Dissolution Methodologies and IVIVC

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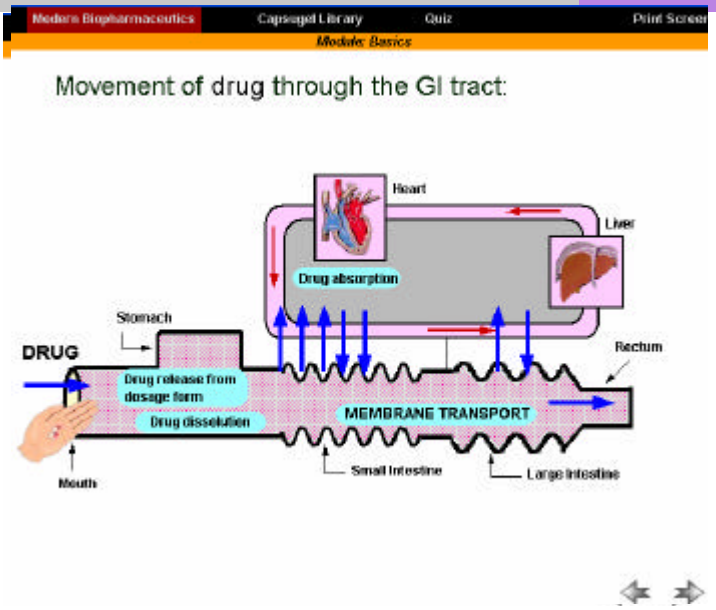
Dissolution Methodologies and IVIVC

- Dissolution testing and BCS
- IVIVC:
  - Definition and Levels
  - Development
    - Calculation of fraction absorbed
    - Mathematical modeling
  - Validation: predictability analysis
  - Approached to obtain IVIVC
    - Non linear Mathematical models
    - Biorelevant Dissolution media
- Curve comparison



Factors influencing dissolution rate

- Noyes Whitney equation

$$\frac{\partial Q}{\partial t} = \frac{A \cdot D}{h} \cdot (C_s - C_t)$$

Factors influencing dissolution rate

Parameter	Physico-chemical characteristic	Physiological variable	In vitro factor
A	Particle size	Presence of surfactants	Presence of surfactants
h		GI motility	Stirring rate System hydrodynamics
D	Molecular size	Viscosity of GI fluids	Viscosity of medium
Cs	hydrophilicity	pH,surfactants	pH, surfactants
Ct		Volume of GI fluids: secretions	Volume of medium

Dissolution test

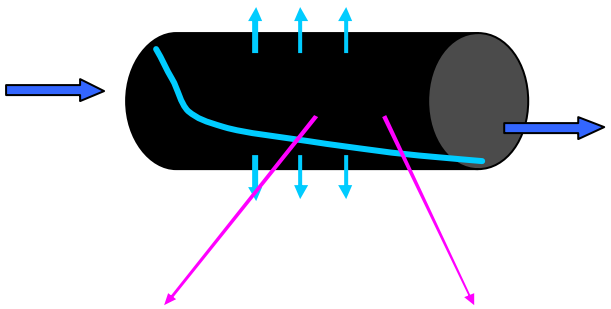
- Quality control:
  - Process control
  - Batch-to-batch quality
- Predictor of Product performance In vivo

BCS

Dissolution test

Biowaiver: permission to use dissolution test as a surrogate of pharmacokinetic data:

- For accepting product sameness under SUPAC-related changes.
- To waive bioequivalence requirements for lower strengths of a dosage form.
- To support waivers for other bioequivalence requirements.



Permeability

Solubility and
Dissolution rate In vivo
Luminal degradation

•Same dissolution profile
•Formulation components do not alter permeability or intestinal transit

Permeability	Volume of aqueous buffer to dissolve the highest dose
	Class I:HS/HP Verapamil, Proparanolol Metoprolol
	Class II:LS/HP Carbamazepine, Ketoprofen, Naproxen
	Class III:HS/LP Ranitidine, Cimetidine, Atenolol
	Class IV: LS/LP Furosemide, Hydrochlorothiazide

BCS Classes

Dissolution Methodology for Immediate Release Products Based on Biopharmaceutics Classification System

Class	Solubility	Permeability	Dissolution Methodology
I	High	High	Single point if NLT 85 % Q in 15 min Multiple point if Q < 85 % in 15 min
II	Low	High	Multiple point
III	High	Low	Same as Class I
IV	Low	Low	Same as Class II

Multiple Point Test: 4 - 6 points each test
Test 1: pH=1, 2 hr., Volume=250 ml
Test 2: Media Change at 0.5, 1, 2 hr. to pH 4.5, 6.5, 8.0
Surfactant media when required to achieve Q=85 %, Volume=900 ml

BCS Classes

In Vitro-In Vivo (IVIV) Correlation Expectations for Immediate Release Products Based on Biopharmaceutics Classification System

Class	Solubility	Permeability	IVIV Correlation Expectation
I	High	High	IVIV correlation if dissolution rate is slower than gastric emptying rate. Otherwise, limited or no correlation is expected.
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate unless dose is very high.
III	High	Low	Absorption (permeability) is rate determing and limited, or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected.

IVIVC Definition

- 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”.

- **Bioequivalent drug products**: Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. (27 CFR 320.1(e)).

