Laplace Transform based Prediction of Drug Concentration in Blood

Jinan Fadhil Mahdi

Medical instruments , Eng. College Electrical and Electronic Engineering Techniques , Middle Technical University , Ministry of Higher Education and Scientific Research

E-Mail: jinanf2008@yahoo.com

Abstract

Performance of an oral dosage form like tablet or capsule is determined by the amount of drug present in the plasma at a given time. Prediction of this in-vivo performance in terms of concentration of drug in blood poses problems. A new technique called convolution which is based on system approach is presented with actual data and details of implementation of the convolution technique. This technique is of great relevance in advanced dosage forms having longer duration of performance like 12, 16 or 24 hours. In the design and development of oral products this technique allows for prediction of the plasma profile without conducting bio studied in human subjects that highly expensive and time consuming.

Keywords: concentration of drug in blood, convolution technique, absorption of drug, Convolution Integral**.**

تحويل لابلاس التنبؤيه استنادا لتركيز الدواء في الدم

جنان فاضل مهدي

الأجهزة الطبية ، كلية التقنيات الهندسية الكهربائية و الكترونيه ، الجامعة التقنية الأوسطى ، وزارة التعليم العالي والبحث العلمي

jinanf2008@yahoo.com

ملخص

يتم تحديد أداء شكل جرعات مثل حبة أو كبسولة من كمية الدواء الموجودة في البلازما في وقت معين . تنبؤا الأداء هذا في الجسم الحي يتم من خلال تركيز الدواء في الدم المصاب . تقنية جديدة تسمى التفاف الجديد وتقوم على تقديم نهج النظام مع بيانات حقيقية وتفاصيل تنفيذ هذه التقنية. هذا الأسلوب هو من ألاهمية الكبيرة في أشكال الدواء المتقدمة وجود مدة أطول من أداء

مثل ١٢ ، ١٦ أو ٢٤ ساعة . في تصميم وتطوير المنتجات تسمح هذه التقنية للتنبؤ بشكل البلازما من دون إجراء دراسة بايولوجية في للجسم البشري التي تكون مكلفة للغاية وتستغرق وقتا .

الكلمات المفتاحية : تركيز الدواء في الدم ، تقنية الالتواء ، امتصاص الدواء ، الإلتواء المتكامل .

1- Introduction

Pharmacokinetics has seen new horizons with the introduction of a very powerful technique from physics called convolution[1]. This technique is being extensively used in a wide variety of field including Mass spectroscopy [2-6], Digital image processing[7,8] Convolution basically accumulates several physical properties like concentration versus time plots originating at different instants of time[9]. Effectiveness of orally administered medicine or drug is determined form the plasma concentration of drug in the blood [10]. When a drug is given orally in the form of a tablet or capsule the amount of drug entering into portal or getting absorbed in the blood as a function of time becomes of interest as this is the deciding factor in determining the effectiveness. Oral solutions usually get absorbed quickly and the resulting plasma concentrations are obvious and have only the disposition or elimination profile.

The absorption of drug depends on several factors including the properties of the dosage form like tablet or capsule which in turn include the characteristics of the constituents and the way the dosage form is made in addition to the properties of the basic drug [10, 11]. As the oral dosage form is administered it passes through the entire gastro intestinal track with time and different regions have different characteristics in terms of pH and viscosity of the fluids and the hydrodynamic conditions, additionally the membranes have varying characteristics towards the absorption of the given drug. Also the drug absorbed undergoes disposition or elimination by different mechanisms including metabolism in many cases. The determination of the net amount of drug present in the blood proves to be a challenge.

2 - Theoretical part

There are several approaches to predict the rate and extent of absorption and elimination of drug among which most popular on is the compartment based approach that considers human body as on two or more compartments. This approach is classical one and has its own limitations [10-12]. The latest approach is the system approach introduced by Aveng Pederson in 1984 [13]. This approach considers the human body as on

single system and this is a compartment independent approach and does not go in conventional way to estimate the absorption and elimination under a given set of conditions. Though this approach does not use the concepts of absorption and elimination coefficient and half life like that in traditional approach it does not disregards any of the physiological realities governing the mechanism of absorption and elimination [14, 15]. All the complex behaviour of the human body to the absorption and elimination of the drug are included in what is called as the Unit Impulse Response or the UIR [16].

UIR is the plasma concentration of drug versus time (fig.1)profile resulting from a unit drug input. It is important to note that this profile or relationship included all the pharmacological realities and contain the information as to how the human body reacts to a given drug over a period of time. Thus UIR if tactfully used can be a perfect representative giving the behaviour of the human body to a given drug and can provide vital information like in-vivo drug absorption allowing estimation of resulting drug levels in plasma as a function of time.

