National and Kapodistrian
University of Athens

# Multiparticulate Drug Delivery Systems: In vitro evaluation with a view to intraluminal performance

21st EAFP Annual Conference, Pre-conference workshop on
*Multiparticulate Drug Delivery Systems – Development Manufacturing and In Vivo Aspects*

14 May, 2015
Athens, Greece

Christos Reppas

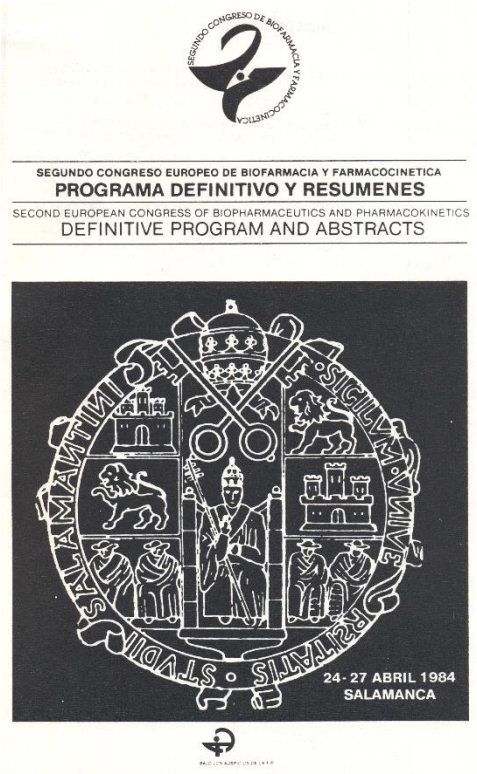
SEGUNDO CONGRESO EUROPEO DE BIOFARMACIA Y FARMACOCINETICA

# PROGRAMA DEFINITIVO Y RESUMENES

SECOND EUROPEAN CONGRESS OF BIOPHARMACEUTICS AND PHARMACOKINETICS

DEFINITIVE PROGRAM AND ABSTRACTS

24-27 ABRIL 1984
SALAMANCA




Panayoti, Thank you for the journey

# Scope of the presentation

*In vitro* testing of prolonged release (and gastro-resistant) multiparticulate dosage forms based on

- current thinking at the European Medicines Agency, and
- relevant experience at the Faculty of Pharmacy, UoA

Guideline on quality of oral modified release products

20 March 2014, EMA/CHMP/QWP/428693/2013, Committee for Medicinal Products for Human Use (CHMP)

## Prolonged release dosage forms

### General remarks

Formulation should be tested for sensitivity/robustness to the expected physiological environment

An in vitro dissolution test that is able to detect changes
which may have an effect on the efficacy/safety of the product
should be developed during scaling up, *the latest*

If scaling up factor exceeds 10 a comparative BA study of lab scale with full scale production batch should be performed,
in order to verify that the chosen dissolution test conditions are appropriate

## Guideline on quality of oral modified release products

20 March 2014, EMA/CHMP/QWP/428693/2013, Committee for Medicinal Products for Human Use (CHMP)

***vs.***

## Implementation of Pharmaceutical Quality by Design in the US

A high quality product is a product free of contamination and reliably delivering the therapeutic benefit promised in the label to the consumer

Woodcock, Am. Pharm. Rev. 1-3 (2004)

The first goal of pharmaceutical QbD is to achieve meaningful product quality specifications that are based on clinical performance

Yu et al. AAPS J 16:771-783 (2014)

***vs.***

## International Conference on Harmonization (ICH) – Quality

documents do not explicitly acknowledge clinical performance–based specifications as a QbD goal

Yu et al. AAPS J 16:771-783 (2014)

The Biopharmaceutics Risk Assesment Roadmap (BioRAM) for Optimizing Clinical Drug Product Performance

Selen et al. J Pharm Sci 103:3377-97 (2014)

# Guideline on quality of oral modified release products

20 March 2014, EMA/CHMP/QWP/428693/2013, Committee for Medicinal Products for Human Use (CHMP)

## Prolonged release dosage forms

### Developing dissolution methods 1(2)

Variations of API and Analytical method validation: refer to ICH guidelines

Use of biorelevant media is encouraged

Volume of medium should preferably ensure sink conditions

Apparatus, Testing conditions, Acceptance criteria: refer to Ph. Eur.

- Dissolution test conditions should cover the physiological pH range (1-7.5 or even 8)
- Appropriate apparatus and intensity of agitation should be used for suitable discrimination
- Inclusion of surfactants should be justified as well as its batch-to-batch quality
- Inclusion of enzymes should be justified, e.g. enzymes for colonic delivery

  (Ph.Eur. prescribes higher than physiologically relevant concentrations of enzymes in SGF and SIF)

# Multiparticulate Drug Delivery Systems: in vitro evaluation with a view to intraluminal performance

**Prolonged release dosage forms**

1. Usefulness of compendial apparatus

2. Importance of luminal composition and residence times

   Also, special populations (alcohol effect)

3. Enzymes for evaluating the performance in the lower intestine

For prolonged release dosage forms, the degree of simulation of luminal hydrodynamics may have a greater impact than with IR dosage forms

Convection becomes more important as particle size increases above ~ 20 microns

Wang et al. Mol Pharm (2012)

(Shear stresses is not an issue for multiparticuate drug delivery systems)

# Intraluminal *vs.* USP II *vs.* USP IV hydrodynamics based on Reylolds number

Reynolds number characterizes the laminar to turbulent transition state of bulk flow

| | Agitation Intensity | Bulk Reynolds number |
|---|---|---|
| Intaluminal | variable | up to about 100 |
| USP II | 25-200 rpm | **2292-31025** |
| USP IV | 20 ml/min | ~10 (23mm Cell)<br>~32 (12mm Cell) |

Diebold, Diss. Tech. 2000
Cammarn & Sakr, IJP 2000
Diebold, 2005
Abrahamsson et al. 2005
Kakhi, EJPS 2009

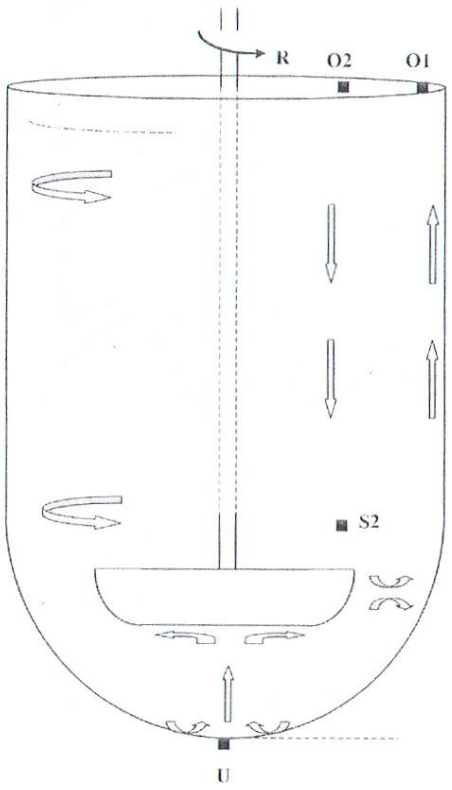
# Intraluminal *vs.* USP II *vs.* USP IV hydrodynamics based on linear flow rates

*Net* volumetric flow rates in the small intestine increase from about 1ml/min in the fasting state to about 3 ml/min in the fed state

Kerlin et al. 1982

Assuming a lumenal diameter of about 3 cm, the *net* linear flow rates should be 0.1cm/min (**0.002 cm/s**) and 0.4 cm/min (**0.007 cm/s**), under fasted and fed state conditions, respectively

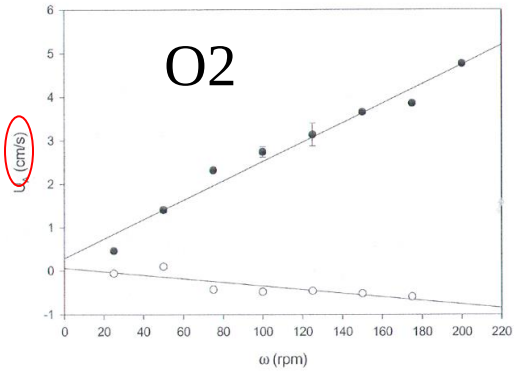
# Linear flow rates vs. rotational speed of the paddle

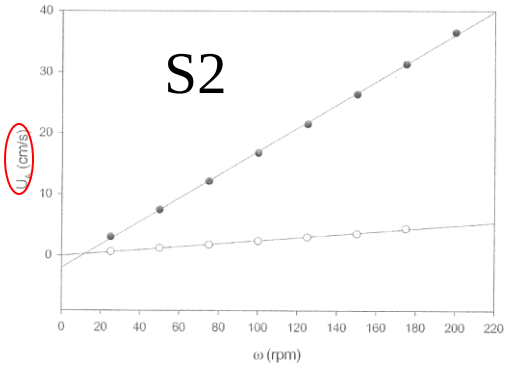


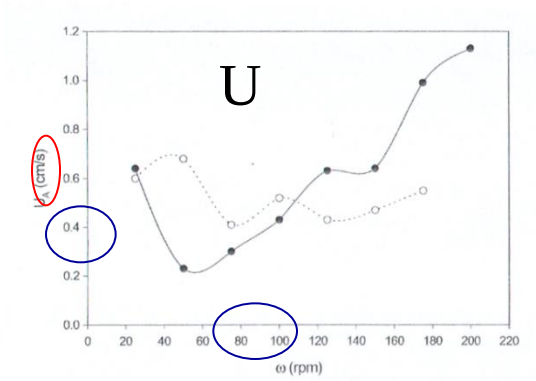

○ USP I

● USP II

Lumenal:
0.002-0.007 cm/s




Diebold, Physiological Parameters relevant to dissolution testing, in Pharmaceutical Dissolution Testing, Taylor & Francis, 2005

