Pharm Res (2014) 31:2529–2538
DOI 10.1007/s11095-014-1349-8

RESEARCH PAPER

In Vitro- In Vivo Correlation's Dissolution Limits Setting

B. Roudier • B. M. Davit • E. Beyssac • J-M. Cardot

Received: 6 January 2014 / Accepted: 24 February 2014 / Published online: 28 March 2014

ABSTRACT

Purpose *In vitro in vivo* correlation (IVIVC) is a biopharmaceutical tool recommended for use in formulation development. When validated, IVIVC can be used to set dissolution limits and, based on the dissolution limits, as a surrogate for an *in vivo* study. The purpose of this paper is to study the various methods used to fix dissolution limits.

Methods Fixing dissolution limits is not a straightforward process; various approaches exist. The classical ±10% of dissolution limits was compared to the recommended ±10% of Cmax and AUC and to an innovative back calculation of the 90% CI. Based on simulated values the influence of the calculation method as well as of the variability of the results and pharmacokinetic processes was investigated.

Results Depending upon the method, the results are different and their comparison leads to possible rules. It appears that the usage of a back calculation of a 90% CI is an accurate and advantageous method when intra-individual variability associated with the drug is low. Those findings are in accordance with the current practice of IVIVC, which is not recommended for highly variable drugs.

Conclusions The approach of using a 90% CI allows the intra-subject variability to be taken into account and fixes limits that ensure a greater chance to show acceptable BE, in case of reasonable intra-subject variability, leading to setting broader *in vitro* dissolution limits compared to classical solutions.

KEY WORDS *in vitro in vivo* correlation (IVIVC) · dissolution limits · biowaiver · prediction · predictability

INTRODUCTION

In vitro dissolution is presently a tool widely used in drug product formulation development and in quality control. Pharmacopeia and regulatory agencies recognize the importance of dissolution as an effective control tool (1–6). With the availability of *in vitro/in vivo* correlations (IVIVC), the importance of dissolution increased as an established and validated correlation and as a tool for predicting *in vivo* results based on *in vitro* data. Use of IVIVC can assist with optimizing drug dosage forms, with the result that the fewest possible trials in man are used during development. Once a valid IVIVC is established, *in vitro* dissolution can be used when the formulation is finalized, or post-approval, as a surrogate for an *in vivo* study for scale-up, formulation and process variations, site changes, and to justify widening of dissolution limit, denoting the importance of setting accurate dissolution limits (7–18).

In vitro dissolution studies are a valid surrogate for *in vivo* data if the process studied *in vitro* is the limiting one and is similar to that existing *in vivo* When release *in vivo* is directly and only dependent of the formulation and its *in vivo* dissolution, the formulators can act, with the advantage that it can be simply studied *in vitro*. The aim of IVIVC is to relate the observed release/dissolution *in vivo*, considered as the limiting

Opinions expressed in this report are those of the authors (BD), and do not necessarily reflect the views of policies of the FDA.

B. Roudier
ESIEE Cités Descartes, BP 99, 93162 Noisy Le Grand Cedex France
e-mail: roudierb@esiee.fr

B. M. Davit
Office of Generic Drugs, US-FDA, 7500 Standish Place
Rockville, Maryland 20855, USA

B. Roudier · E. Beyssac · J.-M. Cardot (✉)
EA4678, Biopharmaceutical Department, Auvergne University
UFR Pharmacie, 28 Place H. Dunant, BP 38
63001 Clermont-Ferrand France
e-mail: j-michel.cardot@udamail.fr

Present Address:
B. M. Davit
Clinical Research, Merck Research Laboratories, One Merck Drive
Whitehouse Station, P.O. Box 100, New Jersey 08889-0100, USA
e-mail: barbara.davit@merck.com

factor, to the *in vitro* observed dissolution which, in turn, is dependent on the formulation. Differences in *in vitro* dissolution could reflect a difference in *in vivo* release from the drug dosage form based on known characteristics. This is of great interest for the identification of the critical quality attribute (CQA).

Various regulatory guidelines and Pharmacopeia chapters refer to IVIVC (1–4,8). In the FDA guideline "Guidance for Industry, Extended Release Oral Dosage Forms" (8), four main cases are generally used to fix the dissolution limits based on the mean dissolution curve and on the clinical/bioavailability lots results and are as follows:

- case 1: in the absence of an IVIVC, dissolution limits are fixed as ±10% of the target dissolution curve;
- case 2: in the presence of a level A correlation, specifications should be established based on average data. The simulated plasma concentration time profile, based on dissolution limits, results in a maximal difference of 20% in the predicted *in vivo* bioequivalence (BE) study parameters, the peak plasma drug concentration (Cmax), representing rate of drug absorption, and area under the plasma drug concentration *versus* time profile (AUC), representing extent of drug absorption;
- case 3 : A Level C correlation is established on both *in vivo* BE parameters (AUC and Cmax) and on multiple dissolution sampling time points. In this case, similar dissolution specifications must insure a maximal difference of 20% in the predicted Cmax and AUC (with a last dissolution point used in the IVIVC of at least 80% dissolved);
- case 4: A single level C correlation based on a single time point is established. In this case, the dissolution limit at this time point must insure that not more than a 20% difference in the predicted AUC and Cmax. In addition, for the other dissolution time points, the range should be ±10% of mean dissolution profile. Reasonable deviations from ±10% may be acceptable if the range at any time point does not exceed 25%.

Based on this information (1–4,8), a Level A correlation can mainly be used as a surrogate of *in vivo* data and dissolution limits calculated based on the IVIVC, reflecting a maximal difference of 20% in the predicted Cmax and AUC. It should be kept in mind that (a) the first line criterion for IVIVC predictability (internal or external) corresponds to a maximum of 10% deviation between observed and predicted values for Cmax and AUC (1–4,8); and (b) the general rule to establish bioequivalence of two formulations implies that both lower and higher limits of the 90% confidence interval (CI) of the adjusted geometric mean Cmax and AUC ratio of test *vs.* reference formulations must be included within CI limits of at least 80% and not more than 125% (1–4), leading obviously to a difference between test and reference which is no greater than 20%. This is why we proposed calculations based on the back-calculation of the 90% CI of Cmax and AUC.

