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Analytical Solutions for Simulation of Mathematical Modelling of Liposomal Drug Release to Tumor by Adomian Decomposition Method.

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Abstract: In this paper, the system of partial differential equations of the thermo sensitive liposome-mediated drug delivery model is solved analytically by applied the Adomian decomposition method with the appropriate initial and boundary condition as well. Also, to determine the effectiveness of suggested models, simulated results were in comparison to the corresponding experimental information , and an important agreement was reached . So that a quantitative analysis is finally done by numerical simulation by adopting the values of all typical parameters to clarify the drug concentrations behavior with increasing time in different cases.
Keywords: Local drug ; Drug delivery ; cancer stem cells ; Adomian decomposition method ; Different locations.

1.Introduction

The system of drug delivery has an important role in controlling the effect of medications because of its effect on drug composition, average release, target organs, working time and ultimately drug toxicity and side effects. It is the composition of the drug in the form of doses or the delivery system of the drug that actually converts research that includes the discovery of medicines and various pharmacological aspects in to a clinical practice [1].TSL or Temperature sensitive liposomes is one of the important systems of drug delivery in order to transfer chemotherapy to the place of the solid tumor. When exposed to temperatures above or at the lipid solid-to-liquid phase transition temperature (often above 40 ° C), it is believed that the pores form inside the sebaceous membrane, leading to the release of the coated medicine [2,3].Thus, the administration of TSL during the moderate increase in temperature applied to the tumor leads to the delivery of treatment through the tumor. It has been exhibited that this treatment strategy significantly reduces tumor size compared with non-thermally sensitive liposomes or conventional chemotherapy [3-5]. While various drugs have been encapsulated in TSL, doxorubicin (Dox) is the most widely investigated agent [6,7] . Dox is a clinical cancer therapy used for a variety of solid tumors [8,9].

The concept of tissue stem cells has extended to the concept of primary cancer cells (cancer stem cells) over the past years. Depending to the current hypothesis, there are a small number of "stem-like" cancer cells that work to reveal the largest portion of malignant cancer cells [10, 11]. Because of the difficult access to cancer stem cells by some classic treatment strategies, it can play a role in relapse of malignant tumors [12, 13]. Cancer stem cells are actually characterized in the context of several various cancers [12, 14]. The mathematical modeling used to delivery of drug and predictability consistently by launching a growing field regarding its importance in the industrial and academic fields is because of its future astronomical potential. Similar to any other scientific discipline, simulations of computer are probably to be

part of future studies in the specialty of pharmacy. By allocating the doses of treatments included in the required medication administration and the target profile for the transfer of treatments, the mathematical prognosis allows to excellent evaluates of the composition needed along with other needs for the dosage forms used. One very difficult aspect is the combination of mathematical models and theories that measure the transfer and release of drugs into tissues and living cells. Different works have been achieved previously on treatment transfer devices regarding optimal design with the help of either numerical simulations / modeling processes or experimental approaches, therapeutic efficacy, and often all procedures are employed [15–17]. Mathematical modeling has shown various visions that are useful in understanding the mechanism of the effect of these physical properties on the transport of therapeutic medicine, and this contributes to the development, presentation and expectation of the treatment strategy in the end [18–20]. Moreover, mechanistically, studied how mathematical modeling of the mass transport of the drug can describe therapeutic responses to chemo-therapy [21,22] and enable the understanding of the process of drug delivery in the human [23]. Nevertheless, for dating, these efforts were limited using the inability to account for temporal and spatial heterogeneity in characteristics of tumor and the drug dosing. The chemo-therapy drug needs for traversing the interstitial, vasculature space (for example, micro-environment and stroma), and cell membranes of cancer for finally reaching intracellular goals. Likely, the capability for characterizing these physical characteristics of tumor must enable clinicians and scientists to not just predict responses, but moreover rationally design therapeutics for the individual cancer patient .Toward the present target, developed the theory of chemo-therapy responses based on the quantitative physical transport characteristics of cells of cancer [24, 25] as well as the solid tumor [26, 27, 28].Work to this end has also resulted in increased understanding of how vasculature structure and the resulting interstitial fluids behavior were included in nanocarriers distribution in the vessels of blood, in vivo [29]. The present generalized model allows us for considering the variety of strategies of treatment, involving the systemic drug delivery by nanocarriers, and helps for predicting the response of tumor for various forms of the drugs delivery by nanocarriers, and helps for predicting the response of tumor for various forms of the drugs delivery approaches before starting the treatment. The present mathematical model proposed focuses on the complex endosomal events as well as the release mechanism of drugs in systemic plasma, tumor plasma , tumor interstitial fluids and stages of intracellular tumor [17].This leads to system of the partial differential equations along with appropriate set of the boundary and initial conditions [17]. In this paper , the Adomian decomposition method (ADM) is applied to find the solution of the model of the liposome drug concentration release to tumor over time in different locations. Hear ,This method was used for the first time to handle the current problem by investigates the solution of partial differential equations which was calculated in the form of the components of an infinite series. The comparison between present results with the experimental data indicate that the efficiency and the reliability of proposed method.

2. Mathematical formulation

Modelling drugs release dynamics in Systemic plasma compartment .

TSL-DOX pass through the wall of blood vessels because of its small size after accumulate, and administration in the extracellular spaces in tumors. Moreover, the liposome is expected to stay stable at temperature of body. When heated locally, encapsulated drugs released from the temperature- susceptible liposome grease quickly when the temperature comes to the point of transition [16, 17] .

There is 2 compartments, tumor compartment and systemic plasma compartment. According to the Starling law, the trans vascular from blood to interstitial flux per tumour volume is defined as

$$F_v = K_v \frac{S}{V} [P_v - P_i - \sigma_T (\pi_v - \pi_i)] \ , \quad (1)$$

where, K_v shows the hydraulic conductivity of the blood vessels wall, *S/V* is surface area of blood vessels per tumour tissue unit volume, P_i and P_v are the respective pressures of interstitial fluid and blood vessels, σ_T is the average of coefficient of osmotic reflection (the measurement of the relative permeability of the specific membranes to the specific solute) for proteins of plasma and finally, π_v and π_i show the respective osmotic pressure of interstitial and plasma fluids.

Equation of liposome-encapsulated drug concentration [C_L^S] can be written as follows [17];

$$\frac{\partial C_L^S}{\partial t} = D_L^S \frac{\partial^2 C_L^S}{\partial x^2} - \gamma_1 \frac{\partial C_L^S}{\partial x} - K_1 C_L^S, \quad (2)$$

where, D_L^S shows the coefficient of diffusion of the liposome-encapsulated drugs in the systemic plasma, γ_1 was advection magnitude and K_1 shows the rate constant of the drug release from the liposome at the systemic plasma.

Equation of free drug concentration[C_F^S]

$$\frac{\partial C_F^S}{\partial t} = D_F^S \frac{\partial^2 C_F^S}{\partial x^2} - \gamma_2 \frac{\partial C_F^S}{\partial x} - K_1 C_F^S, \quad (3)$$

where, D_F^S shows the coefficient of diffusion of the free drugs in the systemic plasma γ_2 is the advection magnitude , and K_1 shows the rate constant of the drug release from the liposome at the systemic plasma.

Firstly at period t = 0, just injected doses of the liposomes-encapsulated drugs are found.

Thus, initial conditions are following: $C_L^S(x,0)=M$, $C_F^S(x,0)=0$.

