Development, Evaluation and Applications of In Vivo In Vitro Correlations

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Food and Drug Administration

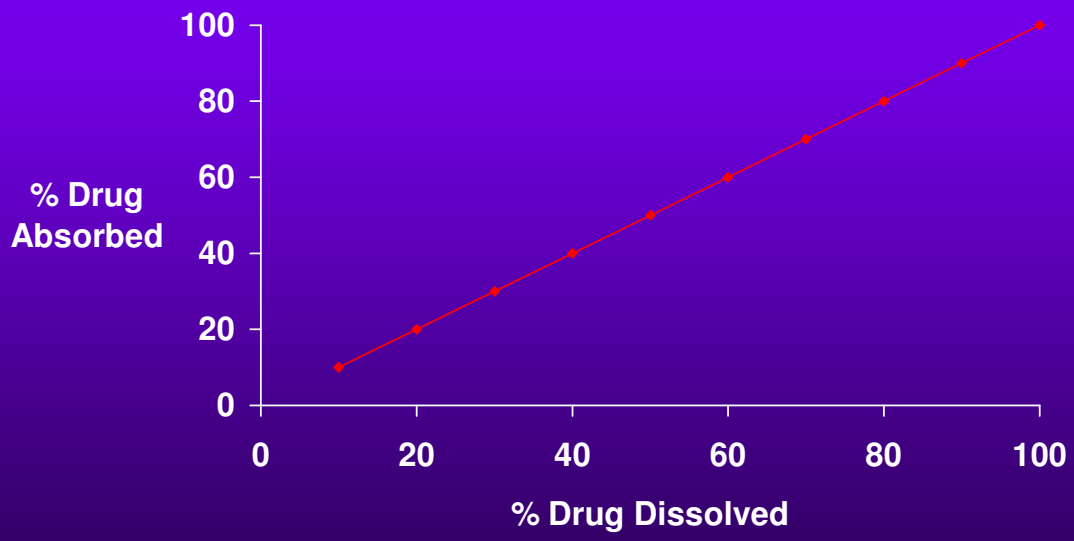
Outline

- Definitions
- General Considerations
- Development of IVIVC
  - Methodology
- Validation of IVIVC
  - Internal vs external predictability
  - Criteria
- Applications of IVIVC
  - Waivers
  - Dissolution specifications
- Conclusion

Level A Correlation

- Is a point to point relationship between in vitro dissolution and the in vivo input rate
- Usually is linear but non linear relationships can exist and are acceptable by the FDA

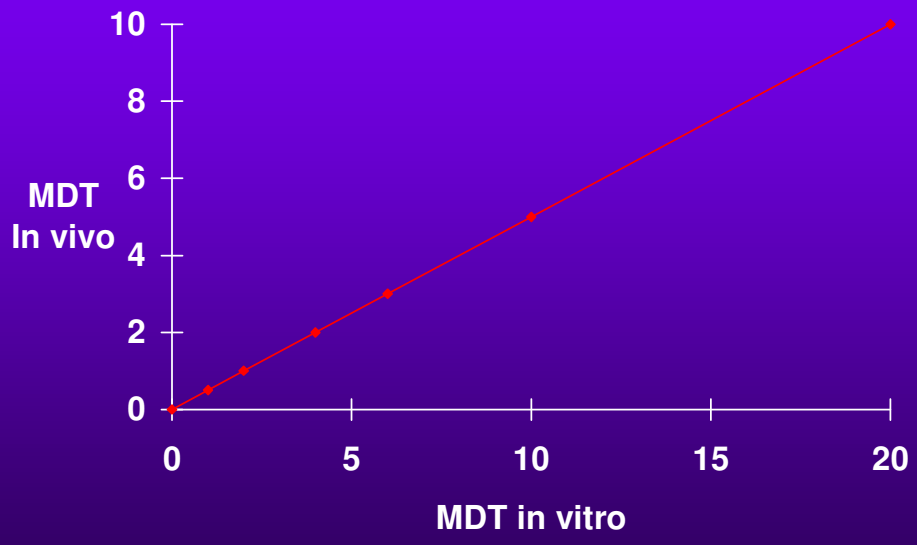
Level A correlation



Level B Correlation

- The mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time
- It utilizes the principle of statistical moment analysis
- not a point to point correlation
- Different profiles can give the same parameters values

Level B Correlation



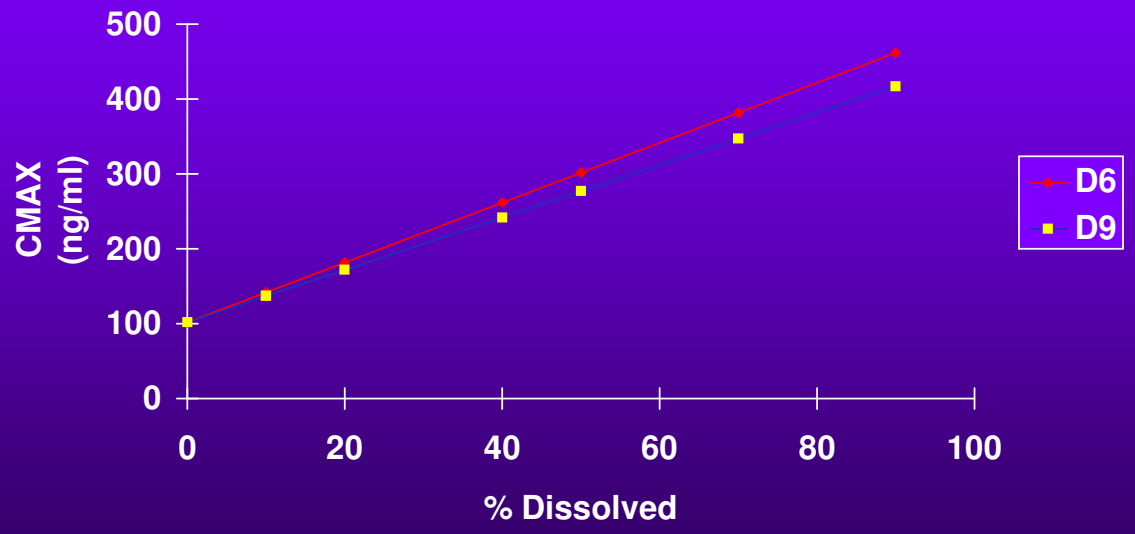
Level C Correlations

- Establish a single point relationship between a dissolution parameter, e.g. % dissolved in 4 hours and a pharmacokinetic parameter such as AUC and CMAX
- Useful in formulation selection and development but not for regulatory purposes

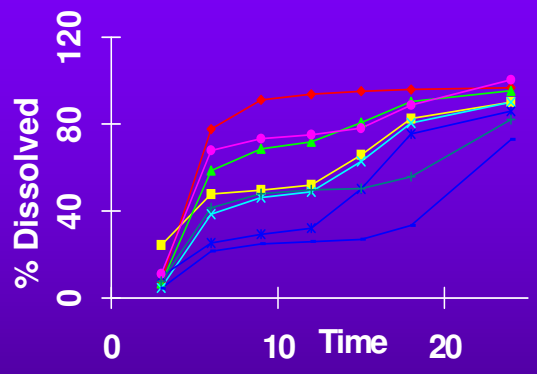
Multiple Level C

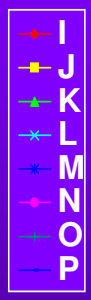
- A multiple Level C correlation relates one or several pharmacokinetic parameters to the amount dissolved at several time points of the dissolution profile

Level C Correlations

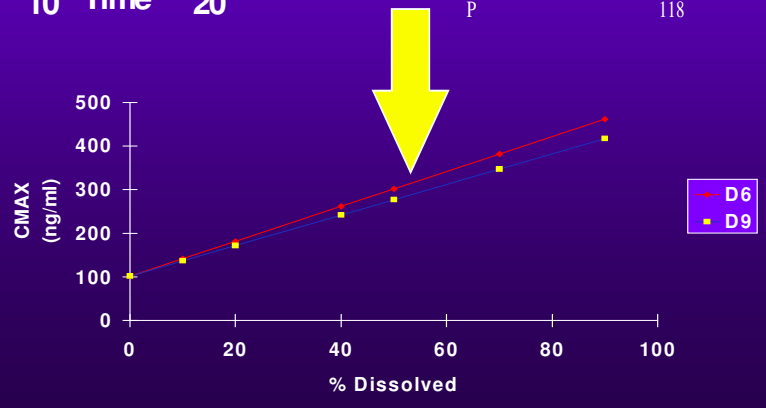


Multiple Level C Correlation





Formulation	CMAX	AUC
I	260	2623
J	192	2547
K	192	2249
L	163	2365
M	125	1980
N	211	2462
O	151	2057
P	118	2034



Level D Correlations

- Rank order correlations are qualitative and are not considered useful for regulatory purposes

