EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 11
447-453
Year: 2017

CONVOLUTION AND DECONVOLUTION BASED APPROACH FOR PREDICTION OF IN-VIVO PERFORMANCE

Nityanand Zadbuke[1]*, A. R. Khan[2], Anil Battase[3] and Sadhana Shahi[4]

[1]Yash Institute of Pharmacy, Aurangabad - 431134, Maharashtra, India.
[2]Postgraduate & Research Centre, Maulana Azad College, Dr. Rafiq Zakaria Campus, Aurangabad- 431001, Maharashtra, India.
[3]Govindrao Nikam College of Pharmacy, Sawarde, Chiplun - 415606, Maharashtra, India.
[4]Government College of Pharmacy, Aurangabad - 431005, Maharashtra, India.

***Corresponding Author: Nityanand Zadbuke**
Yash Institute of Pharmacy, Aurangabad - 431134, Maharashtra, India.

Article Received on 04/09/2017 **Article Revised on 25/09/2017** **Article Accepted on 15/10/2017**

ABSTRACT
In-Vitro In-Vivo Correlation (IVIVC) is a predictive mathematical model describing the relationship between an in vitro property of a dosage form and an in-vivo response. IVIVC play an important role in the pharmaceutical drug development as it serves as surrogate of in-vivo and assists in supporting biowaivers. The aim of present investigation is to use the outcomes of in-vitro studies of the test formulation for prediction of its in-vivo performance and to compare it with the reference to evaluate how close the agreement is? The compartment independent system approach based convolution and deconvolution procedure used for prediction of in-vivo performance. Convolution and deconvolution based prediction requires the availability of a weighting function for the human body system i.e. the unit input response (UIR). IVIVC of reference is used for the in-vivo performance prediction in terms of pharmacokinetic parameters viz. area under the curve (AUC), the maximum observed drug concentration (Cmax) and the time taken to reach the maximum concentration (Tmax). The comparison of the predicted plasma profile of test with reference show excellent agreement. A system approach based simple and practical procedure of convolution and deconvolution to predict in-vivo performance from in-vitro results is described in the present investigation.

KEYWORDS: IVIVC, Compartment independent model, Convolution, Deconvolution, plasma concentration profile.

INTRODUCTION
An in-vitro in-vivo correlation (IVIVC) is a predictive mathematical model describing the relationship between an in vitro property of a dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response.[1, 2] IVIVC play an important role in the pharmaceutical drug development and optimization of it is a time consuming and expensive process. The optimization of pharmaceutical product requires alteration in formulation, composition, equipments, batch sizes and manufacturing process. If such types of one or more changes are applied to the formulation, the in vivo bioequivalence studies in human may required to be done to prove the similarity of the new formulation which will not only increase the burden of carrying out a number of bioequivalence studies but eventually increase the cost of the optimization process and ultimately marketing of the new formulation.

To overcome these problems it is desirable to develop in vitro tests that reflect can bioavailability data. IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development. The main objective of an IVIVC in formulation development is to serve as a surrogate for in vivo performance and assists in supporting biowaivers. The aim of present investigation is to use the outcomes of in-vitro studies of the optimized formulation test and determine its in-vivo performance to compare it with the reference to evaluate how close the agreement is? Nowadays system approach based convolution and deconvolution techniques are available for prediction of in-vivo performance and simulation of the in-vivo performance which are recognized by regulatory agencies around the world.[3]

System approach treats the entire human body as one single system (Fig. 1) 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.[4]

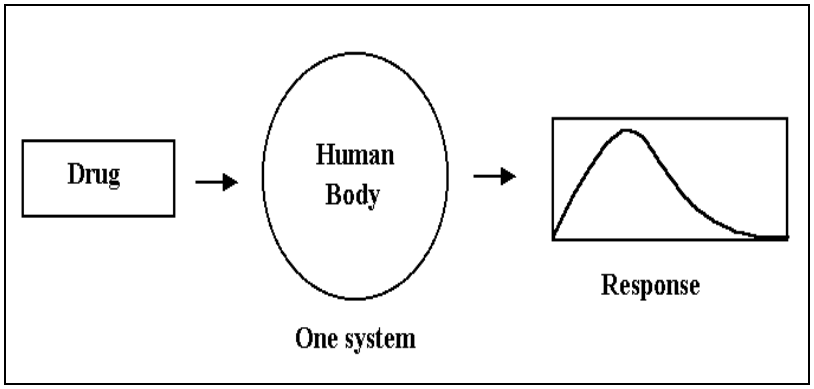

Figure 1: Schematic representation showing the concept of system approach.