The accuracy of the dissolution limits established based on IVIVC is a key factor not only of optimization but also of the use of IVIVC as an *in vivo* surrogate. The aim of this article was to compare these proposed back calculations with the well-established calculations and limits proposed in the FDA guideline.

MATERIALS AND METHODS

Data Used

All calculation were performed using Winnonlin 6.2 in Phoenix® 2.0 (Pharsight, Certara corporation St. Louis, Missouri, USA) and Matlab® 2011b (Matwork, Natick, Massachusetts, USA) under Windows 7.

Two sets of data reflecting slow-release (SR) formulations were used. One was based on a one compartment model and the second on a two compartment model with first order kinetics. Both assumed the simplest level A IVIVC case: high solubility and high permeability drugs presented as a slow release formulation and a one-to-one IVIVC was postulated in order to estimate the link between *in vivo* input (absorption) and dissolution profiles.

Example 1

Example 1 is based on an apparent one-compartment model with first order absorption and no lag time (19). For this first set of simulated data Eq. 1 was used.

$$C(t) = F \times D \times \frac{k_a}{V \times (k_a - k_e)} \times \left(e^{-k_e \times t} - e^{-k_a \times t}\right) \qquad \text{(Eq.1)}$$

The initial drug dependent parameters were set to: elimination rate constant (k_e): 0.05 h^{-1} and the volume of distribution derived from the area (V): 10 L. The formulation-dependent parameter: dose (D=25 mg) is multiplied by absolute bioavailability (F=0.52) to give a value of 13 (FxD), in order to achieve a maximum concentration (Cmax) of 1 at 5 h (Tmax) with an absorption rate constant (k_a) of 0.5 h^{-1}. In a second step, modifications of k_e and k_a, expressed as k_a/k_e ratio, were tested to associate their impact on the calculations. The absorption rate constant (k_a) was then modified according to the results of the forecasted dissolution limits and *vice versa* in order to estimate *in vivo* and *in vitro* impacts.

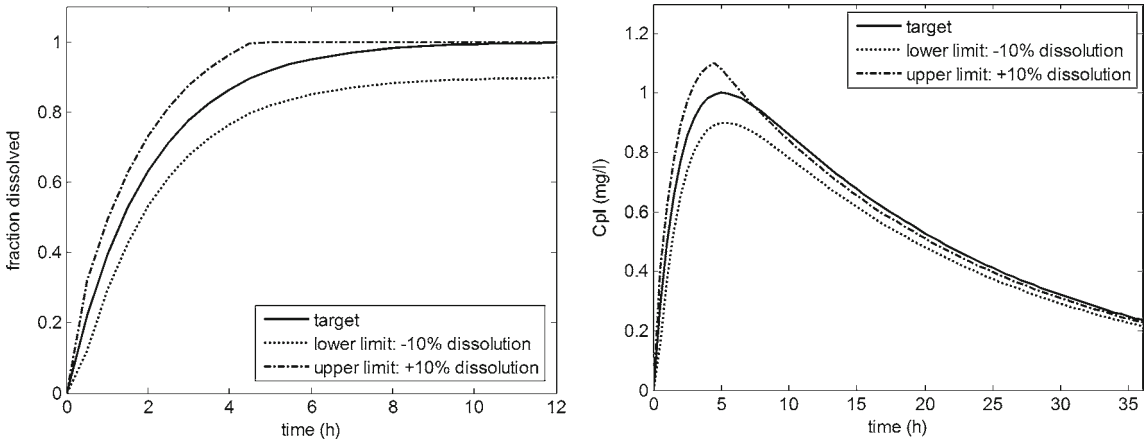


Fig. 1 Profiles obtained with classical simulations: dissolution (*left*) to have ±10% of target dissolution and resulting plasma profile (*right*) according to one compartment model (Eq. 1).

Example 2

Example 2 is composed of a two-compartment model with first order absorption and no lag time (19). The equation used is described in Eq. 2.

$$C(t) = F \times D \times \frac{k_a}{V_c} \times \left(\frac{k_{21}-\alpha}{(k_a-\alpha)\times(\beta-\alpha)} e^{-\alpha \times t} + \frac{k_{21}-\beta}{(k_a-\beta)\times(\alpha-\beta)} e^{-\beta \times t} + \frac{k_{21}-k_a}{(\alpha-k_a)\times(\beta-k_a)} e^{-k_a \times t} \right) \quad \text{(Eq.2)}$$

The initial drug-dependent parameters were set to: elimination rate constant (β) to 0.02 h^{-1}; distribution rate constant (α) to 0.2 h^{-1}; and the volume of distribution of the central compartment (V_c) to 15.9 L. The formulation dependent parameter: dose (D=50 mg) is multiplied by absolute bioavailability (F=0.5), in order to achieve a maximum concentration (Cmax) of 1 at 5 h (Tmax), with an absorption rate constant (k_a) of 0.5 h^{-1}. The micro constants corresponding to the rate from peripheral to central compartment k_{21} was estimated to 0.088 h^{-1} and the corresponding elimination from central compartment k_{10} (corresponding to k_e) calculated to correspond to 0.046 h^{-1}. This value is close to the value of the one-compartment model k_e (0.05 h^{-1}). The similar values of k_a and k_e compared to the one-compartment model allows to compare the results of the two examples. As for the one- compartment model, the influence of the values of α and k_a on the results is investigated as they are the two parameters which control the initial shape of the curve and thus can modify the Cmax.

A single curve that could correspond to the mean value curve is used in both cases. Extensive discussion on this subject can be found in various papers (20–24) as well as the mode of calculation of the BE parameters, the use of arithmetic or geometric mean (20).