General Considerations In Vivo

- Human data are required
- Number of subjects should be sufficient to characterize the bio performance of the drug product
- Data sets I have analyzed included from 6 to 36 subjects

General Considerations In Vivo

- No restrictions on study designs
  - Crossover design preferred
  - Parallel design
  - Cross study comparisons
- Inclusion of a reference treatment such as:
  - Oral solution
  - IV solution
  - Immediate release product

General Considerations In Vivo

- Studies usually are conducted in the fasted state
- When a drug is not tolerated in the fasted state, studies may be conducted in the fed state

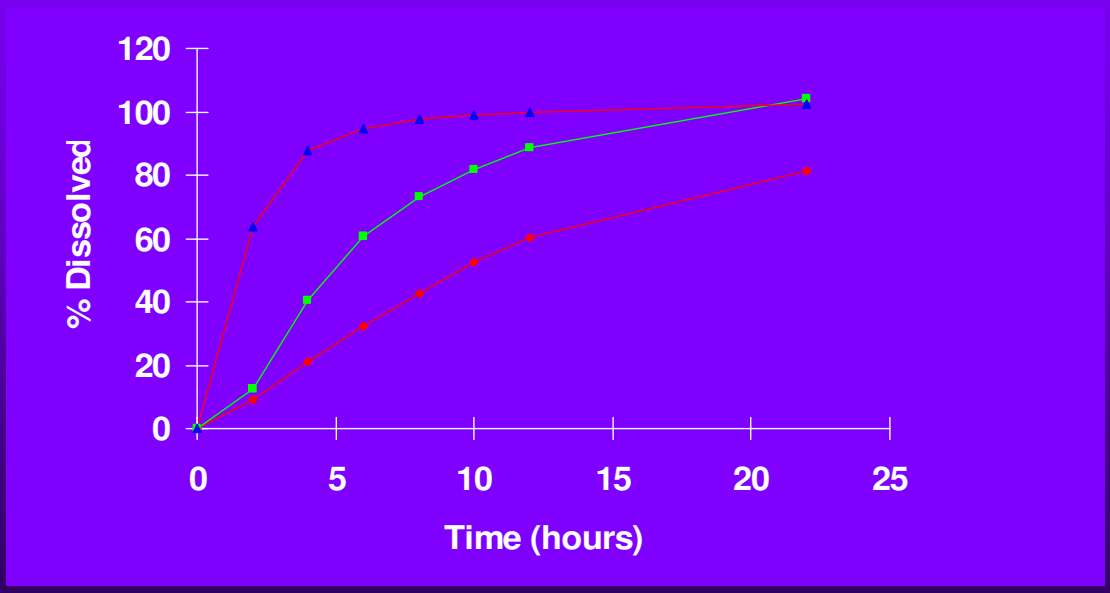
General Considerations In Vitro

- Any in vitro dissolution method can be utilized
- The system once defined should be the same for all formulations tested
- The preferred dissolution appartus is USP apparatus I or II used at compendially recognized speeds
- An aqueous medium either water or buffered solutions not exceeding pH 6.8 is recommended

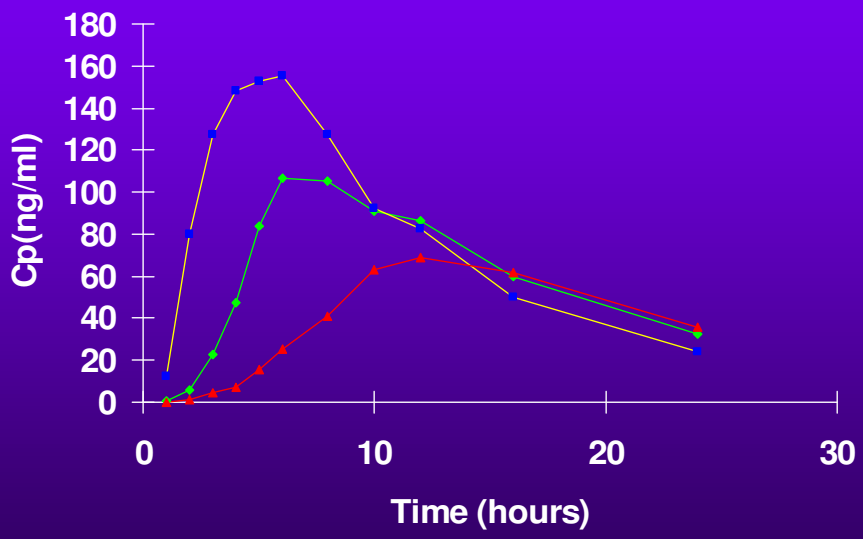
General Considerations In Vitro

- For poorly soluble drugs, addition of a surfactant may be appropriate
- In general non aqueous and hydroalcoholic systems are discouraged
- Dissolution profiles should be obtained from at least 12 units
- The coefficient of variation (% CV) for mean dissolution of a single batch should be less than 10 %

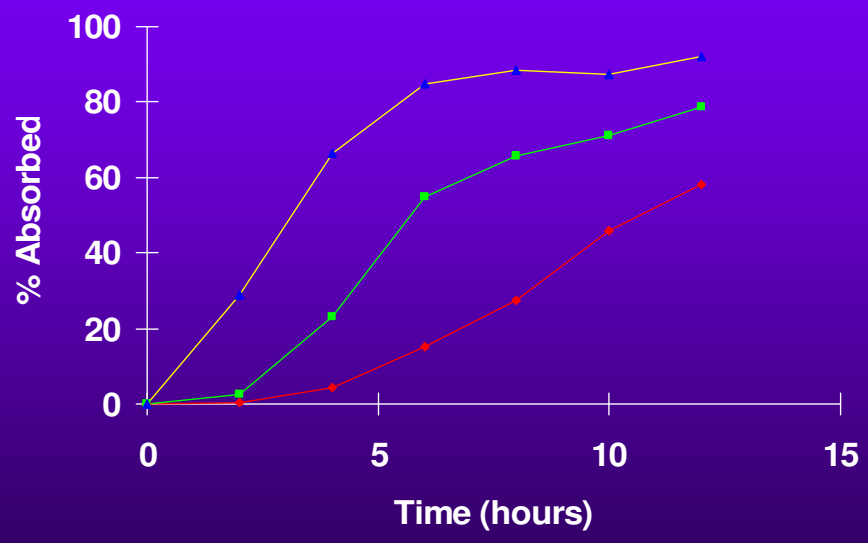
Dissolution Profiles



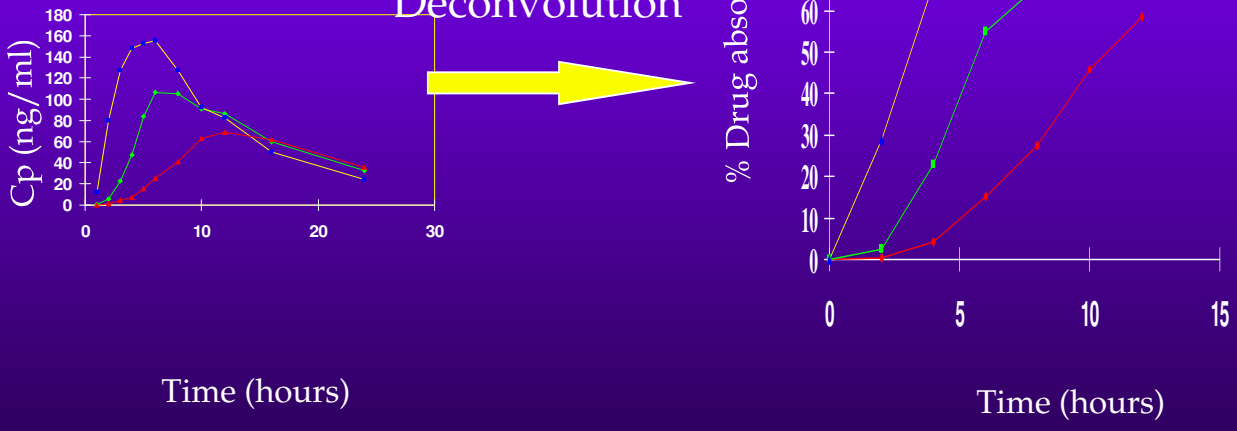
Plasma Profiles



Fraction of Drug Absorbed



Plasma Profiles



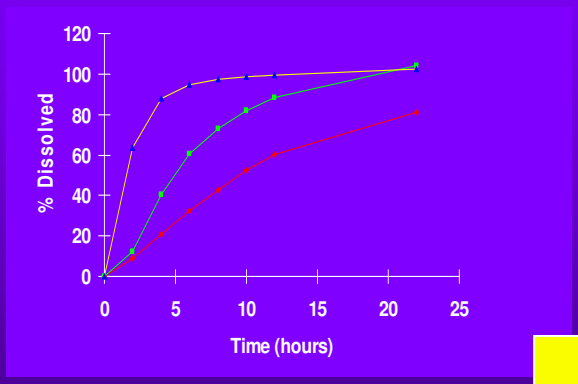
Time (hours)

