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Mathematical Modeling based on Deconvolution for Prediction of In-vivo Drug Absorption

Vijay M. Jadhav[1], Bhausaheb R. Sontakke[2],Nazneen Akthar[3], A. P. Battase[4], Yusuf H. Shaikh[5]

[1] Maulana Azad College of Arts, Science and Commerce, Aurangabad 431001, India
[2] Pratishthan Mahavidyalaya, Paithan District, Aurangabad MH, India
[3] Maulana Azad College of Arts, Science and Commerce, Aurangabad 431001, India
[4] GRN College of Pharmacy, Sawarde, Chiplun, Maharashtra, India
[5] Shivaji Arts, Commerce and Science College, Kannad Dist, Aurangabad MH, India

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Abstract

In pharmaceutical industry the most challenging task is the determination of pharmacokinetic parameters which is of prime importance. In oral Drug Delivery System (DDS) the plasma concentration of drug resulting from a dosage-form is obtained conducting bio-studies where the time, efforts and funds required are very high. Modeling of pharmacokinetic parameters provide a powerful alternative to the bio-studies saving time and money. The results obtained by mathematical modeling are highly dependable and use of system approach based on convolution and deconvolution provides reliable results and are accepted by US FDA also.

We present a systematic approach and procedure for mathematical modeling of the Problem and discuss in-vivo drug absorption. In the prediction of in-vivo absorption of drug as a function of time from a given plasma profile, the only requirement is the Unit Input Response (UIR). The technique presented makes use of System approach and deconvolution. The plasma profile is deconvolved with the UIR which gives the in-vivo rate of drug absorption as a function of time. There are several possibilities of implementation of deconvolution, here we present an actual example of prediction of in-vivo rate of absorption of drug employing system approach and deconvolution using Laplace transform, details and findings are presented

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Introduction

One of the most important areas where mathematical modeling and simulation has an important role is the field of Pharmacy. Pharmacy as a subject requires inputs from a variety of basic sciences and major contribution comes from subjects like pharmacology, biochemistry, chemistry and subjects like engineering and technology. This resulted in limited exposures to other

basic science subjects like mathematics and Physics. The Field of Pharmacy mainly deals with the drugs and its administration including resulting effects. The process of making medicinal products to be administered orally comes under design and development of Oral Drug Delivery System (Oral DDS). 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 component is washed away. A dosage form is administered and blood samples are drawn at suitable predetermined time points after administering the dosage-form. The blood samples are properly labeled according to the time point and volunteer number for storing. These samples are then analyzed for the concentration of drug in blood sample and results are tabulated. The resulting table is subjected to some statistical tests and a plot of plasma concentration of drug as a function of time is constructed which is known as plasma profile.

While making of a dosage-form the design has to comply with requirements laid down by regulatory authorities. In most of the cases it is required to make an oral product which is similar in performance to an existing standard. This amounts to saying that the performance of the product should be as close to the reference as possible (Bio-equivalent) [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.

With the advancements and better understanding of mathematical techniques mathematical approach is being used skillfully in a variety of fields including science, Engineering, technology, research and development. Knowledge, tools and techniques developed in one branch of science has often been applied to other fields in solving problems that are otherwise difficult to handle [6-9]. This equally applies to most of the techniques and methods in mathematics that have been frequently applied in pharmaceutical data modeling and system engineering [10-12]. The use of mathematical techniques and modeling approach in pharmacology instead of animal or disease model is found very effective and reliable [13-15]. Mathematical models make use of mathematical techniques simplifying the real-world problems to provide reliable solutions.

The present work aims at bringing mathematical models into practical use, all that is required is to identify and understand the central phenomena of interest into any branch of science including pharmacokinetics [16, 17]. Pharmacokinetics is a branch of field of Pharmacy that mostly deals with the properties of drug absorption and elimination in order to determine the efficacy of the drug administered. This area is supposed to be most challenging in design development of Drug Dosage System (DDS) like tablets, capsules etc. What is required in prediction of the in-vivo

absorption is a suitable technique to extract the in-vivo absorption, the System Approach and deconvolution provides the answer.

System Approach to Pharmacokinetics

In prediction of in-vivo absorption conventional approach makes use of compartment based models. Here what becomes most important is the characteristics of drug and human body in terms of absorption and elimination of the drug when a certain dose of drug is administered. In conventional approach these properties are site specific in the gastrointestinal tract which are many in number and related information is not readily available hence poses difficulties and the results are poor. In system approach this issue is handled in a tricky way. Here, a unit amount of drug is administered and the resulting plasma concentration versus time table or plot is generated which is called Unit Input Response or Unit impulse Response (UIR). This UIR has all the necessary information regarding how the body behaves with the drug over the entire GIT and hence is a reasonably good representative containing all the realistic information to help prediction of in-vivo properties and performance.