Calculations of Dissolution Limits

The calculation of dissolution limits and their *in vivo* relevance were studied using several simulation methods and as follows:

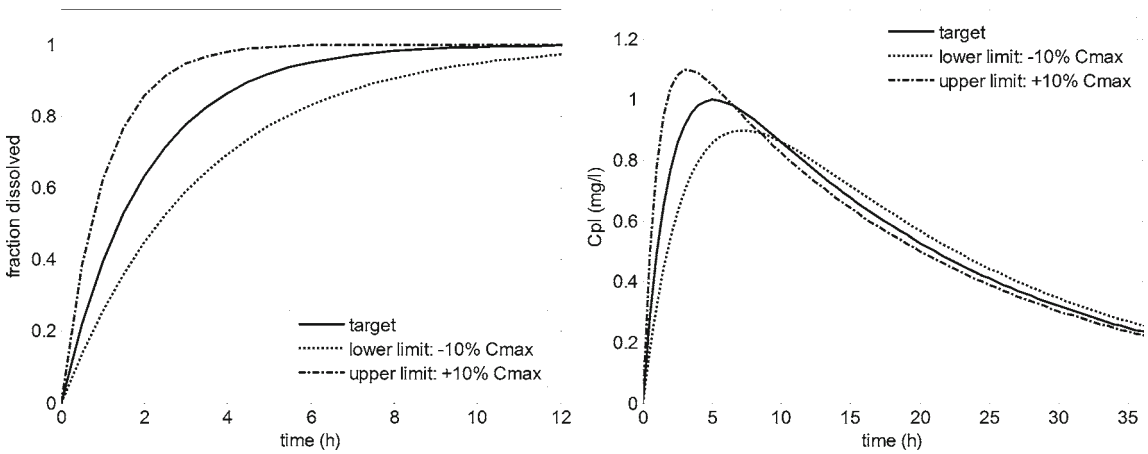


Fig. 2 Profiles obtained with classical simulations: dissolution (*left*) to have ±10% of Cmax and resulting plasma profile (*right*) according to one compartment model (Eq. 1).

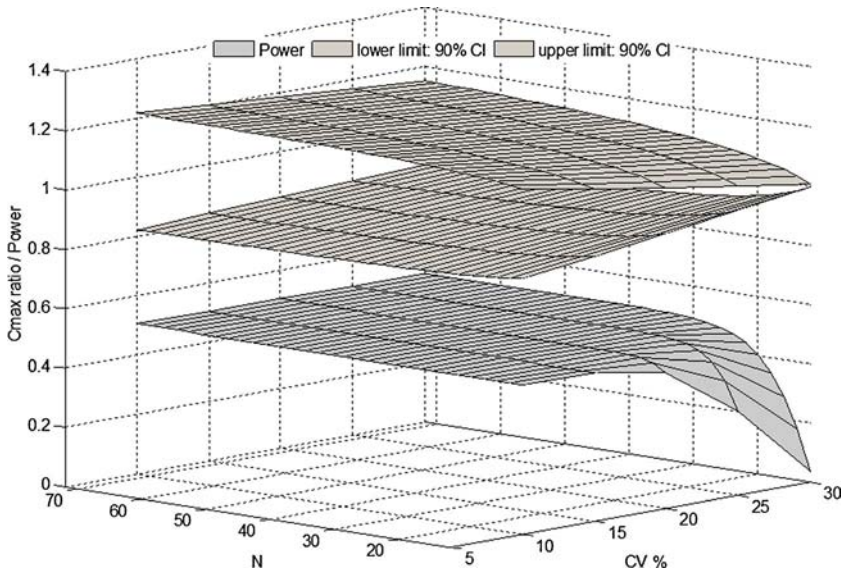


Fig. 3 Cmax ratio (Cmax ref = 1) to insure BE based on methods (iii): back calculation of 90% and resulting power as a function of N and CV of ANOVA.

(i) simulation 1 (noted ±10% dissolution): ±10% from target dissolution curve;
(ii) simulation 2 (noted ±10% Cmax): maximal difference of 10% in the predicted Cmax and AUC (giving a ±20% range);
(iii) simulation 3 (noted 90% CI): method based on the back-calculation of the 90% CI of the Cmax and AUC using data obtained in the *in vivo* bioavailability study (BA) used to establish IVIVC (CV of residual error of ANOVA, reference formulation mean Cmax and AUC and number of subjects);
(iv) simulation 4 (noted 90% CI+power): method based on the back-calculation of the 90% CI (iii) and including a power calculation to insure at least 80% power in the *in vivo* BE study.

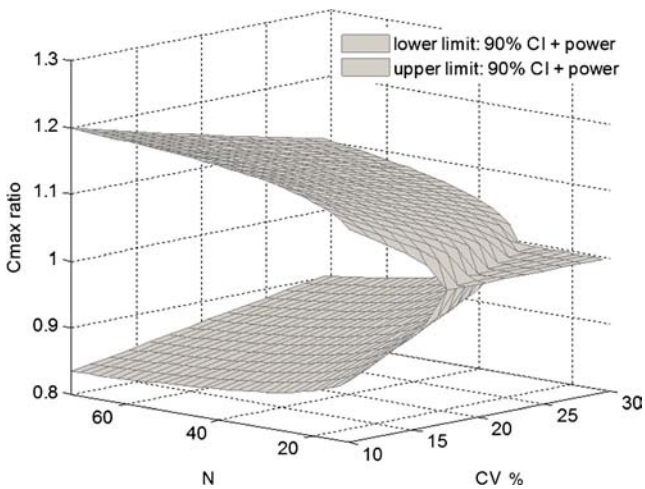


Fig. 4 Cmax ratio (Cmax ref = 1) to insure BE based on methods (iv): back calculation of 90% CI including power≥0.80 as a function of N and CV of ANOVA.