# Simulating the changing luminal pH and maintaining sink conditions

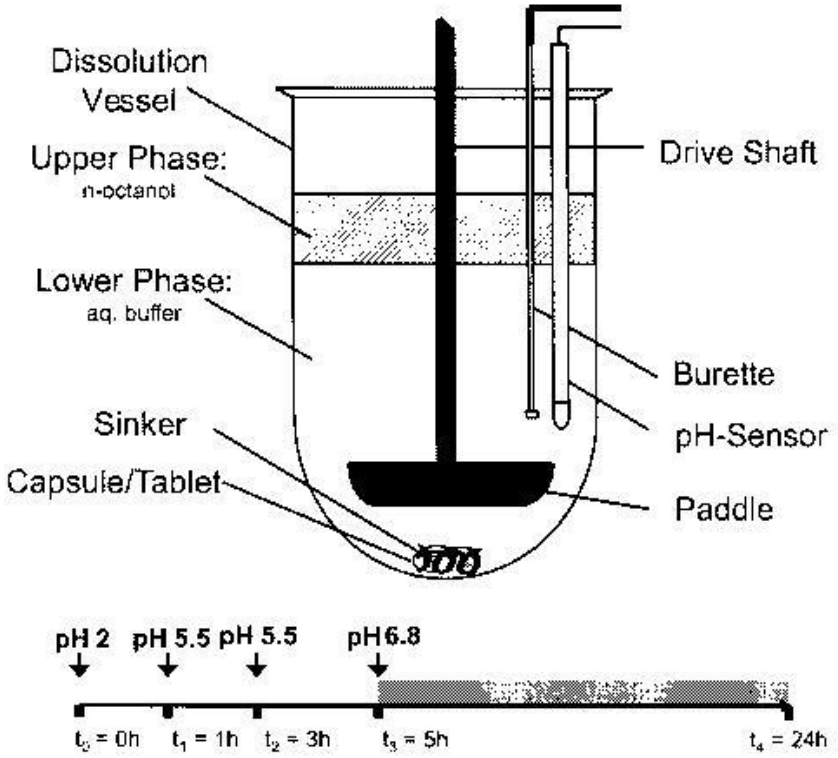



**Fig. 1.** Schematic diagram of a pH-adjusted biphasic dissolution apparatus comprising two immiscible phases (aqueous and *n*-octanol) and a pH-controller to adjust pH of the aqueous phase according to a simulated physiological pH-gradient.

There may be issues when dissolution medium contains micelles

Heigoldt et al. Eur J Pharm Biopharm. 2010

# Linear flow rates vs. volumetric flow rates of the Type IV apparatus (flow – through cell)

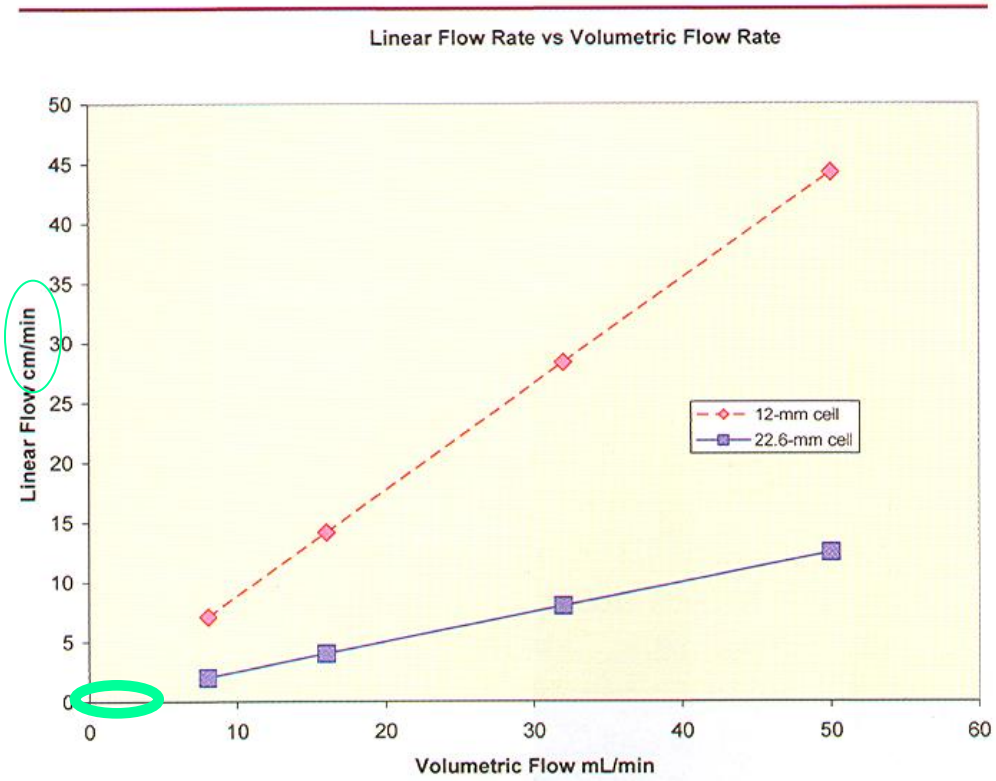



*Figure 1. Comparison of linear flow rates for the 22.6- and 12-mm flow-through cells at identical volumetric flow rates.*

Brown, Diss. Tech. 2005

Lumenal:
0.1-0.4 cm/min

| Tablet - Cell Diameter (mm) | Flow rate, Q (ml/min) | | | | |
|---|---|---|---|---|---|
| | 2 | 4 | 8 | 16 | 32 |
| | Linear flow velocity (cm/min) | | | | |
| 12.6 | 1.6 | 3.2 | 6.4 | 12.8 | 25.7 |
| 22.6 | 0.5 | 1 | 2 | 4 | 8 |

Do we want to apply in vitro flow rates similar to those occurring intralumenally?

Radial loss is not simulated and this is important especially for BCS Class II drugs

# Multiparticulate Drug Delivery Systems: in vitro evaluation with a view to intraluminal performance

**Prolonged release dosage forms**

1. Usefulness of compendial apparatus

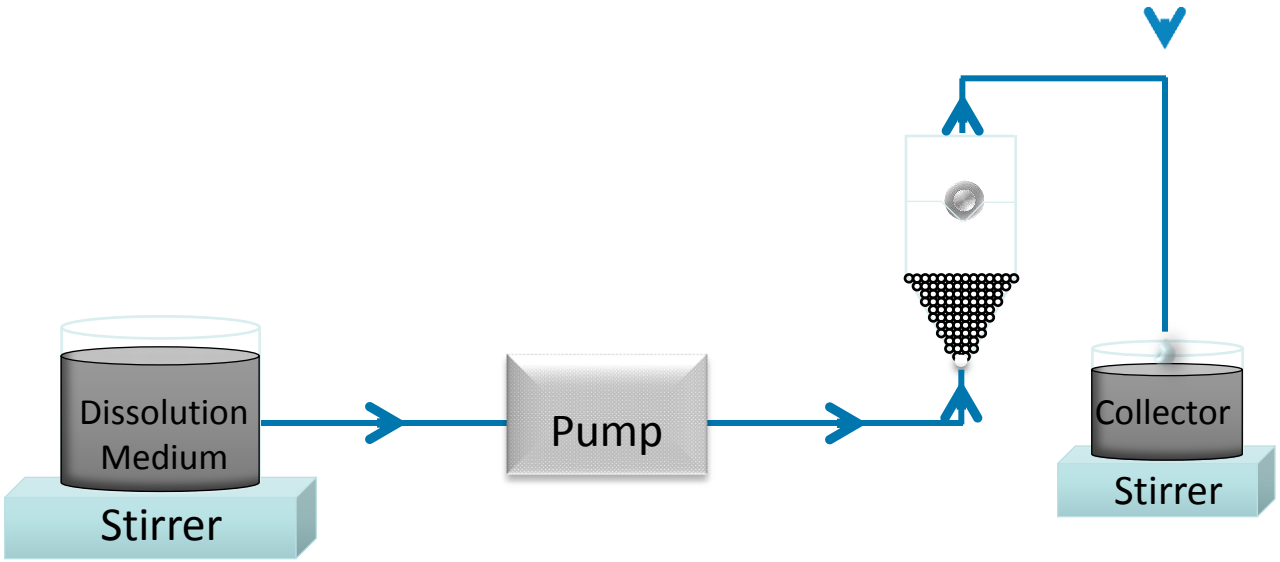
2. Importance of luminal composition and residence times

   Also, special populations (alcohol effect)

3. Enzymes for evaluating the performance in the lower intestine

| Compound | BCS class | Formulations | Dose (mg) | Type of dosage form |
|---|---|---|---|---|
| **Ketoprofen** | II | Oruvail® (Sanofi-Aventis SA) *Controlled Release Capsules* | 200 | Multi-particulate |
| **Mesalamine (Mesalazine)** | IV | Pentasa® (Ferring GmbH) *Prolonged Release Tablets* | 500 | Multi-particulate |

Chatzilias et al. BBBB Conference, Athens, 2013



| Simulated GI region | Simple aqueous media | Biorelevant media* | Period from the beginning of experiment (min) | Duration of exposure (min) | Flow rate (ml/min) |
|---|---|---|---|---|---|
| **Fasted state** | | | | | |
| Stomach | pH 1.8 | FaSSGF | 0-60 | 60 | 8 |
| Duodenum | pH 6.5 | FaSSIF-V2 | 60-105 | 45 | 4 |
| Jejunum | pH 6.8 | $FaSSIF_{jejunum}$ | 105-165 | 60 | 4 |
| Ileum | pH 7.5 | $FaSSIF_{ileum}$ | 165-240 | 75 | 4 |
| Ascending colon | pH 7.8 | FaSSCoF | 240-360 | 120 | 4 |
| **Fed state** | | | | | |
| Stomach | pH 6.4 | $FeSSGF_{early}$ | 0-20 | 20 | 6 |
| | pH 5.0 | $FeSSGF_{middle}$ | 20-80 | 60 | 6 |
| | pH 3.0 | $FeSSGF_{late}$ | 80-120 | 40 | 6 |
| Duodenum | pH 6.0 | $FeSSIF_{early}$ | 120-180 | 60 | 4 |
| Jejunum/Ileum | pH 7.0 | $FeSSIF_{jejunum/ileum}$ | 180-300 | 120 | 4 |
| Ascending colon | pH 6.0 | FeSSCoF | 300-420 | 120 | 4 |