The relationship between the in vitro and in vivo characteristics is expressed mathematically by a linear or nonlinear correlation.[5] However, the plasma concentration profiles cannot be related directly to the in vitro release rate; they have to be converted first to the underlying in vivo release or absorption data, either by pharmacokinetic compartment model analysis or by linear system analysis. The linear system analysis is compartment independent model based on system approach and usually accomplished mathematically by using the convolution and deconvolution method.[6, 7] This method requires the availability of a weighting function for the human body system i.e. the unit input response (UIR). The convolution and deconvolution operations are based on two basic assumptions namely time invariance and superposition.

Convolution is the simple process of adding several plots, mathematically is amounts to integration.[8, 9] The rate at which the drug is coming out as a function of time is denoted by I(t), it is the input rate as a function of time. If the UIR is denoted by U (t) which is plasma concentration time relationship then the plasma concentration profile C(t) resulting from the entire dose I(t) is given by.

$$C(t) = \int_0^t I(x) \cdot U(t-x)dx$$

C(t) is the plasma concentration, I is the drug input rate and U is the UIR, all are represented as a function of time. As the drug is continuously coming out, the instantaneous value of drug release is I(t), at each instance of time this drug will produce certain plasma concentration equal to I(t) times the UIR. The integration actually sums up all such consecutive plasma profiles resulting from the administration of the drug at a rage I(t). Convolution can be performed by various techniques such as Analytical Methods, Laplace Transform Technique or convolution by integral.

The deconvolution is a mathematical procedure that is exactly opposite of convolution.[10, 11] Convolution is used to find out plasma profile from a Unit Input Response (UIR) and a given drug input rate. Deconvolution is used to obtain the in-vivo drug input rate using a UIR and a plasma concentration profile. In pharmacokinetics, this concept is very useful and has been successfully employed for determination of the drug input rates from plasma profiles.

EXPERIMENTAL METHODS AND MATERIALS

We have designed and developed Carbamazepine extended release tablet 200 mg based on osmotic technology by using Single Core Osmotic Pump (SCOP) approach. The optimized formulation (F6) selected as test for the purpose of prediction of the in-vivo performance and comparison with reference listed drug (RLD) Tegretol® XR-Carbamazepine extended release tablets, Novartis. Investigations for test (F6) are carried out for in-vitro performance and drug release profiles. The RLD is related to our design and attempts were made to match the RLD in terms of in-vivo performance. The 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)[12] was used for the purpose of comparison. The available information in the single dose fed study (400mg) of reference was for 168 hours and in-vitro dissolution over a period of 24 hr with four data points. The optimized formulation test (F6) was 200 mg so for the comparison with the reference plasma profile of fed study, test plasma profile can be doubled (test dose is 200mg, reference dose is 400 mg). The following experimental strategy was adopted for the prediction of in-vivo performance of test (F6).

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 IVIVC for the reference, independently for the fed and fasting studies.
3. Use this IVIVC to predict the in-vivo drug absorbed for the test formulation (F6) whose dissolution studies are done.
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 predicted plasma concentration versus time profile of the test (F6) with the reference to assess as to how close be the agreement?

RESULTS AND DISCUSSION

Prediction of in-vivo performance of test (F6) for fed study

When a plasma concentration versus time profile is available, the estimation of the in-vivo drug release rate or cumulative amount of drug absorbed as a function of time requires deconvolution of the plasma concentration versus time profile with Unit Input Response (UIR). The deconvolution is a mathematical process using analytical equation or implementation of numerical deconvolution and it is known that it is a tedious and unstable technical process; therefore we took the assistance of Unisoft Pharma Solutions, Aurangabad, India to carry out the deconvolution.

