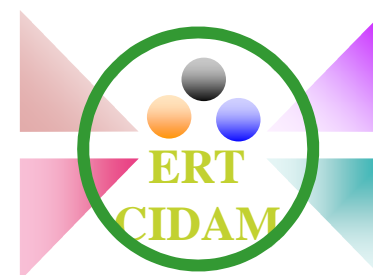


# **In vitro /In vivo correlation and USP4**



**BEYSSAC Eric**  
**Faculty of Pharmacy**  
**ERT CIDAM**



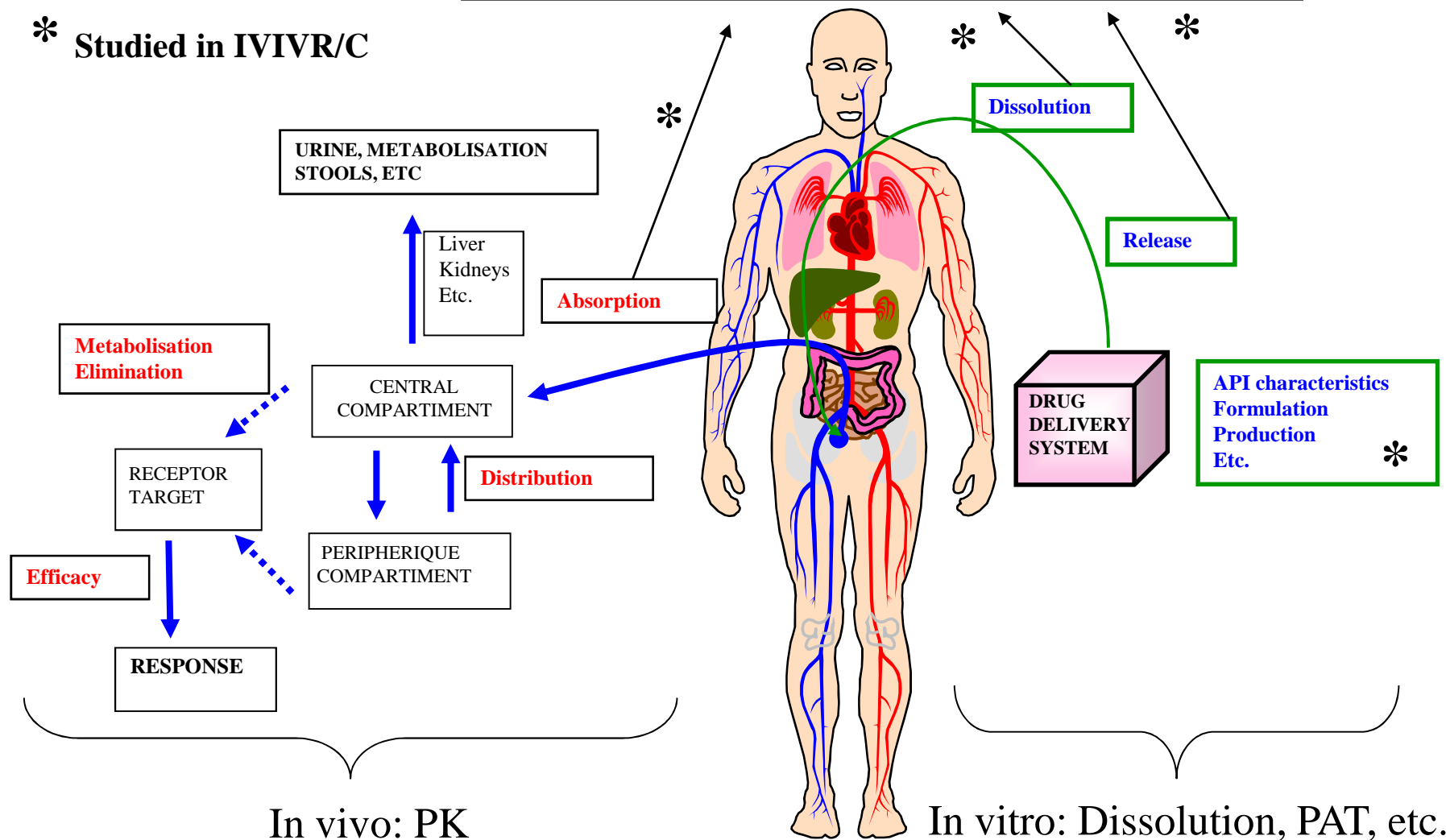
**Université d'Auvergne – Clermont-Ferrand - France**

**SOTAX Workshop**  
**“Apparatus IV Seminar”**

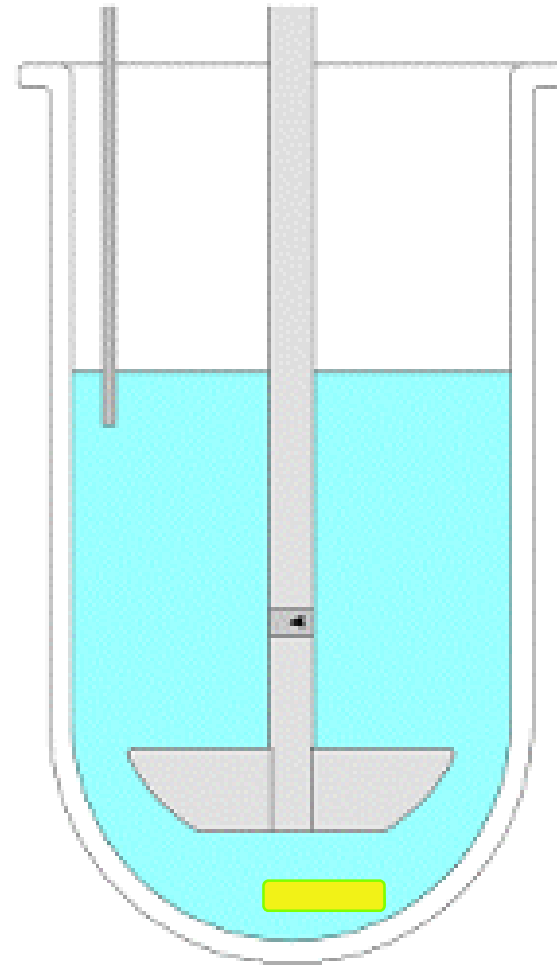
# Introduction and definitions

After oral administration, the slowest phenomenon is observed *in vivo*

\* Studied in IVIVR/C



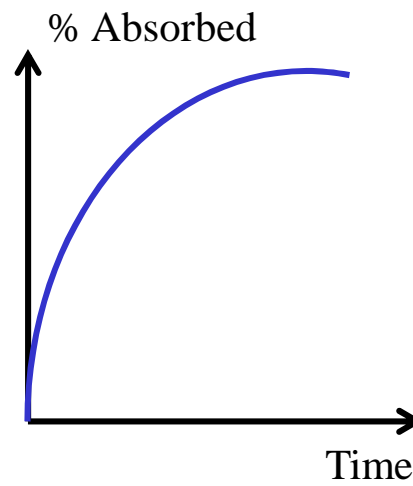
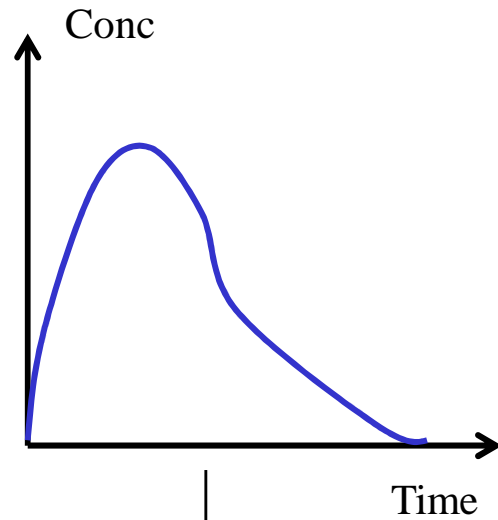
# Correlation ?



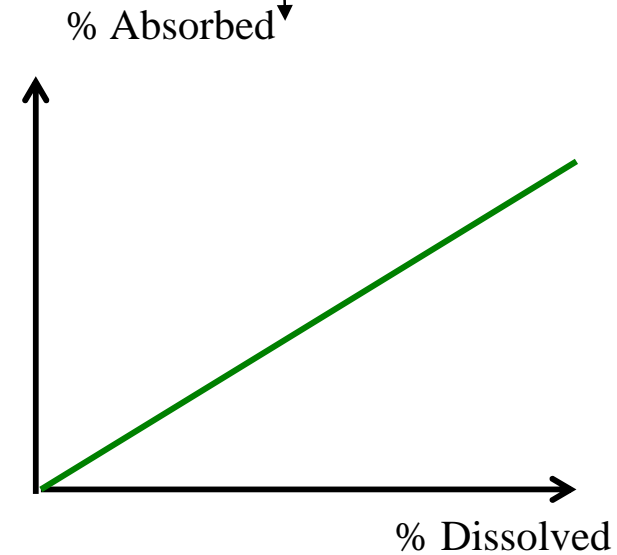
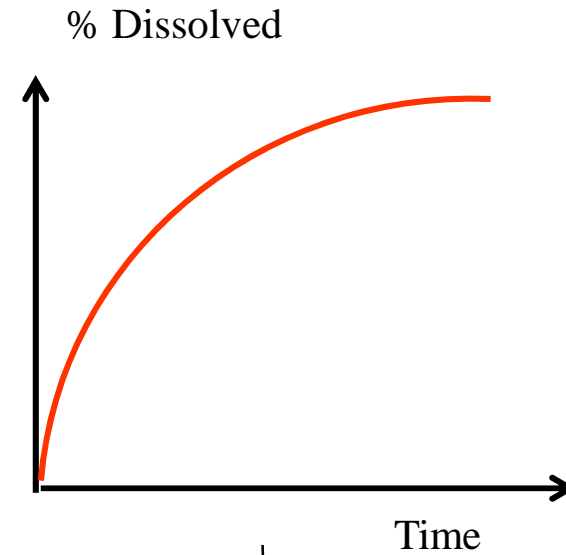
- ❑ **A** : one to one relationship between *in vitro* and *in vivo* data  
ex : *in vitro* dissolution vs. *in vivo* absorption
- ❑ **B** : Correlation based on statistical moments  
ex : *in vitro* MDT vs. *in vivo* MRT or MAT
- ❑ **C** : point to point relationship between a dissolution and a pharmacokinetic parameter  
ex : *in vitro* T50% vs *in vivo* T<sub>max</sub>
- ❑ **Multiple C** : relationship between one or several PK parameters and amount dissolved at several time points

# Correlation

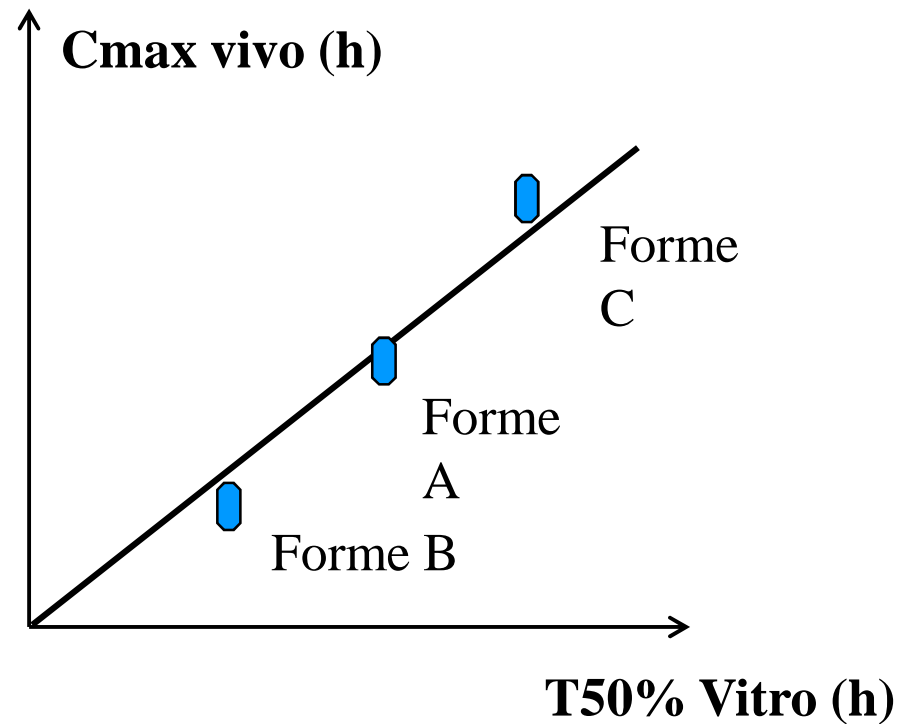
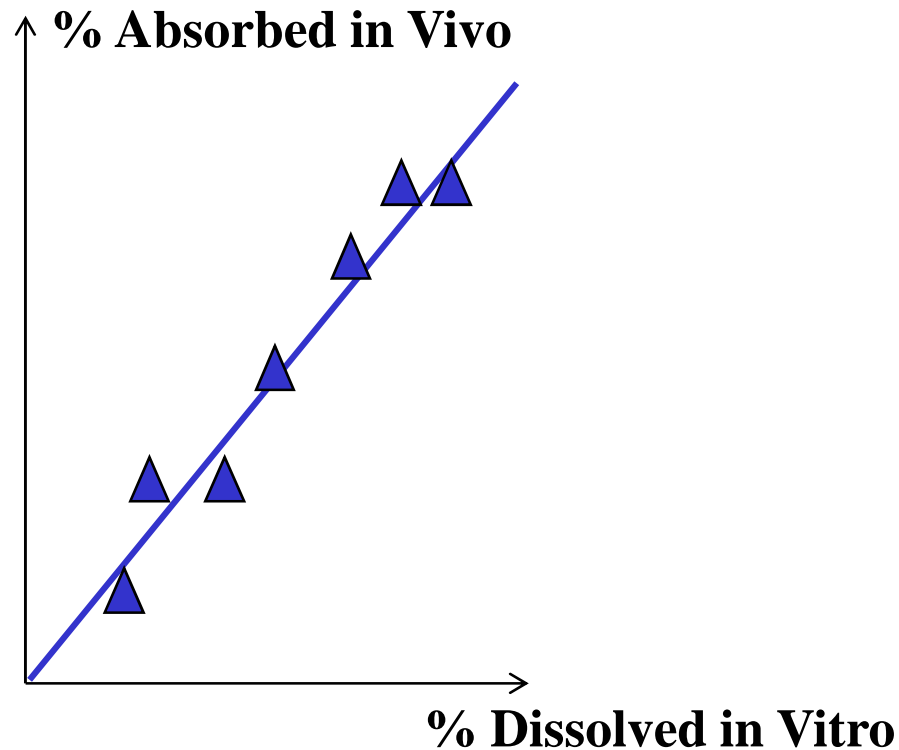
*In vivo*



*In vitro*



# Correlation



Powerfull **A > B > C** Less informative

## Biopharmaceutics Classification System

Class	Solubility	Permeability	Absoption limitation
I	High	High	Gastric emptying
II	Low	High	Dissolution
III	High	Low	Permeability
IV	Low	Low	Case to case

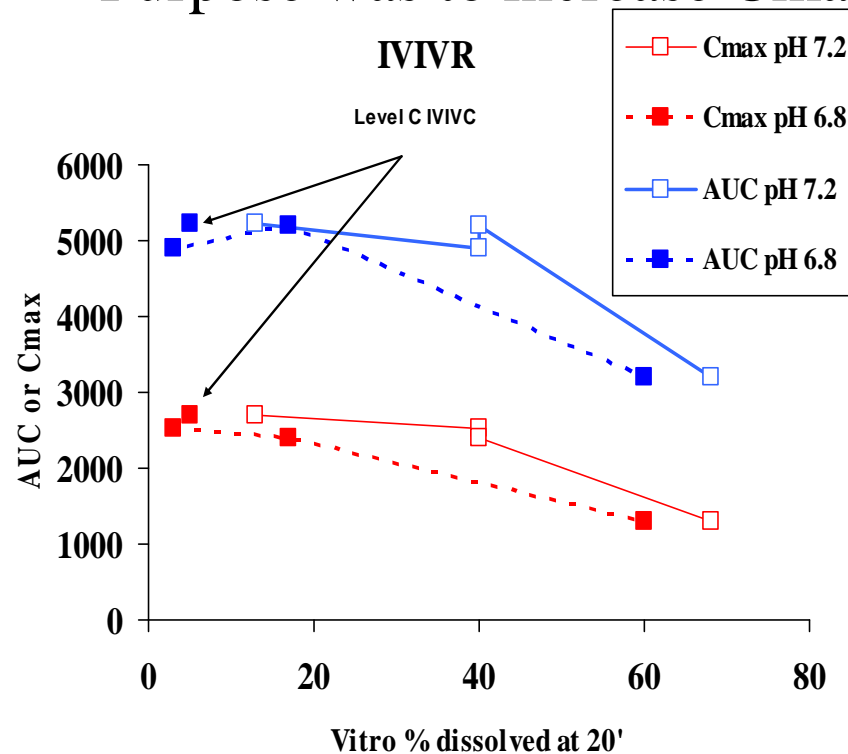
(From : Oral drug absorption : prediction and asessment / edited by Jennifer B. Dressman, Hans Lennernäs-M. Dekker, 2000)

