In vitro-in vivo correlation (IVIVC)

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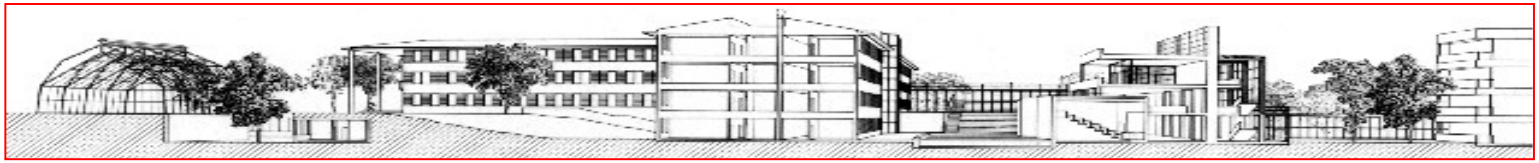


INTRODUCTION

- Key goal in development of dosage form is good understanding of *in vitro* and *in vivo* performance of dosage form
- Formulation optimization requires altering some parameters – bioavailability studies
- Delay in marketing, added in time and cost
- Regulatory guidance developed to minimize the additional bioavailability studies
- The guidance is referred as *in vitro in vivo* correlation

Definition of IVIVC

United State Pharmacopoeia (USP) definition of IVIVC

The establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage Form.

Food and Drug Administration (FDA) definition of IVIVC

An *In-vitro in-vivo* correlation (IVIVC) has been defined by the Food and Drug Administration (FDA) as “a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response”.

BASIC DEFINATIONS ABOUT IVIVC

Mean Residence Time:

- The mean time for which the drug resides in the body. Also known as mean transit time.
- **MRT = AUMC / AUC**
- where, AUMC = Area under first moment Curve (Concentration*time Vs time)
- AUC = Area under curve (Concentration Vs time)
- Both AUMC & AUC can be obtained by using Trapezoidal rule.

Mean Absorption Time:

- The mean time required for drug to reach systemic circulation from the time of drug administration.
- **MAT = MRT $_{oral}$ – MRT $_{i.v.}$**

Mean In-vivo Dissolution Time:

- It reflects the mean time for drug to dissolve in-vivo. For solid dosage form:

Percent Prediction Error:

- % PE = [(Observed value – Predicted value) / Observed value] x 100

FACTORS TO BE CONSIDERD IN DEVELOPING A CORRELATION

1. Biopharmaceutics Classification System (BCS)

BCS guidelines are provided by USFDA, WHO, and EMEA

Class **I:** **HIGH** solubility / **High** permeability,

Class **II:** **LOW** solubility / **High** permeability,

Class **III:** **HIGH** solubility / **LOW** permeability

Class **IV:** **LOW** solubility / **LOW** permeability

BCS Criteria

- **highly soluble drugs:** therapeutic dose is soluble in 250 mL (pH 1 – 7.5)
- **highly permeable drugs:** extent of absorption: > 90%
- (**rapidly dissolving**: no less than 85% within 30 min,

USP II / 50 rpm /pH 1 - 6.8 ; always considered

similar if 85% released in less than 15 min)

Biopharmaceutics Classification System

Class	Solubility	Permeability	IVIVC correlation for IR Products
I	High	High	IVIVC correlation if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation
II	Low	High	IVIVC correlation expected if in in vitro dissolution rate is similar to in vivo dissolution rate , unless dose is very high
III	High	Low	Absorption [permeability] is rate determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected.

Approaches

- Establishing a linear relationship between the in vitro and the *in vivo* parameters

- Using data from previous in-vivo studies to modify the in-vitro to develop IVIVC

Correlations

- **Based on urinary excretion data:** dissolution parameter are related to urinary drug parameters

- **Based on pharmacological response :**acute pharmacological effect such as LD_{50} is related to any of the dissolution parameters.

