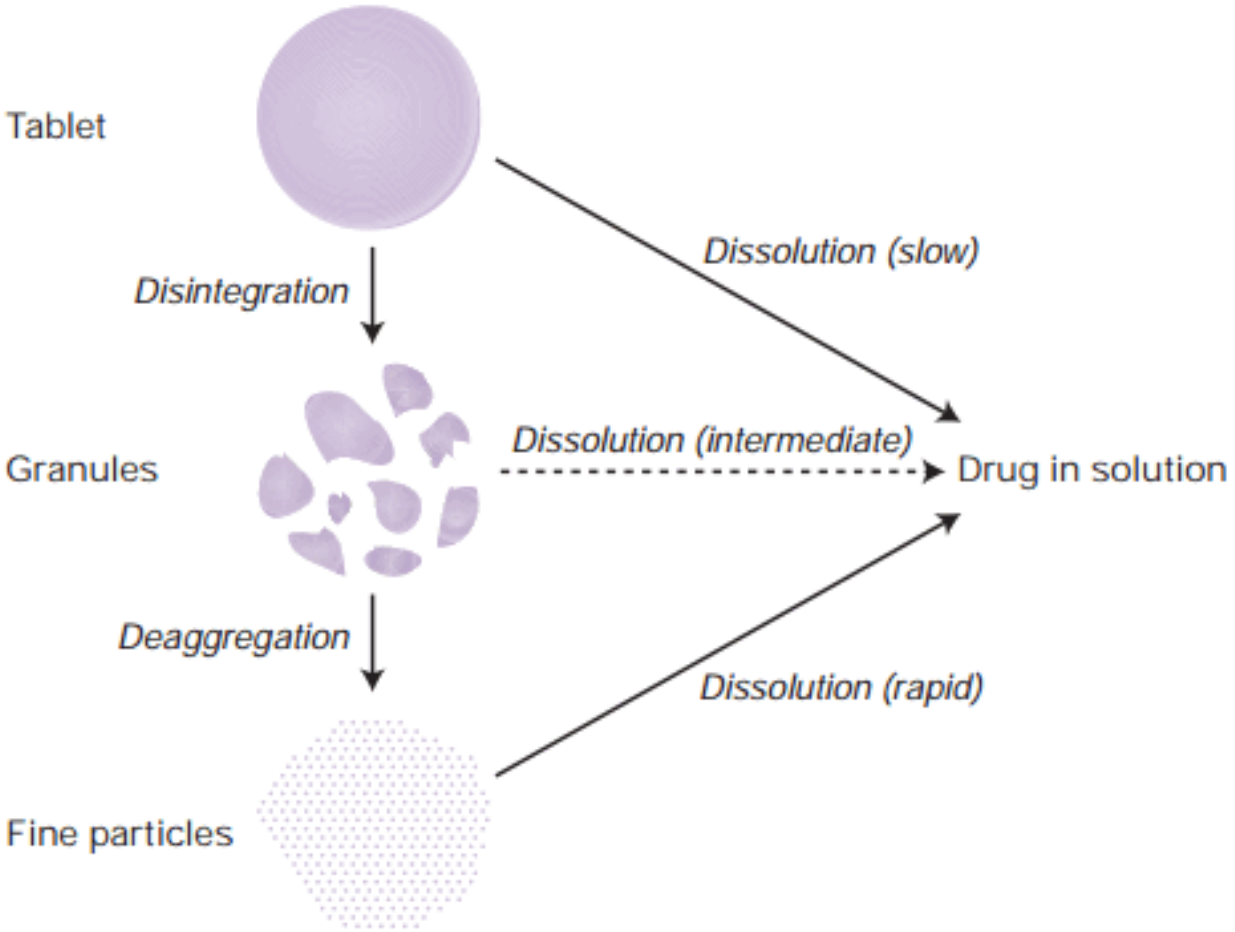
Dissolution profile comparison using different statistical approaches – f_2 bootstrapping

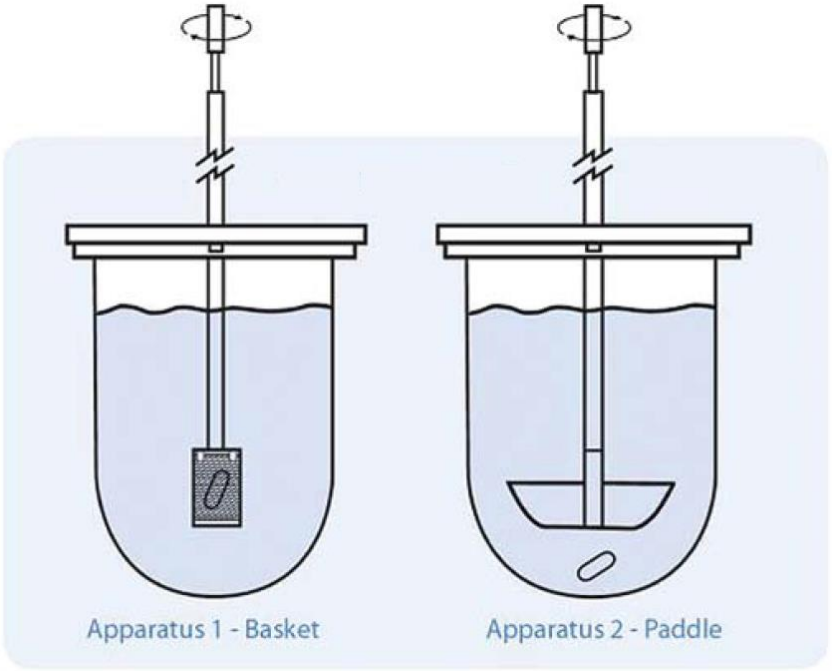
Paulo Paixão
Faculdade de Farmácia, Univ. Lisboa
ppaixao@ff.ulisboa.pt

BioBridges 2019

Dissolution of oral tablets



In vitro dissolution



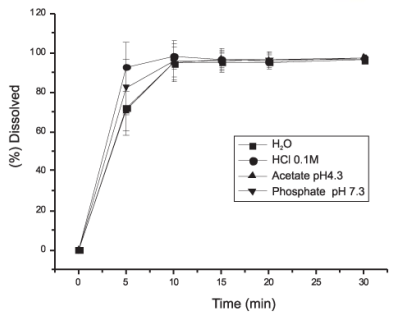


Figure 2. Dissolution profile of ornidazole in different dissolution mediums

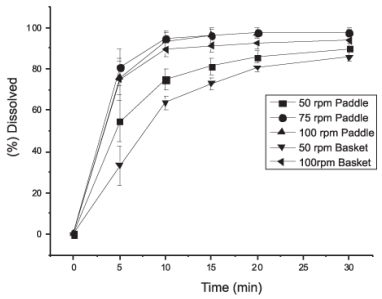


Figure 3. Dissolution profile of ornidazole with different apparatus and stirring

Quím. Nova vol.33 no.2 São Paulo 2010
http://dx.doi.org/10.1590/S0100-40422010000200042

TYPICAL DISSOLUTION PARAMETER OVERVIEW USP APPARATUS 1 AND 2	
Media	• Evaluate Degassed vs. Non-Degassed • Acid (HCl 0.1 – 0.001 N) • Buffers: Acetate (pH 4.1 – 5.5, 0.05 M), Phosphate (pH 5.8 – 8.0, 0.05 M) • Simulated Fluid: Gastric Fed and Fasted, Intestinal Fed and Fasted
Media Volume	• 900 mL, 500 mL (for low dosage strengths) • 1000 mL, 2 L or 4 L (for increased sink) • 200 mL or smaller volumes (as justified)
Surfactants (anionic, cationic, neutral)	• Cetyl trimethylammonium bromide Cetrimide (CTAB) • Polysorbate (Tween™) 20 - 80 • Polyethoxylated alcohols • Polyoxyethylene sorbitan • N,N-dimethyldodecylamine-N-oxide • Hexadecyltrimethylammonium bromide • Polyoxyl 10 lauryl ether • Nonylphenol ethoxylate (Tergitol™) • Cyclodextrins • Lecithin • Methylbenzethonium chloride (Hyamine®) • Sodium dodecyl sulfate (SDS) • Lauryldimethylamineoxide (LDAO) • Brij® • Triton™ X • Cremophor® • Solutol®
Speeds	**Paddle** • 50 rpm (preferred for BCS) • 75 rpm (to eliminate coning/variability) • 25 rpm (for suspensions) • 100 rpm (needs justification for IR, common for ER) **Basket** • 50 - 100 rpm
Temperature	• 37 °C ± 0.5 °C

Utility of in vitro dissolution

Development and Quality

- For selection of the formulation in the development phase
- Selection of the dissolution specifications for product release & stability purposes

Regulatory

- Comparative dissolution data between the bio-batch and innovator batch
- Demonstration of in vivo bioequivalence for several strength(s) of a Finished Pharmaceutical Product may be waived
- Fundamental part on the BCS based waiving concept
- Post-approval amendment applications

Dissolution in bioequivalence in the EMA guideline for BE

- *In vitro* dissolution tests complementary to bioequivalence studies
  - The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study
- *In vitro* dissolution tests in support of biowaiver of strengths
  - Appropriate in vitro dissolution should confirm the adequacy of waiving additional in vivo bioequivalence testing.
- In vitro Dissolution for BCS-based Biowaivers
  - either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics for BCS class I and III

Similarity of dissolution profiles

- Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.
- In case more than 85% is not dissolved at 15 minutes, dissolution similarity may be determined using the f_2 statistic.