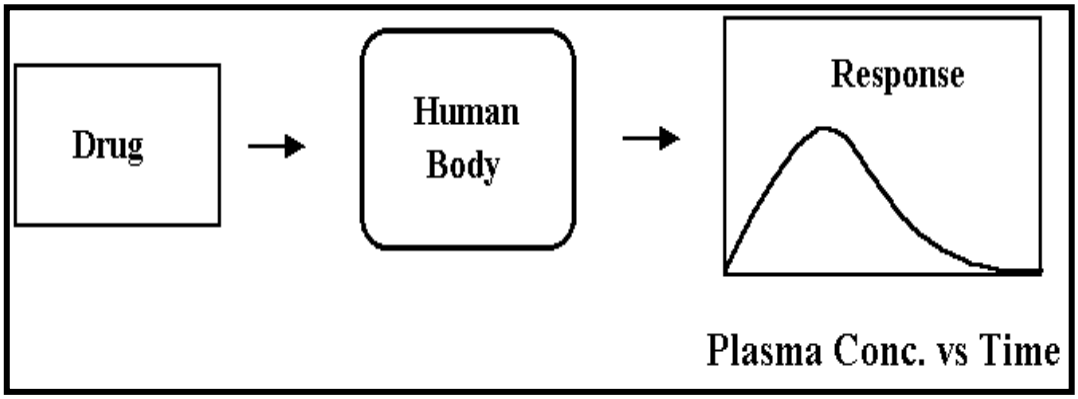

Fig. 1 Block diagram showing the concept of system approach.

This estimation requires information on the dissolution of the dosage form or the dissolution profile or the dissolution curve obtained from in-vitro dissolution studies. If the In-vivo-In-vitro relation Curve (IVIVC) is straight line with slope = 1, the in-vitro dissolution can be used as in-vivo release, if this relation is different, the in-vivo release can be calculated from the in-vitro dissolution by using the IVIVC [17,18].

3 - Convolution Technique

This technique makes use of two important relations, the UIR discussed earlier and the rate at which drug is released from the oral dosage form (tablet or capsule) called the dissolution profile. A dissolution profile is usually of table or plot giving percent of drug released as a function of time [19]. The percent release is converted to amount of drug released and the function is differentiated to obtain the rate of drug release in mg/hr.

This rate at which drug is released from a oral dosage form is represented as I (t).

If PR (t) represents the percent drug release as a function of time then the drug release rate is found as

$$I(t) = \frac{dPR(t)}{dt} \qquad (1)$$

The UIR is the response of the human body to a unit input of drug and can be represented as a function of time U (t). In fact it is a 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, and is most important component of the implementation of the convolution to predict the plasma concentration profile resulting from a dosage form.

4 - Convolution Integral

Convolution is a simple technique of adding two plots which amounts to an integration. The rate at which the drug is coming out as a function of time is denoted by I(t). 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 found by solving the convolution integral

$$C(t) = \int_0^t I(x) \cdot U(t-x)dx \qquad (2)$$

Here x is the dummy variable used for integration. C(t) is the plasma concentration as a function of time, I is the drug input rate (in mg/hr) and U is the UIR in corresponding units, both are represented as a function of time. In advanced dosage forms the drug release is controlled by embedding drug into a matrix or some other technique. The instantaneous value of drug release is I(t), at each instance of time this drug input will produce corresponding plasma concentration equal to I(t) times the UIR(fig.2). The integration actually adds up all such consecutive plasma profiles resulting from the administration of the drug at a rage I(t).