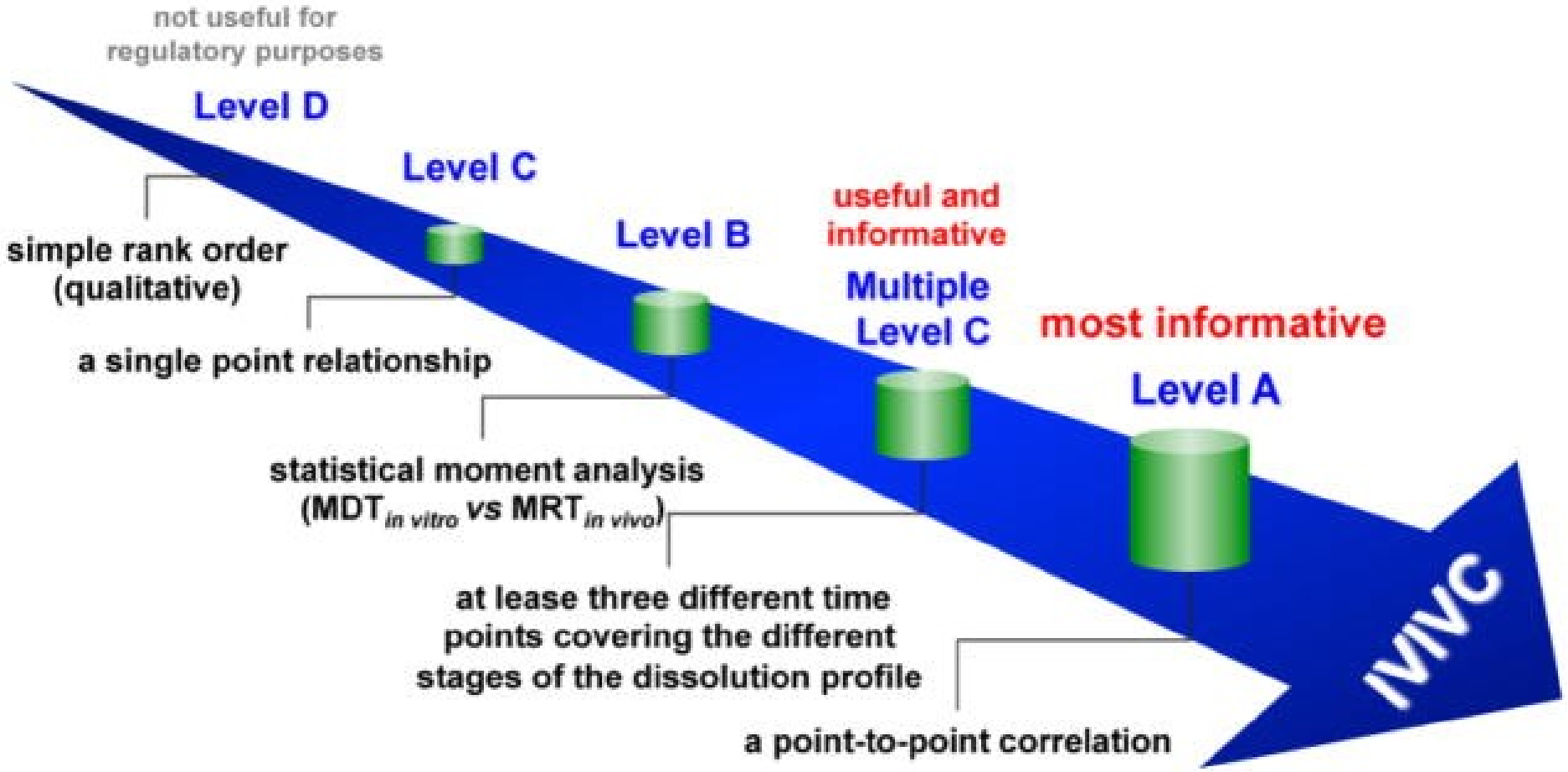
- **Statistical moments theory**: relate MDT to MRT

- **Based on the plasma level data :** here linear relationship between dissolution parameter and plasma level data are established

***In vitro* dissolution parameter**	***In vivo* plasma data parameters**
Time for specific amount of drug to dissolve (e.g. 50% of the dose)	AUC, C_{max}
Amount dissolved at a specific time point	Fraction absorbed, absorption rate constant K_a
Mean dissolution time	Mean residence time , mean absorption time