The f_2 statistic

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

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Not more than one mean value of > 85% dissolved for any of the formulations.
- Twelve individual values for every time point for each formulation
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

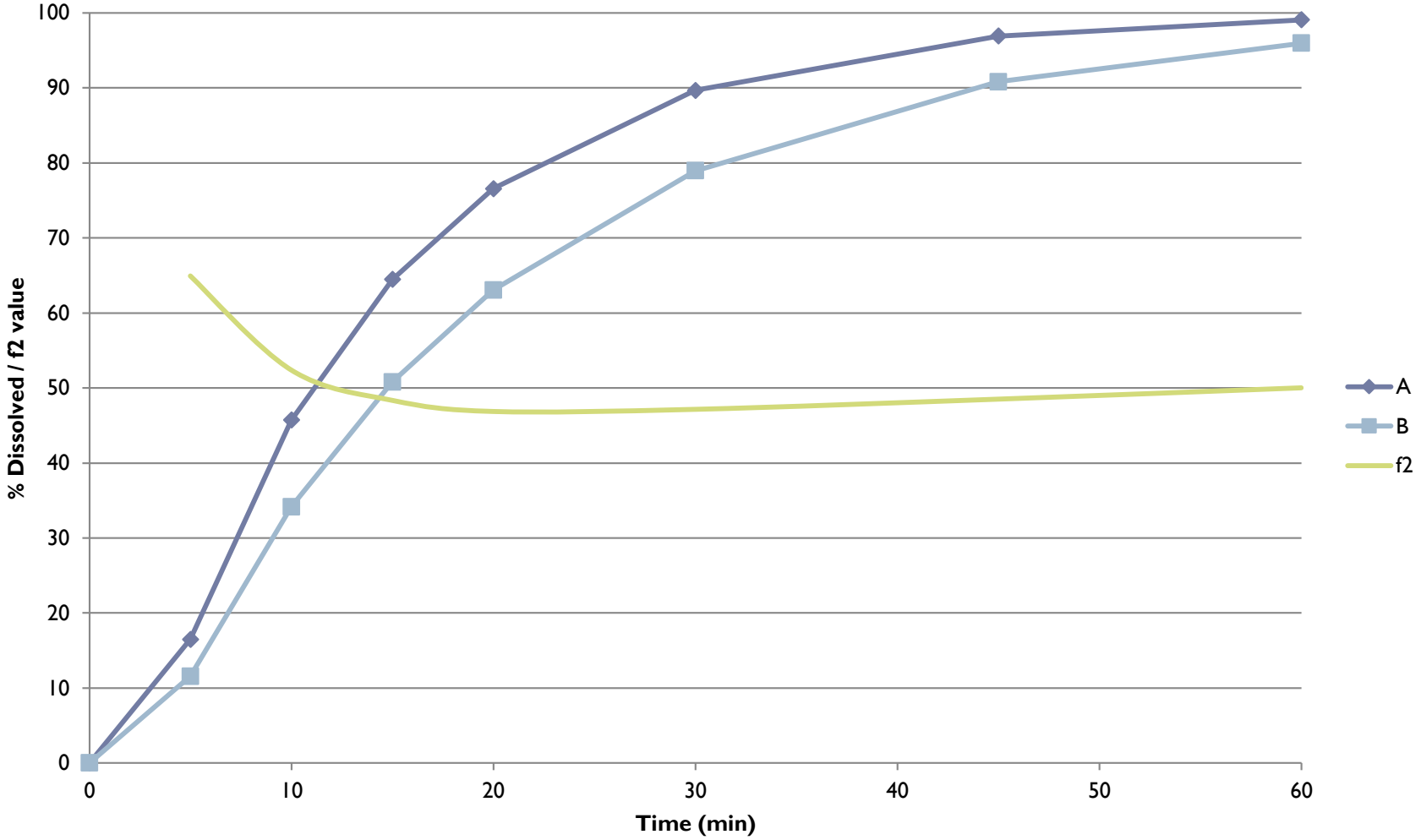
The f_2 statistic

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

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Not more than one mean value of > 85% dissolved for any of the formulations.
- Twelve individual values for every time point for each formulation
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

The f_2 statistic



The f_2 statistic

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

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Not more than one mean value of > 85% dissolved for any of the formulations.
- Twelve individual values for every time point for each formulation
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

The f_2 statistic

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

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Not more than one mean value of > 85% dissolved for any of the formulations.
- Twelve individual values for every time point for each formulation
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

When the f_2 statistic is not suitable, then the similarity may be compared using model-dependent or model-independent methods

Model Dependent Methods

Model	Equation
Zero order Release	$F(\%) = k \times t$
First order Release	$F(\%) = 100 \times [1-e^{(-kt)}]$
Hixson-Crowell cube root law	$F(\%) = 100 \times [1-(1-kt)^3]$
Weibull	$F(\%) = 100 \text{ x } \{1 - e^{[- (t - T1)^{b/a}]}\}$
Korsemeyar and Peppas	$F(\%) = kt^n$

Model Dependent Methods

To allow application of these models to comparison of dissolution profiles, the following procedures are suggested:

1. Select the most appropriate model for the dissolution profiles from the standard, pre-change, approved batches. A model with no more than three parameters is recommended.

2. Using data for the profile generated for each unit, fit the data to the most appropriate model.

3. Compare the statistical distance among the model parameters.

Model Independent Methods - Ratio Tests

- Percent dissolved drug
- AUC

$$AUC = \sum_{i=1}^{n} \left(\frac{F_i + F_{i+1}}{2} \right) (t_{i+1} - t_i)$$

- MDT

$$MDT = \frac{\sum_{i=1}^{n} \hat{t}_i \Delta F_i}{\sum_{i=1}^{n} \Delta F_i}$$

Similarity concluded by the evaluation of the 90%CI of the ratios

Model Independent Methods - Pair-Wise

- Difference factor

$$f_1 = \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i}$$

  - Similar dissolution if values are lower than 15. Similar critics to the f_2 metric

- Bootstrap f_2

  Lower bound of the non-parametric bootstrapping confidence interval (90%) for f_2 index. Similar dissolution if higher than 50.

Model Independent Methods - Pair-Wise

- Rescigno Index - $\xi_i (i = 1,2)$

$$\xi_i = \left[\frac{\int_0^{t_{last}} |F_R(t) - F_T(t)|^i dt}{\int_0^{t_{last}} |F_R(t) + F_T(t)|^i dt} \right]^{1/i}$$

  - The indices lie between zero and one. The value of **ξi** close to zero indicates similarity between mean dissolution profiles.

Model Independent Methods

- Mahalanobis Statistical Distance (MSD)

$$D_M = \sqrt{(\boldsymbol{R}_t - \boldsymbol{T}_t)'\left(\Sigma_{pooled}\right)^{-1}(\boldsymbol{R}_t - \boldsymbol{T}_t)}$$

$$\Sigma_{pooled} = \frac{\Sigma_{test}+\Sigma_{ref}}{2},\ \boldsymbol{R}_t = (R_1, \ldots . R_t)'\ ,\boldsymbol{T}_t = (T_1, \ldots . T_t)'$$

Acceptance by calculating the Upper Bound (D_m^u) of the 90% 2-sided confidence interval (Tsong et. al. 1996) and $D_M^u < \Delta D_M$ with

- $\Delta D_M = \sqrt{\left[(m)'(\sum_{pooled})^{-1}(m)\right]}$ (m=10; 15),
- or ΔD_M = higher historical D_M^u

Use on regulatory grounds

In the past, f_2 was generally accepted as non-applicable conditions were uncommon.

- In present times, the requirement of:
  - Multiple pHs conditions,
  - Limitations on use of surfactants
  - Limitations on the increase of RPM

Resulted on increase in number of dissolution profiles not suitable to be evaluated based on the f_2 metric.

- Typically, the MSD method was used by the applicants

Some simulations…

An immediate release tablet formulation was considered, and the drug release/dissolution model included 1) an initial tablet disintegration period with lag time and 2) the dissolution of the drug particles after disintegration was assumed to follow the Nernst-Brunner equation.

- 1) $$\begin{cases} \frac{dDosage}{dt} = 0 & t < t_{lag} \\ \frac{dDosage}{dt} = -k_{disint} \cdot Dosage & t \geqslant t_{lag} \end{cases}$$

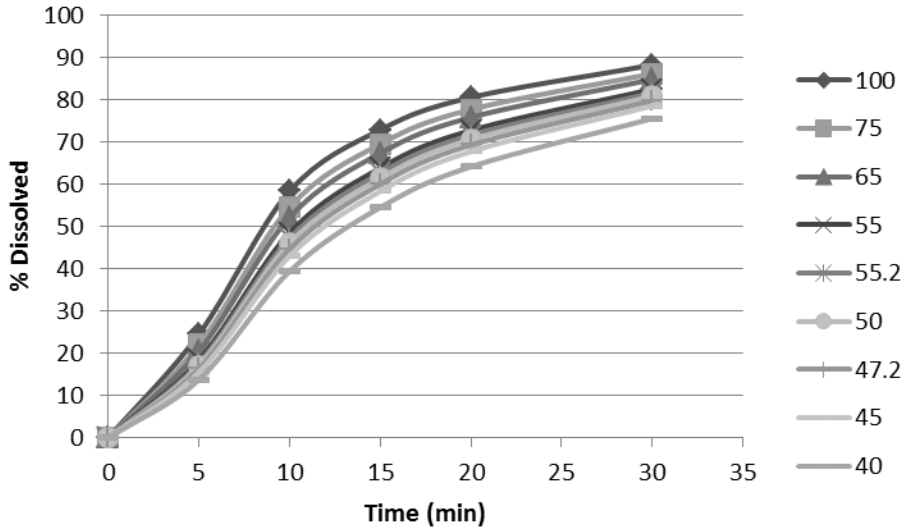
- 2) $$\begin{cases} \frac{dParticles}{dt} = k_{disint} \cdot Dosage - Z_d \cdot Particles \cdot \left(Sol - \frac{Solution}{V}\right) \\ \frac{dSolution}{dt} = Z_d \cdot Particles \cdot \left(Sol - \frac{Solution}{V}\right) \end{cases}$$

Each formulation parameter was considered to vary with an exponential error. An additive residual error was also included.

