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Original Article

Effect of Linear and Non-Linear IVIVC Models on In-Vivo Predictions

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ABSTRACT

Objective: The objective of present investigation is to provide role of in-vitro in-vivo correlation (IVIVC) models on in-vivo performance prediction.

Methods: The investigation demonstrates the development of compartment independent models based on system approach utilizing the concept of deconvolution/convolution. The linear and non-linear IVIVC models are developed to explore the effect on prediction of in-vivo pharmacokinetic parameters.

Results: The linear and non-linear IVIVC models are developed. The in-vivo pharmacokinetic parameters namely area under the curve (AUC), the maximum observed drug concentration (Cmax) and the time taken to reach the maximum concentration (Tmax) are predicted and compared to establish the strength of a IVIVC model in long acting dosage forms.

Conclusion: The investigation explores the effect of correlation models on predictions of in-vivo pharmacokinetic parameters (AUC, Cmax and Tmax).

Keywords: System approach, Linear, Non-linear, IVIVC, In-vivo performance.

1. INTRODUCTION

Nowadays the use and application of concept of in-vitro in-vivo correlation (IVIVC) for pharmaceutical development have been a main focus of attention of pharmaceutical industry, academics and various regulatory agencies. In pharmaceutical development in-vitro in-vivo correlation (IVIVC) plays an important role as it reduces development time to optimize the formulation. The main objective of an IVIVC in formulation development is to serve as a surrogate

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for in-vivo performance and assists in supporting biowaivers.

A well established IVIVC can help to avoid bioequivalence studies by using the dissolution data from the changed formulation, and subsequently predicting the in-vivo concentration-time profile. This predicted profile could act as a surrogate of the in-vivo bioequivalence study. This has extensive cost-saving benefit in the form of reduced formulation development time and rapid implementation of post-approval changes. [1]

The in-vitro in-vivo correlation (IVIVC) has been defined as a predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course (e.g. the time course of the plasma drug concentration or amount of drug absorbed. [2] A good correlation is important in design and development of oral drug delivery systems. A reliable, reproducible and definite tool is needed to correlate the in-vitro dissolution and in-vivo input and would have great advantages in drug development and manufacturing. Plasma concentrations can be predicted from the IVIVC tool and those observed are compared directly. A good IVIVC model should predict the entire in-vivo time course from the in vitro data. Correlation model can be linear or non-linear. [3] Generally, correlations between in-vitro and in-vivo inputs (IVIVC) rely on linear relationships. In a linear correlation, the in-vitro dissolution and in-vivo input curves may be directly super imposable or may be made to be super imposable by the use of a scaling factor. However, non-linear correlations are uncommon, may also be observed, justified and validated. In most correlations, the goal has been to obtain a linear correlation in which the profiles of in-vitro and in-vivo percent inputs versus time are parallel. Rather than achieve linearity by altering in-vitro dissolution tests to match the in-vivo profile or by employing other methods such as time scaling, non-linear correlation could be used to predict in-vivo performance. The application of non-linear IVIVC has been suggested in the literature which appears to indicate curvature and where use of a nonlinear function may be more appropriate than linear regression analysis. [4]

The system approach based convolution and deconvolution techniques are available to develop compartment independent IVIVC models for prediction of in-vivo performance and simulation of the in-vivo performance which are recognized by regulatory agencies around the world. [5] Convolution is the simple process of adding several plots, mathematically is amounts to integration. Mathematically in convolution, in-vitro dissolution data become an input function and plasma concentrations become a weighting factor or function resulting in an output function representing plasma concentrations for the long acting dosage forms. Convolution can be performed by various techniques such as Analytical Methods, Laplace Transform Technique or convolution by integral. [6-8] Deconvolution is a numerical method that is exactly opposite of convolution used to estimate the time course of drug input using a mathematical model based on the convolution integral. The deconvolution technique requires the comparison of in-vivo profile which can be obtained from the blood profiles with in-vitro dissolution data. One of the popular methods of implementing the numerical deconvolution is the PCDCON, a FORTRAN programme available on the internet as an open source for public use. [9-11]

System approach treats the entire human body as one single system and deals with the plasma concentrations resulting from a dosage form with the help of a Unit Input Response (UIR) of the drug. The UIR is the response of the human body to a unit input of drug. In fact it is plasma concentration of the drug resulting from a unit input of the drug. It is important to note that all the processes responsible for the disposition of the drug like elimination, metabolism etc. are included in this plasma profile. Therefore it becomes a dependable representative of the human body reacting to a given drug; this is the most important component of the implementation of the system approach to predict the plasma concentration profile resulting from a dosage form. [12]

There are four levels of IVIVC that have been described in the USFDA guidance, which include levels A, B, C, and multiple C. Out of these Level A correlation is the most informative and very useful from a regulatory point of view. [13,14]

