



ANALYTICAL STUDY OF SINGLE- AND DOUBLE-LAYER COATING SYSTEM FOR CONTROLLED DRUG-RELEASING ORTHOPEDIC IMPLANTS USING DIFFERENTIAL TRANSFORM METHOD

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ARTICLE INFORMATION

Submitted: 29 February, 2024
Revised: 28 November, 2024
Accepted: 30 November, 2024

Keywords:

Orthopedic implants
Drug release
Mathematical models
Differential transform method

ABSTRACT

The analytical study of single- and double-layer coating system for controlled drug releasing orthopedic implants using differential transform method has been presented. Drug release when transported across single- or double-layer boundaries have the potentials of smart fluid properties which can be controlled by various parameters. In the present study, the developed governing model for single- or double-layer coating system for controlled drug-releasing orthopedic implants is a set of coupled partial differential equations for the unsteady diffusion processes with intractable solution. Hence, the solution was obtained with Differential Transform Method and was validated with both Runge-Kutta Order-four numerical scheme and experimental results. Good agreement was established among them. The effects of thickness ratio, diffusion period, porosity term, and effective diffusion coefficient on concentration profile are investigated. From the obtained results, it was observed that increase in the interface layer thickness ratio d of 0.2 to 0.8 resulted in decrease from 1 to 0 (zero) in the concentration profiles for all the different dimensionless durations considered. In addition, augmentation of two (2) layers of varying thickness ratio from $d = 0.2$ to 0.8 in the release parameter resulted in a decrease in the concentration profile to 0 (zero) for the three cases of thickness ratios. The studies show that effective diffusion coefficients for a period of five (5) seconds increases from 0 to 100% is the dominant parameter in the model and so provides considerable flexibility for design process. Hence, the developed model and the obtained solutions provide the benchmark for the optimized and enhanced control of drug-releasing orthopedic implants.

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1.0 Introduction

The subject of drug delivery is indeed a multi-disciplinary area of research that has attracted interest of chemists, mathematicians, engineers, scientists and life scientists for years. In fact, drug delivery controls have received considerable attentions, especially in the designs and uses of tablets (Efentakis *et al.*, 2010). The knowledge also helps in understanding the working principles of various resident drug delivery devices like stent, patch, lense and implants (McGinty, 2014, Lyndon *et al.*, 2014) shown in Figure 1. The applications of these controlled drug releasing orthopedic implants in the field of medicine have introduced innovations and have proven to be successful in its usefulness. It has been a significant advancement in the field of medicine (Goodman *et al.*, 2013). Few examples are plates, prosthetic knee and hip joints, screws and rods placed in the spinal cord, or other parts of the body to stabilize fractures, and for replacement of intervertebral disks. Orthopedic implants have been designed to restore mobility, reduce pain and to improve quality of life (McGinty and Pontrelli, 2015).

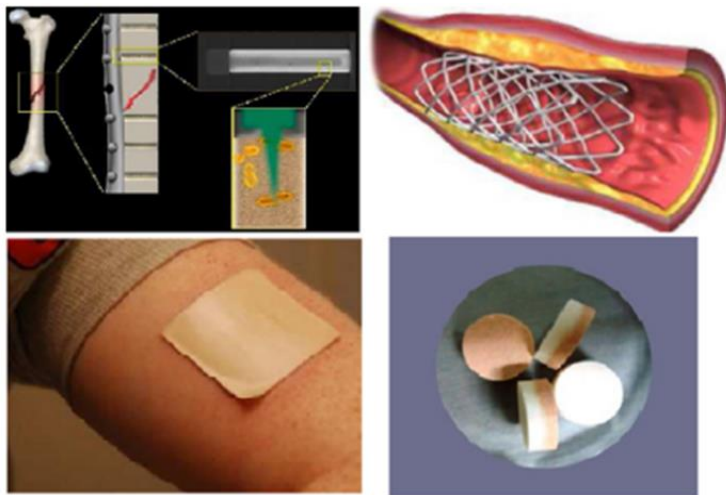


Figure 1: Examples of drug-delivery devices for different applications; implants, patch, stent, lens

Though the application of OIs began as modest mechanical devices, but before long, complications set in. The factors that may be considered include the physical impact of the device on the bone and the soft tissues surrounding the bone; the unavoidable response of the foreign body; the probability of achieving osseointegration and many other complications (McGinty and Pontrelli, 2015). The materials used in the construction of OI must be biocompatible with the human body, and as such quite a number of studies have been conducted to investigate the biocompatibility of these class of biomaterials (Lyndon *et al.*, 2013). Certain studies have been carried out on OI to explore and investigate features such as potential cytotoxic and corrosion resistance effects. Cobalt-chromium and Titanium alloys have been shown to be more durable and less ductile than stainless steel (Zadeh, 2019). Typically, experimental research into techniques to locally distribute medications from OIs as contained a drug inside a small container in the examined device. The various approaches to drug containment that look into changing the surface of the device structure have been studied (Losic *et al.*, 2014, Trajkovski *et al.*, 2012), and putting a coating to the device's surface (Goodman *et al.*, 2013). To enhance the medication release from orthopedic implants, many investigations have been carried out. For instance, modifying an OI's surface structure to serve as a drug reservoir or coating the exterior of an OI with a drug-releasing material (Losic *et al.*, 2014, Mazaheri, *et al.*, 2015). In orthopedic applications, distribution is really nothing new, antibiotics are commonly administered locally (Arruebo *et al.*, 2010, Pozo and Patel, 2009).