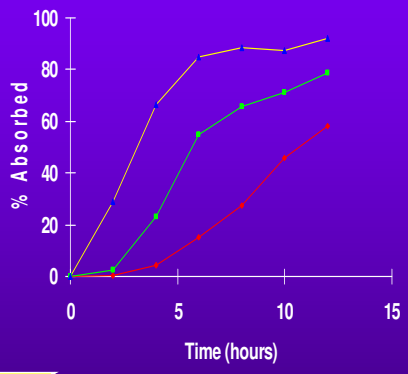
Time (hours)

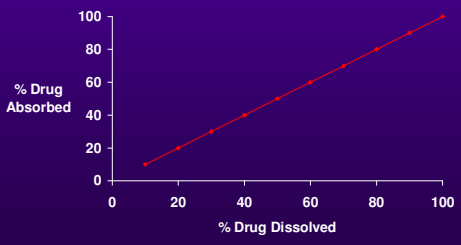
Deconvolution

- Deconvolution of plasma profiles to obtain the fraction of drug absorbed for each corresponding formulation
- Deconvolution techniques such as:
  - Wagner Nelson Method for 1 compartment model
  - Loo-Riegelman Method for 2 compartment model
  - Numerical Deconvolution methods
    - PC Decon Program

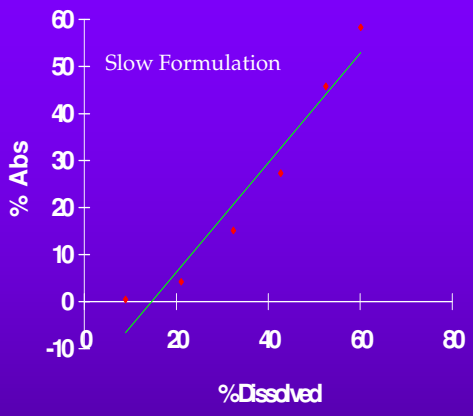
Level A Correlation

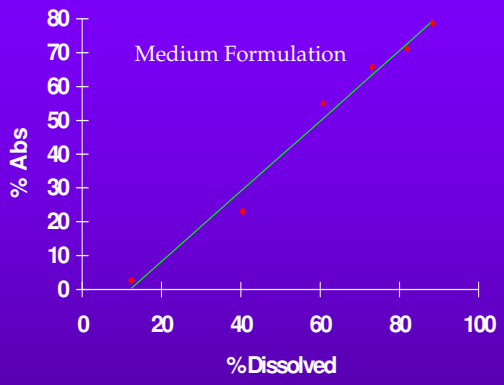


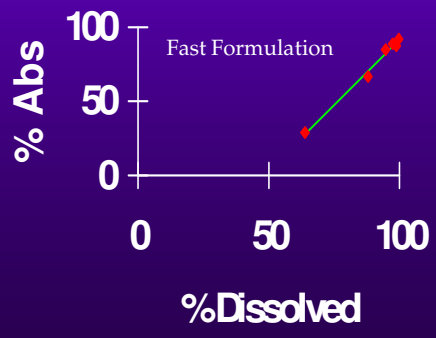


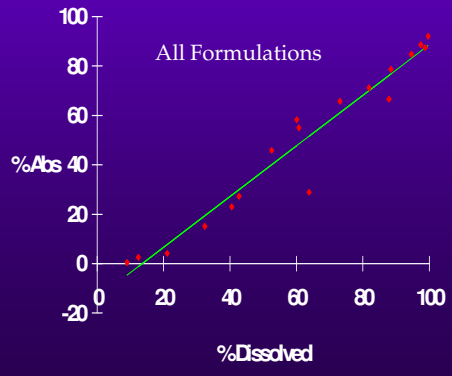


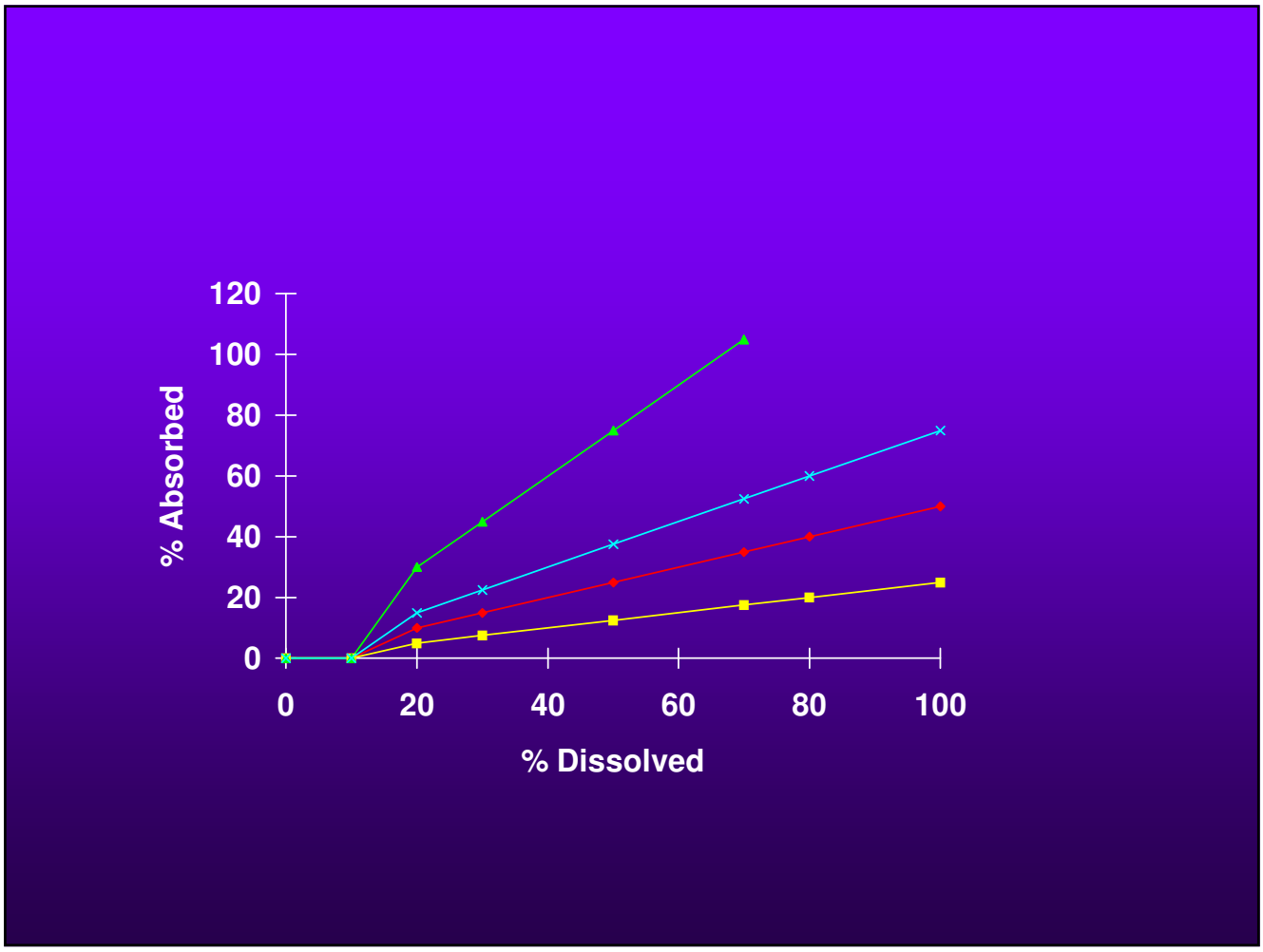
Level A Correlation










120
100
80
60
40
20
0
% Absorbed
0
20
40
60
80
100
% Dissolved

Additional Considerations

- 2 or more formulations with different release rates
- Dissolution independent of dissolution conditions, IVIVC developed with one formulation is acceptable

Additional Considerations

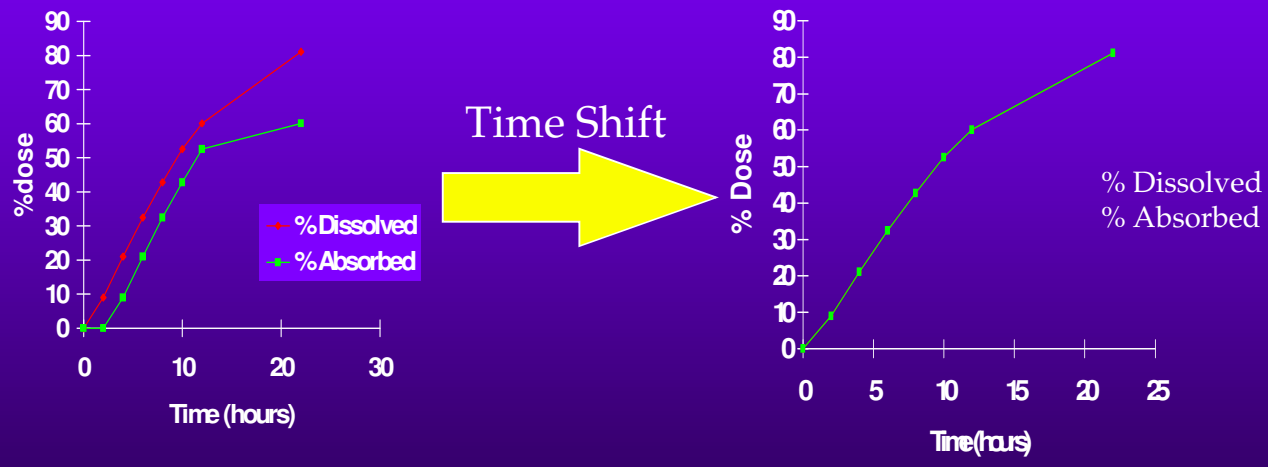
- Highest or lowest release formulations can be dropped out