Level A correlation is usually estimated by a two-stage procedure, deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved and represents a point-to-point relationship between in-vitro dissolution and the in-vivo input rate (e.g. the in-vivo dissolution of the drug from the dosage form). Level A IVIVC is also viewed as a predictive model for the relationship between the entire in-vitro release time course and entire in-vivo response time course. In general, correlations are linear at this level. Although a concern of acceptable non-linear correlation has been addressed, no formal guidance on the non-linear IVIVC has been established. Nowadays, a Level A correlation has been proposed as a surrogate marker for human bioequivalence studies. [15, 16]

The aim of present investigation is to provide role of in-vitro in-vivo correlation models on in-vivo performance (IVIVC) prediction. The linear and non-linear IVIVC models are developed to explore the effect on prediction of in-vivo pharmacokinetic parameters. The in-vivo pharmacokinetic parameters namely area under the curve (AUC), the maximum observed drug concentration (Cmax) and the time taken to reach the maximum concentration (Tmax) are predicted and compared to establish the strength of a IVIVC model in long acting dosage forms.

2. MATERIALS AND METHODS

The following experimental strategy was adopted for the prediction of in-vivo performance of Test (F6) for fasting study-

1. Use the Reference plasma concentration versus time profile to determine the in-vivo drug absorption rate and hence cumulative amount of drug absorbed as a function of time.
2. Compare it with the in-vitro cumulative amount of drug release and thus construct non-linear IVIVC model for the Reference (fasting study).
3. Use this non-linear IVIVC model to predict the in-vivo drug absorption for the Test formulation (F6) using dissolution study.
4. Use this cumulative amount of in-vivo drug absorbed and calculate the rate at which the drug is absorbed in-vivo.
5. Using the in-vivo drug absorption rate from step 4 predict the plasma concentration versus time profile using convolution.
6. Compare the two plasma profiles predicted using linear and non-linear IVIVC model.
7. Compare the predicted plasma concentration versus time profile of the Test (F6) with the Reference to assess as to how close be the agreement?

We used MathCad–11 for the implementation of the convolution and PCDCON programme for numerical deconvolution.

3. RESULTS AND DISCUSSION

The prediction of in-vivo performance of a long acting oral drug delivery system is a tricky task that has to be attended to very carefully taking into account all the vital information available. Such a prediction most of the times suffers from in accuracy because the IVIVC available does not cover the entire time course of dissolution or absorption. One of the most important considerations deciding the strength of the IVIVC is the dissolution method and approach used, a discriminating dissolution method plays the key role. Traditionally, most of the times a linear IVIVC model is attempted which at times covers limited portion of the duration of absorption of drug and thus suffers from limitations and in accurate predictions. In view of this USFDA has made provision for inclusion of non-linear IVIVC model. [17] The main difference between a linear and non-linear IVIVC model is that the in-vivo absorption versus in-vitro data is fitted to a non-linear function like a polynomial function in non-linear IVIVC in contrast to linear IVIVC where the said data is fitted to a straight line. If the in-vivo absorption and in-vitro dissolution are better represented by a non-linear function, it is advisable to use a non-linear IVIVC. It is known that IVIVC is very useful in different ways at different stages of product design, development and for regulatory submissions.

Zadbuke et al [18] designed and developed the optimized oral extended release formulation (F6) of carbamezapine based on osmotic technology and discussed their findings including the prediction of in-vivo performance for fed study of Test (F6) using the system approach involving convolution, deconvolution and IVIVC. [19] They used fed study in-vivo and in-vitro data of Reference available in Center for Drug Evaluation and Research (CDER) Bioequivalence Review of Abbreviated New Drug Application 078115 (ANDA 078115) for the purpose of prediction and comparison. As a continuation of work, we used fasting study in-vivo and in-vitro data of Reference available in ANDA 078115 and predicted in-vivo performance of Test (F6) for fasting study. [20] The dissolution data for Reference Tegretol® XR Tablets 200mg is shown in Table 1.

Table 1: Dissolution data for Tegretol® XR Tablets 200mg (Reference)

Time (hr)	Drug released (%)	Drug released (mg)
0	0	0
3	19	38
6	51	102
12	82	164
24	94	188

We developed and implemented linear IVIVC model for the prediction of in-vivo performance for fasting study. The linear IVIVC model used for the prediction is shown in Figure 1 along with the equation of the linear IVIVC. As shown in Fig. 1 there are few drawbacks of the linear IVIVC model, such as there are only four data points introducing limitation of the availability of the data at the intermediate points that resulted in a lower value of correlation (R^2). The equation of the linear IVIVC is $y = 1.0753 \quad x$ where y is the in-vivo absorption and x is the in-vitro cumulative drug release. The value of R^2 is 0.9491 that is reasonably good however a higher value would have been better.