*pH, buffer capacity, osmolality, bile components, lipid digestion products are simulated in these media (biorelevant media). Experiments were also performed in plain buffers for comparative purposes (plain buffers)

Reppas and Vertzoni. *J. Pharm. Pharmacol.* **64**:919-930 (2012)

# Oruvail® Controlled Release Capsules

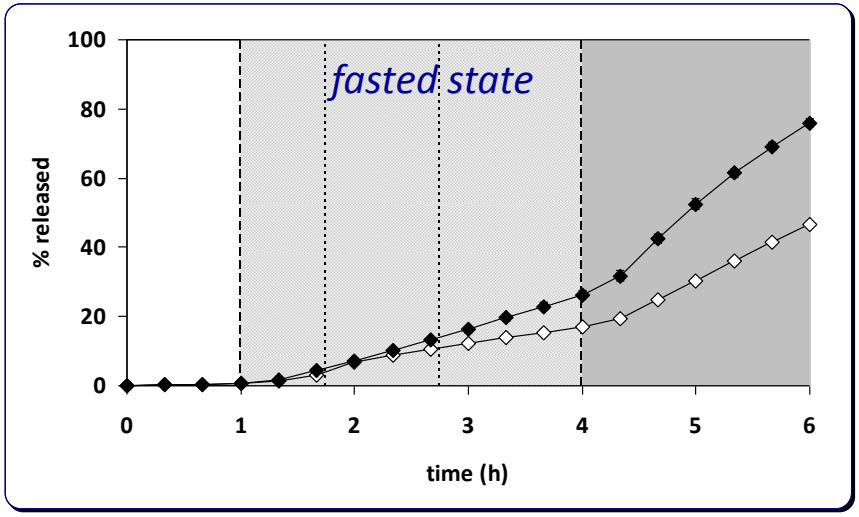
10 min
after the initiation of the experiment

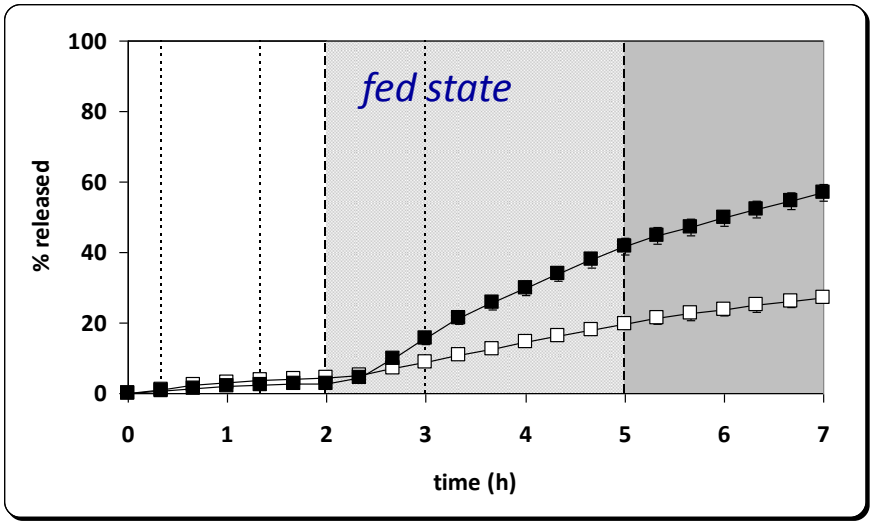
■,♦ Simulated luminal fluids
◊,□ Plain buffers

Gastric Residence

Residence in small intestine

Residence in ascending colon



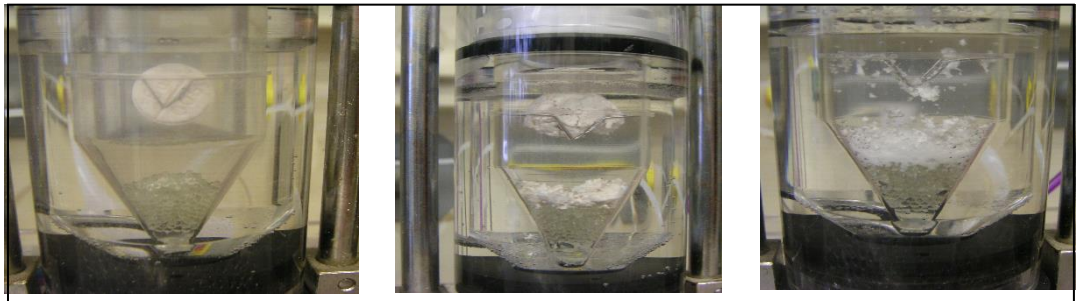




Release of ketoprofen is minimal under simulated gastric conditions

Fasted state: release occurs mostly in the colon / Fed state: release occurs mostly in the small intestine

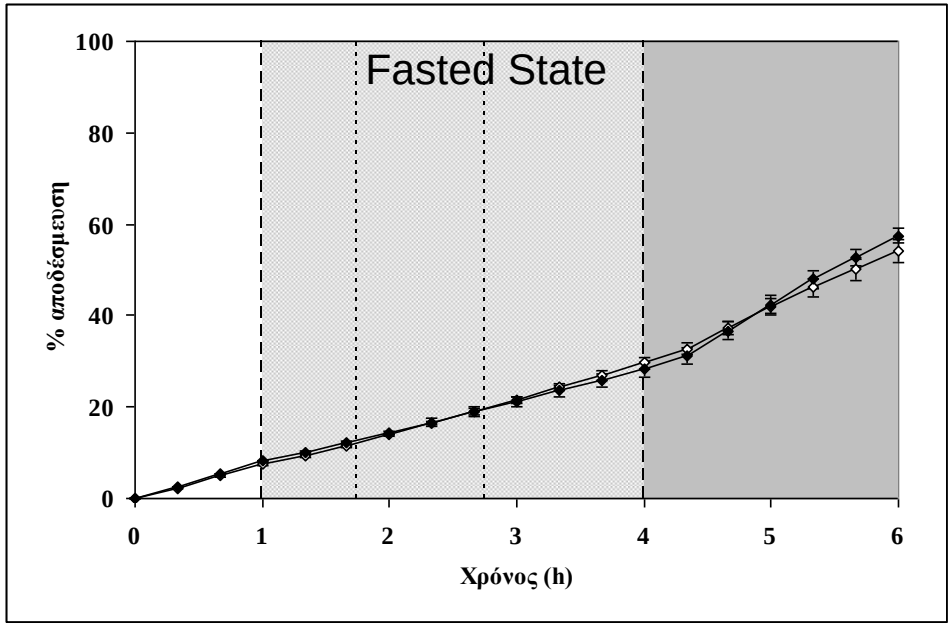
(Relevant in vivo data have not been published)

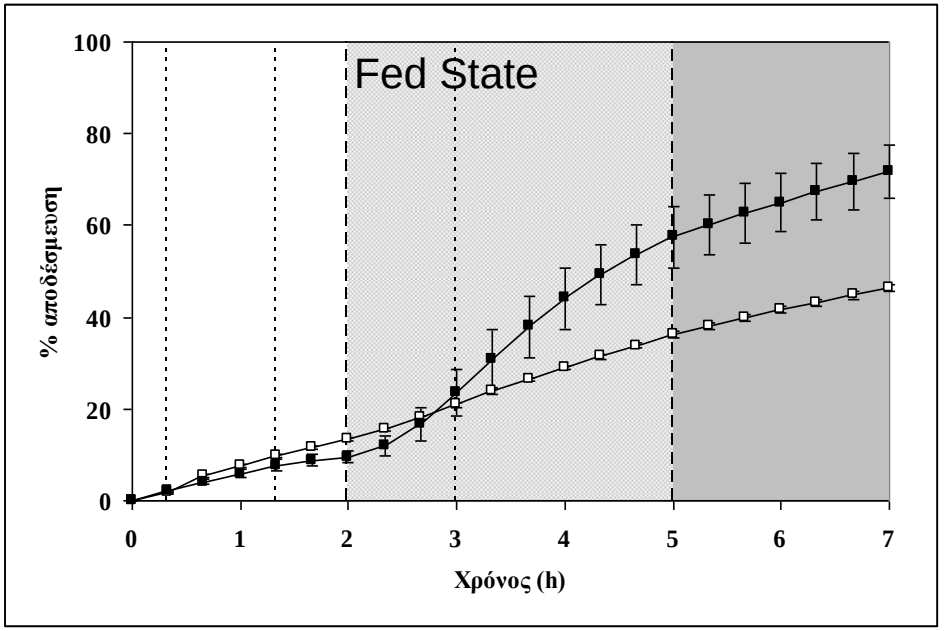
# Pentasa® Prolonged Release Tablets



0 min 10 min 60 min

after the initiation of the experiment




■,♦ Simulated luminal fluids

◊,□ Plain buffers

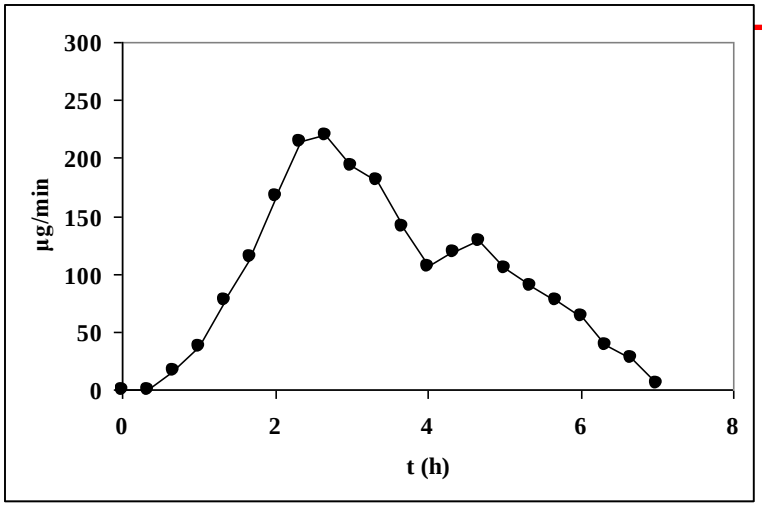
Gastric Residence

Residence in small intestine

Residence in ascending colon

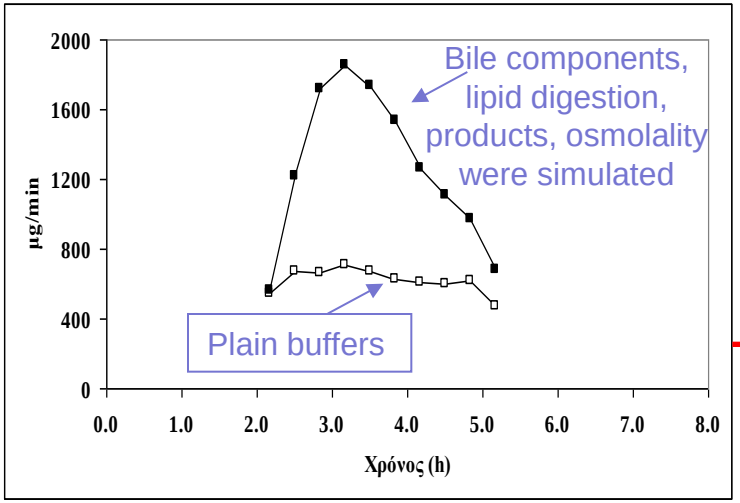
Under fasting state simulating conditions release in plain buffers is identical to that in simulated luminal fluids, but, not under fed state simulating conditions