Additional Considerations

- The in vitro dissolution methodology should adequately discriminate between formulations.
- Dissolution conditions should be the same for all the formulations tested in the bio study
- The dissolution conditions should be fixed before further evaluation of the correlation is undertaken

Scaling Factors

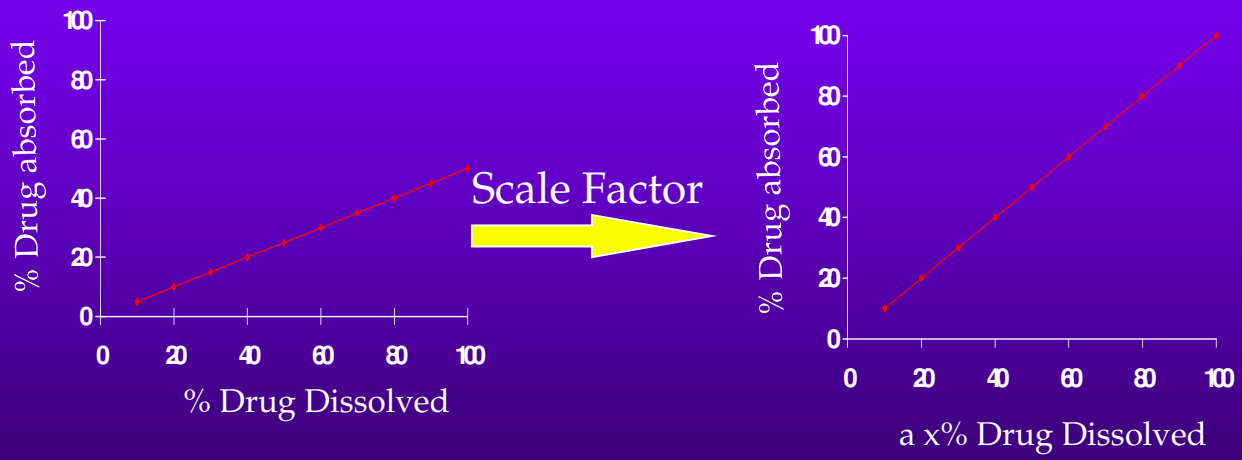
Fabs (t)= Fdiss(t+lag)



Scaling Factors

Fabs = a x Fdiss

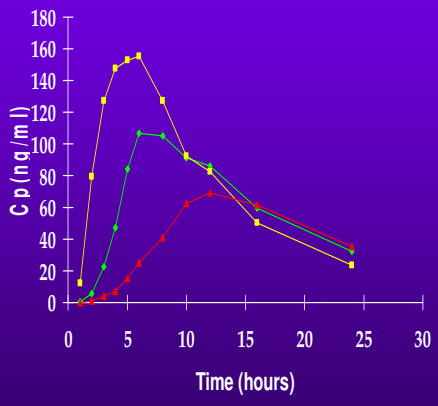
a=0.5



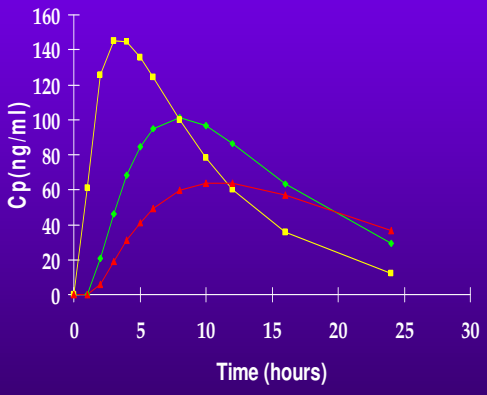
EVALUATION OF PREDICTABILITY OF IVIVC

Plasma profiles

OBSERVED



PREDICTED



Calculate absolute % PE on Cmax & AUC:

(|obs - pred| / obs) * 100

Evaluation Procedures

- **Internal predictability:** Based on data used to define the IVIVC model
- **External predictability:** Based on additional test data sets

Important considerations

- Amount of data used for IVIVC development
- Some combination of 3 or more formulations with adequately different release rates is recommended

Therapeutic index of drug

- Narrow therapeutic index drug
  - Internal and external predictability
- Non-narrow therapeutic index drug
  - Internal predictability
  - External predictability recommended but not necessary if internal pred. criteria are met

Internal Predictability Criteria

- % PE_{abs} (Cmax and AUC)
  - Average of 10% or less with none greater than 15% is acceptable
  - If criteria are not met, proceed to evaluation of external predictability

External Predictability Criteria

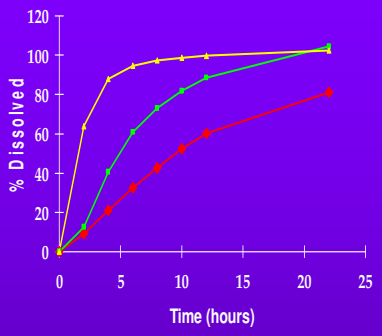
- % PEabs (Cmax and AUC)
  - 10 % or less is acceptable
  - 10-20% is inconclusive
  - Greater than 20% is unacceptable

Predictions

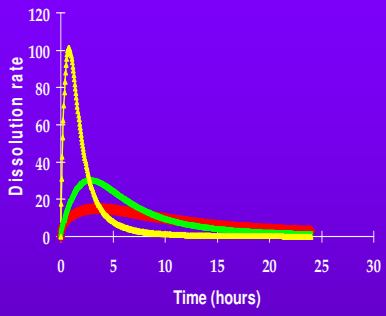
Dissolution → Absorption → Plasma profile

