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On Solution of A Modified Epidemiological Model for Drug Release Systems

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Abstract: In drug delivery systems, mathematical modeling plays an important role in the design of drug carrier systems and facilitates the development of new pharmaceutical products. The ultimate aim is to accurately predict the drug release profile and improve the overall therapeutic efficacy and safety of these drug carrier systems. In this article, we have introduced a operational matrix method, which is based on operational matrix method for solving initial-boundary value problem describing the Higuchi and power law.
Keywords: Drug release systems, Higuchi law, power law, operational matrix method.

INTRODUCTION

The science of drug delivery systems is multidisciplinary, integrating polymer science, pharmaceutical science, clinical, molecular biology and mathematics. Controlled release is a technique in which an active drug is made available to a specified target at a rate and period designed to achieve an intended effect. Such controlled release drug delivery devices offer definite advantages which include a reduced dosing frequency, a decreased incidence and/or intensity of side effects, a more constant and/or prolonged therapeutic effect and an increase in cost effectiveness.

The development and optimization of pharmaceutical products are greatly facilitated by mathematical models [1]. Theoretical modeling of drug delivery significantly improves the understanding of the underlying physical mechanisms governing drug release, while helping to determine the crucial parameters that regulate release rates. Moreover, the predictability offered by mathematical models reduces the number of required experiments, saving time and curtailing costs. Several expressions have been proposed for the description of drug release, such as the Higuchi law [2], the power-law or Peppas model [3, 4, 5] and, more recently, a relatively simple formula containing a stretched exponential function, also known as the Weibull function.
The Higuchi law [2] states that

$$M_t = A\sqrt{D(2c_0 - c_s)t} \qquad (1)$$

where M_t is the cumulstive amount of drug released at time t, A is the surface area of the controlled release device exposed to the release medium, D is the drug diffusivity, c_0 and c_s are the initial drug concentration and the drug solubility, respectively. This law is valid for systems where the drug concentration is much higher than the drug solubility.
The power law [6] states

$$\frac{M_t}{M_\infty} = kt^n \qquad (2)$$

where M_t and M_∞ are the amounts of drug released at times t and infinity, respectively; k is an experimentally determined parameter and n is an exponent that depends on the geometry of the system: it can be related to the drug release mechanisms [7, 8]. In addition to the above two equations, various approaches have been developed that are based on the geometry of the device and the physicochemical drug properties, and they provide a comprehensive, mechanistic interpretation of the drug release kinetics [9, 10, 11].

The Weibull function is sporadically used in drug release studies in spite of its extensive empirical use in dissolution studies [12, 13]:

$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b) \qquad (3)$$

where a and b are constant. This model has the form of a stretched exponential function. It describes experimental disolution data quite well, but put o now there is no physical reasoning for it or a physical meaning of t he constant a and b . Ref. [14] is intented to provide such a physical meaning for the Eq.(3).

CHEBYSHEV POLYNOMIALS

Definition 2.1 The Chebyshev polynomials $T_n(t)$ of the first kind is a polynomials in x of degree n, defined by relation [15, 16]

$$T_n(t) = \cos n\theta, \text{ when } t = \cos\theta$$

If the range of the variable x is the interval $[-1,1]$, the range the corresponding variables θ can be taken $[0,\pi]$. We map the independent variable t in $[0,1]$ to the variable s in $[-1,1]$ by transformation

$$s = 2t - 1 \text{ or } t = \frac{1}{2}(s+1)$$

and this lead to the shifted Chebyshev polynomial of the first kind $T_n^*(t)$ of degree n in x on $[0,1]$ given by [15, 16]

$$T_n^*(t) = T_n(s) = T_n(2t-1).$$

It is of course possible to defined $T_n^*(t)$, like $T_n(t)$, directly by a trigonometric relation. Indeed, we obtained

$$T_n^*(t) = \cos 2n\theta \text{ when } t = \cos^2\theta.$$

The leading coefficient of t^n in $T_n^*(t)$ to be 2^{2n-1}.These polynomials have the following properties [15]:

i) $T^*{}_{n+1}(t)$ has exactly $n+1$ real zeroes on the interval $[0,1]$. The i-th zero t_i is

$$t_i = \frac{1}{2}\left(1 + \cos\left(\frac{(2(n-i)+1)\pi}{2(n+1)}\right)\right),\ i = 0,1,...,n \qquad (4)$$

ii) It is well known that the relation between the powers t^n and the second kind Chebyshev polynomials $T_n^*(t)$ is

$$t^n = 2^{-2n+1}\sum_{k=0}^{n}{}'\binom{2n}{k}T_{n-k}^*(t),\ 0 \le x \le 1 \qquad (5)$$

where $\sum'$ denotes a sum whose first term is halved.