At $x = 0$, for example at the left boundary of plasma of the system, both the free drugs and liposome-encapsulated drugs are eliminated throughout clearance of body. Mathematically, these can be characterized as the following.

$$-D_L^S \frac{\partial C_L^S}{\partial x} = K_{cl}^L C_L^S \quad \text{and} \quad -D_F^S \frac{\partial C_F^S}{\partial x} = K_{cl}^F C_F^S,$$

where, K_{cl}^L and K_{cl}^F are rate constants of the clearance of free and liposomal drugs, respectively, in plasma of the system. At $x = n_l$, for example at the interfaces where the free drug and liposomal drugs introduce in the compartment of tumour from plasma of the system, the following common conditions were occurred in calculation. flux continuity should be assigned at interfaces. Thus,

$$\gamma_1 C_L^S - D_L^S \frac{\partial C_L^S}{\partial x} = \gamma_3 C_L^{TP} - D_L^{TP} \frac{\partial C_L^{TP}}{\partial x}$$

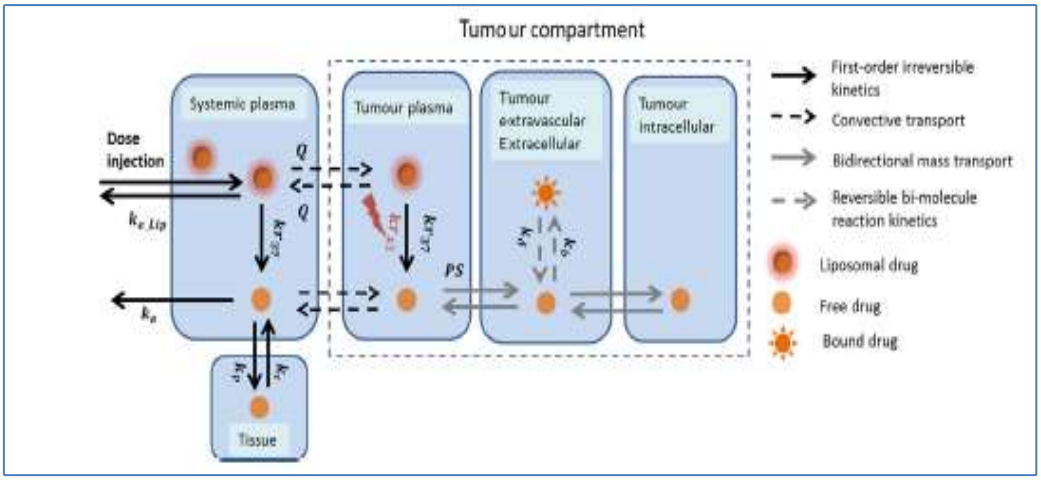


Figure 1: The schematic diagram of the drugs transport to tumour and the releasing liposomal drugs

Modelling drugs transport dynamics in Tumor compartment.

As time elapses, the liposomal in addition to the free drugs enter in to the compartment of tumor from the compartment of systemic plasma. The compartment of tumor is subcategorized in to tumor plasma, tumor interstitial fluids and tumor intracellular. The drug exchange between tumor plasma and tumor interstitial fluids goes on simultaneously, nevertheless in the current work, a particular pathway of transport of drugs is taken in to consideration. The liposome having drugs encapsulation moves from the systemic plasma in to the plasma of tumor as C_L^{TP} . Likewise, free drugs in the systemic plasma enter in to the plasma of tumor as C_F^{TP} .The drugs released from the liposome in interstitial fluids are depicted as free drugs C_F^{TIF}. These free drugs get disseminated through interstitial fluids, bind with the protein found there. Also, free drugs interact with the receptors of surface of the tumor cells and enter in to the tumor intracellular space. No another form of drugs, whether they are bound drugs or liposomal drugs, can enter in to the cells of tumor.

We can represent the tumour compartment by following ;

Partial differential equations of the concentration of liposome encapsulated drugs in plasma of tumour $[C_L^{TP}]$

$$\frac{\partial C_L^{TP}}{\partial t} = D_L^{TP}\frac{\partial^2 C_L^{TP}}{\partial x^2} - \gamma_3\frac{\partial C_L^{TP}}{\partial x} - F_{lp} - K_{rel}C_L^{TP}, \quad (4)$$

where, D_L^{TP} and γ_3 denote the coefficient of diffusion and advection magnitude of the liposomal drug in plasma of tumors, respectively, K_{rel} stands for the rate of release of liposomes, and F_{lp} is the liposomes encapsulated drugs loss because of movement of the liposomes encapsulated drugs in the interstitial fluid throughout the capillary wall and defined as

$$F_{lp} = F_v(1-\sigma_l)C_L^{TP} + P_l\frac{S}{V}(C_L^{TP} - C_L^{TIF})\frac{P_{el}}{e^{P_{el}}-1}, \quad (5)$$

where, σ_l is the coefficient of the osmotic reflection for the particle of the liposomal drug, and P_l the permeability of the vasculature wall to the liposome and $P_{el} = \frac{F_v(1-\sigma_l)}{P_l\frac{S}{V}}$ represents the trans capillary P'eclet number.

Partial differential equations of the concentration of liposomes encapsulated drugs in the interstitial fluid $[C_L^{TIF}]$

$$\frac{\partial C_L^{TIF}}{\partial t} = D_L^{TIF}\frac{\partial^2 C_L^{TIF}}{\partial x^2} - \gamma_4\frac{\partial C_L^{TIF}}{\partial x} + F_{lp} - K_{rel}C_L^{TIF}, \quad (6)$$

where, D_L^{TIF} and γ_4 show the coefficient of diffusion and the advection magnitude of the liposomal drugs in interstitial fluid of the tumour, respectively.

Partial differential equations of free drug concentration in interstitial fluids $[C_F^{TIF}]$

$$\frac{\partial C_F^{TIF}}{\partial t} = D_F^{TIF}\frac{\partial^2 C_F^{TIF}}{\partial x^2} - \gamma_5\frac{\partial C_F^{TIF}}{\partial x} + F_{fp} + K_{rel}C_L^{TIF} + K_d C_B^{TIF} - K_a C_F^{TIF} C_P^{TIF} - K_f C_F^{TIF} R_S^{TC} + K_r C_{BS}^{TIF} \quad (7)$$

where, D_F^{TIF} and γ_5 are the coefficient of diffusion and advection magnitudes of the free drugs in the interstitial fluids, respectively, $F_{fp}$is the free drugs passing capillary walls in interstitial fluids which may be defined as same as (5) with $\sigma_l = \sigma_d, l = d, L = F$, such that σ_d is the coefficient of osmotic reflection for the particle of drug, C_F^{TIF} was concentration of the free drugs in plasma of the tumour shows the vasculature wall permeability to the particle of free drug, K_a , K_f, K_d, and K_d were the association , and dissociation average constants, respectively.

Partial differential equations of concentration of Protein in interstitial fluids $[C_P^{TIF}]$

$$\frac{\partial C_P^{TIF}}{\partial t} = K_d C_B^{TIF} - K_a C_F^{TIF} C_P^{TIF}, \quad (8)$$

Partial differential equations of the concentration of bound drugs in interstitial fluids $[C_B^{TIF}]$

$$\frac{\partial C_B^{TIF}}{\partial t} = D_B^{TIF}\frac{\partial^2 C_L^{TIF}}{\partial x^2} - \gamma_6\frac{\partial C_B^{TIF}}{\partial x} - K_d C_B^{TIF} + K_a C_F^{TIF} C_P^{TIF} + F_{bp}, \quad (9)$$

where, D_B^{TIF} and γ_6 are the coefficient of diffusion and advection magnitude of bound drug in interstitial fluids, respectively, F_{bp}depicts the amount of the bound drugs gained from trans capillary exchange in interstitial fluids, defined as same as (5) with $\sigma_l = \sigma_b, l = b, L = B$, such that σ_b is the coefficient of osmotic reflection for particles of the drug, P_b shows the vasculature wall permeability to particles of the bound drug and $P_{eb} = \frac{F_v(1-\sigma_d)}{P_{be}(\frac{S}{V})}$ represents the trans -capillary P´eclet number.

Partial differential equations of concentration of free drug into plasma of tumour $[C_F^{TP}]$

$$\frac{\partial C_F^{TP}}{\partial t} = K_{rel}C_L^{TP} - V^{TP}F_{fp} + K_{e1}C_F^{TP} - K_a C_F^{TP} C_P^{TP} + K_d C_B^{TP}, \quad (10)$$

where, V^{TP} was a volume fraction of the plasma of the tumour, K_d ,and K_a were dissociation and association averages with the protein, respectively.