# Pentasa® Prolonged Release Tablets




Mean release rate in the lumen of small intestine (duodenum-jejunum-ileum) of adults after administration of the product in the fed state

(Based on Layer P. et al. *Gastroenterology* **108**:1427-1433 (1995))




Non-cumulative in vitro release data in media simulating the conditions of the small intestine and the USP IV apparatus

Actual ***release kinetics*** in the small intestine can be predicted when adequate simulation of composition of luminal contents and of residence times is made

# Multiparticulate Drug Delivery Systems: in vitro evaluation with a view to intraluminal performance

**Prolonged release dosage forms**

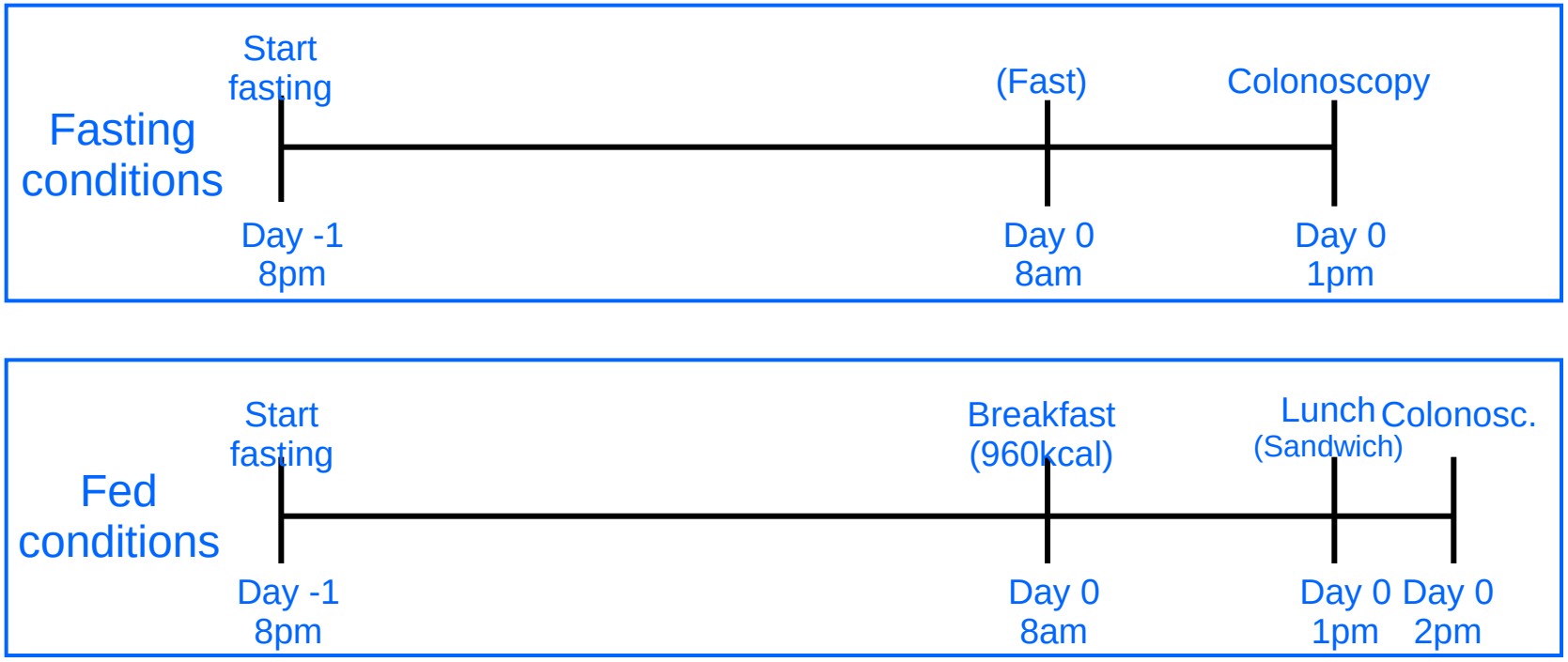
1. Usefulness of compendial apparatus

2. Importance of luminal composition and residence times

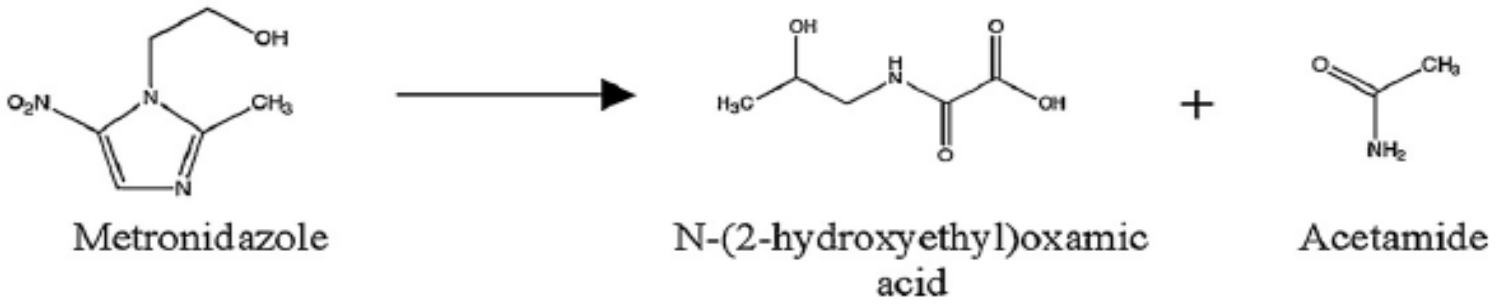
   Also, special populations (alcohol effect)

3. Enzymes for evaluating the performance in the lower intestine

The environment in the ascending colon that
a dosage form should face after administration to healthy young adults
under fasting conditions and together with a meal



# Bacterial degradation of metronidazole in the large intestine




Reaction mediated by anaerobic bacteria in the large intestine

Wadworth and Fitton, 1991; Sousa et al. 2008

# Evaluation of bacterial degradation of therapeutic agents in the ascending colon?

Typically, evaluation is based on data collected in fecal slurry prepared from human feces using water, buffers or normal saline with dilution factors varying from 2 to 10

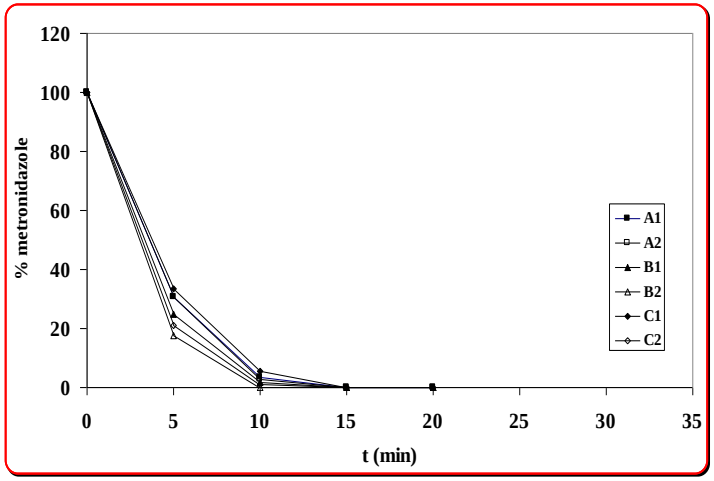
We evaluated two types of media:

- Feces, homogenized with 3.8 parts normal saline

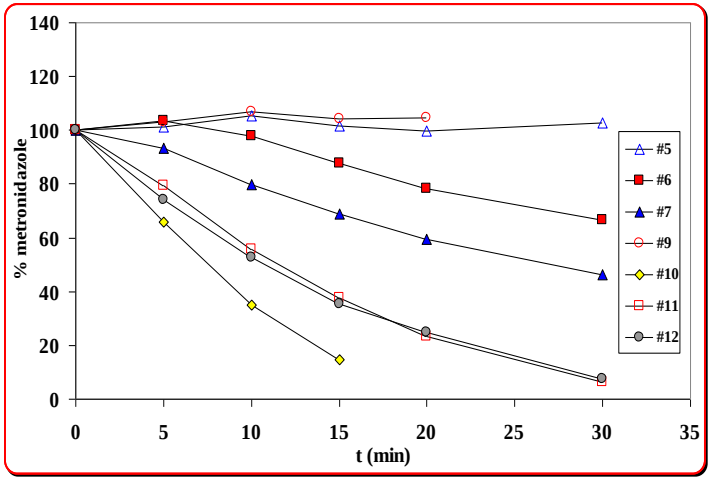
- Precipitates, obtained after ultracentrifugations of individual samples from the lumen of the ascending colon, homogenized with volumes of normal saline equal to the supernatants after ultracentrifugation

# Evaluation of bacterial degradation of metronidazole in fecal material and in material from the ascending colon

Individual fecal materials [n=6
(3 adults, 2 fecal materials from each adult)]




Individual colonic contents prepared from contents of ascending colon collected in the **fasted** state (n=7)