Models were implemented in Berkeley-Madonna

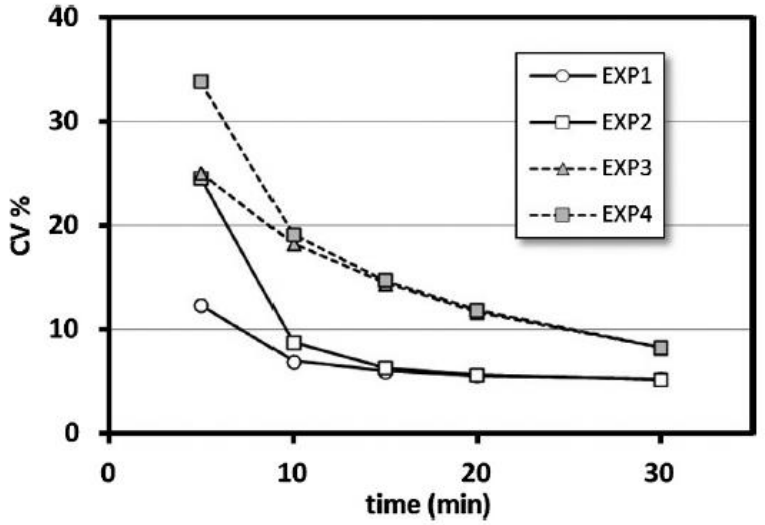
Formulation parameters

f2	100	75	65	55	52.5	50	47.5	45	40
Dosage (mg)	100								
kdisint (min^{-1})	1								
tlag (min)	2								
Zd (mL mg^{-1} min^{-1})	0.090	0.081	0.076	0.069	0.066	0.064	0.061	0.059	0.052
V (mL)	900								
sol (mg/mL)	1								



Variability Parameters

EXP	1	2	3	4
Dosage (CV)	0.05			
Kdisnt (CV)	0.2			
Tlag (CV)	0.05	0.25	0.05	0.25
kd (CV)	0.05	0.05	0.25	0.25
Experimental (SD)	0.001			

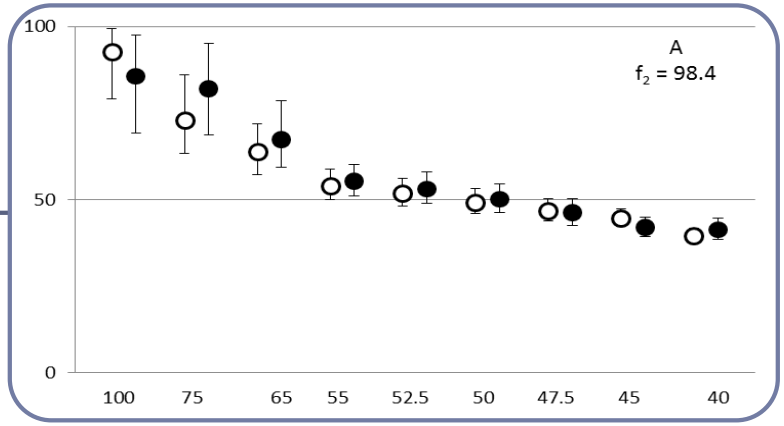


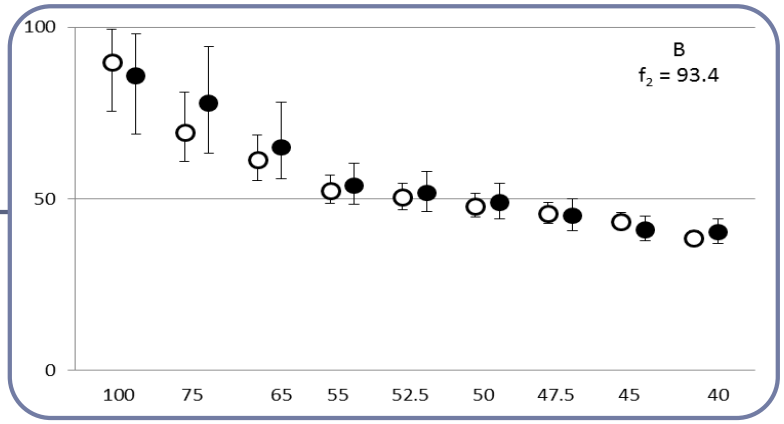
Calculations

- For theoretical f_2 = 100, a total of 12.024 tablets were simulated in each Experimental Condition
  - Ref A = 1-12; Ref B = 13-24
- For theoretical f_2 < 100, a total of 12.000 tablets were simulated in each Experimental Condition
- f_2 values were calculated between $Ref_{A,B}$ and remaining cases (n=12, total of 1000 comparisons) in each theoretical f_2 and experimental condition
- Bootstrap f_2 (90% CI) was calculated between $Ref_{A,B}$ and tablets 25-36 in each theoretical f_2 and experimental condition
- MSD was evaluated between $Ref_{A,B}$ and remaining cases in each theoretical f_2 and experimental condition