## □ IVIVC -IVIVR

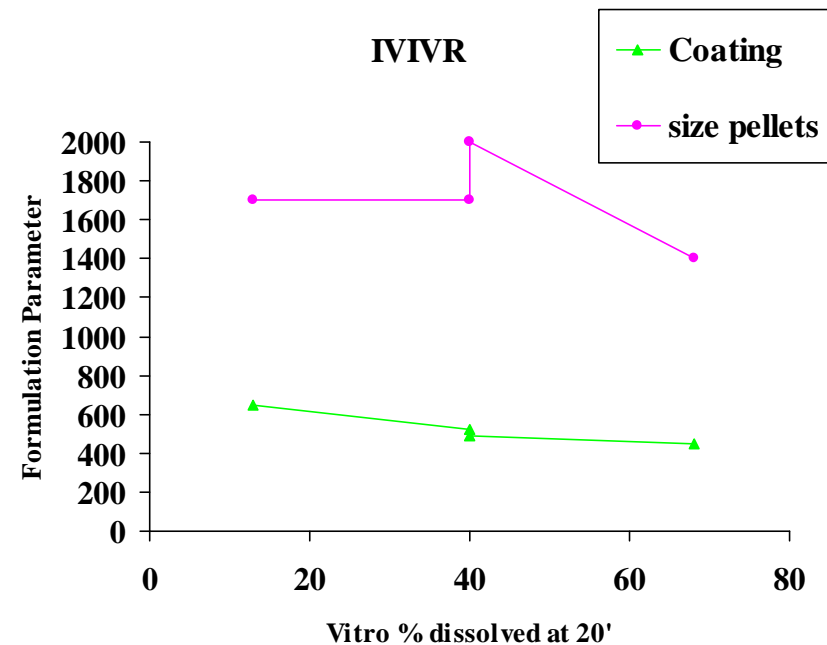
- IVIVC: “**quantitative**” linear mathematical model that is used to simulate in vivo data and for regulatory purposes like **biowaivers** (Ex level A In **vitro** **dissolution** vs **absorption curve**)
- IVIVR: more a “**qualitative**” ranking between in vitro and in vivo data that indicates qualitative tendencies and help in the identification of **key factors**. Ex quantity dissolved at xx minutes (linked with **coating thickness**) vs **Cmax**

## Case study : drug A IVIVR or IVIVC

- Drug A sensitive to low pH
- Purpose was to increase C<sub>max</sub> and AUC in fasted state



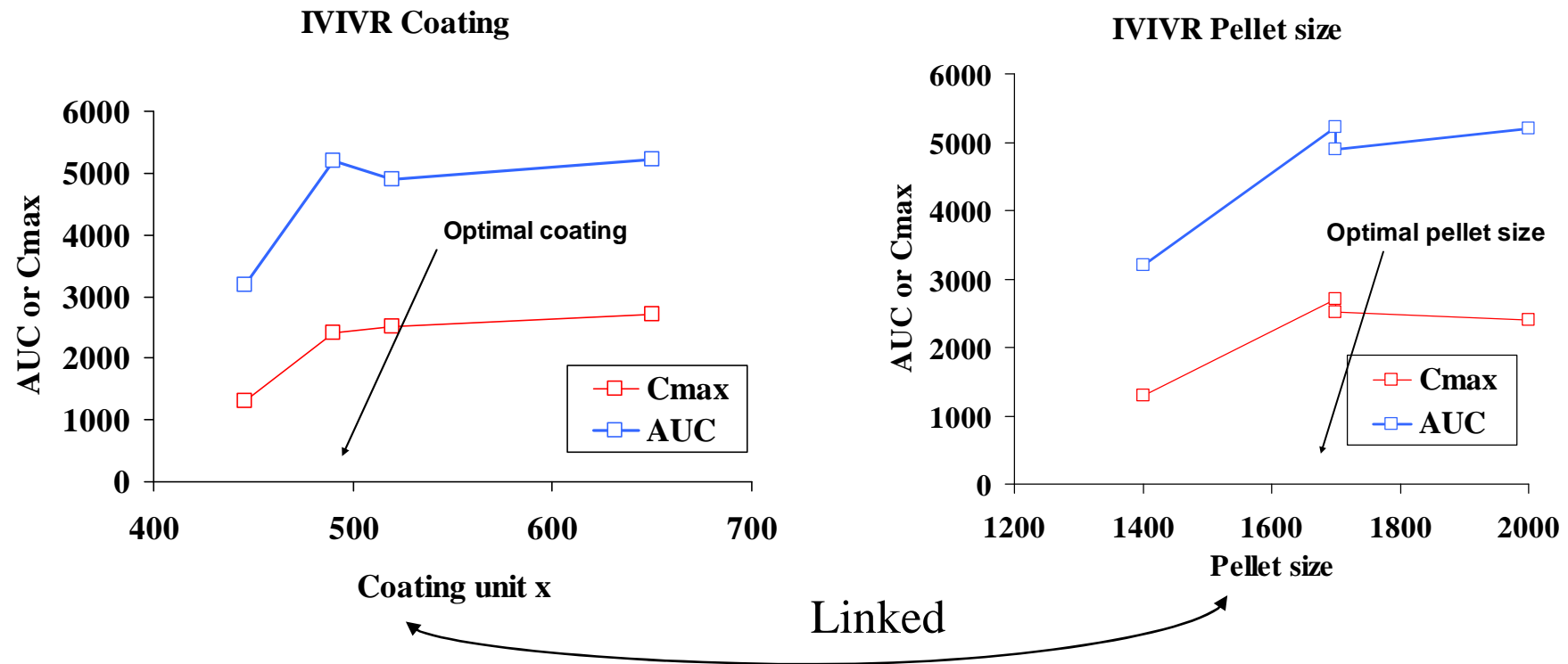
PK Parameters



Formulation Parameters

In vitro dissolution seems to be linked with in vivo results,  
In vitro reflects many other parameters, it is a supra indicator

## Case study : drug A IVIVR or IVIVC



- IVIVR denotes that dissolution was able to show difference between formulations. It is also a way to find the relevant relationship between formulation parameters (pellet size, coating) and efficacy (AUC, Cmax)
- Dissolution is a supra indicator

## □ Gain of IVIVC

- More self understanding than pure Chemometry
- Improves know how about formulation and critical points
- Optimizes development
- De risk BE studies but may be complicated to obtain biowaiver that can be used for dossier

## ☐ Parameters

### Level

### In vitro

### In vivo

☐ A

☐ Dissolution curve

☐ Input (absorption) curves

☐ B

☐ Statistical moments  
(MDT)

☐ Statistical moments  
(MRT, MAT, etc)

☐ C

☐ Desagregation time,  
time to have 10, 50,  
90% dissolved  
dissolution rate  
dissolution efficiency

☐ C<sub>max</sub>/T<sub>max</sub>

K<sub>a</sub>

time to have 10, 50, 90%  
absorbed

AUC (total or cumulative)

## □ Plasma concentration time curve

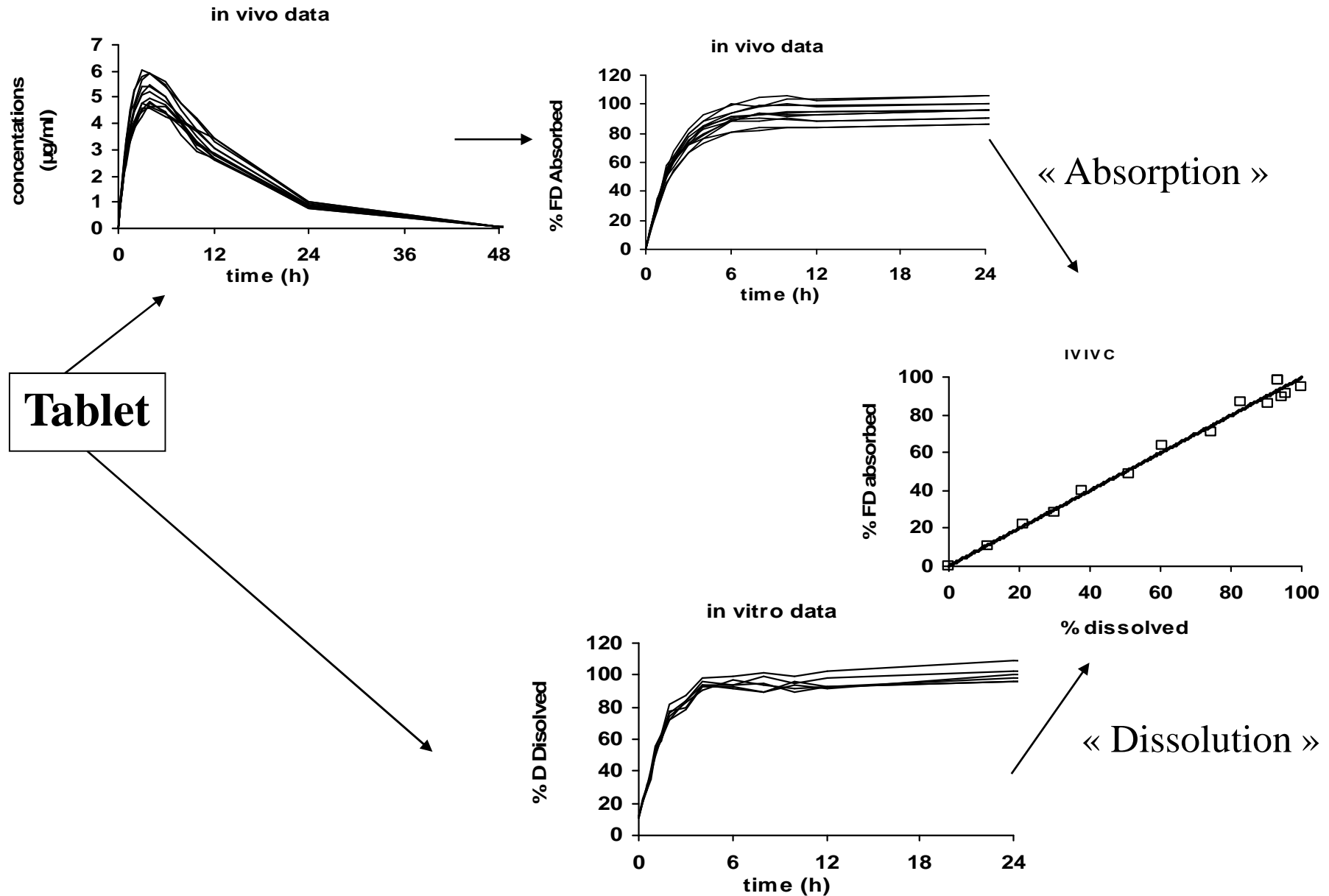
- What is used :
  - absorption curve % FD abs vs. time (Wagner-Nelson, deconvolution etc....)
  - model independent parameters derived from the curve
    - AUC,
    - C<sub>max</sub>
    - T<sub>max</sub> to estimate amount and rate (bioequivalence)
  - model and other parameters
    - Independent parameters

## □ Techniques

- « (3) estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution). »

FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

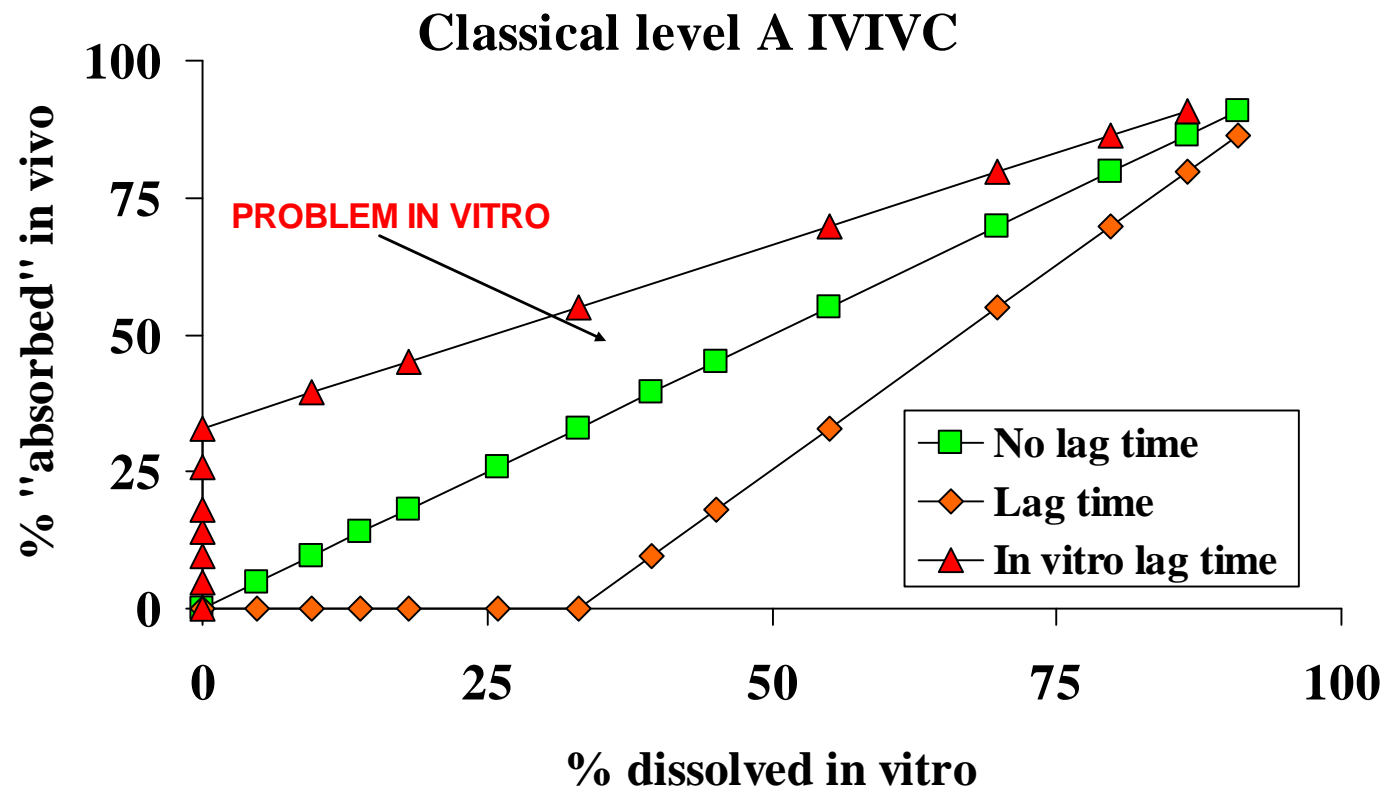
# Development of a correlation



## □ Development of a correlation

Plot % in vitro (x) vs % in vivo (Y) each point represents a similar time

Plot Classical approach same order in vivo and in vitro



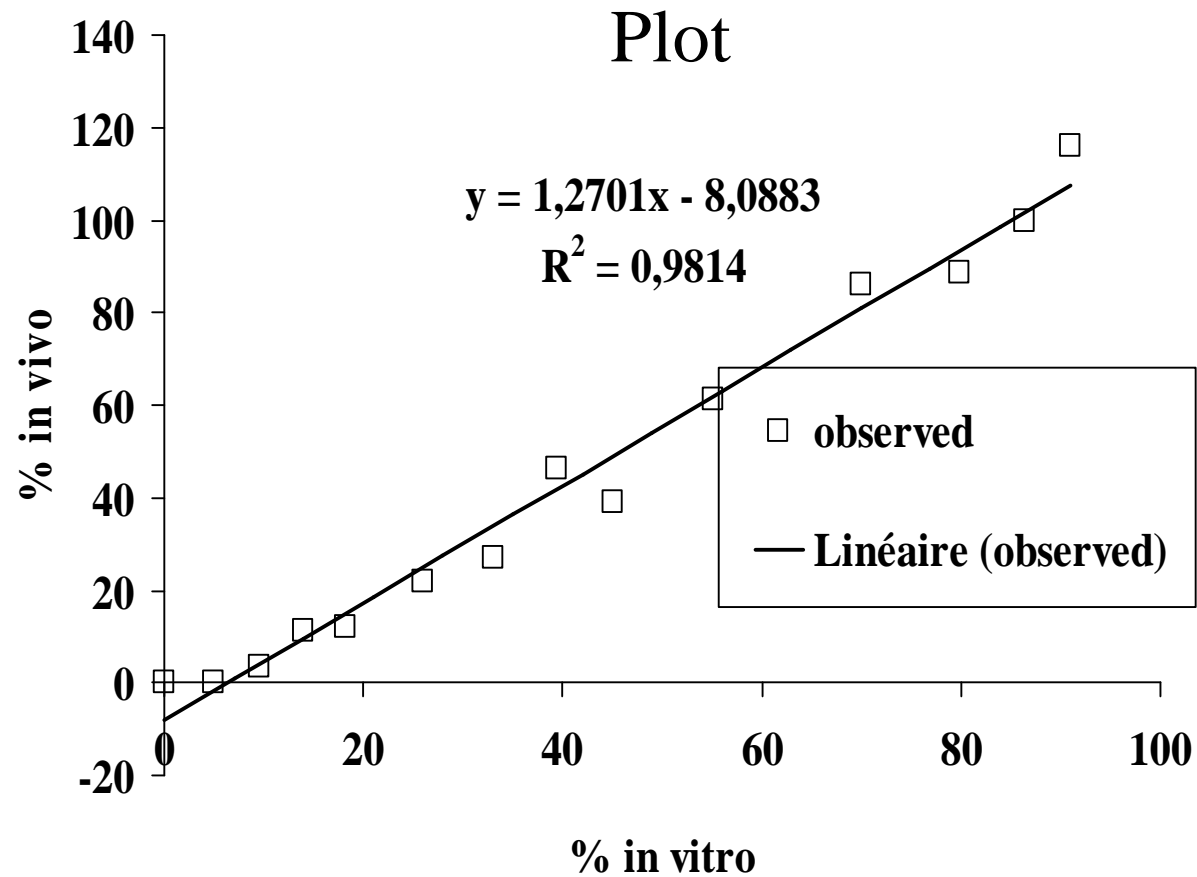
## □ Development of a correlation

Calculate the equation

For each relationship an equation could be calculated but

- Do not modify the original data: no transformation allowed in a first step  $\Rightarrow$  try to modify the dissolution
- Use a simple linear equation  $\text{vivo} = b * \text{vitro} + a$
- Calculate if possible std of each parameters

