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Developing the General Drug Disposition Equation in Linear Pharmacokinetics

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Abstract

This mathematical observation deals with for the first time regarding the application of Mahgoub transform $[M\{F(t)\} = v\int_0^\infty F(t)e^{-vt}dt]$ to predict the general disposition correlation in pharmacokinetics. A general drug disposition formula is developed for the n linear mammillary compartment model along with elimination occurring from every compartment. It is obviously plausible to extract the equation for the central compartment with respect to any linear pharmacokinetics. The obtaining mathematical expression predicts the fate of the intravenous input drug in the mammillary body. To be sum up, by using this presented equation, most drug disposition kinetics can be solved easily. Thus, it is cleared that this mathematical method is obviously helpful to observe the providential information in the computational biology field with the starting point in pharmacokinetics..

Keywords: Compartment model; Mahgoub transform; Pharmacokinetics; Rate constants

Introduction

It is obvious that in pharmacokinetics as well as in mathematical biology we often get linear differential equation, integral, and Integro differential equations, stochastic equations, and others [1-2]. Differential equations often arise in mathematical biology such as growth, and decay problems, pharmacokinetic problems, and the other computational field. The linear and nonlinear pharmacokinetic models in biopharmaceutics are used to predict the fate of the input drug to a mammillary body. In linear pharmacokinetics, simple first order kinetics is used to describe the drug disposition and action. It is also assumed in linear pharmacokinetics [3-4] that the pharmacokinetic parameters do not change for a drug when different dose or multiple doses are applied. So, it is cleared that in linear mammillary pharmacokinetic model, the numerical values of the estimated pharmacokinetic parameters are inevitable to predict the biological half-life, volume of distribution, c_{max}, t_{max}. These are analyzed through experimental data observed from plasma to estimate the effective concentration of the drug to heal diseases of the patient. The determined value of biological half-life i.e., elimination half- life ($t_{1/2}$) is a must to predict the dosage regimen (dose and dosing intervals) for multiple dosage-regimen drug delivery system [5]. It is certified that 97% of the bioavailable drug is eliminated from the body after $5t_{1/2}$. Therefore, in multiple-dosage regimens drug delivery system, the $t_{1/2}$ is an inevitable factor to avoid drug accumulation in the body which produces toxic effect. According to the physicochemical properties of a drug, it may distribute in the mammillary body following one or, two or, three or multi compartment pharmacokinetic model. We developed a mathematical expression for the n linear pharmacokinetic model. This observation is helpful to predict the biological as well as physicochemical parameters of the administered drug through mathematical analysis of the experimental data. Besides, mathematics is an inseparable part of the pharmacokinetics, computational biology modeling as well. As for example, we generally use Laplace transform [6] to solve the differential equations in computational biology problems and pharmacokinetic as well. We also can use the Mahgoub transform mathematical method to solve this problem. Therefore, application of the Mahgoub transform [7] obviously assists to solve many biology related mathematical problems, precisely and correctly. In the present study, we mathematically deduce a general drug disposition correlation for the central compartment in case of linear multi compartment pharmacokinetic model, from which, it is successful that the drug disposition mathematical relationship with respect to variations of compartment model (one, or two, or three, or n) easily extracted precisely and clearly.

It is hardly found the application of Mahgoub transform [7] in computational biology. Thus, it initiates the precise application of Mahgoub transform in pharmacokinetics and mathematical biology as well.

Theory and Discussion

According to mammillary compartment model [8], when a drug is administered as an intravenous bolus dose, the entire drug is present in central compartment (plasma compartment) initially i.e., time is zero. Them it starts to distribute from central compartment (plasma compartment) and transports to peripheral compartment (Figure 1) for moving to the site of drug action and gives pharmacological response. Mammillary compartment model may be one compartment model (Figure 2), two Compartment model (Figure 3 & 4), three compartment model (Figure 5 & 6), as well as multi compartment model (Figure 1) respectively.

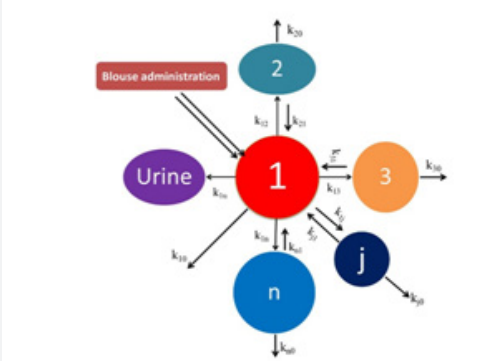

Figure 1: The drug disposition for the n linear pharmacokinetic mammillary model.