Partial differential equations of Protein concentration in tumour plasma $[C_P^{TP}]$

$$\frac{\partial C_P^{TP}}{\partial t} = -K_a C_F^{TP} C_P^{TP} + K_d C_B^{TP}, \quad (11)$$

Partial differential equations of concentration of bound drug in plasma of tumour $[C_B^{TP}]$

$$\frac{\partial C_B^{TP}}{\partial t} = -V^{TP}F_{bp} + K_a C_F^{TP} C_P^{TP} - K_d C_B^{TP}, \quad (12)$$

Partial differential equations of cell surface receptor concentration $[R_S^{TC}]$

$$\frac{\partial R_S^{TC}}{\partial t} = -K_f R_S^{TC} C_F^{TIF} + K_r C_{BS}^{TC} - K_t R_S^{TC} + K_x R_I^{TC} + K_{syn}R_S^{TC}, \quad (13)$$

where, K_t is the rate constant of constitutive internalization, K_x shows the rate constant of the receptor recycling, and K_{syn} shows the surface receptors synthesis rate.

Partial differential equations of cell surface bound drug concentration $[C_{BS}^{TC}]$

$$\frac{\partial C_{BS}^{TC}}{\partial t} = K_f R_S^{TC} C_F^{TIF} - K_r C_{BS}^{TC} - K_e R_S^{TC} + K_x R_I^{TC}, \quad (14)$$

where, K_e represents the internalization rate constant

Partial differential equations of internalized bound drug concentration $[C_{BI}^{TC}]$

$$\frac{\partial C_{BI}^{TC}}{\partial t} = K_e C_{BS}^{TC} + K'_f R_I^{TC} C_{FI}^{TIF} + K'_r C_{BI}^{TC} - (K_{hr} + K_x) C_{BI}^{TC}, \quad (15)$$

where, K_{hr} shows the rate constant of the lysosomal degradation

Partial differential equations of the internalized free drug concentration $[C_{FI}^{TC}]$

$$\frac{\partial C_{FI}^{TC}}{\partial t} = K'_f R_I^{TC} C_{FI}^{TIF} - R_I^{TC} C_{FI}^{TIF} + K'_r C_{BI}^{TC} - K_{hl} C_{FI}^{TC}, , \quad (16)$$

where, K_{hl} the rate constant of the liposomal degradation of the internalized free drug.

Firstly, at the time t = zero, just the injected dosage of liposome-encapsulated drug is obtainable. Also, since interstitial fluid and plasma in the compartment of tumour include the protein, so originally, they have concentration of non-zero. Also, concentrations of the receptor in the tumor intracellular compartment have non-null concentrations originally. However, all other drug embodiments taken in consideration originally have null concentration. Thus, primary conditions come as following:

$C_L^{TP}(x,0)=C_L^{TIF}(x,0)=C_F^{TIF}(x,0)=0, C_P^{TIF}(x,0)=P_0^{TIF}, C_B^{TIF}(x,0)=C_F^{TP}(x,0)=0,$

$C_P^{TP}(x,0)=P_0^{TP}, C_B^{TP}(x,0)=0, R_S^{TP}(x,0)=R_{S0}^{TP}, C_{BS}^{TC}(x,0)=0, C_{BI}^{TC}(x,0)=C_{FI}^{TC}(x,0)=0, R_I^{TC}(x,0)=R_{I0}^{TC}$

However, at interfaces, jump of concentration maybe take place because of the different drug partitioning between tumour compartment and systemic plasma. Like complexities are addressed throughout

$$-D_F^S \frac{\partial C_F^S}{\partial x} = P_1(C_L^{TP} - C_L^S) \quad at\ x= n_1 \qquad -D_L^{TP} \frac{\partial C_L^{TP}}{\partial x} = P_2(C_L^S - C_L^{TP}) \quad at\ x=n_1$$

$$-D_L^{TIF} \frac{\partial C_L^{TIF}}{\partial x} = P_3(C_L^S - C_L^{TIF}) \quad at\ x=n_1 \qquad -D_F^{TIF} \frac{\partial C_F^{TIF}}{\partial x} = P_4(C_F^S - C_F^{TIF}) \quad at\ x=n_1$$

However, since the bound drugs aren't suitable for emerging out of compartments of tumour, so a no flux condition maybe included

$$\gamma_6 C_B^{TIF} - D_B^{TIF} \frac{\partial C_B^{TIF}}{\partial x} = 0 , \quad at\ x=n_1$$

At $x = n_2$, for example, the extreme right boundary of compartment of tumors, certain no flux conditions were studied as liposomes-encapsulated drugs, and the bound drug can emerge out of tumors. Therefore, the following boundary conditions are occurred in the account.

$$\gamma_3 C_L^{TP} - D_L^{TP} \frac{\partial C_L^{TP}}{\partial x} = 0, \quad at\ x = n_2 \quad , \quad \gamma_4 C_L^{TIF} - D_L^{TIF} \frac{\partial C_L^{TIF}}{\partial x} = 0, \quad at\ x = n_2 ,$$

$$\gamma_6 C_B^{TIF} - D_B^{TIF} \frac{\partial C_B^{TIF}}{\partial x} = 0, \quad at\ x = n_2 \quad ,$$

Moreover, due to interaction between C_F^{TIF} and , R_S^{TC} there is feeblepossibility of the existence of C_F^{TIF} at the extreme right boundary, $x = n_2$. Thus, $C_F^{TIF} = 0$ at $x = n_2$.

3.Dimensionless Equations

All the parameters and variables in the mathematical model can be defined in dimensionless forms as [17];

$\overline{C_j^i} = \frac{C_j^i}{M}$,$i = S, T P, TI F, TC, j = L, F,B, P,B S,B I, FI,$ $\overline{R_K^{TC}} = \frac{R_K^{TC}}{M}$, $k = S, I,$ $\bar{x} = \frac{x}{n_2}$, $\bar{t} = \frac{D_L^S t}{{n_2}^2}$

, $\overline{n_l} = \frac{n_l}{n_2}$, $l = 1, 2,$ $\overline{D_m^n} = \frac{D_m^n}{D_L^S}$, $m = L, F,B,$ $n = S, T P, T IF,$ $\overline{F_v} = \frac{F_v n_2^2}{D_L^S}$, $\overline{P_0 \frac{S}{V}} = \frac{P_0 \frac{S}{V} n_2^2}{D_L^S}$, $o = l, fe,$

$be,$

$\overline{K_{rel}} = \frac{K_{rel} n_2^2}{D_L^S}$, $\overline{K_{cl}^L} = \frac{K_{cl}^L n_2}{D_L^S}$, $\overline{K_{cl}^F} = \frac{K_{cl}^F n_2}{D_L^S}$, $\overline{P_{ep}} = \frac{\gamma_p n_2}{D_L^S}$,$p = 1, 2, 3, 4, 5, 6,$ $\overline{Q_q} = \frac{P_q n_2}{D_L^S}$, $q=1, 2, 3, 4,$$\overline{P_0^a}$

$= \frac{P_0^a}{M}$, $a= TP, TIF,$ $\overline{R_b^{TC}} = \frac{R_b^{TC}}{M}$,$b= S_0, I_0,$$D_{a0} = \frac{K_a n_2^2 \ P_0^{TIF}}{D_L^S}$, $D_{a1} = \frac{K_a n_2^2 \ P_0^{TP}}{D_L^S}$,$D_{a2} = \frac{K_f n_2^2 \ R_{S0}^{TC}}{D_L^S}$

,$D_{a3} = \frac{K'_f n_2^2 \ R_{I0}^{TC}}{D_L^S}$,

$\alpha = \frac{K_d}{K_a}$,$\beta = \frac{K_r}{K_f}$, $\delta = \frac{K_r'}{K_f'}$, $B_{p0} = \frac{P_0^{TIF}}{\alpha}$, $B_{p1} = \frac{P_0^{TP}}{\alpha}$, $B_{p2} = \frac{R_{S0}^{TC}}{\beta}$,$B_{p3} = \frac{R_{I0}^{TC}}{\delta}$, $\overline{K_c} = \frac{K_c n_2^2}{D_L^S}$,c=1, e_1, *t*, *x*, *syn*, *e*, *hr*, *hl*.