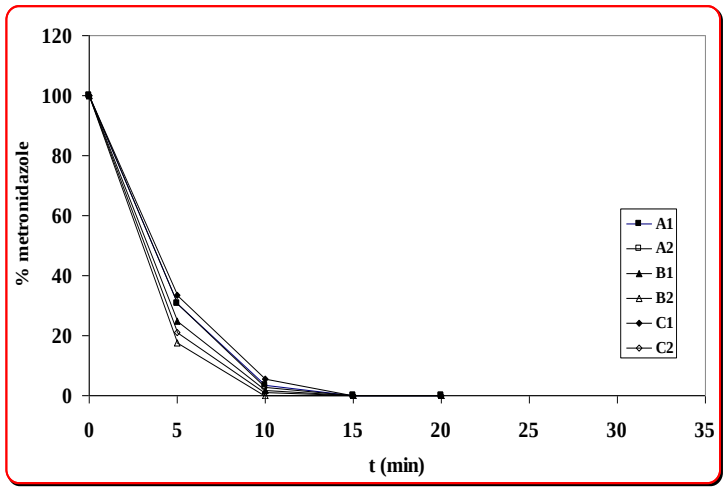

Degradation rate constant in the material from the contents of the ascending colon collected in the **fasted** state is

- ✓ highly variable
- ✓ significantly lower than that observed in fecal material

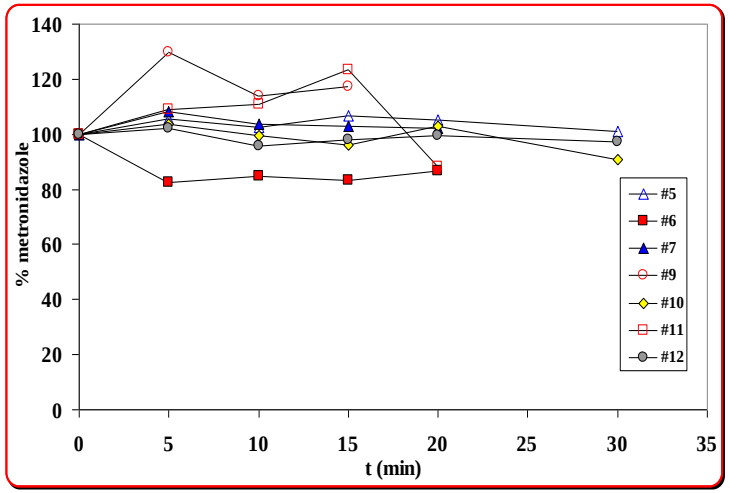
Vertzoni et al. 2011

# Evaluation of bacterial degradation of metronidazole in fecal material and in material from the ascending colon

Individual fecal materials [n=6
(3 adults, 2 fecal materials from each adult)]




Individual colonic contents prepared from contents of ascending colon collected in the **fed** state (n=7)




Practically stable in the material from the contents of the ascending colon collected in the **fed** state

↳ The lack of degradation in the fed state could be related with the arrival of fermentable substrates from the small intestine, i.e. a competitive inhibition mechanism

Vertzoni et al. 2011

**Prolonged release dosage forms**

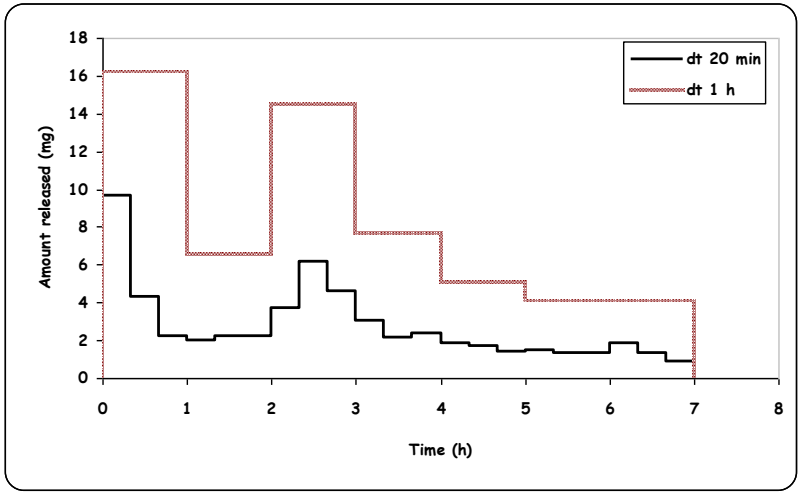
# Developing dissolution methods 2(2)

Evaluation of data variability: At each time point

When release is zero order, specification of rate over a period of time, may be more suitable than cumulative amount dissolved at a given time point

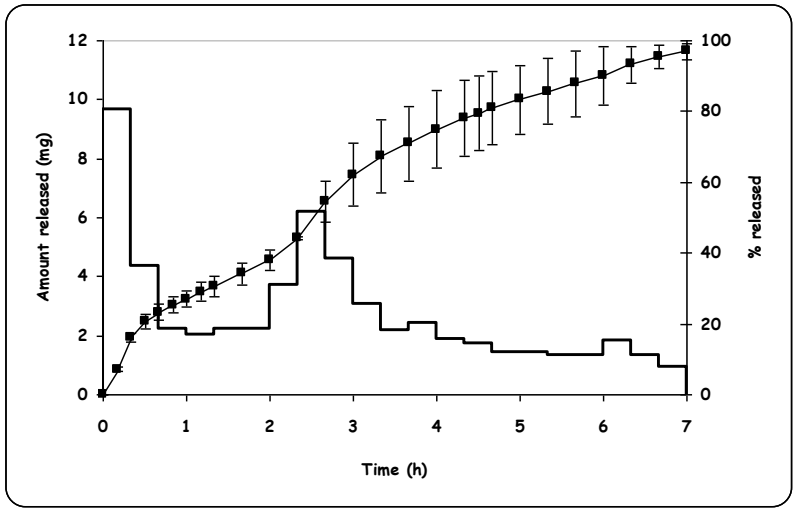
Graphical presentation of dissolution rate over a period of time for an appropriate time interval should additionally be presented

## Amounts dissolved at specific time periods?




Short sampling time intervals equally spaced and the same for all relevant experiments should be used (number of samples?...)

## Cumulative *vs.* non-cumulative data




Cumulative form of data may be less informative on changes of rate of release

Guideline on quality of oral modified release products

20 March 2014, EMA/CHMP/QWP/428693/2013, Committee for Medicinal Products for Human Use (CHMP)

## Prolonged release dosage forms

# Showing discriminatory power of the dissolution test

Three approaches with order of priority:

1. Include batches that failed to show acceptable PK parameters in vivo; together with a validated IVIVC, they aid to set specifications

2. If there are no non-acceptable batches, dissolution data may be compared with average results of the PK parameter estimates on a rank basis

3. If none of the above is applicable, discriminatory power may be shown by deliberately varying an attribute of the API (e.g. particle size)
(this approach may lead to over-discrimination)

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**Prolonged release dosage forms**

# Comparison of dissolution profiles

Similarity of profiles should be established with at least 12 individual values per time point

Model dependent or model independent methods could be used, e.g.

- Linear regression of the percentage dissolved at specified time points (if zero-order release kinetics)
- Statistical comparison of the parameters of the Weibull function
- Calculation of similarity factor or other metric value

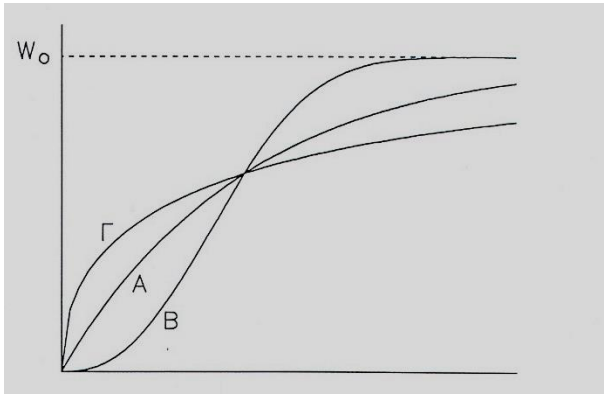
# Model-dependent comparison of cumulative dissolution data sets (a two-step procedure)

Step 1: Characterization of the dissolution process

A) Select physicochemical and/or (semi)empirical models containing assumptions appropriate to their application to the specific data sets
B) Check for over-parameterization and assess goodness of fit
C) Decide which model describes data best

The Weibull function

$$W_t = W_0\left\{1-\exp\left[-\left(\frac{t}{\beta}\right)^c\right]\right\}$$




$A: c = 1$

$B: c \rangle 1$

$\Gamma: c \langle 1$

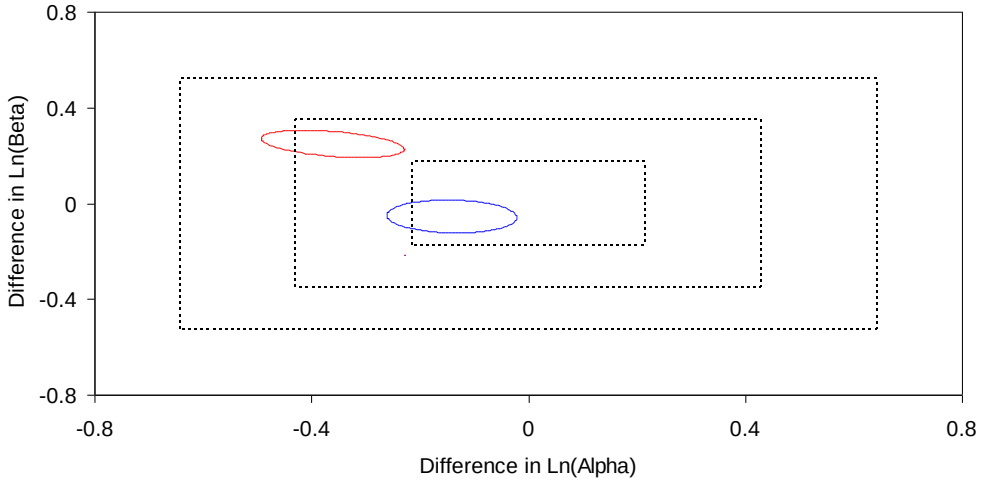
# Model-dependent comparison of cumulative dissolution data sets (a two-step procedure)

