

A Numerical Approach for Solving Modified Epidemiological Model for Drug Release Systems

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Abstract

The mathematical modeling of drug release systems has a significant potential to facilitate product development and to help understanding complex pharmaceutical dosage forms. The findings of the modeling studies can help control some of the parameters to obtain the desired release performance. In this article, we have introduced a Chebyshev collocation method, which is based on collocation method for solving initial-boundary value problem describing the Higuchi and power law.

Keywords: Drug release systems, higuchi law, power law, collocation method.

İlaç Salım Sistemleri için Modifiye Epidemiyolojik Modelin Sayısal Çözümü

Özet

İlaç salım sistemlerinin matematiksel modellenmesi ürün geliştirme ve karmaşık farmasötik dozaj formları anlama kolaylığı sağlamada önemli bir potansiyele sahiptir. Modelleme çalışmaları bulguları, bazı parametrelerin kontrolü, istenilen salım performanslarının elde edilmesine yardımcı olmaktadır. Bu makalede Chebyshev sıralama metodu ile taşıyıcı sistemlerden ilaç salım modeli Higuchi ve güç modeli için nümerik sonuçlar verilmiştir.

Anahtar Kelimeler: İlaç salım sistemleri, higuchi modeli, güç modeli, sıralama metodu

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1. Introduction

In the last 100 years, drug delivery systems have enormously increased their performances, moving from simple pills to sustained/controlled release and sophisticated programmable delivery systems. Meanwhile, drug delivery has also become more specific from systemic to organ and cellular targeting [1]. A good mathematical model can help researchers reduce costs and production time by adding in silico experiments to their database (i.e., filling the gaps between laboratory experiments) and extrapolating to unexplored cases. The results of the mathematical modelings can contribute to the optimal designs of new pharmaceutical devices and treatment schedules to specific diseases and patients[2-4]. Hence, the development of new pharmaceutical products is highly facilitated because the desirable release kinetics can be predicted in advance and thus be better achieved. Despite the complexity of the phenomena involved in drug release mechanisms, the mathematical models commonly used to describe the kinetics of drug release from a large variety of devices are two simple expressions, the Higuchi law and the power law.

The Higuchi law [1] states that

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

where M_t is the cumulative 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 [5] states

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

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 [6,7]. 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 [8-10].

The Weibull function is sporadically used in drug release studies in spite of its extensive empirical use in dissolution studies [11-12]:

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

where a and b are constant. This model has the form of a stretched exponential function. It describes experimental dissolution 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.[13] is intended to provide such a physical meaning for the Eq.(3).

In this article, Chebyshev collocation method [14-18] has been applied for the numerical solution of the mathematical model of drug release Eq.(2-3).

2. 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 [14 ve 20]

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

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 [20 ve 21]

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

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 [21]:

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

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

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

$$t^n = 2^{-2n+1} \sum_{k=0}^n \binom{2n}{k} T_{n-k}^*(t), 0 \leq x \leq 1 \quad (5)$$

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

3. Fundamental relations

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

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

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 [14-18]

$$y(t) = \mathbf{T}^*(t)\mathbf{A}, \quad y'(t) = (\mathbf{T}^*(t))' \mathbf{A} \tag{7}$$

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 $n=0,1,\dots,N$ we find the corresponding matrix relation as follows

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

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

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

4. Method of solution

Using Eq.(11), we obtain the matrix relation of Eqs.(2) and (3)

$$\frac{1}{M_\infty} \mathbf{X}(t)\mathbf{B}(\mathbf{D}^T)^{-1} \mathbf{A}_1 = kt^n \quad (12)$$

$$\frac{1}{M_\infty} \mathbf{X}(t)\mathbf{B}(\mathbf{D}^T)^{-1} \mathbf{A}_2 = 1 - \exp(-at^b) \quad (13)$$

Then, we substitute the collocation points are defined by

$$t_i = \frac{i}{N}, \quad i = 0,1,\dots,N$$

into Eqs.(12) and (13) . Then, we have

$$\frac{1}{M_\infty} \mathbf{X}(t_i)\mathbf{B}(\mathbf{D}^T)^{-1} \mathbf{A}_1 = kt_i^n \quad (14)$$

$$\frac{1}{M_\infty} \mathbf{X}(t_i)\mathbf{B}(\mathbf{D}^T)^{-1} \mathbf{A}_2 = 1 - \exp(-at_i^b) \quad (15)$$

