Prediction of In-Vivo Absorption of Drug Using Mathematical Concept of Deconvolution

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Abstract

Mathematical modeling and prediction of in-vivo performance in terms of the in-vivo drug absorption is of prime importance in the field op pharmacy in relation to the design and development of oral dosage forms. In order to be able to modify the design of a dosage form to comply with certain requirements, the in-vivo absorption characteristics form the basis. The quantitative determination of in-vivo absorption characteristics is not possible, mathematical technique based on system approach, convolution and deconvolution provides the precise answer. We present details of implementation of system approach and deconvolution for the prediction of in-vivo absorption characteristics in terms of rate of absorption of drug and cumulative drug absorbed as a function of time. Plasma concentration versus time profile of a certain product that can be fitted to a bi exponential equation is considered and prediction of the in-vivo absorption rate and cumulative amount absorbed as a function of time is described in detail and findings discussed.

Keywords: *System Approach, In-vivo absorption, Plasma concentration of drug, IVIVC, Deconvolution*

Introduction:

In design and development of oral dosage-form pharmaceutical industry requires characterization of various parameters of interest to pharmaceutical industry [1]. This assumes importance while submission of product details to regulatory agencies like US Food and Drug Administration (US FDA) [2]. Many times it is required to provide in-vitro in-vivo correlation (IVIVC. When a certain drug with certain dosage-form is tested in humans conducting a bio-study on certain number of subjects like 12 or 24 or even more at times it results in a table of values of plasma concentration of drug as a function of time. In such a bio-study the subjects under test are subjected to a washout period where they are kept under controlled conditions so that any residual drug is washed out. Then a dosage form is administered (there are different types of bio-studies) blood samples are drawn at predetermined intervals and stored after proper labeling. The plasma concentration of drug is determined for all the individuals and concentration of drug in blood plasma is measured using suitable technique. The resulting table or plot of plasma concentration of drug as a function of time is constructed which is usually referred to as plasma profile.

In the process of making of a dosage-form the design has to comply with certain requirements, if it is a new design, it has to be within certain range as determined by the laid down conditions. If it is the modification of design, there is some standard plasma profile and the design has to be as close to the reference product as possible [3-5]. This involves the information of what is the rate of absorption of drug at different time point or the in-vivo drug absorption as a function of time. This in-vivo absorption is not always same as the in-vitro drug release, in such cases an IVIVC is needed which is in-vitro in-vivo correlation [6-8]. This relationship helps prediction of in-vivo absorption for a given in-vitro drug release.

The problem is that a plasma profile is available as a reference and the plasma profile of the test product has to mach that of reference. This requires knowledge of in-vivo drug absorption profile for both the test and reference product [9-11]. Determination of these in-vivo absorption profile is not possible with the convention pharmacokinetic models and the results are not reliable [12-15]. Some time back Weng Pederson introduced the concept of System Approach that makes use of mathematical concepts of Convolution and Deconvolution [16]. The relation between the three i.e. the Unit Input Response (UIR or U(t)), the Drug Input Rate I(t) and Plasma Concentration Profile C(t) is :

$$C = I * U \quad (1)$$

or

$$C(t) = I(t) * U(t) = \int_0^t I(t-u) \cdot U(u) du \quad (2)$$

In the above equations ‘C’ is the plasma concentration of drug as a function of time and I is the Unit Input Response (UIR), the plasma concentration of drug as a function of time and ‘I’ is the rate at which the drug is absorbed in-vivo. Equation 1 and 2 represent the convolution equation and the convolution integral respectively. In equation 2, t is the variable for time and ‘u’ is a dummy variable used to evaluate the definite integral. The symbol ‘*’ in equation 1 and 2 is not regular multiplication but stands for convolution of ‘I’ and ‘U’.