Methods for assessing BE[1]

- **Pharmacokinetic study**
- **Pharmacodynamic study**
- **Comparative clinical study**
- **In vitro study**

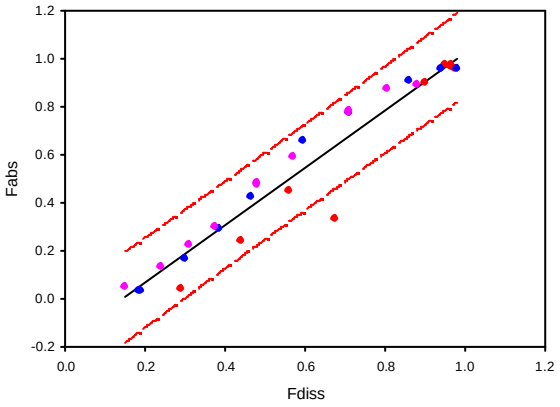
1.GUIDANCE FOR INDUSTRY
Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

- The main objective of developing and evaluating an IVIVC is to establish the **dissolution test as a surrogate** for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post approval changes.

IVIVC Levels

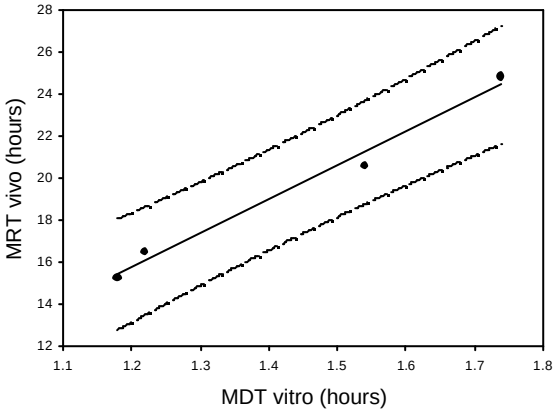
- **L**evel A correlation is a point to point relationship between *in vitro* dissolution and the *in vivo* absorption rate of a drug from the dosage form.
- **L**evel B compares the mean *in vitro* dissolution time (MDTvitro) to the mean *in vivo* dissolution time (MDTvivo).
- **L**evel C is a single point comparison of the amount of drug dissolved at one dissolution time point to one pharmacokinetic parameter.
- **M**ultiple Level C is a correlation involving one or several pharmacokinetic parameters to the amount of drug dissolved at various time points.

Level A correlation



Adapted from Sirisuth N and Eddington N.
Int. J. Generic Drugs (IVIVC series part III)

Level B correlation



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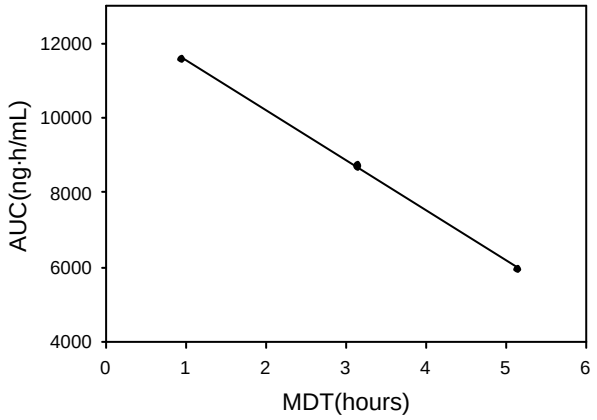
Int. J. Generic Drugs (IVIVC series part III)

Level C correlation



Adapted from Balan G *et al*. *J.Pharm Sci* **90**(8)1176-1185.(2001)

Development of IVIVC: level A

Two steps approach *One step approach*

- develop formulations with different release rates, such as slow, medium, fast;
- obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations

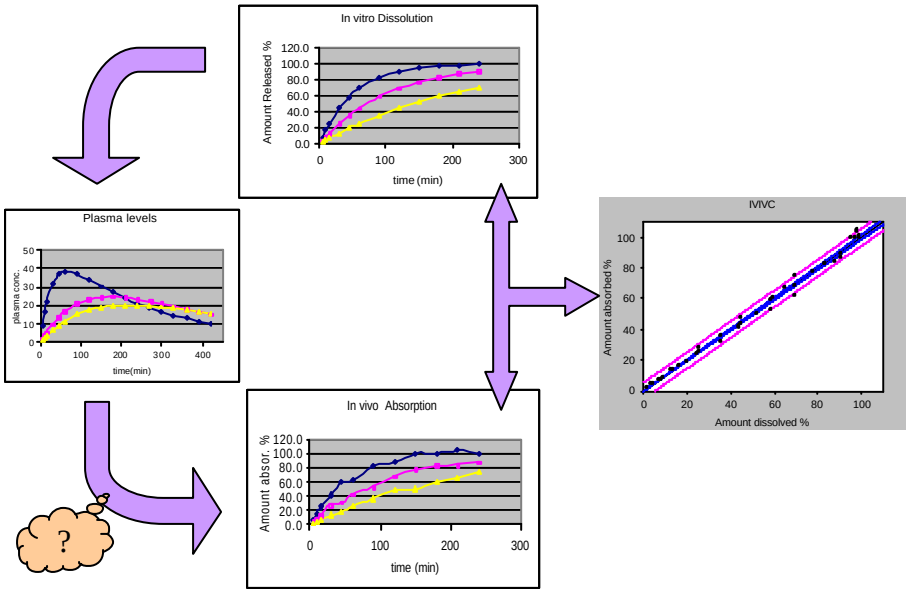
Step 1

- estimate the *in vivo absorption or dissolution time course* using an appropriate technique for each formulation and subject.