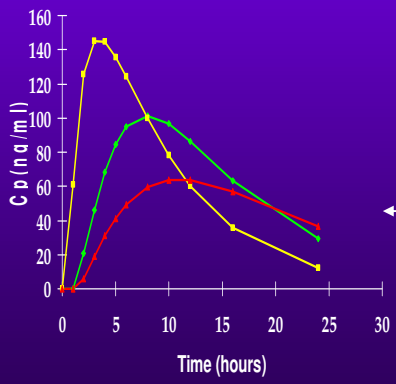
IVIVC model PK parameters

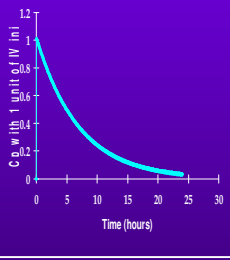
Cumulative diss

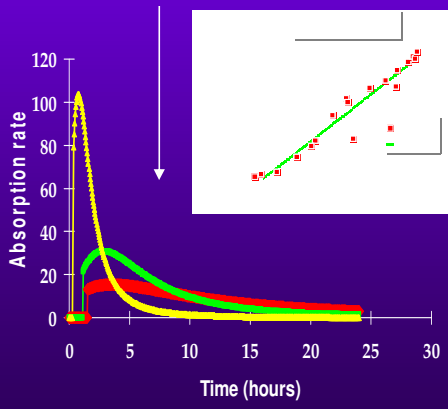


Dissolution rate





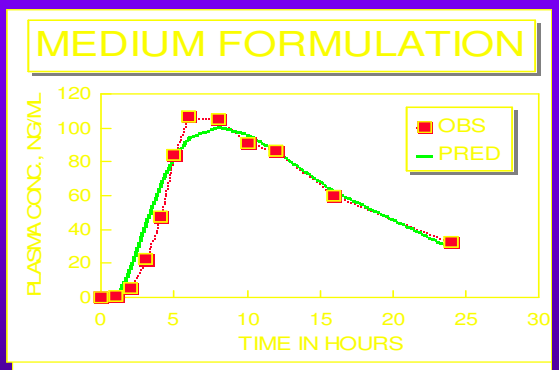


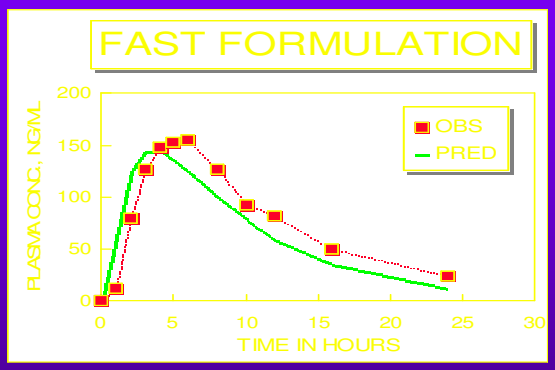


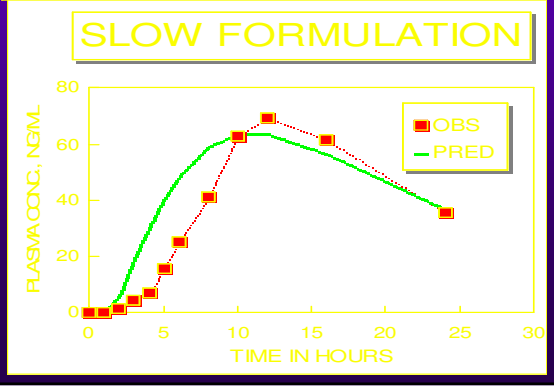
Predicted plasma profiles

Absorption rate

Evaluation of Predictability
INTERNAL

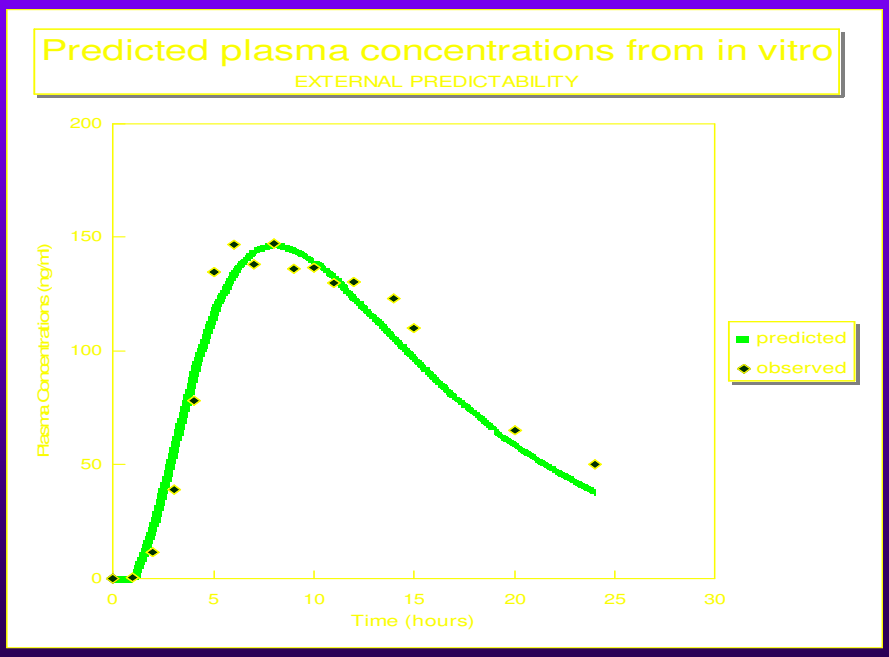






	%PECmax	%PEAUC
MEDIUM	5.14	3.77
FAST	7.08	12.91
SLOW	8.33	10.43
Avg.	6.85	9.04

Evaluation of Predictability
EXTERNAL



%PECmax
0.11

%PEAUC
9.7

Applications of IVIVC

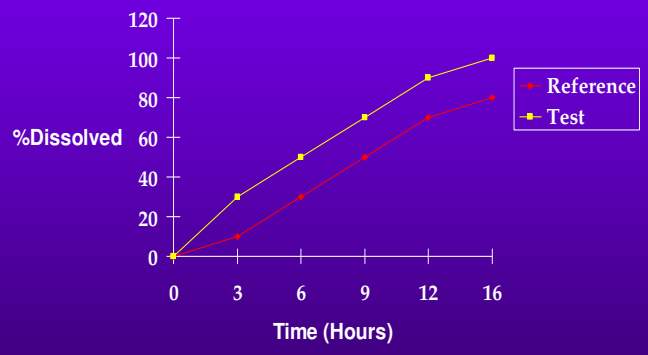
Ideally, one would like to be able to predict the *in vivo* performance of the product from its *in vitro* dissolution

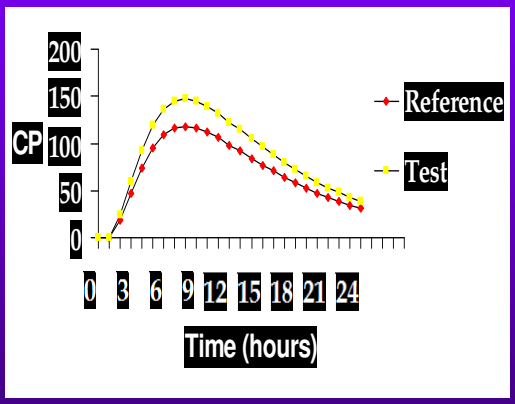
"As a surrogate for bioavailability"