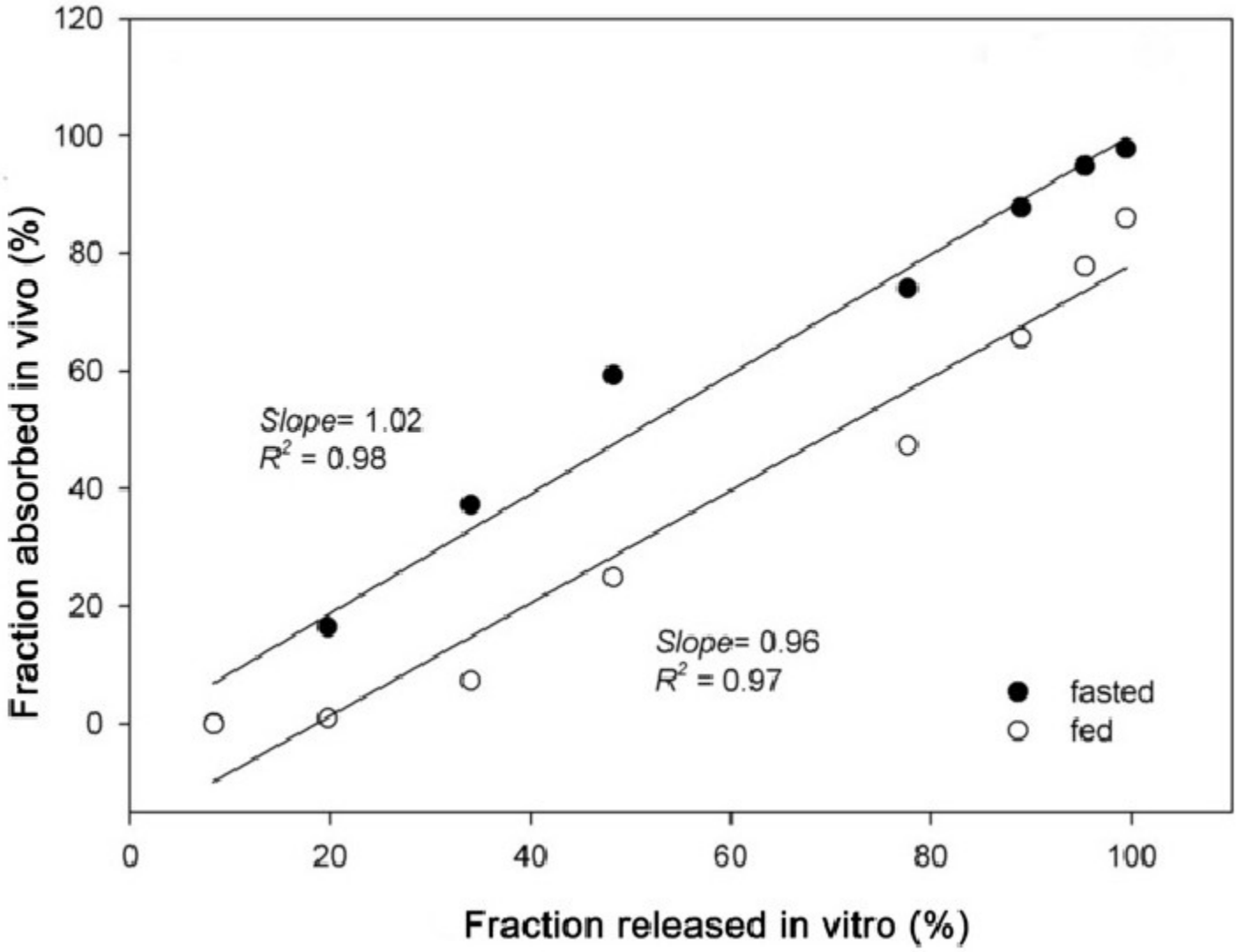
LEVELS OF CORRELATION

- **Level A correlation**
- **Level B correlation**
- **Level C correlation**
- **Multiple level C correlation**
- **Level D correlation**


not useful for
regulatory purposes
Level D
simple rank order
(qualitative)
Level C
a single point relationship
Level B
statistical moment analysis
(MDT in vitro vs MRT in vivo)
useful and
informative
Multiple
Level C
at lease three different time
points covering the different
stages of the dissolution profile
most informative
Level A
a point-to-point correlation
IVIVC