The mean plasma concentrations of single dose fed study of reference are summarized in Table 1 and the same is represented graphically in Fig. 2.

Table 1: Mean plasma concentrations of single dose fed study of reference with a dose of 400 mg.

Time (hr)	Mean Plasma Concentrations (ng/ml) Fed study	Time (hr)	Mean Plasma Concentrations (ng/ml) Fed study
0	0	18	2749.64
1	1.9	20	2682.14
2	177.62	22	2688.79
3	553.70	24	2725.12
4	1023.54	27	2766.51
5	1541.96	30	2630.37
6	1794.81	36	2355.68
7	2022.09	48	1953.97
8	2246.21	72	1298.72
10	2624.61	96	866.98
12	2745.54	120	548.18
14	2760.63	144	395.34
16	2739.39	168	270.90

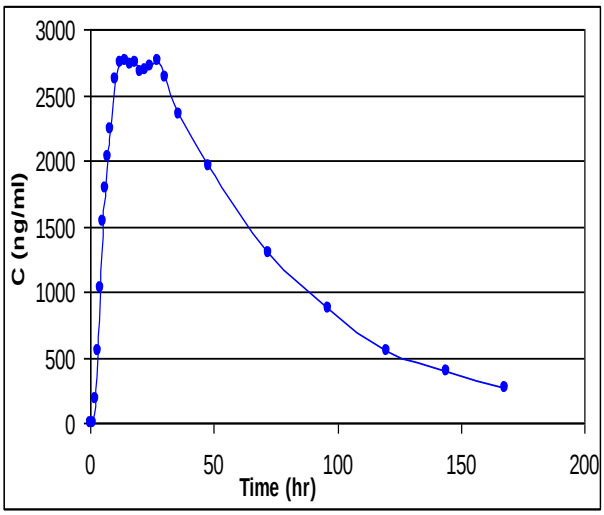

Figure 2: Plasma concentration versus time profile of single dose fed study of reference with a dose of 400 mg.

For the determination of the in-vivo drug absorption the two plasma profiles were deconvolved using the Unit Input Response (UIR) constructed using the trailing part of the plasma concentration profile. The results of deconvolution are represented in Fig. 3.

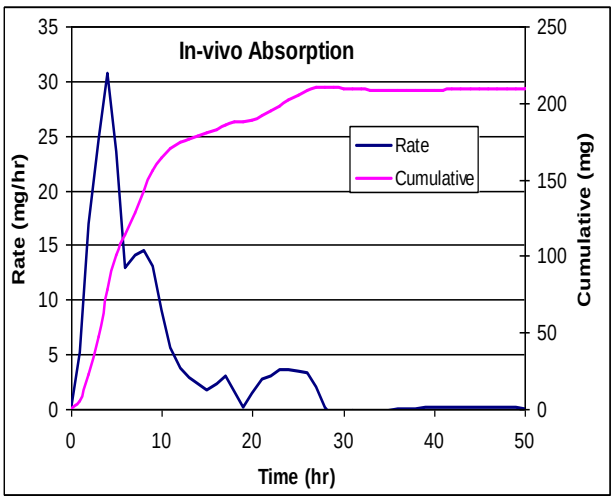

Figure 3: Rate and in-vivo drug absorption reference for fed study obtained from deconvolution, blue line is rate and the pink is the cumulative amount.

The cumulative amount of drug absorbed as a function of time is used for the construction of the IVIVC using the in-vitro drug release data. The dissolution data for the reference is available in CDER Bioequivalence Review (ANDA 078115) summarized in Table 3 and the same is represented graphically in Fig. 4.

Table 3: In-vitro drug release (in % and mg) as a function of time (Reference 200mg).

