IVIVC – a Way to Speed up Development Using Dissolution as a Surrogate Tool

Based on CARDOT J-M., TOMIC I.
in vitro in vivo correlation basis and application to slow release injectable formulation,
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- Definition of IVIVC, Guideline framework
- When IVIVC could be/could not be established
- Estimation of IVIVC, Time scaling, Prediction of concentrations
- Internal vs external Predictability, Determination of target profiles
- Application to non oral formulations

IVIVC

Definition

Legal framework

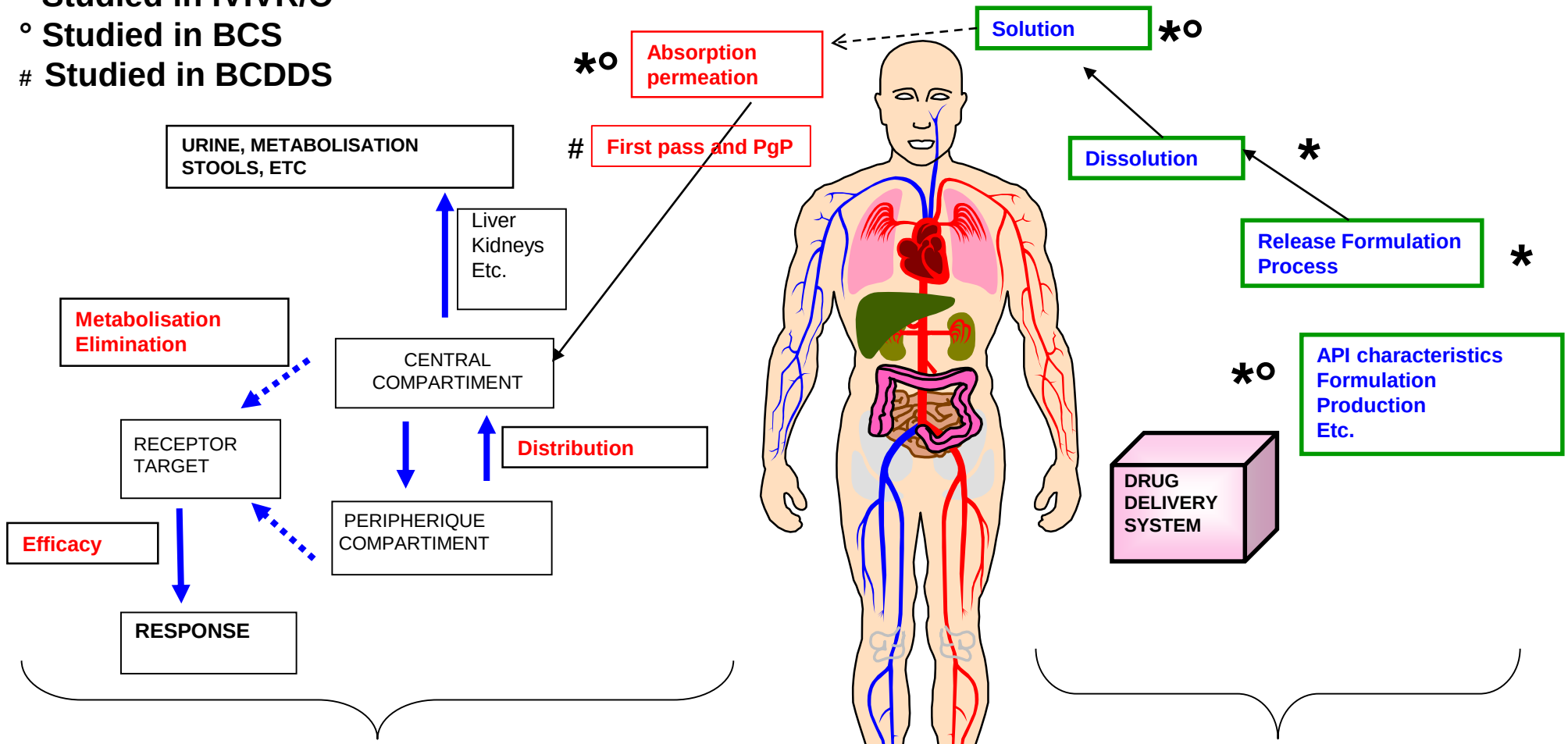
Legal (Main) … not new

- EU-EMA
  - Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CPMP/EWP/280/96 Corr1
  - Guideline on quality of oral modified release products EMA/CHMP/QWP/428693/2013
- US-FDA
  - Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations September 1997
  - Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms September 1997
  - Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms December 1997
- Common
  - ICH Topic Q 8 note for guidance on pharmaceutical development EMEA/CHMP/167068/2004

Administration of drugs

The slowest phenomenon is observed in vivo

*** Studied in IVIVR/C**
° Studied in BCS
 # Studied in BCDDS



In vivo: PK

In vitro: Dissolution, PAT, etc.

Bioavailability Definition

"Bioavailability means the **rate and extent** to which the active substance or active moiety is absorbed from the pharmaceutical form and becomes available at the site of action … (in the general circulation)"

EMEA CPMP/EWP/QWP 1401/88 rev 1

Potential Sources of a Low Oral BA

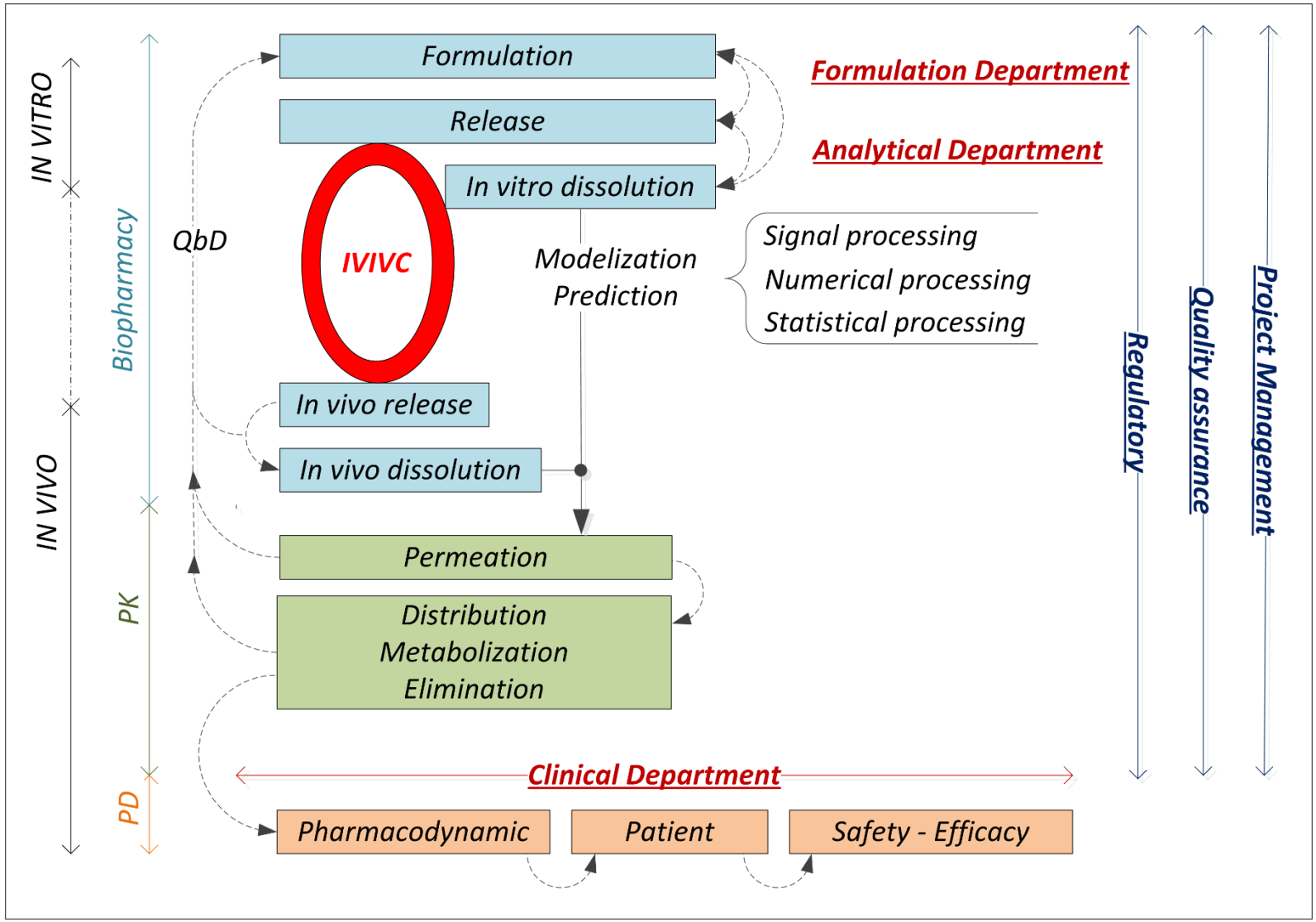
- Release from the dosage form too slow (dosage form, transit time)
- Solubility is limiting (hydrophilicity, pH, volume and type of bio-fluids)
- Dissolution rate API too slow (dose, Particle size, wettability, transit time)
- Absorption is limiting (dose, permeability, type of absorption)
- Permeability (rate) is limiting (lipophilicity, molecular size, -H bounds…)
- Efflux
- Chemical instability in the GIT
- Gut metabolism
- Membrane/Hepatic metabolism

Release/Solubilisation←→Absorption

- That are two main factors studied all along the development of drugs
  - Pharmacokinetics
  - In vitro dissolution
  - BCS
  - Other classifications
  - IVIVC
    - Possible only when in vivo release/dissolution is the limiting factor
    - Possible when that release is controlled by formulation