Thus, we have the fundamental matrix equation of Eqs. (2) and (3)

$$\mathbf{PXB}(\mathbf{D}^T)^{-1} \mathbf{A}_1 = \mathbf{F} \quad (16)$$

$$\mathbf{PXB}(\mathbf{D}^T)^{-1} \mathbf{A}_2 = \mathbf{G} \quad (17)$$

where

$$\mathbf{P} = \begin{bmatrix} 1/M_\infty & 0 & 0 & \dots & 0 \\ 0 & 1/M_\infty & 0 & \dots & 0 \\ 0 & 0 & 1/M_\infty & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 1/M_\infty \end{bmatrix} \quad \mathbf{X} = \begin{bmatrix} 1 & t_0 & t_0^2 & \dots & t_0^N \\ 1 & t_1 & t_1^2 & \dots & t_1^N \\ 1 & t_2 & t_2^2 & \dots & t_2^N \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & t_N & t_N^2 & \dots & t_N^N \end{bmatrix}$$

$$\mathbf{F} = \begin{bmatrix} f(t_0) \\ f(t_1) \\ f(t_2) \\ \vdots \\ f(t_N) \end{bmatrix} \quad \mathbf{G} = \begin{bmatrix} g(t_0) \\ g(t_1) \\ g(t_2) \\ \vdots \\ g(t_N) \end{bmatrix}$$

and where $f(t) = kt^n$, $g(t) = 1 - \exp(at^b)$.

Briefly, Eqs.(16) and (17) can be written in the form[14-19]

$$\mathbf{W}_1 \mathbf{A}_1 = \mathbf{F} \quad \text{or} \quad [\mathbf{W}_1; \mathbf{F}] \quad (16)$$

$$\mathbf{W}_2 \mathbf{A}_2 = \mathbf{G} \quad \text{or} \quad [\mathbf{W}_2; \mathbf{G}] \quad (17)$$

To obtain the solution of Eq. (1) under condition

$$y(a) = \mathbf{X}(a)(\mathbf{D}^T)^{-1} \mathbf{A}_1 = [u_{00} \quad u_{01} \quad \dots \quad u_{0N}] \mathbf{A}_1 = [\lambda] \quad (18)$$

$$y(b) = \mathbf{X}(b)(\mathbf{D}^T)^{-1} \mathbf{A}_2 = [u_{00} \quad u_{01} \quad \dots \quad u_{0N}] \mathbf{A}_2 = [\mu] \quad (19)$$

by replacing the row matrices (19-20) by the last 1 rows of the matrix (21-22) respectively, we have the new augmented matrix,

$$[\tilde{\mathbf{W}}_1; \tilde{\mathbf{F}}] = \begin{bmatrix} w_{00} & w_{01} & \cdots & w_{0N} & ; & f(t_0) \\ w_{10} & w_{11} & \cdots & w_{1N} & ; & f(t_1) \\ \vdots & \vdots & \ddots & \vdots & ; & \vdots \\ w_{N-20} & w_{N-21} & \cdots & w_{N-2N} & ; & f(t_{N-2}) \\ w_{N-10} & w_{N-11} & \cdots & w_{N-1N} & ; & f(t_{N-1}) \\ u_{00} & u_{01} & \cdots & u_{0N} & ; & \lambda \end{bmatrix}$$

$$[\tilde{\mathbf{W}}_2; \tilde{\mathbf{F}}] = \begin{bmatrix} w_{00} & w_{01} & \cdots & w_{0N} & ; & f(t_0) \\ w_{10} & w_{11} & \cdots & w_{1N} & ; & f(t_1) \\ \vdots & \vdots & \ddots & \vdots & ; & \vdots \\ w_{N-20} & w_{N-21} & \cdots & w_{N-2N} & ; & f(t_{N-2}) \\ w_{N-10} & w_{N-11} & \cdots & w_{N-1N} & ; & f(t_{N-1}) \\ u_{00} & u_{01} & \cdots & u_{0N} & ; & \mu \end{bmatrix}$$