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

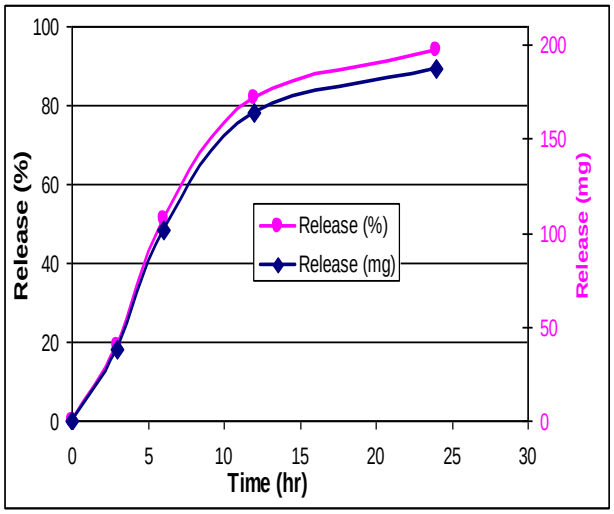

Figure 4: In-vitro dissolution profile of reference 200mg.

As shown in Table 3 in-vitro data for the reference are given at four time points, at these time points the corresponding in-vivo drug absorption can be obtained from deconvolution (Fig. 3). The IVIVC was constructed by plotting in-vivo amount of drug absorbed against in-vitro drug released (Fig. 5).

The points plotted represent actual data for the in-vitro drug released and in-vivo drug absorbed. The straight line joining these points is the best fitting straight line for this data and represents the IVIVC; the equation of the straight line is also shown in the inset along with the value of R^2.

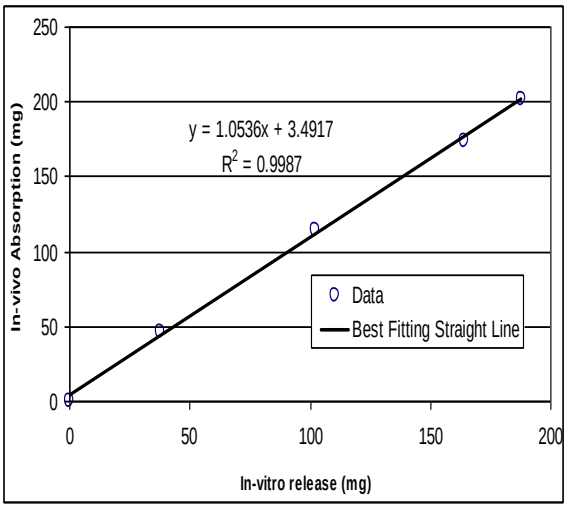

Figure 5: IVIVC for reference (fed study).

It is seen from Fig. 5 that all the points lie well along the straight line indicated by the value of R^2 which is close to unity indicating a good fit. The equation of the linear (straight line) IVIVC is $y = 1.0536x + 3.4917$ and can be used for the prediction of in-vivo absorption from a given in-vitro release. In the equation for IVIVC the variable y stands for the in-vivo amount of drug absorbed and x represents the corresponding amount of in-vitro drug released at that time point.

For the prediction of the in-vivo performance of the test (F6), the in-vitro data of the test is used from which the corresponding amount of drug absorbed as a function of time is obtained using the straight line IVIVC (Fig. 5) and equation of the IVIVC.

Table 4: In-vitro drug release (in % and mg) as a function of time (Test F6).

Time (hr)	In-Vitro Drug Released (%)	In-Vitro Drug Released (mg)
0	0	0
1	4.26	8.52
2	10.32	20.64
3	21.24	42.48
4	34.33	68.66
6	49.89	99.78
8	59.32	118.64
10	68.96	137.92
12	78.66	157.32
16	83.65	167.3
20	88.56	177.12
24	93.12	186.24

The dissolution study summarized in Table 4 is in terms of drug released in % as well as in mg at different time points are represented graphically in Fig. 6.