IVIVC

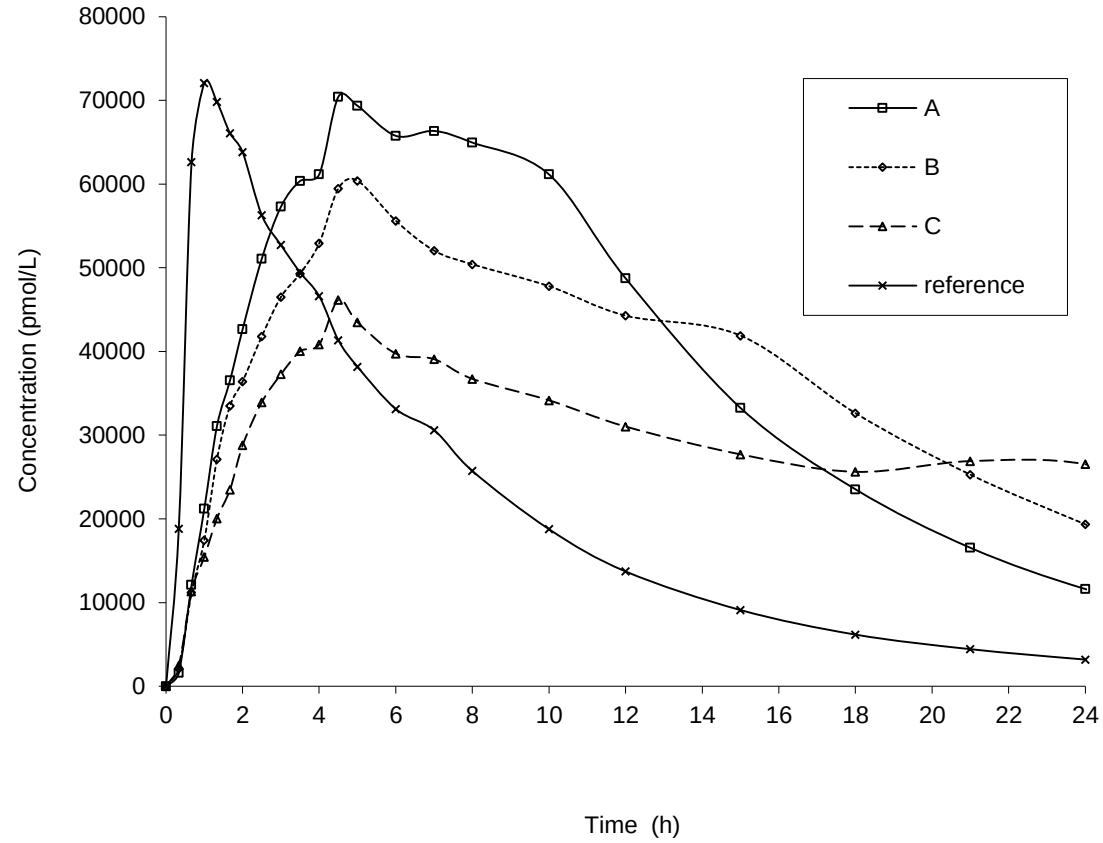
A transversal approach to manage risks



IVIVC

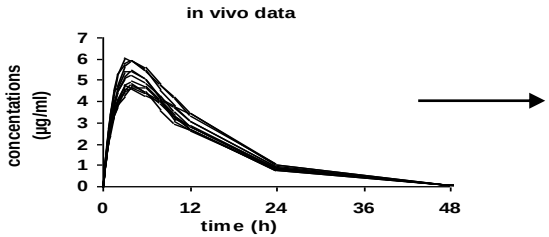
Plasma curves

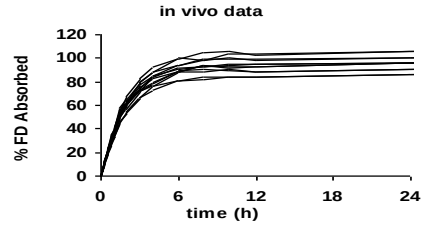
- Same active ingredient
  - Quality
  - Source
  - Batch
  - Difference => different behavior of the formulations
- Or vice versa => optimization of API

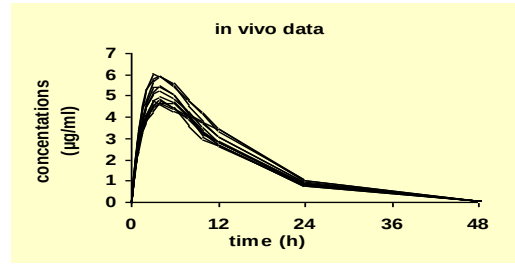


IVIVC in theory

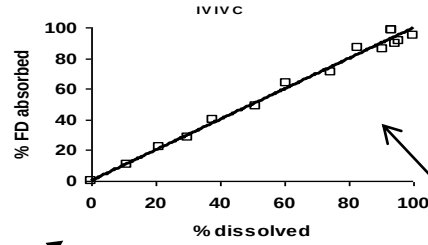
« Absorption »



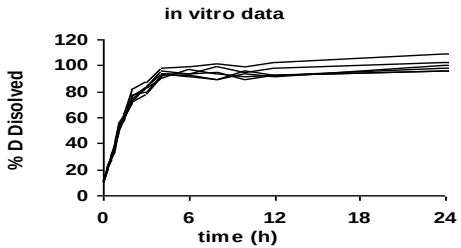




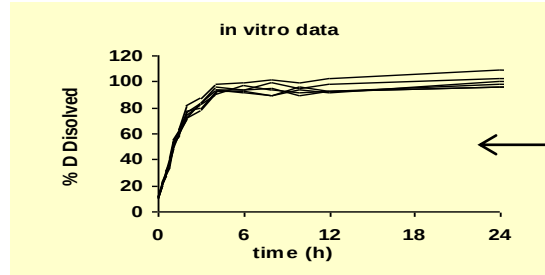
IVIVC



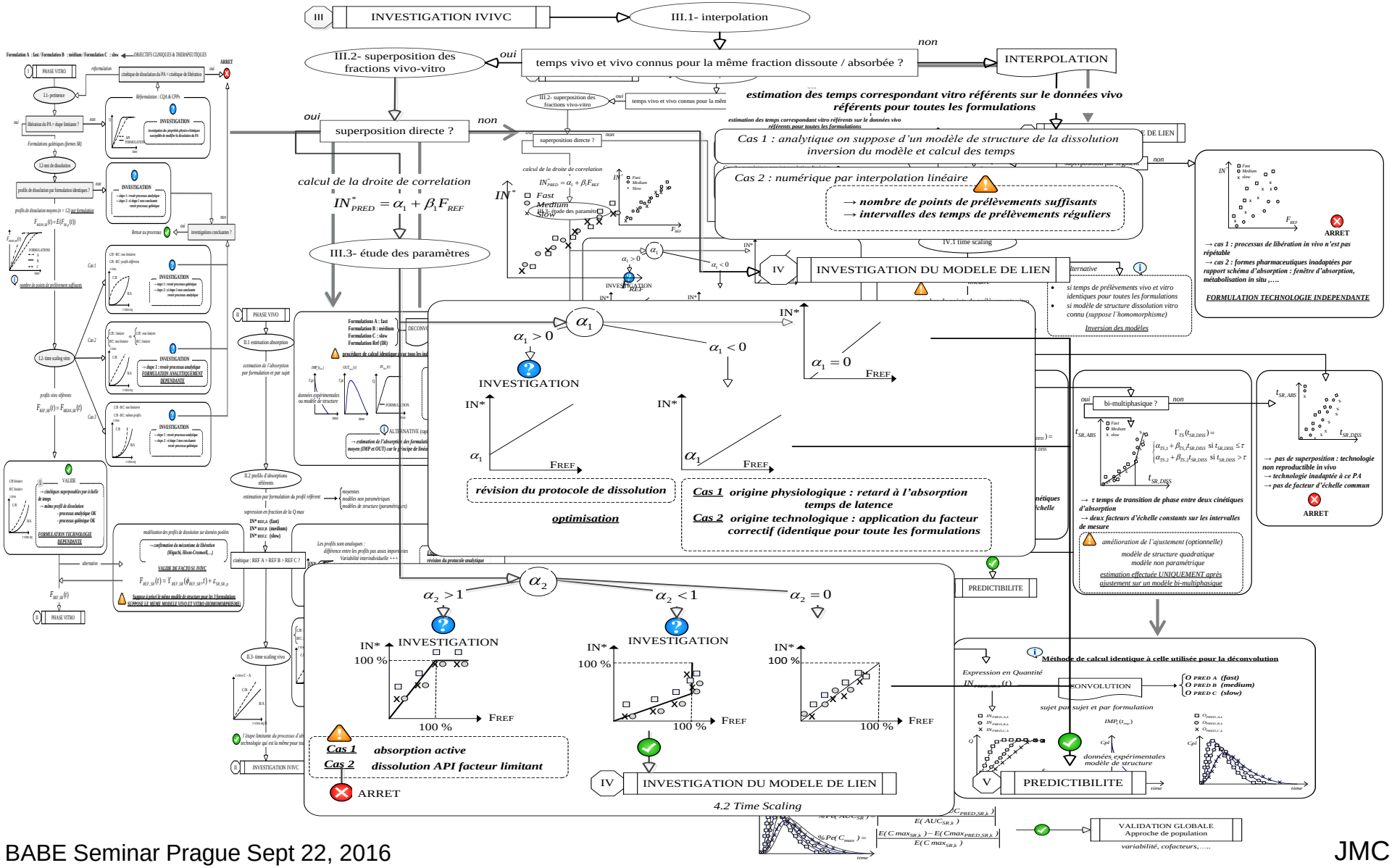
Prediction of a new formulation
Of dissolution limits
Optimisation



« Dissolution »



IVIVC in reality



Trivial aspects

- You can extract the in vivo absorption curve from the in vivo plasma profile => deconvolution for example: Absorption represents the slowest between release, dissolution, and permeation,
- You cannot modify Permeation (trivial)
- Release is the limiting step

