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Defining level A IVIVC dissolution specifications based on individual *in vitro* dissolution profiles of a controlled release formulation

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ABSTRACT

Regulatory guidelines recommend that, when a level A IVIVC is established, dissolution specification should be established using averaged data and the maximum difference between AUC and C_{max} between the reference and test formulations cannot be greater than 20%. However, averaging data assumes a loss of information and may reflect a bias in the results. The objective of the current work is to present a new approach to establish dissolution specifications using a new methodology (individual approach) instead of average data (classical approach). Different scenarios were established based on the relationship between *in vitro-in vivo* dissolution rate coefficient using a level A IVIVC of a controlled release formulation. Then, in order to compare this new approach with the classical one, six additional batches were simulated. For each batch, 1000 simulations of a dissolution assay were run. C_{max} ratios between the reference formulation and each batch were calculated showing that the individual approach was more sensitive and able to detect differences between the reference and the batch formulation compared to the classical approach. Additionally, the new methodology displays wider dissolution specification limits than the classical approach, ensuring that any tablet from the new batch would generate *in vivo* profiles which its AUC or C_{max} ratio will be out of the 0.8–1.25 range, taking into account the *in vitro* and *in vivo* variability of the new batches developed.

1. Introduction

Bioequivalence (BE) concepts have evolved during the last decades globally, allowing the authorization of changes during the development process, variations or post-approval changes, and line extensions of brand-name products and generic products. Bioavailability, measured as maximum plasma concentration (C_{max}), area under the curve (AUC), and time to maximum plasma concentration (t_{max}), is used as a surrogate to demonstrate equivalent biopharmaceutical quality between the test and the reference product [1, 2].

Regulatory authorities have set predefined regulatory requirements for bioequivalence studies and for waiving *in vivo* BE studies using *in vitro* dissolution data (*e.g.*, BCS-based biowaiver and *in vitro-in vivo* correlation (IVIVC)-based biowaivers). In general, for low solubility drug substances where dissolution is the rate limiting step for bioavailability, the possibility of establishing a correlation between *in vitro* dissolution and *in vivo* absorption can be expected (Limberg and Potthast, 2013). An IVIVC is a mathematical model that defines the relationship between the *in vitro* dissolution data and the *in vivo* performance of drug product. The establishment of an IVIVC offers several advantages during the drug development process (Cook, 2012). One of the most relevant uses of the IVIVC is as a surrogate for human bioavailability studies to reduce the number of BE studies needed during the development process and later for post-approval changes (Chowdhury and Islam, 2011; Limberg and Potthast, 2013). Four levels of correlation (A, B, C, and D) have been described based on the predictive

Nonstandard abbreviations: AUC, area under the curve; BE, bioequivalence; CI, confidence interval; CL, clearance; C_{max}, maximum plasma concentration; CR, controlled release; CV, coefficient of variation; f_2, similarity factor; FTFF, the fastest tablet of the fastest dissolving formulation; k_a, *in vivo* absorption rate coefficient; k_d, *in vitro* or *in vivo* dissolution rate coefficient; IIV, inter-individual variability; IVIVC, *in vitro-in vivo* correlation; PK, pharmacokinetic; RUV, residual unexplained variability; STSF, the slowest tablet of the slowest dissolving formulation; t_{max}, time to maximum plasma concentration; V_c, apparent central volume of distribution

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capability of the *in vitro* dissolution profiles to reflect the *in vivo* behavior. However, only a level A IVIVC represents a point-to-point relationship that can be used as a surrogate of *in vivo* studies for regulatory purposes (Chowdhury and Islam, 2011; FDA, 1997; Uppoor, 2001). This IVIVC could also be used to establish the dissolution specifications that guarantee BE (EMA, 2014a; FDA, 1997). Once an IVIVC is developed, dissolution specifications will ensure the safe space of *in vitro* dissolution data that guarantees *in vivo* BE according to the observed *in vitro/in vivo* variability.

Regulatory guidelines (EMA, 2014b; FDA, 1997) define different ways to calculate these dissolution specifications depending on the level of the IVIVC:

- No IVIVC. Any time point should not be greater than ± 10% of the mean profile.
- Level A IVIVC. Specifications should be established based on average data, where the maximum difference allowed in the predicted AUC and C_{max} is 20%.
- Multiple Level C IVIVC. The maximum difference in the predicted AUC and C_{max} should not exceed ± 20% from the mean dissolution profile obtained from the clinical/bioavailability batches (where the last time point should be at least 80% of drug dissolved).
- Single Level C IVIVC. Not more than a 20% difference in the predicted AUC and C_{max} is allowed at the time point used. At other time points, maximum recommended range should be ± 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability batches.