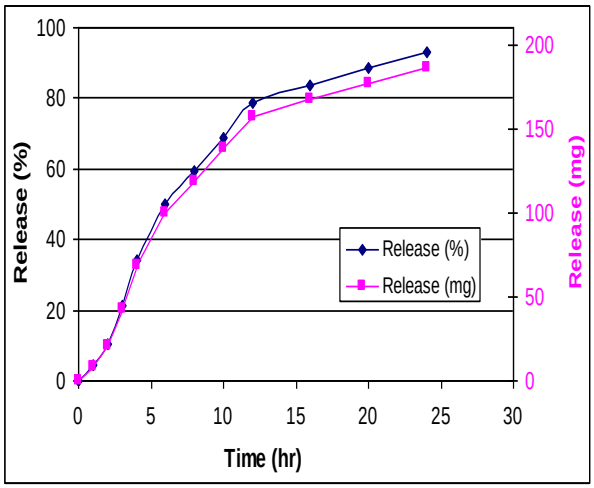

Figure 6: In-vitro dissolution profile of test (F6).

Predicted in-vivo drug absorbed (y) for test (F6)was calculated using the equation of linear IVIVC $y = 1.0536x + 3.4917$ at different time points using the values of in-vitro release (x) and the resulting data of in-vivo drug absorption is shown in last column of Table 6. Second and third column show corresponding in-vitro fraction of drug released.

Table: 6 In-vitro drug released and predicted in-vivo drug absorbed as a function of time calculated from linear IVIVC of fed study for test (F6).

Time (h)	In-Vitro Drug Released (%)	In-Vitro Drug Released (mg)	In-Vivo Drug Absorbed (mg) (Predicted)
0	0	0	0
1	4.26	8.52	12.47
2	10.32	20.64	25.24
3	21.24	42.48	48.25
4	34.33	68.66	75.83
6	49.89	99.78	108.62
8	59.32	118.64	128.49
10	68.96	137.92	148.80
12	78.66	157.32	169.24
16	83.65	167.3	179.76
20	88.56	177.12	190.11
24	93.12	186.24	199.71

The prediction of plasma concentration versus time profile using the in-vivo amount of drug absorbed as a function of time requires convolution. In the process of convolution the rate at which drug absorbed is convolved with the corresponding UIR. To determine the rate at which drug is absorbed in-vivo the cumulative amount of in–vivo drug absorbed is differentiated. Differentiation can be done easily if the cumulative drug absorption is available in the form of analytical functions, in the present case the cumulative amount of drug absorbed in the form of table and hence numerical differentiation works better. We use simple program for differentiation in a mathematical software MathCad–11 which uses spline fitting, interpolation and differentiation.

Table 7: Rate of in-vivo drug absorption obtained from IVIVC (fed study)

Time (hr)	Rate (mg/hr)	Time (hr)	Rate (mg/hr)
0	0	13	4.029
1	9.375	14	1.73
2	17.66	15	0.781
3	27.33	16	1.183
4	24.81	17	2.119
5	15.60	18	2.775
6	11.16	19	3.149
7	9.729	20	3.243
8	9.532	21	3.056
9	10.10	22	2.587
10	10.98	23	1.838
11	10.67	24	0.8078
12	7.678	-	-

The in-vivo drug absorption rate calculated using dissolution study of test (F6) and the IVIVC of reference for fed study is shown in Table 7 which is also represented graphically in Fig. 7. This in-vivo drug absorption rate when convolved with the UIR gives the in-vivo performance in terms of the plasma concentration versus time profile.

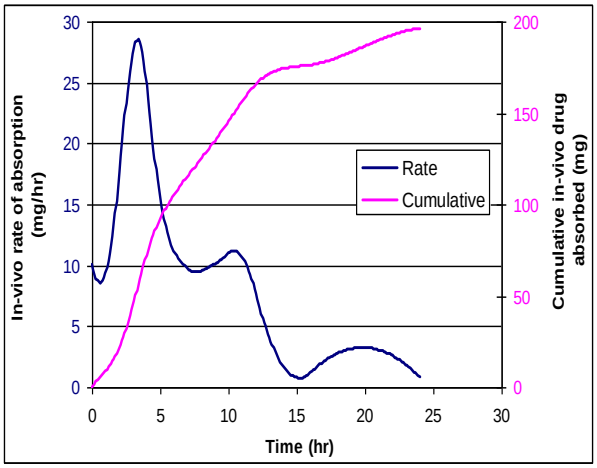

Figure 7: Rate and in-vivo drug absorption of test (F6) for fed study, blue line is rate and pink is the cumulative amount.