The drug release process must be thoroughly understood for regulating the amount released for a precise OI (s) and prudence must be taken when providing treatment, articular antibiotics, below the minimal therapy dosage (Lyndon, *et al.*, 2014). The antibacterial and drug-releasing capabilities of some drug coated polymeric devices were evaluated in an effort to provide solution to the problem of post-surgical infection known with the implant of the orthopedic device, (Arsiwala *et al.*, 2014). Two prevalent approaches for achieving the releasing mechanism are either upgrading existing OIs or developing new device models with the intention of merging medication release with such a device (Gimeno *et al.*, 2013). Recent advances in mathematical modeling studies have focused on drug-releasing OIs in specific medical applications, including coronary stents, and from certain materials and architectures, like nanotubes and porous layers, which could be applied in the production of OI. Therefore, mathematical models with some modifications could be applied to drug-releasing OIs rather than experimental (in vitro and in vivo), which has since come to be accepted as the direction of orthopedic medicine in order to lower costs and shorten trial testing times (Siepmann and Siepmann, 2012). Recent studies have discovered mathematical models that focus solely on the drug-releasing process in OIs. It is beneficial, providing additional insights and understanding, as it was demonstrated by different models such as mathematical models describe drug release mechanisms (McGinty and Pontrelli, 2015). In addition, the release of anti-cancer medications Mitoxantrone (MTX) mesoporous silicon was studied (Tzur-Balter *et al.*, 2013). In recent studies, mathematical models have been developed for drug release from OIs. It reduces the cost of computation and simulation to reduce the challenges of real-life problems (Sobamowo *et al.*, 2022).

In the present study, the Differential Transform Method (DTM) is applied to obtain solution to the problem of nonlinear simulation for the predictions of controlled drug-releasing orthopedic implants. The DTM is an efficient analytical method for obtaining solutions for linear and nonlinear ordinary differential equations. Its principles were developed in 1986 by Zhou (1986). The DTM has been applied in a wide range of studies such as convective flow in free and forced conditions on inclined planes of porous media (Rashidi *et al.*, 2012). Nanofluids flow in both Newtonian and non-Newtonian state (Hatami and Jing, 2016). The DTM has proved to be effective when compared with other analytical methods. These include Homotopy Perturbation Method (Ghafoori *et al.*, 2011) and Adomian Decomposition Method (Cakir and Arslan, 2015). The DTM has been combined with the Laplace Transform Method to overcome the deficiency usually caused by the unsatisfied conditions. Such as in multi-step differential transform method for nonlinear oscillation Erturk (2012), and nonlinear Duffing oscillator with damping effect (Nourazar and Mirzabeigy, 2013). Hence, the main objective of the current study is to develop a predictive mathematical model for controlled drug releasing orthopedic implants and to obtain analytical solutions using the Differential Transform Methods. The Runge-Kutta order four numerical method was applied to validate the obtained analytical solutions. It was also validated with experimental results obtained in past recent studies. The effects of thickness ratio, diffusion period, porosity term, and effective diffusion coefficient ratio parameters on the governing model are then investigated.

2. Model Formulation

One major inclusion in the device for drug delivery is a drug which contains coating of polymeric matrix characteristics that interact with certain release channels. The exact configuration of the device depends on their applications, but the coating of the drug-releasing ones can usually be modeled as a thick slab of width L . Since the thickness of drug-release device coatings is naturally small compared with the dimensions of the lateral coating, and the drug flow is in one direction, the one-dimensional model is assumed in the study as shown in Figure 2.

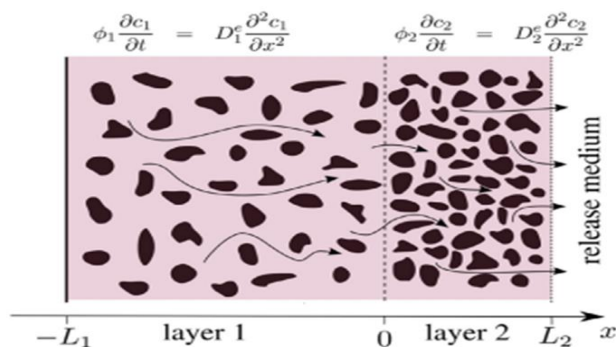


Figure 2: Model's physical geometry

The layers 1 and 2 have thickness or width of L_1 and L_2 , respectively, with $L = L_1 + L_2$ the total coating thickness. Each porous coated layer is represented as a homogeneous material and all concentrations are defined as intrinsically averaged variables c_1 and c_2 . The porosity constant ϕ_1 and ϕ_2 represent the drug concentrations in layers 1 and 2, respectively. Additionally, the molecules are assumed to move along an increasing path length because of the indirect pores pathway represented by a new tortuosity parameter τ_i , $i = 1, 2$.

