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In collaboration with UFR DE PHARMACIE Université Clermont Auvergne

Introducing the concept of time scaling in IVIVC

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September, 2017

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Outline of the presentation

- Brief introduction to IVIVC context
  - Areas that provide input to IVIVCs
  - Applications in pharmaceutical development and in regulatory affairs
- Comment on *in vitro*/*in vivo* time differences
- Levy plots of several examples
- Approach to interpolate dissolution data
- Example
- Potential additional applications for discussion

Introduction to *in vivo in vitro* correlations

- What is it?
  - Mathematical model that describes relationship between in vitro property and in vivo response
- Key assumption: Rate limiting absorption is due to drug product *in vivo* release properties and a method *in vitro* shows the same (or related) rate limitation
- Outcome: The ability to predict, accurately and precisely, expected bioavailability characteristics for a product from dissolution profile characteristics
  - Two step approaches: Level A, B, C correlations
  - One step approaches: *in vitro* data treated as a pharmacokinetic compartment
  - PBPK, others…
- Different to day to day "correlations":
  - *in vivo* and *in vitro* follow same rank order, so in vitro is good enough…
- Overall still a fundamentally empirical method but IVIVc is rapidly becoming theorized and state of the art modeling techniques are increasingly applied
  - E.g. near-physiological in-vitro, direct differential equation convolution, Bayesian approaches

In vitro input

- Analytical method developed to distinguish formulation quality attributes
  - API PSD, release controlling polymer content or grade, others…
  - F2<50, CV 10%, 12 vessels, not more than 1 mean value >85%
- Circular situation:
  - Method considered valid because it separates formulations
  - Formulation differentiating properties are valid because they are detected by method
- Normally not misleading because of high collective experience on critical formulation quality attributes
  - Assume *in vitro* to represent *in vivo:* uncertain
  - New formulation concepts/approaches?
  - Surprises because of factors that were not studied before
- For initial IVIVC exploration: limited dissolution data in 1-2 methods, ideally for 3 release rates

In vivo input

- Small exploratory studies (pilot) to verify
  - Comparative bioavailability of dosed formulations
  - Adequacy of bioanalytical method (e.g. calibration, QC range, LLOQ)
  - Appropriateness of study design (e.g. sampling times enough to characterize absorption, standardization, washouts, etc.)
- Challenge of PK variability potentially exacerbated because of low sample size
  - Cmax and AUC residual variability from ANOVA: observational reference for prediction error estimates
  - Profile shapes: individual displacements left to right, lag times, changes in absorption rates
- For initial IVIVC: limited variable data with or without outliers, ideally with 3 different formulation rates and a fast formulation (for deconvolution: UIR)*

  * Oral immediate release, intravenous in cross-over design, if not must rely on cross-study or published data with associated risk of bias.

Pharm Dev applications

- Select or develop dissolution method that best represents *in vivo* for further development
  - Is the method sufficiently discriminatory to determine optimum formulation?
  - Does the correlation still apply if changes to the formulation are made? Carefully identify what changes pose a risk
  - Ideally pre-define the magnitude of change limits for further development
- Exploration of *in vivo* - *in vitro* relationships provides ideas for further formulation work
  - Useful exploration even if formal correlation cannot be established
  - Confirm or reject Galenical hypothesis (e.g. slowest in vitro is fastest in vivo because release in a different site than others? Tablet size impact on transit? Different release mechanism *in vivo*?)
- Verify design space in Quality by Design
  - support formulation and process understanding
  - established range of process parameters that has been demonstrated to provide assurance of quality/acceptable bioavailability

Regulatory applications

- Justification of product release specifications for Quality Control
- Waive *in vivo* studies for variations
  - With limitations described in FDA Guidance SUPAC-MR, no final guidance on EMA approach (comment in MR Quality Guideline and Statistical Reflection Paper)
- Support certain Letters of Deficiency related to analytical methods
- Recommended by authorities for extended release products since 1990's
  - Included in limited number of applications and many unsuccessful
  - Most common is to submit Level A correlations* (87% of submissions from 2008 to 2015)
    - Two stage by numerical deconvolution 86%
    - Two stage by Wagner Nelson and Loo Reigelman 5.5%
    - One stage approaches about 8%

* *From Suarez-Sharp, 2016*

Regulatory application failures

Table I. Common causes for unsuccessful IVIVCs in FDA submissions

Common causes of IVIVC lack of success				
In vitro dissolution	Formulation	*In vivo* study design	Modeling	IVIVC application
• May need to be physiologically relevant • Lack of systematic approach in the development of a biopredictive method • Inadequate discriminating power for detecting differences in product performance	• Lack of sufficient number of release rates covering a reasonable range • Formulations used in the model construction are not qualitatively the same • Release rate differences are achieved by adding/deleting the release controlling excipients	• Lack of rank-order correlation • Reference formulation not part of the same *in vivo* study when numerical deconvolution is being applied. • Study conducted under fed conditions for drug products with significant food effect • Lack of *a priori* planning on the design of the study • Exclusion of subjects without justification	• Incorrect used of same scaling factor in the correlation step as indicated by slope value differences among the formulation used in the construction of the IVIVC • Inclusion of non-mechanistic terms without adequate justification • Overparameterization of the model • Inconclusive model predictability with unacceptable validation results • Use of mean PK data in the deconvolution step while deconvolution at individual level is applicable • Lack of justification for the model selected to establish the correlation	• Biowaiver request for lower strengths based on IVIVC models constructed and validated with the highest strength while the strengths are not proportionally similar in composition • Calculation of similarity factor instead of IVIVC predicted PK parameters to support CMC changes • Use of invalid extrapolation to support proposed dissolution acceptance criteria • Comparison of the predicted PK parameters to the target formulation rather than to the opposite proposed bound without appropriate justification

* *From Suarez-Sharp, 2016*

Time scaling

- Why?
  - *In vivo* physiological influence of time to absorption events and time to reach systemic circulation
    - Lag times, changes in *in vivo* dissolution/absorption rates
    - Plasma levels also influenced first pass, tissue distribution, clearance, etc.
  - *In vitro* relatively constant.
  - Link minutes/hours to hours/days/weeks, lag times?
- How does it help?
  - Apply a correction for the time difference
  - Allows correlation even if *in vitro* rate is faster than *in vivo* rate
  - Allows to explore if all formulations share the same relationship
    - If not but can establish for test products, could estimate the *in vitro* profile of the optimal test product based on the *in vivo* profile of the reference
    - CANNOT include a formulation with a different time scale in the IVIVC
    - All formulations should have the same time scale relationship for an IVIVC independently if linear or non-linear approaches are pursued

Time scaling: Levy plots

- Traditional tool since 1967! (Levy, 1967)
- Plot times to reach same/similar percentages *in vitro* and *in vivo*

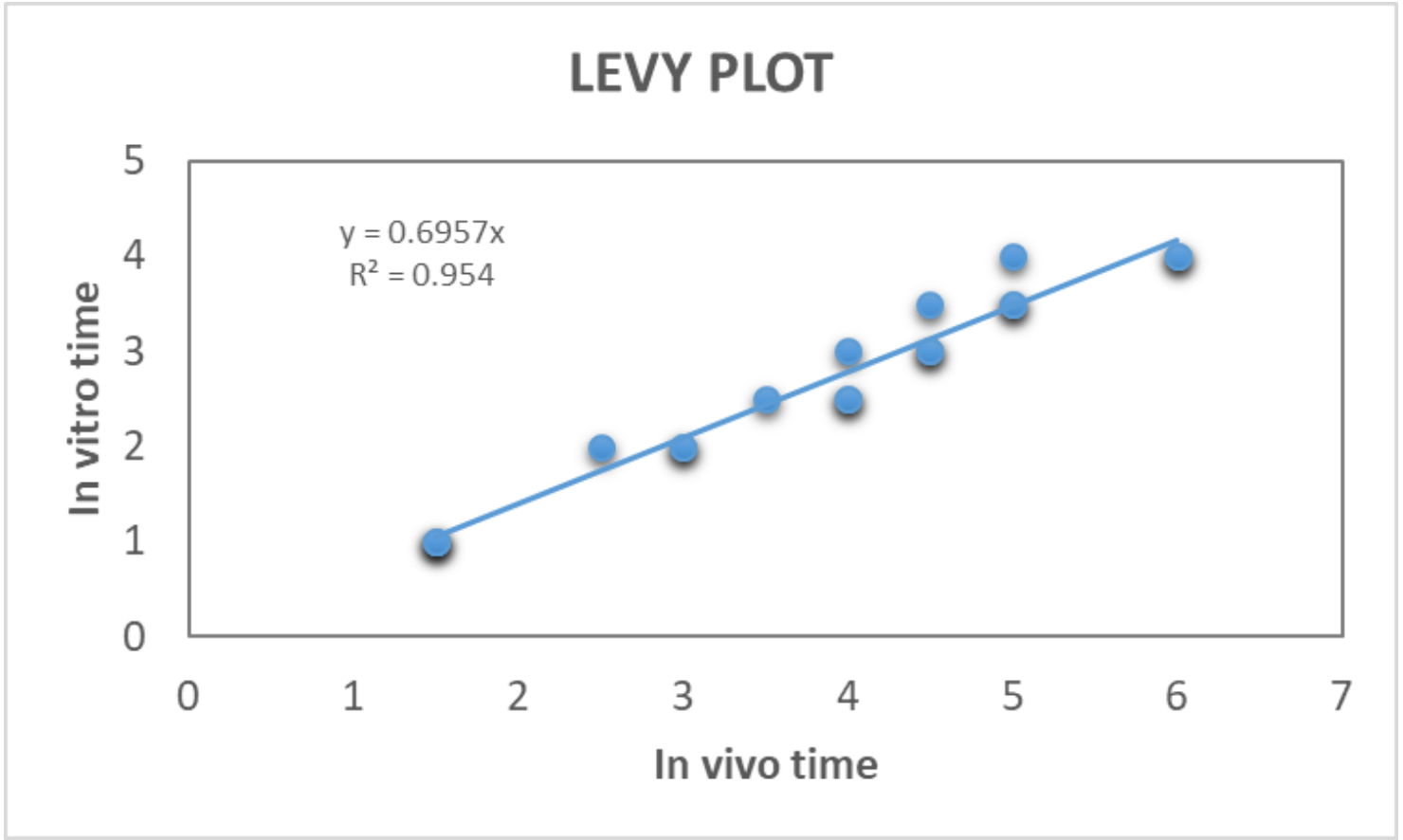
	%D in vitro		
TIME	A	B	C
0	0	0	0
0.5	26	23	14
1	45	41	26
1.5	59	55	36
2	70	65	45
2.5	78	73	53
3	83	79	59
3.5	88	84	65
4	91	88	70
4.5	93	91	74
5	95	93	78
5.5	96	94	81
6	97	96	83