Step 2

- Establish the Link model between in vivo and in vitro variable
- Predict plasma concentration from in vitro data using the Link model

- Predict plasma concentration from in vitro profile using a LINK model whose parameters are fitted in one step
  - •Do not involve deconvolution
  - •Link model is not determined separately
  - •Can be done without a reference (IV bolus, oral solution or IR form)



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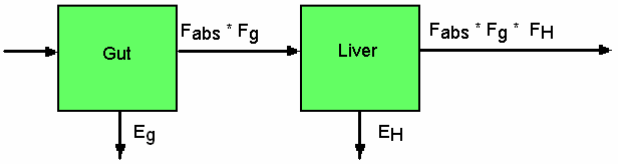
Module: Predicting Fa

Bioavailability after oral administration can be expressed as follows:

$$F_{sys} = F_{abs} * F_g * F_H = F_{abs} * (1 - E_g) * (1 - E_H)$$

where F_{abs} is the fraction of the drug absorbed into the portal system; F_g is the fraction of the absorbed dose that is not eliminated by the gut, and F_H is the fraction escaping first pass metabolism.



Assumptions:
Linear disposition
Linear first pass
Linear absorption

Determining the fraction of dose absorbed

- Model dependent methods
  - Wagner Nelson Equation
  - Loo-Riegelman Method
- Model independent methods
  - Deconvolution

- Wagner Nelson: Mass balance

$$Q_{at} = Q_{ct} + Q_{et}$$

$$Q_{ct} = C \cdot V_d \qquad Q_{et} = k_{el} \cdot V_d \cdot AUC_0^t$$

$$Q_{at} = C_t \cdot V_d + k_{el} \cdot V_d \cdot AUC_0^t$$

$$Q_{a\infty} = k_{el} \cdot V_d \cdot AUC_0^\infty$$

$$\frac{Q_t}{Q_\infty} = \frac{C_t \cdot V_d + k_{el} \cdot V_d \cdot AUC_0^t}{k_{el} \cdot V_d \cdot AUC_o^\infty}$$

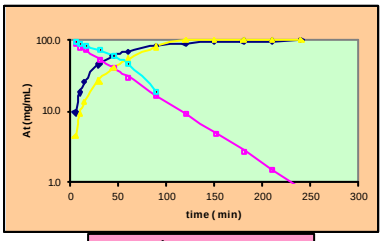
$$Q_{at}/V_d = Q_{ct}/V_d + Q_{et}/V_d$$

- Wagner Nelson: Mass balance

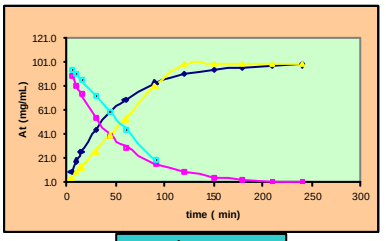
$$A_t = A_c + A_e$$

$$\frac{A_t}{A_\infty} = \frac{C_t + k_{el} \cdot AUC_0^t}{k_{el} \cdot AUC_o^\infty}$$

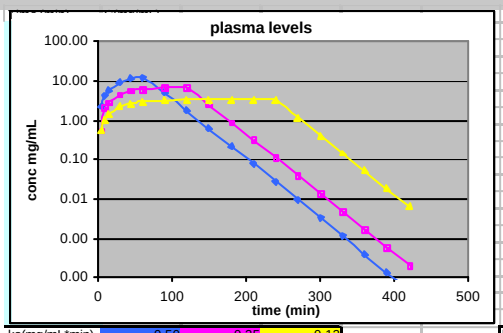
$$1 - \frac{A_t}{A_\infty} = \text{fraction remaining to be absorbed}$$

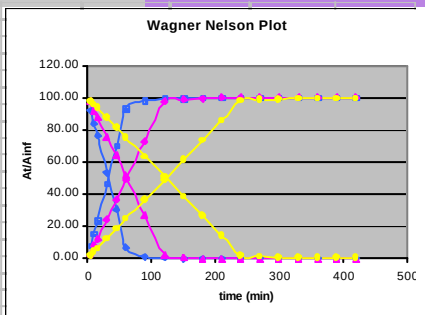


$$\ln(100 - \frac{A_t}{A_\infty}) = \ln 100 - k_a \cdot t$$



$$(100 - \frac{A_t}{A_\infty}) = 100 - k_a \cdot t$$

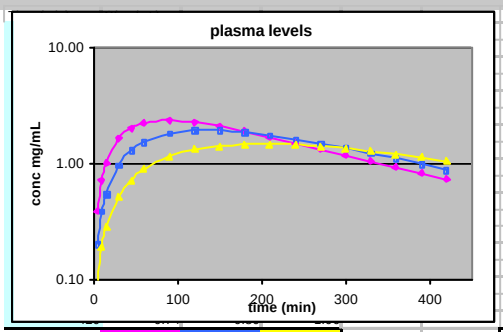


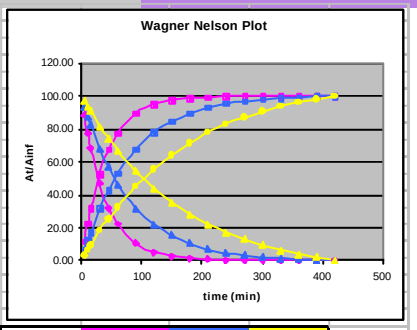


ko(mg/mL*min)	0.50	0.25	0.12
kel(min-1)	0.04	Vd(L)	10
t1/2(min)	19.80		
cinf	14.29	7.14	3.43

ko(calc)	-0.4664	-0.2469	-0.1229

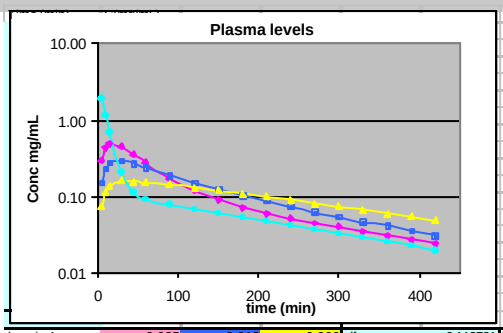
$$(100 - \frac{A_t}{A_\infty}) = 100 - k_a \cdot t$$

