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Wagner-Nelson and Numerical Deconvolution Based Approaches for in-Vivo Performance Prediction

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Abstract: ***Collected information in in-vitro dissolution studies, by means of statistical or mathematical models, can be used to predict the in-vivo performance of dosage forms, e. g. Plasma concentration of drug. This study has a great importance in reducing the number of in-vivo human studies necessary in drug development and batch approval specification limits during drug manufacturing and as a substitute for human in-vivo studies for drug approval. In this study data from previous work for in vitro dissolution profile and in vivo plasma profile were taken and used to perform In Vitro- In Vivo correlation using two methods, Wagner-Nelson and numerical deconvolution. The results shows that Wagner-Nelson has correlation coefficient between %dissolved and %absorbed of 0.85 while the numerical deconvolution shows correlation coefficient of 0.93.***

Keywords: In Vitro–In Vivo Correlation, Deconvolution, Wagner-Nelson, plasma profile

1. Introduction

In vitro- Invivo correlation is A predictive mathematical model describing the relationship between an in-vitro property (usually the extent or rate of drug release), and a relevant in-vivo response (e.g., plasma concentration or amount of drug absorbed). [1] It is established to enable a dissolution test to be used as a surrogate of the bioavailability study. It is basically related the amount of drug dissolved in-vitro to the amount of drug absorbed in-vivo using appropriate mathematical functions and suitable dissolution test conditions [2].

The IVIVC is calculated from in vitro and in vivo data of the same formulation using some mathematical functions based on the type of parameters employed, divided into five categories. The following five levels of IVIVC correlations are narrated in (food and drug administration) FDA guidelines [3].

1. Level A correlation.
2. Level B correlation.
3. Level C correlation.
4. Multiple levels C correlation.

1.1. Level A correlation

This level of correlation is the highest category of correlation and represents a point-to-point relationship between in vitro dissolution rate and in vivo input rate of the drug from the dosage form The percent of drug absorbed may be calculated by means of model-dependent techniques such as the Wagner-Nelson procedure Eqn.(1) or the Loo-Riegelman method or by model-independent numerical deconvolution Eq. (2).

$$\text{Drug absorbed}(\%) = \left[\frac{\left[\frac{C(t)}{k_e}\right] + \text{AUC}_{(0\to t)}}{\text{AUC}_{(0\to\infty)}}\right] \times 100 \ldots (1)$$

The purpose of a Level A correlation is to define a direct relationship of in-vitro data with in-vivo data such that measurement of the in vitro dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. In the case of a level A correlation, an in-vitro dissolution curve can serve as a surrogate for in-vivo performance [4]. A set of dissolution data obtained from one formulation is correlated with a deconvoluted plasma concentration-time data set. This approach is based on the following fundamental equation:

$$C(t) = \int_0^t C_\delta(\tau) F(t-\tau) d\tau \ldots (2)$$

Where, C(t) = Plasma drug concentrations after oral dose at time t, C_δ (t) = Plasma concentrations after an IV dose or a dose of oral solution

A plasma drug concentration-time profile is usually the net effect of two simultaneous processes: (1) absorption of the drug from the GI tract. As absorption is proportional to drug dissolution thus absorption and dissolution are used interchangeably, (2) elimination of the drug from the blood. These two actions, and their net effect, are represented by three profiles and are shown in the Fig. (1) In mathematical terminology, these three curves (profiles) are known as functions, dissolution or absorption as input, blood concentrations as output and the elimination as the weighting factor or function.

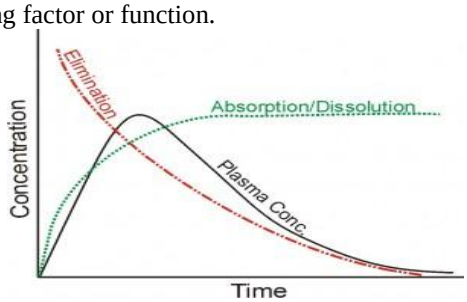

Figure 1: The absorption profile, elimination profile, and the net profile plasma concentration). [4]

Determining output function (plasma blood concentrations), if input function (dissolution results) is available, the procedure will be called convolution technique and inverse of it, that is obtaining input function (absorption/dissolution results) if output function is provided, the procedure will be called deconvolution [5].