The opposite of Convolution is the Deconvolution and the equation representing Deconvolution is:

$$I(t) = C(t)/U(t) \tag{3}$$

The input rate of drug absorption can be determined by solving equation 3 for I(t). As it is opposite of integration it amounts to solving a differential equation and the process becomes simple if the two functions C(t) and U(t) are available in analytical form. If the data is available in tabular form, attempts can be made for fit the data to a suitable equation, at times; fitting the data to piece wise polynomial is also used. In DDS design or modification one needs the information on how the drug is absorbed as a function of time, therefore the Deconvolution of equation 3 has to be solved. There are different methods for performing Convolution and Deconvolution like Laplace transform and numerical methods if the data is in the form of tables [17,18]. The numerical Deconvolution is a very unstable process and needs utmost care. The implementation of Convolution is as follows. For convolution first the Laplace transform of the three functions is to be determined and then the product of the Laplace transform of I and U is found [19, 20]. The inverse Laplace transform of the product of the two Laplace transforms of I and U is the convolution of the said two functions.

Laplace Transform Technique

The Laplace transform of a function f(t) by definition is given by

$$L\{F(t)\} = \int_0^\infty e^{-st} F(t)dt = f(s) \tag{4}$$

Inverse Laplace transform is just the opposite of this and standard tables are available in text books and literature that give Laplace transform and their invers for commonly used mathematical functions. Their multiplication and division rules are also available in literature. The Laplace transform takes a continuous time signal and transforms it to the s-domain.

$$L\{I(t)\} = i(s) \quad L\{(t)\} = U(s) \text{ and } L\{C(t)\} = c(s) \tag{5}$$

Here the main function in time domain is denoted by capital letters and their Laplace transform in s – domain is denoted by lower case letters. The convolution of two functions I(t) and U(t) resulting in the function C(t) is

$$C(t) = I(t) * U(t) \tag{6}$$

In Laplace domain

$$L\{C(t)\} = L\{I(t)\} \cdot \{U(t)\} \tag{7}$$

In s – domain

$$c(s) = i(s) \cdot u(s) \tag{8}$$

It is to be noted that the dot between the last two functions of equations 7 and 8 represents actual multiplication where as the '*' in equation 6 stands for convolution. For deconvolution

$$I(t) = C(t)/U(t) \quad (9)$$

$$L\{I(t)\} = \frac{L\{C(t)\}}{\{U(t)\}} = \frac{c(s)}{u(s)} \quad (10)$$

$$i(s) = \frac{c(s)}{u(s)} \quad (11)$$

The '/' sign in equation 9 is not simple division it represents Deconvolution. The Deconvolution of the two functions C and U in equation 9 is the inverse Laplace transform of i(s) in equation 11.

$$I(t) = L^{-1}\{i(s)\} \quad (12)$$

Using this procedure the in-vivo drug absorption as a function of time i.e. I(t) can be determined which can be compared with the standard and information about what changes in the test product are needed in terms of excipient used and other properties related to dissolution can be controlled.

Implementation of Deconvolution

To demonstrate the validity and importance of predictions using mathematical techniques in pharmacokinetic we consider a plasma profile of certain drug and implement entire procedure of prediction of in-vivo profile. In-vivo profile is the data or plot of the amount of drug absorbed as a function of time [17,19]. The plasma concentration of drug versus time plot is shown in Fig. 1. The plasma profile has a Tmax of 6 hours and Cmax of 278.5 ng/ml. The Area Under the Curve is 3477.41 ng·hr/ml for 0 to 36 hour and AUC (0 – ∞) is 3495.65 ng·hr/ml.