With the assumption of a fast wetted coating and soluble drug, the phenomenon of drug transport can be represented by the following diffusion equations.

$$\text{Diffusion equation for layer 1: } \phi_1 \frac{\partial c_1}{\partial t} - D_1^e \frac{\partial^2 c_1}{\partial x^2} = 0 \quad -L_1 < x < 0, \quad t > 0 \quad (1)$$

$$\text{Diffusion equation for layer 2: } \phi_2 \frac{\partial c_2}{\partial t} - D_2^e \frac{\partial^2 c_2}{\partial x^2} = 0 \quad 0 < x < L_2, \quad t > 0 \quad (2)$$

In the current study, the coating of the medical implant is assumed to discharge drug via pores filled with fluid only. Consequently, the solid phase diffusion is neglected.

The mixed-type boundary conditions are imposed at both ends for a general case

$$K_1c_1 + D_1^e \frac{\partial c_1}{\partial x} = 0 \quad x = -L_1, \quad t > 0 \quad (3)$$

$$K_2c_2 + D_2^e \frac{\partial c_2}{\partial x} = 0 \quad x = L_2, \quad t > 0 \quad (4)$$

With interfacial conditions are given as;

$$P(c_1 - c_2) + D_1^e \frac{\partial c_1}{\partial x} = 0 \quad x = 0, \quad t > 0 \quad (5)$$

$$-D_2^e \frac{\partial c_2}{\partial x} = -D_1^e \frac{\partial c_1}{\partial x} \quad x = 0, \quad t > 0 \quad (6)$$

Subject to initial conditions expressed as;

$$c_1 = c_1^0, \quad -L_1 \leq x \leq 0, \quad t = 0; \quad c_2 = c_2^0, \quad 0 \leq x \leq L_2, \quad t = 0 \quad (7)$$

For the purpose of obtaining a dimensionless model, we introduce the following dimensionless variables:

$$X = \frac{x}{L}, \tau = \frac{D_1^e t}{\phi_1 L^2}, \quad C_1 = \frac{c_1}{c_1^0}, \quad C_2 = \frac{c_2}{c_1^0}, \quad \delta = \frac{L_1}{L}, \\ \chi = \frac{D_2^e}{D_1^e}, \quad C^0 = \frac{c_2^0}{c_1^0}, \quad \phi = \frac{\phi_2}{\phi_1}, \quad \eta = \frac{PL}{D_1^e}, \quad \Gamma_1 = \frac{K_1L}{D_1^e}, \quad \Gamma_2 = \frac{K_2L}{D_1^e} \quad (8)$$

Using Equation (8) on Equations (1-7), the dimensionless governing equations become;

$$\frac{\partial C_1}{\partial \tau} - \frac{\partial^2 C_1}{\partial X^2} = 0 \quad -\delta < X < 0, \quad \tau > 0 \quad (9)$$

$$\frac{\partial C_2}{\partial \tau} - \frac{\chi}{\phi} \frac{\partial^2 C_2}{\partial X^2} = 0 \quad 0 < X < 1 - \delta, \quad \tau > 0 \quad (10)$$

Subject to generalized boundary and interfacial conditions given as:

$$\frac{\partial C_1}{\partial X} + \Gamma_1 C_1 = 0 \quad X = -\delta, \quad \tau > 0 \quad (11)$$

$$\frac{\partial C_1}{\partial X} + \eta(C_1 - C_2) = 0 \quad X = 0, \quad \tau > 0 \quad (12)$$

$$\chi \frac{\partial C_2}{\partial X} = \frac{\partial C_1}{\partial X} \quad X = 0, \quad \tau > 0 \quad (13)$$

$$\chi \frac{\partial C_2}{\partial X} + \Gamma_2 C_2 = 0 \quad X = 1 - \delta, \quad \tau > 0 \tag{14}$$

With initial conditions expressed as;

$$C_1 = 1 - \delta \leq X \leq 0, \quad \tau = 0; \quad C_2 = C^0, \quad 0 \leq X \leq 1 - \delta, \quad \tau = 0 \tag{15}$$

The established diffusion equations will be solved subject to the established initial and boundary conditions in order to obtain the drug transport solutions.

2.1 Analytical Solution to the Developed Models; Differential transform method (DTM)

The governing models and the intermediate boundary conditions in the governing equations necessitate the need for a method that is capable of a solution which transforms differential equations from the original form into another domain for easy and robust representation. The Differential transform method (DTM) is applied to transform a governing differential equation to an algebraic domain and then inverted through series summation method. The solutions of the problems are generated with the governing parameters intact and in place. Few of the DTM recursive relations used in the transformation of the differential equations are shown in the Table I:

Table I: Differential transform method (DTM)

S/N	Original function	Transformed function
1	$Z(t) = U(t) \pm V(t)$	$Z(k) = U(k) \pm V(k)$
2	$Z(t) = \infty U(t)$	$Z(k) = \infty U(k)$
3	$Z(t) \frac{dU(t)}{dt}$	$Z(k) = (k + 1)U[k + 1]$
4	$Z(t) = \frac{d^2U(t)}{dt^2}$	$Z(k) = (k + 1)(k + 2)U[k + 2]$
5	$Z(t) = \frac{d^mU(t)}{dt^m}$	$Z(k) = (k + 1)(k + 2) \dots (k + m)U[k + m]$
6	$Z(t) = U(t) * V(t)$	$Z(k) = \sum_{l=0}^k V[l]U[k - l]$
7	$Z(t) = t^m$	$Z(k) = \delta(k - m) = \begin{cases} 1 & \text{if } k = m \\ 0 & \text{if } k \neq m \end{cases}$
8	$Z(t) = a(\text{const an } t)$	$Z(k) = a\delta(k) = a \begin{cases} 1 & \text{if } k = 0 \\ 0 & \text{if } k \neq 0 \end{cases}$