Methods (i) and (ii) were classical methods proposed in the FDA guideline, whereas methods (iii) and (iv) were innovative. Indeed, those two last methods are based on the results of the BA study used to establish the IVIVC and for the main parameters of interest; Cmax and AUC (up to t or extrapolated to infinity). The residual error variance was extracted from the ANOVA or Mixed-Effects Model used to establish the 90% CI. Using this residual error variance (s_r^2) and the number of subjects (N) associated with the tabulated student t value (t), the lower and higher mean PK parameters to have Cmax and AUC within the BE limits of 80 to 125% were estimated by Eq. 3.1 for the lower and 3.2 for higher.

$$e^{\left[\ln(0.80)+t\times s_r/\sqrt{\mathrm{N}/2}+\ln\left(\overline{m}_{ref}\right)\right]} = lower \qquad \text{(Eq.3.1)}$$

$$e^{\left[\ln(1.25)-t\times s_r/\sqrt{\mathrm{N}/2}+\ln\left(\overline{m}_{ref}\right)\right]} = higher \qquad \text{(Eq.3.2)}$$

In a first step the CV was set to 20% and N = 24 subjects. In a second step, CV (approximation of $\mathrm{CV} = \sqrt{e^{s_r^2}-1}$) was set from 0.1 to 0.3 (10 to 30%), corresponding to the ANOVA residual error, are used in order to estimate the influence of this parameter on the limits calculated assuming subjects between 12 and 72. In a final step (method (iv)), those calculations were redone in order to keep a power equal to 0.8 (80%) at least.

Table I Difference Between Cmax Ratio (Cmax ref = 1) According to Method i, ii, iii, iv and to one compartment model (Eq. 1)

Method	(i)		(ii)		(iii)		(iv)	
$N = 24$	± 10% Dissolution		± 10% Cmax		90% CI		90% IC + power	
CV (%)	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
10	0.899	1.099	0.900	1.100	0.841	1.190	0.862	1.161
15	0.899	1.099	0.900	1.100	0.862	1.161	0.894	1.119
20	0.899	1.099	0.900	1.100	0.883	1.133	0.927	1.079
25	0.899	1.099	0.900	1.100	0.904	1.107	0.972	1.029
30	0.899	1.099	0.900	1.100	0.926	1.081	1.000	1.000

RESULTS

Calculations of Dissolution Limits with Simulated Data corresponding to one compartment (Example 1)

Classical dissolution limits (±10% of target, method (i)) and dissolution limits which would produce a 10% (method (ii)) difference on Cmax are imposed on the data of resulting from initial Eq. 1 to generate Figs. 1 and 2.

If the previous limits based on target dissolution or a 10% difference in Cmax are simple, they cannot prelude the results of a new BA/BE study, as the 90% CI calculations and power depend on the ANOVA error term and on the number of subjects (N). To overcome the problem of possible failure of a new BE study, the method based on 90% CI without power

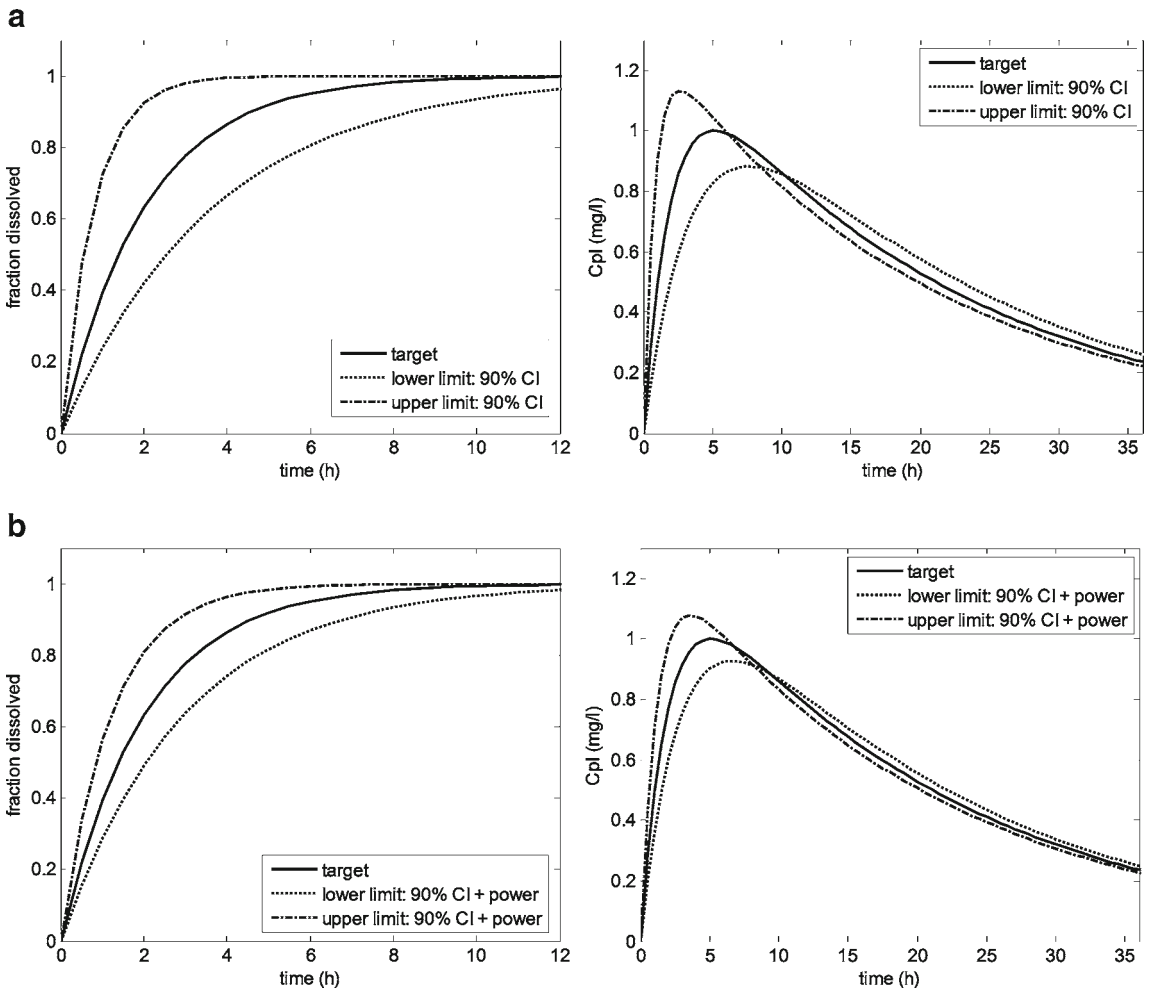


Fig. 5 Dissolution based on a CV of 20% and on a number of subjects of 24, based on the results of Figs. 3 (*up*, method iii) to 4 (*down*, method iv) and corresponding plasma profiles according to one compartment model (Eq. 1).