Match the times at which approximately the same fraction is dissolved or absorbed

	%FA in vivo		
TIME	WN A	WN B	WN C
0	0	0	0
0.5	19	16	10
1	34	29	20
1.5	46	41	28
2	56	50	36
2.5	65	58	43
3	71	65	49
3.5	77	71	55
4	81	75	60
4.5	85	79	65
5	87	83	69
6	92	88	76
8	97	95	87

Time scaling: Levy plots

in vitro time	in vivo time	
	A/B	C
1	1.5	1.5
2	3	2.5
2.5	4	3.5
3	4.5	4
3.5	5	4.5
4	6	5



Formulations A and B share a time scale. The time scale for formulation C is close enough to share a common time scale as is illustrated by the regression line.

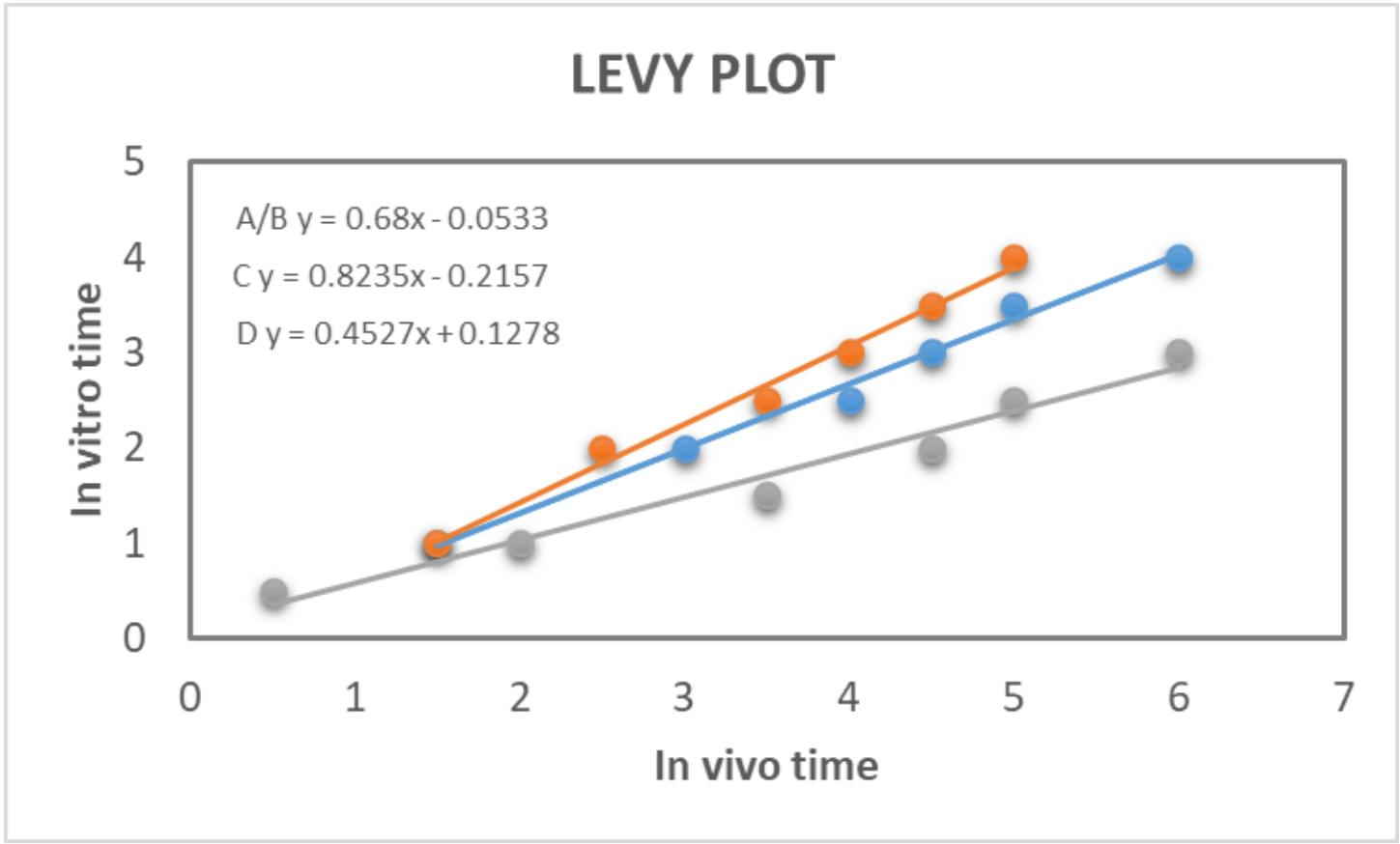
Time scaling: Levy plots

- *Example where formulation differs in relationship*
  - *Formulation D does not have the same time scale, possibly because of different release mechanisms/manufacturing technology/formulation concept*

	%D in vitro			
TIME	A	B	C	D
0	0	0	0	0
0.5	26	23	14	13
1	45	41	26	42
1.5	59	55	36	71
2	70	65	45	89
2.5	78	73	53	97
3	83	79	59	99
3.5	88	84	65	100
4	91	88	70	100
4.5	93	91	74	100
5	95	93	78	100
5.5	96	94	81	100
6	97	96	83	100

	%FA in vivo			
TIME	WN A	WN B	WN C	WN D
0	0	0	0	0
0.5	19	16	10	10
1	34	29	20	20
1.5	46	41	28	31
2	56	50	36	41
2.5	65	58	43	51
3	71	65	49	61
3.5	77	71	55	71
4	81	75	60	82
4.5	85	79	65	90
5	87	83	69	96
6	92	88	76	99
8	97	95	87	100

Time scaling: Levy plots



The LEVY plot shows formulations A,B and C are close enough to share a time scale and D shows a different time relationship.

