Dissolution / Biowaivers / *IVIVC*

Helmut Schütz

Human Guineapigs I

BE as a surrogate for clinical efficacy / safety ('essential similarity')

- We want to get unbiased estimates, *i.e.*, the point estimate from the study sample …

$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$

- … should be representative for the population of patients

$$F_{Pop} = \frac{\mu_{Test}}{\mu_{Reference}}$$

Human Guineapigs II

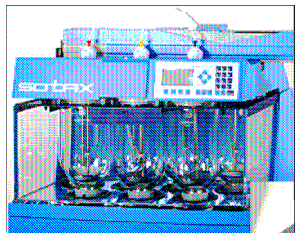
BE as a special case of documented pharmaceutical quality

- The *in vivo* release in the biostudy …

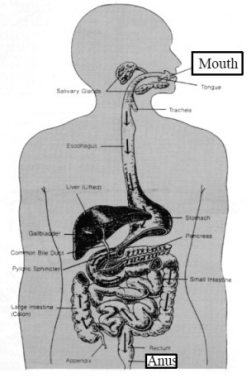
$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$

- … should be representative for the *in vitro* performance

$$f_2 = 50 \cdot \log\left\{\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}\left[\bar{R}(t)-\bar{T}(t)\right]^2}{n}}}\right\}$$



Models *vs.* Reality



Dissolution

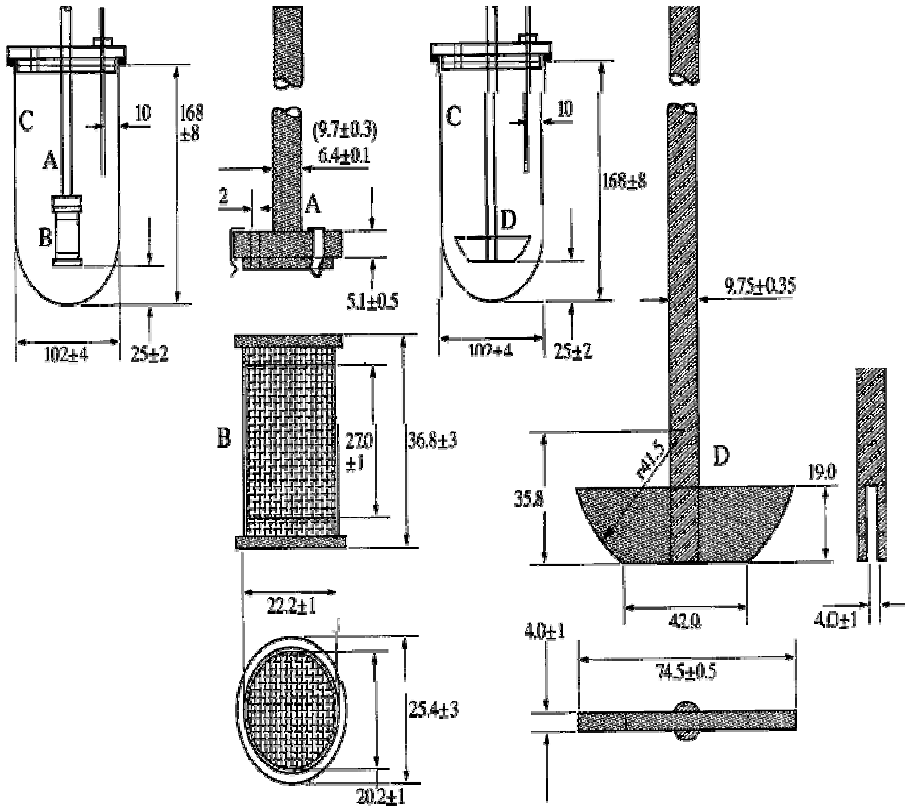
USP Dissolution Apparatus

- Apparatus 1 – Basket (37 ºC)
- Apparatus 2 – Paddle (37 ºC)
- Apparatus 3 – Reciprocating Cylinder (37 ºC)
- Apparatus 4 – Flow-Through Cell (37 ºC)
- Apparatus 5 – Paddle over Disk (32 ºC)
  - Transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless steel disk assembly to hold the transdermal on the bottom of vessel
- Apparatus 6 – Cylinder (32 ºC)
  - Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless steel cylinder element
- Apparatus 7 – Reciprocating Holder
  - For transdermal delivery systems and a variety of dosage forms