Differential transform method (DTM)

$$Z(t) = U(t) \pm V(t), \quad Z(k) = U(k) \pm V(k).$$

$$Z(t) = \infty U(t), \quad Z(k) = \infty U(k).$$

$$Z(t) = \frac{dU(t)}{dt}, \quad Z(k) = (k + 1)U[k + 1].$$

$$Z(t) = \frac{d^2U(t)}{dt^2}, \quad Z(k) = (k + 1)(k + 2)U[k + 2].$$

$$Z(t) = \frac{d^mU(t)}{dt^m}, \quad Z(k) = (k + 1)(k + 2) \dots (k + m)U[k + m]. \quad \text{or } \frac{(k + m)!}{k!} U[k + m].$$

Representing $C_1 = \xi$, $C_2 = \sigma$ and applying Table I to Equations (9) and (10) yield,

$$(k + 1)\xi_{k+1,h} - (h + 1)(h + 2)\xi_{k,h+2} = 0 \tag{16}$$

$$(k + 1)\sigma_{k+1,h} - \frac{\chi}{\phi}(h + 1)(h + 2)\sigma_{k,h+2} = 0 \tag{17}$$

With transformed boundary conditions represented as;

$$\xi_{0,h} = 1, \quad \xi_{k,0} = a, \quad \xi_{k,1} = b, \quad \sigma_{0,h} = C, \quad \sigma_{k,0} = A, \quad \sigma_{k,1} = B \tag{18}$$

Performing iteration on Equations (16) and (17) using Equation (18) gives some of the solution:

$$\text{When } h = 0: \quad \xi_{1,2} = a, \quad \sigma_{1,2} = \frac{A\phi}{\chi}, \quad \xi_{2,2} = \frac{3a}{2}, \quad \sigma_{2,2} = \frac{3A\phi}{2\chi}, \quad \xi_{3,2} = 2a, \quad \sigma_{3,2} = \frac{2A\phi}{\chi} \tag{19}$$

$$\text{When } h = 1: \quad \xi_{1,3} = \frac{b}{3}, \quad \sigma_{1,3} = \frac{B\phi}{3\chi}, \quad \xi_{2,3} = \frac{b}{2}, \quad \sigma_{2,3} = \frac{B\phi}{2\chi}, \quad \xi_{3,3} = \frac{2b}{3}, \quad \sigma_{3,3} = \frac{2B\phi}{3\chi} \tag{20}$$

$$\text{When } h = 2: \quad \xi_{1,4} = \frac{a}{4}, \quad \sigma_{1,4} = \frac{A\phi^2}{4\chi^2}, \quad \xi_{2,4} = \frac{a}{2}, \quad \sigma_{2,4} = \frac{A\phi^2}{2\chi^2}, \quad \xi_{3,4} = \frac{5a}{6}, \quad \sigma_{3,4} = \frac{5A\phi^2}{6\chi^2} \tag{21}$$

Applying the principle of DTM grouping on the term by term solution,

$$C_1 = \sum_{j=0}^8 \sum_{k=0}^8 \xi_{j,k} X^k \tau^j \quad j, k = 1, 2, 3, 4, 5, \dots$$

$$C_2 = \sum_{j=0}^8 \sum_{k=0}^8 \sigma_{j,k} X^k \tau^j \quad j, k = 1, 2, 3, 4, 5, \dots \tag{22}$$

Making necessary substitution, the desired solutions for drug transports become:

$$C_1(X, \tau) = \left(\begin{aligned} &1 + X + 5/6a\tau^3 X^4 + 2/3b\tau^3 X^3 + 3/5b\tau^7 X^5 + b\tau^8 X + 1/7b\tau^7 X^7 + a\tau^7 X^6 \\ &+ 3a\tau^7 X^4 + 4a\tau^7 X^2 + 4/3b\tau^7 X^3 + 7/3a\tau^6 X^4 + \frac{7b\tau^6 X^5}{15} + b\tau^7 X + 1/8a\tau^6 X^8 \\ &+ 1/10b\tau^6 X^7 + 1/2b\tau^2 X^3 + X^8 + a\tau X^2 + 1/42b\tau^3 X^7 + X^6 + 7/6b\tau^6 X^3 + \frac{7a\tau^6 X^6}{10} \\ &+ b\tau^6 X + 7/2a\tau^6 X^2 + 1/15b\tau^5 X^7 + \frac{3a\tau^5 X^8}{40} + b\tau^5 X^3 + \frac{7a\tau^5 X^6}{15} + \frac{7b\tau^5 X^5}{20} \\ &+ 1/24b\tau^4 X^7 + 1/24a\tau^4 X^8 + 7/4a\tau^5 X^4 + b\tau^5 X + 3a\tau^5 X^2 + \frac{a\tau^2 X^8}{112} + 2a\tau^3 X^2 \\ &+ \frac{b\tau^2 X^7}{84} + b\tau^3 X + 5/4a\tau^4 X^4 + \frac{3\xi_{10,3}\tau^8 X^7}{28} + \frac{7a\tau^4 X^6}{24} + \dots \end{aligned} \right) \tag{23}$$