Step 2: Comparison of estimated parameter(s)

Parametric confidence intervals if one parameter is estimated
e.g. the first order dissolution rate constant

Multivariate analysis is appropriate when more than one parameter is estimated
e.g. the rate and shape parameters of the Weibull function

Sathe et al. Pharm. Res. 1996




Simultaneous assessment of difference of the Weibull parameters when 2 test batches were independently compared with a reference batch

Dotted boxes define similarity regions

# Possible problems associated with the application of Weibull function in biorelevant dissolution testing

## Correlation of estimated parameters

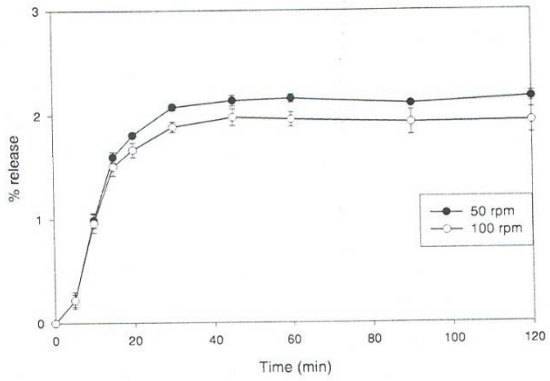
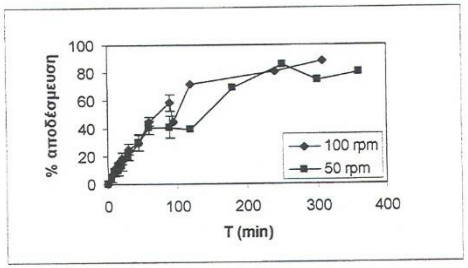


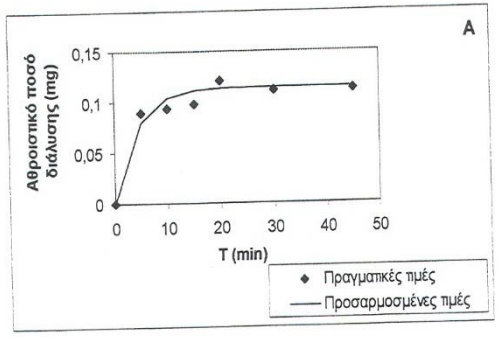

Figure 3-36: Atovaquone tablet dissolution in FeSSIF at 50 and 100 rpm

## Increased data variability




*Σχήμα Γ.6. Μέσες τιμές ± SD για τα δεδομένα του % αθροιστικά διαλυθέντος ποσοστού του troglitazone από δισκία D157/155B σε γάλα σε σχέση με το χρόνο, όταν το πτερύγιο περιστρέφεται με ταχύτητα 100 και 50 rpm.*

## Lack of data at early time-points



# Model-independent comparison of cumulative dissolution data sets (a single-step procedure)

- Various approaches have been considered

- The use of a measure of the absolute or relative "difference" of two profiles is the most challenging (simplicity?) especially when a model-dependent approach is not applicable

# The similarity factor

Moore&Flanner, 1996

$$f_2(t_n) = 50 \log\left[100\left(1/\sqrt{1+\frac{1}{n}\sum_{k=1}^{n} w_k [W_R(t_k) - W_T(t_k)]^2}\right)\right]$$

- ☞ It reflects the squared distance of two data sets
- ☞ Its value increases with the similarity of data sets
- ☞ Evaluation of the index on a confidence interval basis is possible

Shah et al. 1998

# The similarity factor: Key characteristics

- Its evaluation involves comparison of data points and not areas
- A cutoff time limit for its evaluation needs to be designated
  (usually the first datum after 85% completion of the reference data set)
- Caution when data have low variability and the plateau value is not 100
- Cannot be applied when data have high variability and the plateau is not known

# The difference factor

Moore&Flanner, 1996

$$f_1(t_n) = \frac{\sum_{k=1}^{n} \left| W_R(t_k) - W_T(t_k) \right|}{\sum_{k=1}^{n} W_R(t_k)}$$

- It reflects the sum of absolute point differences and it can be any positive number
- Its value increases with the difference of data sets
- Evaluation of the index on a confidence interval basis is possible

# The difference factor: Key characteristics

☞ It can be evaluated using areas so that to reflect the absolute area difference:

$$f_{1,area}(\tau) = \frac{\int_0^{\tau} \left| W_R(t) - W_T(t) \right| \cdot dt}{\int_0^{\tau} W_R(t) \cdot dt}$$

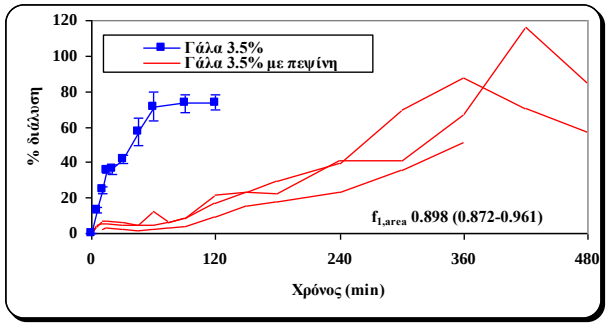
☞ Cannot be evaluated if a reference data set does not exist

☞ A cutoff time limit for its evaluation needs to be designated
(usually the first datum after 85% completion of the reference data set)

☞ Its evaluation requires no consideration of the plateau level

☞ Caution when the plateau is not known

Vertzoni et al EJPB 2003



# The Rescigno index

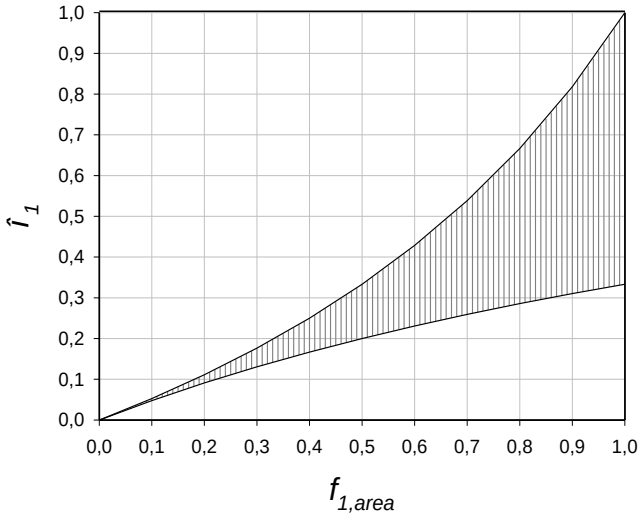
Rescigno, 1992

$$\xi_i(\tau) = \left[ \frac{\int_0^\tau \left| W_R(t) - W_T(t) \right|^i \cdot dt}{\int_0^\tau \left| W_R(t) + W_T(t) \right|^i \cdot dt} \right]^{1/i}$$

- It reflects the absolute area difference (i=1) or the squared area difference (i=2) and its value can be from 0 to 1
- Its value increases with the difference of the two data sets
- Evaluation of the index on a confidence interval basis is possible

# The Rescigno index: Key characteristics

- ☞ It reflects area differences
- ☞ A cutoff time limit for its evaluation needs to be designated
  (usually the first datum after 85% completion of the reference data set)
- ☞ Its evaluation does not require consideration of the plateau level
- ☞Caution when the plateau is not known
- ☞ Many values of the Rescigno index correspond to a single value of the difference factor

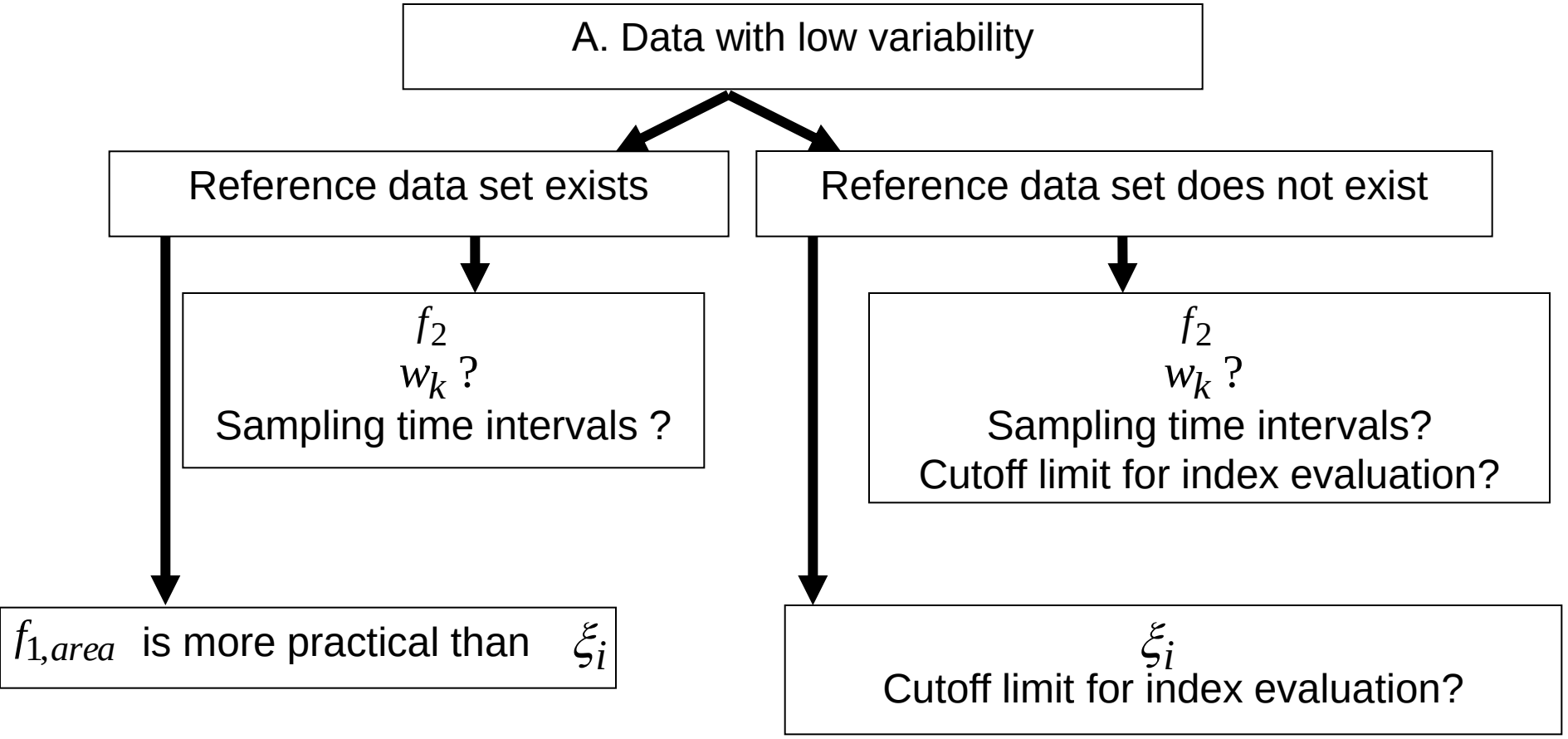



e.g.