Malcolm Ross. *Bioequivalence, Dissolution & IVIVC*. Vienna, 12–14 June, 2017

Dissolution

USP Apparatus 1 and 2



Dissolution

Paddle *vs.* Basket

- **Weakness of Paddle Method**
  - Problems with floating dosage units products
  - Problems with sticking dosage units
  - Use of spiral for holding capsules is subject to variability with operators
  - The phenomenon of cone formation that results from non-dispersion of disintegrated tablets can lead to nonreproducibility of test
- **Weakness of Basket Method**
  - Poor mechanical stability
  - Hindered visual inspection
  - Disintegration-dissolution interaction (slower disintegration keeps the dosage unit in a site of higher agitation, thus increasing dissolution)
  - Poor homogeneity of the bulk fluid due to insufficient stirring or agitation
  - Sensitivity against external vibration, eccentricity, and the presence of baffles such as thermometer or sampling tube
  - Inconvenience for cleaning the set-up after testing

Malcolm Ross. *Bioequivalence, Dissolution & IVIVC*. Vienna, 12–14 June, 2017

Biopharmaceutics Classification System

BCS (Amidon *et al.* 1995)*

- Differentiates drugs based on their solubility and permeability
- Four Classes
  - Class I high permeability, high solubility
    well absorbed, absorption rate higher than excretion
    BCS-based biowaiver generally possible
  - Class II high permeability, low solubility
    BA limited by solvation rate; *IVIVC* possible
  - Class III low permeability, high solubility
    BA limited by permeation rate
    BCS-biowaiver under certain conditions
  - Class IV low permeability, low solubility
    low and highly variable BA

* Amidon GL, Lennernäs H, Shah VP, Crison JR. *A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability*. Pharm Res. 1995;12(3):413–20.

Biopharmaceutics Classification System

BCS (Amidon *et al.* 1995)*

- Two principles
  - If two drug products, containing the same drug, have the same concentration time profile at the intestional membrane surface then they will have the same rate and extent of absorption
  - If two drug products have the same *in vivo* dissolution profile *under all luminal conditions*, they will have the same rate and extent of absorption

* Amidon GL, Lennernäs H, Shah VP, Crison JR. *A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability*. Pharm Res. 1995;12(3):413–20.

Biopharmaceutics Classification System

High Solubility

- Class boundary of *drug* (at the highest dose strenght of IR product)
  - If ≥85% dissolves in ≤250 mL of aqueous media over the pH range of 1 – 6.8 (including pK_a –1, pK_a, pK_a +1).
    - Shake-flask method (or any other if justified)
    - ≥3 determinations at each condition
- Class boundary of *drug product* (at the highest dose strenght)
  - If ≥85% dissolves (*rapidly*: within 30 minutes, *very rapidly*: within 15 minutes) in ≤500 mL (EMA: ≤900 mL) of
    - pH 1.0 – 1.2 (0.1 N HCl or simulated gastric fluid USP without enzymes)
    - pH 4.5 buffer
    - pH 6.8 buffer or simulated gastric fluid USP without enzymes
  - using
    - USP apparatus I (basket) at 100 rpm or
    - USP apparatus II (paddle) at 50 rpm (FDA: 75 rpm if justified)