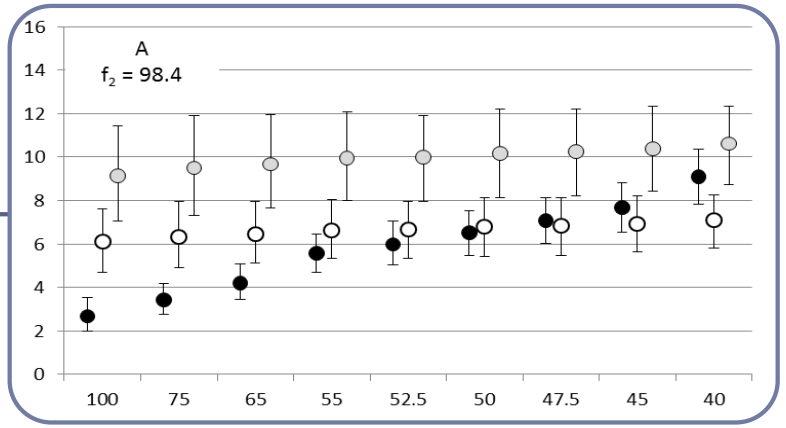
Results EXP 1

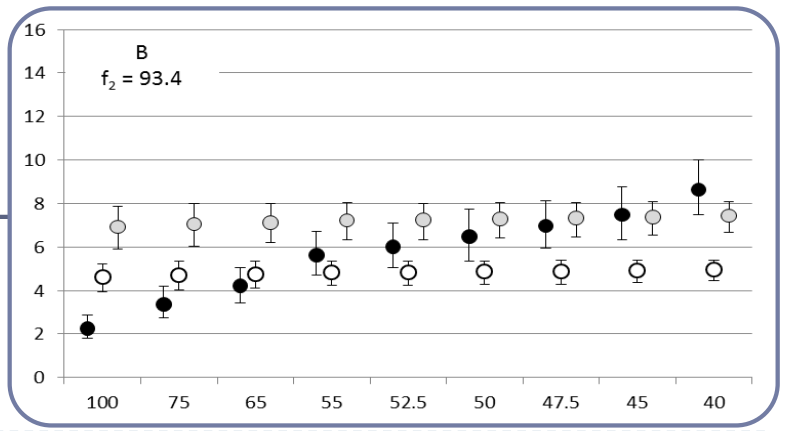
f2



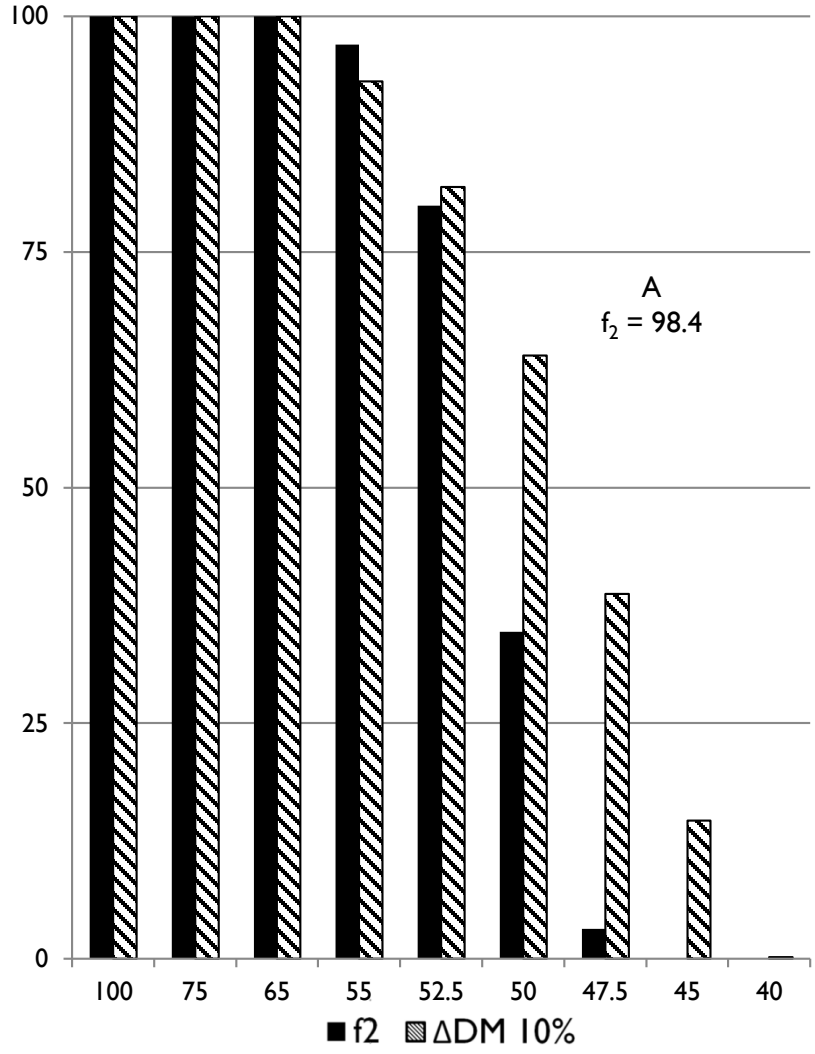


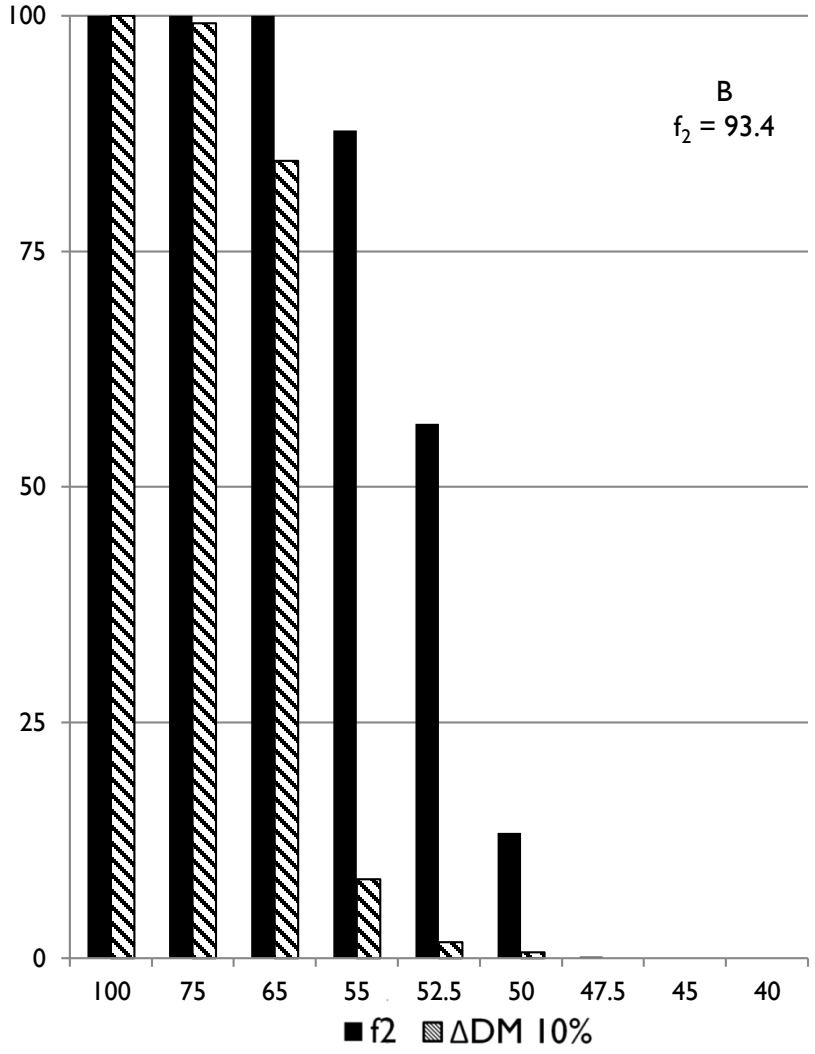
MSD





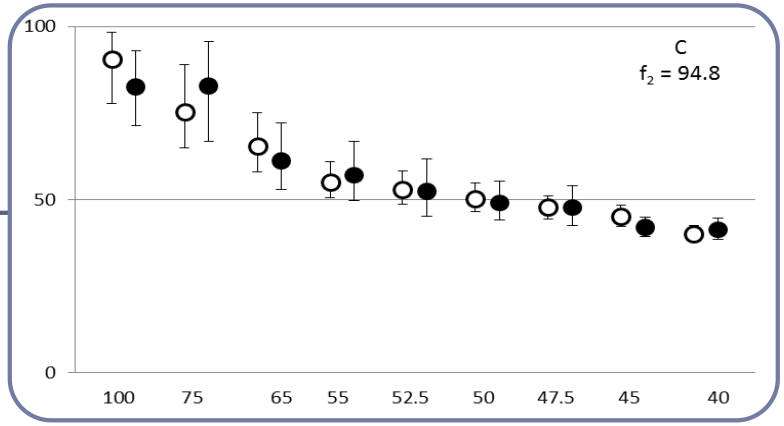
Results EXP 1

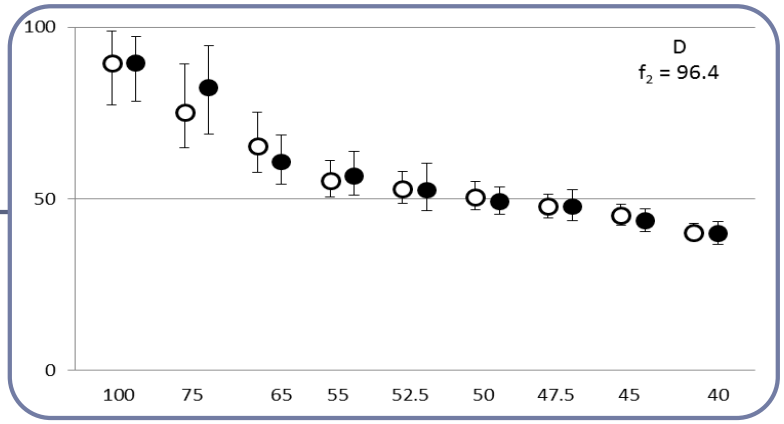




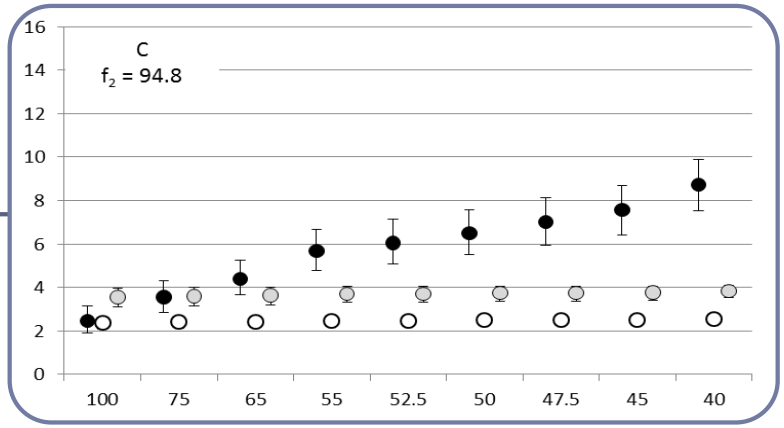
Results EXP 2

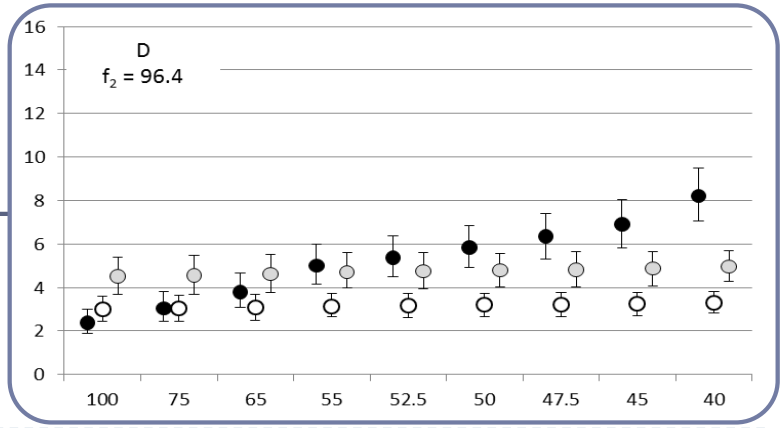
f2



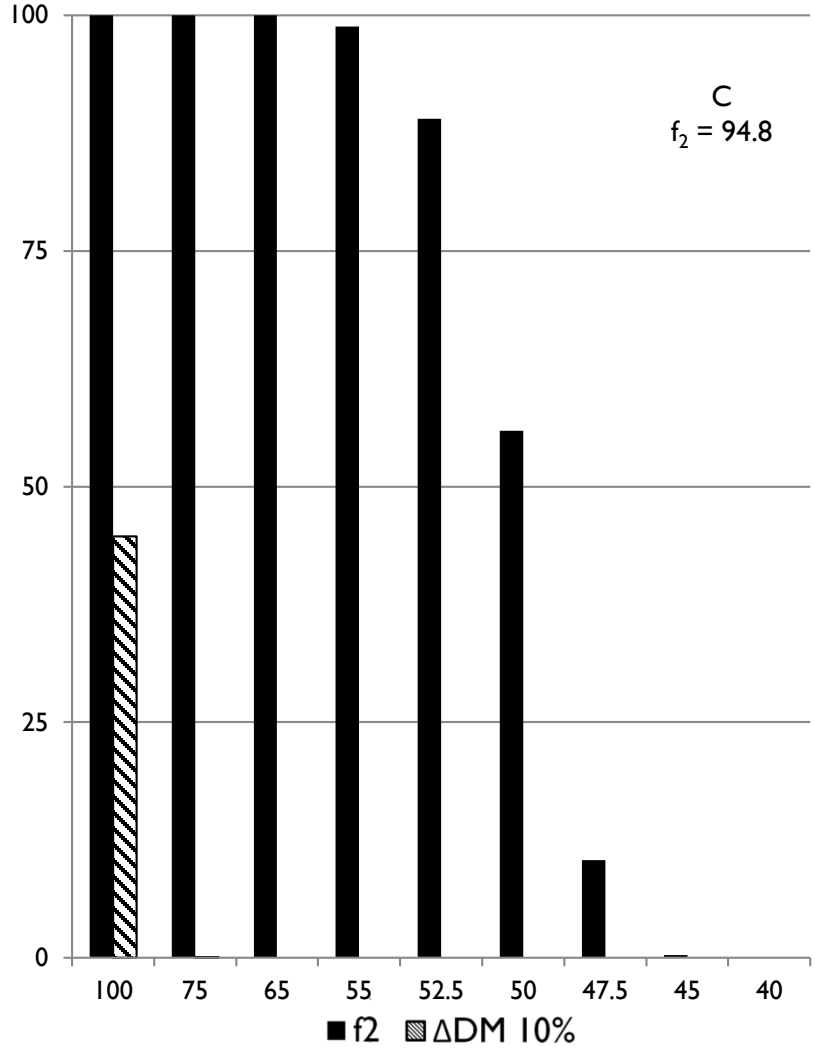


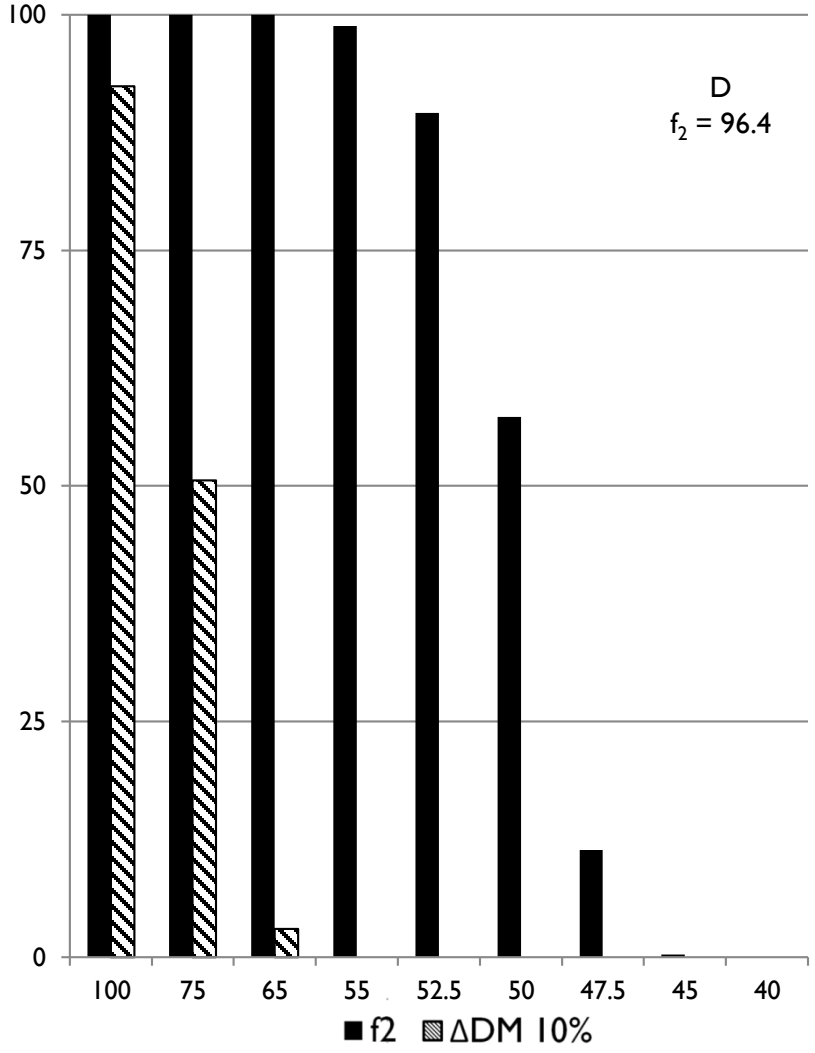
MSD





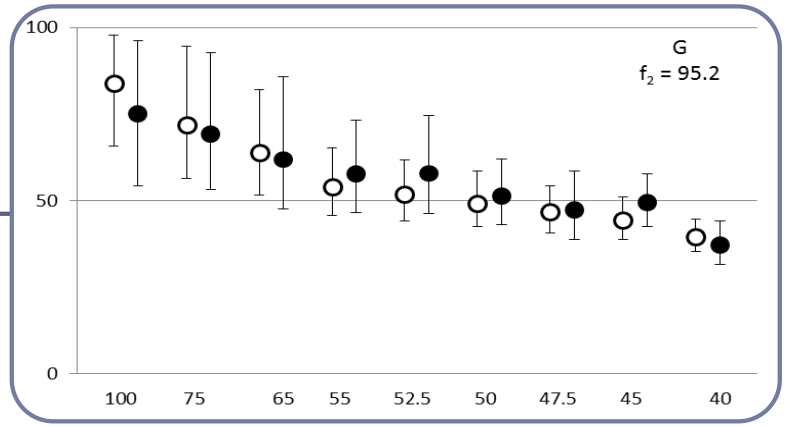
Results EXP 2

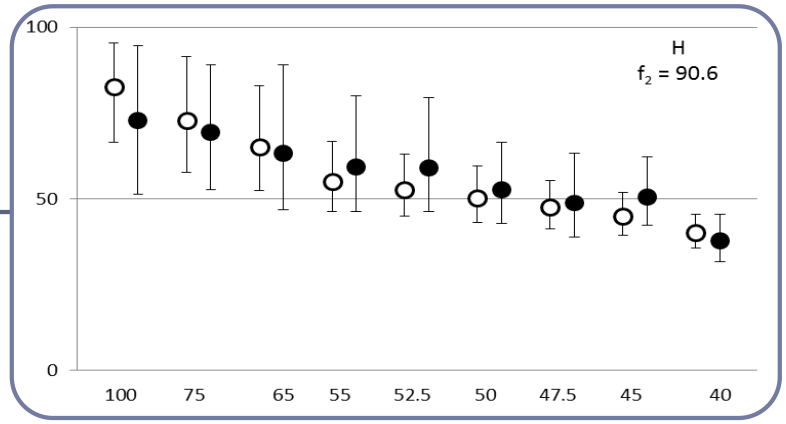




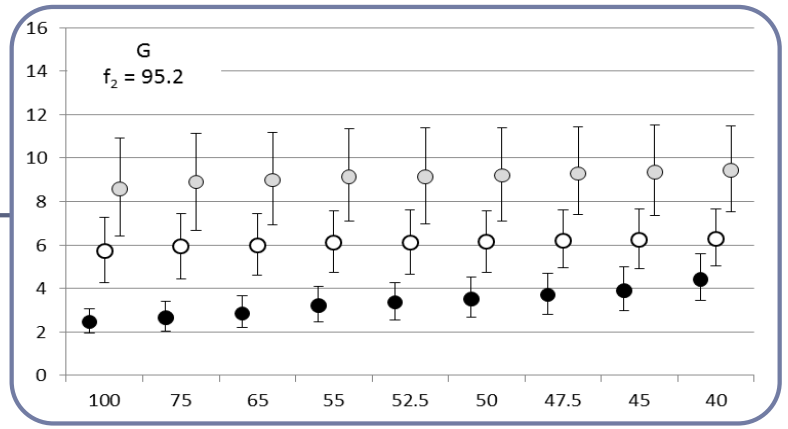
Results EXP 3

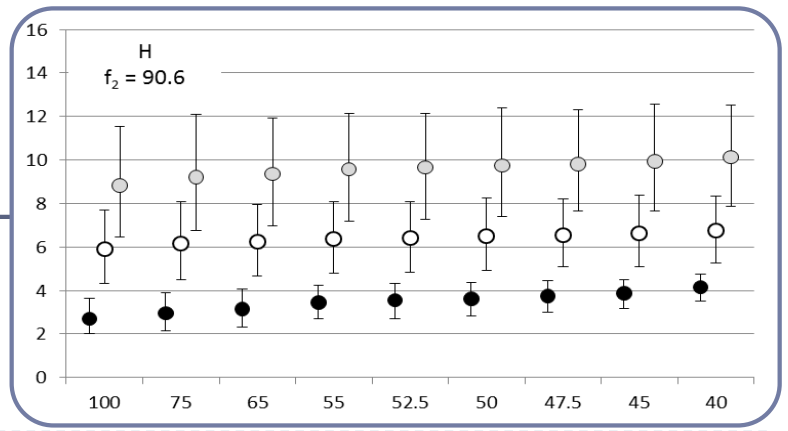
f2



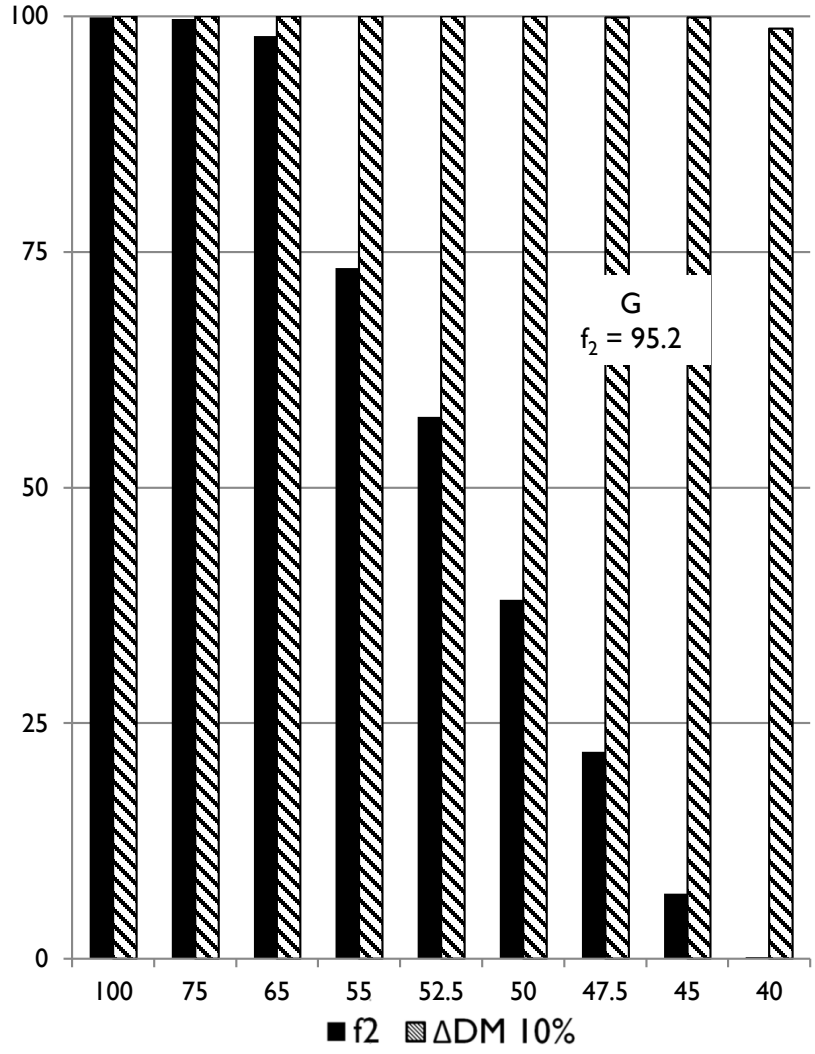


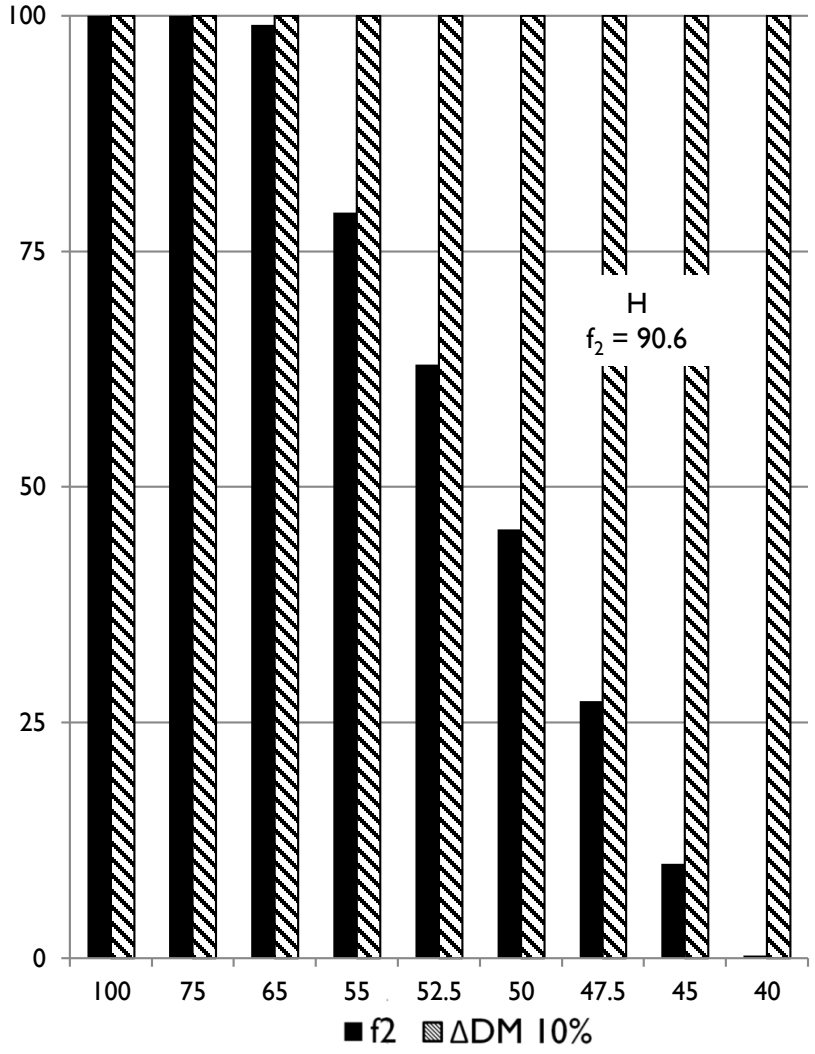
MSD





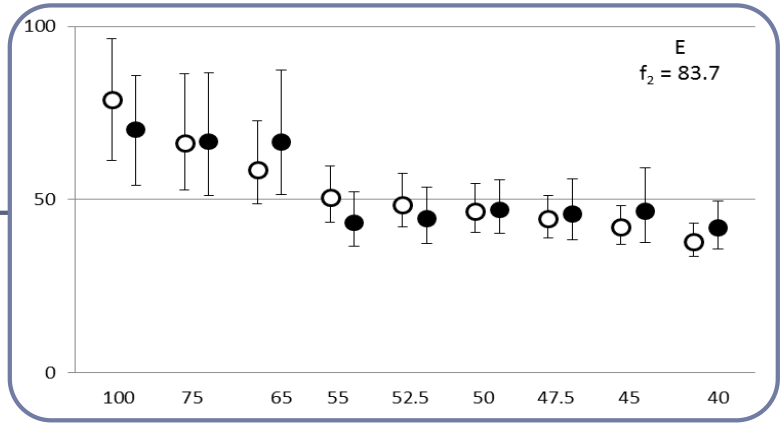
Results EXP 3

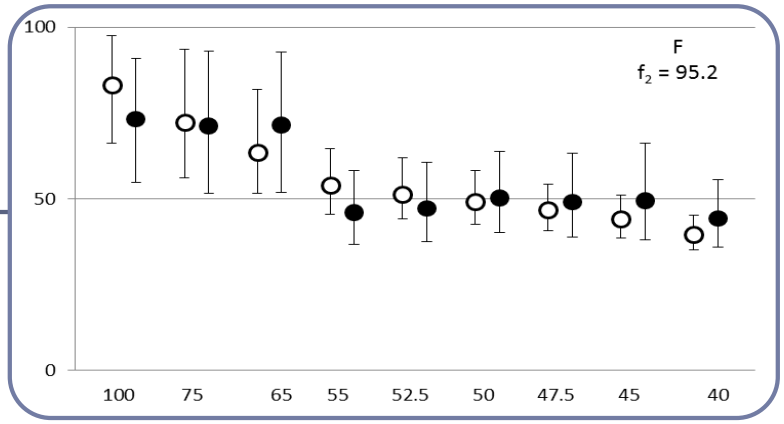




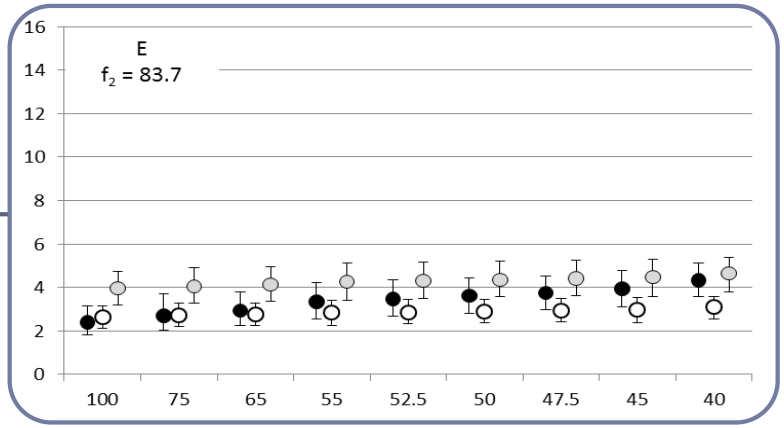
Results EXP 4

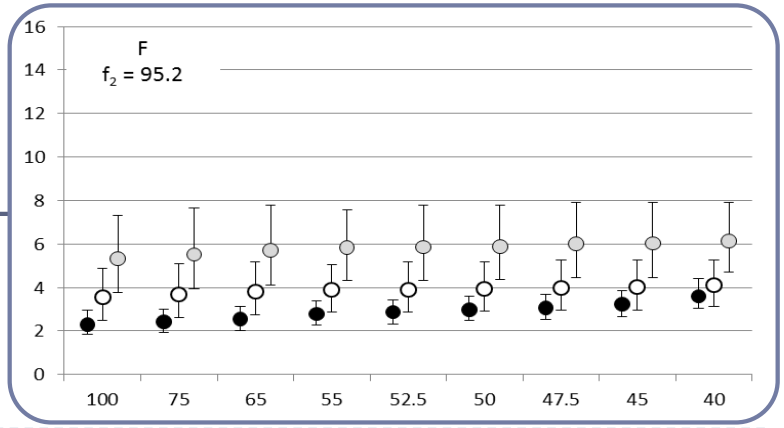
f2



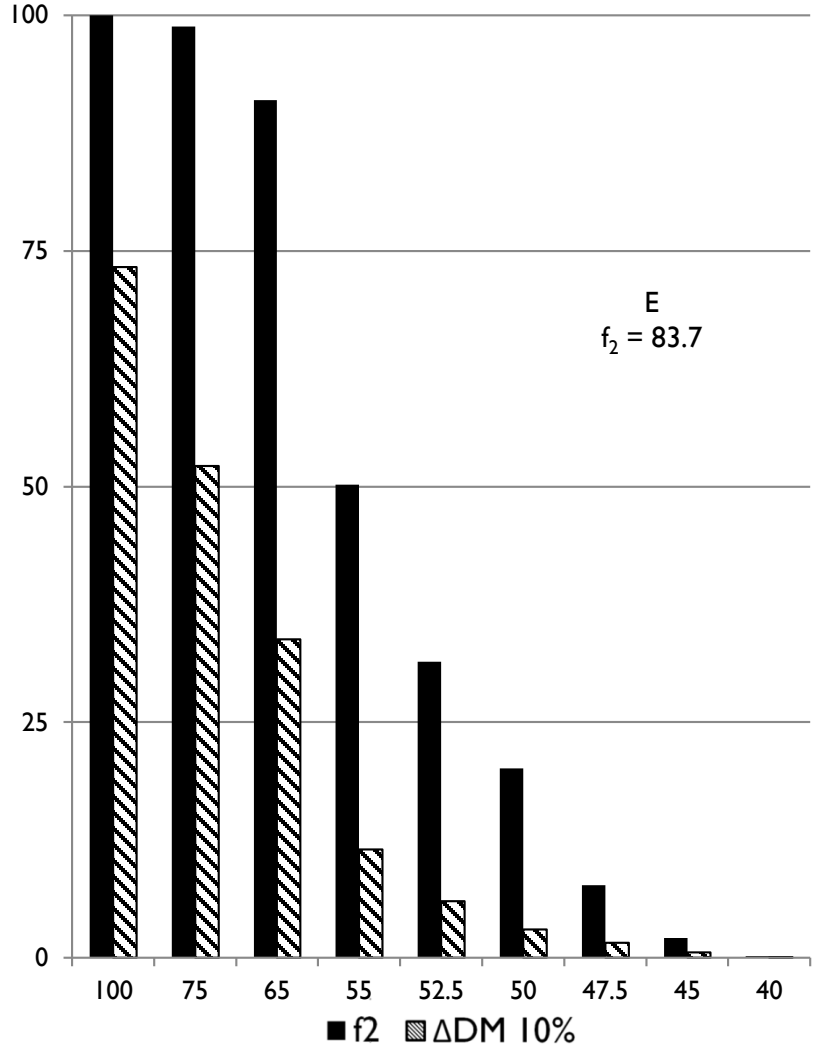


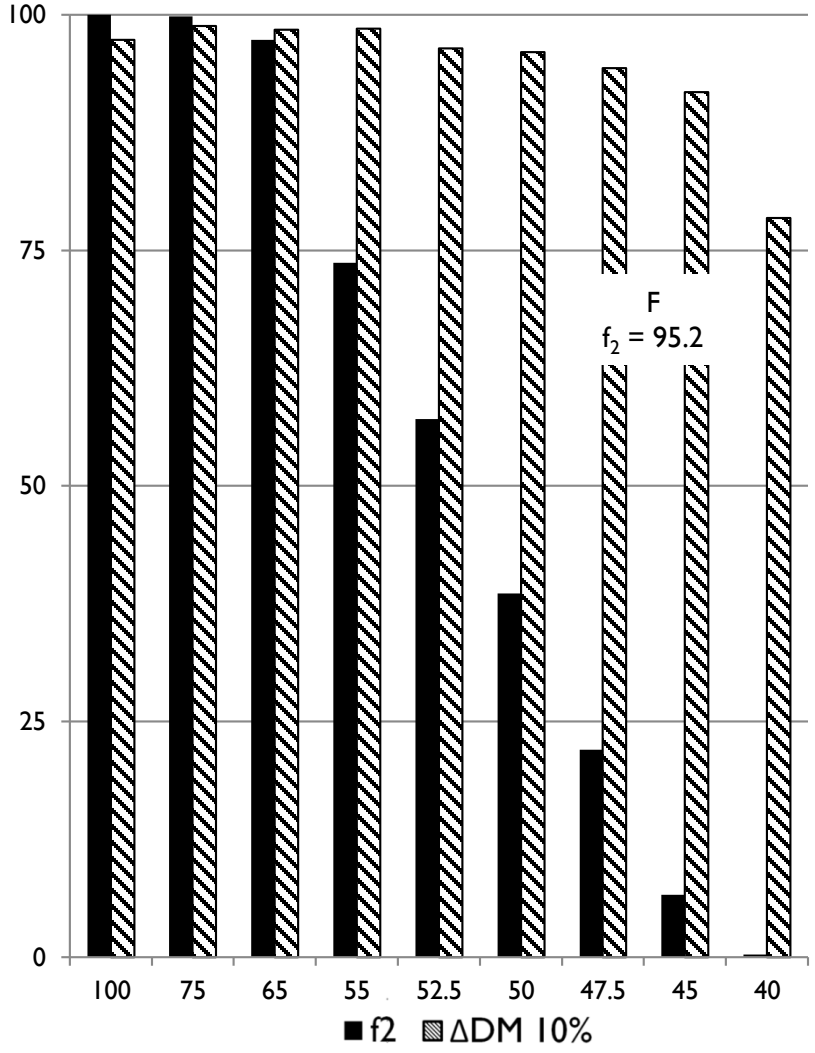
MSD





Results EXP 4





Published works on the matter

European Journal of Pharmaceutics and Biopharmaceutics 112 (2017) 67–74

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Evaluation of dissolution profile similarity – Comparison between the f_2, the multivariate statistical distance and the f_2 bootstrapping methods