Also, the mentioned equation in its form of dimensionless is following:

$$\frac{\partial C_L^S}{\partial t} = D_L^S \frac{\partial^2 C_L^S}{\partial x^2} - P_{e1} \frac{\partial C_L^S}{\partial x} - K_1 C_L^S, \quad (17)$$

$$\frac{\partial C_F^S}{\partial t} = D_F^S \frac{\partial^2 C_F^S}{\partial x^2} - P_{e2} \frac{\partial C_F^S}{\partial x} - K_1 C_L^S, \quad (18)$$

$$\frac{\partial C_L^{TP}}{\partial t} = D_L^{TP} \frac{\partial^2 C_L^{TP}}{\partial x^2} - P_{e3} \frac{\partial C_L^{TP}}{\partial x} - F_{lp} - K_{rel} C_L^{TP}, \quad (19)$$

$$\frac{\partial C_L^{TIF}}{\partial t} = D_L^{TIF} \frac{\partial^2 C_L^{TIF}}{\partial x^2} - P_{e4} \frac{\partial C_L^{TIF}}{\partial x} + F_{lp} - K_{rel} C_L^{TIF}, \quad (20)$$

$$\frac{\partial C_F^{TIF}}{\partial t} = D_F^{TIF} \frac{\partial^2 C_F^{TIF}}{\partial x^2} - P_{e5} \frac{\partial C_F^{TIF}}{\partial x} + F_{fp} + K_{rel} C_L^{TIF} + \frac{D_{a0}}{B_{p0}} C_B^{TIF} - \frac{D_{a0}}{P_0^{TIF}} C_F^{TIF} C_P^{TIF} - \frac{D_{a2}}{R_{S0}^{TIF}} C_F^{TIF} R_S^{TC} + \frac{D_{a2}}{B_{p2}} C_{BS}^{TC} \quad (21)$$

$$\frac{\partial C_P^{TIF}}{\partial t} = \frac{D_{a0}}{B_{p0}} C_B^{TIF} - \frac{D_{a0}}{P_0^{TIF}} C_F^{TIF} C_P^{TIF}, \quad (22)$$

$$\frac{\partial C_B^{TIF}}{\partial t} = D_B^{TIF} \frac{\partial^2 C_B^{TIF}}{\partial x^2} - P_{e6} \frac{\partial C_B^{TIF}}{\partial x} - \frac{D_{a0}}{B_{p0}} C_B^{TIF} + \frac{D_{a0}}{P_0^{TIF}} C_F^{TIF} C_P^{TIF} + F_{be}, \quad (23)$$

$$\frac{\partial C_F^{TP}}{\partial t} = K_{rel} C_L^{TP} - V^{TP} F_{fp} - K_{e1} C_F^{TP} - \frac{D_{a1}}{P_0^{TP}} C_F^{TP} C_P^{TP} + \frac{D_{a1}}{B_{p1}} C_B^{TP}, \quad (24)$$

$$\frac{\partial C_P^{TP}}{\partial t} = - \frac{D_{a1}}{P_0^{TP}} C_F^{TP} C_P^{TP} + \frac{D_{a1}}{B_{p1}} C_B^{TP}, \quad (25)$$

$$\frac{\partial C_B^{TP}}{\partial t} = - V^{TP} F_{be} + \frac{D_{a1}}{P_0^{TP}} C_F^{TP} C_P^{TP} - \frac{D_{a1}}{B_{p1}} C_B^{TP}, \quad (26)$$

$$\frac{\partial R_S^{TC}}{\partial t} = - \frac{D_{a2}}{R_{S0}^{TIF}} C_F^{TIF} R_S^{TC} + \frac{D_{a2}}{B_{p2}} C_{BS}^{TC} - K_t R_S^{TC} + K_x R_I^{TC} + K_{syn} R_S^{TC}, \quad (27)$$

$$\frac{\partial C_{BS}^{TC}}{\partial t} = \frac{D_{a2}}{R_{S0}^{TIF}} C_F^{TIF} R_S^{TC} - \frac{D_{a2}}{B_{p2}} C_{BS}^{TC} - K_e C_{BS}^{TC} + K_x C_{BI}^{TC}, \quad (28)$$

$$\frac{\partial C_{BI}^{TC}}{\partial t} = K_e C_{BS}^{TC} + \frac{D_{a3}}{R_{I0}^{TC}} R_I^{TC} C_{FI}^{TIF} - \frac{D_{a3}}{B_{p3}} C_{BI}^{TC} - (K_{hr} + K_x) C_{BI}^{TC}, \quad (29)$$

$$\frac{\partial C_{FI}^{TC}}{\partial t} = - \frac{D_{a3}}{R_{I0}^{TC}} R_I^{TC} C_{FI}^{TIF} + \frac{D_{a3}}{B_{p3}} C_{BI}^{TC} - K_{hl} C_{FI}^{TC}, \quad (30)$$

$$\frac{\partial R_I^{TC}}{\partial t} = - \frac{D_{a3}}{R_{I0}^{TC}} R_I^{TC} C_{FI}^{TIF} + \frac{D_{a3}}{B_{p3}} C_{BI}^{TC} + K_t R_S^{TC} - (K_{hr} + K_x) R_I^{TC}, \quad (31)$$

The interface, initial, and boundary conditions in the dimensionless method as below:

$C_L^S(x,0)=l, C_F^S(x,0)=C_L^{TP}(x,0)=C_L^{TIF}(x,0)=C_F^{TIF}(x,0)=0, C_P^{TIF}(x,0)=P_0^{TIF}, C_B^{TIF}(x,0)=C_F^{TP}(x,0)=0,$
$C_P^{TP}(x,0)=P_0^{TP}, C_B^{TP}(x,0)=0, R_S^{TP}(x,0)=R_{S0}^{TP}, C_{BS}^{TC}(x,0)=C_{BI}^{TC}(x,0)=C_{FI}^{TC}(x,0)=0, R_I^{TC}(x,0)=R_{I0}^{TC},$

$-\frac{\partial C_L^S}{\partial x} = K_{cl}^L C_L^S$, and boundary conditions $-D_F^S \frac{\partial C_F^S}{\partial x} = K_{cl}^F C_F^S$ at $x=0$

$Pe_1 C_L^S - D_L^S \frac{\partial C_L^S}{\partial x} = Pe_3 C_L^{TP} - D_L^{TP} \frac{\partial C_L^{TP}}{\partial x}$ at $x=n_1$ $-D_F^S \frac{\partial C_F^S}{\partial x} = Q_1(C_F^{TP} - C_F^S)$ at $x=n_1$

$-D_L^{TP} \frac{\partial C_L^{TP}}{\partial x} = Q_2(C_L^S - C_L^{TP})$ at $x=n_1$ $-D_L^{TIF} \frac{\partial C_L^{TIF}}{\partial x} = Q_3(C_L^S - C_L^{TIF})$ at $x=n_1$

$-D_F^{TIF} \frac{\partial C_F^{TIF}}{\partial x} = Q_4(C_F^S - C_F^{TIF})$ at $x=n_1$ $P_{e6} C_B^{TIF} - D_B^{TIF} \frac{\partial C_B^{TIF}}{\partial x} = 0$ at $x=n_2$

$P_{e3} C_L^{TP} - D_L^{TP} \frac{\partial C_L^{TP}}{\partial x} = 0$ at $x=n_2$ $P_{e4} C_L^{TIF} - D_L^{TIF} \frac{\partial C_L^{TIF}}{\partial x} = 0$ at $x=n_2$