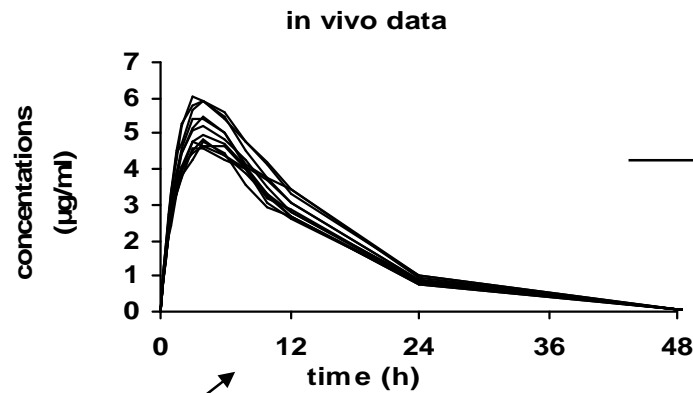
## □ Development of a correlation



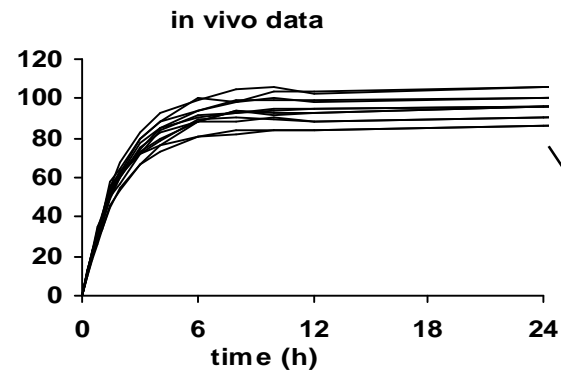
## □ Level A Predictability

- The predictability of correlation should be demonstrated including an estimation of the error
  - internal with initial data
  - external with new test data (validation process)
  - => three to four formulations are needed to initiate and validate the correlation
- Exception if in vitro release is independent of the conditions (apparatus, pH, etc...) : one formulation may be enough (ex : some type of OROS tablets)

# Level A IVIVC

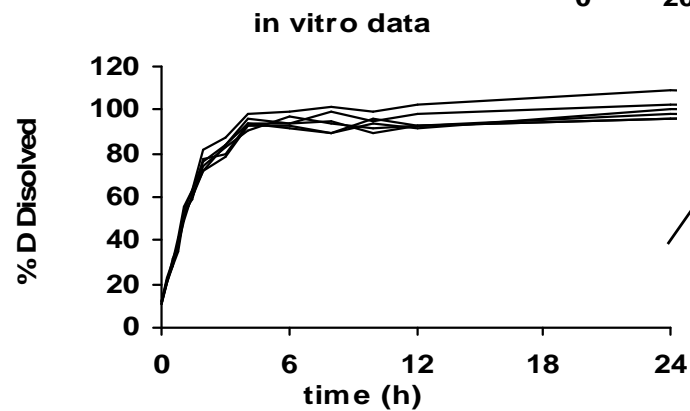
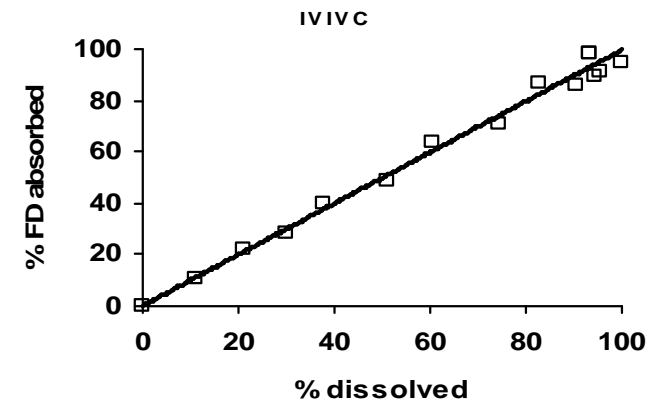


% FD Absorbed



« Absorption »

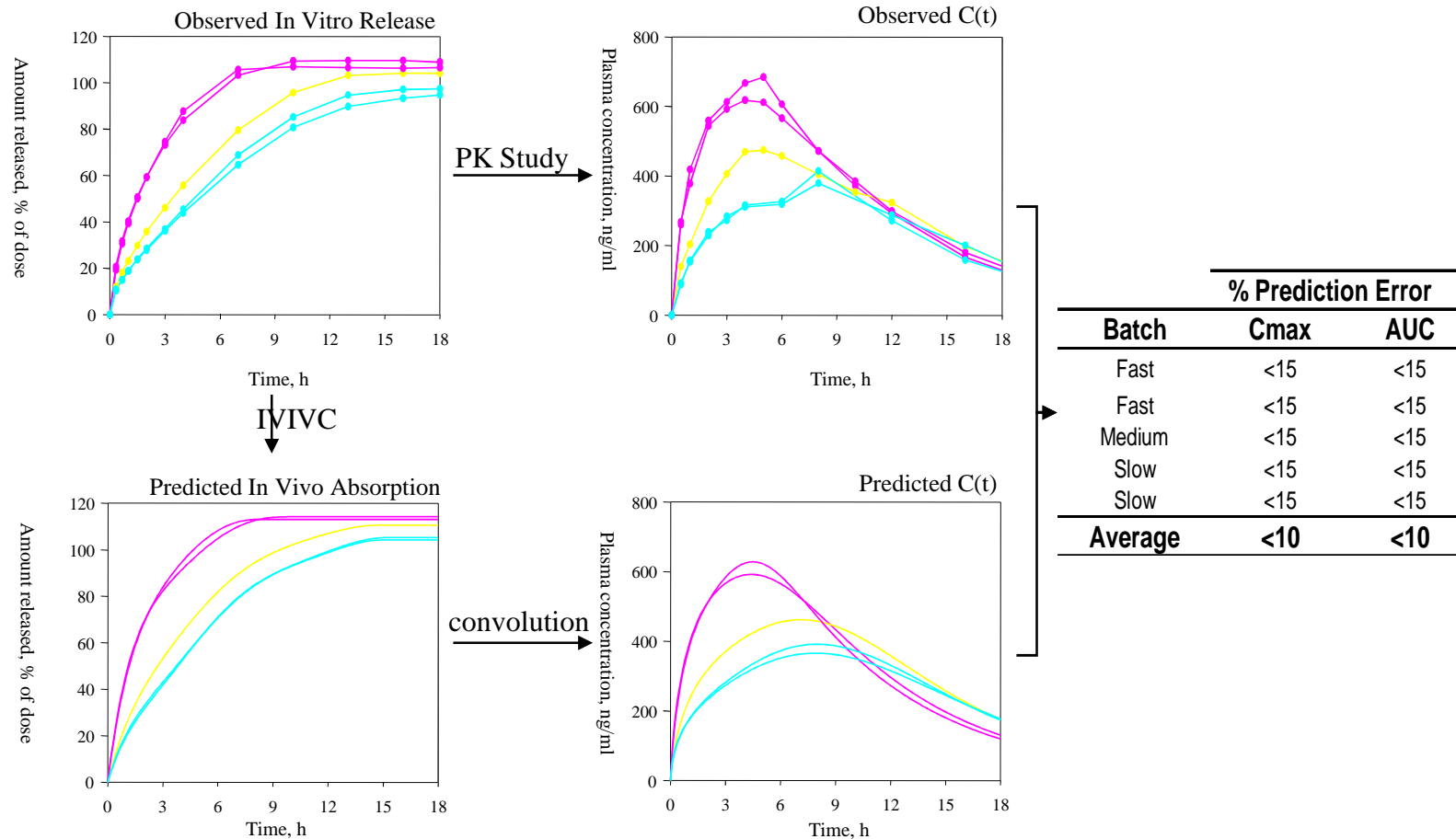
Tablet



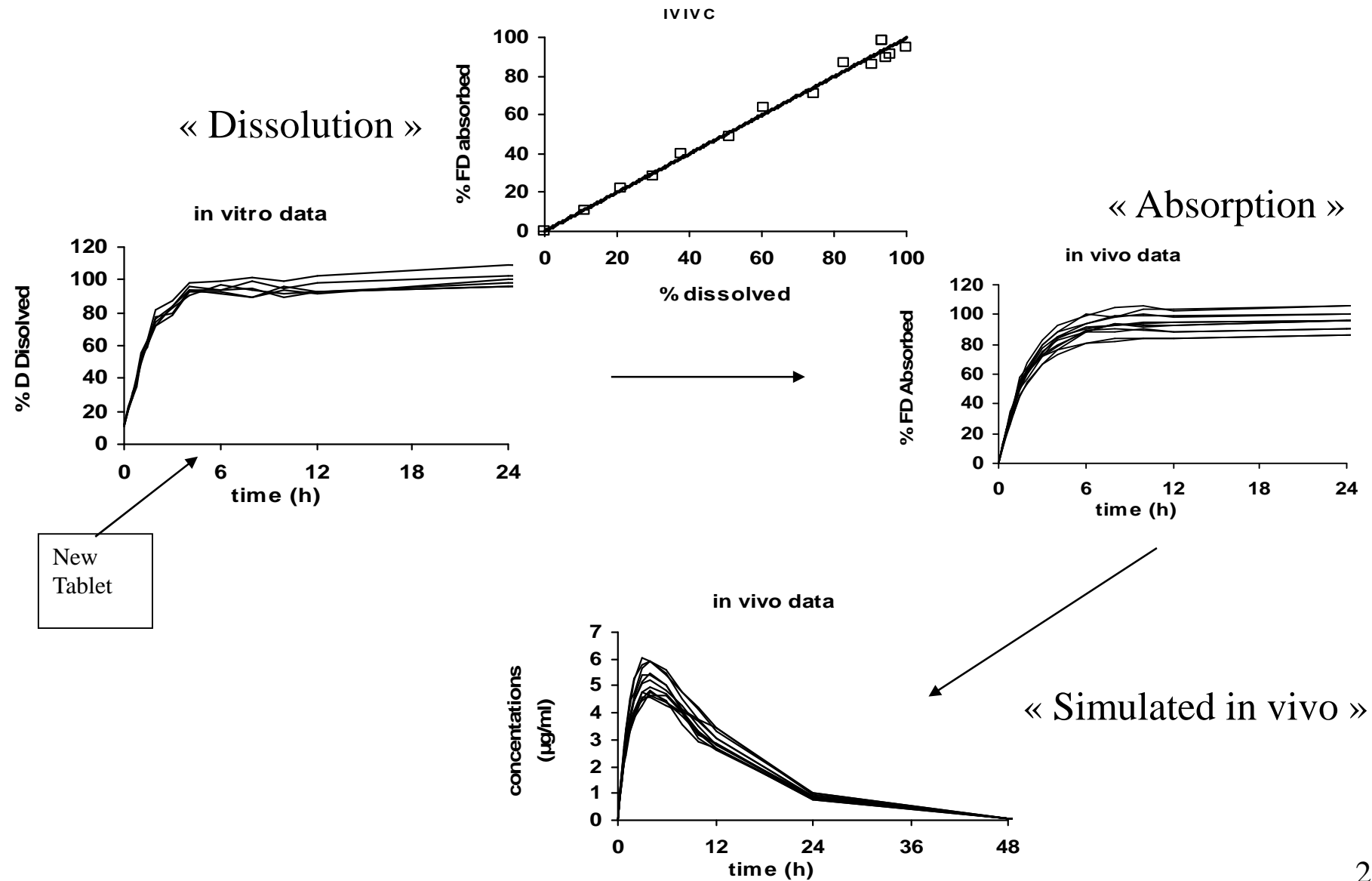
« Dissolution »

# □ Level A Predictability

From T. Schepard



# IVIVC prediction



## IVIVC or IVIVR?

### IR or some MR formulations (like EC)

- More a IVIVR : an in vitro in vivo relationship between in vitro dissolution and PK parameters which underlines a formulation/API and PK parameters relationship
- Coating thickness and T<sub>max</sub> or T<sub>lag</sub>,
- Quantity of binder and C<sub>max</sub> etc...
- Disintegrant and T<sub>max</sub>

➤ IVIVR can't be used as a biowaiver

# EXAMPLE OF IVIVC

## □ In Vitro In Vivo Correlation (IVIVC) for Diclofenac Slow Release Oral Formulations

- Slow release tablets and capsules containing 100 mg of diclofenac:
- Commercially available formulations (brazilian market):
  - M1    M2        and        M3
- Not commercially available formulations:
  - F1    F2        and        F3.

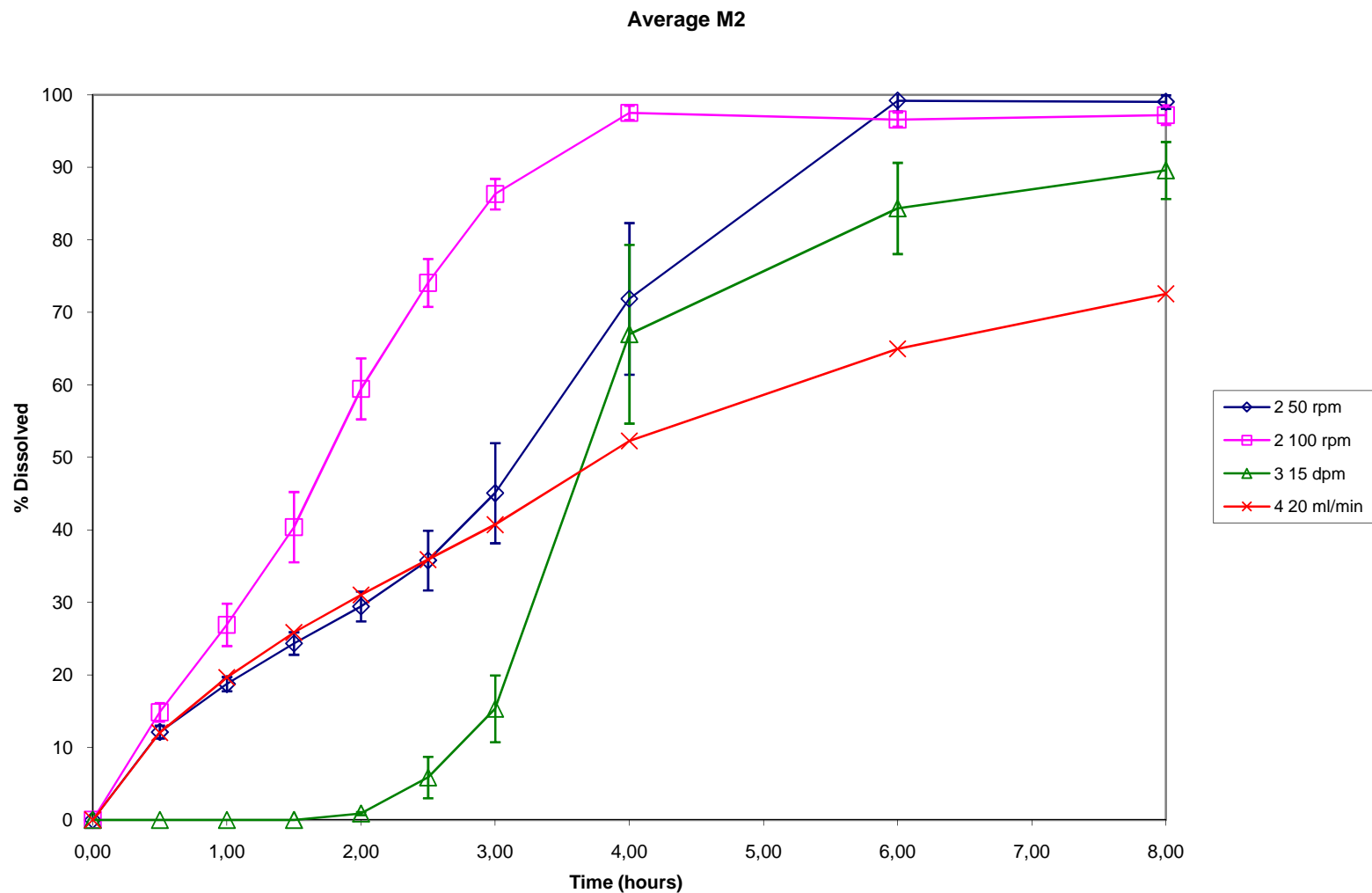
From : Pr. Valentina Porta – College of Pharmaceutical Sciences - University of São Paulo & ERT Cidam - University Auvergne – Clermont-Ferrand – January 2008