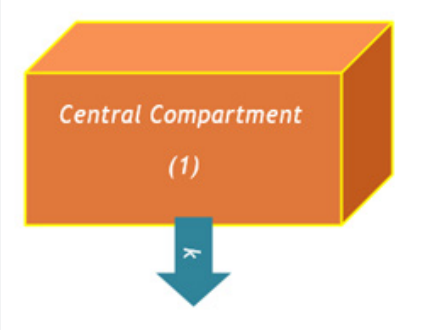

Figure 2: Open one compartment model.

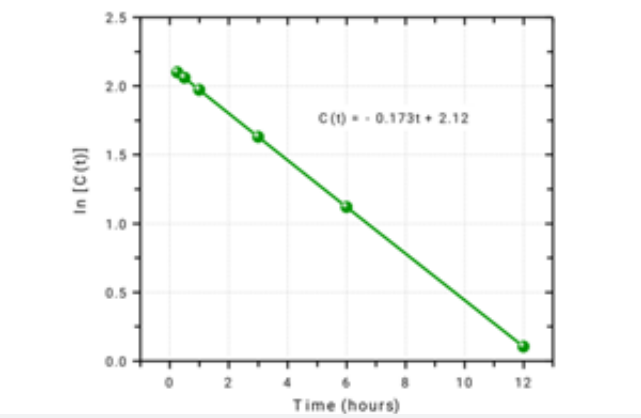

Figure 3: Plasma concentration (logarithm scale) Vs time curve for open one compartment model.

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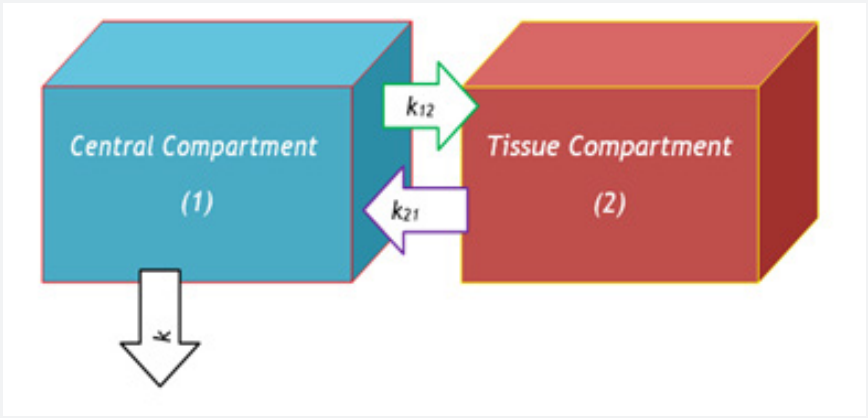

Figure 4: Open two compartment model.

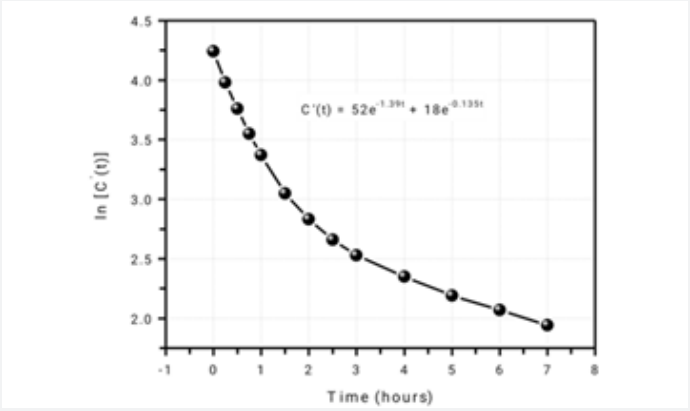

Figure 5: Plasma concentration (logarithm scale) Vs time curve for open two compartments model.