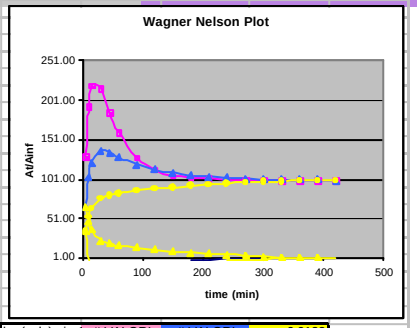




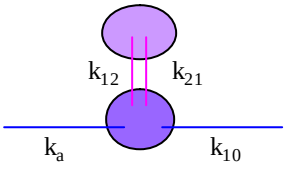
ka min-1	0.025	0.013	0.006		ka(calc)min-1	-0.0250	-0.0126	-0.0069
kel(min-1)	0.004							
t1/2(min)	173.25							
Vd	30.00							
D	100.00							

$$\ln(100-\frac{A_t}{A_\infty}) = \ln 100 - k_a \cdot t$$





ka min-1	0.025	0.013	0.006	alfa	0.113781	ka (calc)min-1	#¡VALOR!	#¡VALOR!	-0.0122
k10(min-1)	0.0600	Vc	30.00	beta	0.004219				
k12 min-1	0.0500								
k21 min-1	0.0080								
D	100.00								



$$A = C + E$$

- Loo-Riegelman: Mass balance

$$\frac{Q_a}{V_c} = \frac{Q_c + Q_e + Q_p}{V_c}$$

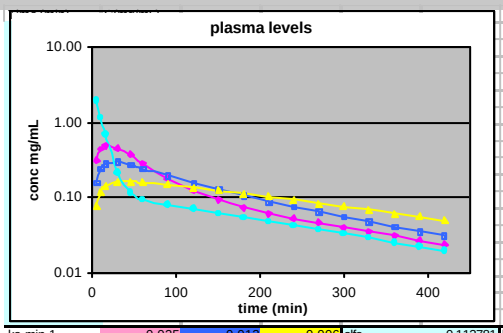
$$A_t = C_t + E_t + P_t$$

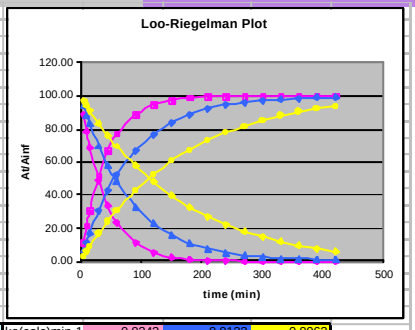
Parameters obtained from IV data
IV and oral administration with the same subjects

$$A_t = C_t + k_{10} \cdot AUC_0^t + P_t$$

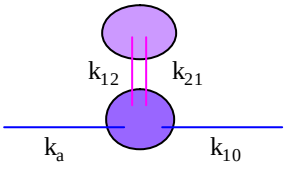
$$P_t = k_{12} \cdot e^{-k_{21} \cdot t} \cdot \int_0^t C \cdot e^{k_{21} \cdot t} \partial t$$

$$P_t = P_{t-1} \cdot e^{-k_{21} \cdot \Delta t} + \frac{k_{12}}{k_{21}} \cdot C_{t-1}(1 - e^{-k_{21} \cdot \Delta t}) + \frac{k_{12}}{2} \cdot \Delta C \cdot \Delta t$$