## ❑ In Vitro In Vivo Correlation (IVIVC) for Diclofenac Slow Release Oral Formulations

- USP Apparatus II: Paddle Apparatus
  - 50 rpm          1000 ml          pH 6.8
  - 100 rpm          1000 ml          pH 6.8
- USP Apparatus III: Reciprocating Cylinder (Bio-Dis)
  - pH 1.2 0- 1h pH 5.4 1h-3h          pH 6.8 3h-8h
- USP Apparatus IV: Flow – Through Cell
  - 20 ml/min close system          1000 ml pH 6.8

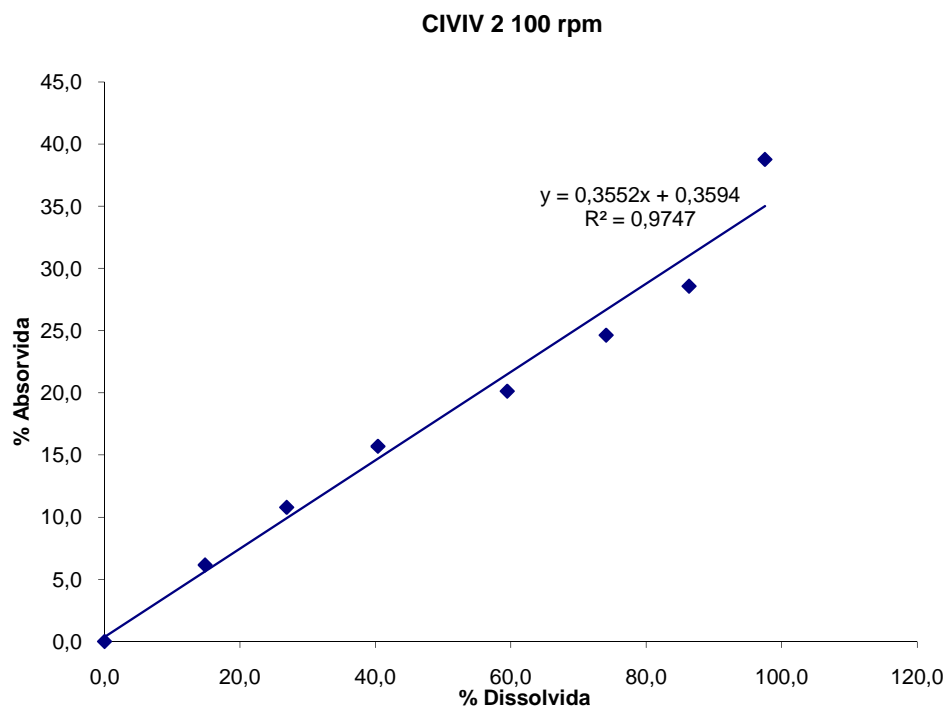
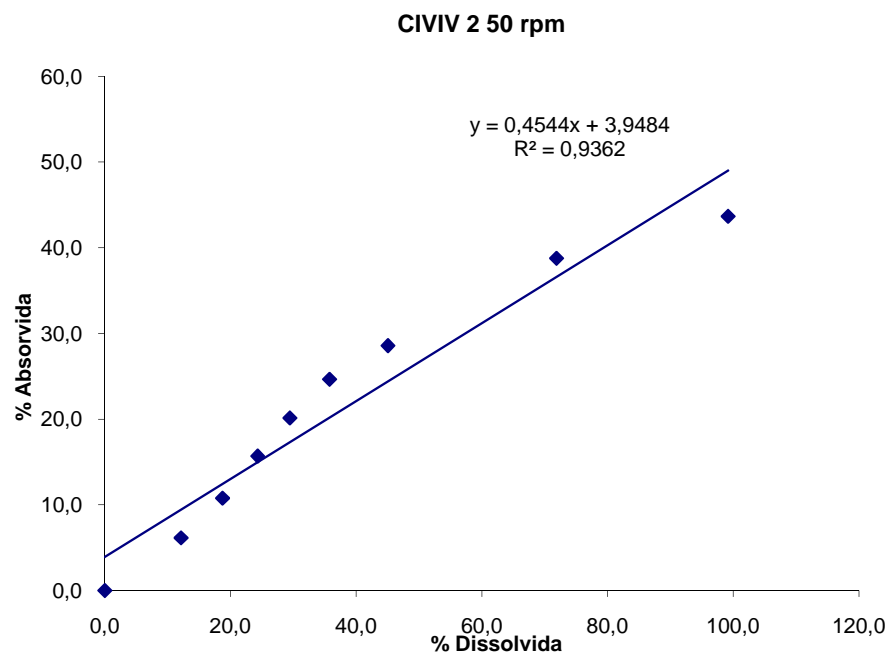
From : Pr. Valentina Porta – College of Pharmaceutical Sciences - University of São Paulo & ERT Cidam - University Auvergne – Clermont-Ferrand – January 2008

## Form M2



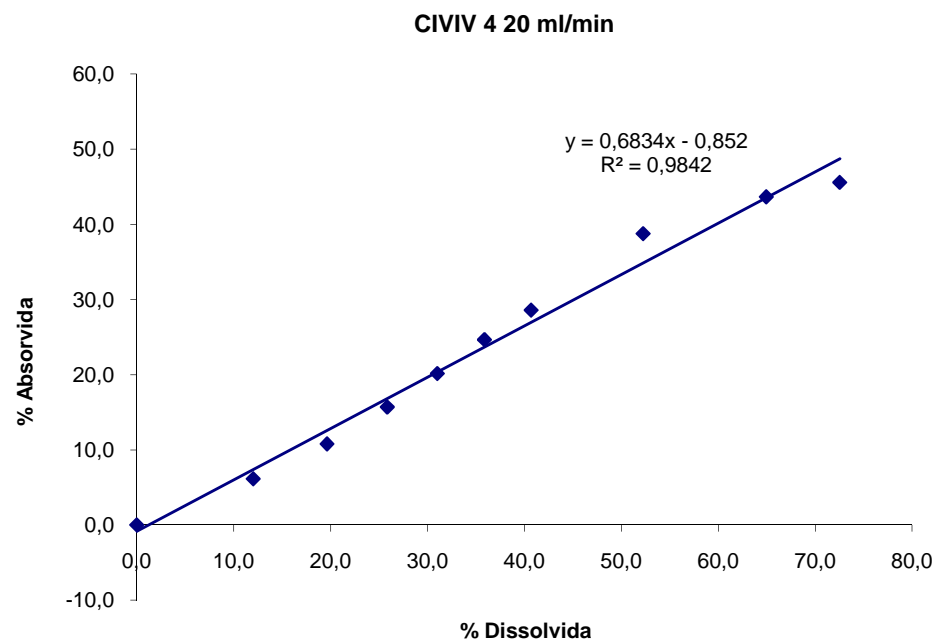
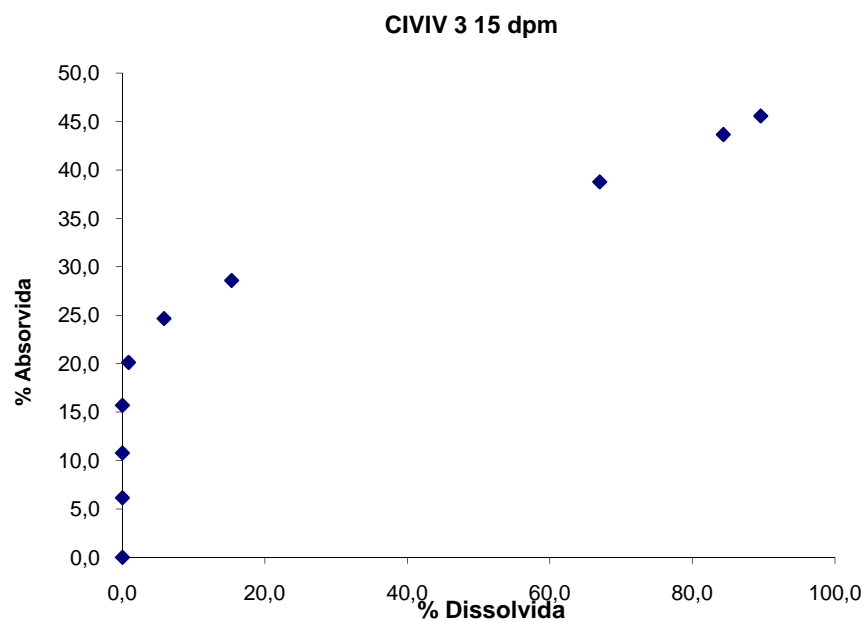
From : Pr. Valentina Porta – College of Pharmaceutical Sciences - University of São Paulo & ERT Cidam - University Auvergne – Clermont-Ferrand – January 2008

## Form M2 IVIC



From : Pr. Valentina Porta – College of Pharmaceutical Sciences - University of São Paulo & ERT Cidam - University Auvergne – Clermont-Ferrand – January 2008

## Form M2 IVIC



From : Pr. Valentina Porta – College of Pharmaceutical Sciences - University of São Paulo & ERT Cidam - University Auvergne – Clermont-Ferrand – January 2008

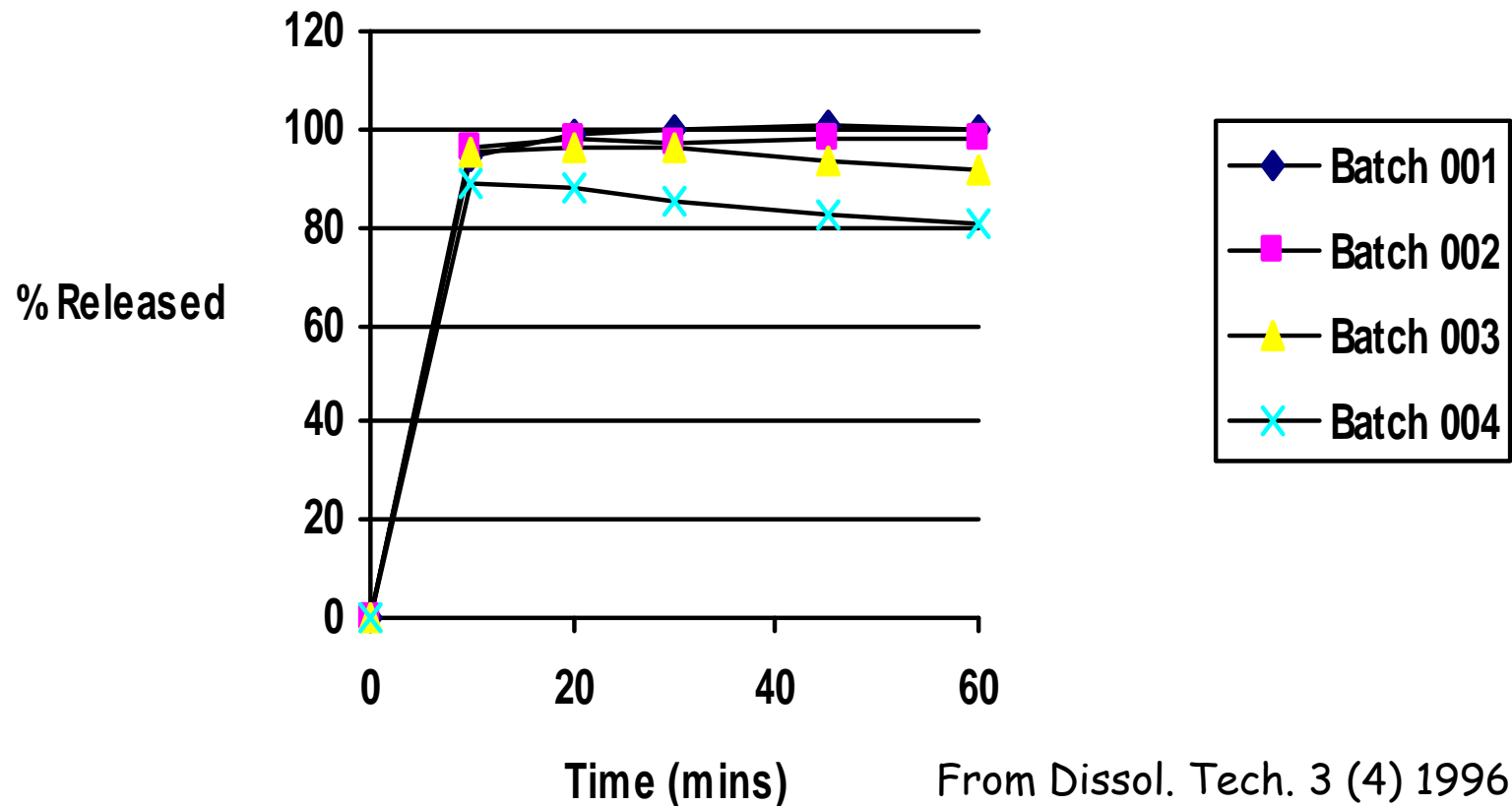
# EXAMPLE OF IVIVR

## □ Example of an IVIVR :

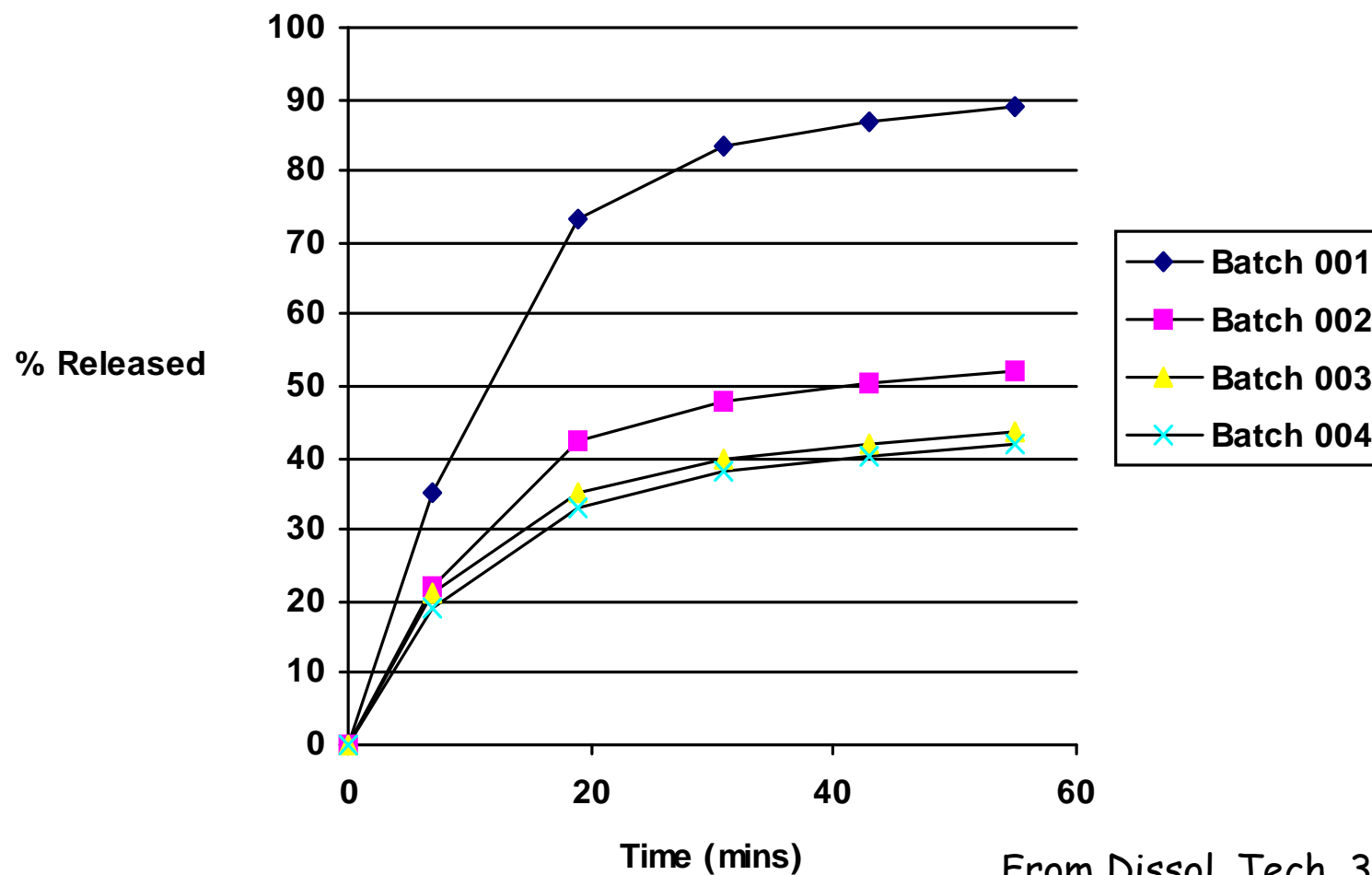
- Troglitazone
  - BCS class II, weak acid.
  - Amorphous solid dispersion formulation used to increase bioavailability
  - Dose 200mg (Tablet)
  - Solubility 2 $\mu$ g/mL in water, 68 $\mu$ g/mL in FaSSIF, 300 $\mu$ g/mL in FeSSIF