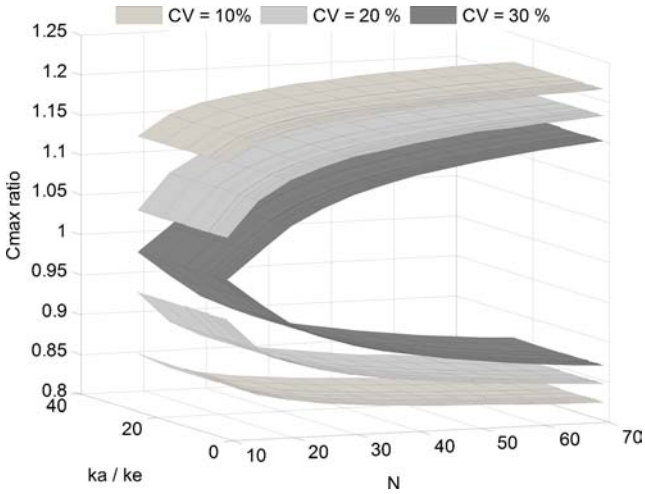


Fig. 6 Influence of the ratio k_a/k_e on the lower and upper ratio of Cmax as a function of N and CV, using method (iv) and according to one compartment model (Eq. 1).

calculation (method iii) are presented in Fig. 3 as a function of N and CV.

Figure 3 clearly shows that power is below 0.8, and achieves 0.5 at most. In order to be compliant with the current practice of including a number of subjects to maintain BE study power of at least 80%, the limits must be recalculated to include this parameter (method iv). Equations 3.1 and 3.2 were recomputed and well as the *post hoc* power in order to recalculate the limits of the 90% CI that will be associated with a power of at least 80%. This calculation would correspond to the calculation of the parameter needed to perform a new BE study based on previous results. The results are presented in Fig. 4, using an approach similar that used to generate Fig. 3 except that the power curve is not displayed as always at least equal to 80%. The results of Fig. 4 are always lower than the data obtained in Fig. 3.

The Table I displays, for N = 24 subjects and CV ranging from 10 to 30%, the Cmax limits calculated using the various methods.

It is clearly visible that method (i) and (ii) result in similar values. Methods (iii) and (iv) bring advantages in cases of low CV.

Figure 5 displays the various dissolution profiles, based on a CV of 20% and N of 24 subjects, associated with the plasma concentration based on the results of Fig. 3 and 4.

As presented in Figs. 1, 2 and 5, the differences in the dissolution profiles derived using the various *in vivo* constraints are lower at the early sampling times comparing to ±10% of dissolution. That is linked with the calculation methodology.

The influence of absorption rate on the values of Cmax and the resulting 90% CI limits obtained with method (iv) are presented in the Fig. 6 as a function of N and CV. The variations of k_e and k_a which control the shapes of the curves do not change the previous findings

Calculations of Dissolution Limits with Simulated Data Corresponding to Two Compartments Model (Example 2)

A similar approach as for one compartment was used for the two compartment model. The results corresponding to be initial set of parameters and calculations are presented in Fig. 7 for methods (i) to (iv) corresponding to Figs. 1, 2 and 5 in case of one comparment model. The results observed denoted differences of dissolution limits indicating the direct influence of the distribution parameter on the absorption profiles. As for 1 compartment model, the differences in the dissolution profiles derived using the various *in vivo* constraints are lower at the early sampling times comparing to ±10% of dissolution. That is linked with the calculation methodology.

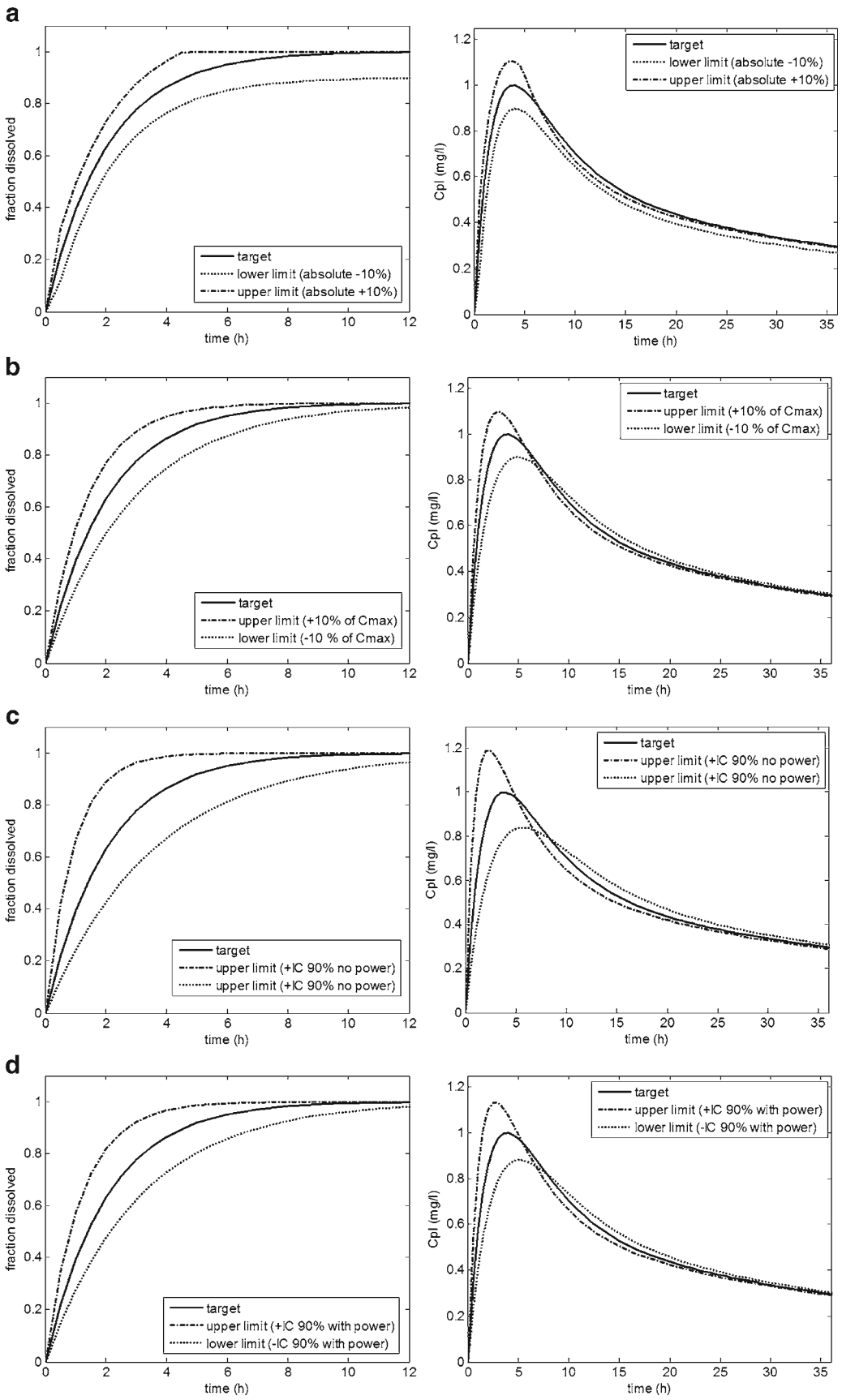
In the next step the influence of the ratio k_a/α was studied as they are the two parameters which control the initial shape of the curve and thus can modify the Cmax. When $\alpha > k_a$, the results correspond to a one-compartment model; thus, the ratio studied was selected to be between one and 60. The variations of α and k_a do not change the previous findings and confirm the results observed for one compartment model (results not shown).