$$C_2 = \left(C + \frac{B\phi^3\tau X^7}{210\chi^3} + 1/3 \frac{B\phi\tau X^3}{\chi} + 2 \frac{A\phi\tau^3 X^2}{\chi} + 2/3 \frac{B\phi\tau^3 X^3}{\chi} + 1/2 \frac{B\phi\tau^2 X^3}{\chi} + \frac{A\phi^3\tau^7 X^6}{\chi^3} \right. \\
 + 1/7 \frac{B\phi^3\tau^7 X^7}{\chi^3} + 1/28 \frac{\sigma_{10,2}\phi^3\tau^7 X^8}{\chi^3} + 4 \frac{A\phi\tau^7 X^2}{\chi} + 4/3 \frac{B\phi\tau^7 X^3}{\chi} + 3 \frac{A\phi^2\tau^7 X^4}{\chi^2} \\
 + 3/5 \frac{B\phi^2\tau^7 X^5}{\chi^2} + 1/20 \frac{B\phi^2\tau X^5}{\chi^2} + 3 \frac{A\phi\tau^5 X^2}{\chi} + \frac{A\phi^4\tau X^8}{336\chi^4} + A\tau + A\tau^2 + A\tau^3 \\
 + A\tau^4 + A\tau^5 + A\tau^6 + A\tau^7 + B\tau^2 X + B\tau X + B\tau^8 X + \frac{7B\phi^2\tau^5 X^5}{20\chi^2} + 1/10 \frac{B\phi^2\tau^2 X^5}{\chi^2} \\
 + 1/2 \frac{A\phi^2\tau^2 X^4}{\chi^2} + \frac{15A\phi^2\tau^8 X^4}{4\chi^2} + 3/4 \frac{B\phi^2\tau^8 X^5}{\chi^2} + 1/4 \frac{\sigma_{10,2}\phi^2\tau^8 X^6}{\chi^2} + B\tau^4 X + B\tau^7 X \\
 + B\tau^3 X + 1/30 \frac{A\phi^3\tau X^6}{\chi^3} + B\tau^5 X + B\tau^6 X + 1/15 \frac{B\phi^3\tau^5 X^7}{\chi^3} + \frac{3\sigma_{10,4}\phi^2\tau^8 X^8}{56\chi^2} + \frac{7A\phi^3\tau^5 X^6}{15\chi^3} + \\
 1/12 \frac{A\phi^3\tau^2 X^6}{\chi^3} + 1/24 \frac{B\phi^3\tau^4 X^7}{\chi^3} + 1/24 \frac{A\phi^4\tau^4 X^8}{\chi^4} + 9/2 \frac{A\phi\tau^8 X^2}{\chi} + 3/2 \frac{B\phi\tau^8 X^3}{\chi} \\
 + 7/2 \frac{A\phi\tau^6 X^2}{\chi} + 7/6 \frac{B\phi\tau^6 X^3}{\chi} + 7/3 \frac{A\phi^2\tau^6 X^4}{\chi^2} + \frac{7B\phi^2\tau^6 X^5}{15\chi^2} + \frac{7A\phi^3\tau^6 X^6}{10\chi^3} \\
 + 1/10 \frac{B\phi^3\tau^6 X^7}{\chi^3} + 1/8 \frac{A\phi^4\tau^6 X^8}{\chi^4} + \frac{B\phi\tau^5 X^3}{\chi} + 7/4 \frac{A\phi^2\tau^5 X^4}{\chi^2} + \frac{A\phi\tau X^2}{\chi} + \frac{7A\phi^3\tau^4 X^6}{24\chi^3} \\
 \left. + CX + CX^2 + CX^3 + CX^4 + CX^5 + CX^6 + CX^7 + CX^8 + 5/6 \frac{B\phi\tau^4 X^3}{\chi} + \dots \right) \tag{24}$$

Equations (23) and (24) are the desired analytical solutions for the drug diffusion models. These solutions can be used to predict transport and mass transfer of the drug through the porous layers. The equations will be treated and then used for simulation and parametric studies. Furthermore, the obtained spatial terms of the series solutions will be converted into an approximate polynomial or exponential functions. These approximate functions will then be solved numerically together with the given boundary conditions to obtain the values of a , b , A and B . These values are substituted into the series solution and then used to visualize and investigate the intermediate conditions.

3. Results and Discussion

In this study, an analytical solution for controlled drug releasing orthopedic implants for biomedical applications has been obtained using the differential transform method (DTM). The obtained analytical results are validated using the Fourth Order Runge Kutta numerical method and presented in Table 2. The obtained analytical solutions were further validated with experimental results in a related past study and showed in Figure 3. Additionally, Figure 3 depicts the validation of the present study the experimental result of Berg (2012) good agreements established. This further demonstrate the capability of the employed analytical scheme for handling the problem of drug delivery for single and double interface layers.