LEVEL A CORRELATION

- Highest category of correlation
- Linear correlation
- Superimposable in vitro and in vivo input curve
- Or can be made superimposable by use of a constant offset value
- Represents point to point correlation between in vitro dissolution time course and in vivo response time course
- Utilizes all the dissolution and plasma level data available to develop correlation
- Most informative and useful from a regulatory perspective


120
100
80
60
40
20
0
0
20
40
60
80
100
Fraction absorbed in vivo (%)
Fraction released in vitro (%)
Slope= 1.02
R2 = 0.98
Slope= 0.96
R2 = 0.97
fasted
fed

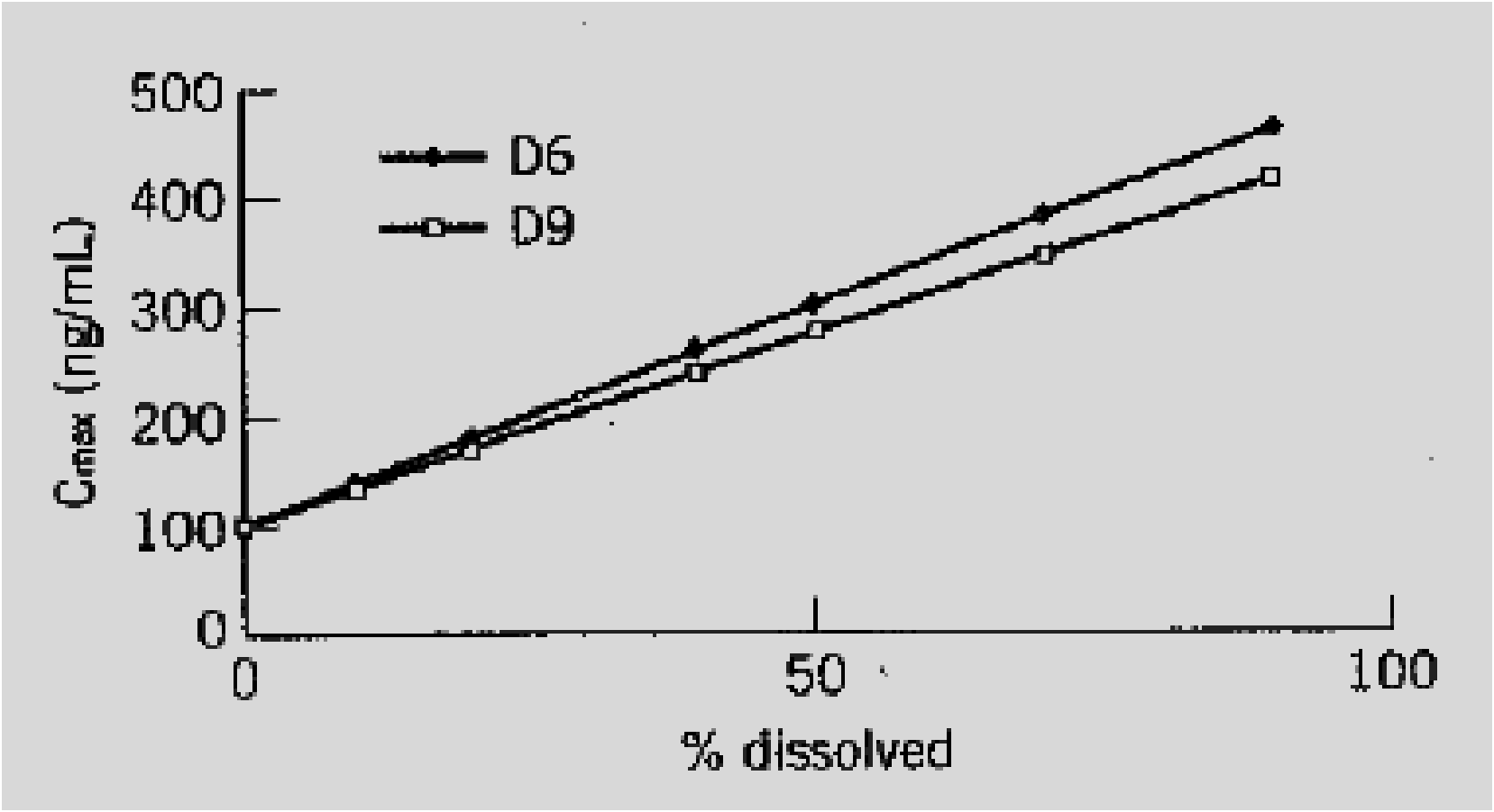
Level B correlation

- Utilizes the principle of statistical moment analysis

  MDT vitro is compared with MRT vivo
- No point to point correlation
- Does not reflect the actual in vivo plasma level curves
- Thus we can not rely to justify the formulation modification, mfg site change and excipient source change.

Level C correlation

- Dissolution time point ($t_{50\%}$,$t_{90\%}$) is compared to one mean pharmacokinetic parameter
  (C_{max} ,t_{max} ,AUC)
- Single point correlation
- Weakest level of correlation as partial relationship b/w absorption and dissolution is established
- Useful in the early stages of formulation development


500
400
300
200
100
0
C_{max} (ng/mL)
D6
D9
0
50
100
% dissolved

Multiple level C correlation

- It reflects the relationship b/w one or several pharmacokinetic parameter of interest and amount of drug dissolved at several time point of dissolution profile
- Based on
  - Early
  - Middle
  - Late stage

Significance of *ivivc*

- The main objective of developing and evaluating an IVIVC is to enable the dissolution test to serve as a surrogate. It reduces the number of bio-equivalence required for approval as well as during scale up and post approval changes (SUPAC).
- IVIVC shortens the drug development period, economizes the resources and leads to improved product quality.