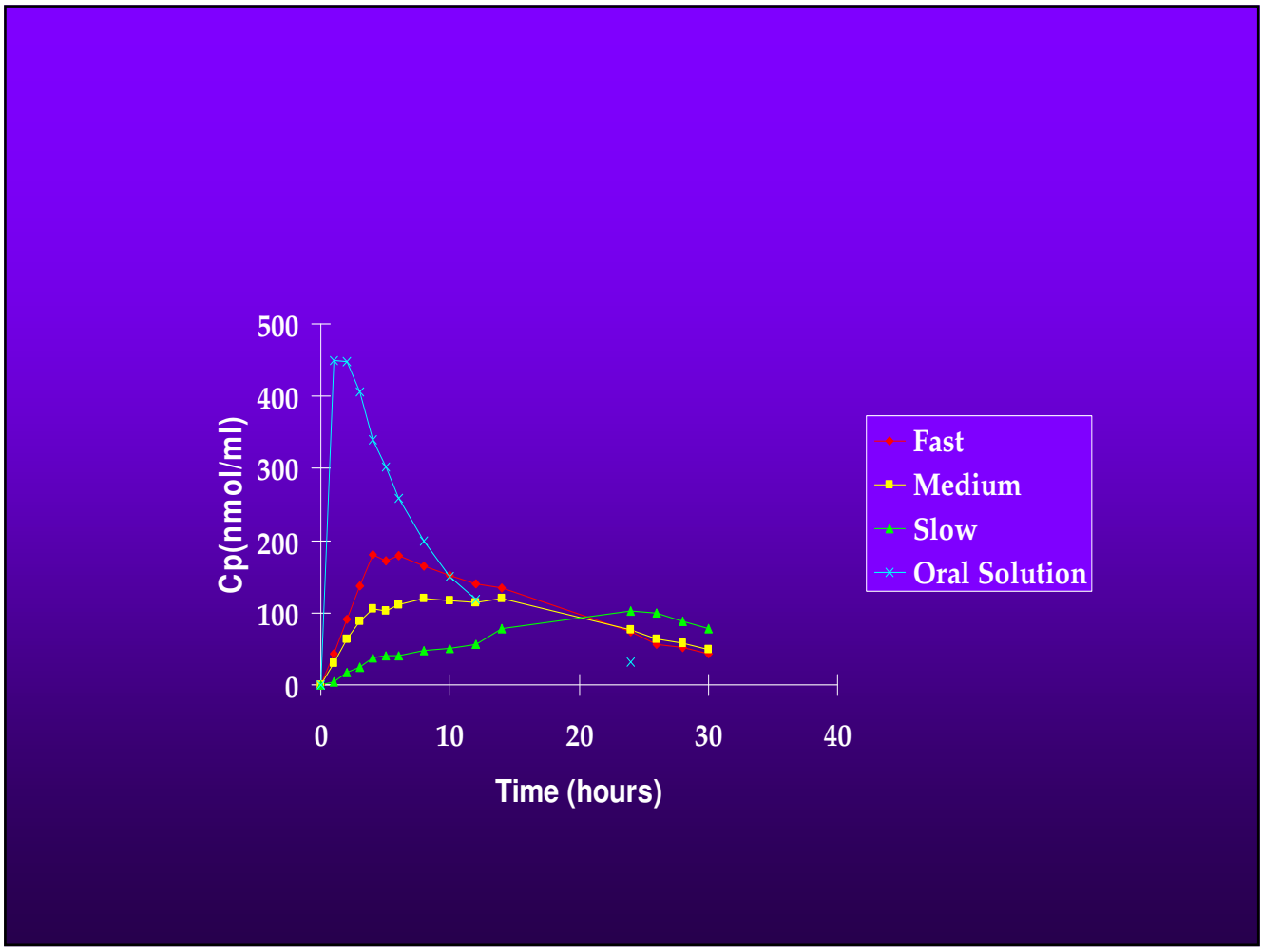
Types of Waivers

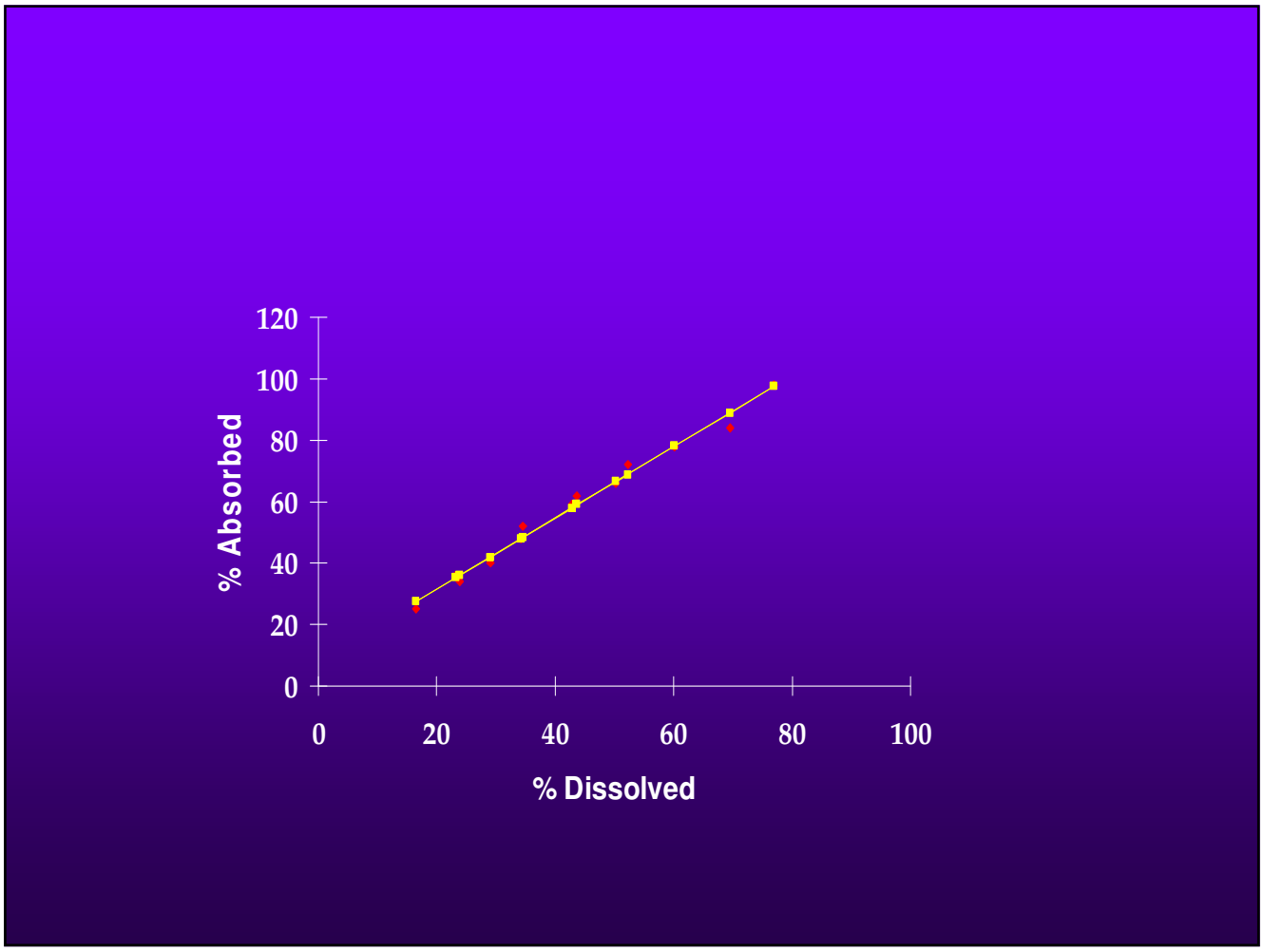
- Waivers for Bioavailability Studies:
  - Manufacturing site changes
  - Equipment changes
  - Method of manufacture
  - Source of raw materials
  - Formulation changes

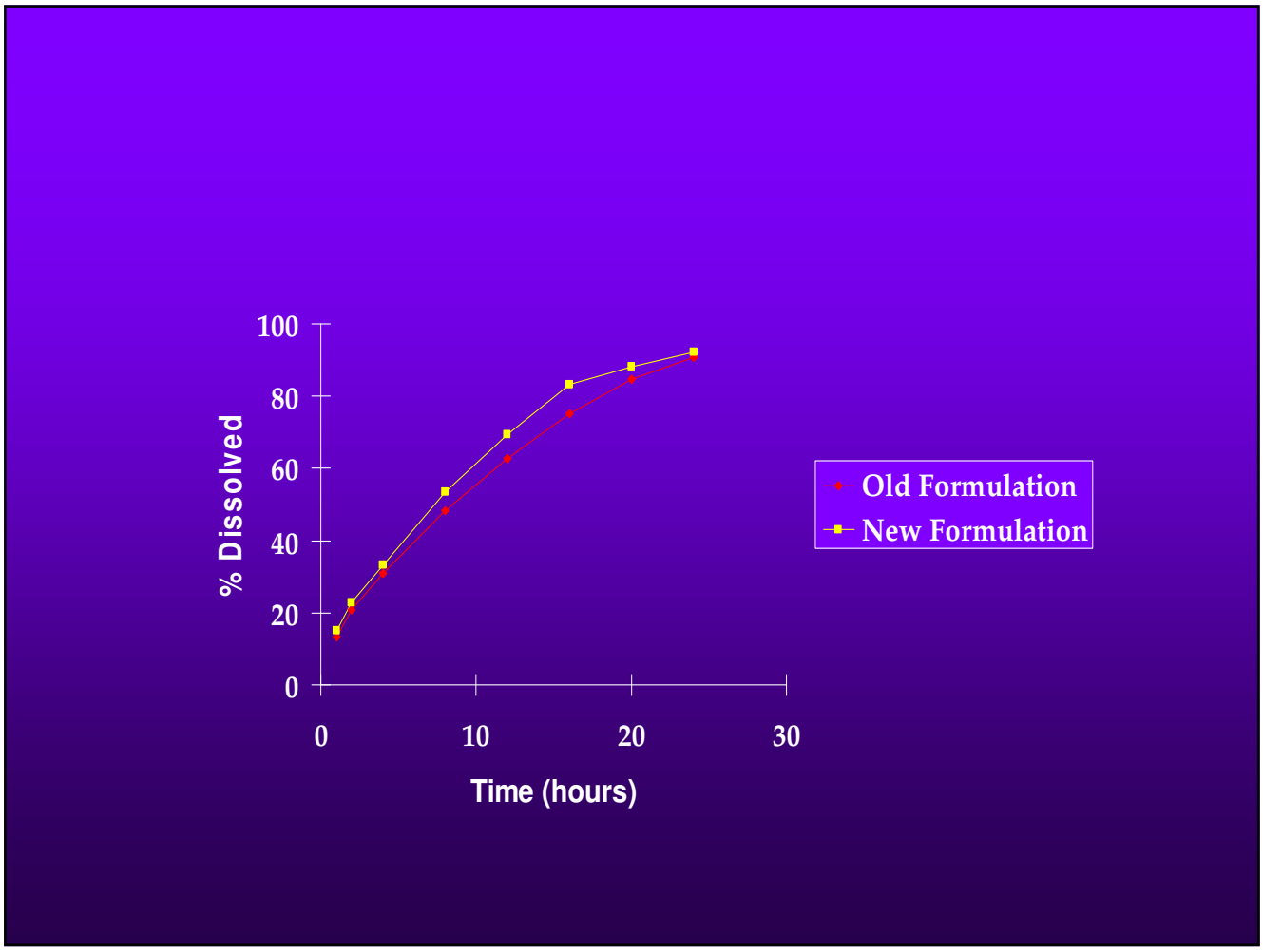
Criteria for Granting Biowaivers with an IVIVC