The Dissolution Analytical Working group of the IQ Consortium also put forward another two approaches (Hermans et al., 2017):

- A clinically established "safe space" for dissolution can be established when formulation/process variants demonstrate acceptable PK performance, but the dissolution method can discriminate those variants.
- *In silico* IVIVe (*in vitro - in vivo* extrapolation). The link between the *in vivo* dissolution and the observed pharmacokinetic response is established *via* the use of a physiologically based absorption/pharmacokinetic model, and the model is used to identify dissolution profiles that are projected to ensure the desired clinical performance.

According to the above-mentioned requirements, dissolution specifications are established based on the mean *in vitro* dissolution profile and all batches whose *in vivo* simulated profiles are within ± 20% in C_{max} and AUC will be considered bioequivalent. However, there is evidence suggesting that the use of mean profiles instead of individual information could lead to a biased analysis and less accurate predictions (Cardot and Davit, 2012; Gaynor et al., 2009; González-García et al., 2017; Roudier et al., 2014). This issue is of special relevance for IVIVC-based biowaived batches where some individual profiles within the same batch could overcome the ± 20% difference boundary in the predicted *in vivo* C_{max} and AUC parameters.

Therefore, the purpose of this work is to compare the classical approach (the use of mean data) with a new methodology in which we have used individual data in order to assess the probability of declaring bioequivalence for a new batch based on an IVIVC of a controlled release (CR) formulation. Furthermore, we have evaluated the impact of these two different methodologies on the establishment of dissolution specifications.

2. Material and methods

2.1. IVIVC development

Slow, medium, and fast dissolving drug formulations were used to develop the IVIVC. Dissolution data sets were generated for 12 units (*e.g.* tablets) based on a first-order dissolution model (Gibaldi and Feldman, 1967) and forced to show a similarity factor (f_2) below 50 between the medium and fast/slow formulation.

A level A IVIVC using differential equations (Rossenu et al., 2008) was established using these three drug formulations, where the link between *in vitro* and *in vivo* performance of the drug products was related between *in vitro* and *in vivo* dissolution rate coefficients (k_d). It was assumed that the dissolution process was the rate limiting step of *in vivo* absorption and bioavailability, where the k_d of each formulation was lower compared to the absorption rate coefficient (k_a). Two types of scenarios were drawn:

- Linear relationship between $k_{d,\ in\ vitro}$ and $k_{d,\ in\ vivo}$ (Scenarios 1, 2, 3)
- Non-linear relationship between $k_{d,\ in\ vitro}$ and $k_{d,\ in\ vivo}$ based on a sigmoid function (Scenarios 4, 5, 6)

In vitro individual data for each formulation were simulated randomly, using inter-individual variability (IIV) on k_d through an exponential model. Residual unexplained variability (RUV) on the *in vitro* dissolved fractions was also considered.

Plasma profiles were generated using a one compartment model with first order dissolution, absorption, and elimination kinetics. Twelve individual units were considered for each formulation or batch. IIV on pharmacokinetic parameters was not included in order to avoid any influence on the dissolution performance of drug formulation or batch. *In vitro* dissolution and *in vivo* pharmacokinetic parameters used in the establishment of the level A IVIVC were the same in both linear and non-linear relationships, but the link equation parameters were different. Study design characteristics and parameters used in the development of the level A IVIVC are summarized in Table 1.

2.2. Batch suitability

Once the level A IVIVC was established, in order to assess the impact of the different mathematical approaches on concluding BE of a new batch, six additional batches (12 units each) were simulated following the same dissolution model according to the following rules: (i) three new batches with different k_d among them, but within the range of medium and slow formulations (Batch 1, 3, and 5), and (ii) three new batches with different k_d among them, but within the range of medium

Table 1
Parameters used in establishment of the level A IVIVC.