- A means of assuring the bioavailability of active ingredients from a dosage form.
- Supports and or validates the use of dissolution methods and specifications
- IVIVC assists in supporting biowaivers.

Bioavailability studies in developing IVIVC

- Performed to characterize the plasma conc. versus time profile
- Performed with sufficient no. of subjects
- Appropriate deconvulation technique is to be applied for IVIVC

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

Wegner Nelson method

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

Loo – Riegelman method

Factors to be considered while developing IVIVC

1. Stereochemistry
2. First pass effect
3. Food effect

Applications

- To ensure batch-to-batch consistency in therapeutic efficacy of a drug product based *in vitro* test
- To develop a new dosage form with desired *in-vivo* performance
- Validating dissolution specifications & development of bio- waiver guidelines
- To estimate the magnitude of the error in predicting the *in-vivo* bioavailability results from *in-vitro* dissolution data

LEVELS OF CORRELATION

Level A

- Highest category correlation representing point- to-point relationship between *in vitro* and *in- vivo* parameters

- *In vitro* dissolution & *in- vivo* absorption rate curves are superimposable

- *In vitro* dissolution curve serves as a alternate for *in vivo* testing & can accurately predict its therapeutic efficacy

Level B

- Not a point-to-point correlation utilizing principles of statistical moment analysis

- Here mean dissolution time is compared to either the mean residence time or in vivo dissolution time.

- Cannot justify changes in manufacturing or modification in formula based on level B correlation

- In vitro data cannot be used for in-vivo quality control standards

Level C

- It is a single point correlation. Relates one dissolution time point ($T_{50\%}$) to one PK parameter such as AUC, T_{max} , C_{max}