DISCUSSION

The present study presented and compared methods to establish dissolution limits based on IVIVC. The main outcomes are based on using a simulated SR formulation of a highly soluble and permeable drug, and indicated that the dissolution limits based on various techniques could lead to different predicted PK parameters. As the aim of setting dissolution limits is to validate possible biowaivers and *in vivo* surrogates, it is important to estimate dissolution limits in which therapeutic equivalence exists for all formulations resulting in the lower and higher dissolution limits. As therapeutic effects are not easily assessed, these simulations are based on BE of formulations. BE is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available …" (3). Thus, equivalence of both Cmax and AUC is essential for a successful *in vivo* study outcome.

Various papers (9–11,15–18,25–29) described the importance and possible predictive techniques for dissolution, as well as the importance of having an accurate dissolution technique. In 2000, Modi (16) investigated for specific drugs the limits of dissolution which would ensure BE and arrived at ±10% as limits.

Fig. 7 Dissolution based on a CV of 20% and 24 subjects, and corresponding plasma profiles according to two compartments model (Eq. 2).


a
fraction dissolved
time (h)
target
lower limit (absolute -10%)
upper limit (absolute +10%)
Cpl (mg/l)
time (h)
target
lower limit (absolute -10%)
upper limit (absolute +10%)
b
fraction dissolved
time (h)
target
upper limit (+10% of Cmax)
lower limit (-10 % of Cmax)
Cpl (mg/l)
time (h)
target
upper limit (+10% of Cmax)
lower limit (-10 % of Cmax)
c
fraction dissolved
time (h)
target
upper limit (+IC 90% no power)
upper limit (+IC 90% no power)
Cpl (mg/l)
time (h)
target
upper limit (+IC 90% no power)
upper limit (+IC 90% no power)
d
fraction dissolved
time (h)
target
upper limit (+IC 90% with power)
lower limit (-IC 90% with power)
Cpl (mg/l)
time (h)
target
upper limit (+IC 90% with power)
lower limit (-IC 90% with power)

Figures 3, 4, 6 and Table I highlight the importance of intra-subject variability and the number of subjects (N). The calculations performed indicate that using limits based on the calculation of CI brings advantages in some circumstances compared to using fixed limits, but are more drastic in other circumstances. As a function of CV and N for methods (ii) and (iv), Table II shows that, depending on the calculation technique, different outcomes and chances to be bioequivalent exist. The various graphs and Table II clearly show that the limits based on the 90% CI values are larger when intra-subject variability is low (low CV).

Methods (i) and (ii) provided results close together (Table I) than confirming the results presented by Modi (16). The limits based on 90% CI are somewhat obvious. When the CV increases, N must be increased to insure BE. For high CV the approaches using the back-calculated 90% CI is more restricting than the classical approaches. When the power is included in the calculation of the 90% CI, the advantage compared to using a fixed calculation of ±10% of Cmax is only visible up to a CV around 17.5% for N = 24 subjects. The comparison of the two modes of calculations based on the 90% CI led, as presented in Figs. 3 and 4, to higher limits with method (iii) compare to (iv). However this method does not insure a power greater than 80% in the case of a new study to be performed. The outcome of both approaches based on CI is the observation that the limits vary depending of the quality of the initial data. Method (iv) is more conservative compared to method (iii) and is more adventitious in the case high N and low CV compared to methods (i) and (ii).

As shown in the simulations, the differences in dissolution curves based on calculations associated with *in vivo* determinations are lowest at the initial sampling times, due to the methodology used for the calculations. That is clearly illustrated by Figs. 1, 2, 5, and 7. This fact would be a handicap, as in this case, the early dissolution time sampling times allowed only an extremely low variability. Since this most likely is an artifact due to calculation methodology, enlarging these early differences in dissolution rate might not impact the *in vivo* behaviors if it is below the dissolution time which is influencing Cmax values. The difference between the fixed ±10% of the target dissolution profile and the calculated dissolution limits based on other methods are less marked when absorption is faster. The crossing of the calculated *versus* observed dissolution curves and the maximum difference between the calculated *versus* observed dissolution limits occurred earlier when absorption is fast. In the initial stage the ±10% of the target dissolution profile is larger than the calculated. Based on convolution, the impact of modified (enlarged dissolution limits at early time) on PK parameters (Cmax and AUC) is neglectable for a first order absorption. A simple approach could be taken. When the limits calculated using method (i) are larger in the initial times than the values obtained by method (iv): the largest of the two is selected to define the final limits. After the initial times the opposite relation is observed:

Table II Method (ii) vs (iv) Giving the Higher Limits as a Function of N and CV, in Grey Limit for Method (iv) which Insure BE

N	CV %				
	10	15	20	25	30
12	IV	II	II	II	II
18	IV	II	II	II	II
24	IV	IV	II	II	II
36	IV	IV	IV	II	II
48	IV	IV	IV	II	II
60	IV	IV	IV	IV	II
72	IV	IV	IV	IV	IV

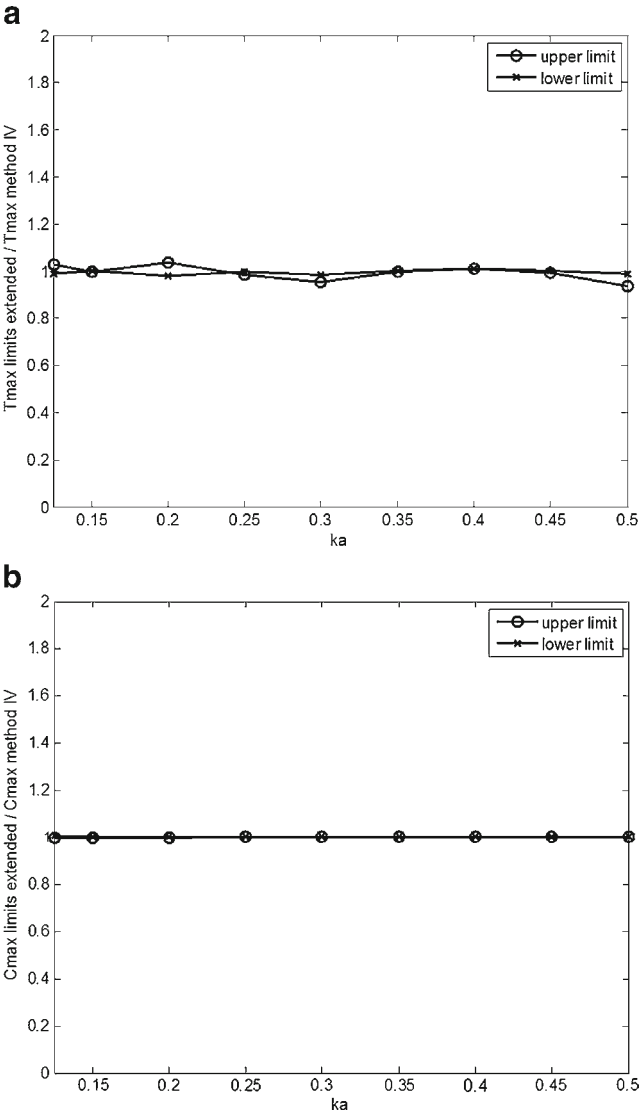


Fig. 8 Influence of the enlargement of dissolution according to method (i) and (iv) on resulting Tmax (*up*) and Cmax (*down*): ratio after enlargement/method (iv) for CV = 15% and *N* = 24 according to one compartment model (Eq. 1).

method (iv) limits broader than method (i)), and limits defined by method (iv) are kept. After setting those limits, a convolution is performed and the outcome of the absence of impact of enlargement on the final *in vivo* Cmax and AUC confirmed. Example is given in Fig. 8 for a one compartment model with a first order absorption associated with a CV=15% N=24: ratio of Cmax and Tmax after enlargement vs before enlargement as a function of the absorption rate constant values. No impact is noticed in this case. Anyway if an impact is noticed then the limits must be reevaluated.

Based on the previous findings and examples, the CI methods allow defining wider dissolution limits than the classical setting when the intra-subject variability is acceptable. This method allows also calculating and defining *a priori* the number of subjects and dissolution limits with all the required conditions to be fulfilled in the case of the *in vivo* BE study. For example, with 36 subjects, the method based on a 90% CI associated with the power calculation presented an advantage until an intra-subject CV is 20% or greater.

However the IVIVC must never be seen as a method to fix more drastic limits than those that would have been established with ±10% of the dissolution of the target formulation. IVIVC trials must never be punishable and the broader limits either based on the dissolution of the target formulation (±10% of the dissolution) or IVIVC must be selected by the authorities except in case of possible side effects or absence of efficacy linked with to inadequate concentrations. The case of narrow therapeutic range drugs is interesting as in this case the safety/efficacy risk for subject is important. No global consensus existed on the approach to treat those drugs (2,3). In Europe possibility exists to restrict the 90% CI limits to 90.0–111.1%. For USA the FDA recommends, unless otherwise indicated by a specific guidance, that the traditional BE limit of 80–125% is kept providing the sponsor submitted additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. Usually the narrow therapeutic index drugs are not highly variable; in other words, intra-subject variability is very low. For Europe the adapted 90% CI bounds (*i.e.* 0.90–1.11, for AUC and Cmax), could be used to calculate the lower and higher possible dissolution limits, leading in this case to results that must be compared to the actual proposed specifications and evaluated in both cases (according mainly to safety concern). For FDA the standard case, in absence of specific recommendation, is more complex as many factors are proposed to be taken into consideration (in addition to the 90% CI based on standard limits) such as reference scaling or comparison of variances. In this case a standard approach to calculate dissolution limits could not be set up even if possibly the method (iv) reflects better the reality of a new study.

The fixing of dissolution limits is the ideal case for applying the one-step process known as convolution-based IVIVC (29–34), as all the key parameters which could influence IVIVC are determined in the early two-stage approach used to initiate the IVIVC.

All the current findings must be confirmed using other types of pharmacokinetic models such as sigmoidal or zero-order absorption and other types of IVIVC relationship such as nonlinear IVIVC with time-scaling.