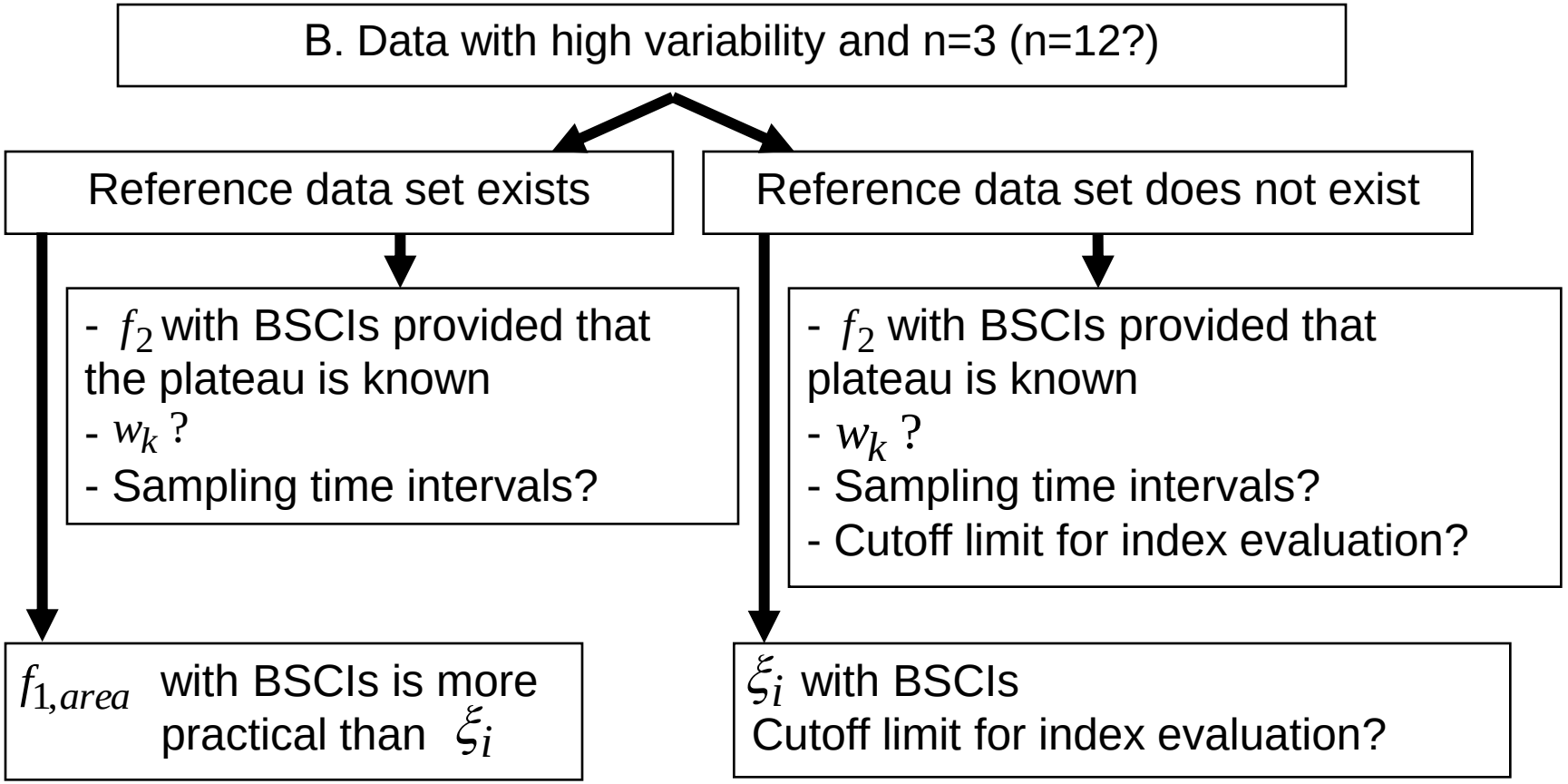
$f_{1,area} = 0.20$ corresponds to $0.091 \leq \xi_1 \leq 0.111$

Vertzoni et al EJPB 2003

# Comparison of two (cumulative) dissolution data sets with indices



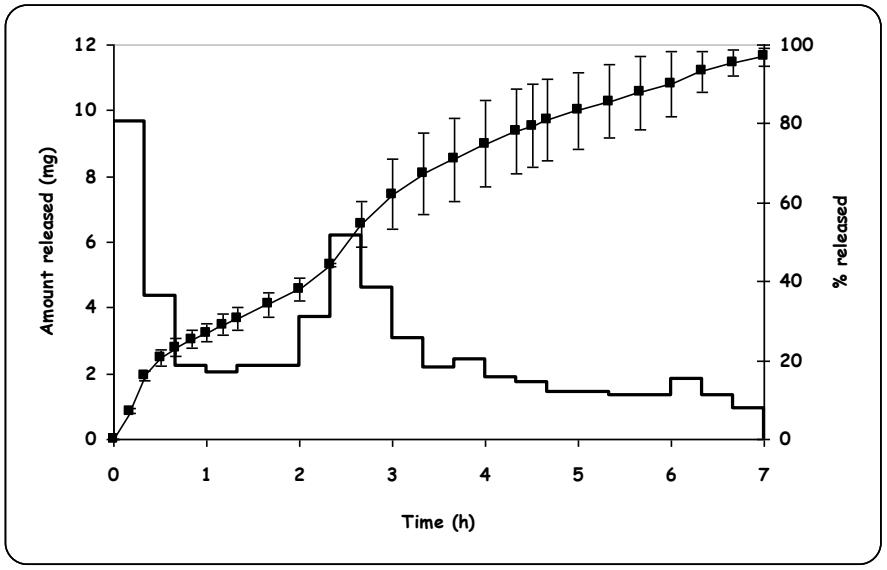
# Comparison of two (cumulative) dissolution data sets with indices



# Comparison of release data collected with the flow-through apparatus (open-loop) with model-dependent procedures

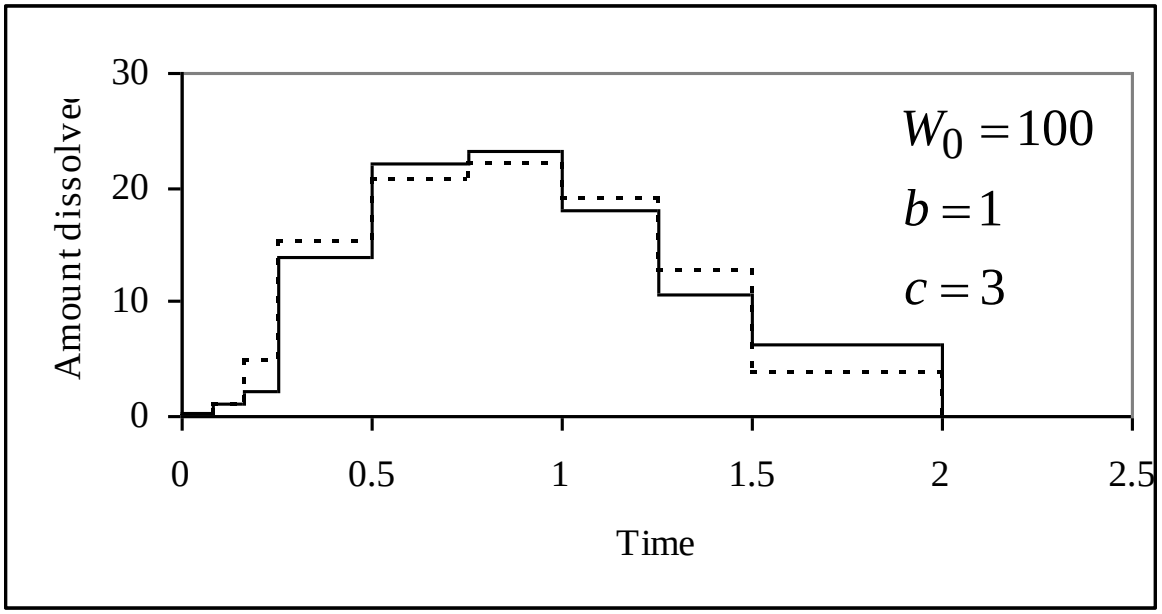
Step 1: Characterization of the dissolution process

The least square criterion for drawing the best-fitted curve through a set of errant data is only valid if errors are independent



# A method for characterization of the kinetics from flow-through (open-loop) data sets

$$W(t_{j-1}, t_j) = W(t_j) - W(t_{j-1}) = W_0 \left\{ \left\{ 1 - \exp\left[ -\left( \frac{t_j}{b} \right)^c \right] \right\} - \left\{ 1 - \exp\left[ -\left( \frac{t_{j-1}}{b} \right)^c \right] \right\} \right\}$$




Dotted line: Data with SD=4

Continous line: Fitted line

# Comparison of release data collected with the flow-through apparatus with model-dependent procedures

Step 2: Comparison of estimated parameter(s)