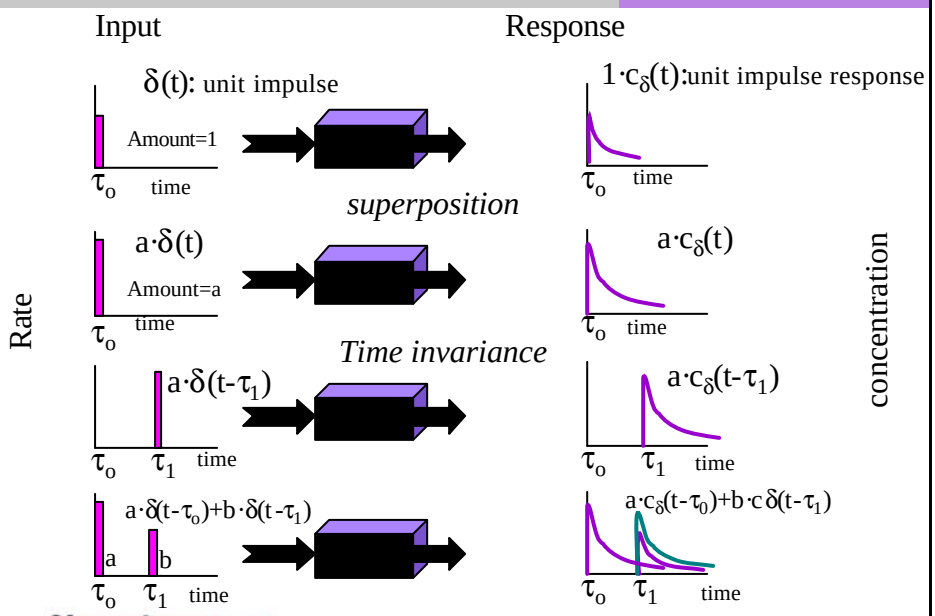


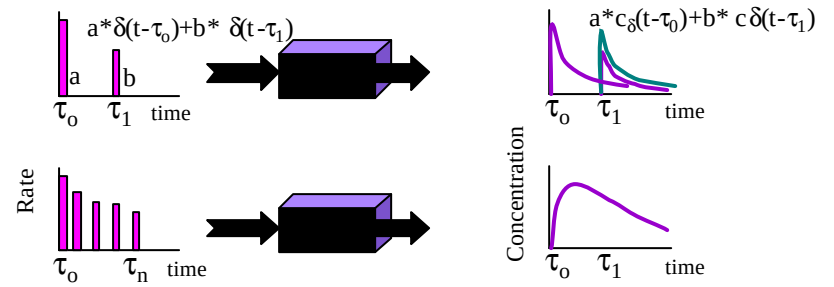


ka min-1	0.025	0.013	0.006	alfa	0.113781	ka(calc)min-1	-0.0242	-0.0122	-0.0062
k10(min-1)	0.0600	Vc	30.00	beta	0.004219				
k12 min-1	0.0500								
k21 min-1	0.0080								
D	100.00								



$$A = C + E + P$$





Amount= $f(\tau_n)\Delta\tau$

C(t)= $[f(\tau_o)\,\Delta\tau]\cdot c_\delta(t-\tau_o)+$
$[f(\tau_1)\,\Delta\tau]\cdot c_\delta(t-\tau_1)+\ldots.$
$[f(\tau_n)\,\Delta\tau]\cdot c_\delta(t-\tau_n)=$

$$c(t)=\sum_{n=0}^{n=n,t=t} f(t)\cdot c_d(t-t_n)\cdot\Delta t$$

$$\Delta t \rightarrow 0$$

$$c(t)=\int_0^t f(t)\cdot c_d(t-t)\cdot dt$$

response impulse Unit impulse response

Methods of Deconvolution

Convolution: solving c(t) given f(t) and $c_\delta(t)$
Deconvolution: solving f(t) given $c\delta(t)$ and c(t)
or solving $c\delta(t)$ given f(t) and c(t)

- Analytic: Laplace transforms
- Implicit: deconvolution by curve fitting
- Numeric: point-area

Laplace transform

$$\ell\{f(t)\} = F(s) = \int_0^\infty e^{-s\cdot t} \cdot f(t) \cdot \partial t$$

- Analytic: Laplace transforms

$$c(t) = \int_0^t f(t) \cdot c_d(t-t) \cdot dt$$

response input Unit impulse response

$$c(t) = \ell^{-1}\left[\ell[f(t)] \cdot \ell[c_d(t)]\right]$$

$$\ell[c(t)] = \left[\ell[f(t)] \cdot \ell[c_d(t)]\right]$$

$$C(s) = F(s) \cdot C_d(s)$$

$$f(t) = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t} \quad \ell[f(t)] = \frac{F \cdot D \cdot k_a}{(s+k_a)}$$

$$c_d(t) = \frac{1}{D} \cdot \left(\frac{D}{V_d} \cdot e^{-k_{el} \cdot t}\right) \quad \ell[c_d(t)] = \frac{1}{V_d \cdot (s+k_{el})}$$

$$\ell[f(t)] \cdot \ell[c_d(t)] = \frac{F \cdot D \cdot k_a}{V_d \cdot (s+k_a) \cdot (s+k_{el})}$$

$$\ell^{-1}\left[\frac{F \cdot D \cdot k_a}{V_d \cdot (s+k_a) \cdot (s+k_{el})}\right] = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k_{el})} \cdot (e^{-k_{el} \cdot t} - e^{-k_a \cdot t})$$

Implicit: deconvolution by curve fitting

$$c_d(t) = \frac{1}{D} \cdot \left(\frac{D}{\square} \cdot e^{\square \cdot t}\right)$$

$$c(t) = \frac{F \cdot D \cdot k_a}{\square \cdot (\square - k_a)} \cdot \left(e^{-k_a \cdot t} - e^{\square \cdot t}\right)$$

Simultaneous fit

$$f(t) = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t}$$

Numeric: point-area

$$c(t) = \int_0^t f(t) \cdot c_d(t - t) \cdot dt$$

Assuming f(τ)= R= constant in an interval: $T_{i-1} < \tau < T_i$

$$c(Tn) = \sum_{i=1}^{n} R_i \int_{T_{i-1}}^{Ti} c_d(Tn - t) \cdot dt$$

By substitution of variables, solving for Rn, if Δτ is constant

$$R_n = \frac{c_n - \sum_{i=2}^{n} R_{i-1} \cdot AUC_{d\,n-i+1}^{n-i+2}}{AUC_0^1}$$

$$R_1 = \frac{c_1}{AUC_0^1}$$

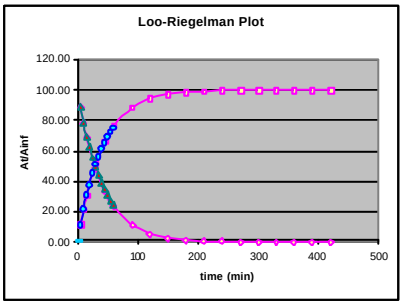
$$R_2 = \frac{c_2 - (R_1 \cdot AUC_1^2)}{AUC_0^1}$$