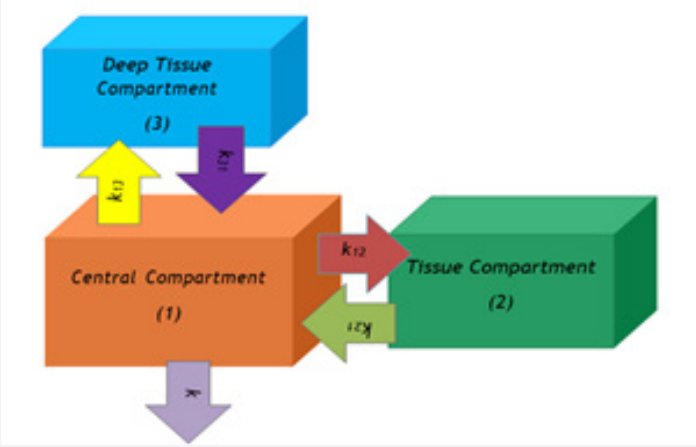

Figure 6: Open three compartment model.

Methodology

We have derived the relationships by applying Mahgoub Transform and Mahgoub Inverse Transform [9]. Mahgoub transform H = H(v) of a function F = F(t) is defined by $M\{F(t)\} = v\int_o^\infty F(t)e^{-vt}dt$. The integral is evaluated with respect to t, so the limits are substituted. The is left are in terms of v or 1. If M{F(t)} = H(v) then F(t) is called the inverse Mahgoub transform of H(v) and mathematically it is defined as $F(t) = M^{-1}\{H(v)\}$, where

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M^{-1} is the inverse Mahgoub transform operator. We have that $H(e^{-kt}) = v/(v+k)$, $H(1) = 1$, written in the inverse transform notations, $M^{-1}[v/(v+k)] = e^{-kt}$; $M^{-1}(1) = 1$, respectively. If a function $F = F(t)$, the transform of its derivative F' can be expressed in terms of the Mahgoub transform of: $M\{F'(t)\} = vH(v) - vF(0)$.

Proof

According to pharmacokinetic model (Figure 1).

$$dc_1/dt = - k_{11}c_1 + k_{21}c_2 + k_{31}c_3 + \ldots\ldots\ldots + k_{n1}c_n$$

$$dc_2/dt = k_{12}c_1 - k_{22}c_2$$

$$dc_3/dt = k_{13}c_1 - k_{33}c_3$$

……

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$$dc_n/dt = k_{1n}c_1 - k_{nn}c_n$$

here, c_1 is concentration of drug in central compartment (plasma compartment); c_2, c_3……., c_n are the concentration of drug in peripheral compartments respectively at time t and k_{ij} is the first order rate constants. Besides, k_{ii} is the sum of the exit rate constants from compartments i.

Initial conditions: At time, t is zero

$$c_1(0) = C_0,\ c_2(0) = c_3(0) = \ldots\ldots\ldots = c_n(0) = 0$$

Mahgoub transform for the mathematical model,

$$vH_1(v)-vC_0 = - k_{11}H_1(v)+k_{21}H_2(v)+k_{31}H_3(v)+\ldots\ldots\ldots + k_{n1}H_n(v)$$

$$vH_2(v) = k_{12}H_1(v) - k_{22}H_2(v);\ \text{Or}\ H_2(v) = k_{12}H_1(v)/(v+k_{11})$$

$$vH_3(v) = k_{13}H_1(v) - k_{33}H_3(v);\ \text{Or},\ H_3(v) = k_{13}H_1(v)/(v + k_{22})$$

……

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$$vH_n(v) = k_{1n}H_1(v) - k_{nn}H_n(v);\ \text{Or},\ H_n(v) = k_{1n}H_1(v)/(v + k_{nn})$$

Therefore,

$$H_1(v)\ [(v+k_{11}) - k_{12}k_{21}/(v+k_{22}) - k_{13}k_{31}/(v+k_{33}) - \ldots\ldots - k_{n1}k_{1n}/(v + k_{nn})] = vC_0$$

Or,

$$H_1(v)[(v+k_{11})\ (v+k_{22})\ (v+k_{33})\ \ldots\ (v+k_{nn}) - k_{12}k_{21}(v+k_{33})\ \ldots\ldots (v+k_{nn}) - k_{13}k_{31}(v+k_{22})\ \ldots\ldots\ (v+k_{nn}) - \ldots\ldots\ldots\ldots - k_{1n}k_{n1}(v+k_{22})\ (v+k_{33})\ \ldots\ldots\ldots] = (v+k_{22})\ (v+k_{33})\ \ldots\ldots\ldots(v+k_{nn})\ vC_0$$