Study design characteristics		
	In vitro	*In vivo*
Sampling times (h)	0, 0.083, 0.167, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 28, 32, 48	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 24, 28, 32, 48
No. of individuals	12	12

Study design parameters		
Parameter	Value	IIV (%)
k_d (slow formulation) (h^{-1})	0.1	5
k_d (medium formulation) (h^{-1})	0.3	5
k_d (fast formulation) (h^{-1})	0.8	5
K_a (h^{-1})	1.13	0
V_c (L)	1	0
CL (L/h)	0.08	0
In vitro RUV (%)	1	–
In vivo RUV (%)	3	–

CL, clearance; h, hours; k_a, *in vivo* absorption rate coefficient; k_d: *in vitro* dissolution rate coefficient; IIV, inter-individual variability; L, liters; RUV, residual unexplained variability; V_c, central volume of distribution.

and fast formulations (Batch 2, 4, and 6) from the developed IVIVC.

For each batch, simulation (n = 1000) of a dissolution assay with 12 units was generated through the Monte Carlo simulation approach. With the aim of clarifying the conclusions, we assumed complete absorption of the dosage form. Thus, dissolution performance of each batch was assessed on C_{max} only. Twelve thousand *in vitro* dissolution profiles per batch were obtained. Then, using the IVIVC link, *in vivo* time course profiles were calculated as follows:

1. *Classical approach*: 1000 C_{max} ratios of the batch formulation and reference were obtained from the mean 1000 *in vivo* profiles using 1000 mean *in vitro* dissolution profiles.
2. *Individual approach*: 12,000 *in vivo* profiles from the 12,000 *in vitro* dissolution profiles were generated. Then, according to rules i) and ii), the slowest tablet of the slowest dissolving formulation (STSF) or the fastest tablet of the fastest dissolving formulation (FTFF) for each dissolution assay (n = 1000) were selected. If the k_d of the new batch was within the range of medium and fast formulation the FTFF was selected, otherwise the STSF was chosen. Thus, 1000 ratios from the mean C_{max} of the reference formulation and the C_{max} of the STSF or FTFF tablet were determined.

The percentage of BE batches was computed for each approach. BE of a new batch was concluded when the C_{max} ratio between new batch formulations and the reference was within ± 20%.

2.3. Dissolution specification

For the classical approach (using mean data), *in vitro* dissolution limits of each formulation were computed using the batch whose ratio was the closest to ± 20%. On the other hand, using the individual approach, the STSF and FTFF whose ratio was exactly (to four significant digits) ± 20% were selected in order to establish the *in vitro* dissolution specifications.

2.4. Bioequivalence studies

In order to assess the influence of the two methodologies used, and to establish dissolution specification that would guarantee that all dissolved units from the new batch will be BE (its AUC or C_{max} ratio will be within of the 0.8–1.25 range), Monte Carlo simulations (n = 1000) of crossover BE studies with 24 healthy simulated subjects per study were performed. Each simulated subject received an oral dose of 100 mg of the test and reference formulations, with a wash-out period between the administrations. Samples were collected at 0, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16 h after a single dose administration of the drug. The simulated subjects were distributed into two sequence-groups of 12 volunteers each.

In vitro k_d of the test formulation ranged within the k_d values of the STSF and FTFF that previously set the dissolution specifications. Moderate (30%) intra-individual variability was applied to pharmacokinetic parameters in order to generate different conditions to allow the assessment of *in vivo* performance of the drug formulation: i) 30% intra-individual variability on k_a; ii) 30% intra-individual variability on clearance (CL); iii) 30% intra-individual variability on k_a and CL.

2.5. Software

The simulations were performed using NONMEM 7.3 (Bauer, 2011). Graphical and statistical analyses were performed using R software (http://cran. r-project.org, version 3.3.2) and RStudio® (version 1.0.136).

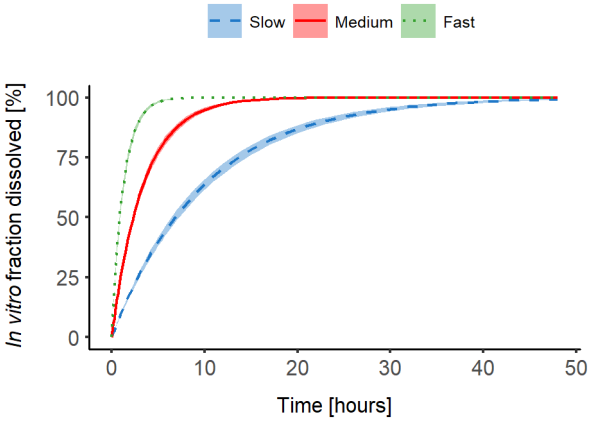

Fig. 1. Mean *in vitro* profiles for IVIVC formulations.