which corresponds to a system of $(N + 1)$ algebraic equations for the $(N + 1)$ unknown Chebyshev

coefficients $\mathbf{A}_1, \mathbf{A}_2$. If $rank \tilde{\mathbf{W}}_1 = N + 1, rank \tilde{\mathbf{W}}_2 = N + 1$, we obtain the coefficient matrix $\mathbf{A}_1, \mathbf{A}_2$

$$\mathbf{A}_1 = \tilde{\mathbf{W}}_1^{-1} \tilde{\mathbf{F}} \tag{20}$$

$$\mathbf{A}_2 = \tilde{\mathbf{W}}_2^{-1} \tilde{\mathbf{G}} \tag{21}$$

The coefficients matrix $\mathbf{A}_1, \mathbf{A}_2$ substituting in Eq.(6), we obtain the approximate solutions for Eqs.(2) and (3).

We can easily check the accuracy of the method. Since the truncated shifted Chebyshev series (6) is an approximate solution of Eqs.(2) and (3), when the solution $y(t)$ and its derivatives are substituted in Eq.(2) and (3), the resulting equation must be satisfied approximately; that is [14-20], for $x = x_q \in [0,1], q = 0,1,2,\dots$

$$E_1(t_q) = \left| \frac{y'(t)}{M_\infty} - kt^n \right| \cong 0 \tag{22}$$

$$E_2(t_q) = \left| \frac{y'(t)}{M_\infty} - 1 + \exp(at^b) \right| \cong 0 \tag{23}$$

5. 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. (2) and (3), respectively.

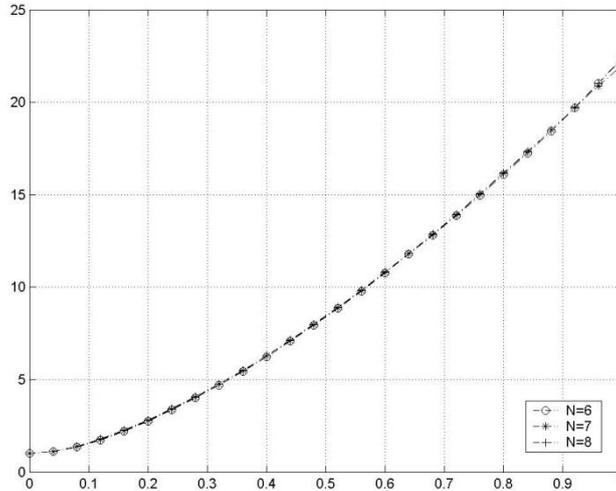


Fig.1. Numerical solutions of Eq.(2) for various N.

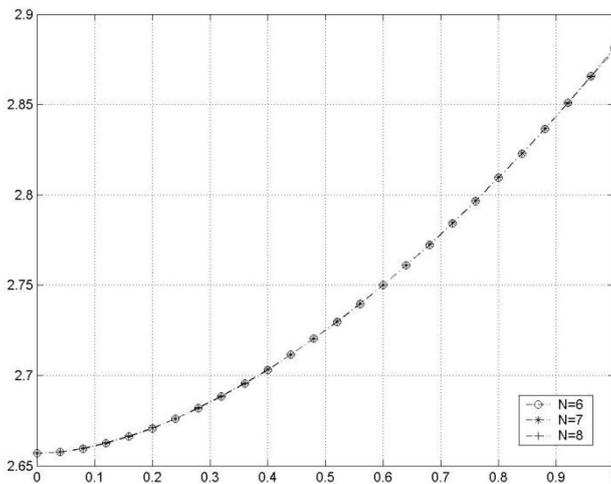


Fig.2. Numerical solutions of Eq.(3) for various N.

6. Conclusion

Mathematical modelling, whose development requires the comprehension of all the phenomena affecting drug release kinetics [10], has a very important value in controlled drug release systems optimisation. The model can be simply thought as a “mathematical metaphor of some aspects of reality [11] that, in this case, identifies with the ensemble of phenomena ruling release kinetics. 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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