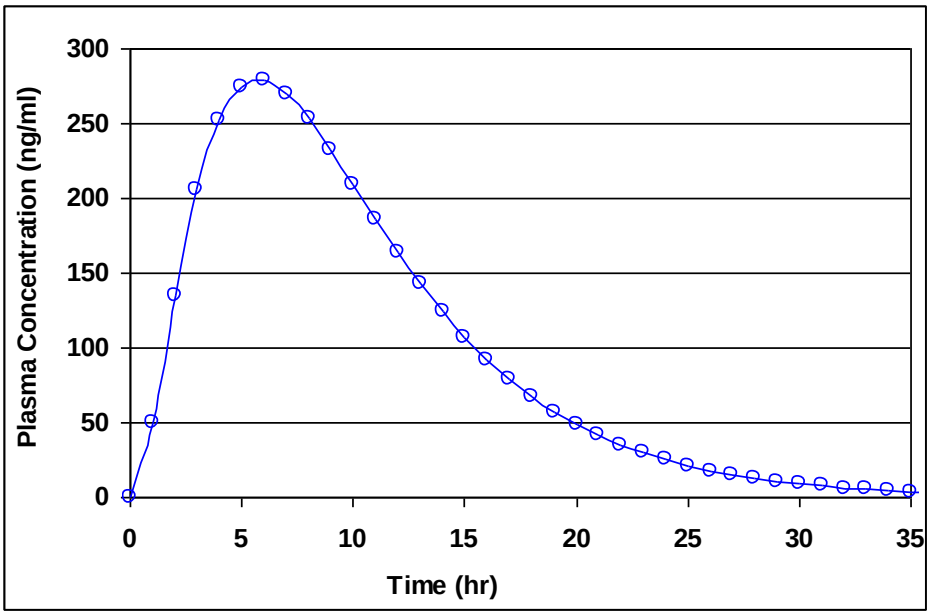

Fig. 1 Plasma concentration of drug versus time plot, the plasma profile

The plasma profile has a finite value till about 36 hours and what is desired is to estimate the amount of drug absorbed as a function of time. This requires implementation of the mathematical procedure of Deconvolution as discussed earlier. For the implementation of

Deconvolution shown in equation 9 – 12 which in turn requires the UIR or U(t). The UIR can be obtained using trailing part of the plasma profile shown in Fig. 1 after a time where absorption phase of the drug is over and normalizing the AUC to unit dose or 1 mg of drug. The plasma profile is fitted to a suitable analytical function and so is the UIR data. The equation fitting to the plasma concentration of drug versus time is given in equation 13 and the equation best fitting to the UIR data obtained from the trailing part of the plasma profile where the absorption phase is over is given in equation 14.

$$C(t) = 1738.078e^{-0.1749t} - 2286.33e^{-0.32t} + 548.25e^{-0.78t} \quad (13)$$

$$U(t) = 7.31e^{-0.32t} \quad (14)$$

The Laplace transform of the two functions respectively is

$$L\{C(t)\} = \frac{-1.29999976874723233e-19 \cdot s + 152.6031945}{(s+0.32)\cdot(s+0.1749)\cdot(s+0.78)} \quad (15)$$

$$L\{U(t)\} = \frac{7.31}{s+0.32} \quad (16)$$

Dividing right hand side of equation 15 by right hand side of equation 16 and simplifying and then splitting into partial fractions we get

$$I(s) = \frac{4.572664e-19}{(s+0.32)} + \frac{34.5}{s+0.1749} - \frac{34.5}{s+0.78} \quad (17)$$

Taking the inverse Laplace transform of equation 17 gives the equation of the in-vivo drug input rate I(t) as

$$I(t) = 2.094\times10^{-19}\cdot e^{-0.32*t} + 34.5\cdot e^{-0.1749t} - 34.5\cdot e^{-0.78t} \quad (18)$$

The in-vivo rate of drug absorption shown in equation 18 is presented graphically in Fig. 2.

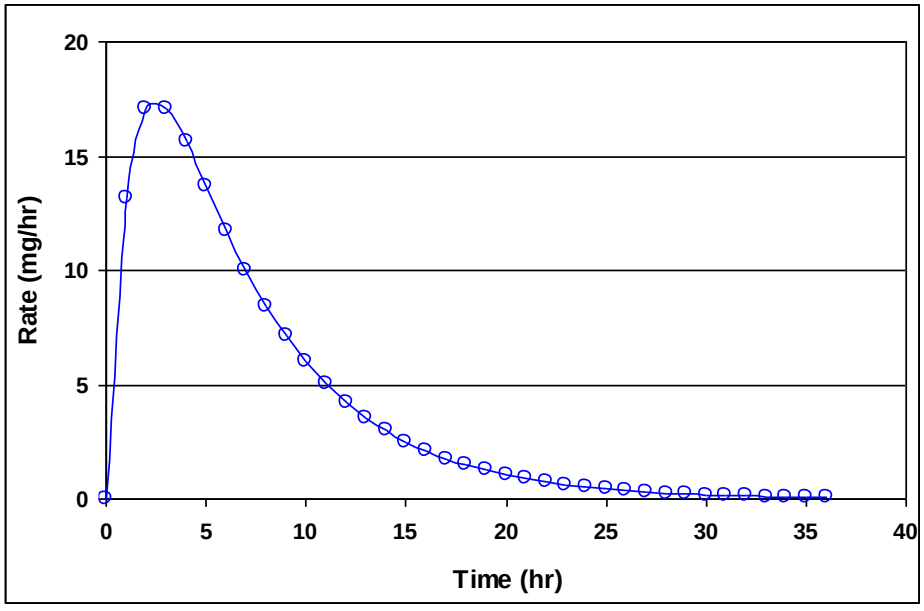

Fig. 2 Plot of In-vivo drug absorption as a function of time (Input rate)