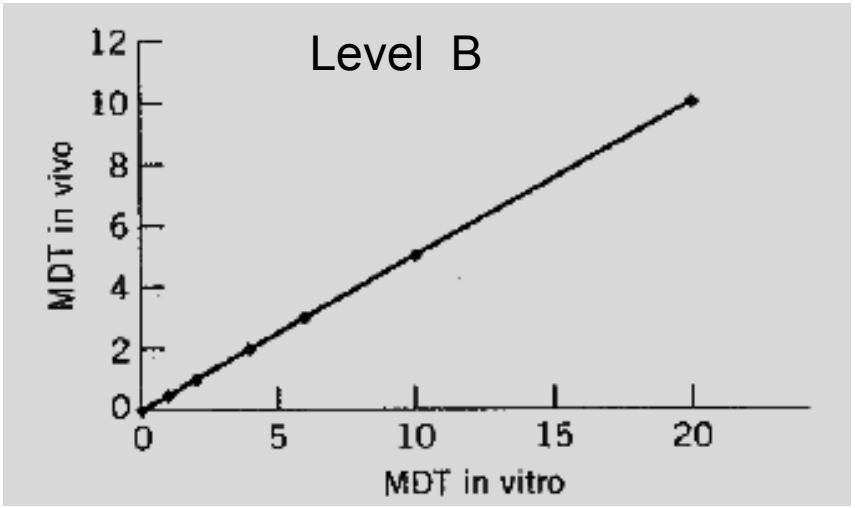
- Useful as a guide in formulation development or QC

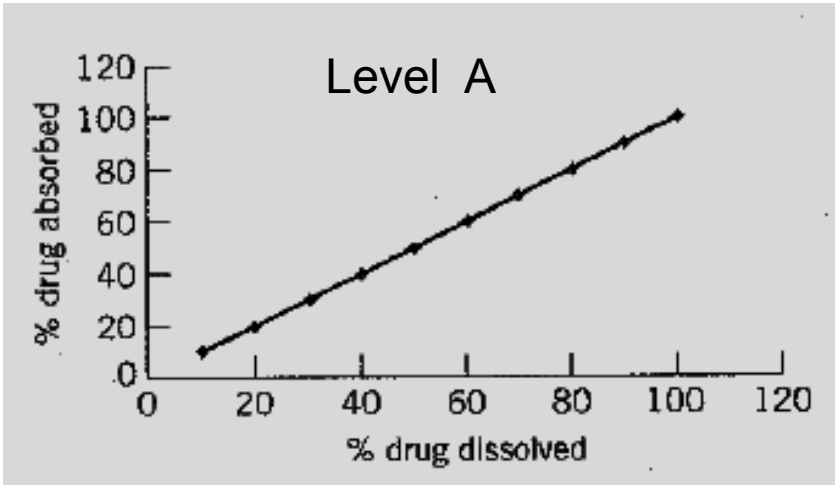
Multiple level C

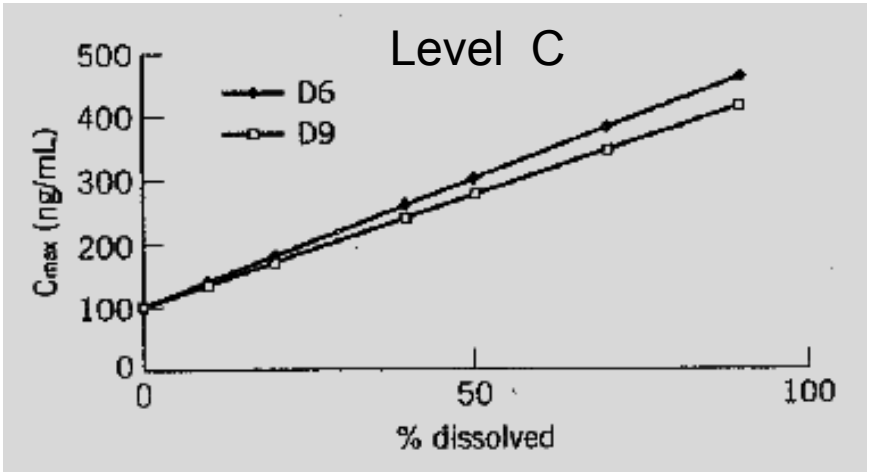
- Correlation involving one or several PK parameter to the amount of drug dissolved at various time point

Levels of IVIVC

- **Level A –** point-point; first deconvolution to get *in vivo* %drug absorbed, then compare with %dissolved
- **Level B** – Statistical moments; MRT or MDT *in vivo* vs. MDT *in vitro*
- **Level C** – single point; PK parameter vs. %dissolved







Malinowski and Marroum, Encyclopedia of Contr. Drug Deliv.