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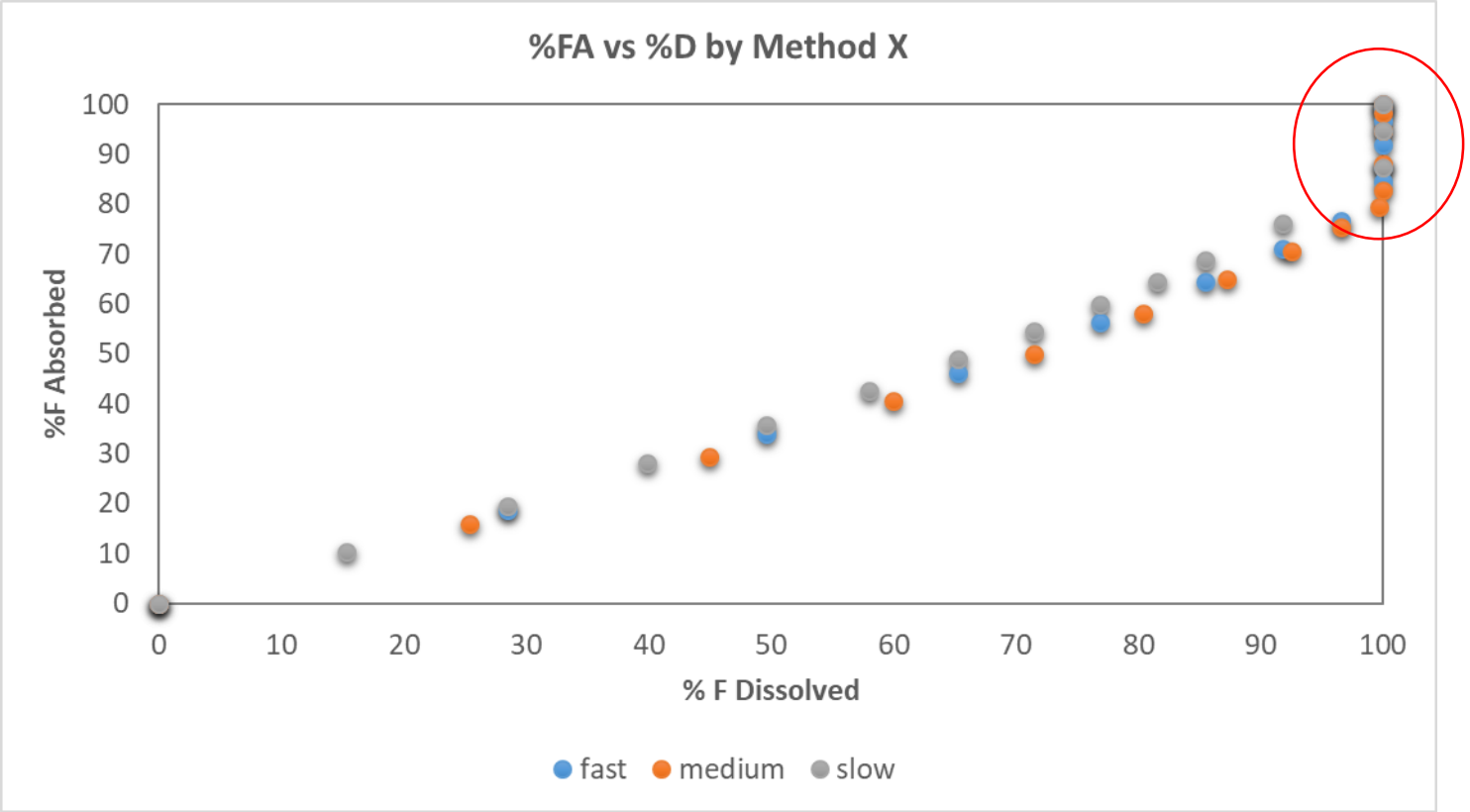
Time scaling: Levy plots

- *Example where the plot corrects for fast method*



The plot shows dissolution reaches 100% faster than Fraction Absorbed. This situation is a standard candidate to explore time scaling.

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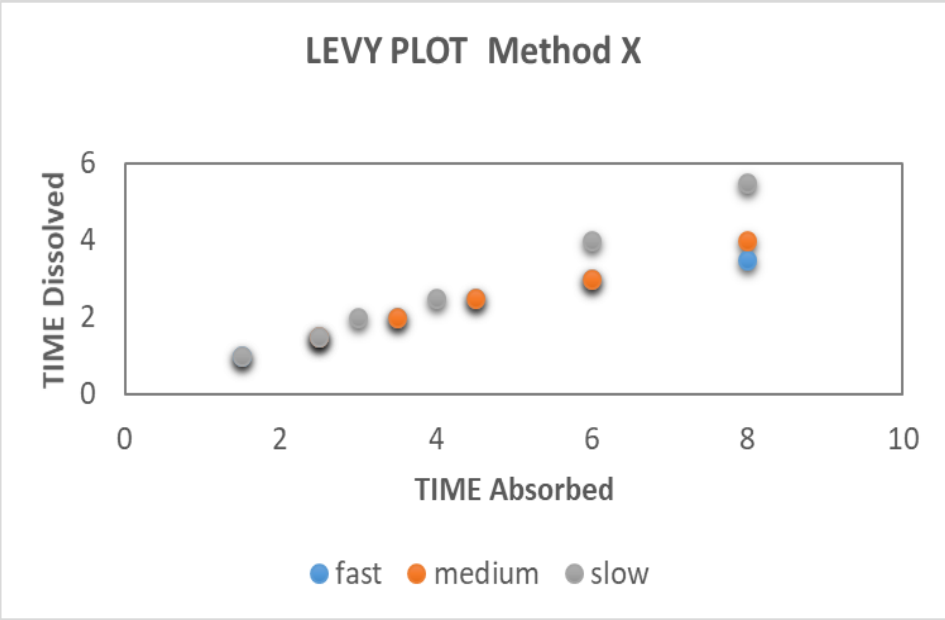
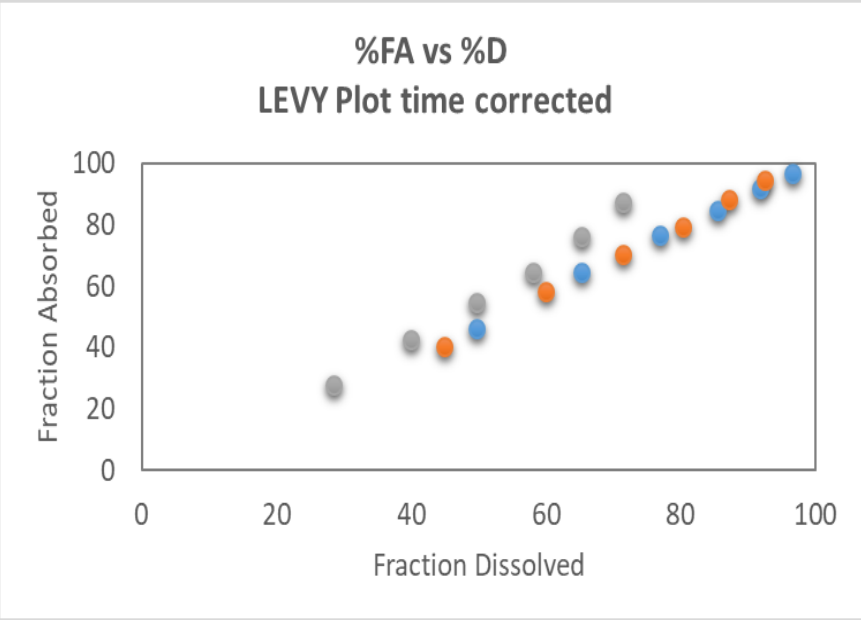
Time scaling: Levy plots





The LEVY plot highlights the difference in time scale for the slow formulation. The dissolution method is not representative of in vivo even applying time scaling.

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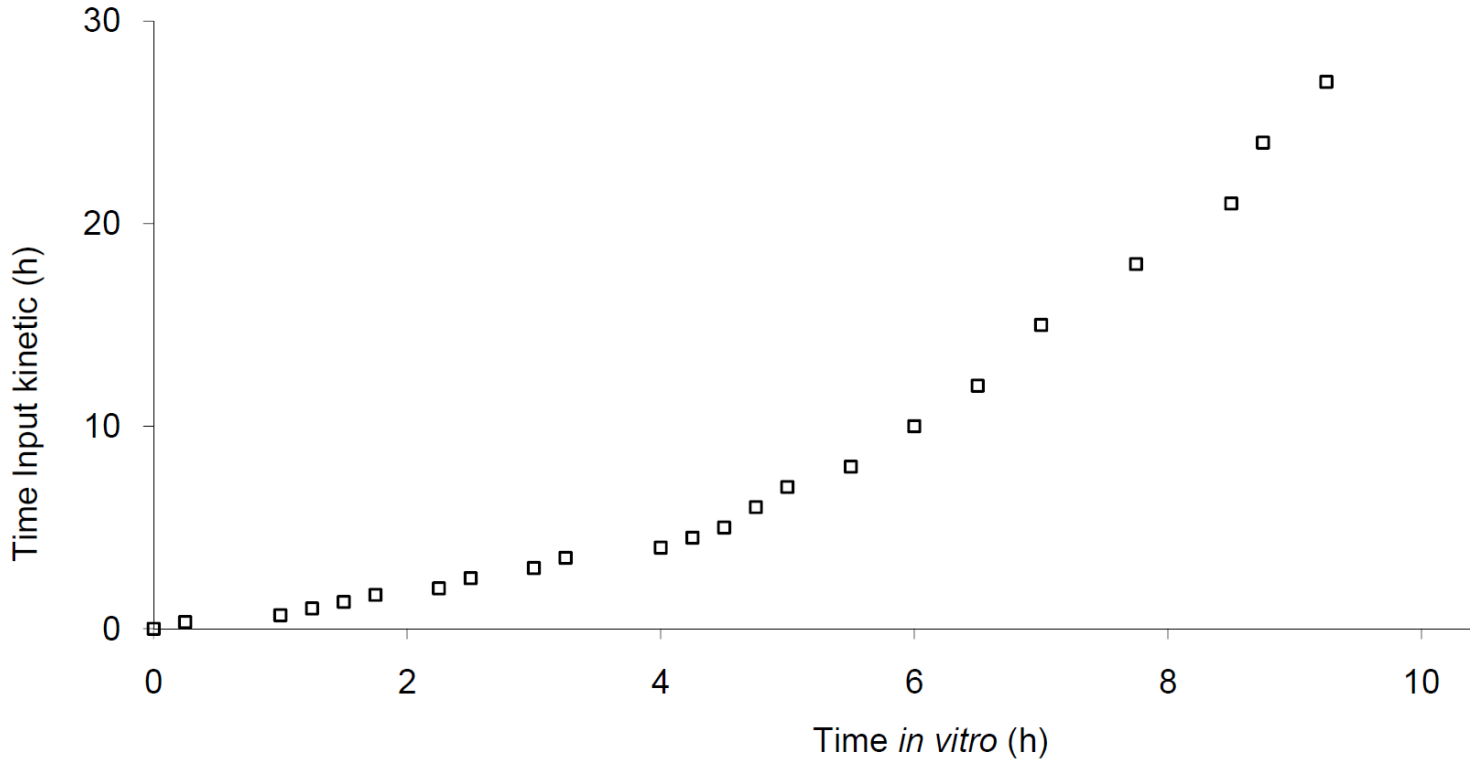
Time scaling: Levy plots