Paulo Paixão *, Luís F. Gouveia, Nuno Silva, José A.G. Morais

Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisboa, Portugal

ARTICLE INFO

Article history:
Received 9 August 2016
Revised 3 October 2016
Accepted in revised form 28 October 2016
Available online 17 November 2016

Keywords:
Similarity of dissolution profiles
f_2 metric
Bootstrap f_2 method
Model-independent multivariate statistical distance
Variability in dissolution profiles
Regulatory acceptance of dissolution similarity

ABSTRACT

A simulation study is presented, evaluating the performance of the f_2, the model-independent multivariate statistical distance and the f_2 bootstrap methods in the ability to conclude similarity between two dissolution profiles. Different dissolution profiles, based on the Noyes-Whitney equation and ranging from theoretical f_2 values between 100 and 40, were simulated. Variability was introduced in the dissolution model parameters in an increasing order, ranging from a situation complying with the European guidelines requirements for the use of the f_2 metric to several situations where the f_2 metric could not be used anymore. Results have shown that the f_2 is an acceptable metric when used according to the regulatory requirements, but loses its applicability when variability increases. The multivariate statistical distance presented contradictory results in several of the simulation scenarios, which makes it an unreliable metric for dissolution profile comparisons. The bootstrap f_2, although conservative in its conclusions is an alternative suitable method. Overall, as variability increases, all of the discussed methods reveal problems that can only be solved by increasing the number of dosage form units used in the comparison, which is usually not practical or feasible. Additionally, experimental corrective measures may be undertaken in order to reduce the overall variability, particularly when it is shown that it is mainly due to the dissolution assessment instead of being intrinsic to the dosage form.

The AAPS Journal, Vol. 18, No. 6, November 2016 (© 2016)
DOI: 10.1208/s12248-016-9971-5

Research Article

Assessment of the Regulatory Methods for the Comparison of Highly Variable Dissolution Profiles

Victor Mangas-Sanjuan,[1] Sarin Colon-Useche,[2] Isabel Gonzalez-Alvarez,[1] Marival Bermejo,[1] and Alfredo Garcia-Arieta[3,4]

Received 20 May 2016; accepted 2 August 2016; published online 29 August 2016

Abstract. The objective is to compare the performance of dissolution-profile comparison methods when f_2 is inadequate due to high variability. The 90% confidence region of the Mahalanobis distance and the 90% bootstrap confidence interval (CI) of the f_2 similarity factor (f_2-bootstrap) were explored. A modification of the Mahalanobis distance (new *D*-Mahalanobis) in which those points >85% were not taken into account for calculation was also used. A population kinetic approach in NONMEM was used to simulate dissolution profiles with the first-order or Weibull kinetic models. The scenarios were designed to have clearly similar, clearly non-similar or borderline situations. Four different conditions of variability were established: high (CV = 5%) for inter-tablet (IIV) and inter-batch variability (IBV) associated to the dissolution parameters (k_d or MDT) using an exponential model. Forty-four (44) scenarios were simulated, considering different combinations of IIV, IBV and typical dissolution parameters. The dissolution profiles simulated using a first-order model modified the profile slope. The Weibull model allows profiles with different shapes and asymptotes and crossing each other. The results show that the f_2-bootstrap is the most adequate method in cases of high variability. The method based on the 90% confidence region of the Mahalanobis distance (*D*-Mahalanobis) is not able to detect large differences that can be detected simply with f_2 (*i.e.* low specificity and positive predictive value due to false positives). The new *D*-Mahalanobis exhibits superior sensitivity to detect differences (*i.e.* specificity as a diagnostic test), but it is not as good as the f_2-bootstrap method.