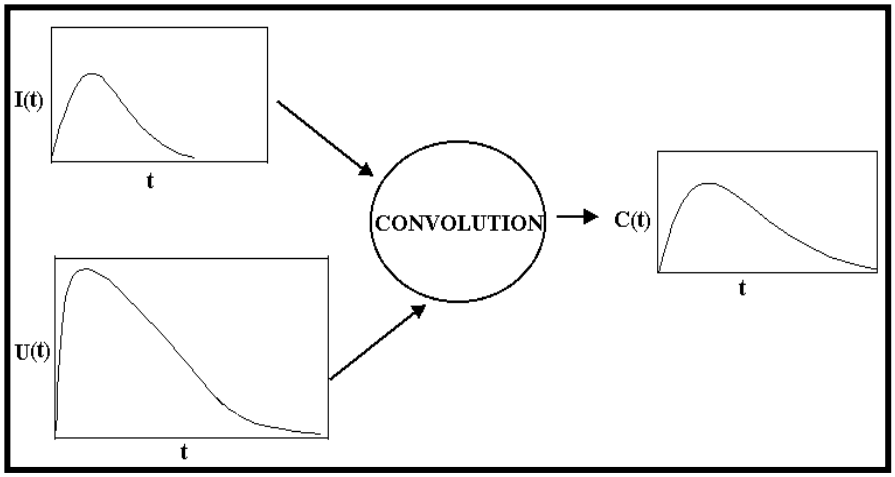

Fig. 2 Block diagram of the concept of convolution by combination the drug input rate I(t) and the UIR to obtain plasma concentration profile C(t).

At times the functions I(t) and U(t) may not be simple relations and implementation of integral shown in equation 2 is not possible. In such cases analytical equations for I(t) and U(t) can be used to implement the convolution with the help of Laplace transform technique

$$C(t) = L^{-1}\left[L\{U(t)\} \cdot L\{I(t)\}\right] \tag{3}$$

L{U(t)} and L{I(t)} are the Laplace transforms of *U(t)* and *I(t)*respectively and *C(t)* is the resulting plasma concentration as a function of time. If the two functions *U(t)* and *I(t)* are available as analytical expressions, their Laplace transform can be found from standard Laplace transform tables from any related text book. Simply take Laplace transform of the two functions, multiply them together and take the inverse Laplace transform L^{-1} as shown in equation 3.

In most of the practical situation, it is not easy to represent U (t) or I(t) in the form of a mathematical expression in order to implement the integration, in such situations the integration in equation 2 can be solved by using numerical methods available in standard mathematical software like MathCAD or Mat lab. In a typical case if the two functions are given by:

$$I(t) = 3e^{-0.2t} - 3e^{-0.6t} \tag{4}$$

$$U(t) = 5e^{-0.3t} - 5e^{-0.5t} \tag{5}$$

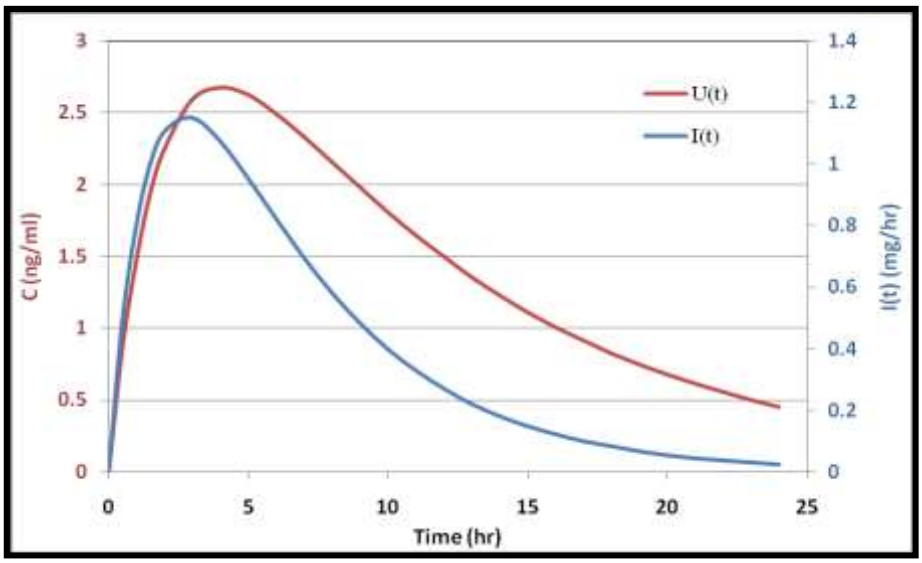

Fig. 3: Drug input rate I (t) and the UIR temporal variation from equation (3) and (4).

The two functions I(t) the drug input rate and the UIR U(t) shown in equation (4) and (5) are plotted in Fig. 3 both are double exponential curves, at times, the UIR could be a single exponential function having only decaying part without a rising part.