# Dissolution results - Troglitazone early clinical batches - USPII (paddle) method

Tablet Batch Number	Relative Bioavailability
001	98
002	87
003	73
004	58

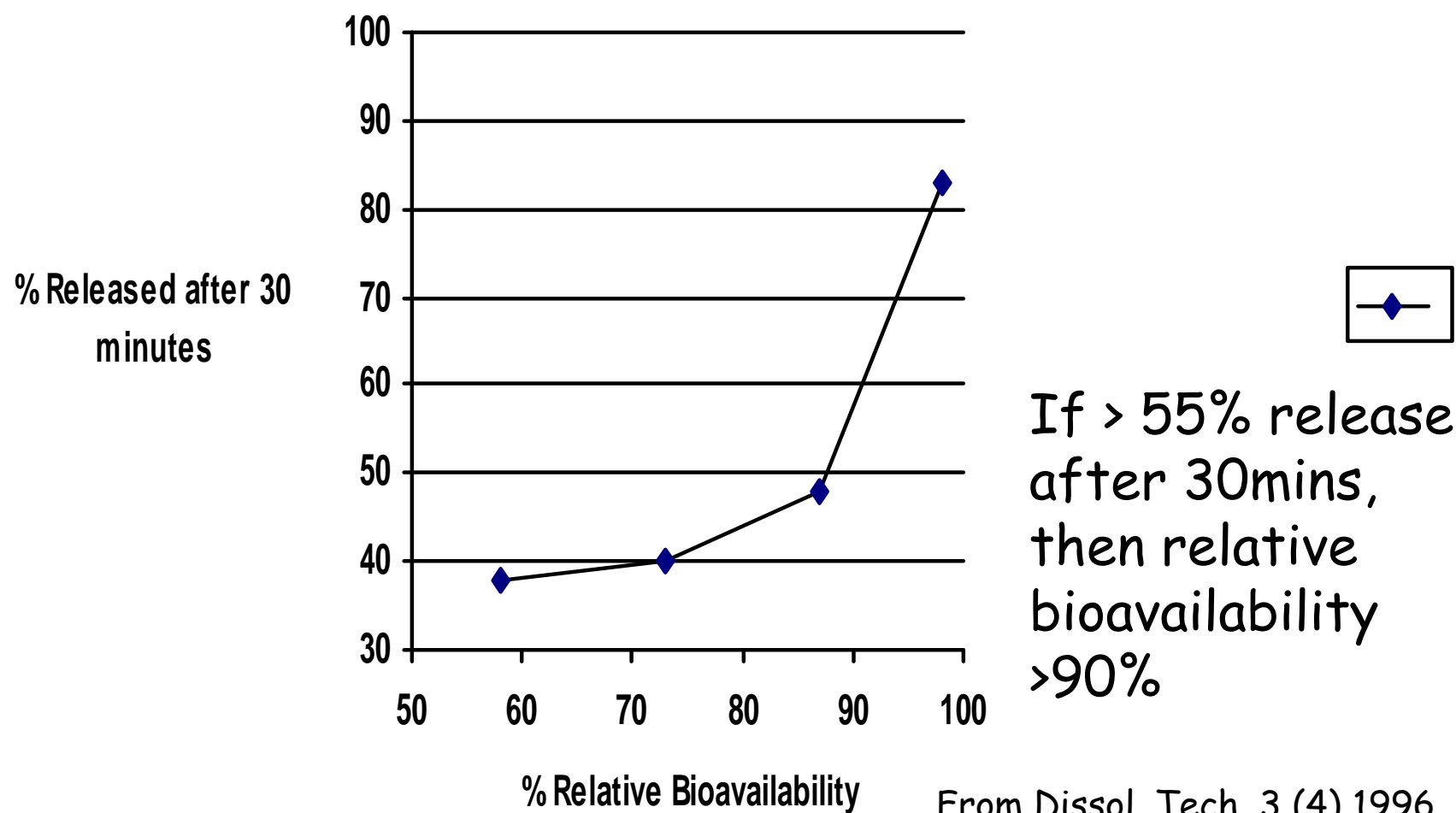


# Dissolution of early clinical batches using USP IV



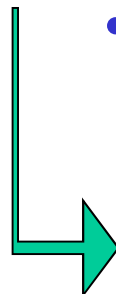
From Dissol. Tech. 3 (4) 1996

# Correlation between %released after 30mins in the USP4 test and relative bioavailability in man



# APPLICATION OF USP4 FOR GENERIC DEVELOPMENT

## ❑ Developing a discriminatory method

- 
- Distinguish the good from the bad products with intentional change
  - Ensure good knowledge of batches (formulation, processing, API characteristics, Excipients...etc)
  - Use characterisation technique in combination
  - Know what you are measuring
  - Link dissolution results with other characterisation data
  - Know your method variability and batch to batch variability

## ❑ Case Study : development of a generic tablet of antidepressant drug

Drug soluble in water and buffer

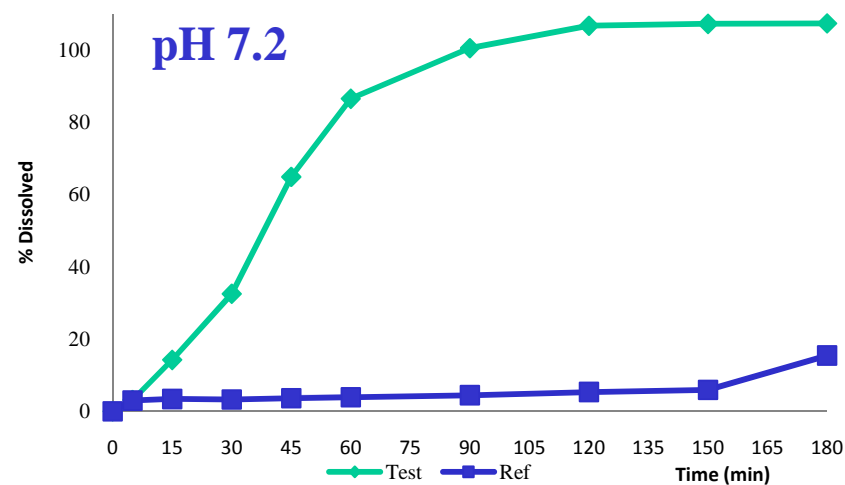
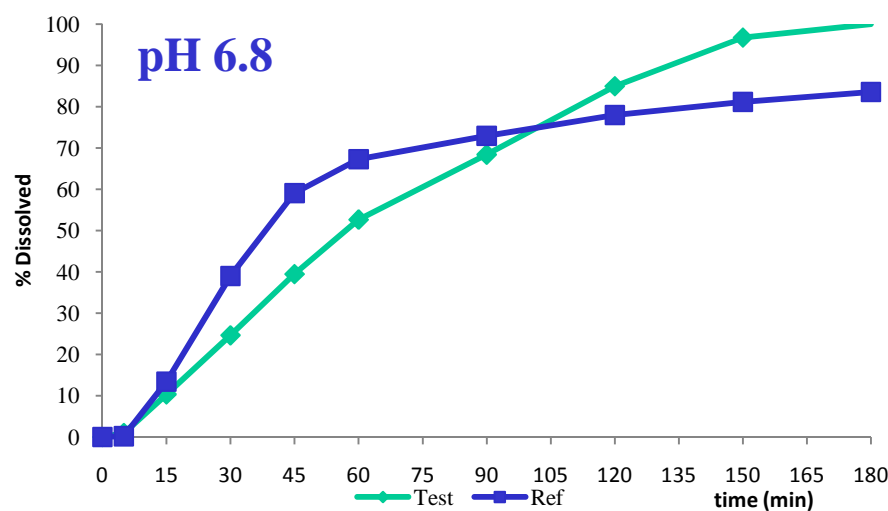
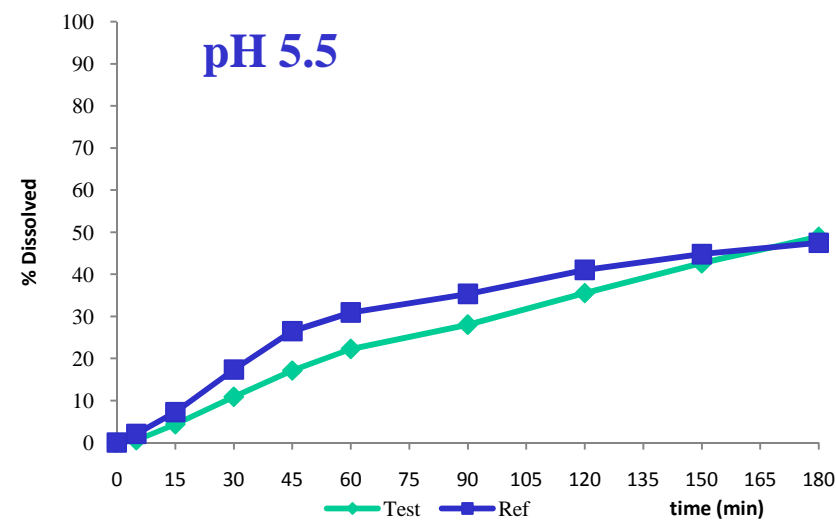
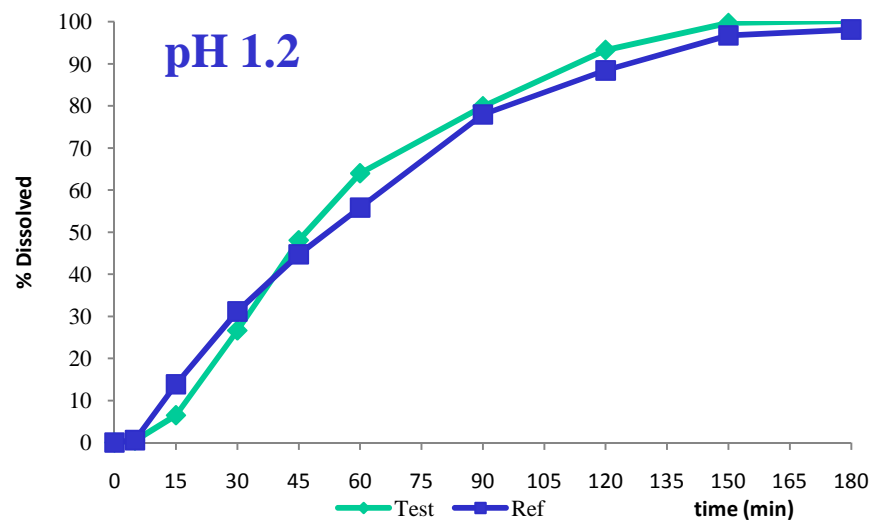
Drug totally absorbed after oral administration with no first pass effect

Partition coefficient in favor of a lipophilic compound

No specific absorption mechanism

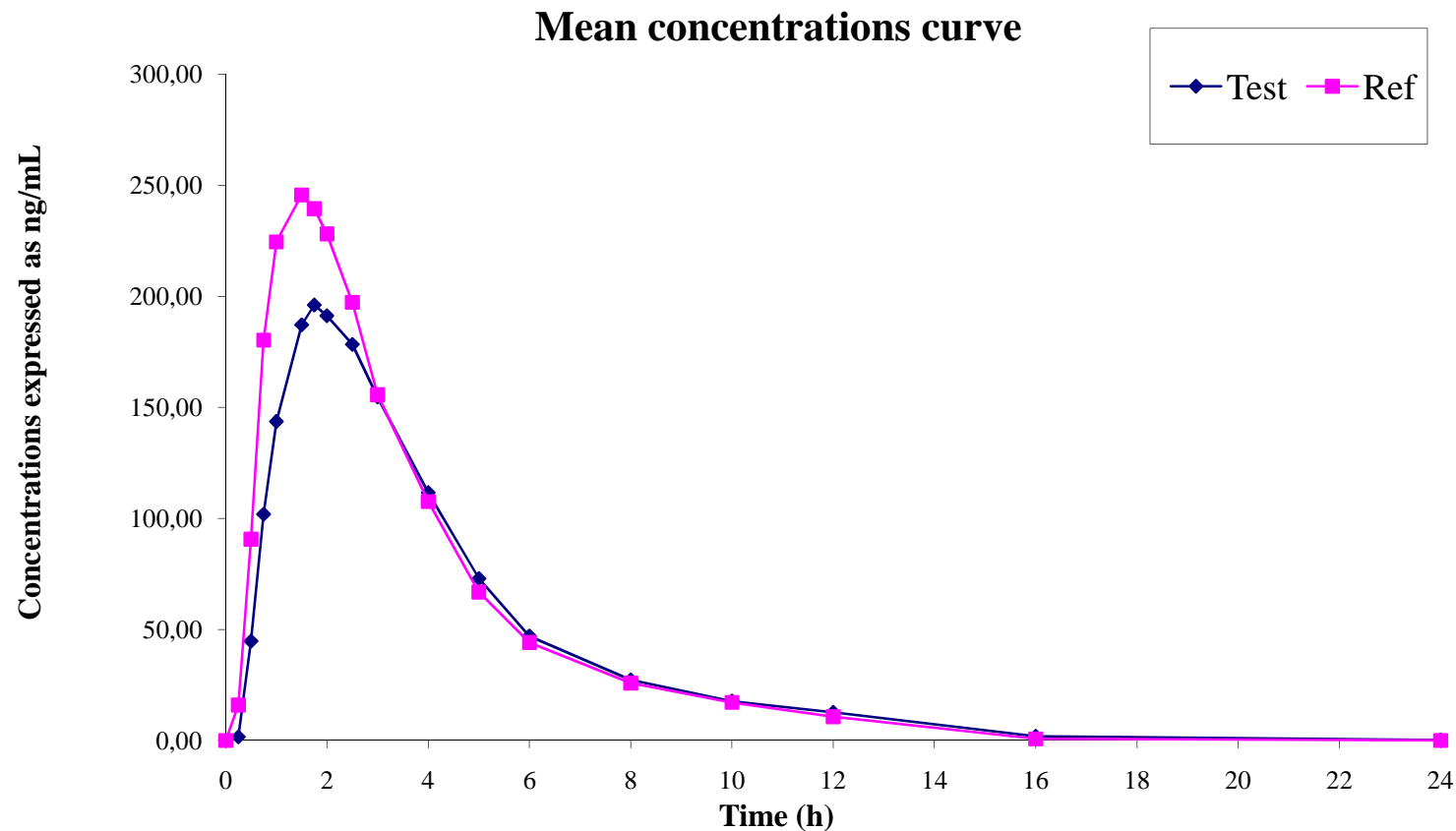
Comparison of the Test formulation developed and the Reference *in vitro* and *in vivo*

## Case Study : development of a generic tablet of antidepressant drug



# ❑ Case Study : development of a generic tablet of antidepressant drug

In vivo experiment → no Bioequivalence



## ❑ Case Study : development of a generic tablet of antidepressant drug

Development of a discriminatory dissolution method with increased pH as dissolution medium and the USP4 as apparatus.

pH 1.2 from T0 to T15 min

pH 5.5 from T15 min to T30 min

pH 6.8 from T30 min to T180 min

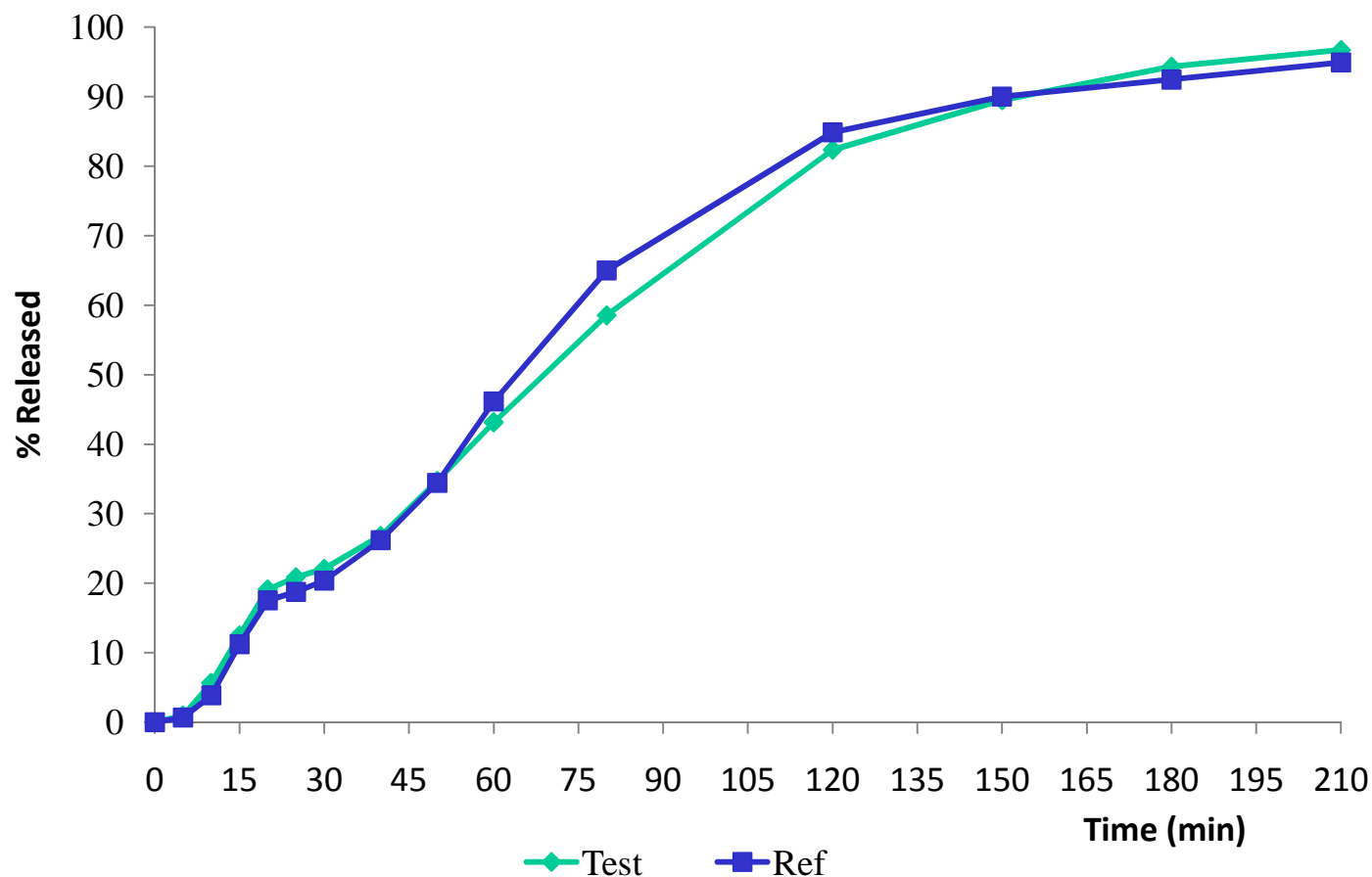
pH 7.5 from T180min to T210 min

Use of the dissolution method to develop the generic and select the formulation with the same in vitro release as the reference