$P_{e6} C_B^{TIF} - D_B^{TIF} \frac{\partial C_B^{TIF}}{\partial x} = 0$ at $x=n_2$ $C_B^{TIF} = 0$ at $x=n_2$

4. Method of solution

Also, the above governing equations are completed by helping Adomian decomposition method (ADM) . The method is named after the scientist who discovered it, namely G. Adomian [21]. ADM is widely applied because it is a kind of analytical approximation method that is integrated between the analytical exact method and analytical approximate methods called the semi-analytical method. It is active and powerful in solving nonlinear ordinary and partial differential equations based on the calculation Adomian polynomials for non-linear terms [28-30]. Let us consider the following equation:

$$Lu + Nu + Ru = g\,(x) \tag{32}$$

The linear terms decomposed in $L + R$, whereas the non-linear terms are observed using N , where L and R are facilely invertible linear operators and g is a given function; from (32) we have

$$(\text{or R})u = g\,(x) - Nu - R(\text{or L})u. \tag{33}$$

To begin the ADM analysis [18, 21], a linear differential operators with respect to t and x and its inverse are respectively defined as

$$L = \frac{\partial(.)}{\partial t} \qquad L^{-1} = \int_0^t (.)\, dt \tag{34}$$

$$R = \frac{\partial^2(.)}{\partial x^2} \qquad R^{-1} = \int_0^x \int_0^x (.)\, dx dx \tag{35}$$

And the nonlinear term with assume that $N(u) = \Psi\,(u)$ can be decomposed by an infinite series of polynomials

$$(u) = \sum_{i=0}^{\infty} A_n\,(u_0, u_1, \ldots, u_n), \tag{36}$$

where A_n are the Adomian's polynomials [7] defined as

$$A_n = \frac{1}{n!}\frac{d^n}{d\lambda^n}[\Psi(\sum_{i=0}^{\infty} \lambda^i u_i)]_{\lambda=0}, \qquad n=0,1,2,\ldots \tag{37}$$

Now, applying the inverse operators(34) and (35) to both sides of (33) with equation(37) then via the initial or boundary conditions, we find the following two recurrence relations;

$$\begin{array}{ll} (A) & (B) \\ u_0 = u(x,0) + L^{-1}(g) & u_0 = u(0,t) + x\frac{\partial u(0,t)}{\partial x} + L^{-1}(g) \\ u_1 = -L^{-1}(R(u_0) - L^{-1}\,(A_0) & u_1 = -R^{-1}(L(u_0) - R^{-1}\,(A_0) \\ u_2 = -L^{-1}(R(u_1) - L^{-1}\,(A_1) & u_2 = -R^{-1}(L(u_1) - R^{-1}\,(A_1) \\ . & . \\ . & . \\ . & . \\ u_n = -L^{-1}(R(u_{n-1}) - L^{-1}\,(A_{n-1}) & u_n = -R^{-1}(L(u_{n-1}) - R^{-1}\,(A_{n-1}) \end{array} \tag{38}$$

Thus each term of u is solved and the general solution of equation (34) obtained depending to ADM as the following infinite series:

$$u = \sum_{n=0}^{\infty} u_n \tag{39}$$

However, for some problems [31] the current series can't be calculated, so we must use the solution approximation from the truncated series

$$U_M = \sum_{n=0}^{M} u_n \text{ with } \lim_{M\to\infty} U_M = u \tag{40}$$

Now, the series solutions of equations (17-31) by applying recurrence relations of ADM in group (A) or group(B) of equation(38) are;

$$C_L^S(x,t) = \sum_{n=0}^{3} C_{L\,n}^S = (1 - 3681.9\,x^4)e^{-K_1 t}\,. \tag{41}$$

$$C_F^S(x,t) = \sum_{n=0}^{3} C_{F\,n}^S = \sum_{i=0}^{6} a_i x^i\, e^{-K_1 t} - 1 + (xa_1 - a_3 x^3)\,. \tag{42}$$

$$\begin{aligned} C_L^{TP}(x,t) = \sum_{n=0}^{3} C_{Ln}^{TP} &= \sum_{i=0}^{6} 1 - e^{-K_1 t} c_i x^i + (644.44)x + (6.80E\text{-}13)x^2 \\ &+ (5.50E\text{-}7)x^3 + (5E\text{-}22)x^4 + (2.41E\text{-}16)x^5 + (1.50E\text{-}21)x^6\,. \end{aligned} \tag{43}$$

$C_L^{TIF}(x,t)=\sum_{n=0}^{3} C_{Ln}^{TIF}=\sum_{i=0}^{6} 1-\ e^{-K_1 t}c_i x^i - 100x -\ (6.76E-13)x^2$
$-(2.07E-5)x^3 -\ (4.97E-22)x^4 - (2.41E-16)x^5 - (1.50E-31)x^6$. (44)

$C_F^{TIF}(x,t)=\sum_{n=0}^{3} C_{Fn}^{TIF}=\sum_{i=0}^{6} d_i x^i\, e^{-K_1 t} - 1$ -17.05x – (1.14*E-17)*x^2 (45)

$C_P^{TIF}(x,t) =\sum_{n=0}^{3} C_{Pn}^{TIF} =\sum_{i=0}^{6} Q_{1i} * e^{-K_1 t} + Q_{2i}x^i\, t + Q_{3i}x^i$. (46)

$C_B^{TIF}(x,t)=\sum_{n=0}^{3} C_{Bn}^{TIF} =\sum_{i=0}^{6} E_i x^i\, e^{-K_1 t} + 1 + 5800x + (-5.00E6)x^2 + (16.50)x^3 -$
$(7.10E7)x^4 - (9.19E-17)x^5 - (5.43E-11)x^6 - (7.80E-10)x^7 - (1.31E-24)x^8$
(47)

$C_F^{TP}(x,t)=\sum_{n=0}^{3} C_{Fn}^{TP} =\sum_{i=0}^{6}(\ f_i + h_i t + g_i e^{-K_1 t})x^i + \sum_{i=1}^{2} p_i x^i\, t^2$. (48)

$C_B^{TP}(x,t) = \sum_{n=0}^{3} C_{Bn}^{TP} =\sum_{i=0}^{6}(\ r_i + z_i t + o_i t^2 + L_i t^3 + n_i e^{-K_1 t})x^i$. (49)

$C_{BS}^{TC}(x,t)=\sum_{n=0}^{3} C_{BSn}^{TC} = 1 - e^{-K_1 t} + \sum_{i=0}^{6}(A_{1i} + A_{2i}\, e^{-K_1 t} + A_{3i}t + A_{4i}t^2)x^i$. (50)

$C_P^{TP}=1+\sum_{i=0}^{6}(G_{1i}e^{-K_1 t} + G_{2i} + G_{3i}\, t + G_{4i}t^2 + G_{5i}t^3 + G_{6i}t^4)x^i + \sum_{i=0}^{2} G_{7i}\, x^i t^5$. (51)

$C_{RS}^{TC}(x,t) = \sum_{n=0}^{3} C_{RSn}^{TP} =\sum_{i=0}^{6}(H_{1i}\, e^{-K_1 t} + H_{2i} + H_{3i}t + H_{4i}t^2 + H_{5i}t^3 + H_{6i}t^4)x^i$. (52)

$C_{BI}^{TC}(x,t)=\sum_{n=0}^{3} C_{BIn}^{TC} =\sum_{i=0}^{6}(\ B_{1i}\, e^{-K_1 t} + B_{2i} + B_{3i}t^3 + B_{4i}t^2 + B_{5i}t + B_{6i}t^4)x^i$. (53)

$C_{FI}^{TC}(x,t)=\sum_{n=0}^{3} C_{FIn}^{TC} =\sum_{i=0}^{6}(\ N_{1i}\, e^{-K_1 t} + N_{2i}t + N_{3i}t^2 + N_{4i}t^3 + N_{5i}t^4 + N_{6i}t^5 + N_{7i}t^6)x^i$ (54)

$C_{RI}^{TC}(x,t)=\sum_{n=0}^{3} C_{RIn}^{TC} =\sum_{i=0}^{6}(F_{1i}\, e^{-K_1 t} + F_{2i} + F_{3i}t + F_{4i}t^2 + F_{5i}t^3 + F_{6i}t^4 + F_{7i}t^5 + F_{8i}t^5)$
(55)

where the coefficients values of all above equations are listed in appendix.