Table 2: Validation of DTM with Numerical method

C(X)	t = 0.01			d = 0.10			d = 1.00		
	Numerical	DTM	Residue	Numerical	DTM	Residue	Numerical	DTM	Residue
0.00	1.0000	1.0000	0.0000	0.5000	0.5000	0.0000	0.2000	0.2000	0.0000
0.05	1.0000	1.0000	0.0000	0.5000	0.5000	0.0000	0.2000	0.2000	0.0000
0.10	1.0000	1.0000	0.0000	0.5000	0.5000	0.0000	0.2000	0.2000	0.0000
0.15	1.0000	1.0000	0.0000	0.5000	0.5000	0.0000	0.2000	0.2000	0.0000
0.20	0.9997	0.9997	0.0000	0.4999	0.4999	0.0000	0.1999	0.1999	0.0000
0.25	0.9990	0.9990	0.0000	0.4995	0.4995	0.0000	0.1998	0.1998	0.0000
0.30	0.9971	0.9971	0.0000	0.4986	0.4985	0.0001	0.1994	0.1994	0.0000
0.35	0.9927	0.9927	0.0000	0.4964	0.4963	0.0001	0.1985	0.1985	0.0000
0.40	0.9837	0.9839	0.0002	0.4919	0.4919	0.0000	0.1967	0.1967	0.0000
0.45	0.9673	0.9676	0.0003	0.4837	0.4837	0.0000	0.1935	0.1935	0.0000
0.50	0.9394	0.9399	0.0005	0.4699	0.4697	0.0002	0.1879	0.1879	0.0000
0.55	0.8952	0.8959	0.0007	0.4478	0.4476	0.0002	0.1790	0.1790	0.0000
0.60	0.8298	0.8309	0.0011	0.4153	0.4149	0.0004	0.1660	0.1660	0.0000
0.65	0.7396	0.7413	0.0017	0.3703	0.3698	0.0005	0.1479	0.1479	0.0000
0.70	0.6246	0.6268	0.0022	0.3131	0.3123	0.0008	0.1249	0.1249	0.0000
0.75	0.4907	0.4933	0.0026	0.2462	0.2454	0.0008	0.0981	0.0981	0.0000
0.80	0.3504	0.3532	0.0028	0.1761	0.1752	0.0009	0.0701	0.0701	0.0000
0.85	0.2212	0.2237	0.0025	0.1114	0.1106	0.0008	0.0442	0.0442	0.0000
0.90	0.1193	0.1213	0.0020	0.0603	0.0597	0.0006	0.0239	0.0239	0.0000
0.95	0.0528	0.0540	0.0012	0.0268	0.0264	0.0004	0.0106	0.0106	0.0000
1.00	0.0183	0.0189	0.0006	0.0093	0.0092	0.0001	0.0037	0.0037	0.0000

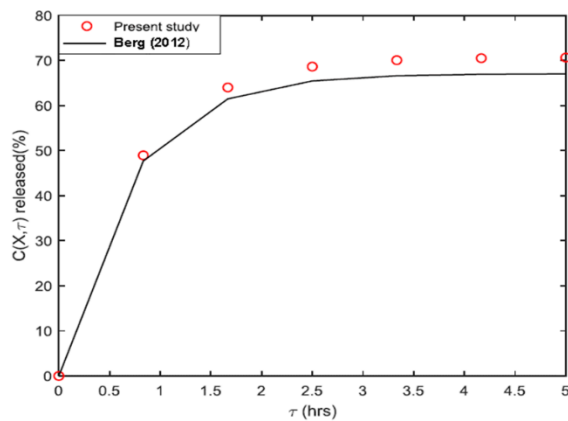


Figure 3: Validation of the present study with the experimental work of Berg (2012)

3.1 The Effects of Short and Long Transport Durations on Drug Release Concentration Profiles

The effects of short and long transport durations on drug release concentration profiles for the case of perfect contact interface are shown in Figures 4 and 5. This is equivalent to the transport phenomenon in a single layer material. For the baseline case, the dimensionless concentration profiles at four durations are considered. As a result of the perfect contact initiated at the interface ($C_1 = C_2$), the results of concentration show that the concentration are not sensitive to the interface location for both short and long durations of the transport processes. The percentage mass transfer in the individual layers do vary with thickness ratio, d , but the release curves do not.

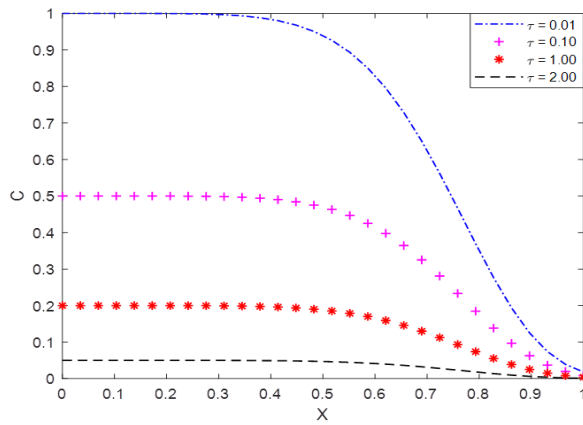


Figure 4: Effect of perfect contact during drug release on concentration profiles for short durations