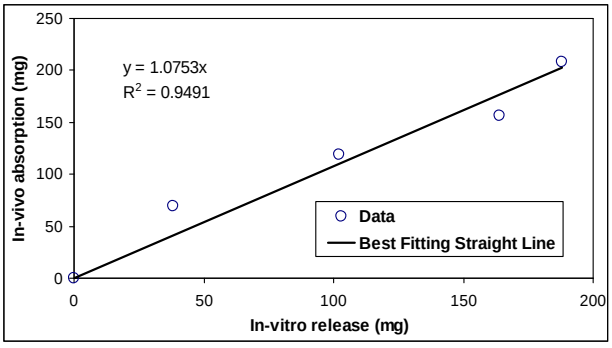

Fig. 1: Linear IVIVC model for Reference (fasting study) used for prediction of in-vivo performance

The comparison of the predicted plasma profile of Test (F6) with Reference (fasting study) by using linear IVIVC model is shown in Fig. 2.

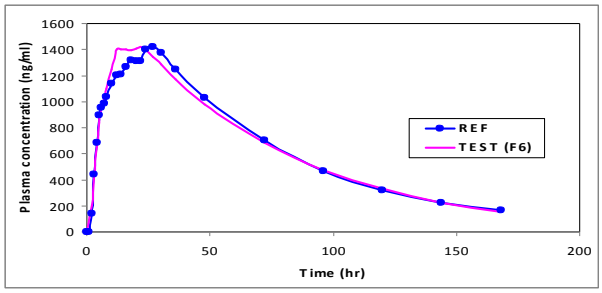

Fig. 2: Comparison of predicted plasma profile from linear IVIVC model of Test (F6) with Reference (fasting study)

The comparison of the pharmacokinetic parameters with linear IVIVC model is shown in Table 2.

Table 2: Comparison of predicted pharmacokinetic parameters of Test (F6) with Reference (fasting study) obtained from linear IVIVC model

Parameters	Test (F6) Fasting study (Predicted)	Reference (Fasting Study)	T/R (%)
AUC 168 (ng hr/ml)	109166	109431	99.76
Cmax (ng/ml)	1418.00	1422.14	99.71
Tmax (hr)	22	27	81.48

As is seen from Fig. 2, the predicted plasma concentration versus time profile of Test (F6) is similar to the Reference in several terms however the plasma concentration between 8 to 50 hrs is slightly different and initial rising part of the test is appreciably different from that of the Reference. Also it is observed that the Zadbuke et al, predictions of the fed study are very much in agreement [21], however the same in-vitro study is not giving consistent results for fasting study by using linear IVIVC. This suggested that the difference in prediction could be due to the poor linear IVIVC model shown in Figure 1. Therefore to investigate this issue we attempted construction of non-linear IVIVC model for the fasting study using the concept of non-linear IVIVC. Using the same data of in-vitro dissolution and in-vivo absorption we constructed a non-linear IVIVC model as shown in Fig. 3.

The data of the non-linear IVIVC was fitted using least square fit to a third degree polynomial equation $y = 0.000079 \quad x^3 - 0.023282 \quad x^2 + 2.676035 \quad x$ and the value of R^2 is 0.9977 indicating a good fit to data. This equation was used to calculate the in-vivo absorption of drug corresponding to in-vitro drug release and is shown in Table 3.

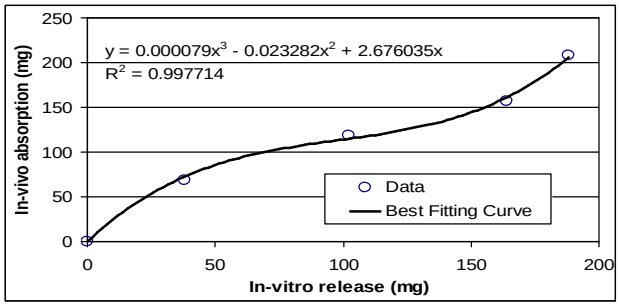

Fig. 3: Non-linear IVIVC model for fasting study of Reference fitted to a third degree polynomial used for prediction of in-vivo performance

Using the last column of Table 3 giving the cumulative in-vivo amount of drug absorbed the rate of drug absorption is calculated using numerical differentiation of the cumulative data, the resulting rate of in-vivo absorption of drug as a function of time is shown in Fig. 4.