3. Results

3.1. IVIVC development

Mean *in vitro* dissolved fraction *versus* time from the three formulations (fast, medium, and slow) are depicted in Fig. 1. Plasma concentrations were calculated using the *in vitro* dissolved fraction and according to the linear (Scenarios 1–3) or non-linear (Scenarios 4–6) IVIVC link model. Fig. 2 represents the mean *in vivo* profiles for each type of formulation included in the development of the IVIVC. Table 2 includes the 90% confidence interval (CI) for C_{max} demonstrating that neither the slow nor the fast formulation were BE to the medium

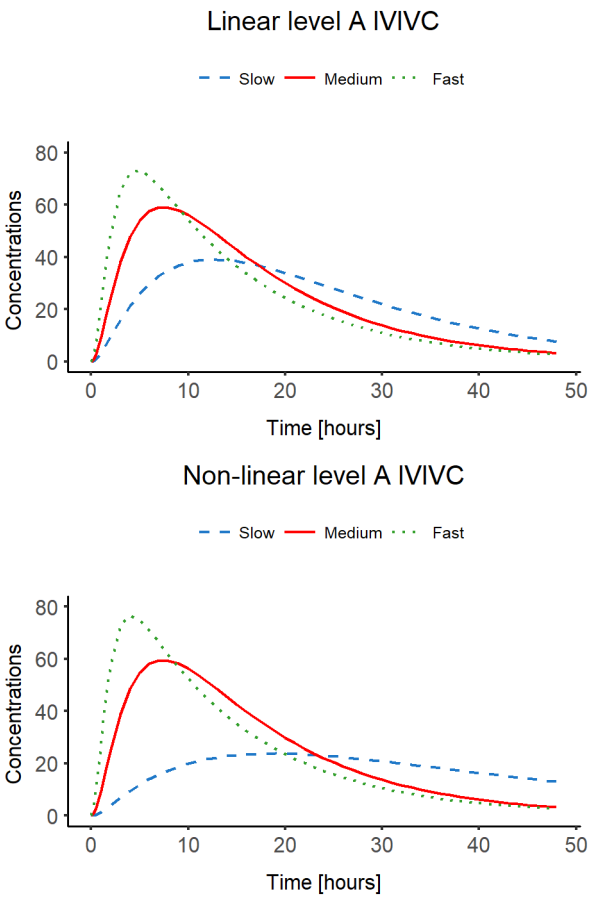

Fig. 2. Plasma *in vivo* profiles obtained through IVIVC link (top linear IVIVC, bottom non-linear IVIVC).

Table 2
90% CI for the BE studies performed comparing slow-medium and fast-medium formulations used in the establishment of the level A IVIVC.

Formulations	Linear level A IVIVC	Non-linear level A IVIVC
Slow formulation	63.52%–68.87%	38.07%–40.70%
Fast formulation	120.68–129.04%	127.84%–129.59%

formulation.

3.2. Batch suitability

Fig. 3 represents the mean *in vivo* PK profile obtained from the mean *in vitro* dissolution profile for the reference formulation and the six batches considered. The C_{max} ratio between each batch and the reference formulation from the mean *in vivo* PK profile are summarized in Table 3, showing that all batches were within the regulatory threshold of ± 20% for both types of level A IVIVC. One thousand simulations were performed using the mean *in vitro* dissolution profile (classical approach) and the STSF/FTFF (individual approach). Fig. 4 depicts the *in vivo* PK profiles of the reference and the six batches according to the classical and individual approaches obtained from the linear and non-linear IVIVC developed. When the classical approach was applied, 1000 time-course *in vivo* profiles were obtained from the mean *in vitro* dissolution profile of each dissolution assay (12 units) simulated (n = 1000). Otherwise, the individual approach was allowed to generate 1000 PK profiles from the slowest/fastest unit (STSF/FTFF) of each dissolution assay simulated (n = 1000). Fig. 5 shows the results of

Table 3
C_{max} ratios obtained between the reference formulation used in the development of a level A IVIVC and the six new batches simulated (Batch 1–6).