$$R_3 = \frac{c_3 - (R_1 \cdot AUC_2^3 + R_2 \cdot AUC_1^2)}{AUC_0^1}$$

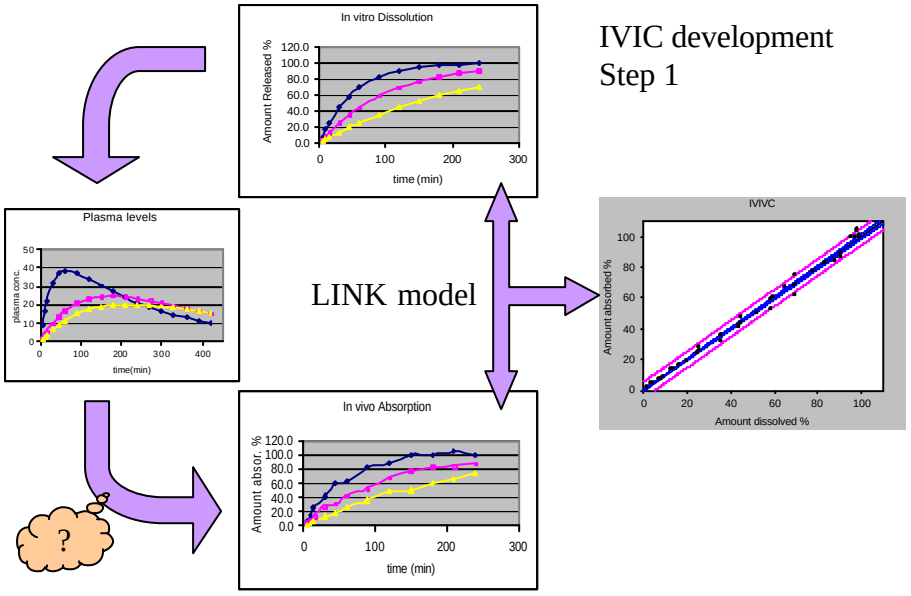
$$R_4 = \frac{c_4 - (R_1 \cdot AUC_3^4 + R_2 \cdot AUC_2^3 + R_3 \cdot AUC_1^2)}{AUC_0^1}$$

Point area

Time (min)	C(mg/mL)	25	AUC(Tn-1-Tn		
5	2.250	14.51	98.77	AUC(T0-T1)	
10	3.302	8.56	57.68	AUC(T1-T2)	
15	3.699	5.19	34.38	AUC(T2-T3)	
20	3.749	3.27	21.16	AUC(T3-T4)	
25	3.621	2.18	13.63	AUC(T4-T5)	
30	3.411	1.56	9.34	AUC(T5-T6)	
35	3.169	1.19	6.87	AUC(T6-T7)	
40	2.924	0.98	5.44	AUC(T7-T8)	
45	2.688	0.86	4.60	AUC(T8-T9)	
50	2.468	0.78	4.10	AUC(T9-T10)	
55	2.266	0.73	3.78	AUC(T10-T11)	
60	2.083	0.70	3.57	AUC(T11-T12)	
		R*dT	Suma(R*dT)	*100	100-A
R1	0.02278	0.11392	0.1139	11.39	88.61
R2	0.02012	0.10060	0.2145	21.45	78.55
R3	0.01777	0.08884	0.3034	30.34	69.66
R4	0.01384	0.06918	0.3725	37.25	62.75
R5	0.01494	0.07471	0.4473	44.73	55.27
R6	0.01225	0.06127	0.5085	50.85	49.15
R7	0.01083	0.05413	0.5627	56.27	43.73
R8	0.00956	0.04782	0.6105	61.05	38.95
R9	0.00845	0.04226	0.6527	65.27	34.73
R10	0.00747	0.03734	0.6901	69.01	30.99
R11	0.00660	0.03300	0.7231	72.31	27.69
R12	0.00583	0.02917	0.7523	75.23	24.77



$$R_n = \frac{c_n - \sum_{i=2}^{n} R_{i-1} \cdot AUC_{d\ n-i+1}^{\ n-i+2}}{AUC_0^1}$$



IVIC development
Step 1

Dual Step method:

Step1:

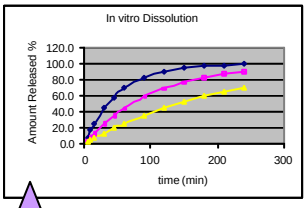
1. IV bolus: Obtain Unit Impulse Response (UIR)
2. Oral administration
3. Deconvolution of oral curve using UIR to obtain Input function in vivo *f(t)vivo*
4. Dissolution In vitro: *f(t)vitro*
5. LINK model: relationship between in vitro variable and in vivo
   f(t)vivo=Link(f(t)vitro)

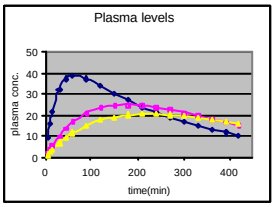
Step 2:

1. Predict plasma concentration from in vitro data using link model
   *C(t)=(Link(f(t)vitro)*UIR*

References to obtain UIR. Input function

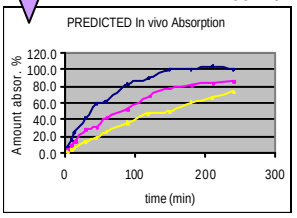
- IV bolus,
  - UIR: disp;
  - Input function: diss+abs+1st pass: availability rate
- Oral Solution,
  - UIR (abs +1st pass)
  - Input function: release rate
- IR dosage form,
  - UIR (diss from IR+ abs + 1st pass)
  - Input function: release rate from MR