Use of the method as a tool for development, IVIVC and quality control

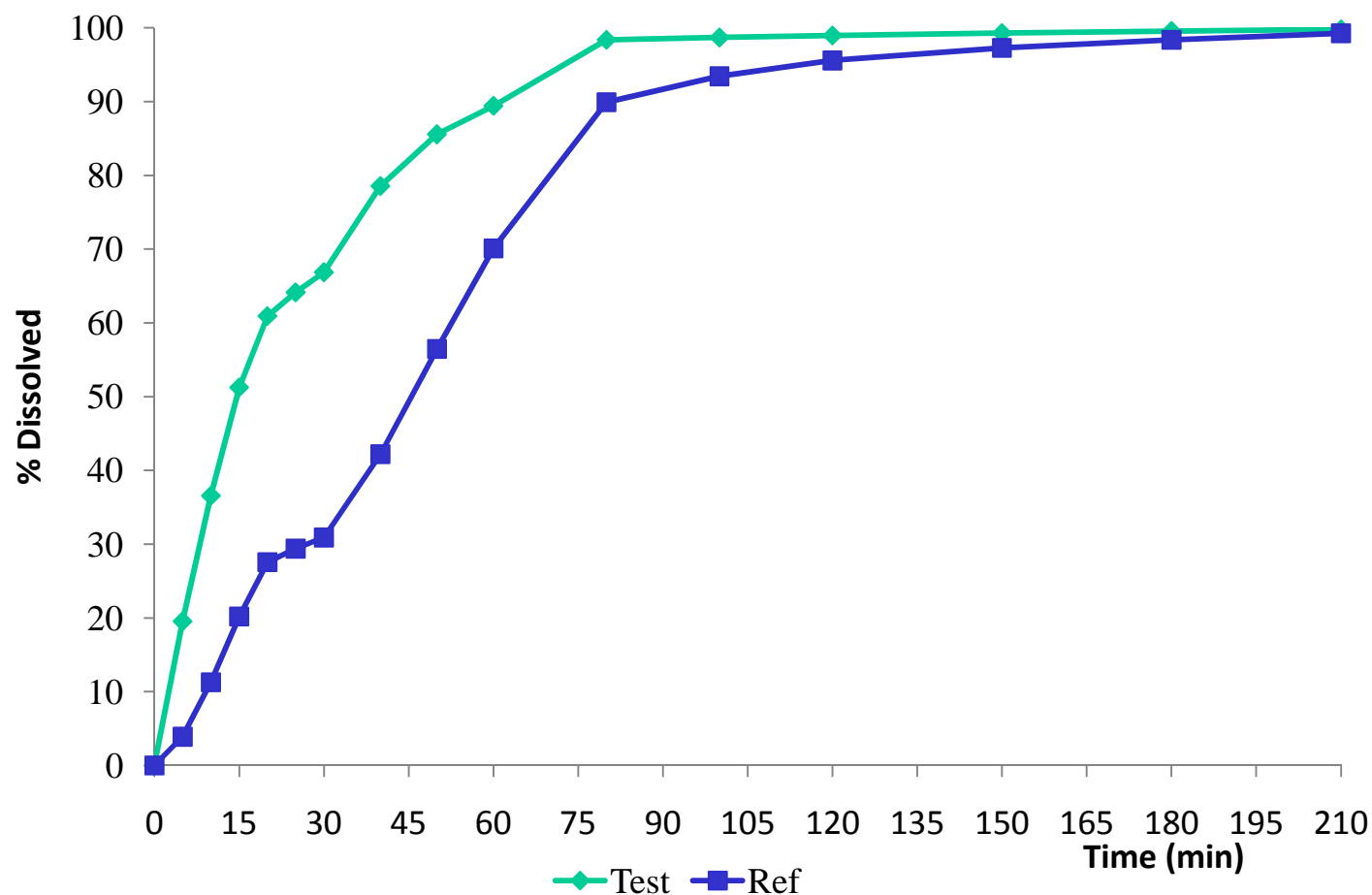
## ❑ Case Study : development of a generic tablet of antidepressant drug

Method : USP 4 – pH variation flow rate 4 ml/min

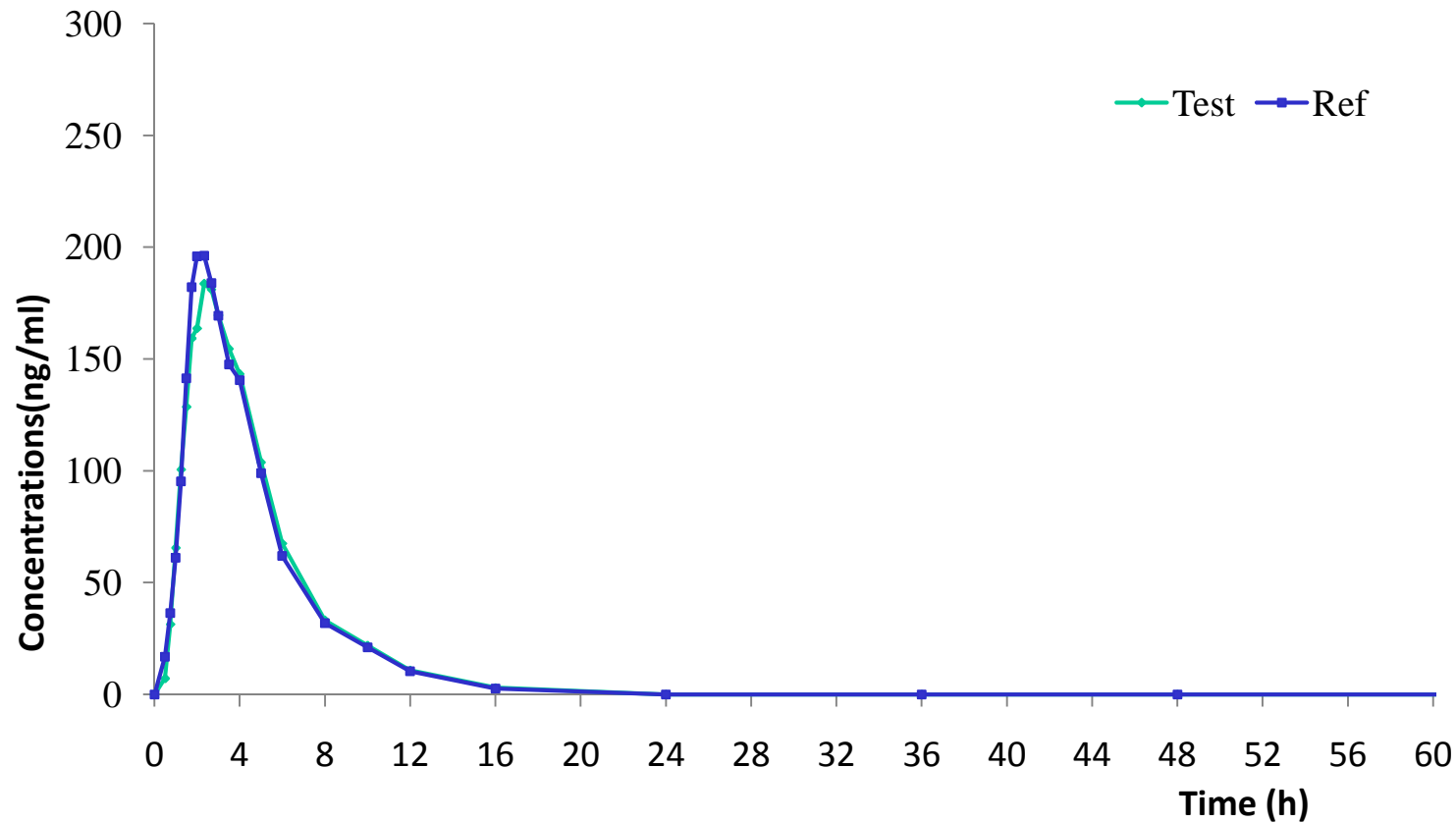


## ❑ Case Study : development of a generic tablet of antidepressant drug

Method : USP 4 – pH variation flow rate 20 ml/min



## ❑ Case Study : development of a generic tablet of antidepressant drug

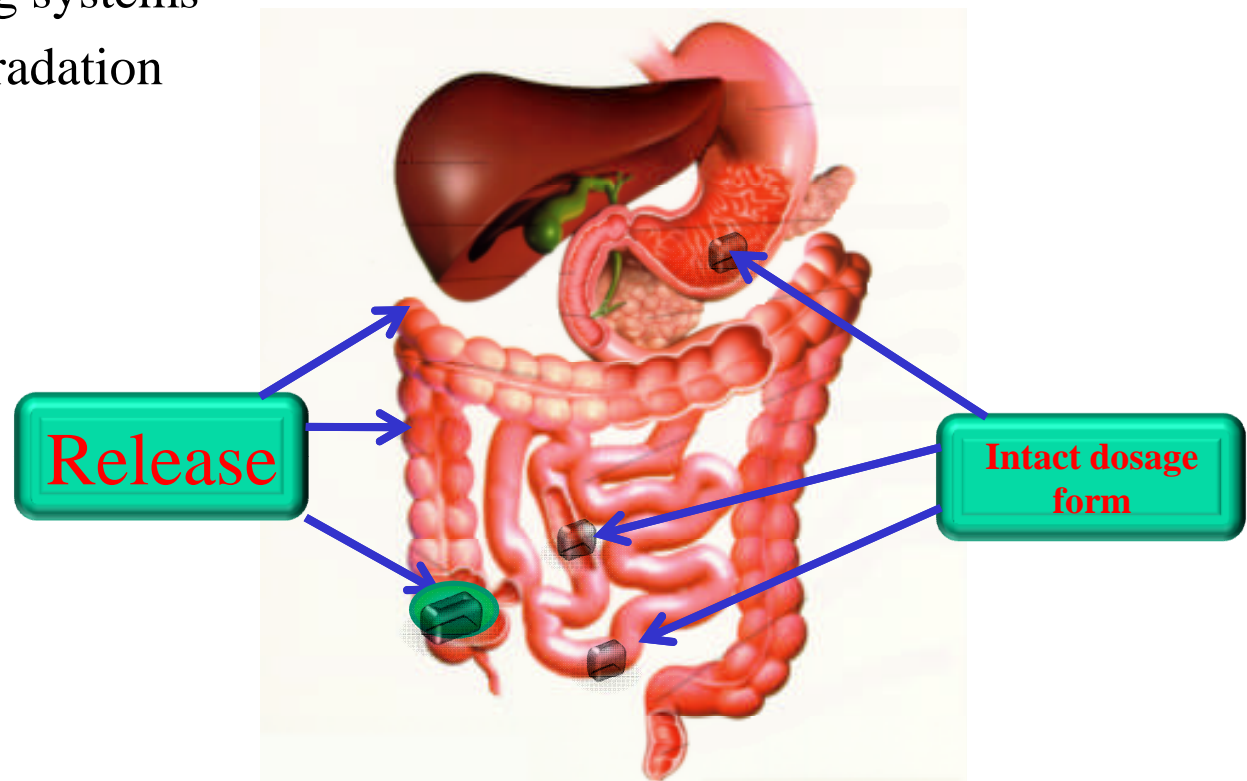


In vivo experiment → Bioequivalence

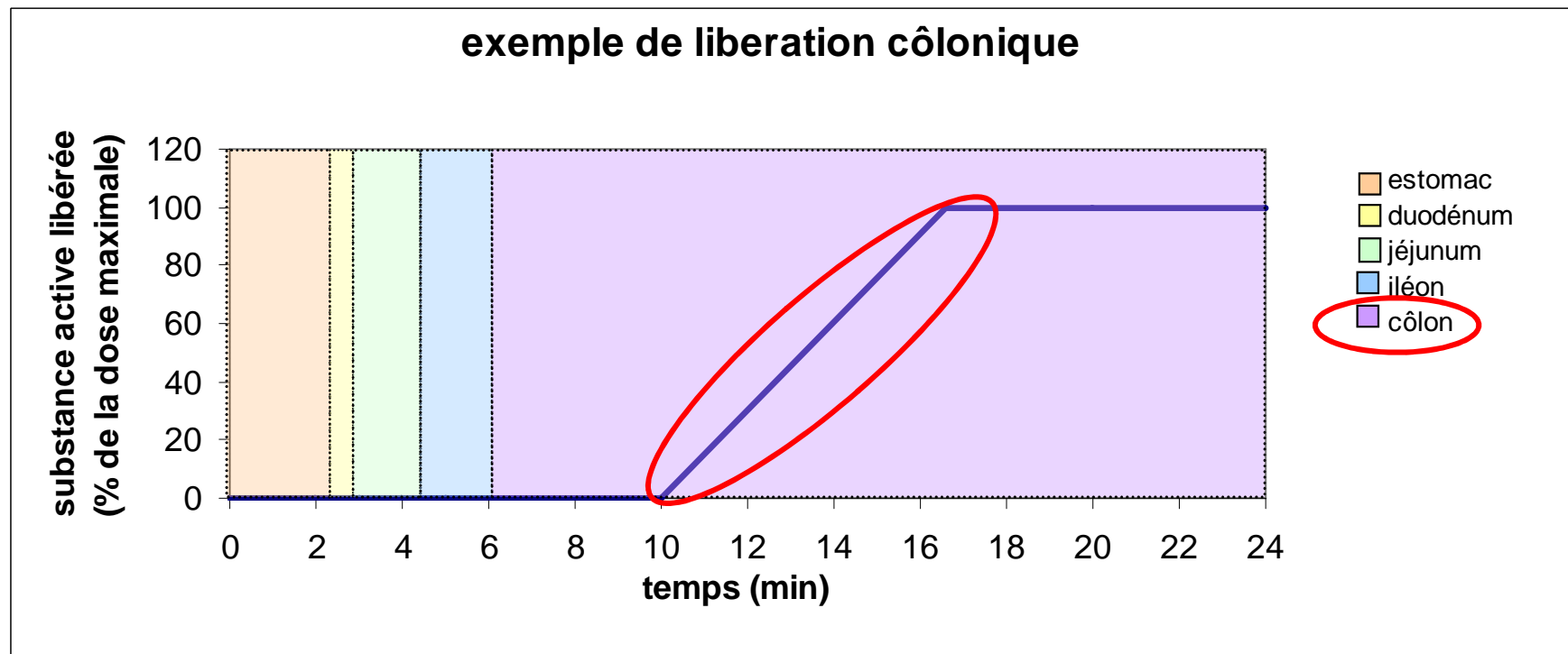
APPLICATION OF USP4  
FOR  
COLONIC DELIVERY DOSAGE  
FORMS

## ❑ Case of colonic delivery modified release dosage form

- Drug release when the drug enters the colon
- Specific Mechanism of release
  - Release function of pH
  - Multiple coating systems
  - Release by degradation