To demonstrate a correlation, fraction absorbed in vivo should be plotted against the fraction released in vitro. If this relationship becomes linear with a slope of 1, then curves are superimposable, and there is a 1:1 relationship which is defined as point-to-point or level A correlation. Under these circumstances, the correlation is considered general and could be extrapolated within a reasonable range for that formulation of the active drug entity. The relationship between in vitro dissolution, expressed by the kinetics x = f(t), and in vivo input kinetics, expressed by the relation y =f(t), would be linear, in Eqs. (3), (4).

$$y = ax + b \quad \ldots (3)$$

$$\%\text{ in vivo input }(t) = a.\%\text{ in vitro input }(t) + b \quad \ldots (4)$$

Where a and b are the intercept and slope of the regression line, respectively.

2. Result and Discussion

2.1. Deconvolution Based IVIV Correlation:

First of all to find data of accumulative percent released in vitro at time point similar to that of bioavailability test calculated by parameter estimation technique using the Matlab program. Data from previous work for in vitro dissolution profile and in vivo plasma profile for sustained release dicclofenac sodium were takento perform IVIV Correlation

There are two types of level A IVIVC as follows:

2.1.1. Model dependant approach (Wagner-Nelson method)

The data would be fitted to a single compartment model(as shown above), the % absorbed were calculated using Eq.(1),Table(1) shows % dissolved and % absorbed using wagner nelson equation knowing that All calculations were made using MATLAB package (version R2012b).

Table 1: % dissolved and % absorbed using Wagner-Nelson method.

% Dissolved	% absorbed
0	1.822
0.89	9.113
1.18	16.92
2.04	32.24
2.39	51.63
21.87	74.06
33.8	86.12
64.01	99.7
74.81	100
94.8	96.19
101.2	97.27

The percent dissolved represents the data obtained from dissolution test (mean of seven tablets), while percent absorbed obtained by calculating the total area under the curve and the cumulative area under the curve using cumulative integration then Eq.(1)applied to each time point.

Percent dissolved plotted against time, Fig.(1):

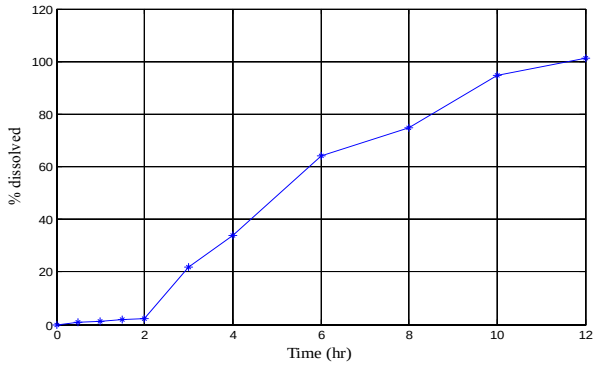

Figure 1: Percent Dissolved against Time

percent absorbed using Wagner-Nelson method plotted against time Fig(2):

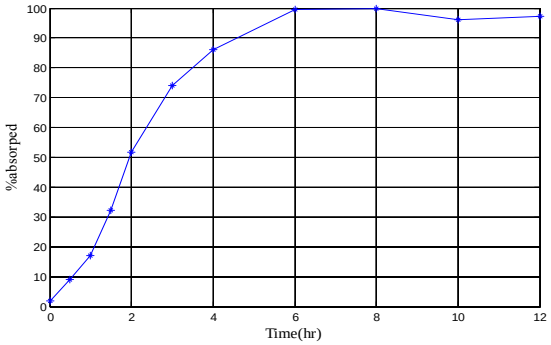

Figure 2: Percent Absorbed Versus time using Wagner-Nelson Method

The percent absorbed using Wagner-Nelson method is sensitive to the AUC and k_e.

Percent absorbed plotted against percent dissolved as shown in Fig. (3):

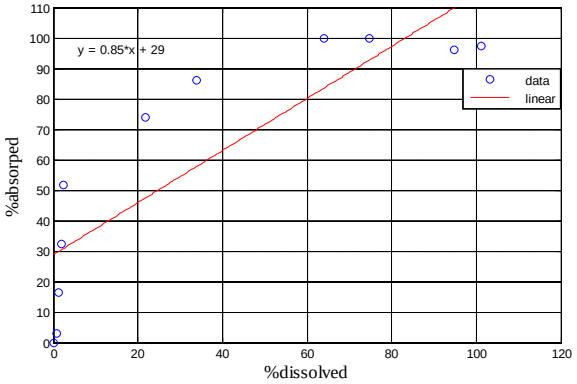

Figure 3: IVIVC using Wagner-Nelson Approach

Linear fitting made, slope and regression coefficient obtained for the correlation was nearer to 1.0 indicating good correlation from level A modeling. A point to point link from level A which is a keystone of an acceptable and reliable correlation was achieved.