- *Example of non-linear Levy plots*



- Associated to absorption rate from small intestine and from colon
- Common to all tested formulations, can be applied for time scaling

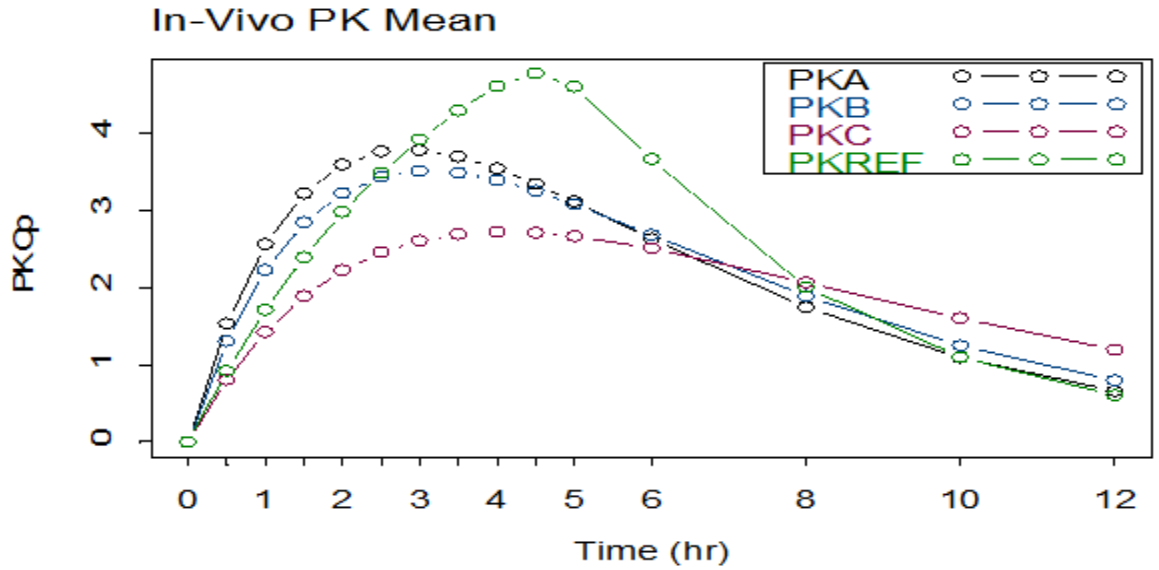
** From Hemmingsen, 2011*

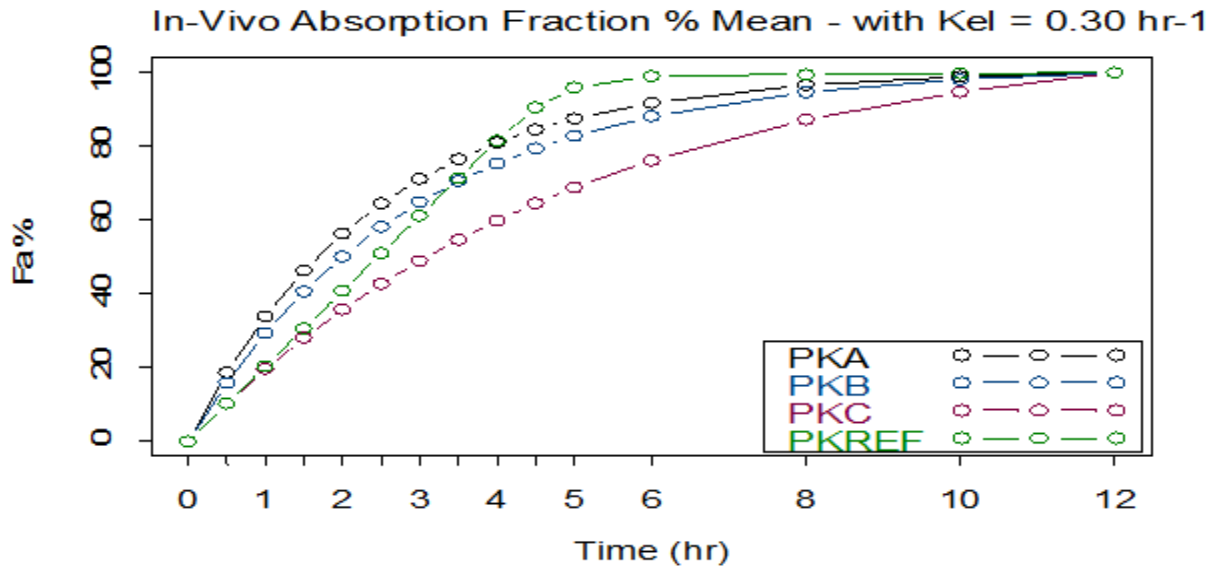
Questions and comments?

Time scaling: Levy plots

- Challenges of Levy plot time scaling
  - Difficult to match %FD with % FA
  - Exclusion of data that do not match reduces robustness
  - **Approximation** of percentages and interpolation of %FD
- New approach
  - Model dissolution data
    - Weibull $Disso(t)=Finf\ (1- \exp[-(t/MDT)^{b}])$
  - Apply inverse function to obtain those times In-Vitro that “would” correspond to the fraction absorbed (%FA) In-Vivo
    - Inverse Weibull Time scaling $=-Ln(-Abs/Finf+1)^{(1/b)}xMDT$
  - Estimate *in vitro* time for each given %FA