## ❑ Case of colonic delivery modified release dosage form

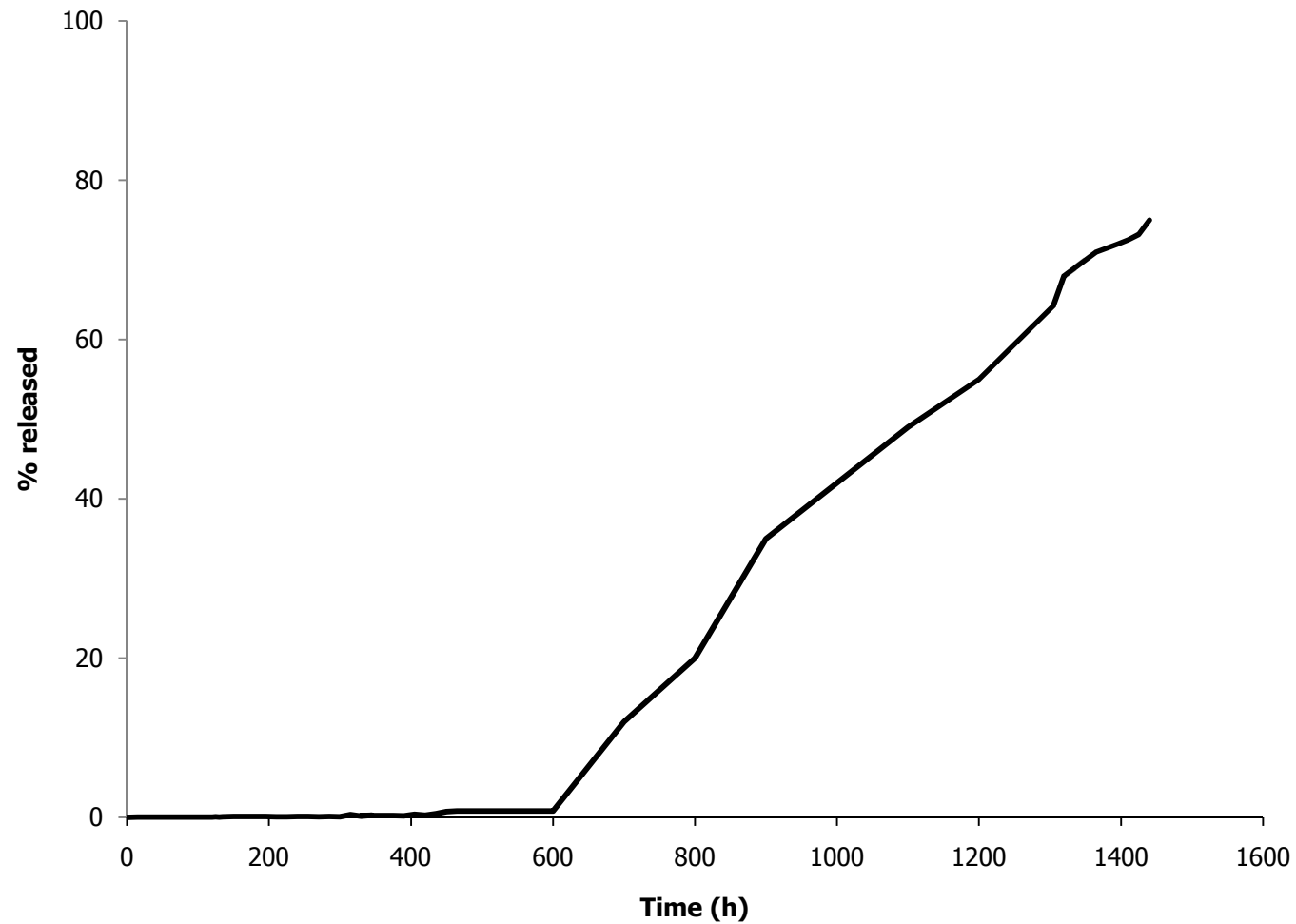


## ❑ Case of colonic delivery modified release dosage form

- USP4 with change pH
  - pH 1.2 simulation of stomach
    - » 30 to 120 min
  - pH 4.5 simulation of duodenum
    - » 15 to 60 min
  - pH 6.8 simulation of jejunum
    - » 60 to 120 min
  - pH 7.2 simulation of ileum
    - » 60 to 120 min
  - pH 5.8 simulation of colon
    - » Up to 300 min



## ❑ Case of colonic delivery modified release dosage form



APPLICATION OF USP4  
FOR  
MULTIPARTICULATE DOSAGE  
FORMS

## **❑ Dissolution of multiparticulate drug dosage forms : pellets in hard gelatin capsule**

The main difference between two formulations can be :

- The density of the pellets which is caused by the use of different core materials
- The thickness of the coated substance
- The sensibility to pH of the coated membrane

The in vitro dissolution test must be able to detect real differences between the formulations.

## **❑ Potential problems for multiparticulate drug dosage forms with the USP 1 and 2 apparatus**

- Slower release for heavy pellets compared to the lighter one
- Formation of a heap of the heavy pellets at the bottom of the USP vessel due to the stagnant zone under the center of the paddle
- Evaluation of pH sensitive release drug dosage forms and simulation of the continuous change of pH in gastrointestinal tract

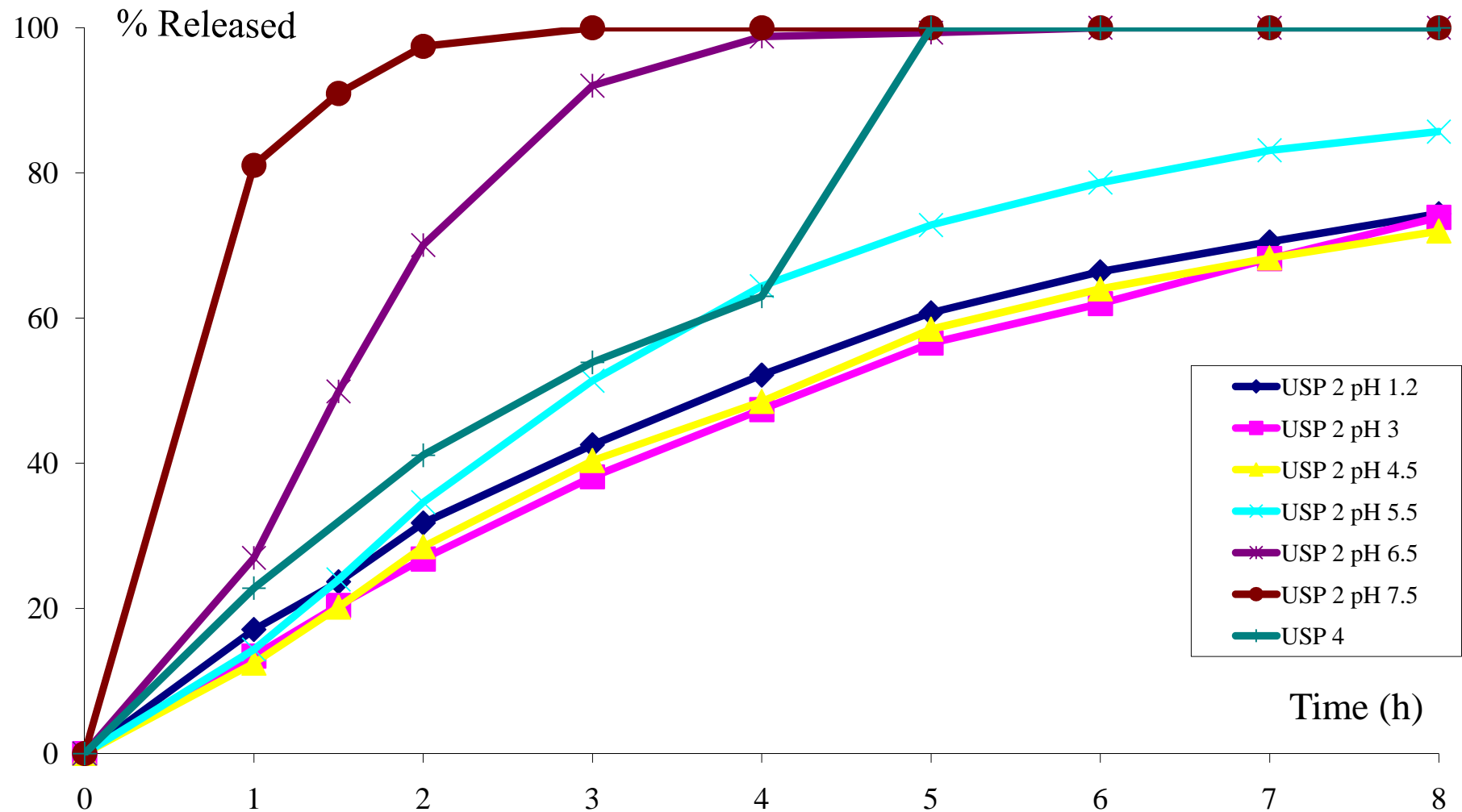
## ❑ Evaluation of a pH sensitive multiparticulate drug delivery system

- Drug : Theophylline
- Dosage form : coated micropellets release function of pH
- Dose : 300 mg

### Dissolution conditions

- USP 2 1000 ml 60 rpm  
pH 1.2, pH 3, pH 4.5, pH 54.5, pH 6.5, pH 7.5
- USP 4 cell Ø 22.6 mm  
increasing pH : 0-1h pH 1.2, 1h-4h pH 4.5, 4h-8h pH 7.2

## □ Evaluation of a pH sensitive multiparticulate drug delivery system



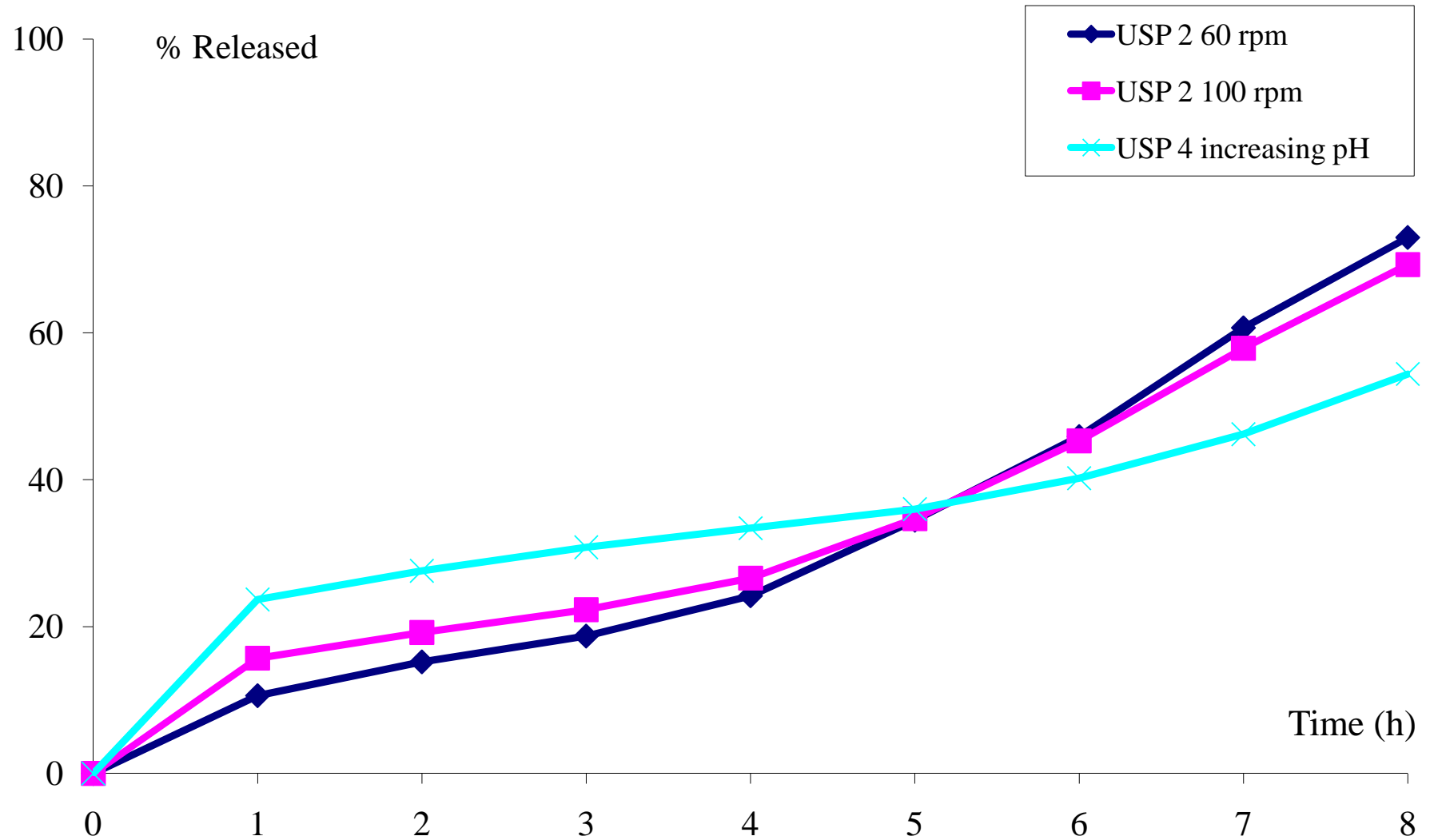
## ❑ Evaluation of a multiparticulate drug delivery system

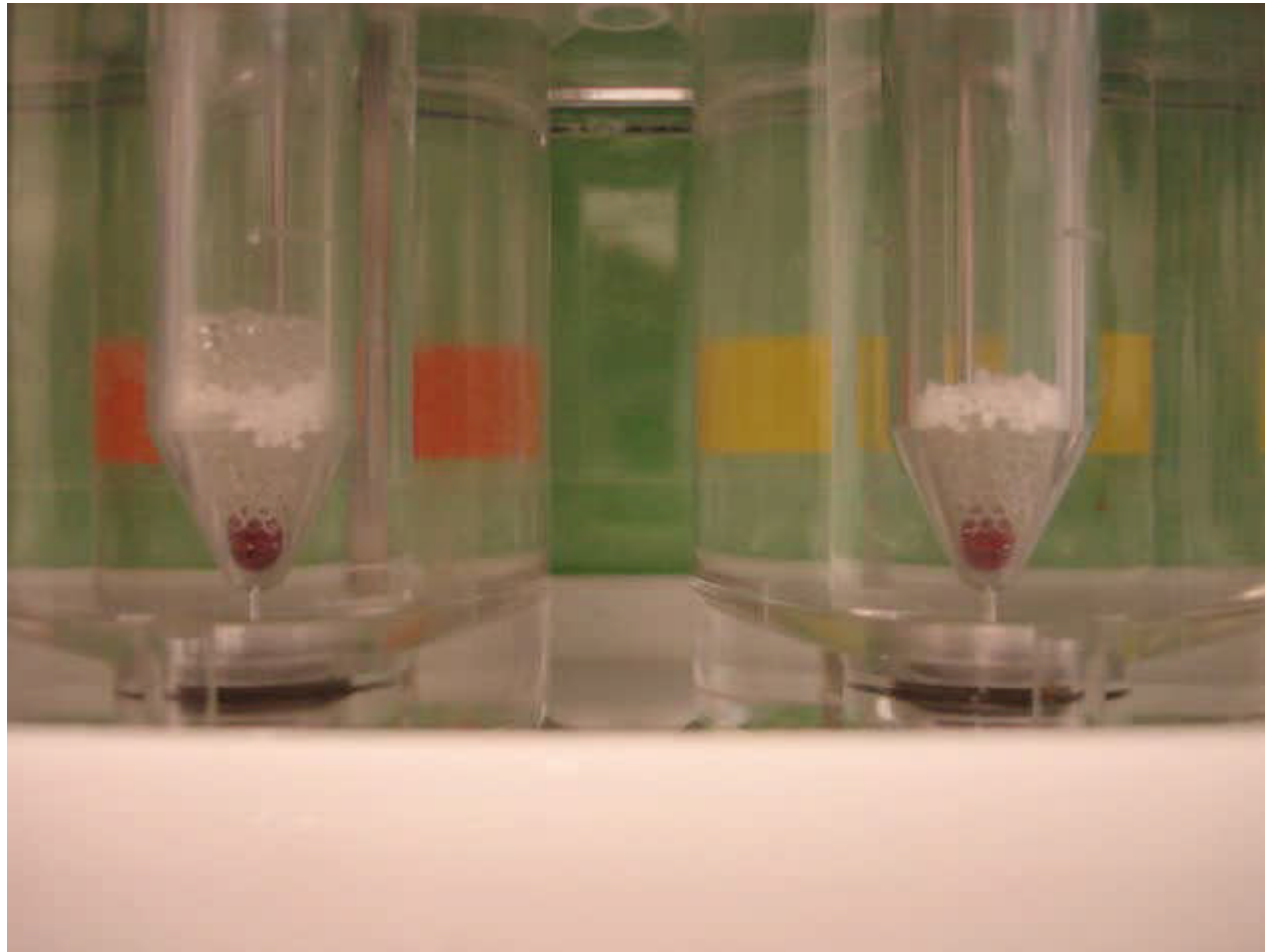
- Drug : Diltiazem
- Dosage form : coated micropellets sustained release
- Dose : 300 mg

### Dissolution conditions

- USP 2 60 rpm
- USP 2 120 rpm
- USP 4 cell Ø 22.6 mm  
increasing pH : 0-1h pH 1.2, 1h-3h pH 5.3, 3h-8h  
pH 7.2

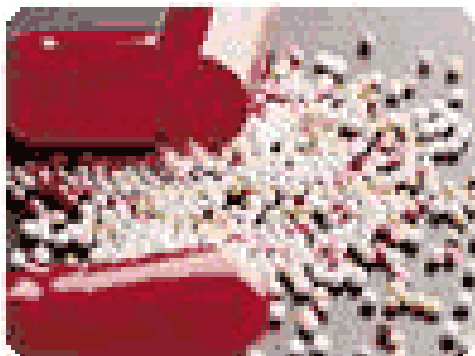
## □ Evaluation of a multiparticulate drug delivery system