KEY WORDS: dissolution profile comparison; f_2 bootstrap; f_2 similarity factor; *in vitro* dissolution; Mahalanobis distance.

Note

Comparison of Dissolution Similarity Assessment Methods for Products with Large Variations: f_2 Statistics and Model-Independent Multivariate Confidence Region Procedure for Dissolution Profiles of Multiple Oral Products

Hiroyuki Yoshida,*[,a] Hiroko Shibata,[b] Ken-ichi Izutsu,[a] and Yukihiro Goda[a]

[a] *Division of Drugs, National Institute of Health Sciences; 1–18–1 Kamiyoga, Setagaya-ku, Tokyo 158–8501, Japan; and* [b] *Division of Biological Chemistry and Biologicals, National Institute of Health Sciences; 1–18–1 Kamiyoga, Setagaya-ku, Tokyo 158–8501, Japan.*

Received November 21, 2016; accepted February 21, 2017

The current Japanese Ministry of Health Labour and Welfare (MHLW)'s Guideline for Bioequivalence Studies of Generic Products uses averaged dissolution rates for the assessment of dissolution similarity between test and reference formulations. This study clarifies how the application of model-independent multivariate confidence region procedure (Method B), described in the European Medical Agency and U.S. Food and Drug Administration guidelines, affects similarity outcomes obtained empirically from dissolution profiles with large variations in individual dissolution rates. Sixty-one datasets of dissolution profiles for immediate release, oral generic, and corresponding innovator products that showed large variation in individual dissolution rates in generic products were assessed on their similarity by using the f_2 statistics defined in the MHLW guidelines (MHLW f_2 method) and two different Method B procedures, including a bootstrap method applied with f_2 statistics (BS method) and a multivariate analysis method using the Mahalanobis distance (MV method). The MHLW f_2 and BS methods provided similar dissolution similarities between reference and generic products. Although a small difference in the similarity assessment may be due to the decrease in the lower confidence interval for expected f_2 values derived from the large variation in individual dissolution rates, the MV method provided results different from those obtained through MHLW f_2 and BS methods. Analysis of actual dissolution data for products with large individual variations would provide valuable information towards an enhanced understanding of these methods and their possible incorporation in the MHLW guidelines.

Key words dissolution test; generic product; dissolution similarity; f_2 statistic; bootstrap analysis; multivariate ANOVA

Follow-Up Discussions

The AAPS Journal, Vol. 19, No. 4, July 2017 (© 2017)
DOI: 10.1208/s12248-017-0063-y

Research Article

Dissolution comparisons using a Multivariate Statistical Distance (MSD) test and a comparison of various approaches for calculating the measurements of dissolution profile comparison

J-M. Cardot,[1,4] B. Roudier,[2] and H. Schütz[3]

Received 16 November 2016; accepted 20 February 2017; published online 28 March 2017

Abstract. The f_2 test is generally used for comparing dissolution profiles. In cases of high variability, the f_2 test is not applicable, and the Multivariate Statistical Distance (MSD) test is frequently proposed as an alternative by the FDA and EMA. The guidelines provide only general recommendations. MSD tests can be performed either on raw data with or without time as a variable or on parameters of models. In addition, data can be limited—as in the case of the f_2 test—to dissolutions of up to 85% or to all available data. In the context of the present paper, the recommended calculation included all raw dissolution data up to the first point greater than 85% as a variable—without the various times as parameters. The proposed MSD overcomes several drawbacks found in other methods.

KEY WORDS: dissolution; multivariate statistical difference; MSD; Weibull; f_2.

Received: 15 November 2017 | Revised: 16 March 2018 | Accepted: 1 July 2018
DOI: 10.1002/bimj.201700257

RESEARCH PAPER

Biometrical Journal

Equivalence analyses of dissolution profiles with the Mahalanobis distance

Thomas Hoffelder

Global Biostatistics & Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany

Correspondence
Thomas Hoffelder, Global Biostatistics and Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 55216 Ingelheim am Rhein, Germany.
Email: thomas.hoffelder@boehringer-ingelheim.com

Abstract

For some postapproval changes, the manufacturer has to demonstrate that the dissolution profile of the drug product before the change is statistically equivalent to the dissolution profile after the change. Guidelines suggest the so-called similarity factor f_2 as standard approach for the equivalence analysis. f_2 is a statistically questionable transformation of the Euclidean distance between both profile means and does not allow a control of the type I error rate. An alternative multivariate distance measure for quantifying the dissimilarity between both profile groups is the Mahalanobis distance. Current equivalence procedures based on the Mahalanobis distance implicate some practical problems in the dissolution context: either one chooses an exact method but the determination of a product independent equivalence margin will not be practically feasible or one chooses an approximate alternative that suffers from the bias of the Mahalanobis distance point estimate. This paper suggests the T2EQ approach for dissolution profile comparisons. T2EQ is a practically feasible equivalence procedure based on the Mahalanobis distance with an internal equivalence margin for comparing dissolution profiles. The equivalence margin is compliant with current dissolution guidelines. The operating characteristics (size, robustness, and power) are investigated via simulation: T2EQ meets the needs of both authorities and industry: not affected by the bias of the point estimate the type I error rate can be reliably controlled for various distribution assumptions and the power of T2EQ exceeds the power of methods recently discussed in the literature. These results were presented for the first time at CEN-ISBS 2017.

Received: 15 November 2017 | Revised: 5 February 2018 | Accepted: 24 March 2018
DOI: 10.1002/sim.7689

RESEARCH ARTICLE

WILEY Statistics in Medicine

Regulatory assessment of drug dissolution profiles comparability via maximum deviation

Kathrin Moellenhoff[1] | Holger Dette[1] | Evangelos Kotzagiorgis[2] | Stanislas Volgushev[3] | Olivier Collignon[2,4]

[1] Department of Mathematics, Ruhr-Universität Bochum, Bochum 44801, Germany

[2] European Medicines Agency, 30 Churchill Place, Canary Wharf, London E14 5EU, UK

[3] Department of Statistical Sciences, University of Toronto, Toronto, ON M5S, Canada

[4] Competences Center in Methodology and Statistics, Luxembourg Institute of Health, Strassen 1445, Luxembourg

Correspondence
Holger Dette, Department of Mathematics, Ruhr-Universität Bochum, Bochum 44801, Germany.
Email: holger.dette@rub.de

Olivier Collignon, European Medicines Agency, 30 Churchill Place, Canary Wharf London E14 5EU, UK.
Email: olivier.collignon@lih.lu; olivier.collignon@ema.europa.eu

Funding information
European Union Seventh Framework Programme [FP7 20072013], Grant/Award Number: 602552; Deutsche Forschungsgemeinschaft [SFB 823]

In drug development, comparability of dissolution profiles of 2 different formulations is usually assessed using the similarity factor f_2. In practice, the drug dissolution profiles are deemed similar if the f_2 exceeds 50, which occurs when a 10% maximum difference in the mean percentage of the dissolved drug at each time point between test and reference formulation is obtained. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) use of the f_2 is however restricted by a set of validity conditions. If some of these conditions are not satisfied, the f_2 is not considered suitable, and alternative statistical methods are needed. In this article, we propose an inferential framework based on the maximum deviation between curves to test the comparability of drug dissolution profiles. The new methodology is applicable regardless whether the validity criteria of the f_2 are met or not. Contrary to the f_2, this approach also integrates the variability of the measurements over time and not only their average. To benchmark our method, we performed simulations informed by 3 real case studies provided by the European Medicines Agency and extracted from dossiers submitted to the Centralised Procedure for Marketing Authorisation Application. In the scenarios of the simulation study, the new method controlled its type I error rate when the maximum deviation was greater than the similarity acceptance limit of 10%. The power exceeded 80% for small values of the maximum deviation, while the test was more conservative for intermediate ones. Our results were also very robust to sampling variations. Based on these positive findings, we encourage applicants to consider the new maximum deviation–based method as a valid alternative to the f_2, especially when the validity criteria of the latter are not met.

Current EMA position

Question and answer on the adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles

Draft agreed by Biostatistics Working Party	June 2018
Adopted by CHMP	26 July 2018

Keywords	Bioequivalence, dissolution profiles, f2, Mahalanobis distance, biowaiver

The aim of this question-and-answer document is to provide clarification about the suitability of the Mahalanobis distance as a tool to assess the comparability of drug dissolution profiles and to a larger extent to emphasise the importance of confidence intervals to quantify the uncertainty around the point estimate of the chosen metric (e.g. the f2 factor or the Mahalanobis distance).

Conclusions

- f_2 metrics are a convenient way to evaluate the similarity of dissolution profiles
- f_2 metrics are not suitable for data with high variability (as expected)
- MSD is also not suitable for the same conditions
- f_2 Bootstrapping is a convenient way to evaluate similarity in dissolution profiles with high variability
- Current Regulatory view proposes the use of f_2 Bootstrapping for high variability conditions.

Thank you

Paulo Paixão
Faculdade de Farmácia, Univ. Lisboa
ppaixao@ff.ulisboa.pt