As is seen from equation 3 first the Laplace transform of the two functions in equation (3) and (4) are obtained referring to standard Laplace transform. The corresponding Laplace transform of the two functions are shown in equations (6) and (7).

$$I(s) = L\{I(t)\} = \frac{3}{s+0.2} - \frac{3}{s+0.6} \tag{6}$$

$$U(s) = L\{U(t)\} = \frac{5}{s+0.3} - \frac{5}{s+0.5} \tag{7}$$

The next step is to multiply the two Laplace transforms in the equations (6) and (7) and take the inverse Laplace transform of the product.

$$L^{-1}\left[\left(\frac{3}{s+0.2} - \frac{3}{s+0.6}\right)\cdot\left(\frac{5}{s+0.3} - \frac{5}{s+0.5}\right)\right] \tag{8}$$

$$15\cdot L^{-1}\left[\left(\frac{1}{s+0.2} - \frac{1}{s+0.6}\right)\cdot\left(\frac{1}{s+0.3} - \frac{1}{s+0.5}\right)\right] \tag{9}$$

As in the case of Laplace transform, the inverse Laplace transform of the equation (8) can be found from standard tables of Laplace transforms and is given by

$$C(t) = 100 \cdot (e^{-0.2t} - e^{-0.6t}) + 200 \cdot (e^{-0.5t} - e^{-0.3t})$$

On simplification

$$C(t) = 100 \cdot (e^{-0.2t} - e^{-0.6t} + 2e^{-0.5t} - 2e^{-0.3t}) \qquad (10)$$

Equation (10) is the predicted plasma concentration as a function of time as obtained by convolution of the drug input rate I(t) and UIR U(t). The plot of the plasma concentration C(t) as a function of time t is shown in Fig. 4.

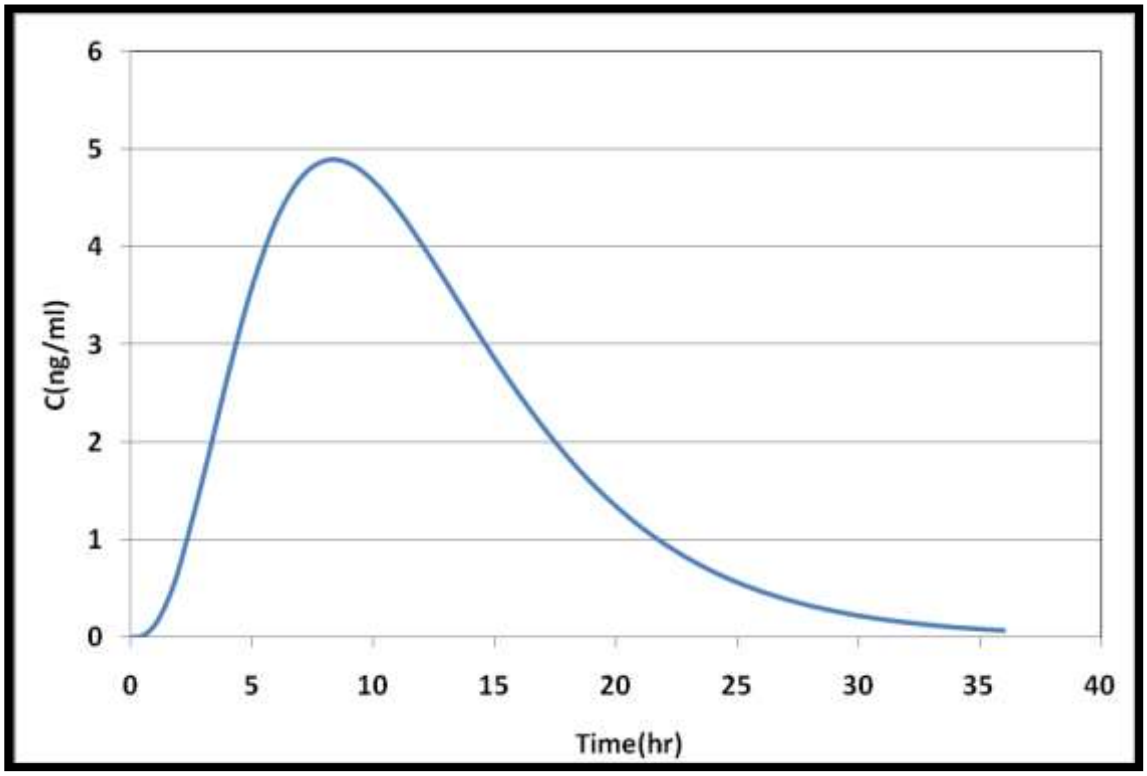

Fig. 4: Plasma concentration C(t) versus time plot from convolution.

As is expected the results of convolution using Laplace transform technique are in very good agreement with those obtained using integration method.

5 - Conclusion

We successfully demonstrated a simple new approach for prediction of in-vivo plasma concentration of drug versus time plot. The approach is based on convolution using Laplace transform technique. The predicted plasma profile very well compare with one obtained using analytical expression and integration. This technique is very useful in design and development of oral products and allows for prediction of the plasma concentration versus time profile without conducting bio studied in human subjects that highly expensive and time consuming.