CONCLUSION

Our findings are based on simulated one and two compartment model assuming a first order absorption, linear pharmacokinetics, and 1:1 IVIVC. The introduction of the IVIVC allowed use of dissolution as a surrogate of an *in vivo* study, and is based on using the IVIVC to establish the dissolution limits. Up until now the limits are linked with a maximal difference of 20% in the predicted Cmax and AUC. The classical approach, in absence of IVIVC, fixes the dissolution limits at ±10% of the actual dissolution and gives results close to the limits fixed using ±10% of Cmax and AUC. The approach of using a 90% CI allows the intra-subject variability to be taken into account and fixes limits that ensure a greater chance to show acceptable BE, in case of reasonable intra-subject variability, leading to setting broader *in vitro* dissolution limits compared to classical solutions.

REFERENCES

1. EMA Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Forms B: Transdermal Dosage Forms, 2000.
2. EMA, Guideline on the investigation of bioequivalence, January 2010.
3. FDA Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003.
4. FDA Guidance for Industry Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and In vivo Bioequivalence Documentation U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) May 1997.
5. ICH Steering Committee, Draft consensus guideline on development Q8 step 4, August 2009.
6. United States Pharmacopeial Convention, Inc., " Dissolution" <711>.
7. United States Pharmacopeial Convention, Inc., "In Vitro In Vivo Evaluation of Dosage Forms" <1088>.
8. FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In vivo Correlations U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) September 1997.

9. Cardot JM, Beyssac E. In vitro/in vivo correlations: scientific implications and standardisation. Eur J Drug Metab Pharmacokinet. 1993;18:113–20.
10. Cardot J-M, Beyssac E, Alric M. In vitro- in vivo correlation Importance of dissolution in IVIVC. Dissolution Technol. 2007;14: 15–9.
11. Cardot J-M, Beyssac E. In vitro/in vivo correlations: encyclopedia of pharmaceutical technology. In: Swarbrick J, Boylan JC, editors. Informa Healthcare. 3rd ed; 2006;1:1062–72.
12. Devane J. The impact of in vitro-in vivo relationships on product development. Adv Exp Med Biol. 1997;423:241–60.
13. Emami J. In vitro - in vivo correlation: from theory to applications. J Pharm Sci. 2006;9:169–89.
14. Farrell C, Hayes S. IVIVC for oral drug delivery: immediate release and extended release dosage forms in pharmaceutical product development. In: Chilukuri DM, Sunkara G, Young D, editors. Vitro-in vivo correlation. New York: Marcel Dekker; 2007. p. 125–40.
15. Hayes S, Dunne A, Smart T, Davis J. Interpretation and optimization of the dissolution specifications for a modified release product with an in vivo-in vitro correlation(IVIVC). J Pharm Sci. 2004;93:571–81.
16. Modi NB, Lam A, Lindemulder E, Wang B, Gupta SK. Application of in vitro-in vivo correlations (IVIVC) in setting formulation release specifications. Biopharm Drug Dispos. 2000;21:321–6.
17. Pabst G. Revalidation of the in vitro specification limits after an in vitro-in vivo correlation. Arzneimittelforschung. 1998;48(5A):584–8.
18. Siewert M. Perspectives of in vitro dissolution tests in establishing in vivo/in vitro correlations. Eur J Drug Metab Pharmacokinet. 1993;18(1):7–18.
19. Gibaldi M, Prescott L. Handbook of clinical pharmacokinetics. New-York: ADIS Press; 1983.
20. Cardot J-M, Davit BM. In vitro- in vivo correlations: tricks and traps. AAPS J. 2012. doi:10.1208/s12248-012-9359-0.
21. Bigora S, Piscitelli D, Dowell J, Butler J, Farrell C, Devane J, *et al.* Use of nonlinear mixed effects modelling in the development of in vitro-in vivo correlations. Adv Exp Med Biol. 1997;423:207–15.
22. Dowell JA, Hussain A, Devane J, Young D. Artificial neural networks applied to the in vitro-in vivo correlation of an extended-release formulation: initial trials and experience. J Pharm Sci. 1999;88:154–60.
23. Kortejarvi H, Malkki J, Marvola M, Yliperttula M, Pajunen P. Level A in vitro-in vivo correlation (IVIVC) model with Bayesian approach to formulation series. J Pharm Sci. 2006;95:1595–605.
24. Rossenu S, Gaynor C, Vermeulen A, Cleton A, Dunne A. A nonlinear mixed effects IVIVC model for multi-release drug delivery systems. J Pharmacokinet Pharmacodyn. 2008. doi:10.1007/110928-008-9095-3.
25. Banakar UV, Makoid MC. Drug dissolution and bioavailability. Lancaster: Technomic Publishing Company; 1994.
26. Elkoshi Z. Dissolution specifications based on release rates. J Pharm Sci. 1999;88(4):434–44.
27. Okumu A, DiMaso M, Löbenberg R. Dynamic dissolution testing to establish in vitro/in vivo correlations for montelukast sodium, a poorly soluble drug. Pharm Res. 2008;25(12):2778–85.
28. Rohrs BR, Skoug JW, Halstead GW. Dissolution assay development for in vitro-in vivo correlations: theory and case studies. In: Advances in experimental medicine and biology; in vitro-in vivo correlations, vol. 423. New York: Plenum Press; 1997. p. 17–30.
29. Dunne A, Gaynor C, Davis J. Deconvolution based approach for level A in vivo-in vitro correlation modeling: statistical considerations. Clin Res Regul Aff. 2005;22:1–14.
30. Dunne A, O'Hara T, Devane J. Approaches to IVIVR modelling and statistical analysis. Adv Exp Med Biol. 1997;423:67–86.
31. Gillespie WR. Convolution-based approaches for in vitro-in vivo correlation modeling. In: Advances in experimental medicine and biology, in vitro-in vivo correlations, vol. 423. New York: Plenum Press; 1997. p. 53–65.
32. Buchwald P. Direct, differential-equation-based in-vitro-in-vivo correlation (IVIVC) method. J Pharm Pharmacol. 2003;55: 495–504.
33. Gaynor C, Dunne A, Davis J. A comparison of the prediction accuracy of two IVIVC modelling techniques. J Pharm Sci. 2008;97:3422–32.
34. O'Hara T, Hayes S, Davis J, Devane J, Smart T, Dunne A. In vivo-in vitro (IVIVC) modeling incorporating a convolution step. J Pharmacokinet Pharmacodyn. 2001;28:277–98.