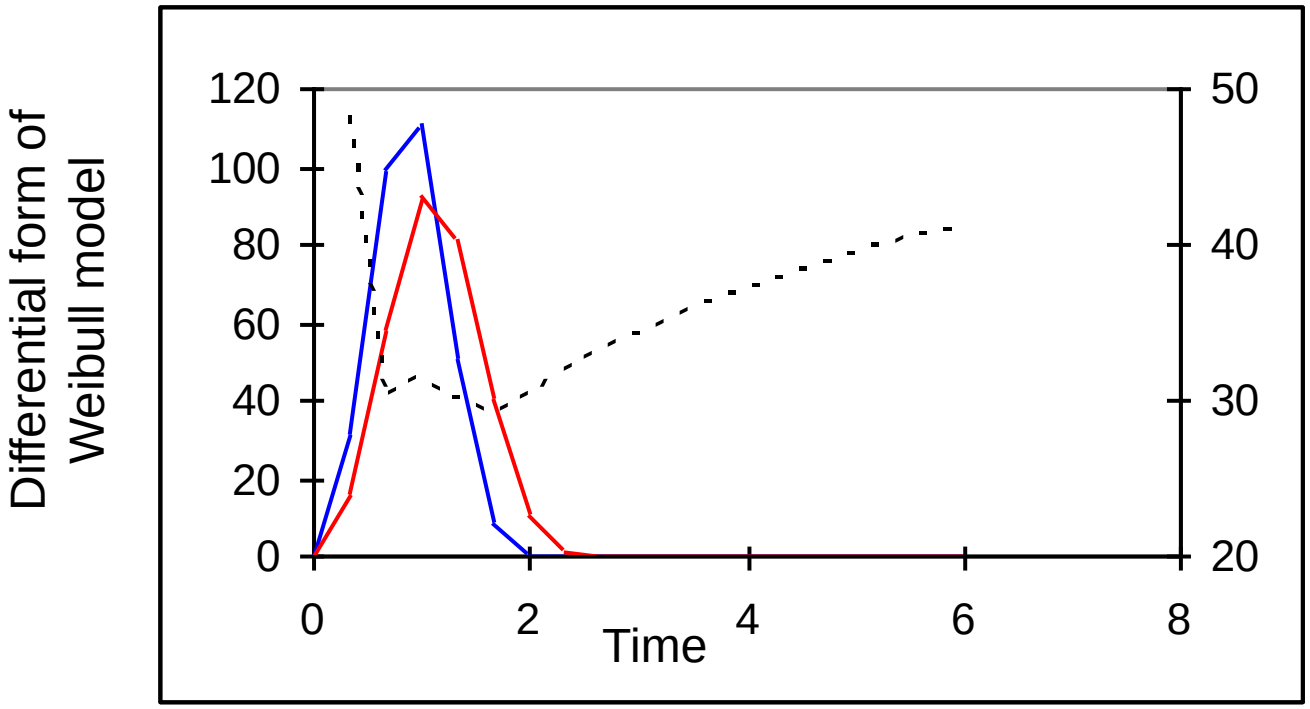
The multivariate technique proposed by Sathe et al. (1996) can lead to wrong conclusions when *c* is low. This is in accordance to the low precision of estimation when c is low

Vertzoni et al. 2005

# Comparison of release data collected with the (open-loop) flow-through apparatus with model-independent procedures

Application of the similarity factor to flow-through data

- ☞ A scaling procedure must be applied
- ☞ Index value continues to change after completion of the process




$W_0 = 100$

$c = 3$

$b_{red} = 1.25$

$b_{blue} = 1$

Application of the difference factor and the Rescigno index to flow-through data

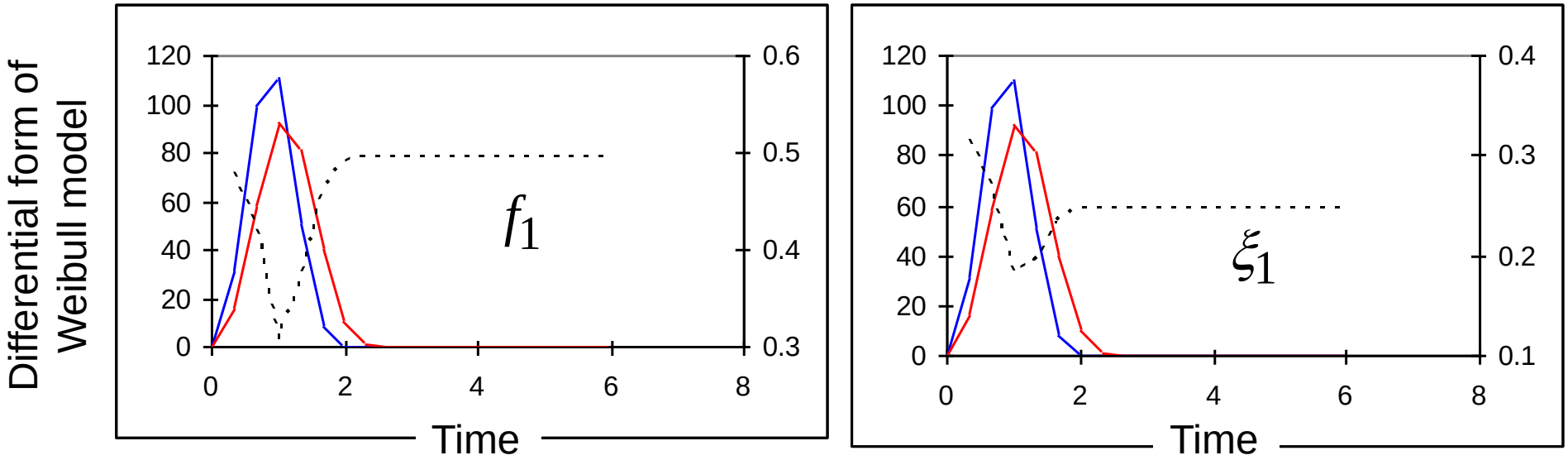
These indices do not change after completion of the process

$$W_0 = 100$$

$$c = 3$$

$$b_{red} = 1.25$$

$$b_{blue} = 1$$



Application of the difference factor and the Rescigno index
to flow-through data on a confidence interval basis

☞ Bootstrap confidence intervals can lead to wrong conclusions in cases where c is low (faster than first order)and the test is faster than the reference data set

## General conclusion for flow-through data comparisons

The comparison of flow-through data can be safely performed with multivariate model-dependent procedures (unless fitting procedure is problematic) and with the difference factor or the Rescigno index (unless the process is very fast at early stages and becomes very slow as it approaches completion whereas the test is faster than the reference data set)

# To what extent the value of a direct curve comparison index reflects differences in PK parameters for the assessment of BE?

The ability of DCCIs to predict differences in PK parameters used for the assessment of BE varies with disposition kinetics and appears to be limited when absorption of the drug is relatively slow compared to the elimination process

Dalmara et a. AAPS poster, Chicago, 2012

Guideline on quality of oral modified release products

20 March 2014, EMA/CHMP/QWP/428693/2013, Committee for Medicinal Products for Human Use (CHMP)

**Prolonged release dosage forms**

# In vitro – in vivo comparison

Development of Level A IVIVC is encouraged, because
- It reduces the number of in vivo studies during product development,
- It helps setting specifications,
- It facilitates regulatory approval (e.g. SUPAC variations)
  - Therapeutic index will be considered for waiving in vivo study
  - A list with NTI/Critical Dose Drugs is not provided by EMA
  - (lists have been published by Health Canada, FDA, WHO, and Danish, Japanese,South African reg agencies!)
- It gives confidence in the use of dissolution testing

Notes:
- If Level B or C correlations are established, in vivo BA BE studies are still needed
- Multiple Level C correlations are not mentioned
- A Level A IVIVC cannot serve as a basis for claiming BE between products from different MA applicants, based on in vitro data only!

## How to develop and evaluate predictability of an IVIVC model

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- Deconvolution or Convolution based approaches

- An IVIVC is adequately accurate when the entire (average) concentration-time curve is well predicted and prediction errors for each of the relevant
PK parameters [(observed-predicted)/observed]
are with acceptable limits,
i.e. <15% for each formulation and on average <10% for each parameter

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# Setting specifications – General remarks

A specification should be set using a discriminatory dissolution test

A minimum of 3 points should be included in the specification
one early (to exclude dumping)
one to ensure compliance with the shape of the profile (usually at ~50% release)
one to ensure that the majority of API is released (>85%, i.e. Q=80%)

When zero order release, a specification for the rate over a period of time for a given time interval is more appropriate than the cumulative amount dissolved

When a lag time, a relevant specification is mandatory

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## Setting specifications without a previously established IVIVC

Acceptable variation around each time point should generally not exceed ±10% of labeled content (total variability 20%)
(highly variable drug products?)

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# Setting specifications after establishing an IVIVC (4 steps)

Dissolution profiles are generated from the proposed limits, e.g. by using an appropriate Mathematical function (Weibull, Hill, etc.)

Plasma profile is calculated for the proposed upper and lower dissolution limits (assuming dissolution reflects absorption profile!) and the observed dissolution data for the to-be-marketed (reference) product

The corresponding $C_{max}$ and “AUC” values for the proposed upper and lower limits and the ref product are calculated and the ratios (upper/lower, upper/reference, lower/reference)

All batches within the lower and upper dissolution spec limits should be BE to one another.
IVIVC should preferably quantify variability so that decision be based on CI basis.
If not, the criteria for BE limits should be tighter, e.g. mean concn-time data predicted for upper and lower specification should be less than 20%

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**Prolonged release dosage forms**

# Setting specifications after establishing an IVIVC

Notes:

For drugs that are absorbed throughout the GI lumen AUC is often similar for formulations with widely varying dissolution rates and the specification is driven by $C_{max}$ (In such case, limits of ±10% in cumulative dissolution may be possible at particular time points for $C_{max}$)

Sensitivity of $C_{max}$ to changes in dissolution depends on the PK properties of the API (short half life, high sensitivity to changes in dissolution!)

## Gastro-resistant dosage forms

### General remarks

Single unit dosage forms are discouraged
(variable gastric residence times, dose dumping, erratic absorption profiles)

Dissolution at pH 3-5 should also be tested (not only at pH 2!)

Setting specifications:
1. At least 2 points should be included
    - one early (to exclude release in acidic medium, <10% dissolved after 2h)
    - one to ensure that majority of API has been released in a (near) neutral medium
2. Acceptance criteria as in PhEur

Thank you for your attention

I will be happy to answer questions