	C_{max} ratios	
	Linear level A IVIVC	Non-linear level A IVIVC
Batch 1/reference formulation	82.6%	80.8%
Batch 2/reference formulation	118%	118%
Batch 3/reference formulation	86.1%	86.0%
Batch 4/reference formulation	113%	115%
Batch 5/reference formulation	92.0%	88.4%
Batch 6/reference formulation	108%	107%

the number of suitable batches (within ± 20%) using the classical and individual approach. According to the results from the classical approach, the C_{max} ratio from the six batches fulfill the ± 20% range under linear level A IVIVC. Similar results were observed for Batches 2–6 when non-linear level A IVIVC was developed, but only 78.6% of the simulations with Batch 1 achieved a C_{max} ratio within the ± 20% difference (Fig. 5). However, when the individual approach was applied under linear level A IVIVC, a significant number of simulations with Batches 1 and 2 were outside of the ± 20% limits: 53.3 and 58.1%, respectively. Greater differences between the classical and individual approaches were observed for the non-linear relationship (scenarios 4–6), where the suitable number of batches of Batch 1 and 2 diminished to 0.3 and 15.5%, respectively. Additionally, 23.1% of the simulations with Batch 3 resulted in a C_{max} ratio greater than ± 20% compared to the reference formulation. The dissolution performance of Batch 3 was

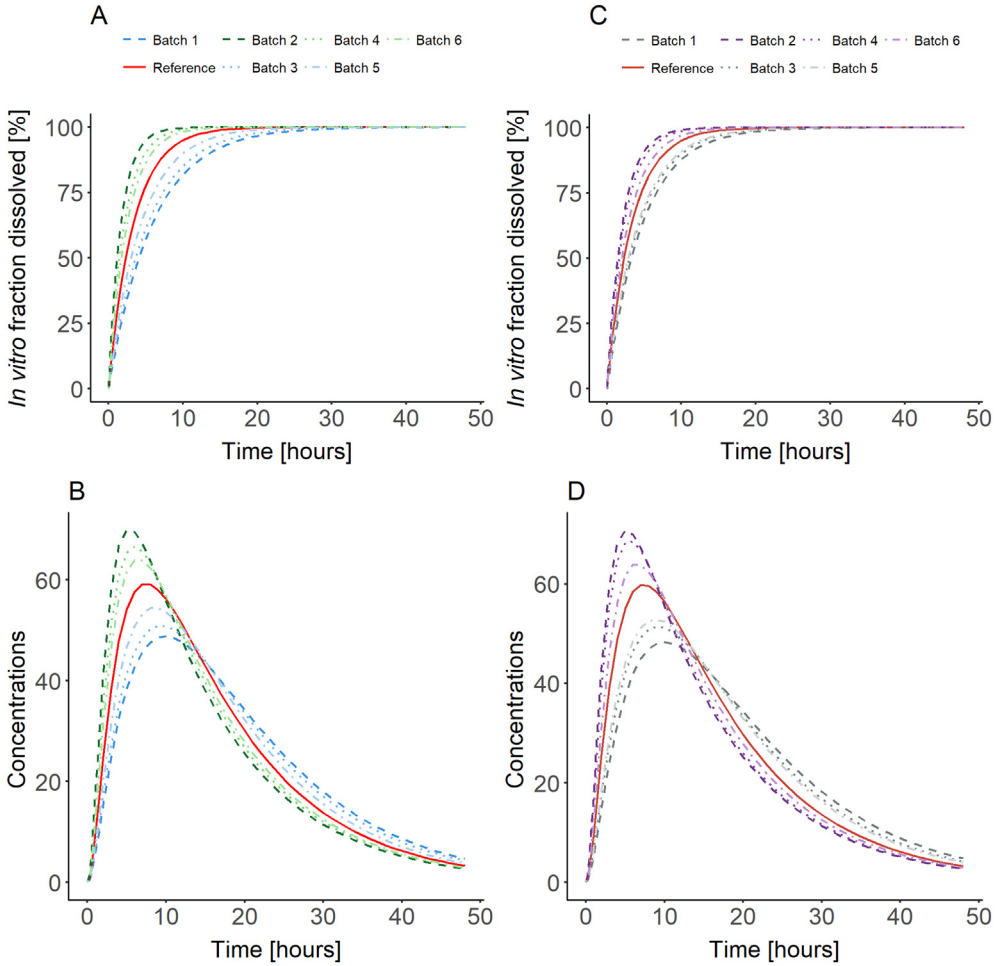

Fig. 3. Mean *in vitro* (top) and *in vivo* (bottom) profiles of the new batches (left linear scenarios, right non-linear scenarios).