In system approach the human body is considered as one single system and the effect of administration of the dosage form is determined with the help of mathematical technique known as deconvolution. This process needs two things i.e. the plasma profile of the dosage form and the UIR. If C(t) is the plasma profile, I(t) the drug input rate and U(t) represents the UIR then the three functions are related as:

$$C = I * U \tag{1}$$

If I and U are known then C and be determined, If C and U are known then I can be determined from:

$$I = C / U \tag{2}$$

In equation 1 and 2 representing convolution and deconvolution respectively, the symbol '*' stands for convolution and '/' stands for deconvolution respectively.

For the determination of in-vivo drug absorption profile or the drug input rate I equation 2 can be used as C and U are known and the problem simplifies to determination of I.

Mathematically equation 1 describing convolution and can be written in mathematical form as shown below, however there are other approaches possible for this purpose.

$$C(t) = I(t) * U(t) = \int_0^t I(t-u) \cdot U(u) du \tag{3}$$

In equation 3 'u' is the dummy variable used for the purpose of integration which gets eliminated on solving the integral. As deconvolution is the reverse process of convolution the

equation 2 can be written in the form of a differential equation subjected to respective boundary conditions. Instead of using direct integration or differential equation approach the convolution and deconvolution can easily be implemented using Laplace transform technique. Laplace transform of a function F(t) is defined as:

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

The convolution of the two functions I and U is given by

$$L\{C(t)\} = L\{I(t)\} \cdot L\{U(t)\} \tag{5}$$

The value of C(t) is given by inverse Laplace transform of the right hand side of equation 5.

And the deconvolution is given by:

$$L\{I(t)\} = \frac{L\{C(t)\}}{\{U(t)\}} = \frac{c(s)}{u(s)} \tag{6}$$

$$i(s) = \frac{c(s)}{u(s)} \tag{7}$$

$$I(t) = L^{-1}\{i(s)\} \tag{8}$$

For the prediction of In-vivo Drug Absorption I(t) what is needed is the C(t) the plasma profile and the UIR U(t) and implementation of Deconvolution discussed above in equation 8.

If the plasma concentration versus time data is available and the UIR is also available in the form of a table or graph, the two can be fitted to a suitable function for implementation of deconvolution. If the UIR is denoted by 'U' and the drug input rate by 'I' then the resulting plasma profile i.e. the plot or table of Plasma concentration of drug 'C' versus time can be found using Convolution shown in equation 1 and 3. This process requires convolution of two functions the UIR 'U' representing the behavior of human body towards the drug by way of various processes involving absorption, elimination, metabolism etc. which is in fact response of the human body to a unit input of drug. And the other one, 'I' which is the input rate of drug or the rate at which the drug is absorbed as a function of time. If the plasma concentration profile resulting from the administration of the oral dosage-form is available and represented by 'C' and it is required to determine in-vivo absorption profile in the form of rate of drug absorption as a function of time, deconvolution has to be done with UIR as shown in equation 6, 7, 8.

Here we present actual example as a case study for the prediction of in-vivo drug absorption rate from a plasma concentration profile. The approach used is deconvolution of the plasma concentration versus time data with unit input response (UIR). Both the Plasma profile and UIR are represented by analytical equations 9 and 10 and hence, use of Laplace technique is convenient and

straight forward. The data used for plasma profile is shown in Table – 1 and plot of the same along with fitting line is shown in Fig. 1, equation of the fitting curve is given in equation 9

Table – 1 Plasma Profile data for equation 9

T	C		T	C
0.0	0.0000		13.0	0.2904
1.0	0.6549		14.0	0.2177
2.0	1.5175		15.0	0.1627
3.0	1.9883		16.0	0.1213
4.0	2.0783		17.0	0.0903
5.0	1.9293		18.0	0.0671
6.0	1.6682		19.0	0.0498
7.0	1.3778		20.0	0.0370
8.0	1.1033		21.0	0.0274
9.0	0.8646		22.0	0.0203
10.0	0.6673		23.0	0.0151
11.0	0.5093		24.0	0.0112
12.0	0.3857		–	–