Biopharmaceutics Classification System

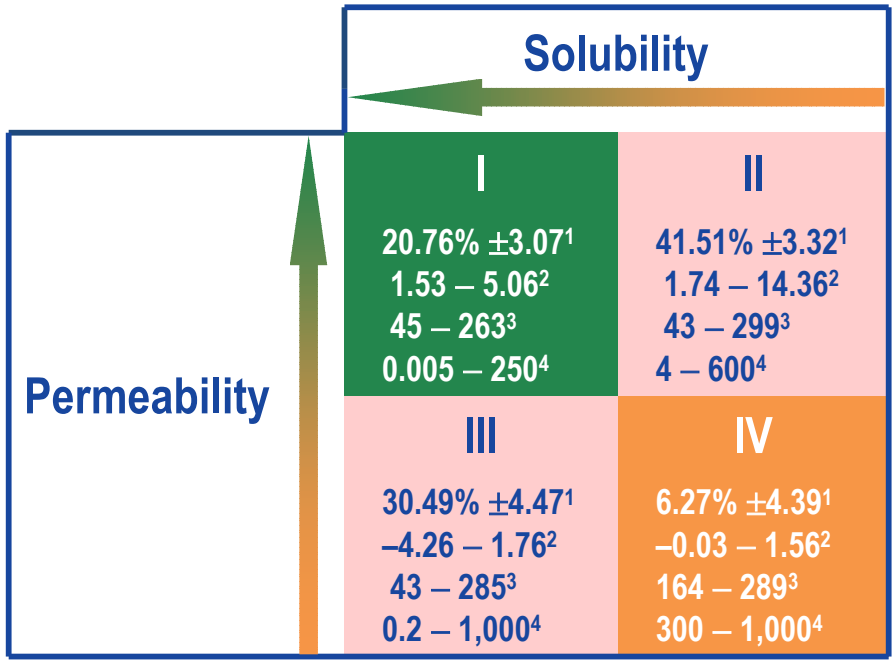
High Permeability

- Class boundary
  - PK studies in humans (FDA: preferred, EMA: mandatory)
    - Mass balance studies
      - » Unlabeled, stable isotopes or a radiolabeled drug substance to document extent of absorption
      - » If high permeability is demonstrated, additional data to document stability in the GIT required, unless ≥85% excreted unchanged in urine
    - Absolute BA studies
      - » Oral dose *vs.* IV dose
      - » If *F* ≥85%, additional data to document stability in the GI fluid is not required
  - Intestinal Permeability (EMA: supportive only)
    - *in vivo* intestinal perfusion studies in humans
    - *in vivo* or *in situ* intestinal perfusion studies using suitable animal models
    - *in vitro* permeation studies using excised human or animal intestinal tissues
    - *in vitro* permeation studies across a monolayer of cultured epithelial cells

Biopharmaceutics Classification System

Details*

- Percent of 185 drugs[1] / logP[2] / melting point (°C)[3] / dose (mg)[4]



* Wolk O, Agbaria R, Dahan A. *Provisional in-silico biopharmaceutics classification (BCS) to guide oral drug product development.* Drug Res Dev Ther. 2014;8:1563–75.

Biowaivers

Biowaiver

- The biostudy can be *waived* (*i.e.*, has not to be performed) if similarity *in vitro* (dissolution) can be demonstrated
- Two types
  - Proportionality biowaiver
    - If BE (*in vivo*) is demonstrated of (generally) the highest strength, BE for lower strength(s) can be waived

Biowaivers

Biowaiver

- BCS-based biowaiver (IR solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form)
  - Not acceptable for NTIDs and when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product
  - No BE-study for IR drug products has to performed if
    - For BCS Class I drug products
      - the drug substance is highly soluble and permeable,
      - both test and reference products are rapidly dissolving, and
      - excipients that might affect BA are qualitatively and quantitatively the same. The use of the same excipients in similar amounts is preferred.
    - For BCS Class III drug products
      - the drug substance is highly soluble,
      - both test and reference products are very rapidly dissolving, and
      - excipients that might affect BA are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

Dissolution Similarity

Biowaiver possible if similarity in vitro demonstrated

- f_2
- If not applicable, alternatives are acceptable and under discussion (workplan 2017 of the PKWP and BSWP)
  - Similarity acceptance limits must be pre-defined and not greater than 10%
  - Dissolution variability of T and R should be similar, though the one of T could be lower
  - Software must validated

Difference factor f_1, similarity factor f_2

Difference factor f_1

- Percent difference between dissolution profiles at each time point
- Measurement of the relative error between the curves

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

Similarity factor f_2

- Logarithmic reciprocal square root transformation of the sum of squared error
- Measurement of the similarity in the percent dissolution between the curves

$$f_2 = 50 \cdot \log\left\{100 \cdot \left[1 \Big/ \sqrt{1 + \frac{1}{n}\sum_{t=1}^{t=n}(R_t - T_t)^2}\right]\right\}$$

Example 9.1

Calculation

n	3
$\Sigma (R_t - T_t)$	10
$\Sigma \lvert R_t - T_t \rvert$	10
$\Sigma (R_t - T_t)^2$	38
ΣR_t	258
f_2	71.6
f_1	3.9

t (min)	R_t (%)	T_t (%)	$\Delta (R_t - T_t)$	$\Delta \lvert R_t - T_t \rvert$	Δ^2
15	83	78	5	5	25
30	85	83	2	2	4
45	90	87	3	3	9

Difference factor f_1, similarity factor f_2

Certain conditions must be fullfilled for the application of f_2

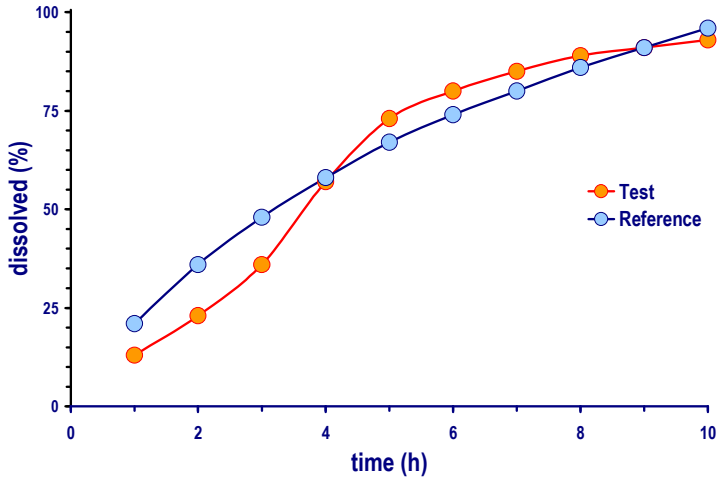
- f_2 *not required* if product releases ≥85% in all three media
- 12 units of test and reference product
  R_t and T_t are their arithmetic means
- *CV* should not be >20% at ≤15 minutes
- *CV* should not be >10% at other time points
- Sampling time points after 85% release:
  - FDA Only one measurement included for test product
  - EMA Not more than one mean value of >85% dissolved for each formulation
  - WHO Maximum of one time-point should be considered after 85% dissolution of the comparator (Brand/Reference/Innovator) product has been reached