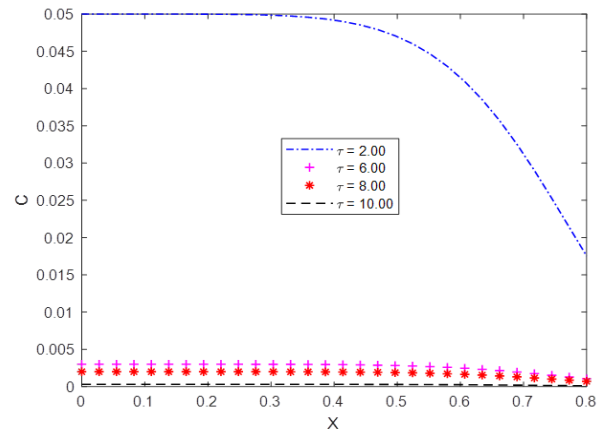


Figure 5: Effect of perfect contact during drug release on concentration profiles for long durations

3.2 Effects of Drug Release Due to System Parameters Variation

The effects of drug release due to system parameters variation is further established by assuming that layers 1 and 2 have similar microstructure parameters ($\chi = \phi = 1 = C^0$). Consequent upon the infinite sinks' boundary conditions at the release medium, drugs are swiftly released from the second layer in the early stages, whereas there is delay before drugs concentrations in the first layer drop from initial values. The release of drugs from the first layer continues at a slower rate than in the second layer. Consequently, there are alterations in both the durations and shapes of release in the layers. From the plots, it is obvious that at $\tau = 3$ and $\tau = 4$, all of the drugs have been released from the system. Continuous increase in the drug release duration beyond these limits produces negligible influences on the concentration profiles.

The dimensionless concentration profiles for imperfect contacts at the interface of the two layers are illustrated in Figures 6 - 8. These helps explore the effects of varying relative microstructural parameters between the two layers for different time at imperfect contact points $d = 2, d = 5, d = 8$. From the plots, it is evident that continuous increase in interface layer thickness ratio introduce corresponding decrease in the concentration profiles for all the different dimensionless durations considered. The inference of this phenomenon is that the variation of the microstructure of the two layers causes alteration in the drug release shape profile and that drug delivery is ensured in specific time period.

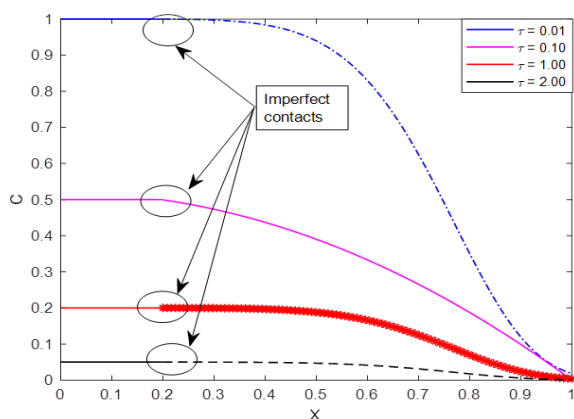


Figure 6: Effect of varying relative microstructural parameters between the two layers for different time at $d = 0.2$

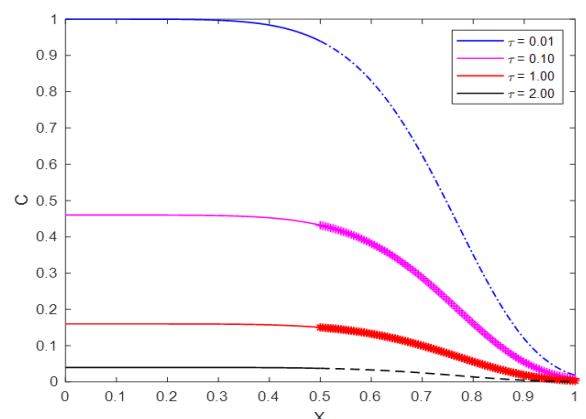


Figure 7: Effect of varying relative microstructural parameters between the two layers for different time at $d = 0.5$

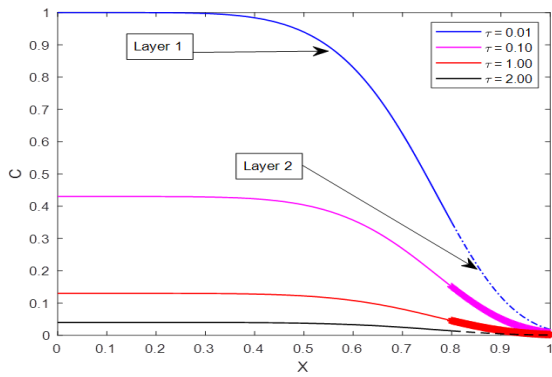


Figure 8: Effect of varying relative microstructural parameters between the two layers for different time at $d = 0.8$.

3.3 Effects of Drug Release Parameter on Concentration Profile for Single and Double Layers

The effects of drug release parameter on concentration profile for single and double layers with perfect and imperfect contacts at interface are shown in Figures 9 and 10. From the plots, it can be deduced that two layers with perfect contact interface condition can be approximated as a single layer. This is so because the concentration profiles for the aforementioned cases are similar. However, this is not the case when considering imperfect contact interface conditions. Generally, an augmentation in the release parameter results in a decrease in the concentration profile for the three cases of thickness ratios considered.