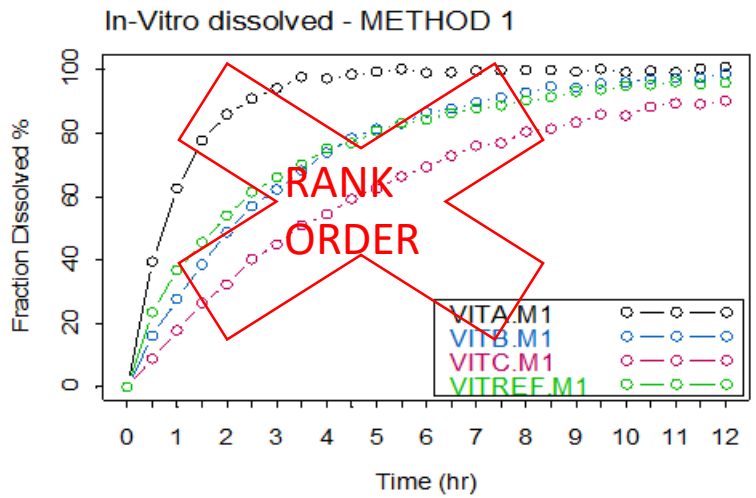
Time scaling: Levy plot and Weibull

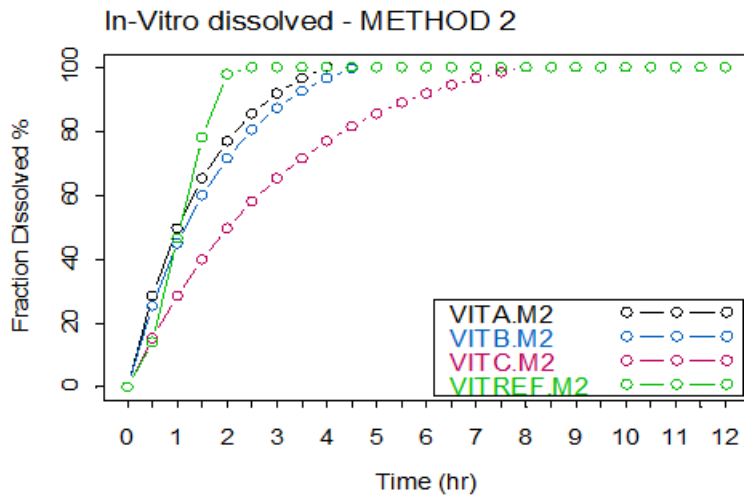


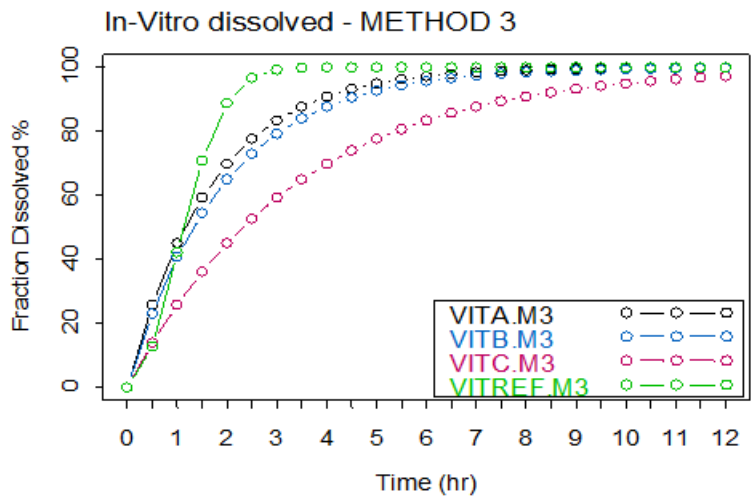


Wagner Nelson

Time scaling: Levy plot and Weibull







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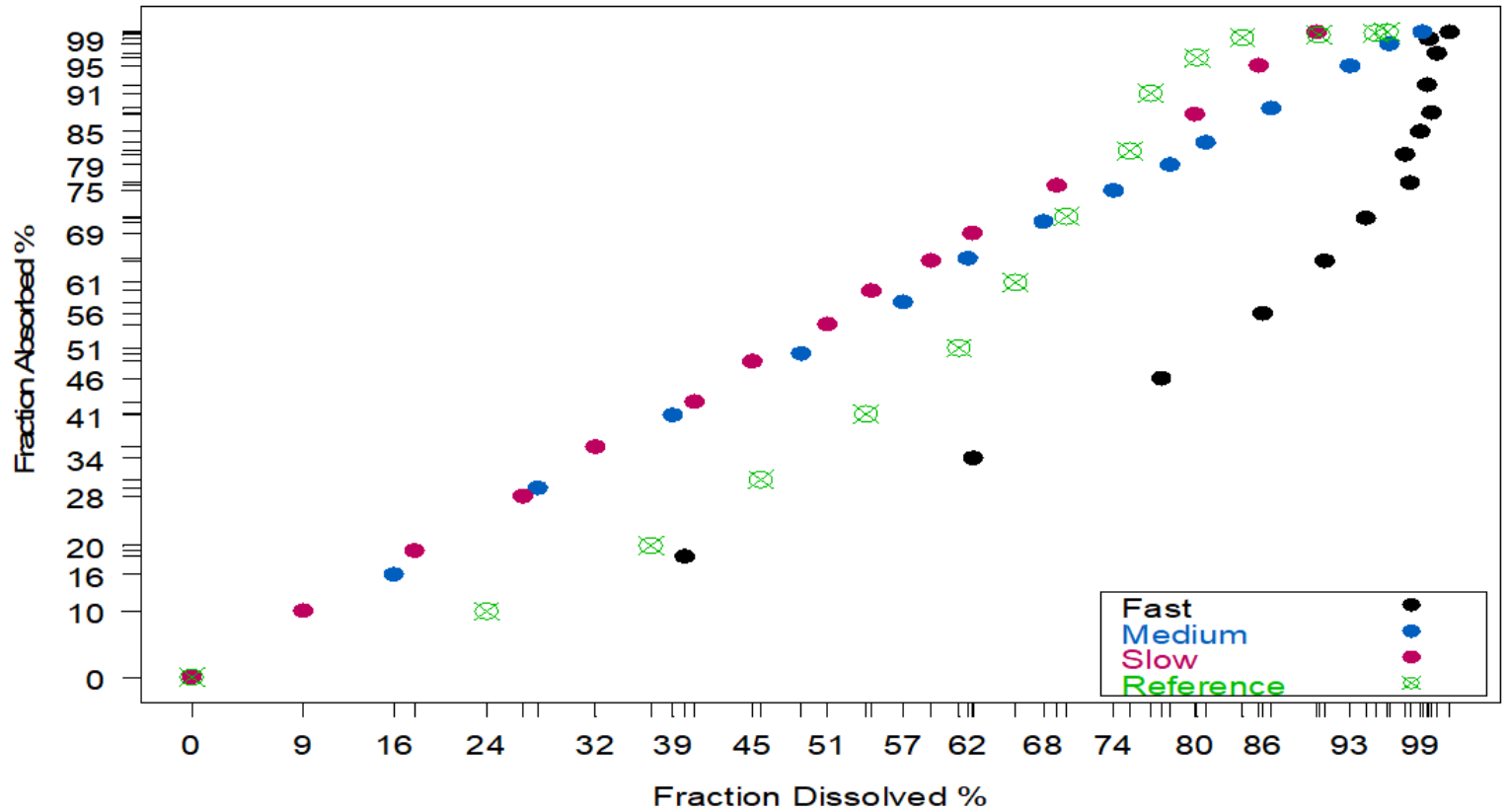