Example 9.2

Different release characteristics

- Although f_1 (2.1) and f_2 (57.7) suggest similarity, the comparison is not suitable because the profiles display different release kinetics

t (h)	R_t (%)	T_t (%)	$\Delta (R_t - T_t)$	$\Delta \lvert R_t - T_t \rvert$	Δ^2
1	21	13	8	8	64
2	36	23	13	13	169
3	48	36	12	12	144
4	58	57	1	1	1
5	67	73	-6	6	36
6	74	80	-6	6	36
7	80	85	-5	5	25
8	86	89	-3	3	9
9	91	91			
10	96	93			



Reference: Zero order?
Test: Sigmoidal (Hill or Weibull?)

Vivian Gray, *Dissolution Workshop*. 10 December 2010.

Alternatives (?)

Suggested if variability (especially in early time points) is high

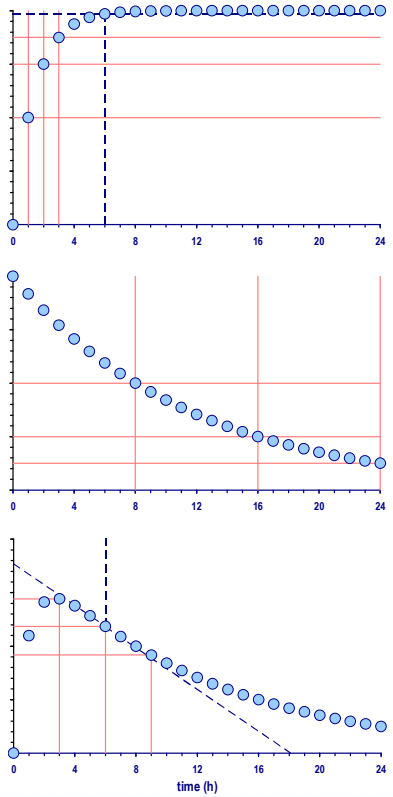
- Multivariate statistical distance (MSD)[1]
  - MSD is estimated
    - Its 90% confidence interval calculated
    - The upper limit compared to the similarity limit
  - A subset of MSD is the Mahalanobis' Distance (MD)[2]
    - Currently explored by the EMA's PKWP and Biostatistical Working Party
- Model-dependent approaches
  - Select a suitable model (quadratic, logistic, probit, Hill, Weibull, …)
  - Similarity region is specified based on the variability
  - Calculate MSD and CI as above

1 Cardot J-M, Roudier B, Schütz H. *Dissolution comparisons using a Multivariate Statistical Distance (MSD) test and a comparison of various approaches for calculating the measurements of dissolution profile comparison.* AAPS J. 2017;19(4):1091–101.
2 Mangas-Sanjuan V, Colon-Useche S, Gonzalez-Alvarez I, Bermejo M, Garcia-Arieta A. *Assessment of the Regulatory Methods for the Comparison of Highly Variable Dissolution Profiles.* AAPS J. 2016;18(6):1550–61.

Excursion into A(D)ME

In vivo curve can be described by absorption (A) and elimination (metabolization + excretion)

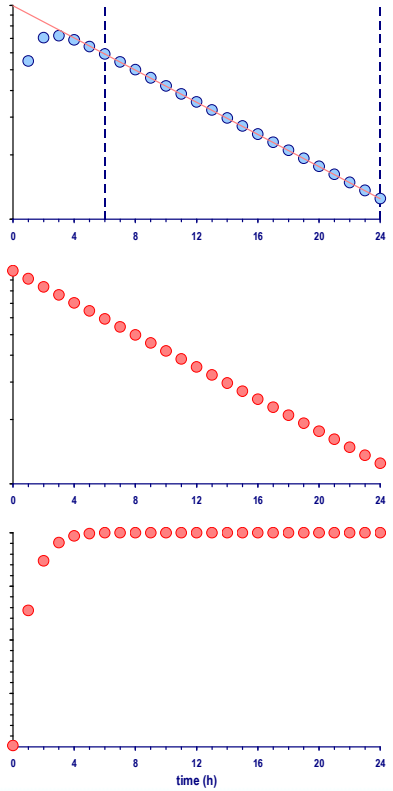
- One-compartment model does not have D (distribution)
  - Example: $t_{½a}$ 1 h, $t_{½e}$ 8 h
    - After 3×$t_{½a}$ (3 h) 87.5% are absorbed
    - After 3×$t_{½e}$ (24 h) 87.5% are eliminated
    - In the *in vivo* curve the inflection point (where the curve changes from concave to convex) is seen at 2×t_{max} (6 h)
      At this time absorption is essentially complete (98.44%) and the *in vivo* curve practically represents elimination only
- We can get *in vivo* absorption by subtracting the estimated elimination