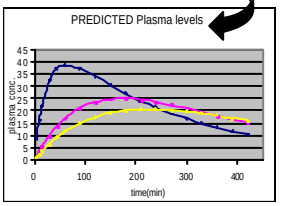




f(t)vivo=Link(f(t)vitro)

*C(t)=(Link(f(f(t)vitro)*UIR*





IVIC : step 2 and predictability analysis

% Prediction error		
	Cmax	AUC
Fast	<15%	<15%
Med	<15%	<15%
Slow	<15%	<15%
Average	<10%	<10%

- Internal validation
- External validation

Approaches to obtain an IVIVC

1. Look for an appropriate mathematical model to describe the relationship between in vitro-in vivo dissolution

2. Choose different dissolution conditions to match in vivo dissolution profile

Level A correlation: Approach 1. Example of non linear relationships

Proportional Odds models

$T_{vit\ or\ viv}$: Time to go into solution ⟶ Random variable

$F_{(t)vit\ or\ viv}$: Distribution function=fraction of dose dissolved at time t

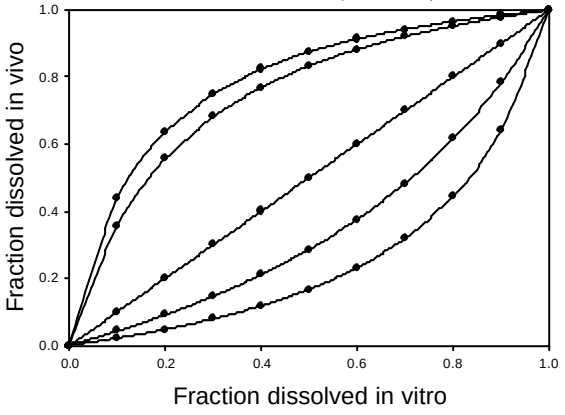
$$\log\left(\frac{F_{(t)viv}}{1-F_{(t)viv}}\right)=\log(a)+\log\left(\frac{F_{(t)vit}}{1-F_{(t)vit}}\right)$$

Adapted from *Dunne A. et al. J Pharm Sci*. **86**(11)1245-1249(1997)

Level A correlation: Approach 1. Example of non linear relationships

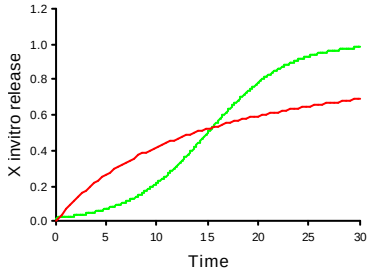
Proportional Odds models

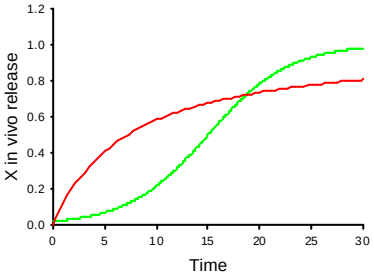
$$\log\left(\frac{F_{(t)viv}}{1-F_{(t)viv}}\right)=\log(a)+\log\left(\frac{F_{(t)vit}}{1-F_{(t)vit}}\right)$$

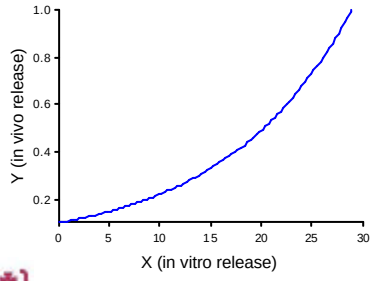


Adapted from *Dunne A. et al. J Pharm Sci*. **86**(11)1245-1249(1997)

Autonomic vs non autonomic relationships







Biorelevant Dissolution Media: Approach 2

Fasted State simulated intestinal Fluids			Fed State simulated intestinal Fluid	
pH	6.8	6.5	pH	5.0
Osmolality (mOsmol)	280-310±10	270±10	Osmolality(mOsmol)	635±10
Na Taurocholate	5 mM	3 mM	Na Taurocholate	15 mM
Lecithin	1.5 mM	0.75 mM	Lecithin	3.75 mM
KH_2PO_4	0.029 mM	3.9 g	Acetic Acid	8.65 g
KCl	0.22M	7.7 g	KCl	15.2 g
NaOH	qs pH 6.8	qs pH 6.5	NaOH	Qs pH 5.0
Deionized Water	qs 1 liter	qs 1 liter	Deionized Water	Qs 1 liter

- From *Galia E et al . Pharm Res* 15(5) 698-705 (1998)
- From *Dressman J et al. Pharm Res* 15(1) 11-22 (1998)

Component	Concentration (mM)				
	FaSIMS	FESIMS	FeSIES	FaSSIF	FeSSIF
Taurodeoxycholate	5	10	10	-	-
Taurocholate	-	-	-	3	15
KH_2PO_4	-	-	-	29	-
CH_3COOH	-	-	-	-	144
Dodecanoic Acid	0.25	10	20	-	-
Monocaprin	-	3	10	-	-
Sesame oil	-	-	70	-	-
Lecithin	0.25	0.6	3	0.75	3.75
Lysolecithin	0.75	2.4	3	-	-
NaCl	142	85	85	-	-
KCl	-	-	-	103	204
pH	5 to7.5	5 to 7.5	5	6.5	5
Visual description	Clear	Pearlescent at pH 5; Clear at pH 7.5	Pearlescent w/TG; Cloudy without TG	Sightly cloudy	Clear