Or

$$H_1(v)\left[\prod_{i=1}^{n}(v+k_{ii}) - \ldots\ldots\ldots - k_{13}k_{31}\prod_{\substack{i=2\\ i\neq 3}}^{n}(v+k_{ii}) - \ldots\ldots\ldots - k_{1n}k_{n1}\prod_{\substack{i=2\\ i\neq n}}^{n}(v+k_{ii})\right] = vC_0\prod_{i=2}^{n}(v+k_{ii})$$

$$H_1(v) = \frac{vC_0\prod_{i=2}^{n}(v+k_{ii})}{\prod_{i=1}^{n}(v+k_{ii}) - \sum_{j=2}^{n}k_{1j}k_{j1}\prod_{\substack{i=2\\ i\neq j}}^{n}(v+k_{ii})}$$

Therefore,$H(v)=C_0\times$(general disposition equation)

1. Case-1: When the drug is administered intravenously as a bolus dose that follows open one compartment model (Figure 2).

Therefore, $H(v) = C_0 \times$ (general disposition equation)

2. Case 1: When the drug is administered intravenously as a bolus dose that follows open one compartment model (Figure 2)

Let the intravenous bolus dose of a drug D0 be administered to a mammillary body. The initial plasma concentration of the drug is C0. The drug is eliminated from the central compartment at a rate constant k. Here,

$$k_{11} = k\ [\text{since, } n = 1]$$

$$H_1(v) = C_0v/(v+k),$$

$$\text{Or, } C(t) = C_0e^{-kt} \ldots\ldots\ldots\ldots (2)$$

3. Case 2: When the intravenous administered drug follows open two Compartment model (Figure 4).

If the intravenous injected dose is D0, the drug is distributed in the peripheral compartment following open two compartment model, the pharmacokinetic rate constants are k_{12}, k_{21} and drug is eliminated from the central compartment at a rate constant k. Now, we get from the general mathematical expression (n = 2),

$$k_{11} = k+k_{12},\ k_{22} = k_{21}$$

$$[(v+k_{12}+k)(v+k_{21}) - k_{12}k_{21}]\ H_1(v) = v(v+k_{21})C_0$$

$$\text{Or, } [v_2+(k+k_{12}+k_{21})v+kk_{21}]\ H_1(v)= v(v+k_{21})C_0$$

$$\text{Now, let } k+k_{12}+k_{21} = a+b,\ kk_{21} = ab$$

$$\text{So, we get that, } H_1(v) = v(v+k_{21})C_0\ /\{(v+a)(v+b)\}$$

$$\text{Or, } H_1(v) = C_0[v(a-k_{21})\ /\{(a-b)(v+a)\} + v(k_{21}-b)/\{(a-b)(v+b)\}]$$

$$\text{Or, } H_1(v) = \{C_0(a-k_{21})/(a-b)\}v/(v+a) + \{C_0(k_{21}-b)/(a-b)\}v/(v+b)\}$$

By using inverse Mahgoub transform,

$$C'(t) = Ae^{-at} + Be^{-bt} \qquad (3)$$

$$\text{where, } A = C_0(a-k_{21})/(a-b);\ B = C_0(k_{21}-b)/(a-b)$$

$$k+k_{12}+k_{21} = a+b,\ kk_{21} = ab$$

4. Case 3: When the intravenously injected drug follows open three compartment model (Figure 6).

If the intravenous injected dose is D_0, the drug is distributed in the peripheral compartment following open three compartment model, the pharmacokinetic rate constants are k_{12}, k_{21}, k_{13}, k_{31} and drug is eliminated from the central compartment at a rate constant k. We get from the general equation (n = 3),