Excursion into A(D)ME

Reconstructing *in vivo* absorption (residual method)

- Fit elimination (λ_z from $2\times t_{max}$ or later to t_z)
- Predict *in vivo* elimination
- *In vivo* absorption is the *in vivo* curve minus the predicted elimination



Different other methods exist

- One-compartment model
  - Wagner-Nelson

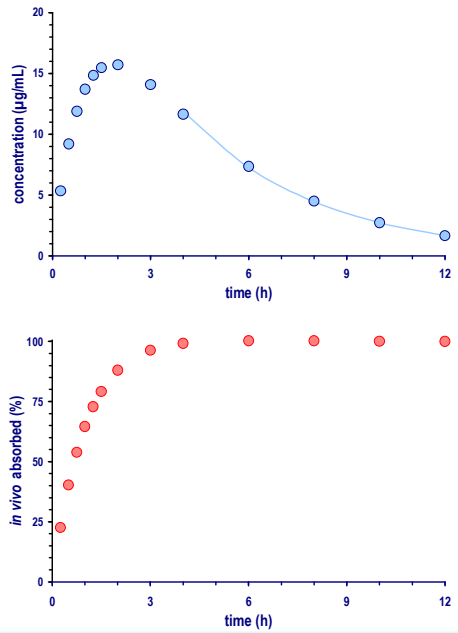
$$abs(\%) = 100\frac{C_t + k_{el}\cdot AUC_{0-t}}{k_{el}\cdot AUC_{0-\infty}}$$

- Two-compartment model
  - Loo-Riegelman (needs true elimination from iv); the distribution phase is reconstructed

Example 9.3

D 100 mg, V 4 L, F 1, k_a 1 h^{-1} ($t_{½}$ 0.69 h), k_{el} 0.25 h^{-1} ($t_{½}$ 2.77 h)

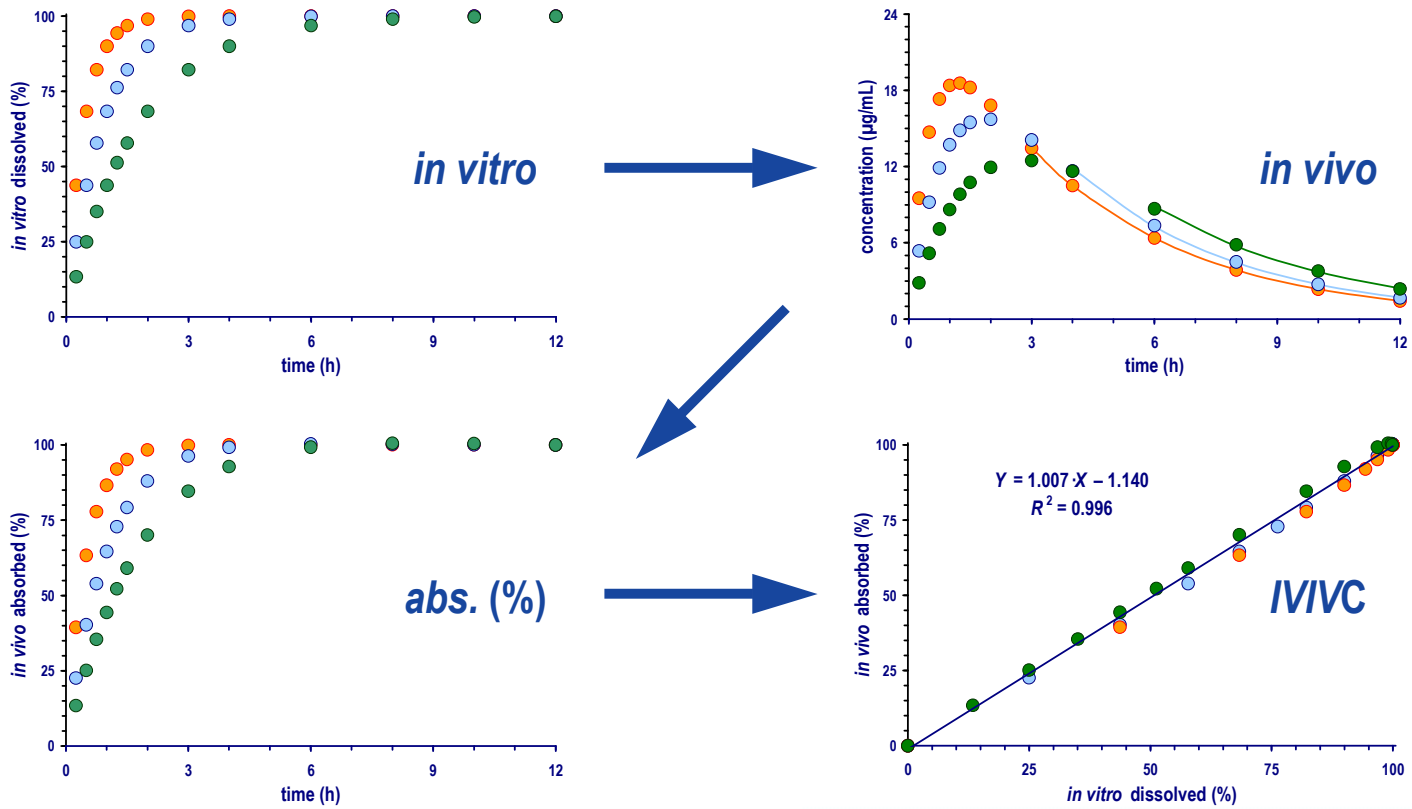
- Lin-up/log-down trapezoidal method for AUC_{0-t}
- λ_z (estimated from 4 to 12 hours) = 0.2444
- $AUC_{0-\infty} = AUC_{0-12} + C_{12} / \lambda_z = 99.68$