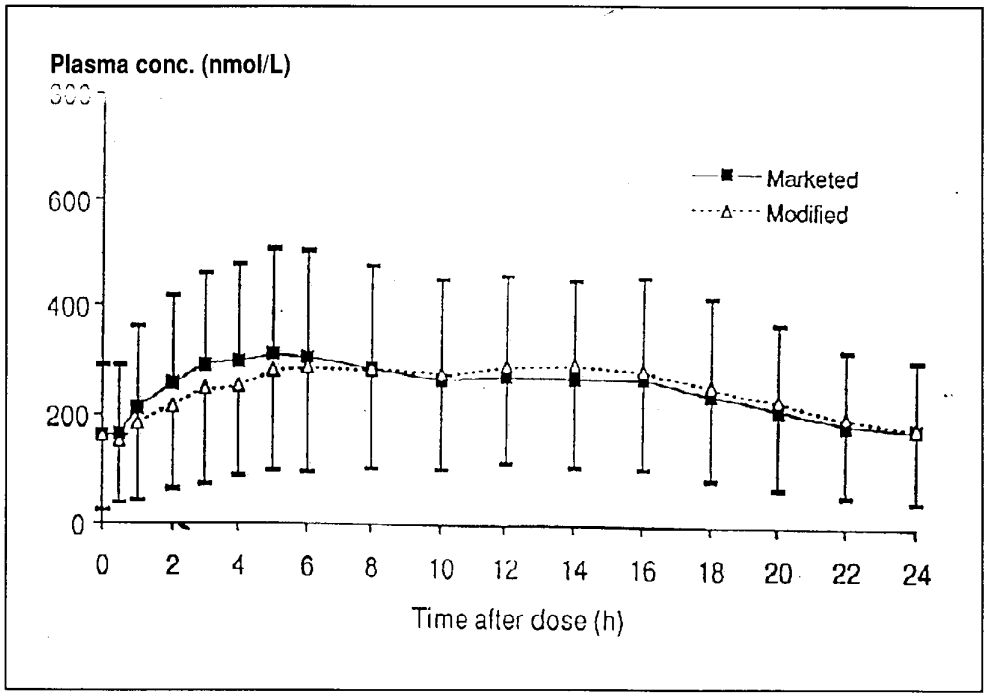



500
400
300
200
100
0
Cp(nmol/ml)
0
10
20
30
40
Time (hours)
Fast
Medium
Slow
Oral Solution


120
100
80
60
40
20
0
% Absorbed
0
20
40
60
80
100
% Dissolved


100
80
60
40
20
0
% Dissolved
0
10
20
30
Time (hours)
Old Formulation
New Formulation

Results (Continued):



	Modified Formulation	Original Formulation	90 % CI
AUC	6129	6073	98-108
CMAX	316	327	93-103
CMIN	160.7	165	
TMAX	10.1	6.14	
Flss	.67	.73	

Level C Correlation

- Data obtained from 36 healthy volunteers
- Eight formulations consisting of different ratios of slow and fast releasing beads
- 4 way incomplete block crossover design

  multiple dose study

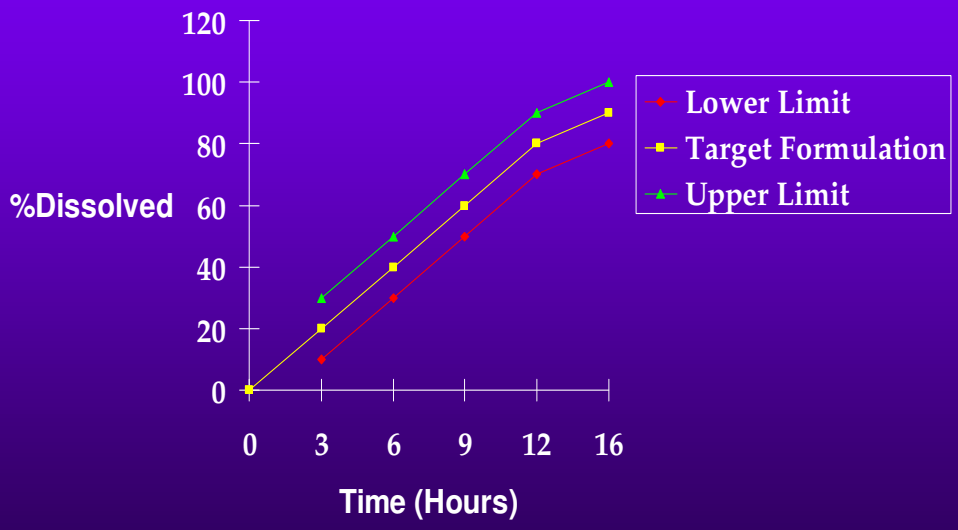
Relationship between % dissolved at various times and certain PK parameters of interest

Parameter	Linear Correlation Equation	R values	P values
AUC	3022.7+(14.32*D6)	0.782	0.0110
	3041.1+(12.18*D9)	0.704	0.0154
	3038.47+(11.79*D12)	0.679	0.0171
CMAX	101.8+(4.01*D6)	0.970	0.000
	102.3+(3.5*D9)	0.965	0.000
	99.26+(3.43*D12)	0.967	0.000

Dissolution Specifications With No IVIVC

- Minimum of 3 points required
- Last time point should be the time where 80% of claimed labeled amount is dissolved
- Specifications set to pass at stage 2 level of testing of the USP acceptance criteria

Dissolution Specifications



Dissolution Specifications

- Ideally, all lots within the lower and upper limit of the specifications are bioequivalent
- Minimally, these lots should be bioequivalent to the clinical trials lots or an appropriate reference standard

Dissolution Specifications

- Variability should no longer be a primary consideration

- Specifications wider than 20 % are acceptable only when evidence is submitted that lots with mean dissolution profiles that are allowed by the upper and lower limits are bioequivalent

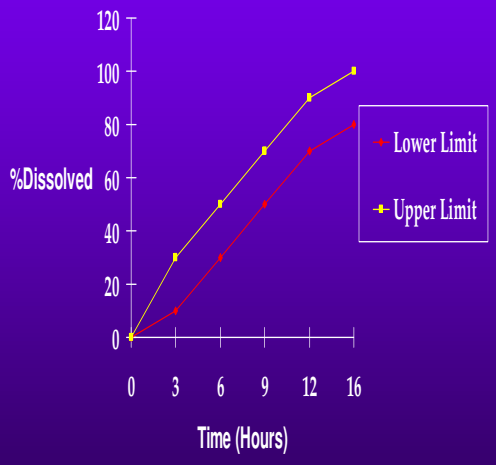
Dissolution Specifications

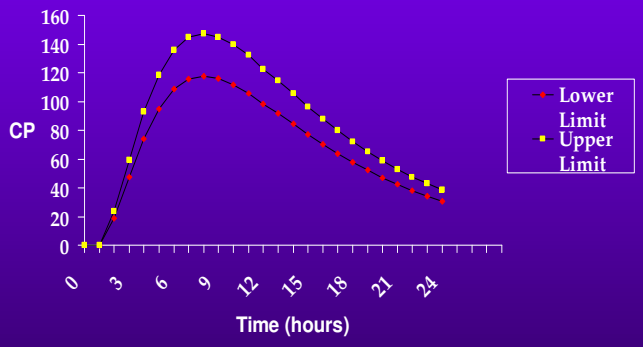
- Impart meaning to the *in vitro* dissolution profile
- Justify the specifications and acceptance criteria

Dissolution Specifications with IVIVC

- IVIVC should be used to set the specification
- External validation is not required to use the IVIVC for setting specifications
- Wider specifications based on what the correlation predicts

Dissolution Specifications with an IVIVC





Dissolution Specifications with a Level C Correlation

- One time point correlation:
  - Use that point to establish the specification in a way that you have a maximum difference of 20 % in the mean predicted CMAX or AUC
  - The other points should be no more than 20 % wide with the clinical/bio profile considered to be the target profile to achieve

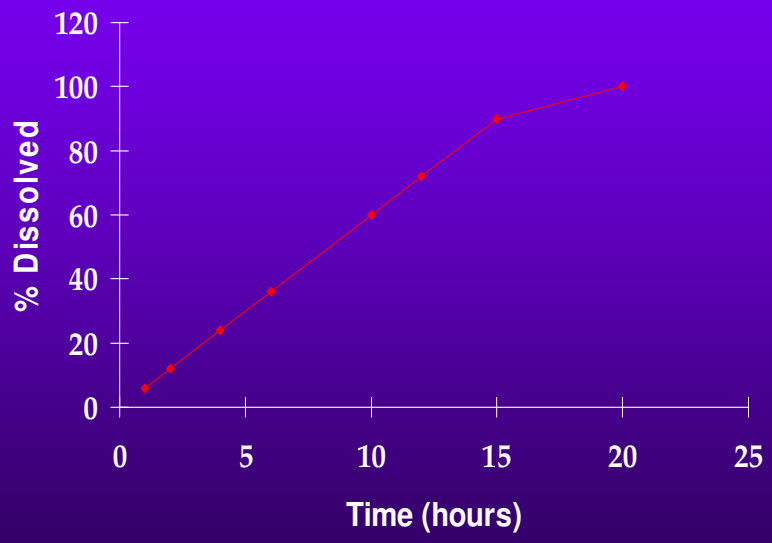
Dissolution Specifications with a Level C Correlation

- Multiple Level C Correlation:
  - establish specifications at each time point in a way to have a maximum difference of 20 % in the mean predicted CMAX or AUC whichever is tighter