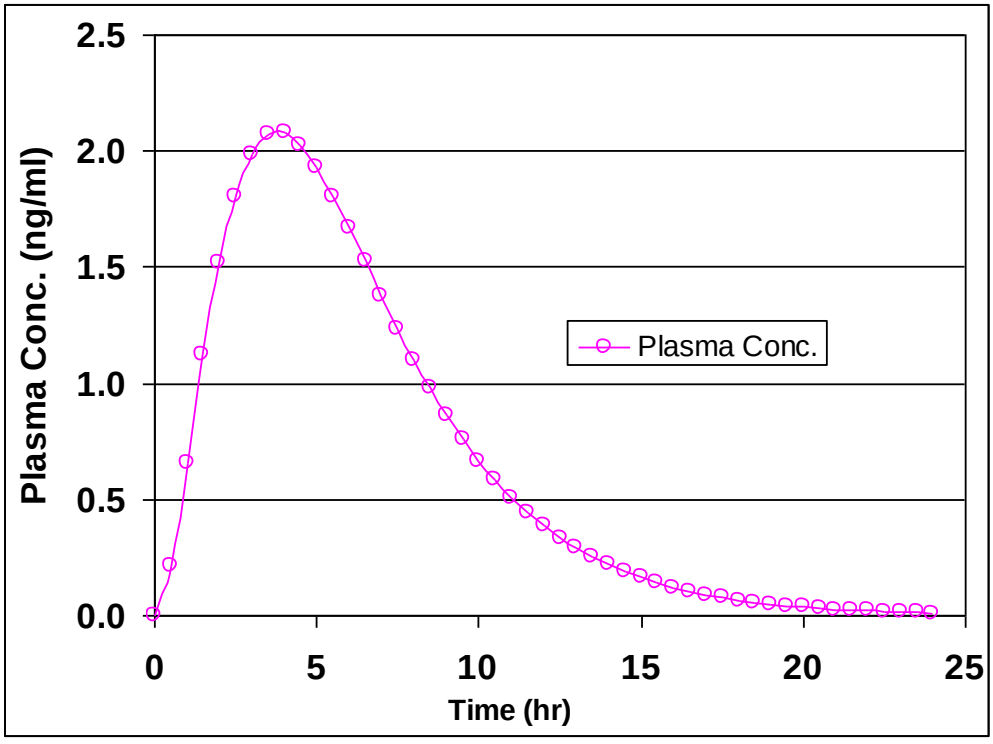

Fig. 1 Plasma profile from equation 9 and Table – 1

$$C(t) = 25e^{-0.8t} - 40e^{-0.612t} + 15e^{-0.3t} \quad (9)$$

$$U(t) = 1.6e^{-0.5t} \quad (10)$$

Table – 2 The UIR data from equation 10

T	C		T	C
0	1.6000		13	0.0024
1	0.9704		14	0.0015
2	0.5886		15	0.0009
3	0.3570		16	0.0005
4	0.2165		17	0.0003
5	0.1313		18	0.0002
6	0.0797		19	0.0001
7	0.0483		20	0.0001
8	0.0293		21	0.0000
9	0.0178		22	0.0000
10	0.0108		23	0.0000
11	0.0065		24	0.0000
12	0.0040		–	–