Adapted from *Luner P. and Vander Kamp D. et al. J. Pharm Sci* 90(3) 348-359(2001)

Biorelevant Dissolution Media: Approach 2

Fasted State simulated Gastric Fluid	
HCl	0.01-0.05 N6.5
Na Lauryl sulfate	2.5 g
NaCl	2 g
Distilled Water	qs 1 liter

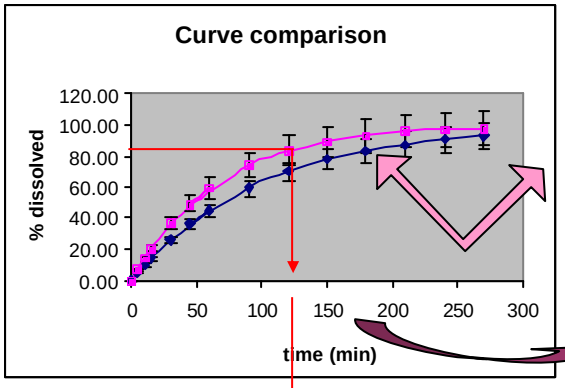
From *Dressman J et al. Pharm Res* 15(1) 11-22 (1998)

Dissolution curve comparison

- Model independent approach:
  - f1: difference factor
  - f2 similarity factor

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n} \cdot \sum_{t=1}^{n} \left(R_t - T_t\right)^{-05}\right] \cdot 100\right\}$$

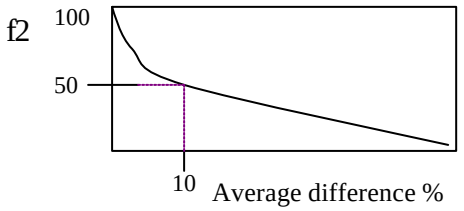
$$f_1 = \left\{\frac{\sum_{t=1}^{n} \left|R_t - T_t\right|}{\sum_{t=1}^{n} R_t}\right\} \cdot 100$$



- Three to four or more dissolution data point availables
- Coefficient of variation of the earlier data points less than 20% and in later data points not more of 10%
- Same data points for reference and test

- Only one data point after 85% dissolution of one of the products

- A f2 value =50 ensures sameness of the two curves. (An average difference between two profiles of 10% at all sampling data points corresponds to an f2 value of 50)

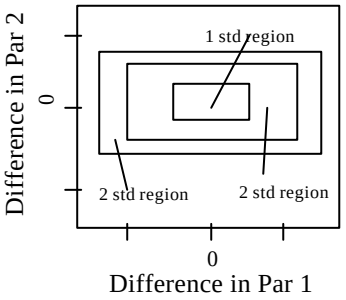


Dissolution curve comparison

- Model dependent approach.
  - Select the most appropriate model for the dissolution profiles from the reference batches.
  - A similarity region is set based on variation of parameters of the fitted model from the reference batches.
  - Calculate the MSD in model parameters between test and reference batches.
  - Estimate the 90% confidence region of the true difference between the two batches.
  - Compare the limits of the confidence region with the similarity region.

Reference batches

$Batch_1$	Par1	Par2	$Batch_2$	Par 1	Par2
Unit $_1$ 1	$Par_1$11	$Par_1$21	Unit $_2$ 1	$Par_2$11	Par $_2$ 21
Unit $_1$ 2	Par $_1$ 12	Par $_1$ 22	Unit $_2$ 2	$Par_2$12	Par $_2$ 22
…	…	…	…		…
Unit $_1$ n	Par $_1$ 1n	Par $_1$ 2n	Unit $_2$ n	$Par_2$1n	Par $_2$ 2n
Average ± SD					



Pooled SD=Sqrt((var 1+var2/2)+var(interbatch))
Construct similarity region

$Batch_{Test}$	Par1	Par2	$Batch_{Ref}$	Par 1	Par2
Unit $_1$ 1	$Par_1$11	$Par_1$21	Unit $_2$ 1	$Par_2$11	Par $_2$ 21
Unit $_1$ 2	Par $_1$ 12	Par $_1$ 22	Unit $_2$ 2	$Par_2$12	Par $_2$ 22
…	…	…	…		…
Unit $_1$ n	Par $_1$ 1n	Par $_1$ 2n	Unit $_2$ n	$Par_2$1n	Par $_2$ 2n
Average ± SD					

$$D^2 = \left[\left(X_T - X_R \right)^t \cdot S_{pooled}^{-1} \cdot \left(X_T - X_R \right) \right]$$

$$T^2 = K \cdot D^2$$

$$K = \left(\frac{N1 + N2 - P - 1}{(N1 + N2 - 2) \cdot P} \right) \cdot \left(\frac{N1 \cdot N2}{N1 + N2 - P} \right)$$

$$CR = \left\{ K \cdot \left[(Y - (X_T - X_R))^t \cdot S_{pooled}^{-1} \cdot (Y - (X_T - X_R)) \right] \right\}$$

$$CR \leq F_{(P, N1+N2-P-1, 0.90)}$$

D^2= squared Mahalanobis distance (M)
T^2=Scaled M distance (Hotelling T^2)
K= scaling factor
Nn=number units of lot n
P= number of parameters
CR= confidence region
Xn= vectors of mean parameters of test and ref.
S^{-1}pooled=inverse of pooled sample variance-covariance matrix

Contrast CR with similarity region