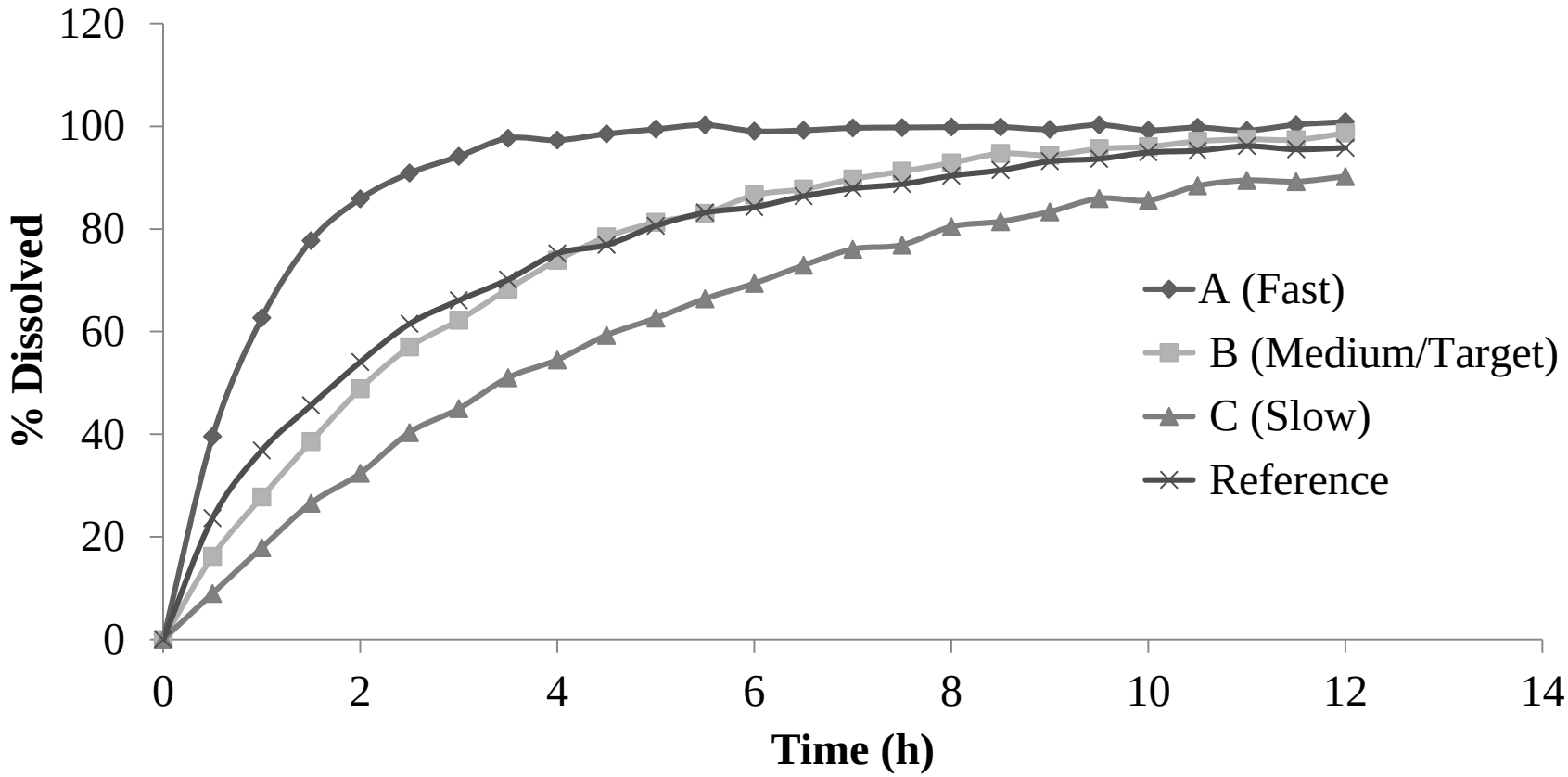
⇒All formulations have the same release principle/mechanism

⇒you may have to adapt the dissolution test!

⇒You may have to “time scale” between in vivo and in vivo

Example

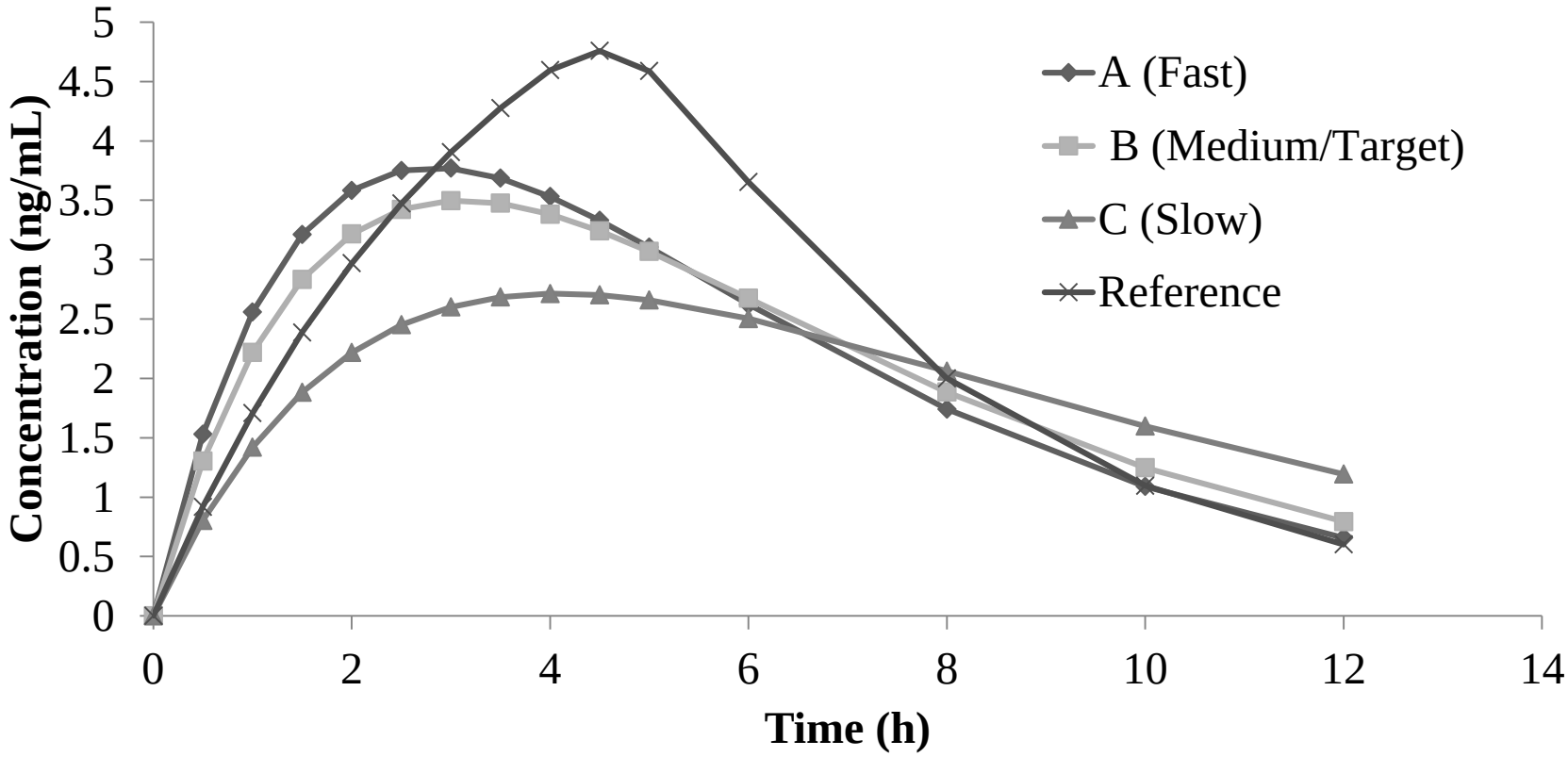
Pilot study: dissolution prior in vivo



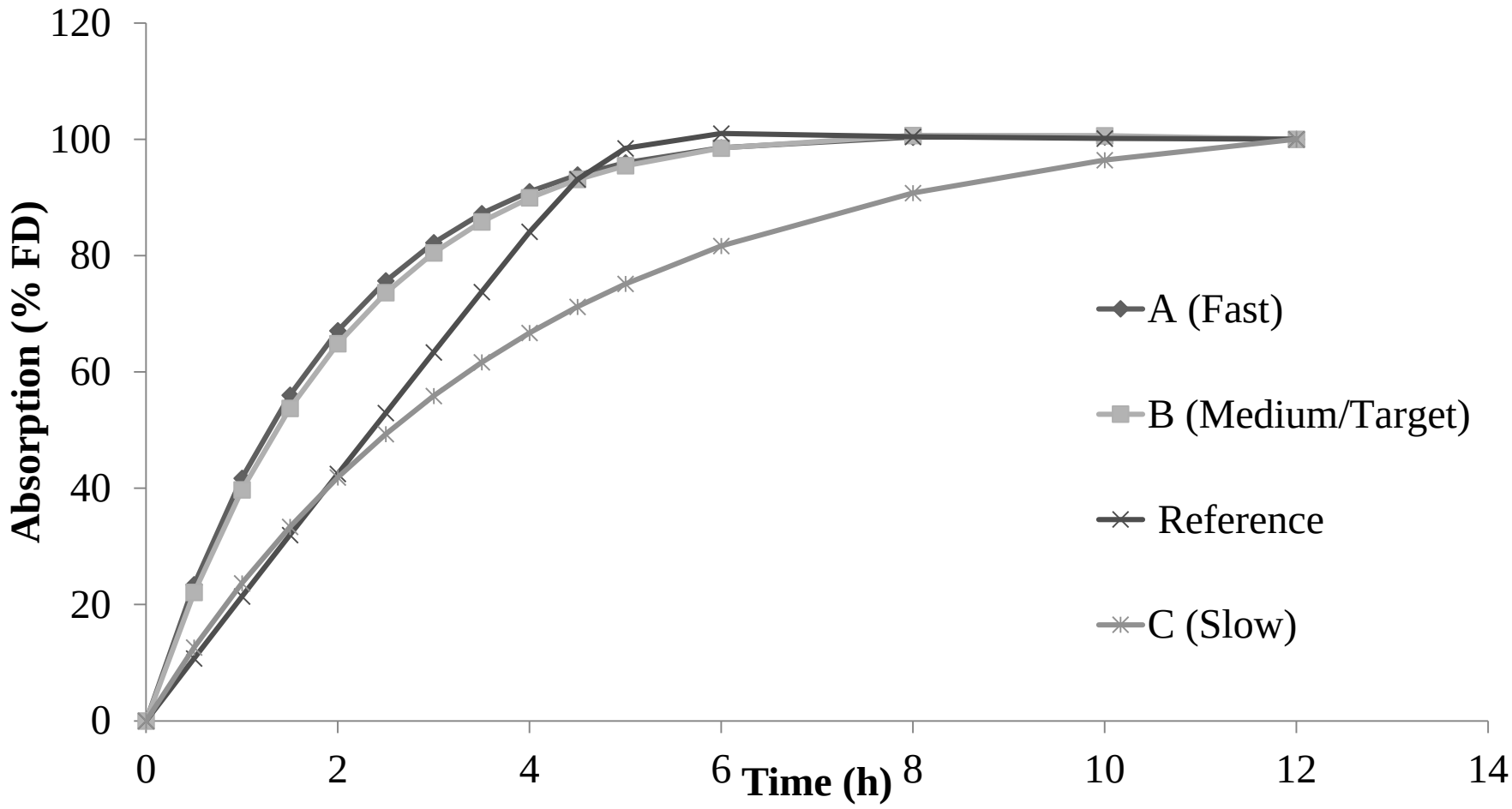
BE study

- BE study failed with 3 test formulations vs reference
- Aim
  - how based on the « bad » results could we forecasted the best strategy
  - Make from the failed study a starting point to re evaluate the data and to bring hypothesis