Time scaling: Levy plot and Weibull

- Method 1: Fast product and reference are different



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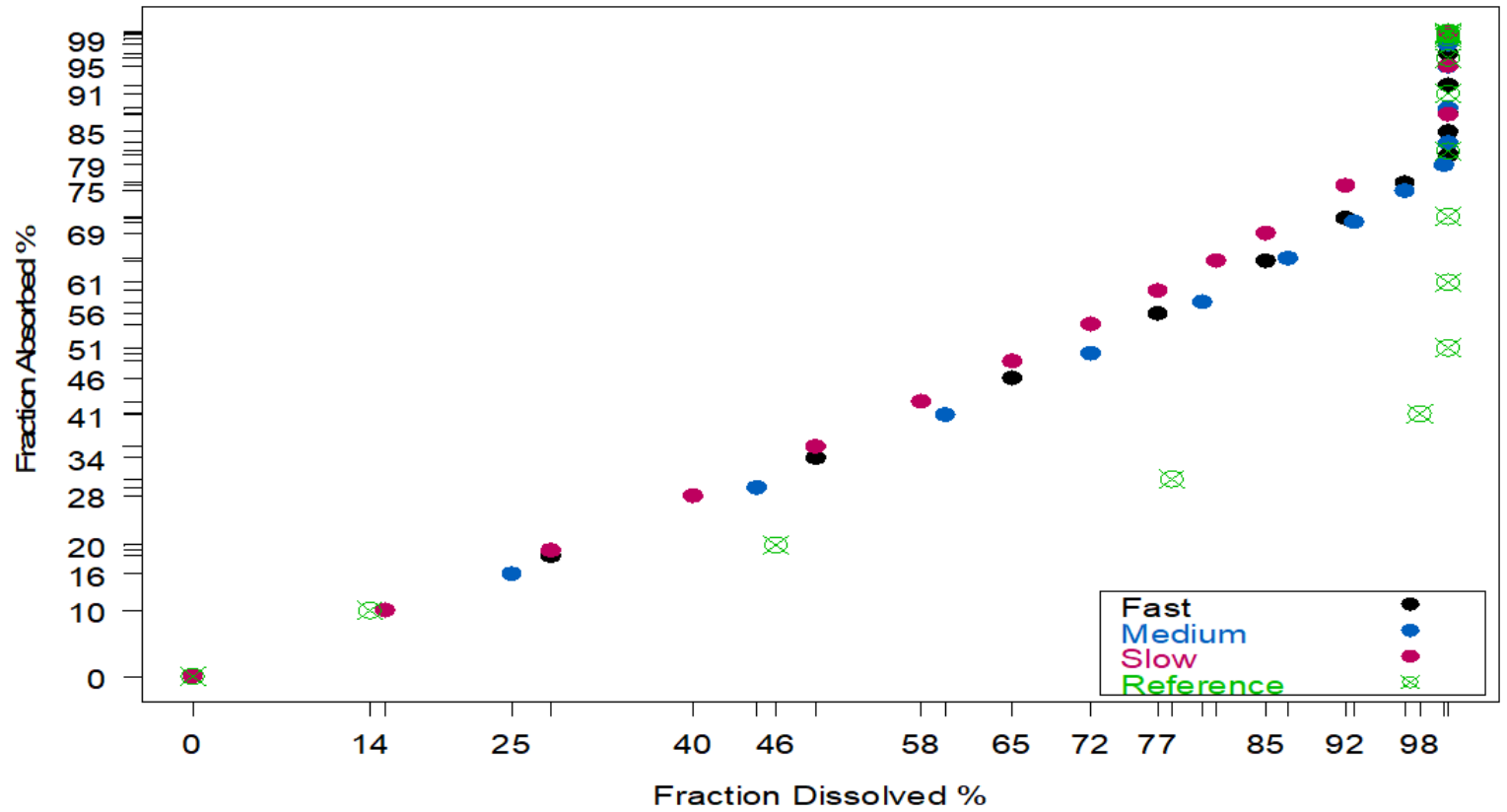
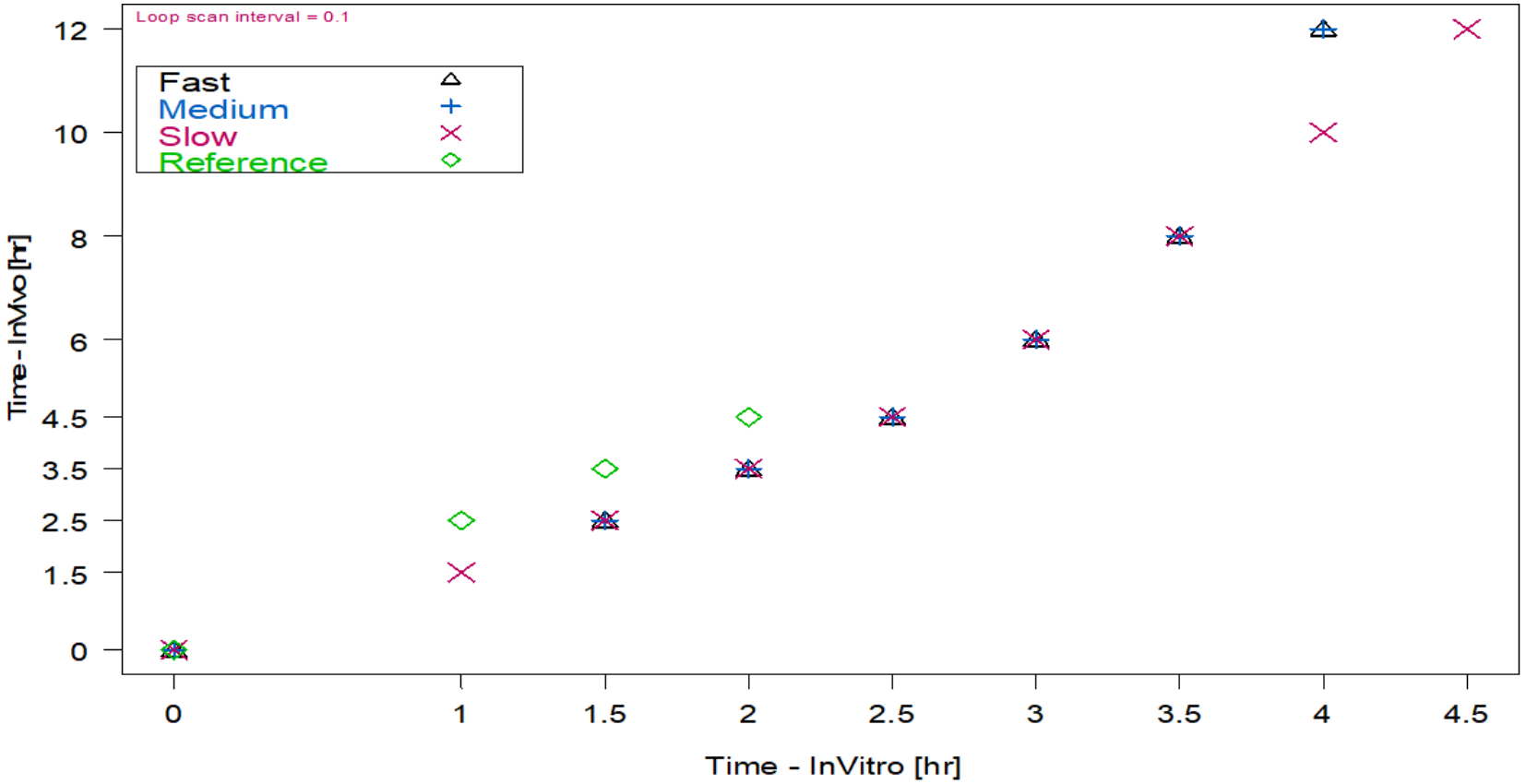
Time scaling: Levy plot and Weibull