References

1 - Tuomas Tallinen, Jun Young Chung, François Rousseau, Nadine Girard, Julien Lefèvre & L.Mahadevan, 'On the growth and form of cortical convolutions' Nature Physics, (2016), doi:10.1038/nphys 3632.

2 - Chien Nguyen, John Mark Christensen and James W Ayres, 'Verapamil sustained release: New formulation and convolution', Pharmaceutical Development and Technology 17(2):148-57, October 2010.

3 - Jelena Parojcic, Svetlana Ibric, Zorica Djuric, Milica Jovanovic, Owen I. Corrigan, 'An investigation into the usefulness of generalized regression neural network analysis in the development of level A in vitro–in vivo correlation' European Journal of Pharmaceutical Sciences Volume 30, Issues 3–4, March 2007, Pages 264–272.

4 - Marija Ilić, Jelena Duris, Ivan Kovačevic, Svetlana Ibric, Jelena Parojcic, 'In vitro – in silico – in vivo drug absorption model development based on mechanistic gastrointestinal simulation and artificial neural networks: Nifedipine osmotic release tablets case study' European Journal of Pharmaceutical Sciences Volume 62, 1 October 2014, Pages 212–218.

5 - Parojčić J. , Durić Z., Jovanović M., Ibrić S., Grbić S., Predicting in vivo behaviour of sustained release matrix tablet formulation: numerical convolution versus artificial neural network ana lysis. 6th Central European Symposium on Pharmaceutical Technology and Biotechnology, Siofok/Hungary, Eur J Pharm Sci 2005; 25S1:170-172.

6 - Dromey R.G., Morrison J.D., 'Inverse convolution in mass spectrometry' International Journal of Mass Spectrometry and Ion Physics, Volume 6, Issues 3–4, March–April 1971, Pages 253-261.

7 - Robert G. Keys. 'Cubic Convolution Interpolation for Digital Image Processing' IEEE Transactions On Acoustics, Speech, And Signal Processing, Vol. Assp-29, No. 6, December 1981.

8 - Michael Unser, Senior Member, IEEE, Philippe and Leonid Yaroslavsky, 'Convolution-Based Interpolation for Fast, High-Quality Rotation of Images' IEEE transactions on Image Processing Vol. 4, No. 10 October 1995.

9 - Louis A. Pipes, Lawrence R. Harvill, "Applied Mathematics for Engineers and Physicists": Third Edition –Reprint of the McGraw-

Hill, New York, third edition, 1970.

10 - Wagner J. G., Do you need a pharmacokinetic model, and, if so which one? J. Pharmacokin. Biopharm. 3: 457-478, 1975.

11 - Cutler D., Linear system analysis in pharmacokinetics. J. Pharmacokin. Biopharm. 6: 227-241, 1978.

12 - Veng-Pedersen P., Linear and Nonlinear system approaches in parmacokinetics: How much do they have to offer? I. General considerations. J. Pharmacokin. Biopharm. 16:413-472, 1988.

13 - Veng-Pedersen P., Theorems and implications of a model independent elimination/distribution function decomposition of linear and some nonlinear drug dispositions: I. Derivation and theoretical analyses. J. Pharmacokin. Biopharm. 12: 627-648, 1984.

14 - Veng-Pedersen, P., System approaches in parmacokinetics: I. Basic concepts. J. Clin. Pharmacology. 28: 1-5, 1988.

15 - Veng-Pedersen P., System approaches in parmacokinetics: II. Applications. J. Clin. Pharmacology. 28: 97-104, 1988.

16 - Amidon G., Paul M., and Welling P., Model-independent methods in pharmacokinetics: Theoretical considerations. Math. Biosci. 25: 259-272, 1975.

17 - Veng-Pedersen P., Linear and Nonlinear system approaches parmacokinetics: How much do they have to offer? II. Response mapı operator (RMO). J. Pharmacokin. Biopharm. 16: 543-571, 1988.

18 - Gillespie W. R., and Veng-Pedersen P., Theorems and implications of a model independent elimination/distribution function decomposition of linear and some nonlinear drug dispositions: II. Clearance concepts applied to the evaluation of distribution kinetics. J. Pharmacokin. Biopharm. 13: 441-451, 1985.

19 - Mohamed Ali Lassoued , Fathia Khemiss , Souad Sfar, Comparative Study of Two In Vitro Methods for Assessing Drug Absorption, J Pharm Pharmaceut Sci (www.cspsCanada.org) 14(1) 117 - 127, 2011 .