Table 1. Values of Parameter

The Parameter		The Value	The reference
σ_T	avg. osmotic reflection coefficient for plasma prote	0.820	[34, 35-37]
$\sigma_d(free)$	avg. osmotic reflection coefficient for free drugs	0.150	[37, 38]
π_v	The osmotic pressure of the plasma	2666 Pa	[34, 35-37]
P_l	The vasculature wall permeability to the liposomes	3.42 *l0^{-7} cm/s	[39, 40]
P_{fe}	The vasculature wall permeability to the free drugs	3.0 *l0^{-4}cm/s	[37, 41]
P_v	The pressure of blood vessels	2080 Pa	[34, 35-37]
K_v	The hydraulic conductivity	2.10 * l0^{-9}s^{-l}cm/Pa .s	[34, 35-37]
K_{cl}^F	The clearance average constant of the free drugs	1.1 *l0^{-3}s^{-l}	[42]
K_{hl}	The lysosomal degradation average constant	1.67 * l0^{-4}s^{-l}	[43]
K_e	The internalization average constant	2.75 * l0^{-3}s^{-l}	[44]
K_t	The constitutive internalization rate constant	5 * l0^{-4}s^{-l}	[43]
n_1	The interface position	10^{-3}cm	—
K'_r	The dissociation average constant	2* l0^{-2}s^{-l}	[45, 46]
K_f	The association average constant	107 (mol cm^{-3}S)$^{-l}$	[37]
K'_f	The association average constant	2*106(mol cm^{-3}S)$^{-l}$	[47]
$\gamma_j, j=1-6$	advection magnitude	10^{-4}* 10^{-3}cm/s	[48]
K_1	drug release average constant at systemic plasma	10^{-5}s^{-l}	[49]

Table 2. Values of Parameter

Parameter		The value	the reference
σ_l	avg. osmotic reflection coefficient for the liposomal drugs	0.950	[48]
σ_d *(bound)*	avg. osmotic reflection coefficient for the bound drugs	0.820	[37, 38]
π_i	The osmotic pressure of interstitial fluids	2000 Pa	[34, 35-37]
P_{be}	The vasculature wall permeability to the bound drugs	$7.80 * l0^{-7} s^{-1}$cm/s	[38, 40]
K_{rel}	drug release rate constant	$0.0078\ s^{-1}$	[48]
S/V	surface of blood vessels at tumour compartment area per volume	$200\ cm^{-l}$	[34, 35-37]
V^{TP}	volume fraction	0.07452	[41]
K_{cl}^{L}	clearance average constant of the liposomal drugs	$2.228 *l0^{-4} s^{-l}$	[41]
K_{hr}	lysosomal degradation average constant	$3.670*l0^{-5} s^{-l}$	[43]
K_x	recycling rate constant	$9.670*l0^{-4} s^{-l}$	[43]
K_r	plasma clearance rate constant	$11*l0^{-3} s^{-l}$	[41]
K_d	dissociation average constant	$103\ S^{-l}$	[48]
K_a	The association average constant	$107(mol\ cm^{-3} S)^{-l}$	[43]
P_i, *i = 1 - 4*	The mass transfer coefficient	10^{-7}–10^{-6} cm/s	[50]
D_p, *p=L ,F,B*	The diffusion coefficient	10^{-8}– $10^{-6} cm^2/s$	[51, 52-54]
n_2	boundary position of compartment of tumour	10^{-2}	—

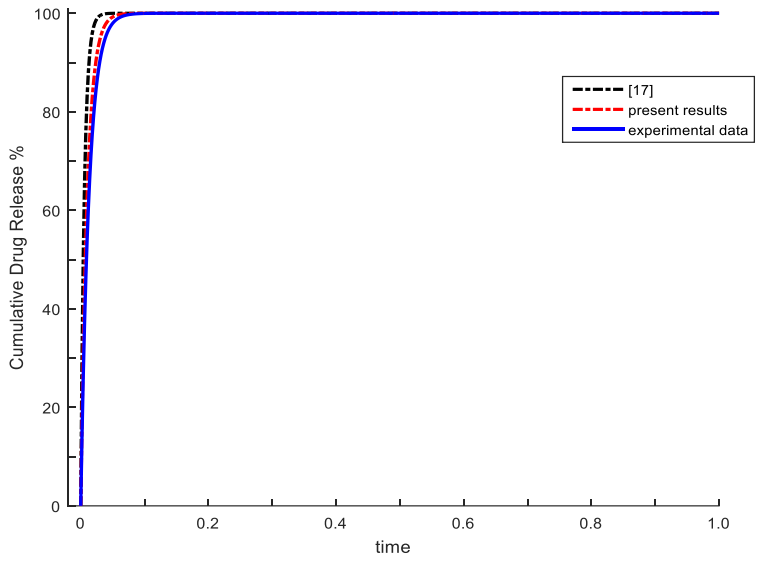


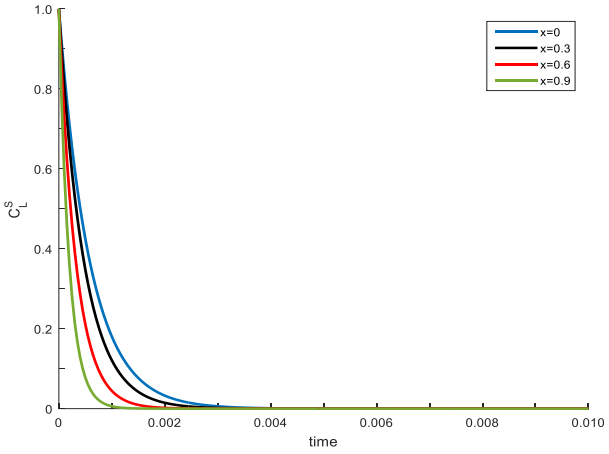
Fig.2: Comparison of the experimental data with the current results [33] .

5. Numerical simulation and discussion

The systematic quantitative analysis was achieved to locally drug delivery according to parameters of the model listed in Table l and 2 in more details with characterization of pharmacokinetic aspects. The representation of graphic of the drug concentrations in its various embodiments were showed in the well case in Figures 1 - 11 so that the underlying governing the physical phenomena was illustrated.

When seen the results in Figure 2, it can be observed that against the onset, the data of tests match exactly, whereas against the termination , there is the small deviation between the current mathematical model profile and its counterpart of tests [33]. The rationale behind this consequence is that the present model seeks with free drugs being transported to biological tissues while the

framework of tests [33] lacks in the transport of drugs. These results proved that the applied of Adomian decomposition method for solving problems of nonlinear partial equations is a powerful tool to obtain solutions without a need for large size of computations. Additionally, the numerical results which obtained using the current approach indicate the high accuracy degree. We showed that the procedure of decomposition is quite efficient for determining the exact solutions .And applicability of ADM for solving the partial differential equations of mathematical model to deliver drugs to the tumor over time in different locations.