## ❑ Development of a multiparticulate drug delivery system

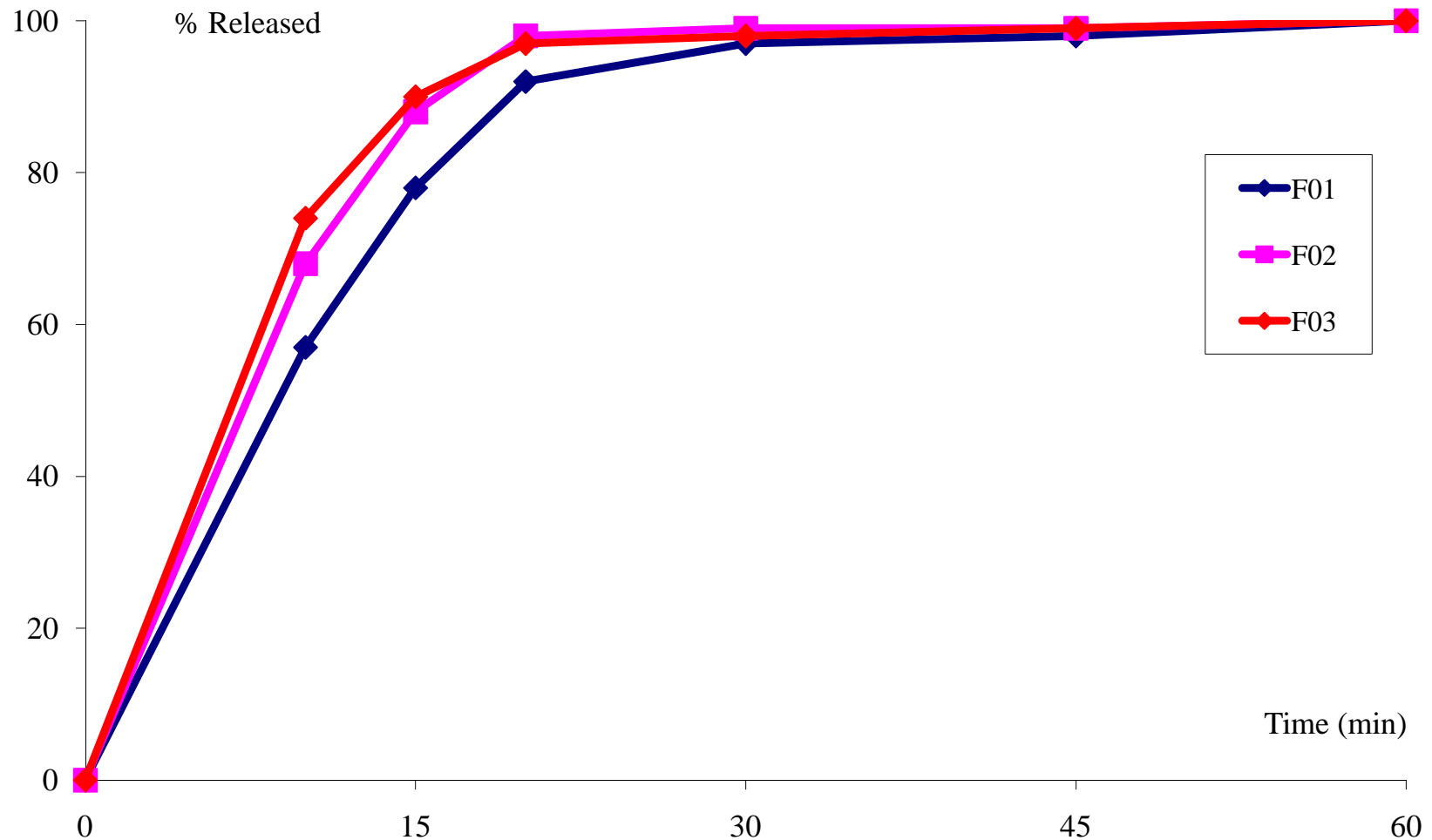
- pH sensitive release pellets in hard gelatin capsule
- Mixture of non coated and coated pellets
- Immediate release : complete release at pH 1.2 in 30 min
- Delayed release : sustained release at pH > 5.5



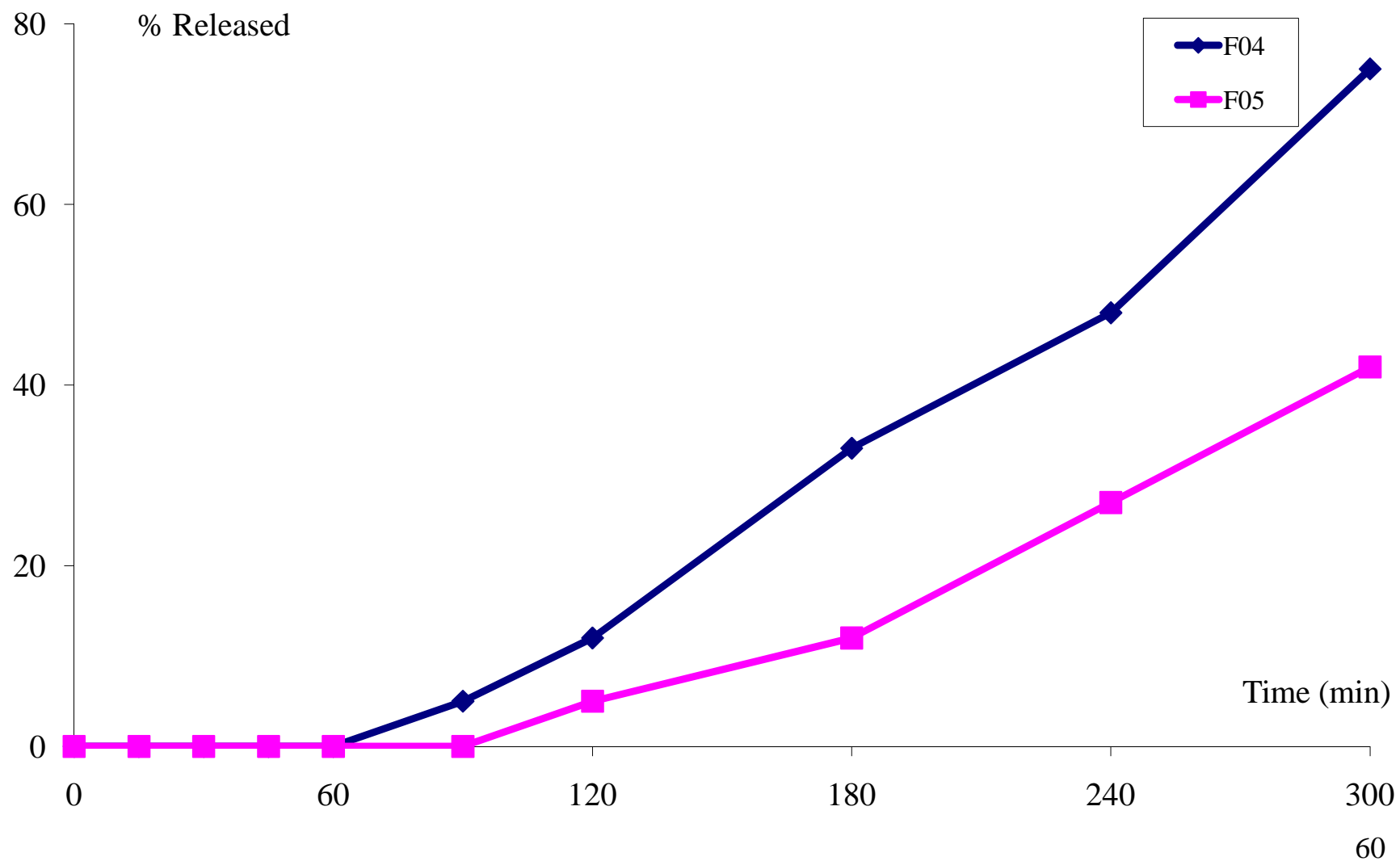
□ Non coated pellets

USP 2

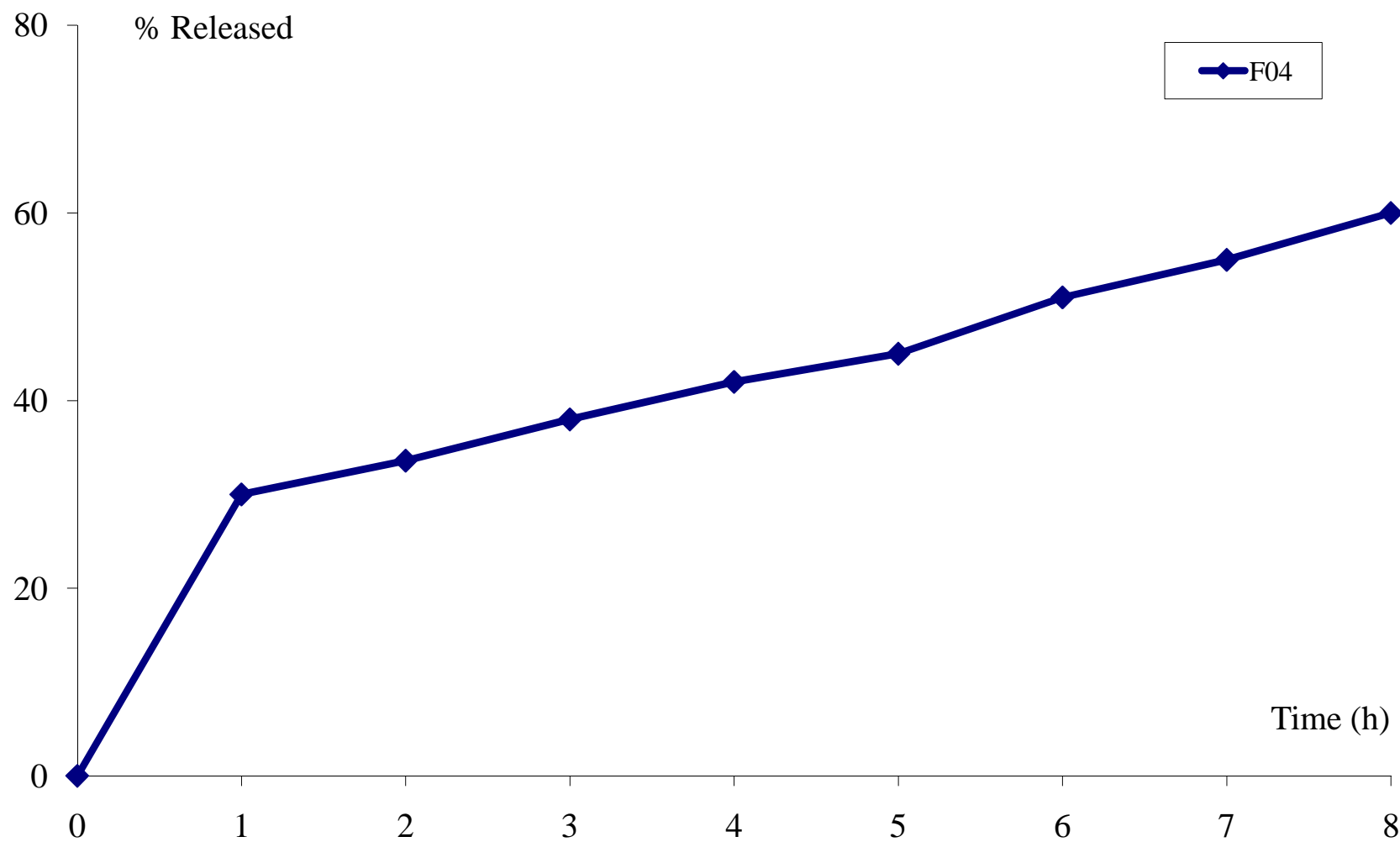
pH 1.2



**Coated pellets USP 2 pH 1.2**



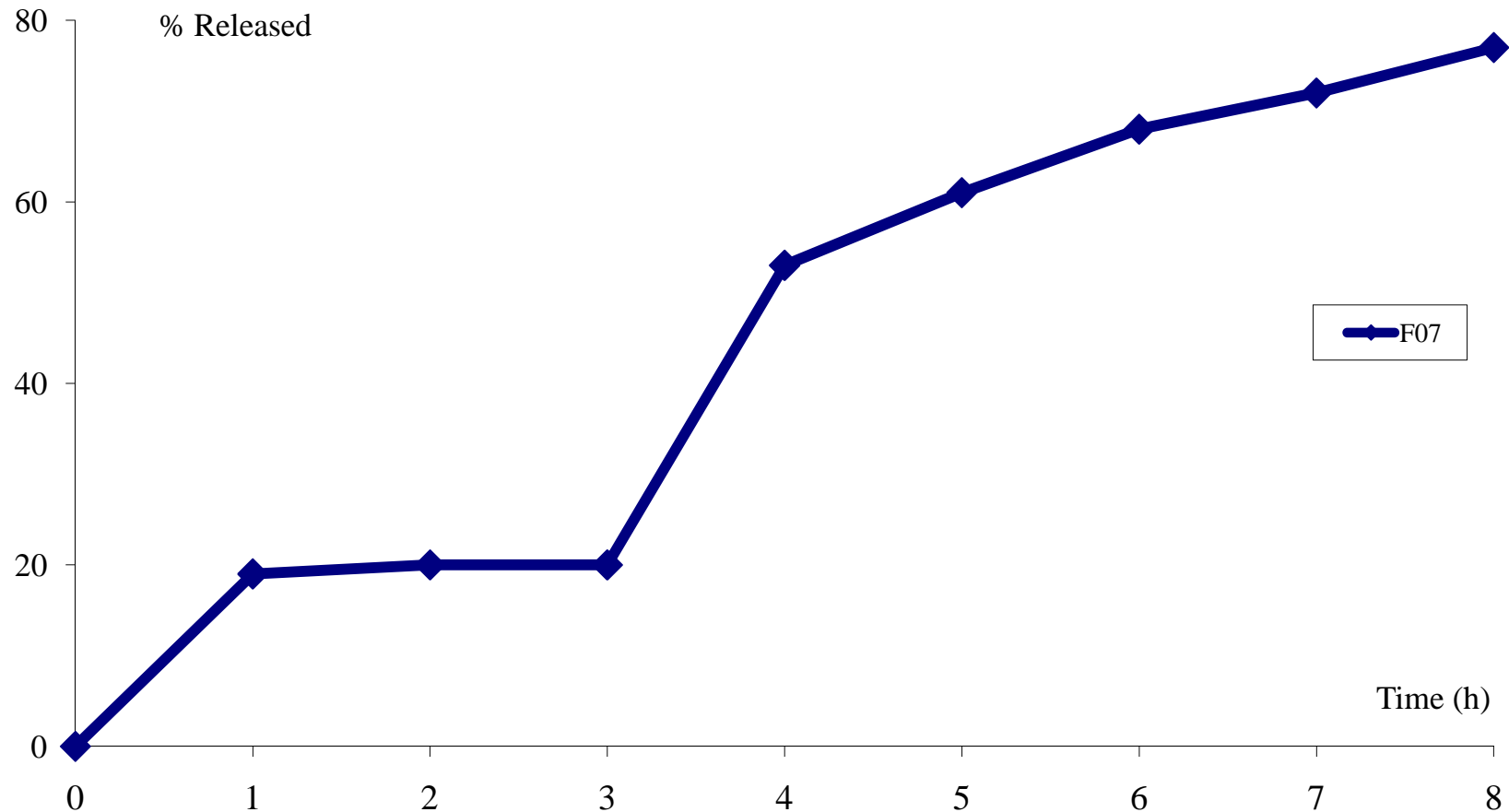
**Coated pellets USP 2      pH 7.1**



❑ 20% uncoated pellets + 80% coated pellets

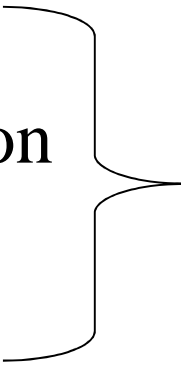
❑ pH 1.2 → 1 hour    pH 4.5 → 2 hours    pH 7.1 → 5 hours

Flow-through cell method



# CONCLUSION

# Gain of IVIVC/IVIVR

- ❑ Multi factorial tool  $\Rightarrow$  information needed in various domains, improvement of the knowledge about formulation and drug
    - API
    - Formulation, production
    - In vitro dissolution
    - PK
  - ❑ Optimizes and accelerates development and line extension
  - ❑ De risk BE studies
  - ❑ Can be used as a biowaiver
- 
- Team Work

## ❑ **IVIVC/IVIVR powerful tool**

- To develop new drug or formulation,
  - To facilitate the development description and rational,
  - To find key factors
  - To gain time and guaranty of the in vivo performances,
  - To facilitate certain regulatory determinations.
- Cost limited vs the full development or could generate benefit

# Special Thanks to

- ❑ Research Team ERT CIDAM – Faculty of Pharmacy – Auvergne University – Clermont-Ferrand



# Special Thanks to

□ **sotax**

□ **SPS**

*Pharma Services*