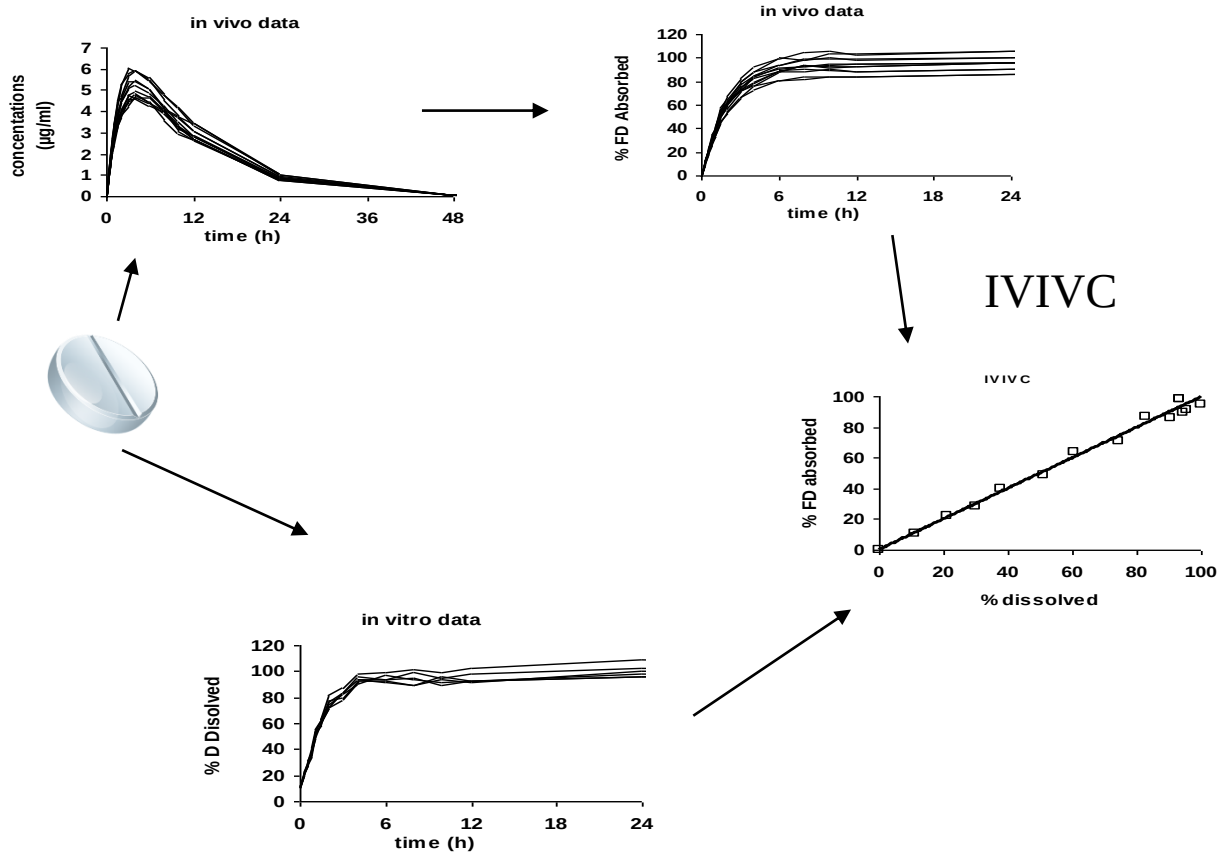
Plasma Curve



« Absorption » input curve

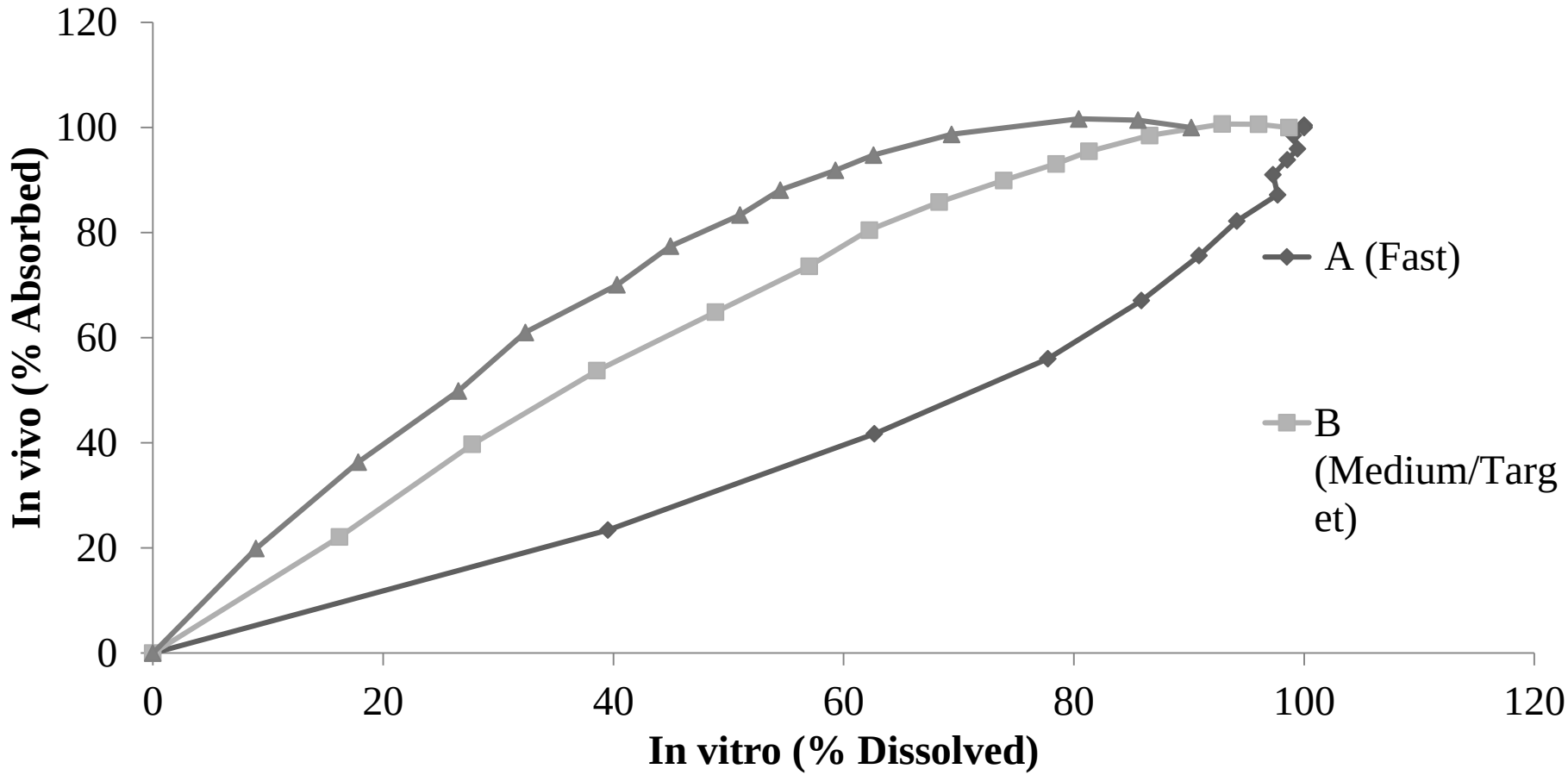


« Absorption »



« Dissolution »

IVIVC with current dissolution



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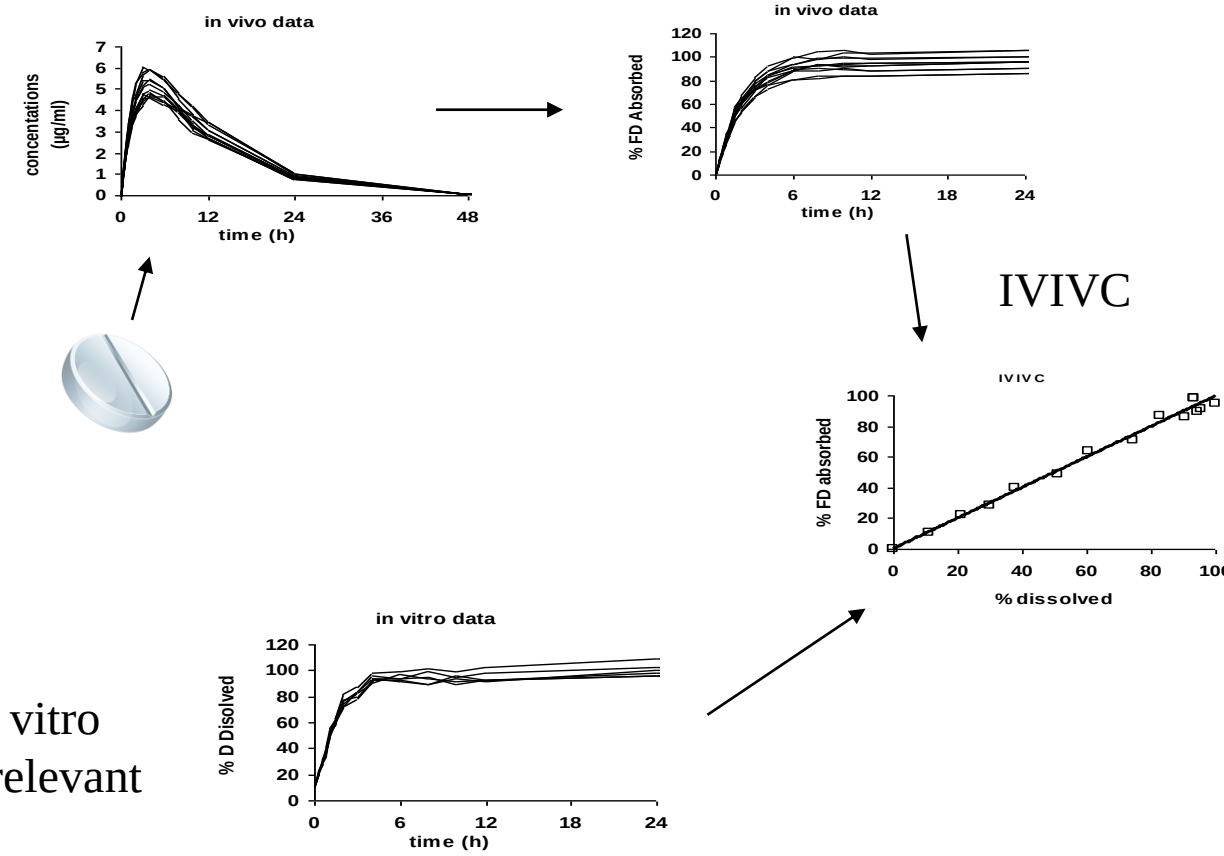