t (h)	C (mg/mL)	AUC_{0-t}	abs (%)
0.00	BQL	–	–
0.25	5.35	0.67	22.63
0.50	9.20	2.49	40.26
0.75	11.89	5.12	53.94
1.00	13.70	8.32	64.58
1.25	14.84	11.89	72.84
1.50	15.47	15.68	79.22
2.00	15.71	23.47	88.03
3.00	14.09	38.36	96.31
4.00	11.65	51.19	99.17
6.00	7.36	69.87	100.31
8.00	4.50	81.50	100.23
10.00	2.73	88.88	100.08
12.00	1.66	92.68	100.00

IVIVC (Level A)

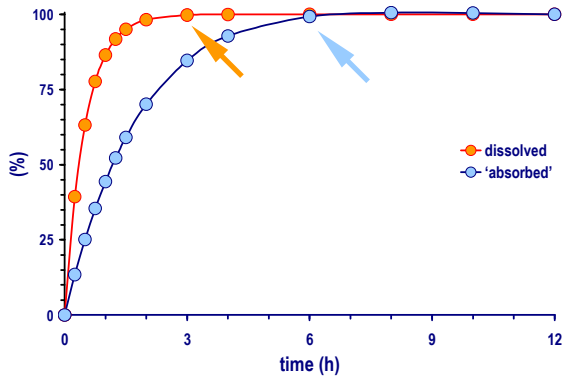
Three candidate formulations (fast, intermediate, slow)

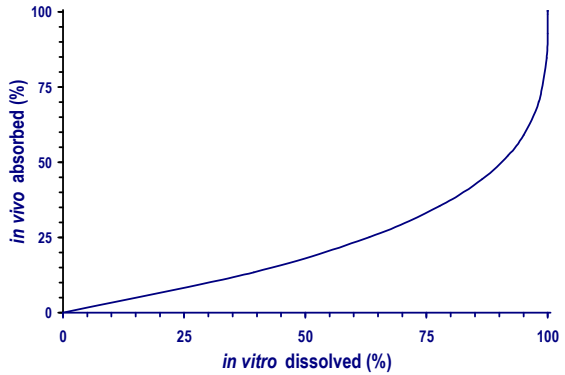


IVIVC (Level A)

Different rates *in vitro* / *in vivo*

- Not suitable for IVIVC (nonlinear relationship)