Traditionally and also from the point of view of taking a decision regarding what modification in the drug absorption as a function, along with the drug absorption rate, the cumulative amount of drug absorbed as a function of time is found to be very useful. The cumulative amount of drug absorbed in-vivo as a function of time can be obtained integrating the in-vivo rate of drug absorption as a function of time from equation 18. Plot of cumulative amount of drug absorbed as a function of time is shown in Fig. 3.

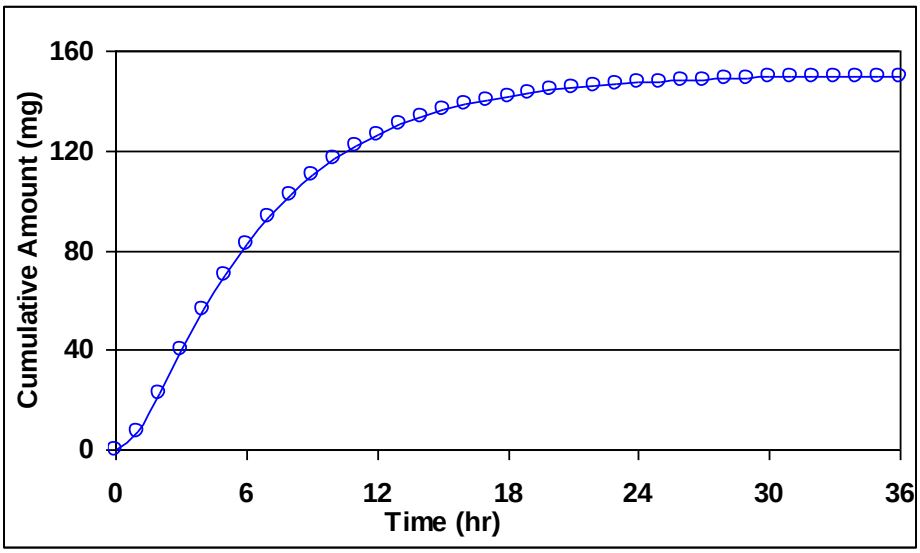

Fig. 3 Plot of cumulative amount of drug absorbed in-vivo as a function of time

The cumulative amount of drug absorbed in-vivo is shown in Fig. 3 which is obtained by integrating the equation 18. The cumulative amount of drug absorbed as a function time shows the after the absorption phase is over, after about 20 hours, the amount of drug absorbed plot becomes flat and the total amount of drug absorbed is about 150 mg which is consistent with the data used.

Results and discussion

In the field of pharmacy, particularly in the design and development of oral dosage forms like tablets and capsules, to comply with the requirements it becomes very important to know the in-vivo performance in terms of the drug absorption as a function of time. The existing techniques in pharmacokinetics, other than the one presented here, are incapable of providing realistic and reliable result. We demonstrated that for a product with 150 mg of drug and given plasma performance, the system approach and Deconvolution can be very useful and reliable to predict in-vivo drug absorption which is of key importance is product design and development. This can be used to control at what time how much drug is to be released or absorbed. This becomes extremely important for long acting dosage-forms like slow release, sustained release etc.

ACKNOWLEDGEMENT

Principal Maulana Azad College, Aurangabad 431008 for providing research facility. Unisoft Pharma Solutions, Aurangabad for sharing important information techniques and tools and training. Principal Dr. Anil P Battase, GRN College of Pharmacy, Sawarde, Chiplun 415606, Maharashtra, India and Dr. Nityanand Zadbuke, Manager (F&D), RV Lifesciences Limited, Aurangabad, for sharing useful information and guidance from time to time related to system approach and pharmaceutical applications.

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