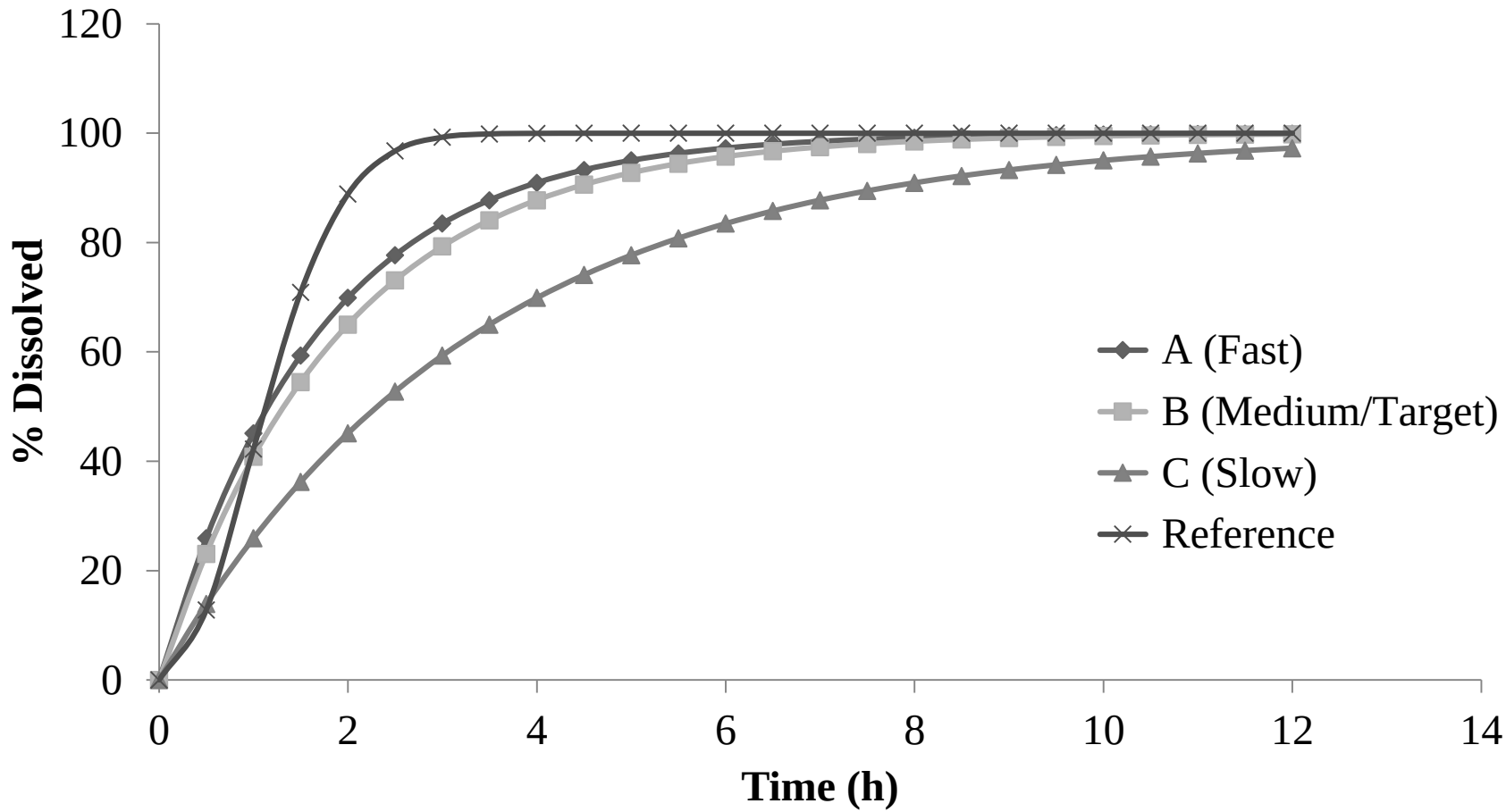
Generate various in vitro method to find the relevant dissolution

« Dissolution »

Dissolution

- After the in vivo results numerous new dissolutions were tried
  - USP 1
  - USP 2
  - USP 3
  - USP 4
- USP 3 and 4 gave the best results

Dissolution curve USP 4



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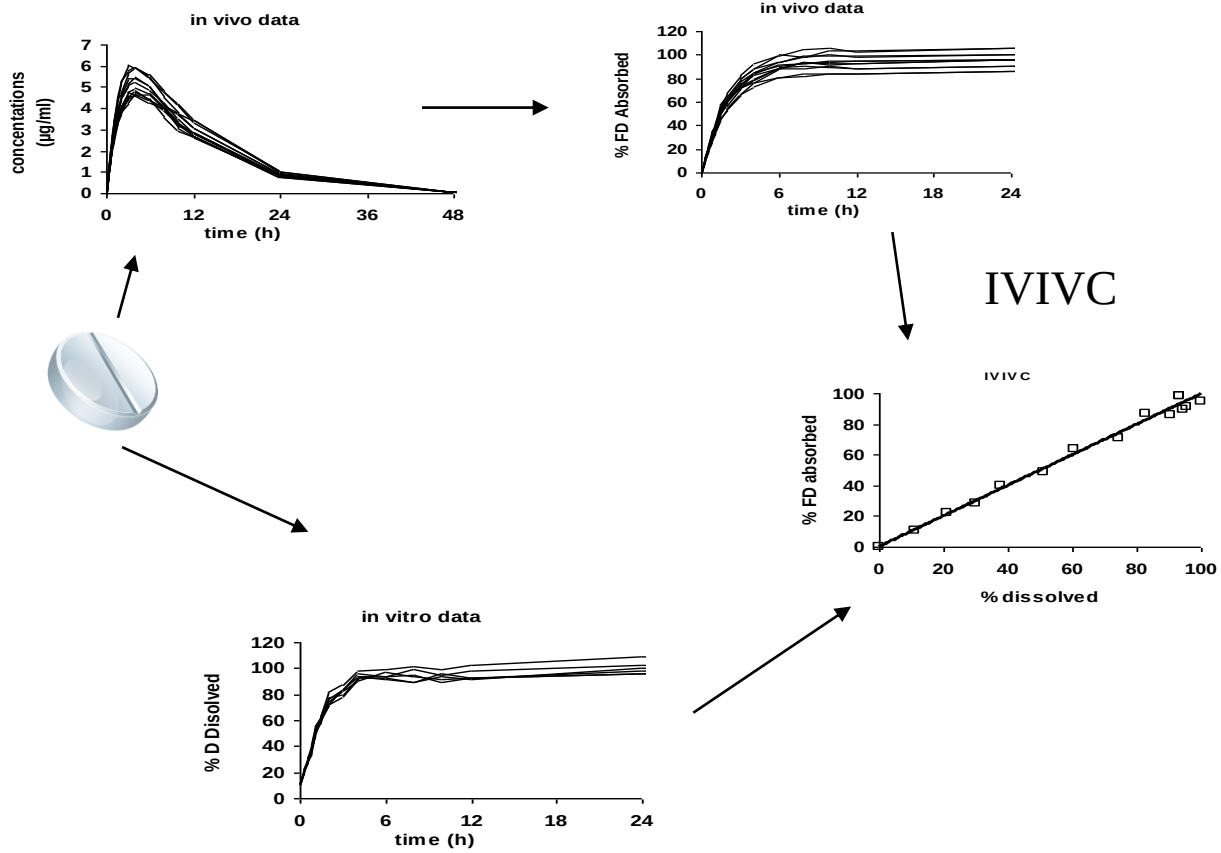
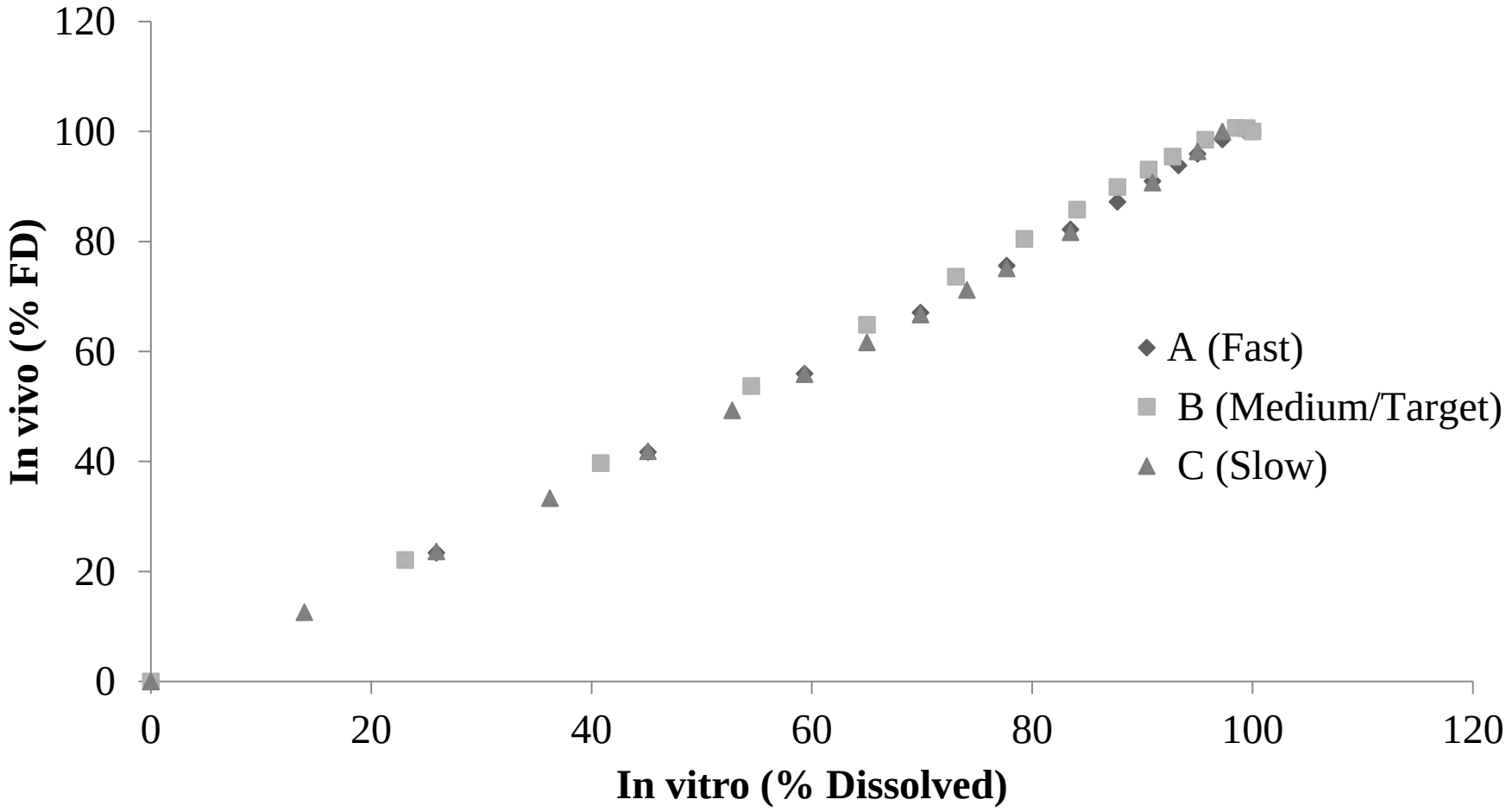