2.1.2. The Model Independent Approach (Numerical Deconvolution)

Since no intravenous data was available from this study, they had to be taken from the literature (Willis et al.,1979) to perform numerical deconvolution. Therefore, the

deconvoluted data cannot be interpretedas 100% accurate. By fitting the intravenous plasma drugconcentration–time data to the 'Exponential Decay' regression, bi-exponential functions were found todescribe the profile appropriately Eq. (5). The unit impulse response wasthen obtained from the coefficients of bi-exponential equation

v= 10.21*exp (-16.28*t) + 1.868*exp (-0.9417*t)…(5)

Where v is the intra-venous concentration at sampling time points.

Fig.(4) shows the plasma concentration versus time of intra-venous injection.

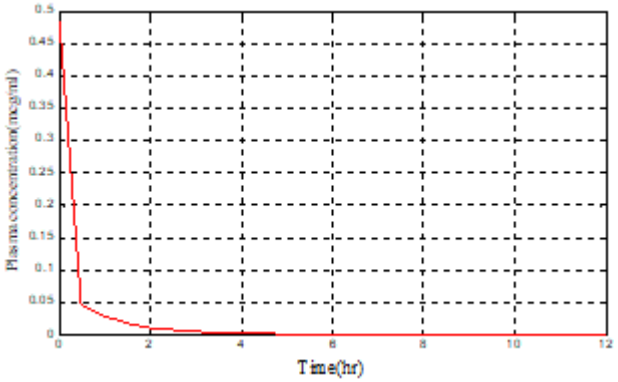

Figure 4: Plasma Concentration Versus Time of Intra-Venous Injection

The plasma concentration data deconvoluted with the unit impulse response and the percent absorbed shown in Table (2)

Table 2: Deconvolution Results

Time	%absorbed
0	4.14
1	12.23
1.5	19.27
2	25.18
2.5	30.82
3	53.85
4	75.58
6	87.02
8	98.88
10	105.49
12	102.48

Accumulative percent absorbed of DS using numerical deconvolution ploted against time as shown in Fig. (5)

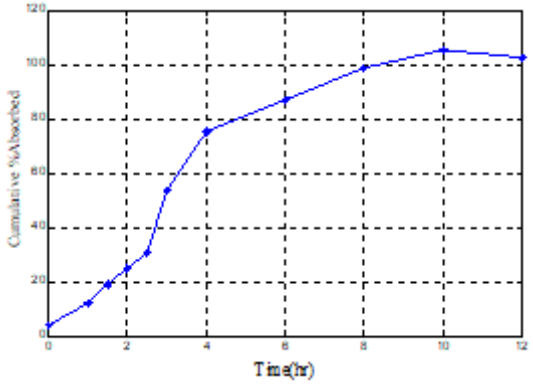

Figure 5: Accumulative Percent Absorbed of DS using Numerical Deconvolution.

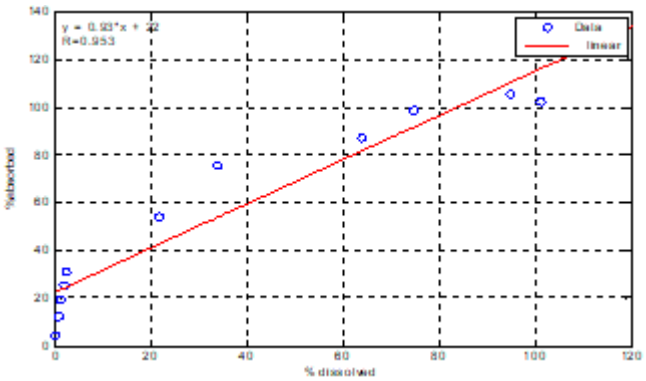

Figure 6: IVIVC using Numerical Deconvolution

Then linear fitting made, the slope was 0.93 and the regression coefficient 0.95 as shown in fig. (6), it's clear that numerical deconvolution gave higher correlation than wagner-nelson method this may be due to the fact that wagner nelson method highly sensitive to AUC and k_e in the another hand, numerical deconvolution is more general model and not depend on by how many compartments plasma concentration versus time profile represented.

3. Conclusion

A point-to-point link from level A which is a keystone of an acceptable and reliable correlation was achieved because the correlation coefficient was nearer to 1, From the results of the current study, IVIVC developed by level A correlation makes Diclofenac sodium dissolution profile meaningful, the numerical deconvolution model gave a higher correlation between in-vitro and in-vivo release profile than Wagner-Nelson method where the slope were 0.93 and the regression coefficient 0.95, this may be due to that wagner-nelson method is sensitive to AUC (area under the curve) and Ke(elimination rate constant).

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