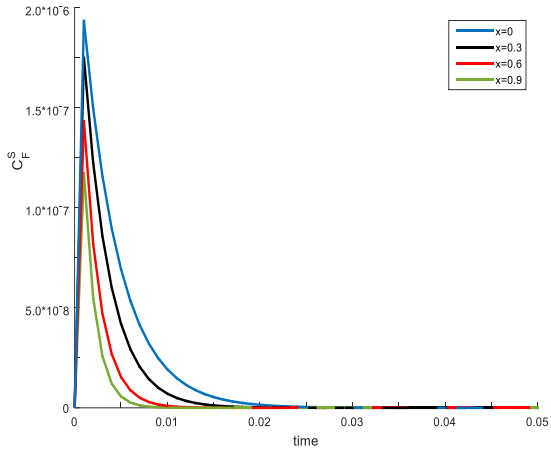


Fig.3:Profiles of time variant concentration of C_L^S at different locations.

Fig.4:Profiles of time variant concentration of C_F^S at different locations.

Fig.3and Fig.4 are describes the profiles of period-variant concentration of liposomes-encapsulated drugs in the systemic plasma(C_L^S) and free drugs(C_F^S) of four different axial sites distributed across. The rate of decrease of concentration of the liposomes-encapsulated drugs from its most concentration immediately becomes higher and higher as resulting by releasing free drugs , they entry in to tumor plasma. On another hand C_F^S acquires and grows certain band in accordance to the particular immediate of time followed using the gradual descend for periods rest. Fig.5represents the time-variant concentration profiles of liposome encapsulated drug C_L^{TP}in tumor plasma for deferent axial sites stretched on the full domain .As time elapses, the liposomal in addition to free drugs crosses in to the compartment of tumour from the compartment of systemic plasma. The liposome having drugs en-capsulation moves from the systemic plasma in to the

plasma of tumour as C_L^{TP} .An increase in concentration initially within the tumor plasma because of distribution of liposome from the systemic plasma to tumor plasma. Also, the concentration gradually decreases due to the release of the drug as free forms and the net loss of fatty liposome because of the exchange of drugs between the parts of the sub-tumor through the capillaries. Figure 6 describes the profiles of period-variant concentration of liposome encapsulated drugs in interstitial fluid C_L^{TIF} for deferent axial sites stretched on the full domain. In the tumor compartment, the exchange of liposome encapsulated drugs takes place between interstitial fluids and plasma due to the exchange of drugs through the capillaries. As a result of the spread of C_L^S, its concentration in interstitial fluid increases .The released drugs from the liposome in interstitial fluids was depicted as free drugs (C_F^{TIF}). These free drugs get disseminated through interstitial fluids . The interstitial fluids contain the big portion of free drugs (C_F^{TIF}), since just the free drug can cross the compartment of tumor cell.

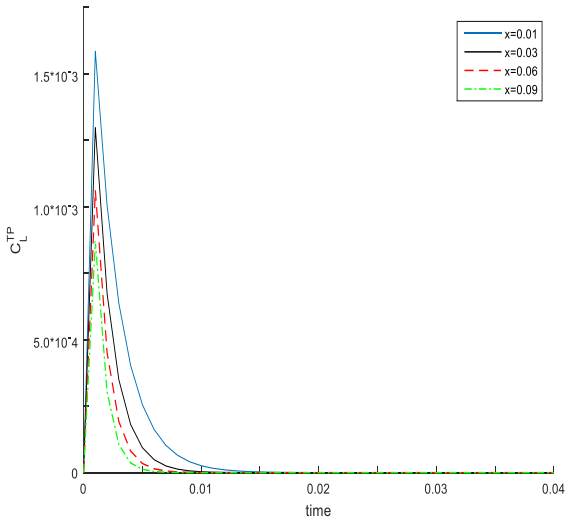


Fig.5: Profiles of period variant concentration of C_L^{TP} at various sites.

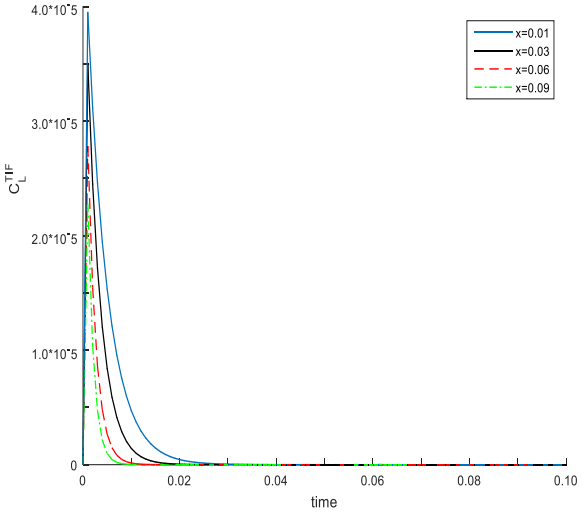


Fig.6: Profiles of time variant concentration of C_L^{TIF} at various sites

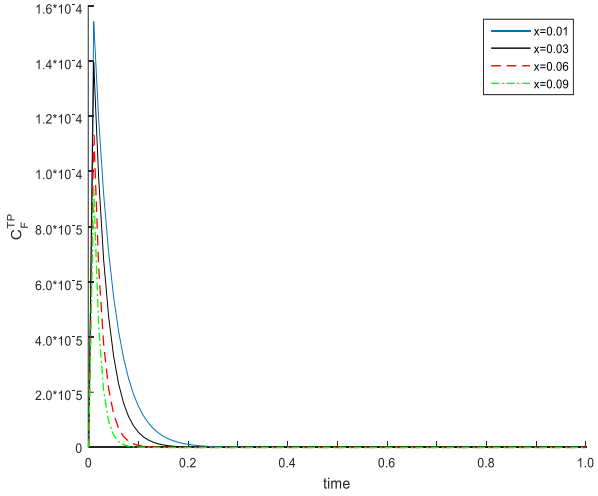


Fig.7: Profiles of period variant concentration of C_F^{TP} at various sites sites

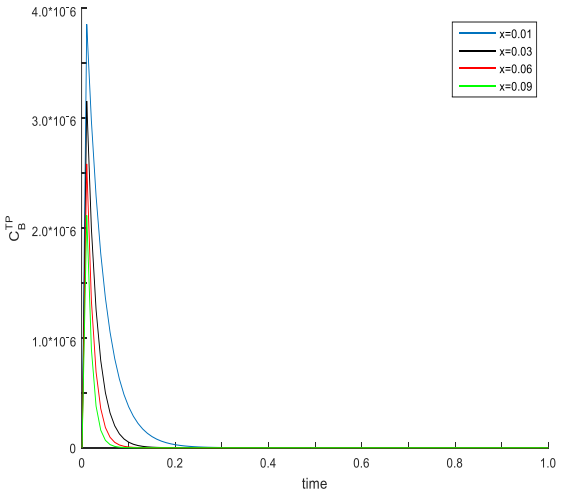
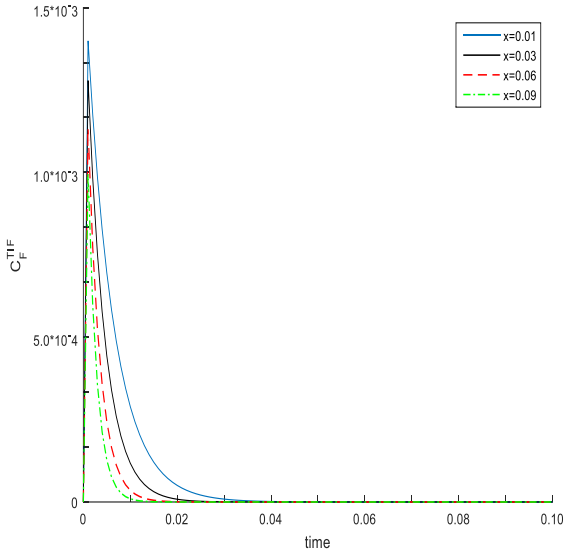


Fig .8: Profiles of period variant concentration of C_B^{TP} at various sites

Fig.7 shows the profiles of period-variant concentration of free drugs in tumor plasma (C_F^{TP}) for deferent axial sites stretched on the full domain. the free drugs in systemic plasma crosses in to

the plasma of tumor as C_F^{TP}.The increase in concentration occurs as a result of the release rate of liposome and free drugs leaks from the systemic plasma to plasma of tumor**.** Fig. 8 shows profiles the period-variant concentration of the bound drugs in tumor plasma $C_B^{TP}$for deferent axial sites stretched on the full domain .The free drugs bind with the protein found there. Also , free drugs interact with receptors of the surface of cells of tumor and cross in to tumor intracellular spaces. No another drug forms, whether it is bound drugs or liposomal drugs, can cross in to cells of tumor .Where the exchange of bound drugs between the sub-sections of the tumor through the capillaries and the effect associated with the formation of a free pharmaceutical protein compound .