« Dissolution »

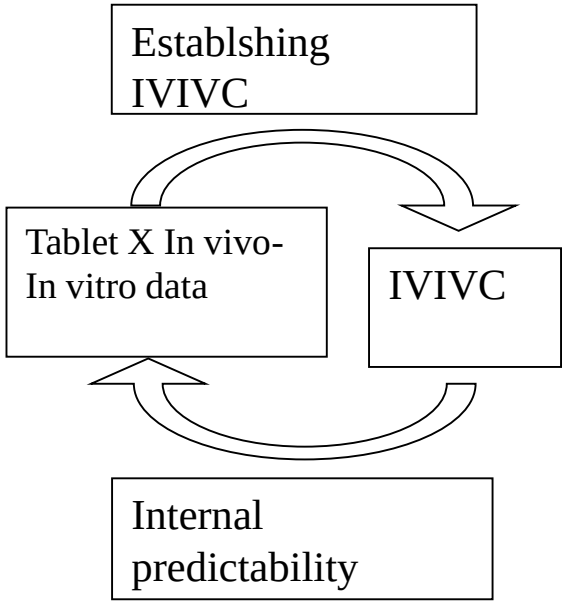
IVIVC common to all formulations

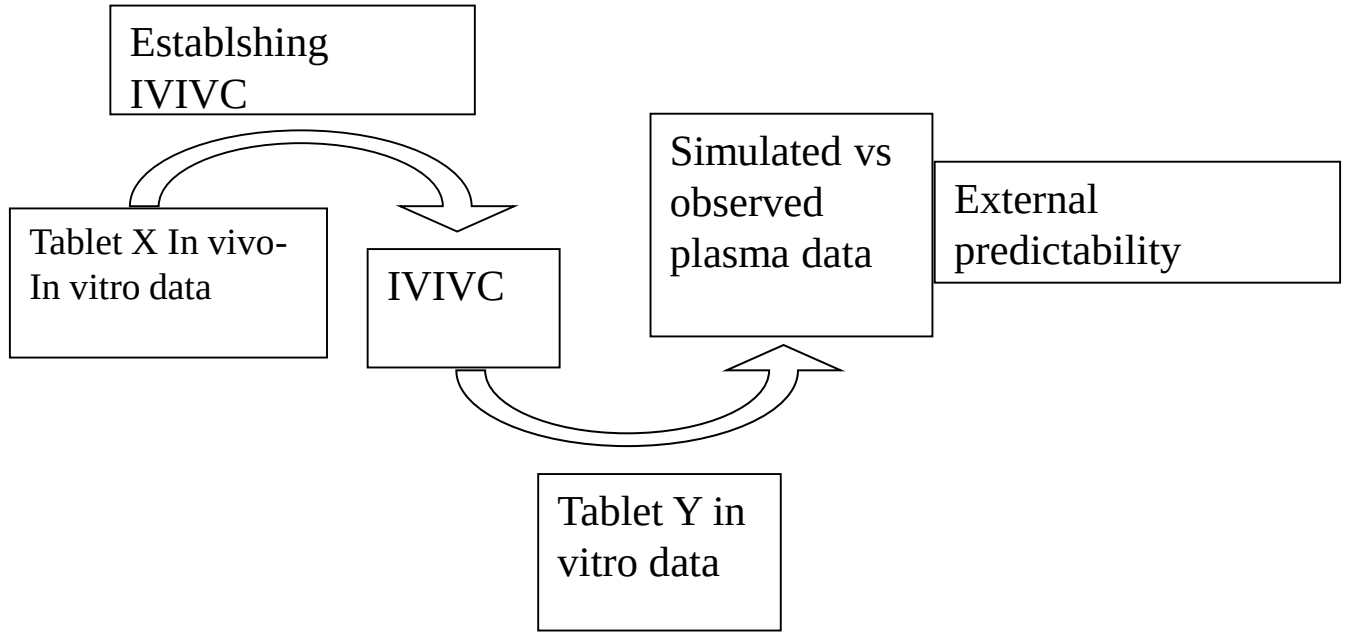


Predictability and prediction

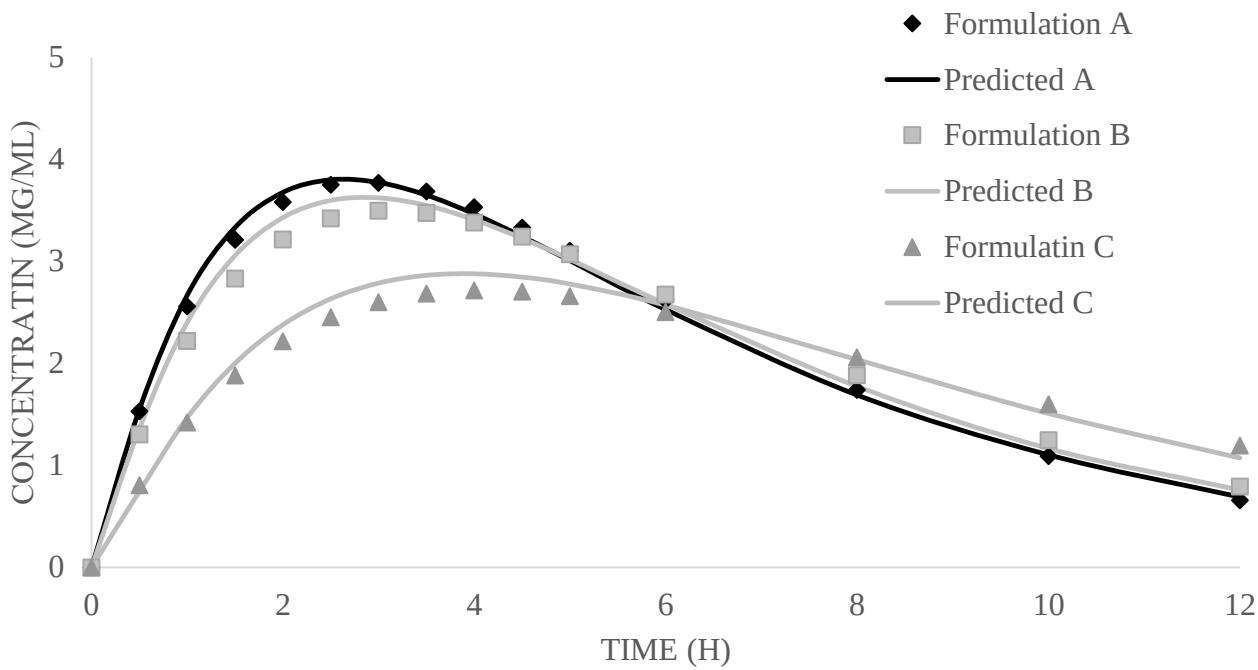
Definition

- Capacity to predict accuratly the data
- Based on BA/BE criteria: AUC and Cmax
- At least 3 formulations with either different rate or different batch etc..
- Max 10% as a mean on each parameters, with none of individual > 15%


Establshing IVIVC
Tablet X In vivo- In vitro data
IVIVC
Internal predictability


Establshing IVIVC
Tablet X In vivo- In vitro data
IVIVC
Simulated vs observed plasma data
External predictability
Tablet Y in vitro data