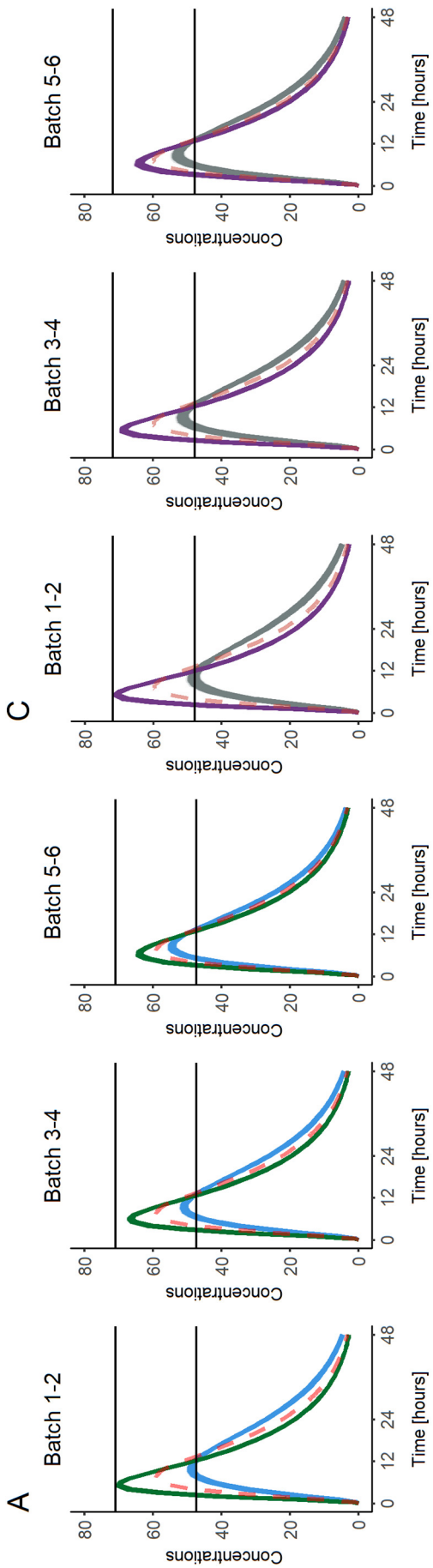

Fig. 4. *In vivo* plasma profiles obtained using a linear and non-linear level A IVIVC models when the classical and individual approaches were applied, where A represents linear IVIVC and classical approach, B represents linear IVIVC and individual approach, C represents non-linear IVIVC and classical approach, and D represents non-linear IVIVC and individual approach. Blue/grey (linear/non-linear) dashed areas represent batch 1 (left), batch 3 (middle), and batch 5 (right), respectively; red solid line represents the reference formulation; green/purple (linear/non-linear) dotted areas represent batch 2 (left), batch 4 (middle) and batch 6 (right), respectively. Horizontal lines represent the acceptance interval of 80.00–125.00%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

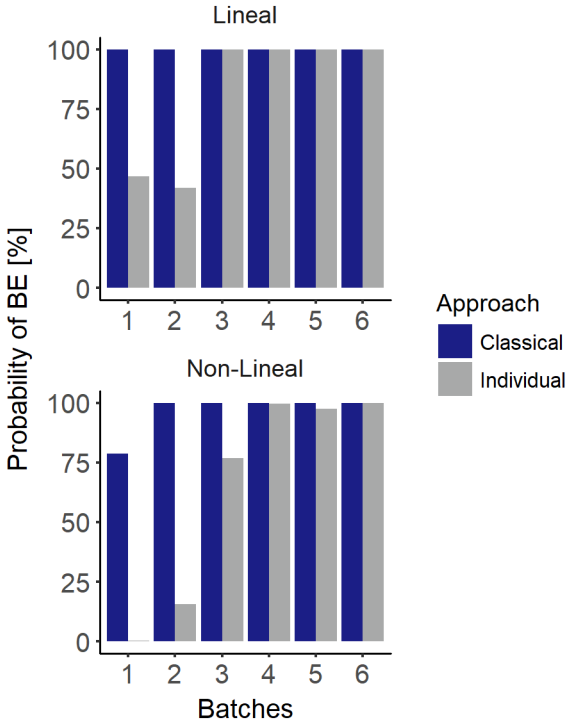

Fig. 5. Suitable batches calculated by the classical and individual approach based on Monte Carlo simulations of a cross-over BE study (n = 1000).

more similar to the reference formulation than Batches 1 and 2, but differences were not detected when the classical approach was applied.