- Method 2: Too fast, candidate for time scaling if better method not found



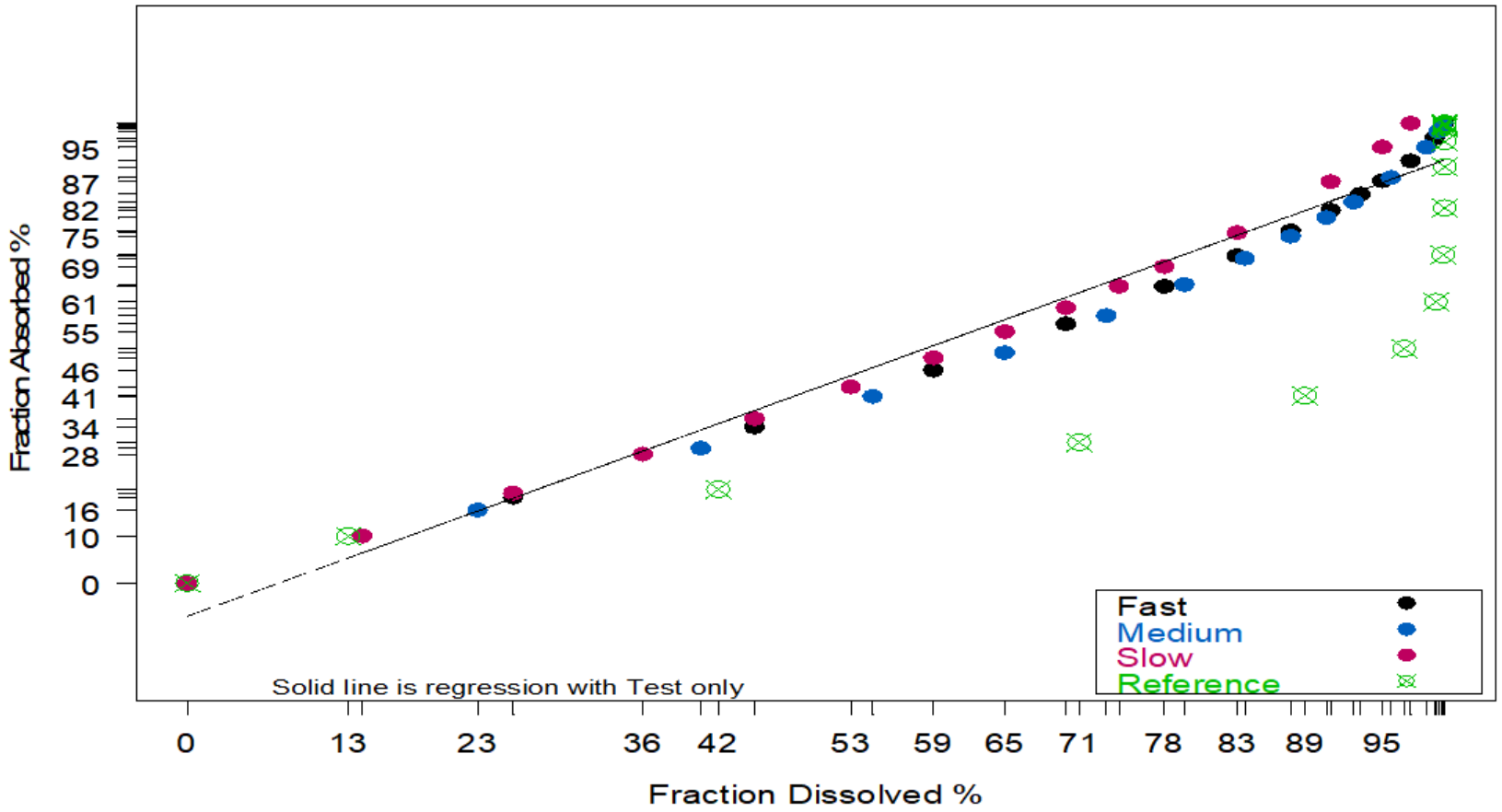
Time scaling: Levy plot and Weibull

- Method 2: Levy plot is not common to three forms



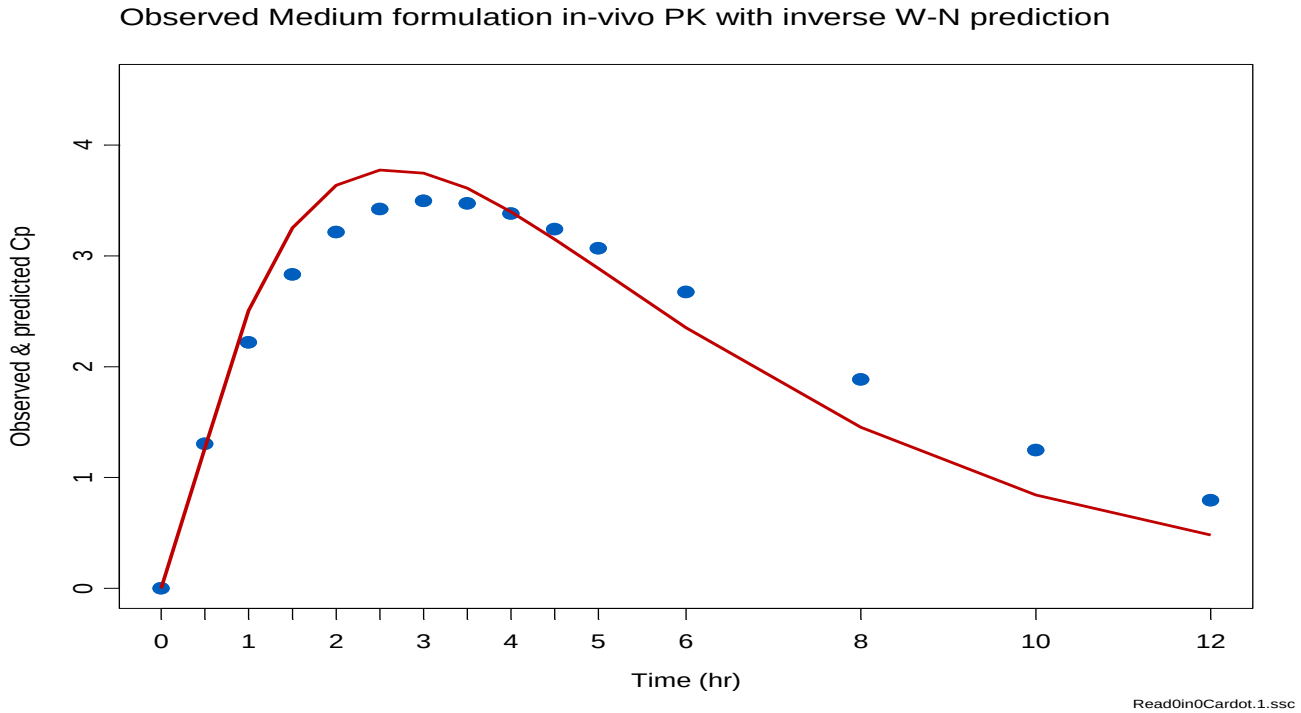
Time scaling: Levy plot and Weibull

- Method 3: Common for all forms. Is it really linear?



Time scaling: Levy plot and Weibull

- Prediction error of IVIVC
  - Applying linear correlation
  - Complies with guideline requirements but can be improved



	Estimated	Observed	Prediction error
Cmax	3.8	3.5	-7.9
AUC t	24.9	26.7	6.6

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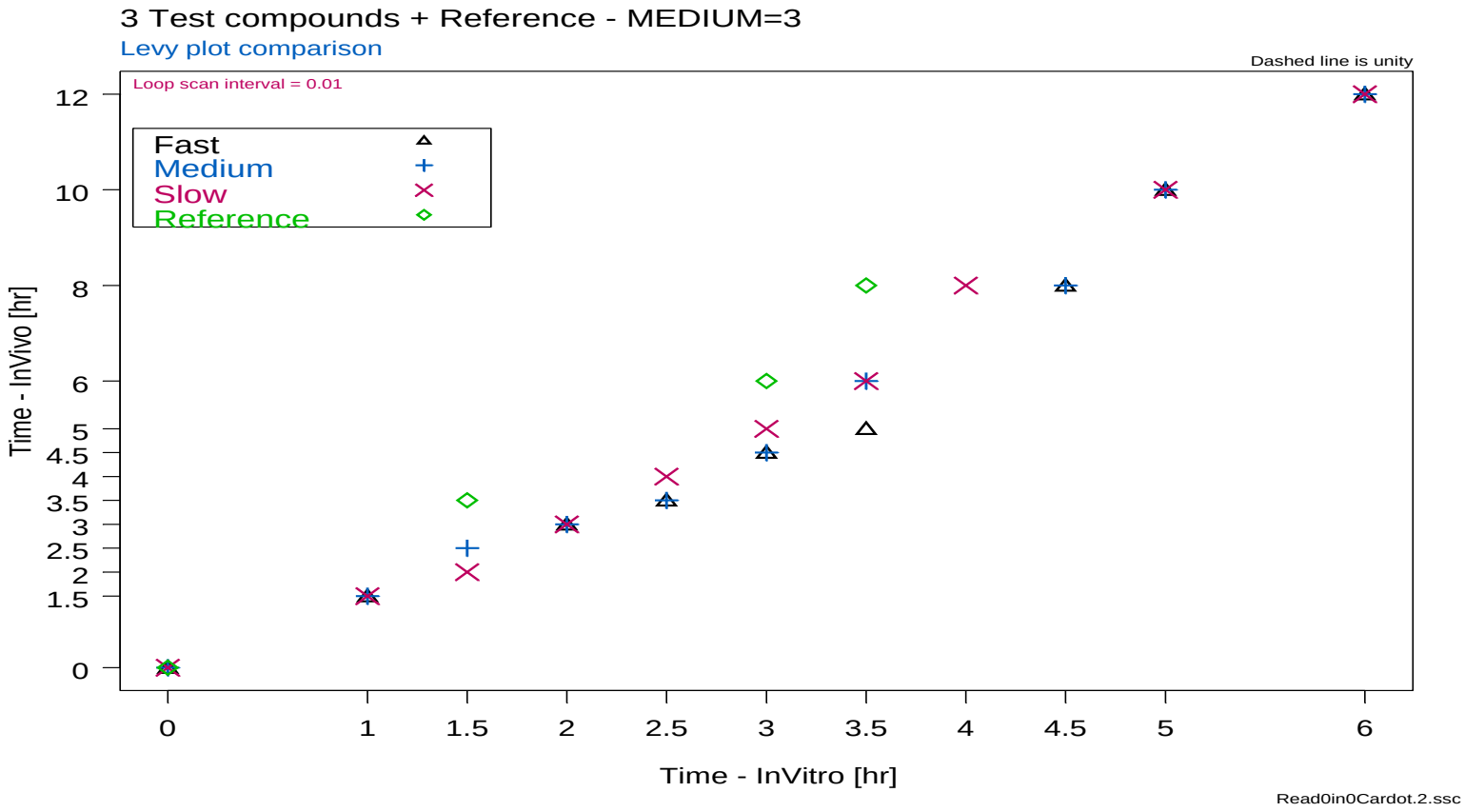
Time scaling: Levy plot and Weibull

- Method 3: Linear Levy plot for test products



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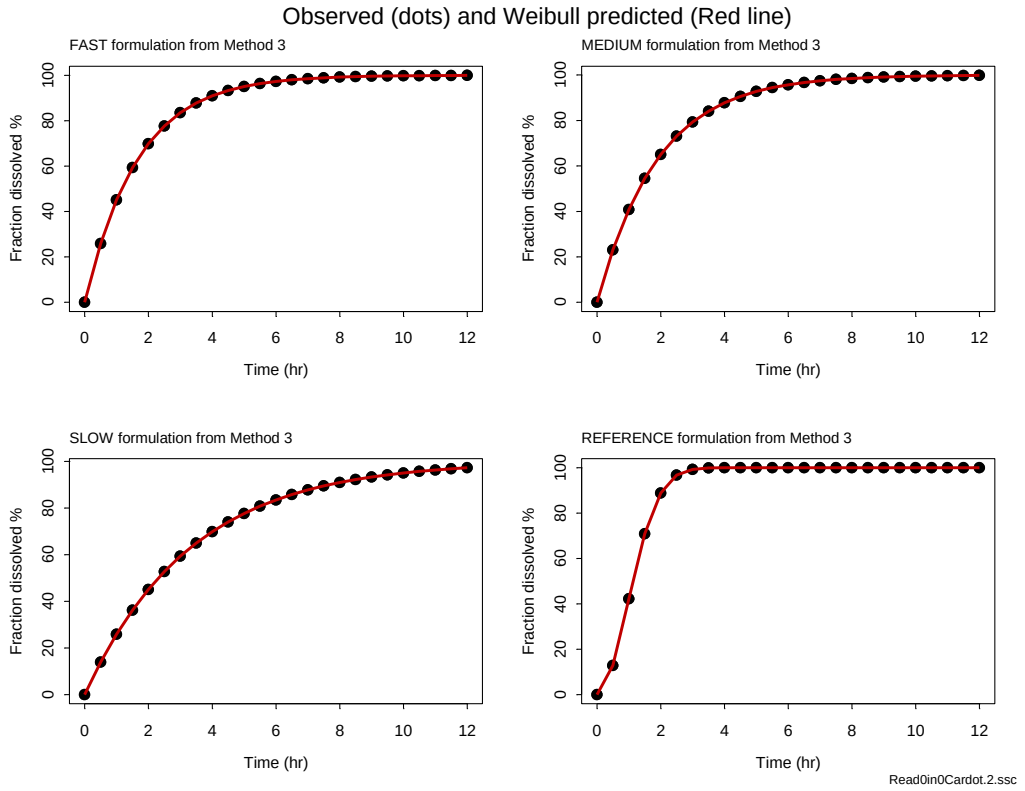
Time scaling: Levy plot and Weibull

- Method 3: Weibull model
  - Weibull Disso(t)=Finf (1- exp[-(t/MDT)^{b}])