Table: 3 In-vitro drug release and predicted in-vivo drug absorbed as a function of time calculated from non-linear IVIVC of fasting study for Test (F6)

Time (hr)	In-vitro drug released (%)	In-vitro drug released (mg)	In-vivo drug absorbed (mg) (Predicted)
0	0	0	0.00
1	4.26	8.52	21.16
2	10.32	20.64	46.01
3	21.24	42.48	77.72
4	34.33	68.66	99.55
6	49.89	99.78	113.70
8	59.32	118.64	121.70
10	68.96	137.92	133.47
12	78.66	157.32	152.37
16	83.65	167.3	165.98
20	88.56	177.12	182.55
24	93.12	186.24	201.16

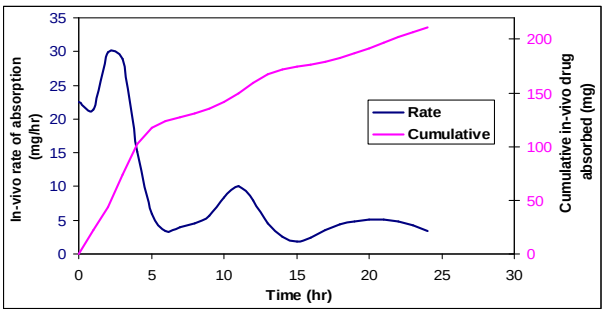

Fig. 4: Predicted rate and cumulative in-vivo drug absorption of Test (F6) for fasting study, blue line is rate and pink is the cumulative amount

The rate of in-vivo absorption of drug was used for prediction of the resulting plasma concentration versus time profile using convolution with Unit Input Response (UIR). The resulting plasma concentration versus time profile of Test (F6) and Reference for fasting study is shown in Fig. 5. It is clearly seen that both the plasma profiles go hand in hand and there is a strong agreement, both qualitatively and quantitatively. It is also seen that the predictions made using a non-linear IVIVC model are more close to the Reference plasma concentration profile than that obtained using a linear IVIVC model. Comparison of the pharmacokinetic parameters obtained from non-linear IVIVC model of Test (F6) and Reference for fasting study is depicted in Table 4. Fig. 6 shows that predicted plasma concentration profile of Test (F6) obtained using non-linear IVIVC model closely resembles the Reference plasma profile as compared to that obtained using linear IVIVC model.

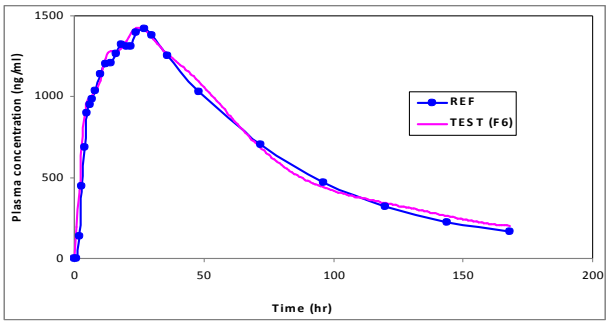

Fig. 5: Comparison of predicted plasma profile from non-linear IVIVC model of Test (F6) with Reference (fasting study)

Table: 4 Comparison of predicted pharmacokinetic parameters of Test (F6) with Reference (fasting study) obtained from non-linear IVIVC model

Parameters	Test (F6) (Fasting Study) (Predicted)	Reference (Fasting Study)	T/R (%)
AUC 168 (ng hr/ml)	112782	109431	103.1
Cmax (ng/ml)	1427	1422.14	100.3
Tmax (hr)	25	27	92.59

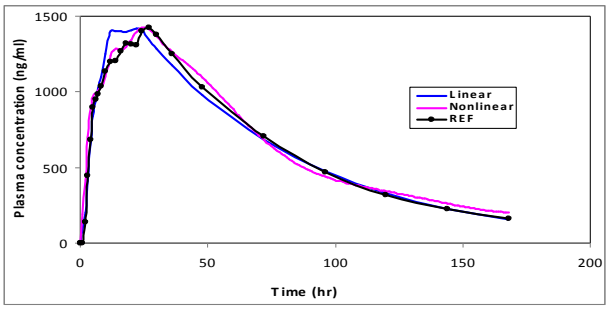

Fig. 6: Comparison of the plasma profile of Reference with Test (F6) obtained using predictions based on linear and non-linear IVIVC models

4. CONCLUSION

The present investigation explores the effect of correlation models on predictions of in-vivo pharmacokinetic parameters (AUC, Cmax and Tmax). The linear and non-linear IVIVC models are developed. We successfully demonstrated the prediction of the in-vivo performance of a Test formulation using the in-vitro study and the Unit Input Response (UIR) along with the IVIVC of the Reference. It is also shown that the predictions made using non-linear IVIVC model are far superior to those made using a traditional linear IVIVC model. Detailed procedure of the implementation of the technique based on system approach employing convolution and deconvolution is presented. A comparison of the pharmacokinetic parameters of interest while comparing the performance is also presented to establish the strength of a non-linear IVIVC model in long acting dosage forms.

5. ACKNOWLEDGEMENT

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