Prediction based on IVIVC Internal

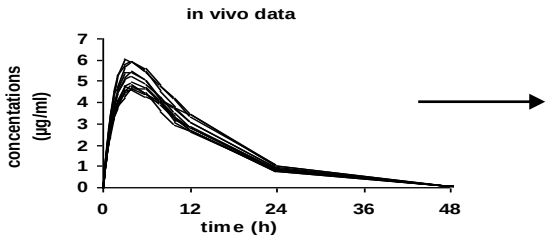


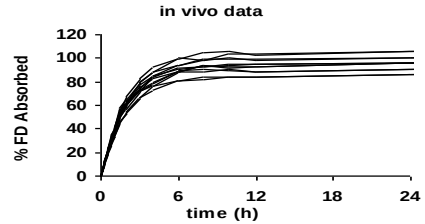
	formulation A	Formulation B	Formulation C	Mean
Cmax	0.82	3.60	6.03	3.48
AUC Inf	3.80	1.88	3.36	3.01

Prediction of target profile

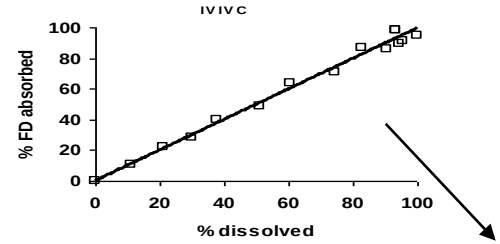
- Based on the ivivc and on the in vivo reference absorption could predict in vitro dissolution curve to mimic reference
- Then plan a DOE
- Select the best results
- Go in vivo

« Absorption »





IVIVC



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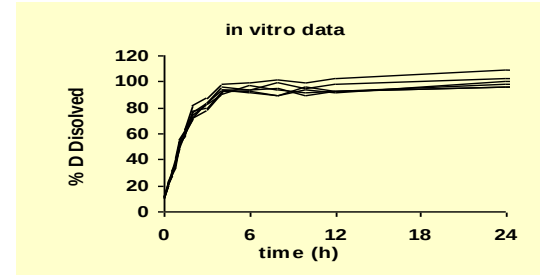


New target formulation

- Result of DOE => now you know your CQA
- Will served as external predictability

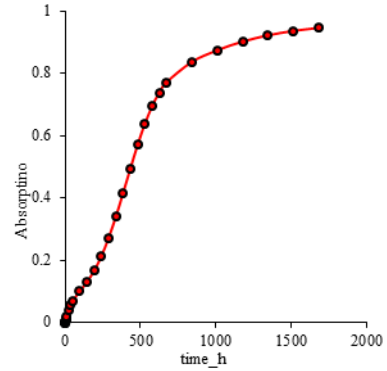
Non oral formulations

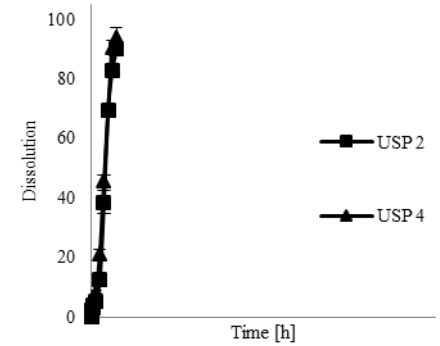
IVIVC could be used

- For parenteral
  - Suspension
  - Implants
  - Depot
- For IUD, Vaginal ring
- For TTS
- For DPI/MDPI
- Etc…

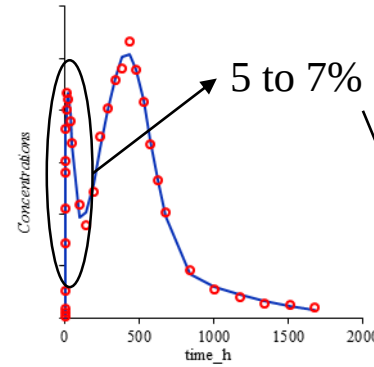
Example of long acting drugs

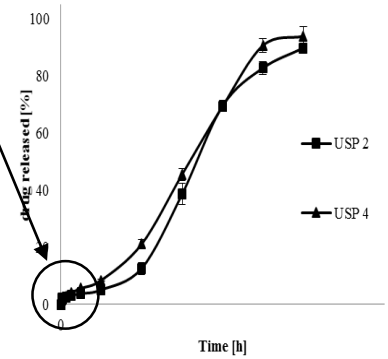
- Problem is often the time scaling … difference between in vitro and in vivo time scale
  - In vivo release over 70 days
  - In vitro dissolution over hours





- Burst possible … but its often linked with low quantities



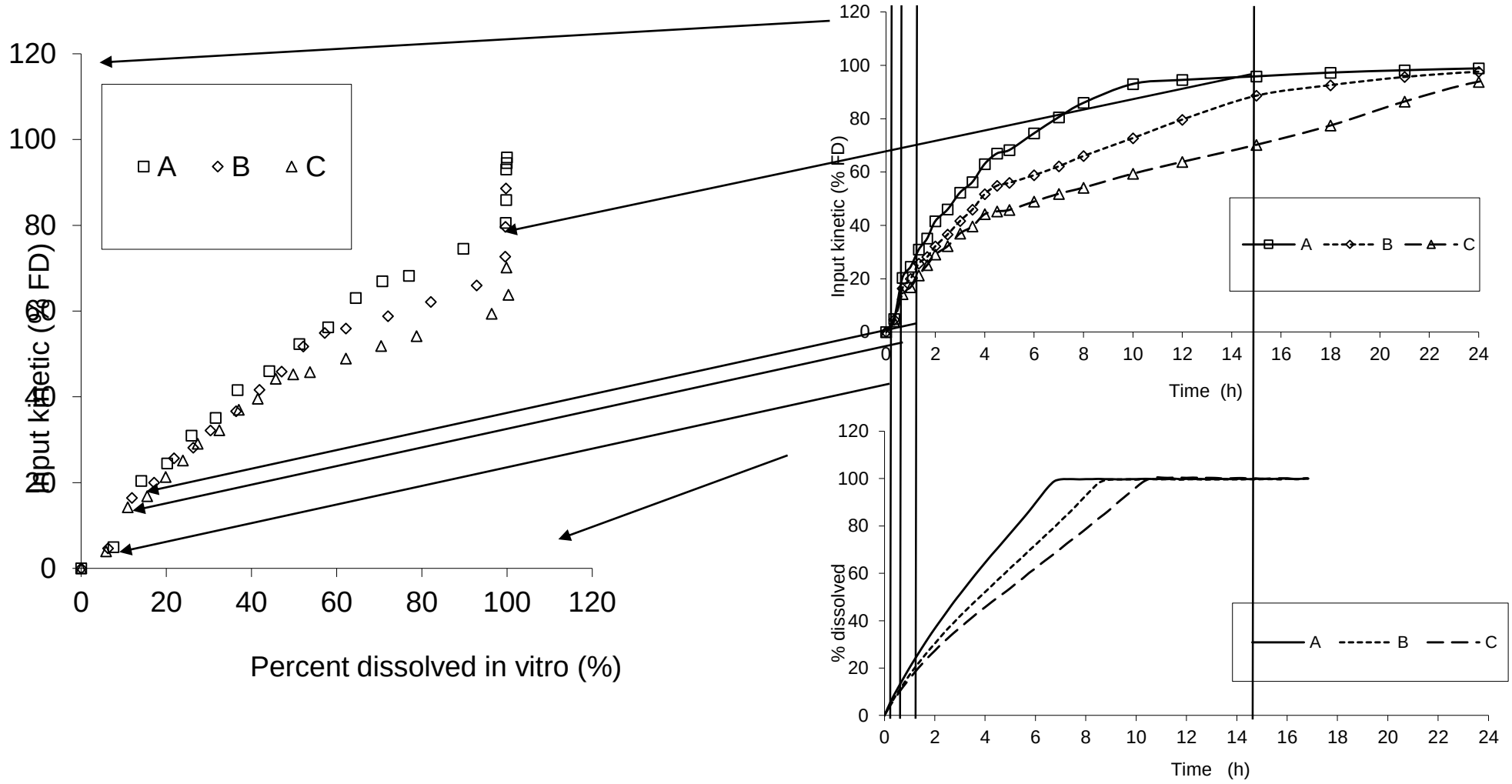


Time scaling … funny game

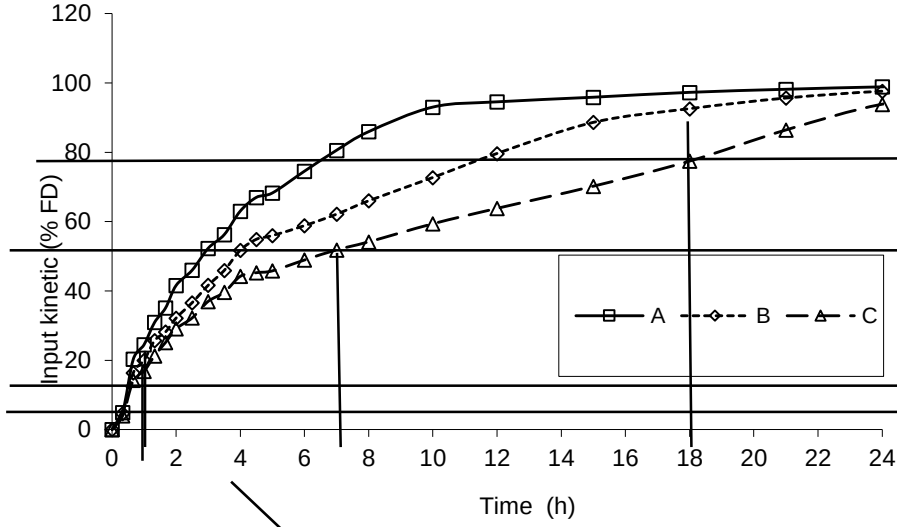
- Time scaling => find the time in vitro correspond to what was observed as absorption in vivo
- Post time scaling IVIVC => in vitro=in vivo… 1:1 relationship!