Convolution can be implemented in different ways like Laplace transform when the two functions are available in analytical equation form, however in the present case the two data are available in tabular form and under such circumstances numerical convolution is convenient.

We used MathCad–11 for the implementation of the convolution, a screenshot of the MathCad window is shown in Fig. 8. The MathCad-11 uses the data of UIR and the in-vivo drug absorption rate and convolves the

two and the result is saved in a tabular form in Microsoft Excel file for further use. The result of convolution is shown in Fig. 9.

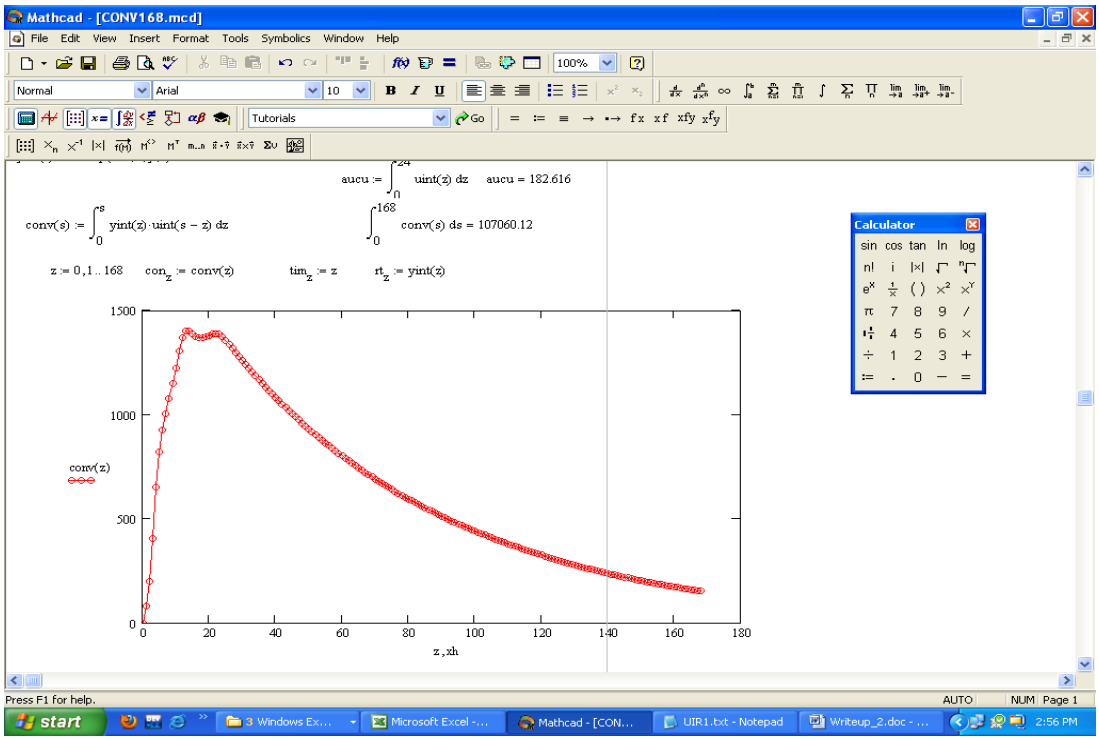

Figure 8: A typical screenshot of MathCad implementation of convolution

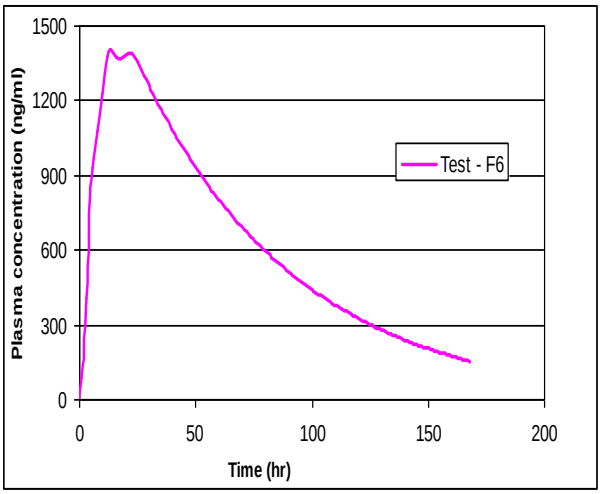

Figure 9: Predicted plasma concentration profile for the test (F6) (fed study).