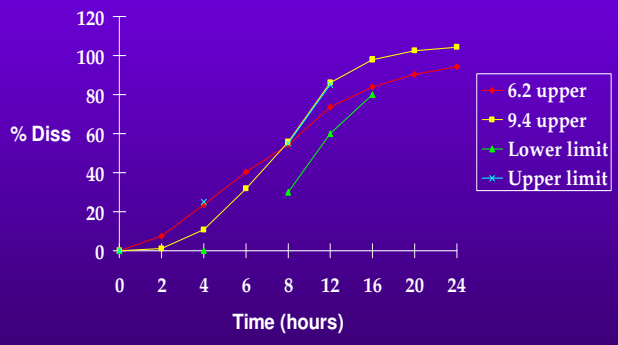
Release Rate Specifications

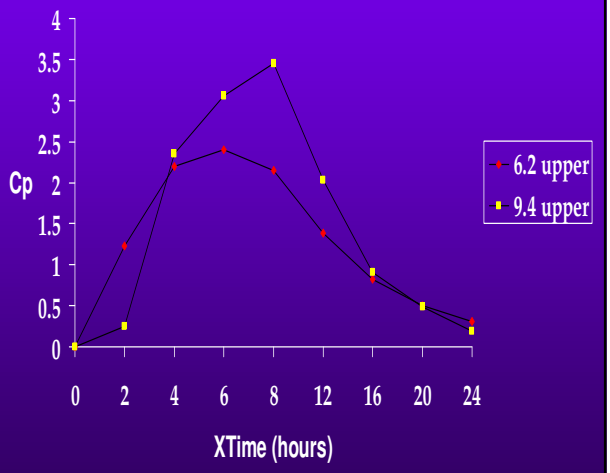
- If the release characteristics of the formulation can be described by a zero order for some period of time and the dissolution profile appears to fit a linear function over that time then
  - A release rate specification to describe the dissolution characteristics could be established

Zero Order Release Rate

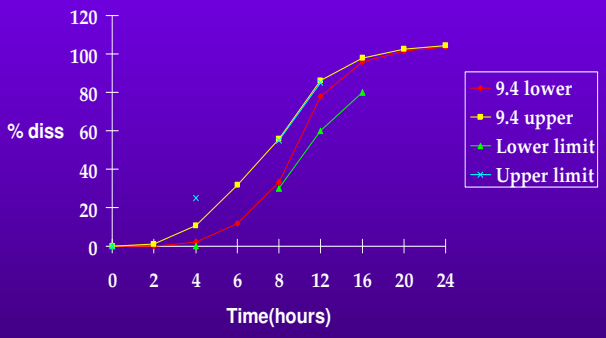


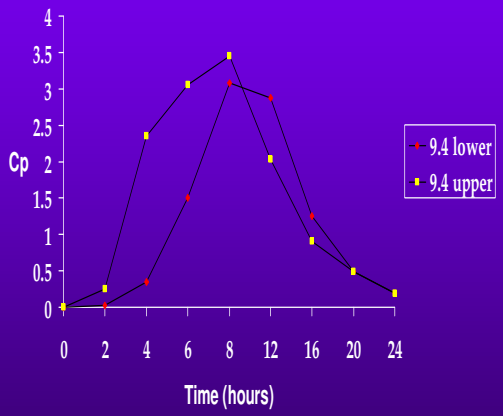
Release Rate Specification





Release Rate Specification





Level A Correlation not Involving Deconvolution

- Correlation was obtained from in vivo data obtained from 6 different studies
- Media Consisted of PH 1.5 for the first 1.5 hours then PH 6.8 buffer for the remainder of the 24 hours

Input Function

- WEIBULL FUNCTION:

Ft= Dose(1-exp-((t-tl)/td)^beta)

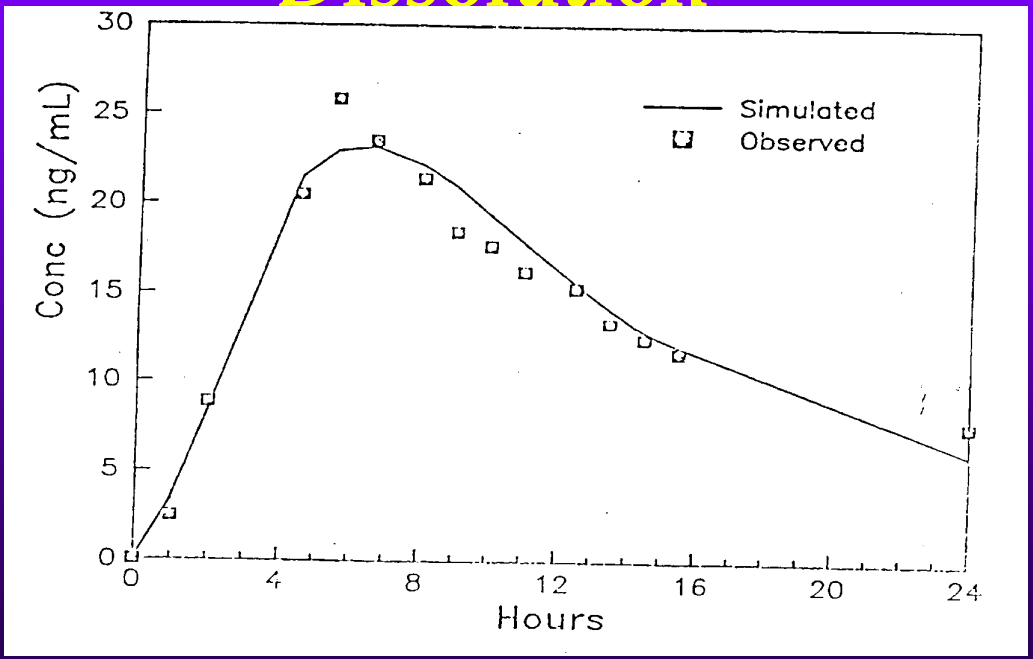
where Dose= labelled dose.

t and tl time and lag time for dissolution.

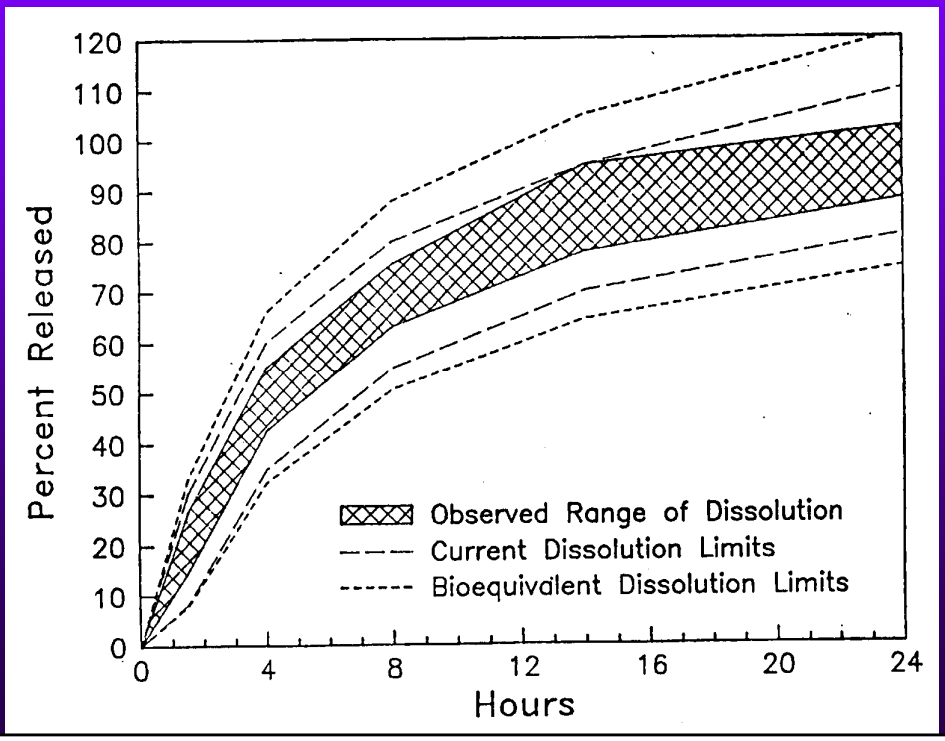
td= time required for 63.2 % of the drug to dissolve.

beta= unitless number ranging from 0 to1.

Plasma Profile Observed And Predicted from Dissolution



Dissolution Limits



Level A Correlation

Table 1

Dosage Strength (Protocol Used In)	Average In-Vitro Slope (%/hr)	Average In-Vivo Slope (%/hr)
95 mg, Batch E-11685 (#84, 85, 87)	6.15 (0.26)	6.17 (0.43)
95 mg, Batch E-12175 (#92, 94)	6.48	6.62 (0.43)
190 mg, Batch E-11687 (#86, 87, 88, 91)	5.35 (0.14)	5.28 (0.27)
190 mg, Batch E-11067 (#63)	5.89	5.91 (0.50)
285 mg, Batch E-12387 (#92)	6.22 (0.11)	6.55 (1.0)
380 mg, Batch E-12385	6.1 (0.07)	6.12 (0.87)

Predicted Plasma Profiles For the Upper and Lower Specification