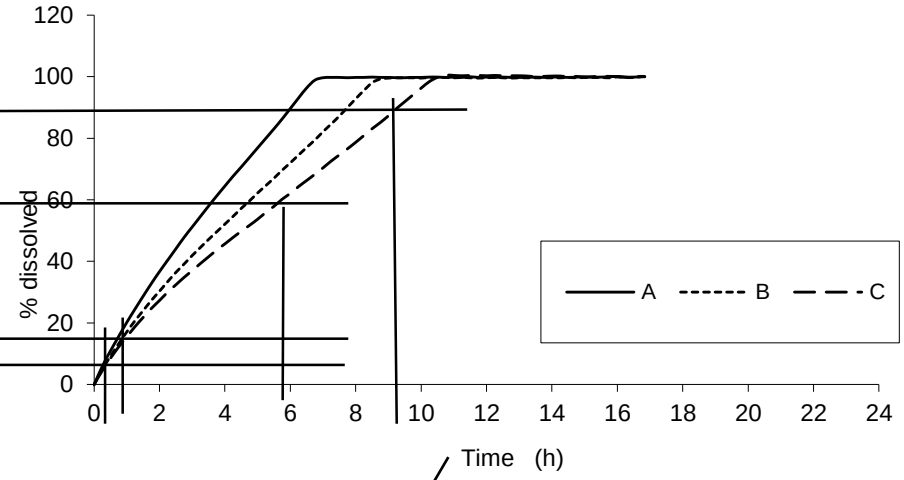
IVIVC without time scaling

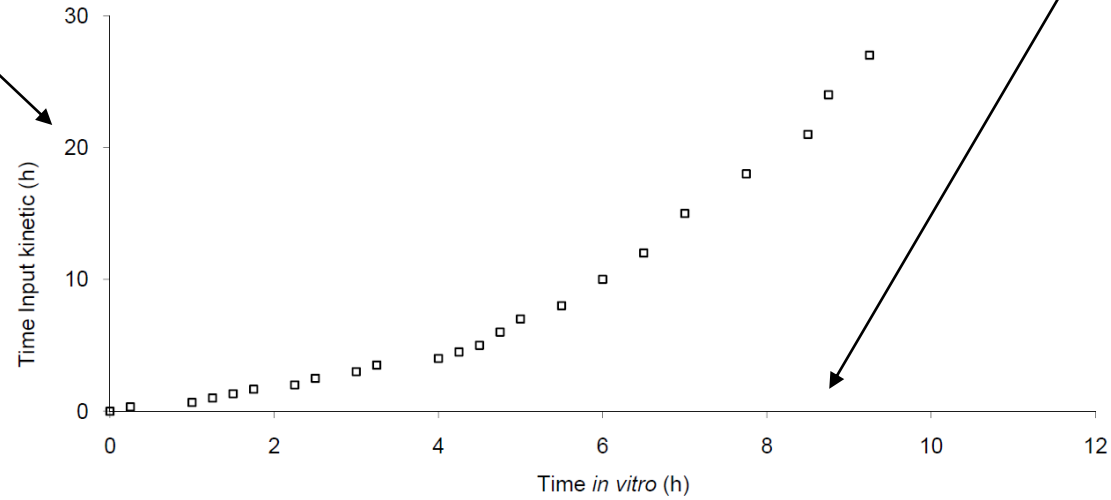
(mean data presented)



time scaling
(mean data presented)



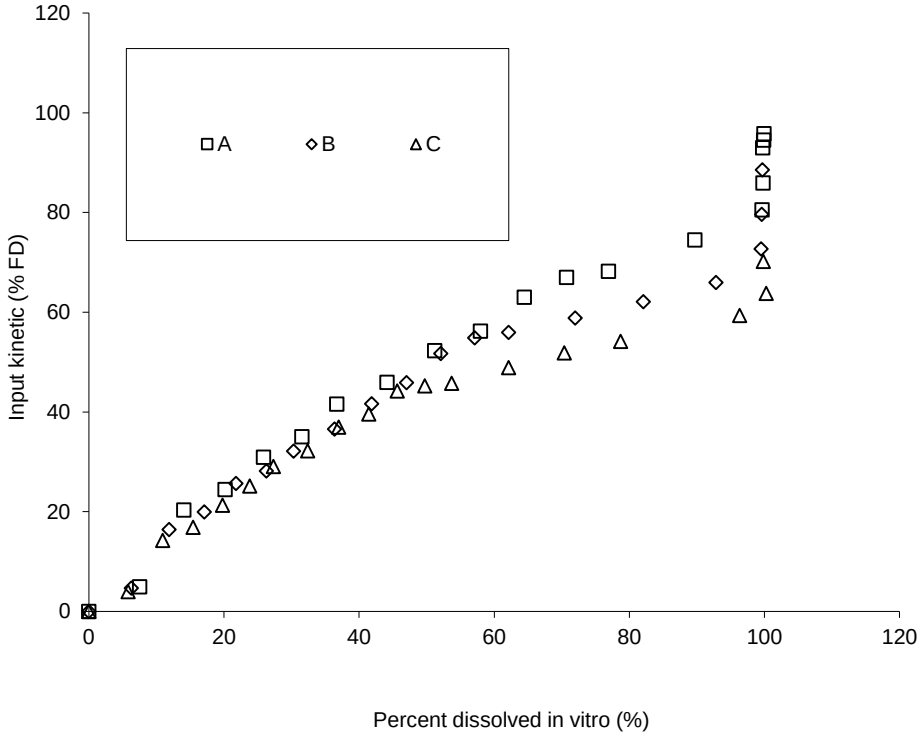




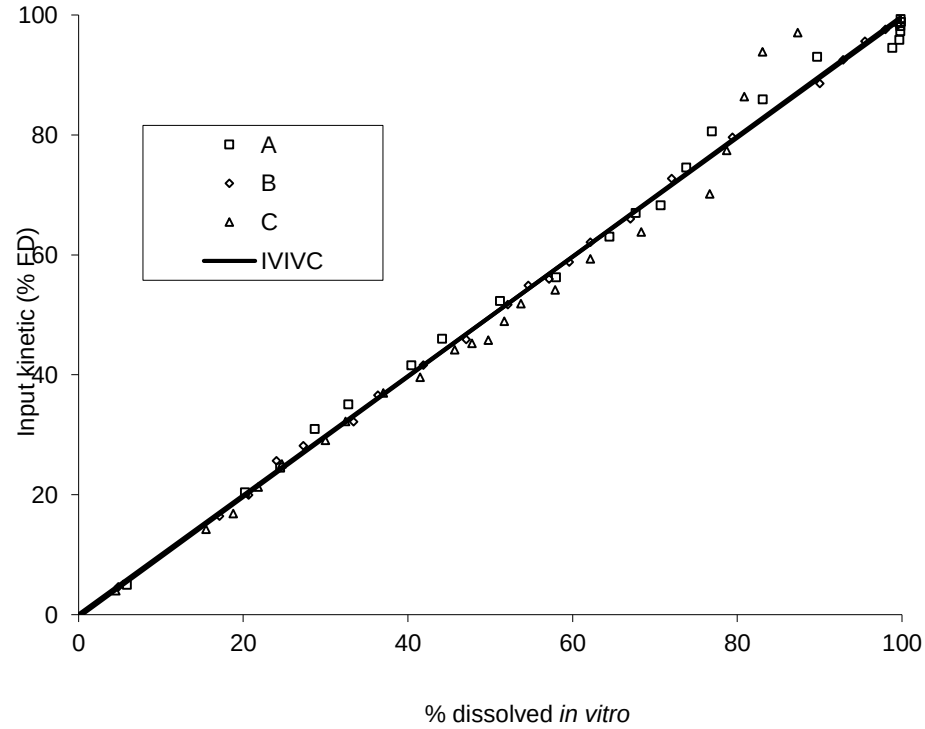
IVIVC with time scaling

(mean data presented)

Without time scaling



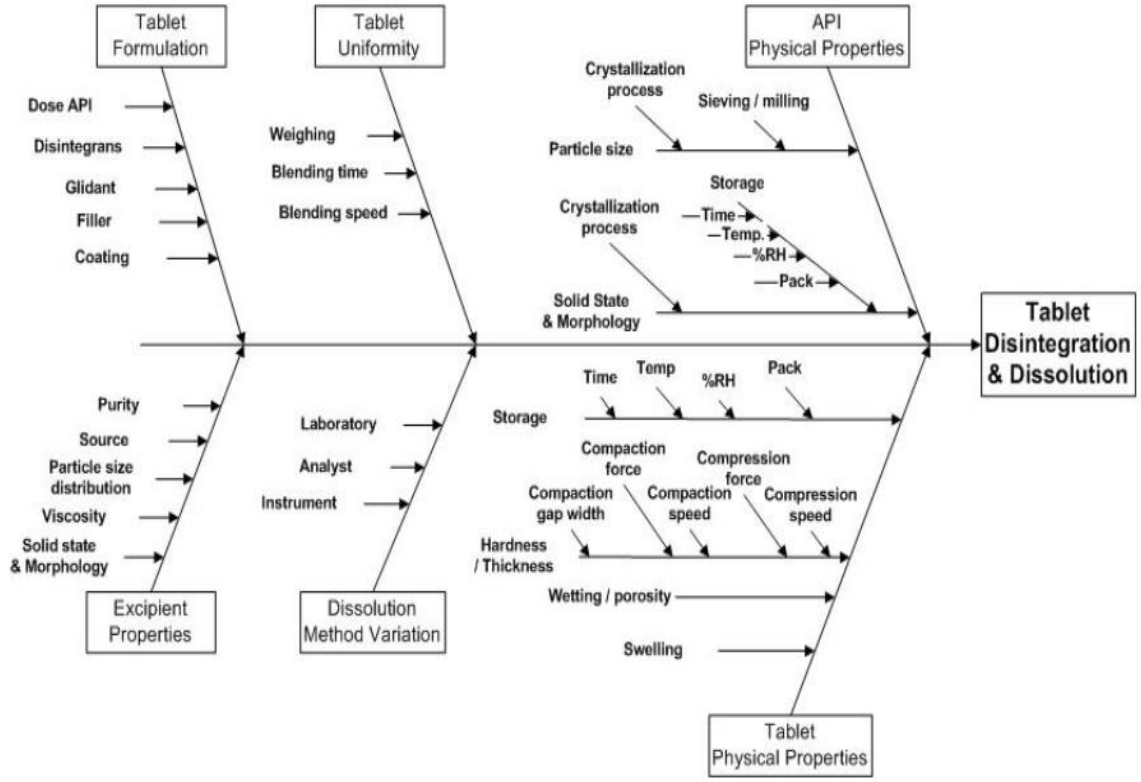
With time scaling



Conclusion

Can we trust prediction

- Only if based on
  - know how of CQA
  - relevant hypothesis
    - API
    - Formulation
    - Physiology
    - Previous data
    - Validation
    - Etc…



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Strategic jigsaw