FUNDAMENTAL RELATIONS

In the begining, let assume that Eq.(2-3) has the approximate solution of the truncated Chebyshev polynomial series as:

$$y(t) = \sum_{n=0}^{N} a_n T_n^*(t),\ T_n^*(t) = \cos(n\theta),\ 2t - 1 = \cos\theta \qquad (6)$$

Let us consider Eq. (2-3) and find the matrix forms of the equation. First we can convert the solution $y(t)$ defined by a truncated shifted Chebyshev series (3) and its derivative $y^{(k)}(t)$ to matrix forms [15, 16, 17, 18, 19]

$$y(t) = \mathbf{T}^*(t)\mathbf{A},\ \ y'(t) = \left(\mathbf{T}^*(t)\right)'\mathbf{A} \qquad (7)$$

where

$$\mathbf{T}^*(t) = [T_0^*(t)\ T_1^*(t) \dots T_N^*(t)]$$

$$\mathbf{A} = [a_0\ a_1 \dots a_N]^T$$

By using the expression (5) and taking n=0,1,…,N we find the corresponding matrix relation as follows

$$(\mathbf{X}(t))^T = \mathbf{D}(\mathbf{T}^*(t))^T \quad \textit{and} \quad \mathbf{X}(t) = \mathbf{T}^*(t)\mathbf{D}^T \qquad (8)$$

where

$$\mathbf{X}(t) = [1\ t \dots t^N]$$

$$\mathbf{D}=\begin{bmatrix} 2^{0}\binom{0}{0} & 0 & 0 & 0 & \dots & 0 \\ 2^{-2}\binom{2}{1} & 2^{-1}\binom{2}{0} & 0 & 0 & \dots & 0 \\ 2^{-4}\binom{4}{2} & 2^{-3}\binom{4}{1} & 2^{-3}\binom{4}{0} & 0 & \dots & 0 \\ 2^{-6}\binom{6}{3} & 2^{-5}\binom{6}{2} & 2^{-5}\binom{6}{1} & 2^{-5}\binom{6}{0} & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 2^{-2N}\binom{2N}{N} & 2^{-2N+1}\binom{2N}{N-1} & 2^{-2N+1}\binom{2N}{N-2} & 2^{-2n+1}\binom{2N}{N-3} & \dots & 2^{-2N+1}\binom{2N}{0} \end{bmatrix}$$

Then, by taking into account (7) we obtain

$$\mathbf{T}^{*}(t)=\mathbf{X}(t)(\mathbf{D}^{-1})^{T} \tag{9}$$

and

$$(\mathbf{T}^{*}(t))^{(1)}=\mathbf{X}^{(1)}(t)(\mathbf{D}^{-1})^{T}$$

To obtain the matrix $\mathbf{X}^{(k)}(t)$ in terms of the matrix $\mathbf{X}(t)$, we can use the following relation:

$$\mathbf{X}^{(1)}(t)=\mathbf{X}(t)\mathbf{B}^{T} \tag{10}$$

where

$$\mathbf{B}=\begin{bmatrix} 0 & 0 & 0 & \dots & 0 \\ 1 & 0 & 0 & \dots & 0 \\ 0 & 2 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & 0 & N & 0 \end{bmatrix}$$

Consequently, by substituting the matrix forms (8) and (9) into (5) we have the matrix relation

$$y^{'}(t)=\mathbf{X}(t)\mathbf{B}^{1}(\mathbf{D}^{T})^{-1}\mathbf{A} \tag{11}$$

METHOD OF SOLUTION

Approximating $y'(t)$, $y(t)$ by the shifted Chebyshev polynomials as

$$y'(t)\approx\mathbf{X}(t)\mathbf{B}(\mathbf{D}^{T})^{-1}\mathbf{A}$$

$$y(t)\approx\mathbf{X}(t)(\mathbf{D}^{T})^{-1}\mathbf{A}$$

Using matrix representation of approximate solution and its derivatives, Eqs (2) and (3) can be written as:

$$\frac{1}{M_{\infty}}\mathbf{X}(t)\mathbf{B}(\mathbf{D}^{T})^{-1}\mathbf{A}_{1}\approx f(t) \tag{12}$$

$$\frac{1}{M_{\infty}}\mathbf{X}(t)\mathbf{B}(\mathbf{D}^{T})^{-1}\mathbf{A}_{2}\approx g(t) \tag{13}$$

where $f(t)=kt^{n}$, $g(t)=1-\exp(-at^{b})$. The residual $R_{N}(t)$ for Eqs.(12) and (13) can be written as

$$R_{N}(t)\approx\frac{1}{M_{\infty}}\mathbf{X}(t)\mathbf{B}(\mathbf{D}^{T})^{-1}\mathbf{A}_{1}-\mathbf{F}^{T}\mathbf{X}(t)(\mathbf{D}^{T})^{-1} \tag{14}$$

$$R_{N}(t)\approx\frac{1}{M_{\infty}}\mathbf{X}(t)\mathbf{B}(\mathbf{D}^{T})^{-1}\mathbf{A}_{2}-\mathbf{G}^{T}\mathbf{X}(t)(\mathbf{D}^{T})^{-1} \tag{15}$$

where

$$f(t)\approx\mathbf{F}^{T}\mathbf{X}(t)(\mathbf{D}^{T})^{-1}$$

$$g(t)\approx\mathbf{G}^{T}\mathbf{X}(t)(\mathbf{D}^{T})^{-1}$$

Applying typical Tau method in [17-21], Eqs.(14) and (15) can be converted in $N-1$ linear equations by applying

$$\left\langle R_N(t), T_n^*(t) \right\rangle = \int_0^1 R_N(t) T_n^*(t) dt = 0\,,\ n = 0,1,\ldots,N-1 \qquad (16)$$