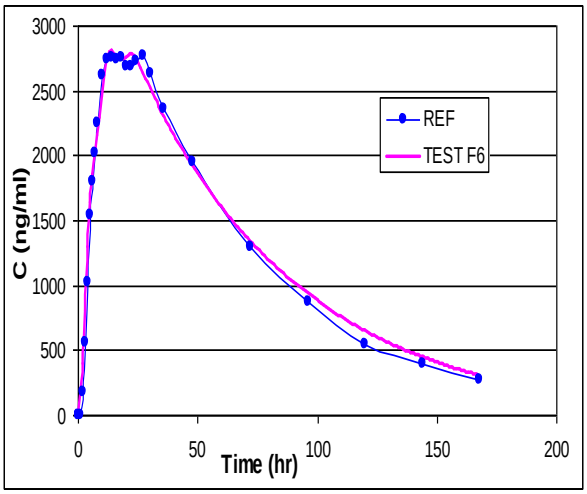

Figure 10: Comparison of predicted plasma profile of test (F6) with reference (fed study).

As the dose of test (F6) is 200 mg and the reference is 400 mg for comparison of plasma profile of both under fed study, the predicted plasma profile of test (F6) has to be adjusted i.e. doubled according to the dose of reference. The comparison of scaled up (2x) predicted plasma profile of the test F6 (200 mg) with reference (400 mg) for fed study is represented in Fig. 10.

Figure 10 shows that there is an excellent agreement between the test (F6) and reference as the two plasma concentration profiles almost super impose indicating that the test (F6) nicely compares with the reference. Comparison of the pharmacokinetic parameters of test (F6) and reference for fed study is summarized in Table 8.

Table 8: Comparison of pharmacokinetic parameters (fed study).

Parameter	Test (F6) (Fed Study) 2x (Predicted)	Reference (Fed Study)	T/R (Ratio)
AUC 168 (ng hr/ml)	214116	208502	1.02
Cmax (ng/ml)	2806	2760	1.01
Tmax (hr)	14	14	1.00

CONCLUSION

The present work utilized system approach based technique of convolution and deconvolution to evaluate the in-vivo performance of selected optimized formulation test (F6). Dissolution studies showed promising results as the in-vitro dissolution was close to the reference, however the dissolution study for the reference was available in literature had only four data points, a dissolution study with more data points would have been more useful.

For the in-vivo performance prediction we used the IVIVC of the reference. The IVIVC was constructed using the in-vitro study of the reference available in literature and the in-vivo drug absorption determined using deconvolution of the plasma concentration profile with the UIR (Unit Input Response). The IVIVC for the fed study was nicely fitting to a straight line.

The in-vivo performance of the test was determined using the in-vitro study of the test and finding out the in-vivo drug absorbed as a function of time using IVIVC. The predicted in-vivo information so obtained was in the form of cumulative amount of drug absorbed as a function of time. This data was converted to corresponding in-vivo drug absorption rate as a function of time using numerical differentiation in MathCad-11 software. The predicted plasma concentration versus time profile was obtained by using convolution of the absorption rate with the UIR. The resulting plasma concentration profiles of test were compared with those of the reference.

For fed study, the comparison of the predicted plasma profile of test (F6) with reference show excellent agreement as the tow plots almost superimpose indicating similarity of performance. The predicted pharmacokinetic parameters of test (F6) viz. AUC, Cmax and Tmax are 214116 ng hr/ml, 2806 ng/ml and 14 hr respectively.

A system approach based simple and practical procedure of convolution and deconvolution to predict in-vivo performance from in-vitro results is described in the present investigation.

ACKNOWLEDGEMENT

We thank to Unisoft Pharma Solutions, Aurangabad and Principal, Government College of Pharmacy Aurangabad for support and institutional facility.

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