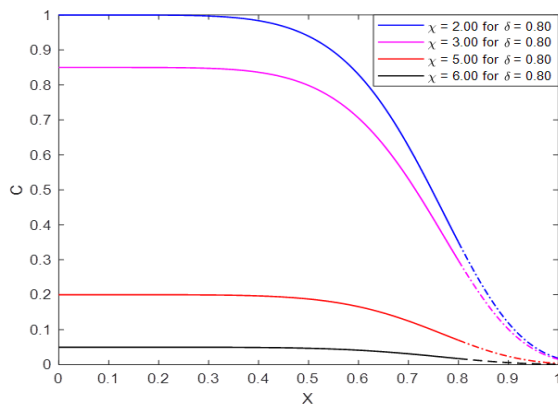


Figure 9: Effect of release parameter on concentration profile for the case of perfect contact at interface

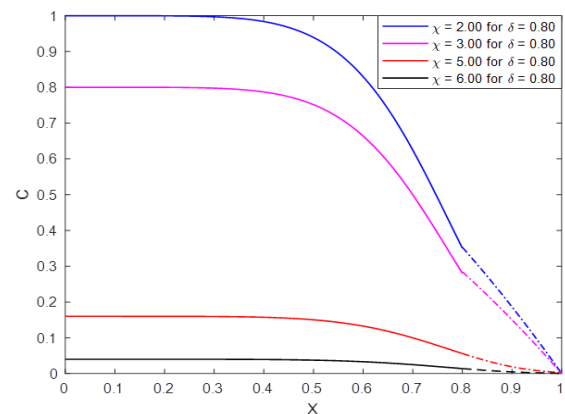


Figure 10: Effect of release parameter on concentration profile for the case of imperfect contact at interface

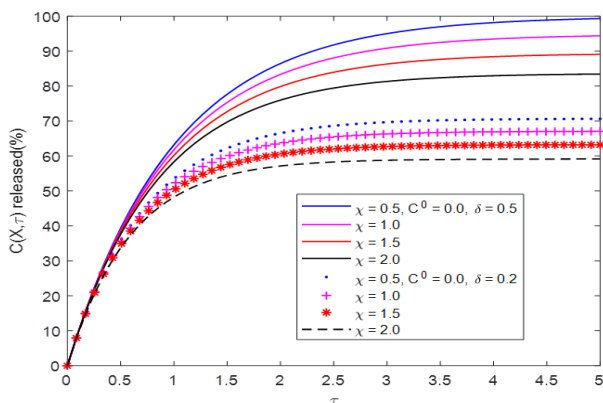


Figure 11: Super-imposed plot showing the effect of diffusion coefficient on conc. history for cases 1 and 2

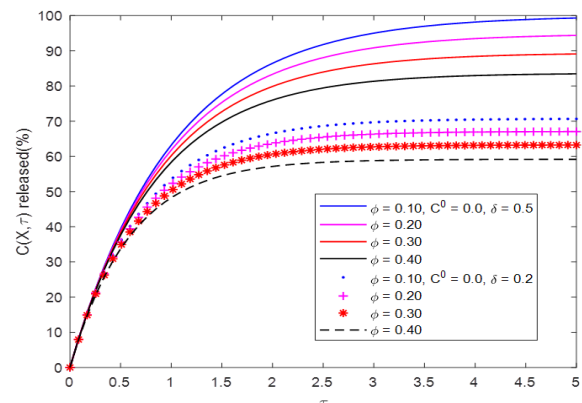


Figure 12: Super-imposed plot showing the effect of porosity term on concentration history for cases 1 and 2

3.5 Effects of Diffusion Coefficient, Porosity and Thickness Ratios on Concentration History

The effects of diffusion coefficient and porosity on concentration history for specified initial loading parameter are presented in Figures 11 and 12 respectively. From the plots, it is apparent that the porosity and diffusion coefficient terms have synonymous impacts on concentration history. An increase in the two parameters may be used to reduce the concentration history. However, this reduction in concentration history may be further strengthened by reducing the magnitude of the thickness ratio. These parameters can be used interchangeably to achieve the desired concentration profiles and concentration history.

4. Conclusion

In this study, the modeling and simulations of the predictive mathematical model for controlled drug release orthopedic implants using differential transform method has been presented. The obtained solution was validated with Runge-Kutta order four numerical method and results from past experimental study. The solution was applied to investigate the effects of thickness ratio, diffusion period, porosity term, initial loading and effective diffusion coefficient ratio parameters. It was observed that continuous increase in interface layer thickness ratio resulted in corresponding decrease in the concentration profiles and augmentation in the release parameter resulted in a decrease in the concentration profile for thickness ratios. Hence, the developed model and the obtained solutions provide the benchmark for the optimized and enhanced control of drug-releasing orthopedic implants (OI). The parametric studies also show that effective diffusion coefficients ratio (χ) may be the dominant parameter in the model and so provides considerable flexibility and tuneability from a design/manufacturing point of view. The analytical solution in this work also provides better understanding of the relationship between the physical properties of the problem investigated.

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