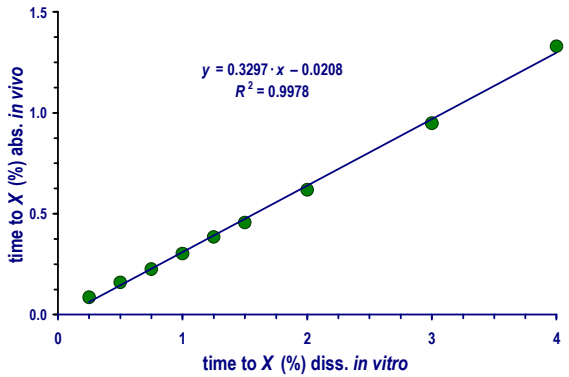


t (h)	*diss* (%)	*abs* (%)
0.00	0.00	0.00
0.25	39.35	13.44
0.50	63.21	25.14
0.75	77.69	35.44
1.00	86.47	44.37
1.25	91.79	52.22
1.50	95.02	59.04
2.00	98.17	70.10
3.00	99.75	84.66
4.00	99.97	92.82
6.00	100.00	99.27
8.00	100.00	100.57
10.00	100.00	100.43
12.00	100.00	100.00

IVIVC (Level A)

Different rates *in vitro* / *in vivo*

- Modify the dissolution method (*e.g.*, less agitation) to get a better match
- Establish a Levy plot (time to get % dissolved or absorbed); use interpolation to find dissolution times which match absorption



- Calculate new *in vitro* sampling times

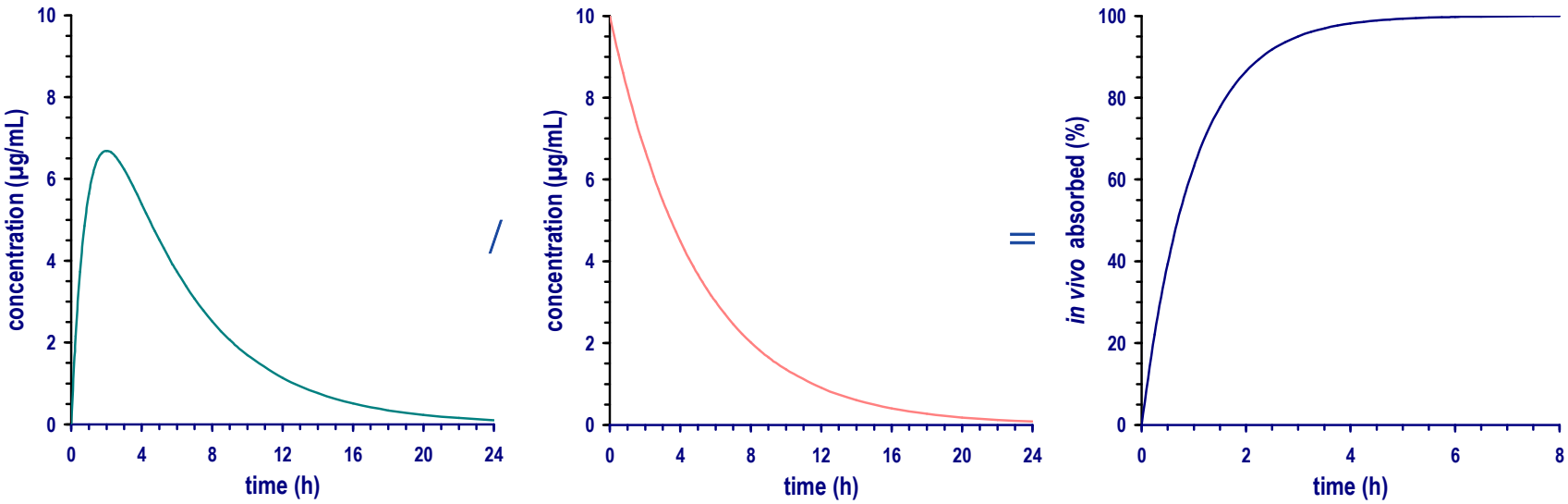
$$t_{in\ vitro} = t_{in\ vivo} \times 0.3297 - 0.0208$$

in vivo		*diss. time*	
t (h)	*abs* (%)	(h)	(h:mm)
0.00	0.00	0.00	0:00
0.25	13.44	0.06	0:03
0.50	25.14	0.14	0:08
0.75	35.44	0.23	0:13
1.00	44.37	0.31	0:18
1.25	52.22	0.39	0:23
1.50	59.04	0.47	0:28
2.00	70.10	0.64	0:38
3.00	84.66	0.97	0:58
4.00	92.82	1.30	1:17
6.00	99.27	1.96	1:57

IVIVC (Level A)

Alternative to Wagner-Nelson and Loo-Riegelman

- **Deconvolution:** Derive *in vivo* input curve from *in vivo* profile. Only method which is can be applied if there are more than two compartments. Notation: $f = g / h$

