEL	*IN VITRO*	*IN VIVO*
A	Dissolution curve	Input(absorption curves)
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(cmax), observed at time(tmax), absorption constant(ka), time to have 10,50,90% absorbed, AUC(total or cumulative)

A: one-to-one relationship between *in vitro* and *in vivo* data,
e.g., in vitro dissolution vs. *in vivo* absorption

B: correlation based on statistical moments, e.g., *in vitro* MDT vs. *in vivo* MRT or MAT

C: point-to-point relationship between a dissolution and a pharmacokinetic parameter, e.g., *in vitro* T50% vs. *in vivo* T max,

Multiple C: relationship between one or several PK parameters and amount dissolved at several time points.

THANK YOU