1. Estimate Finf, MDT and b
For each formulation

2. Apply the inverse function
Time=-Ln(Abs/Finf+1)$^{(1/b)}$xMDT

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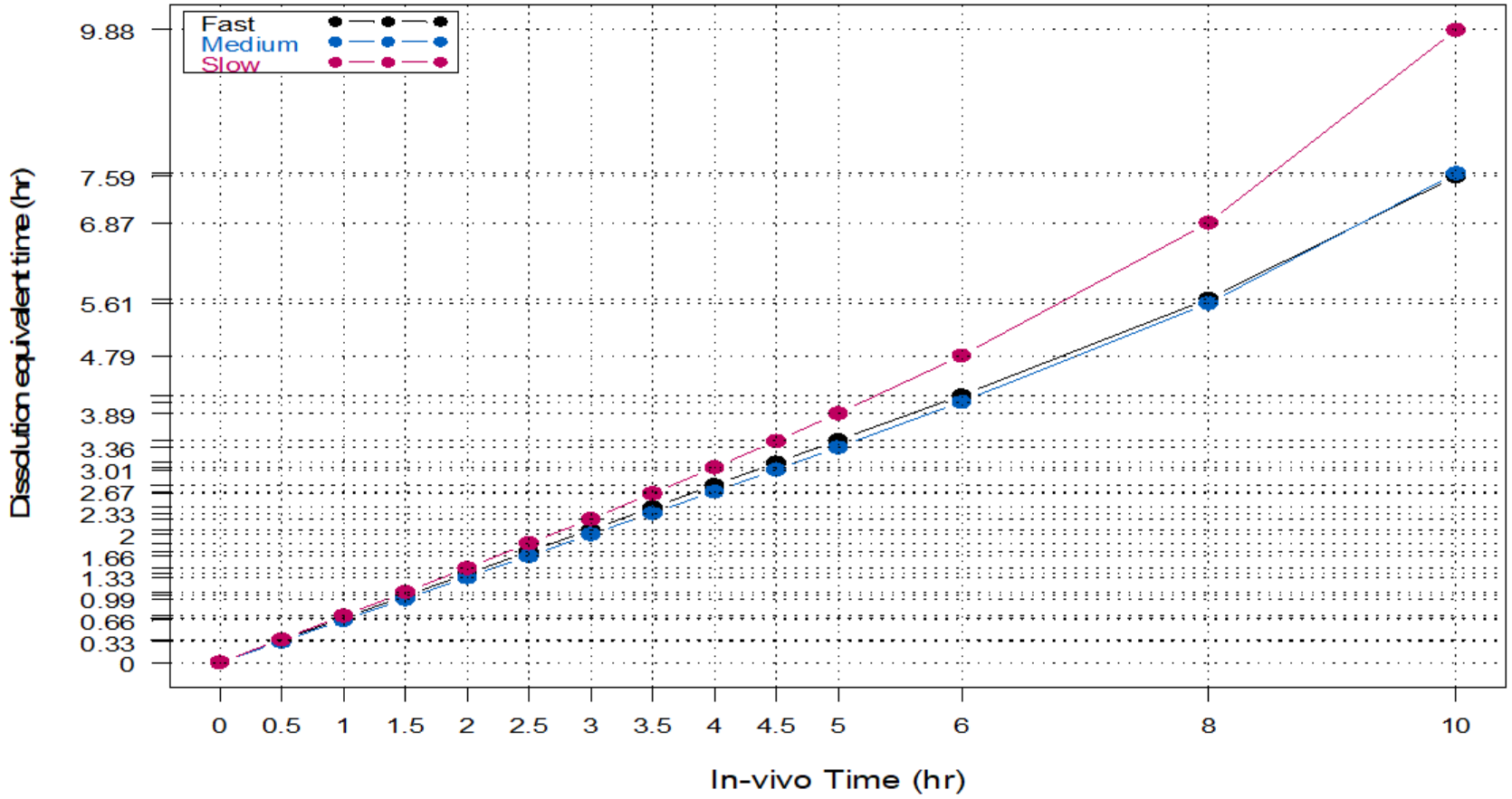
Time scaling: Levy plot and Weibull

- LEVY plot of all formulations for method 3 AFTER by Inverse Weibull interpolation



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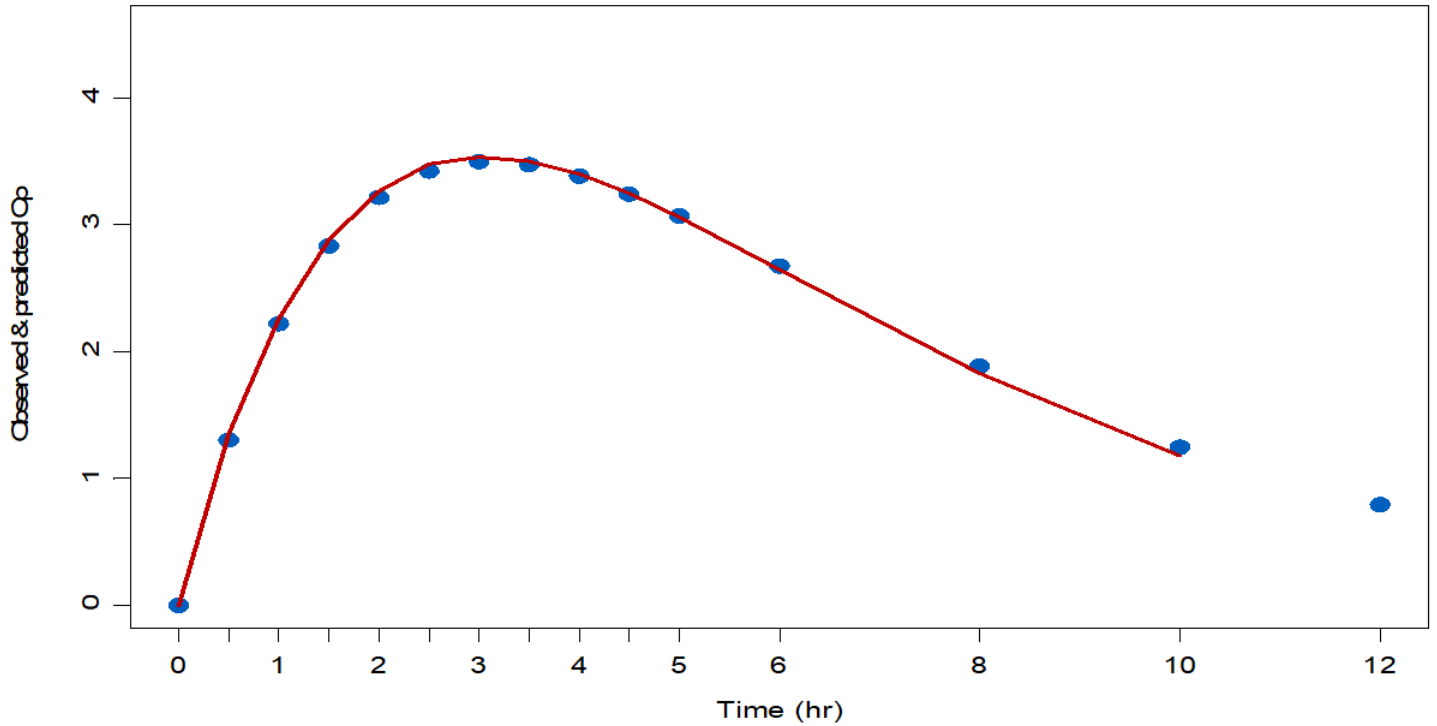
Time scaling: Levy plot and Weibull

- Application of a common time scale
  - Use mean or median depending on data characteristics

Time in vivo	Estimated in vitro time by Inverse Weibull			
	A	B	C	**Mean**
0.00	0.00	0.00	0.00	0.00
0.50	0.35	0.33	0.36	0.35
1.00	0.69	0.66	0.73	0.69
1.50	1.04	0.99	1.10	1.04
2.00	1.38	1.32	1.47	1.39
2.50	1.73	1.66	1.85	1.75
3.00	2.07	1.99	2.24	2.10
3.50	2.42	2.33	2.64	2.46
4.00	2.77	2.67	3.04	2.83
4.50	3.11	3.01	3.46	3.19
5.00	3.46	3.36	3.89	3.57
6.00	4.17	4.06	4.79	4.34
8.00	5.68	5.61	6.87	6.05
10.00	7.58	7.64	9.87	8.36

Time scaling: Levy plot after Inverse Weibull time scaling

- Prediction error of IVIVC using time scaling with Inverse Weibull
  - Applying inverse Weibull to estimate *in vitro* time
  - Improvement in prediction



Formulation B	Predicted	Observed	Prediction error
Cmax	3.5	3.5	-1.1
AUC t	26.4	26.7	1.1

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Questions and comments?

Time scaling: Discussion points

- What if the analytical method with IVIVC is too long and complex and original IVIVC batches have expired?
  - Use batches from specification extremes and one target
  - Obtain dissolution data in development method and in optimized QC method
  - Observe if all fit linear relationship in Levy plot
  - Apply common time scaling and establish the correlation between methods
- Does a process change introduce a risk of falling outside the IVIVC?
  - Dissolution of new manufacturing method batch in QC and IVIVC method
  - Observe if fits in the same linear relationship in Levy plot
  - Different relationship is clue of change in release mechanism which should be explored further

Thank you for your attention