3.3. Dissolution specification

The batches whose C_{max} ratios were closest to ± 20% (Batches 1 and 2) were used to establish the dissolution limit specifications (Table 4). The classical approach provides narrower specification limits because it is established based on the mean *in vitro* dissolution profile that is closest to ± 20%, whereas the individual approach provides the dissolution specification limits that exactly achieved ± 20% difference on C_{max} between reference and new batch.

3.4. Bioequivalence studies

One thousand Monte Carlo simulations were generated using linear and non-linear IVIVC models and according to the different scenarios of *in vivo* variability in k_a and/or CL mentioned above. Based on the dissolution limits previously established using the individual approach proposed in this article, 100% of the 90% CI of C_{max} estimated between the reference formulation and the new batch simulated were within the 0.8–1.25 limits when linear and non-linear IVIVC models were applied. These results confirmed dissolution specification limits would guarantee bioequivalent units within the batch when 30% of intra-individual variability on PK and *in vitro* dissolution parameters were accounted for, even in the worst *in vivo* case scenario (30% in k_a and CL).

Table 4
Dissolution specifications for the different methodologies.

	Dissolved [%]	Classical approach [min]	Individual approach [min]
Linear level A IVIVC	25	30–120	30–120
	50	75–270	60–300
	85	165–780	165–840
Non-linear level A IVIVC	25	30–90	30–90
	50	90–210	75–225
	85	210–600	195–600

4. Discussion

In this paper a new methodology based on an individual approach has been proposed and successfully applied to establish dissolution specifications from a level A IVIVC, which was developed using a one-stage method. It considers the *in vitro* and *in vivo* variability of batches and, as a consequence, it displays wider dissolution specification limits than the classical approach, ensuring that any tablet from the new batch would generate *in vivo* profiles which its C_{max} ratio will out of the 0.8–1.25 range. The widening of the dissolution specification limits could be accomplished because individual data is used instead of average data. The use of the classical approach, which assumes a maximal difference of 20% in the predicted AUC and C_{max} using average data, might result in considering non-BE units within the batch as BE. Averaging data implies loss of information and use of the geometric mean might not be an adequate approach due to extreme values (Cardot and Davit, 2012). For these reasons, this new approach makes use of the individual data to ensure BE for all tablets.

When comparing the linear and non-linear relationship between the *in vitro* and *in vivo* dissolution, it is observed that non-linear conditions narrow the dissolution specification limits. Nonetheless, 100% of the Monte Carlo simulations achieved a BE conclusion, even in the non-linear scenario when 30% intra-individual variability in k_a and CL was considered. The aforementioned highlights the shortcomings of the current methods that are employed to define the dissolution specification limits based on IVIVC, mostly when there is non-linearity between *in vitro* and *in vivo* dissolution or when the IIV is relevant.

The current constraint regarding the use of average data in the establishment of dissolution specifications has been highlighted in this analysis (Fig. 5), showing the regulatory and clinical implications of declaring BE batches that contain non-BE units. Based on the most different batches (Batch 1 and Batch 2), only 46.7% (Batch 1) and 41.9% (Batch 2) of the simulated batches in the linear level A IVIVC were declared BE compared to 100% simulated batches using the classical approach. These differences between the classical and the individual approach largely increase when a non-linear level A IVIVC is developed. On the other hand, when batches similar to the reference formulation are developed (Batches 3–5), the individual approach achieved equal results to the classical approach. This demonstrates the new methodology proposed is more restrictive and accurate to declare BE of a new batch based on a level A IVIVC.