Here,

$$k_{11} = k+k_{12}+k_{13},\ k_{22} = k_{21},\ k_{33} = k_{31}$$

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$$Or, [v^3+(k+k_{12}+k_{21}+k_{13}+k_{31})v^2+(kk_{21}+k_{21}k_{31}+kk_{31}+k_{12}k_{31}+k_{13}k_{21})v+kk_{21}k_{31}]H_1(v)=vC_0(v+k_{21})(v+k_{31})$$

$$If, k+k_{12}+k_{21}+k_{13}+k_{31} \text{ is } p+q+r; kk_{21}+k_{21}k_{31}+kk_{31}+k_{12}k_{31}+k_{13}k_{21} \text{ is } pq+qr+rp, \text{ and } kk_{21}k_{31} \text{ is } pqr$$

$$So, we get that, [v^3+(p+q+r)v^2+(pq+qr+rp)v+pqr]H_1(v)=v(v+k_{21})(v+k_{31})C_0$$

$$Or, H_1(v)=v(v+k_{21})(v+k_{31})C_0/\{(v+p)(v+q)(v+r)\}$$

$$Or, H_1(v) = Pv/(v+p) + Qv/(v+q) + Rv/(v+r)$$

Here,

$$P=C_0(p-k_{21})(p-k_{31})/\{(p-q)(p-r)\}, Q=C_0(q-k_{21})(q-k_{31})/\{(q-p)(q-r)\}, R=C_0(r-k_{21})(r-k_{31})/\{(r-p)(r-q)\}$$

$$Hence, C^{''}(t) = Pe^{-pt} + Qe^{-qt} + Re^{-rt} \ldots\ldots\ldots\ldots (4)$$

$$k = pqr(P+Q+R)/(Pqr+Qrp+Rpq)$$

Calculation and Results

According to pharmacokinetic compartment model solution [10-15].

For one compartment open model (Figure 3),

$$k = 0.173h^{-1}.$$

For two compartments model (Figure 5),

$$A = 52; B = 18; a = 1.39; b = 0.135; k = 0.41h^{-1}; k_{12} = 0.657h^{-1}; k_{21} = 0.458h^{-1}$$

For three compartments model (Figure 7)

$$P = 28; Q = 10.5; R=14; p = 0.63; q = 0.46; r = 0.077; k = 0.21h^{-1}; k_{12} = 0.01h^{-1}; k_{21} = 0.52h^{-1}; k_{13} = 0.14h^{-1}; k_{31} = 0.18h^{-1}$$

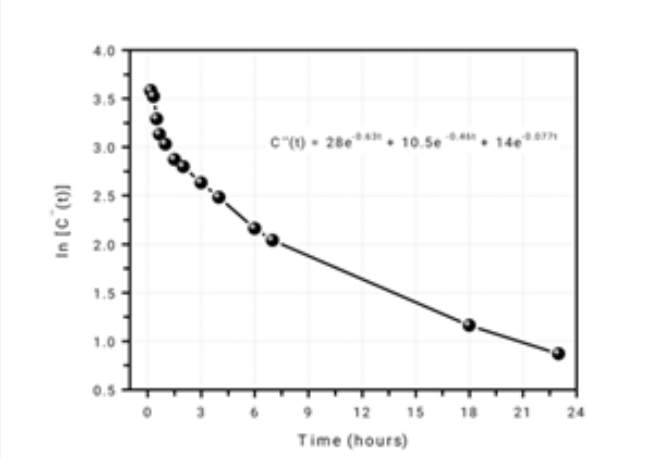

Figure 7: Plasma concentration (logarithm scale) Vs time curve for open three compartments model.

Conclusion

The mathematical expressions are derived from the general drug disposition equation for the central compartment in n linear compartment model ([$C(t) = C_0e^{-kt}$], [$C'(t) = Ae^{-at} + Be^{-bt}$], [$C''(t) = Pe^{-pt} + Qe^{-qt} + Re^{-rt}$]). These mathematical expressions can predict the drug concentration in plasma compartment for one, two, and three compartment open model, respectively in the mammillary body. We can also predict the numerical value of pharmacokinetic factors (k_{12}, k_{21}, k, k_{13}, k_{31}) through the observation of various mathematical hybrid constants (p, q, r, P, Q, R, a, b, A, B) for the respective compartment model. So, it is cleared that this mathematical observation is successful to predict intuitive information about the bioavailable drug disposition for n-compartment mammillary model. Thus, this mathematical method initiates a successful point of view to observe the providential information in the computational biology field as well as in pharmacokinetics.

Declaration of Interests

The author declares no competing financial and non-financial interests.

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