The initial conditions are given by

$$y(a) = \mathbf{X}(a)(\mathbf{D}^T)^{-1}\mathbf{A}_1 = \begin{bmatrix} u_{00} & u_{01} & \ldots & u_{0N} \end{bmatrix}\mathbf{A}_1 = \begin{bmatrix} \lambda \end{bmatrix} \qquad (17)$$

$$y(b) = \mathbf{X}(b)(\mathbf{D}^T)^{-1}\mathbf{A}_2 = \begin{bmatrix} u_{00} & u_{01} & \ldots & u_{0N} \end{bmatrix}\mathbf{A}_2 = \begin{bmatrix} \mu \end{bmatrix} \qquad (18)$$

Therefore, we obtained the N sets of linear equations with N unknowns by Eq.(16) and Eq.(17) or Eq.(18). Using the Maple 13, we write the program and solve the N sets of linear equations with N unknowns, and so approximate solution $y_N(x)$ can be calculated.

NUMERICAL RESULTS

We take the values of $k = 4$, $n = 0{,}5$ in Eq.(2) and $a = -0.049$, $b = 0{,}72$ in Eq.(3). Using in Section (3) and Section (4), we obtain the numerical results for Eqs.(2)-(3) and the numerical results is plotted in Figs. (1) and (2), respectively.

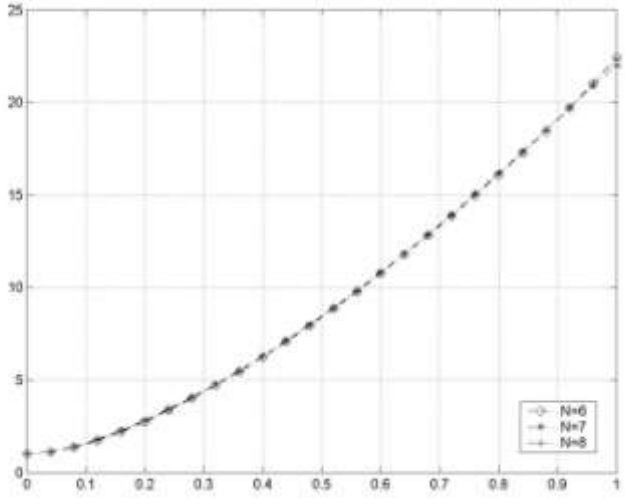

Fig. 1: Numerical solutions of Eq.(2) for various N.

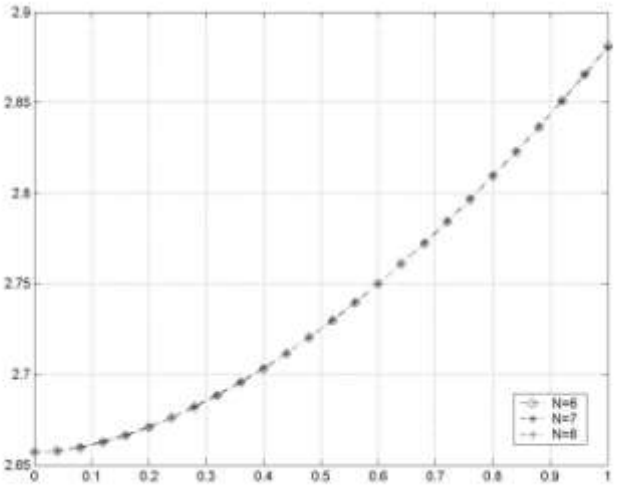

Fig. 2: Numerical solutions of Eq.(3) for various N.

CONCLUSION

Controlled release systems are systems that release the drug in a controlled fashion to maintain an appropriate concentration for a long period of time. Delivery systems of this type will have an impact on the quality of life of patients as well as providing a potentially safer way of delivering correct dosages. Mathematical modeling of the drug release process plays an important role in the design of controlled release systems as it can be used to study various design parameters and avoid excessive experimentation. Furthermore, given the significant advances in computer simulation technology, numerical modeling is increasingly becoming an integral part of research and development in this area. Although extensive experimental studies have been carried out in this field in the recent years, modeling of these systems is currently lacking. Numerical modeling relies on careful representation of the physical situation, and it requires a thorough understanding of drug release kinetics, as well as mathematical expressions and modeling tools. For this generality, mathematical modelling is widely employed in different disciplines such as genetics, medicine, psychology, biology, economy and obviously engineering.

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