As a limitation of the present work, the simulated conditions and scenarios are empirical and not related to any specific drug. However, the drug product conditions employed assumed a BCS class II drug, where the *in vivo* dissolution was the rate limiting step of *in vivo* absorption and bioavailability due to the high dependency of the drug product on the drug solubility, formulation factors, and *in vivo* luminal environment (Gonzalez-Garcia et al., 2015). All these elements provide the ideal basis for the development of an IVIVC (Balan et al., 2000; Corrigan et al., 2003; Ghosh et al., 2008; Honorio Tda et al., 2013; Ilic et al., 2014; Jantratid et al., 2009; Kovacevic et al., 2009; Lue et al., 2008; Macha et al., 2009; Okumu et al., 2008, 2009; Ostrowski et al., 2010; Rossi et al., 2011; Saibi et al., 2012; Shono et al., 2009; Sunesen et al., 2005; Tashtoush et al., 2004; Veng-Pedersen et al., 2000; Wei and Lobenberg, 2006). *In vivo* variability on PK parameters was not considered during the development of both level A IVIVCs in order to only assess the influence of dissolution variability on the establishment of dissolution specifications, as IIV on PK parameters would have impacted equally to the methodologies compared. More complex *in vitro* dissolution models (Abuhelwa et al., 2016; Locher et al., 2016; Ramteke et al., 2016; Weiss et al., 2014) have not been included in the current analysis in order to simply compare the predictability of both methodologies, but future analyses should incorporate them in order to

account for complex dissolution kinetics. On the other hand, the analysis included only the assessment of dissolution performance on C_{max} because we assumed complete absorption of the dosage form and, therefore, no differences in AUC would be expected. Additionally, moderate *in vivo* variability was considered in k_a and/or CL in order to reflect real conditions of a BE study. The influence of higher and lower *in vivo* variability on PK parameters was not assessed to reduce the number of simulated scenarios.

The establishment of an IVIVC offers several advantages during the drug development process (Cook, 2012), with one of the most relevant uses of the IVIVC being a surrogate for BE studies due to post-approval changes (Chowdhury and Islam, 2011; Limberg and Potthast, 2013). As described in the guidelines (EMA, 2012; FDA, 1997), a level A IVIVC is established by i) a two-stage procedure, where the *in vivo* absorption is obtained through deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved (Gonzalez-Garcia et al., 2015; Loo and Riegelman, 1968; Margolskee et al., 2016; O'Hara et al., 2001; Qiu et al., 2016; Suverkrup et al., 1989; Vaughan and Dennis, 1978; Wagner and Nelson, 1963, 1964; Young, 1997; Yu et al., 1996), and ii) one-stage procedures, which directly relate *in vivo* - *in vitro* data (Costello et al., 2011; Gaynor et al., 2011; Gillespie, 1997; O'Hara et al., 2001; Veng-Pedersen et al., 2000) and are mathematically more stable than two-stage methods (Dunne et al., 2006; Gaynor et al., 2008; Veng-Pedersen et al., 2000).

Roudier et al. proposed calculations based on the back-calculation of the 90% CI of C_{max} and AUC in order to solve the limitations of using average data when a level A IVIVC is developed as an *in vivo* surrogate of a new batch/formulation (Roudier et al., 2014). This takes into consideration the intra-subject variability and leads to wider *in vitro* dissolution limits compared to the classical approach in the same line as the present work. However, the dissolution limits allow that 10% of the units from a batch overcome the BE limits, whereas the individual approach guarantees all units within the same batch are BE because dissolution limits are set based on the STSF and FTFF. This result was confirmed in this article when one thousand batches were simulated and used in cross-over BE studies, assuming different *in vivo* variability on PK parameters and none of the simulated batches generated a 90% CI outside of 80–125%.

FDA and EMA regulatory guidelines have been adapted to increase the applicability of IVIVC as a surrogate of the *in vivo* performance (EMA, 2012; FDA, 1997). However, both still consider the use of average data and allow an arbitrary limit of 20% in C_{max} and AUC. The *in vitro* and *in vivo* variability is an inherent element of the experimental studies and not taking it into consideration suggests a very simple vision of the *in vitro* and *in vivo* behavior of drug products.

4.1. Conclusion

In conclusion, an individual approach has been proposed to establish dissolution specifications using a level A IVIVC, ensuring BE of all units within the new batch developed. This methodology takes into consideration the *in vitro* and *in vivo* variability observed, providing dissolution specification limits that ensure *in vivo* ratios exactly between 80 and 125. Thus, the widening of dissolution specifications is a consequence of using individual data, but the approach ensures the BE of all tablets, which is not always achieved using the classical approach.

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