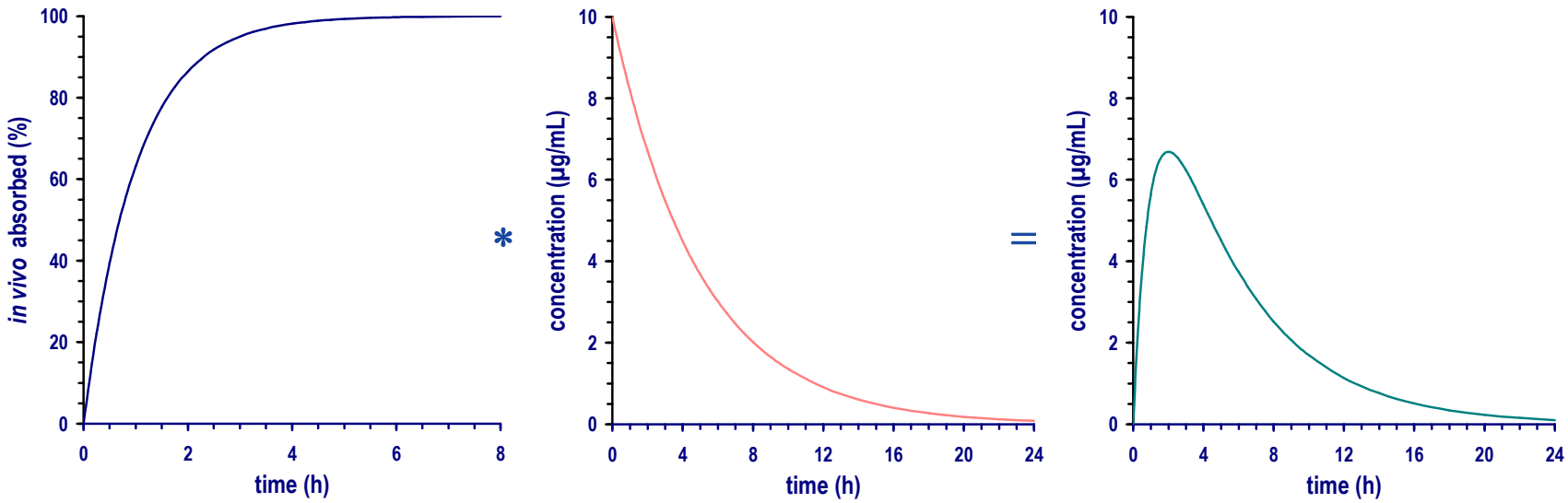


Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Level A)

Alternative to Wagner-Nelson and Loo-Riegelman

- **Convolution:** Derive *in vivo* profile from simulated *in vivo* input curve (obtained by IVIVC). Notation: $f = g * h$



Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Level A)

Deconvolution / Convolution

- Already mathematically demanding for continous functions – even more complicated if only data-pairs are available
  - Numeric methods require equidistant supporting points
    Must interpolate / impute data
  - Requires additionally to % absorbed, the rate of absorption *dA* / *dt* (method by Vaughan, Denis 1978)
  - Requires six to ten (!) sampling points in the absorption phase ($\leq 2 \times t_{max}$)

Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC (Levels B and C)

Level B

- Correlation of statistical moments describing *in vitro* and *in vivo* profiles
  - Mean dissolution time (*MDT*) with mean residence time (*MRT*) and mean absorption time (*MAT*)
    Problem: *MRT* depend to a large part on distribution / elimination
    Requires IV (or at least solution) data to obtain *MAT*

Level C

- Correlation of single-point metrics
  - % dissolved (at least 80%) up to an certain time point with a PK metric (*e.g.*, C_{max}, truncated *AUC*)
  - Few 'working' examples (*e.g.*, glibenclamide)

Jean-Michel Cardot. *IVIVC Workshop*. Mumbai, 27 – 29 January 2012.

IVIVC: Conclusion

Quite often what one thinks to be 'different' (based on a QC dissolution method) turns out to be similar *in vivo*

- Modify formulations, perform *in vivo* pilot studies until you see a difference *there*
  - Then (!) develop a discriminatory *in vitro* method which is able to predict *in vivo* absorption
    - Try different agitation speeds, use surfactants, change the apparatus, and – if nothing helps – explore biorelevant media
    - The final *in vitro* method likely has nothing in common with the one used in QC.

      If Earl Grey with a sip of milk is predictive, use it! (Jean-Michel Cardot)
- Once you established a discriminatory method, modify formulations to find one which matches the reference
  - This does not (!) guarantee that your best candidate will behave *in vivo* like the reference
  - Another pilot (T *vs.* R) makes sense (to estimate *CV* and *GMR*)

Dissolution / Biowaivers / *IVIVC*

Thank You!
Open Questions?

Helmut Schütz

BEBAC

Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria

helmut.schuetz@bebac.at