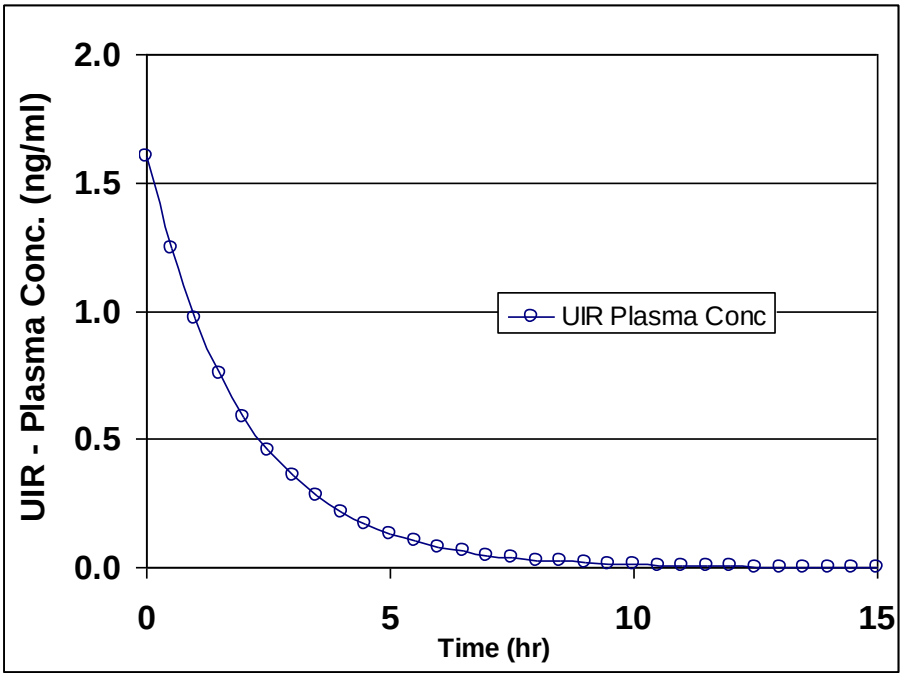

Fig. 2 Plasma profile from equation 10 and Table – 2

The UIR data and its plot are shown in Table – 2 and Fig. 2 respectively and the corresponding equation is given in equation 3. Using the analytical equation for the plasma concentration profile shown in equation 9 and 10 and performing deconvolution according to equations 6 – 8 we get the desired in-vivo drug absorption rate in analytical form as shown in equation 11 and corresponding data is shown in Table – 3 whose plot is given in Fig. 3.

$$I(t) = 1.875e^{-0.3t} - 4.6875e^{-0.8t} + 2.8e^{-0.612t} \quad (11)$$

Table – 3 Data representing rate of drug absorption obtained from deconvolution

T	I (mg/hr)		T	I (mg/hr)
0	0.0000		13	0.0388
1	0.8011		14	0.0286
2	0.9060		15	0.0211
3	0.7835		16	0.0156
4	0.6158		17	0.0115
5	0.4638		18	0.0085
6	0.3426		19	0.0063
7	0.2509		20	0.0047
8	0.1832		21	0.0035
9	0.1339		22	0.0026
10	0.0979		23	0.0019
11	0.0718		24	0.0014
12	0.0527			

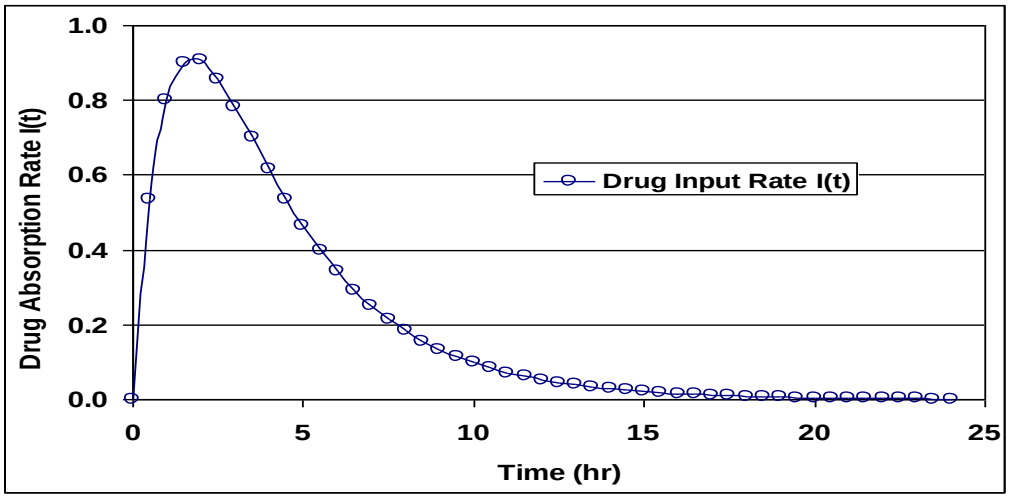

Fig. 3 Drug Input Rate or Drug Absorption Rate I(t) obtained by deconvolution as shown in equation 11 and Table – 3

Results and Discussions

In pharmaceutical industry one of the most challenging tasks is to be able to predict the drug absorption rate for a given product. Once this is known similar or modified products can be made by adjusting the dissolution profile by the use of suitable excipient and manufacturing technique. For this purpose we made use of mathematical technique of deconvolution and implemented the same using Laplace Transform. The plasma concentration data and UIR fitted to analytical equation and the deconvolution was carried out. Detailed procedure has been demonstrated with the help of standard data. The Laplace transform can be found from tables of Laplace transform given in standard books on mathematics. As this is a mathematical procedure the validity has been checked by implementing the reverse process of convolution between the drug input rate and UIR which nicely reproduced the plasma profile which confirms the mathematical procedure and strength of the system approach which otherwise is not that simple.

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