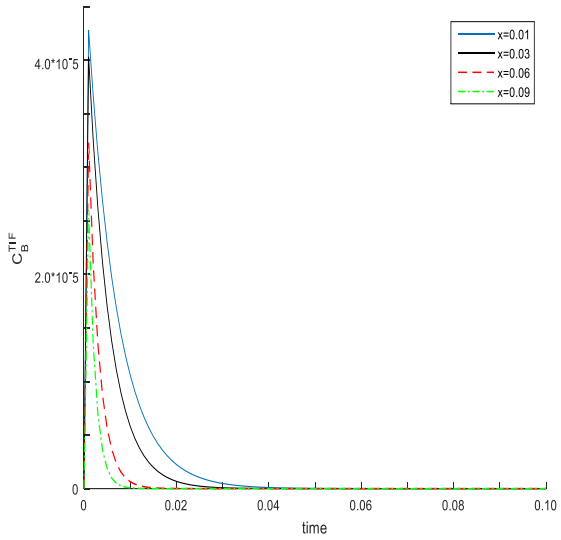


Fig.9:Profiles of period variant concentration of C_F^{TIF} at various sites. Fig.10: Profiles of period variant concentration of C_B^{TIF} at various sites

Figs.9 and 10 are represents the profiles of time-variant concentration of free drug (C_F^{TIF}) and represents the profiles of period-variant concentration of bound drugs (C_B^{TIF}) in interstitial fluid for deferent axial sites stretched on the full domain. $C_F^{TIF}$is peaked because of liposome and the free drug of the tumor that crosses the wall of capillaries into the interstitial fluid and then decreases because of its relation with the proteins and receptors of the surfaces of cancer cells .Free drug (C_F^{TIF}) binds with the proteins (C_P^{TIF}) in interstitial fluids for forming the free drug-protein complexes, like bound drugs (C_B^{TIF}) . Bound drug (C_B^{TIF}) peaks because of its interaction with the free exchange of drugs and drugs across borders to the interstitial fluid of tumor plasma. Over time, C_B^{TIF} decreases because of the dissociation of the drug-protein complexes in interstitial fluids of the tumor.

Conclusions

The simulation of the phenomena of drugs transport and the release of mathematical modelling drugs show to be too important as it helps in release kinetics prediction, which has a useful value in optimization of forms of the drug dosage. Also, the systematic quantitative analysis was achieved to locally drug delivery to tumors over time at different locations successfully, based on parameters of the model obtained with Table (l&2) with the full characterizing the pharmaco-kinetic aspect

.The results obtained show that the ADM is quite efficient to determine the precise analytical approximate solutions. The approach provides the powerful tool to obtain the solutions without a need for large size of computations. In addition, The ability and power of the Adomian decomposing method (ADM) confirm that there is no need to effort device for investigating the solution of a non-linear system of partial differential equations and reliable. It provides the analyst with an easily computable, readily verifiable and rapidly convergent sequence of analytic approximate functions for the solution.

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Appendix

No of Equations	coefficients values						
42	a_0 =1	a_1 =0.014	a_2 =3.7E+12	a_3 =7.8E+13	a_4 =1.6E+25	a_5 =6.7E+34	a_6 =1.9E+36
43	b_0 = 1	b_1 = 644.44	b_2 = 0.0055	b_3 = 2.40	b_4=0.51E-5	b_5=0.19E-2	b_6=1.90E-5
44	c_0 = 1	c_1 = 100	c_2 = 0.6E-2	c_3 = −0.40	c_4=−0.5E-5	c_5 = 0.3E-3	c_6=1.9E-9
45	d_0 = 1	d_1 = 17.1	d_2=1.1E-17	d_3=-3.8E-16	d_4=-2.8E-10	d_5=5.6E-9	d_6=1.04E-13
46	Q_{10}=- Q_{30} =1.7E+14	Q_{11}= −Q_{31} =2.9E+19	Q_{12}= −Q_{32} =2.5E +26	Q_{13}= −Q_{33} = - 2.8E+15	Q_{14}= −Q_{34} =1.2 E +22	Q_{15}= −Q_{35} =0.015	Q_{16}= -Q_{36} =1.7E+5
	Q_{20}=2.9E+16	Q_{21}=5.07E+17	Q_{22}=1.4E +19	Q_{23}=4.9E +13	Q_{24}=2.1 E +20	Q_{25}=0.00027	Q_{26}=161.57
47	l_0=1	l_1=5800	l_2=5E + 16	l_3=16.5	l_4=7.1E-7	l_5=9.2E − 17	l_6=5.4E-11
48	f_0= g_0 = 1	f_1=-g_1 = -0.45E-2	f_2= -g_1 =-3814.05	f_3=-g_3 =-8.2E-21	f_4= -g_4 =-7.3E-15	f_5= -g_5 =1.5E-13	f_6 = -g_6 =2.7E-18
	h_0=1.72E+6	h_1=0.79E-4	h_2=65.7	h_3=1.4E-22	h_4=1.3E-16	h_5=-2.5E-15	h_6= -5.7E-30
	p_1=-7.5E-7	p_2=-7.8E-22	–	–	–	–	–
49	r_0=1	r_1=4.58E+13	r_2=3.8E+11	r_3 =8.2E-13	r_4=1458.2	r_5=-0.14 E -4	r_6=-0.02
	z_0=1	z_1=-7.9E+11	z_2=-6.6E+9	z_3=-1.4E-14	z_4=-1.25	z_5=25.1	z_6=0.5E-2
	o_0=1.48 E +20	o_1= 6.81E+9	o_2=5.7E+7	o_3=1.2E-16	o_4=0.01	o_5=-0.21	o_6=-0.4E-5
	L_0 =-8.54E+17	L_1=-3.91E+7	L_2=-4.5E-16	L_3=-7E-11	L_4=-0.6E-4	L_5=0.12E-2	L_6=2.8E-8
	n_0=-1	n_1=-4.6E+5	n_2=-3.8E+11	n_3=-0.82E-4	n_4=-73.9	n_5=1458.2	n_6=0.03
50	A_{10}=-A_{20}=1	A_{11} = -A_{21} =1.7E+9	A_{12} = -A_{22} = -1.5E+16	A_{13} =A_{23} =-3.2E-8	A_{14} =-A_{24} =-63.96	A_{15} =-A_{25} =1279.2	A_{16} =-A_{26} =0.02
	A_{30}=-1.72E+6	A_{31}=-2.9E+7	A_{32}=2.5E+14	A_{33}=5.5E-10	A_{34} = 1.1	A_{35}=-22.1	A_{36}=-0.4E-3
	A_{40}=3.38E+7	A_{41}=5.8E+8	A_{42}=-4.97E+15	A_{43}=-1.1E-8	A_{44} =0.95E-2	A_{45}=0.2	A_{46}=4.3E-16
51	G_{10}=1	G_{11} =4.6E+21	G_{12} =3.8E+27	G_{13} =8224.1	G_{14} =7.3E+9	G_{15}=-1.5E+11	G_{16} =-2.7E+6
	G_{20}=1.7E+30	G_{21}=7.9E+19	G_{22}=6.6E+25	G_{23}=0.007	G_{24}=1.3E+8	G_{25}=2.5E+9	G_{26}=-46557.1
	G_{30}=-1.5E+28	G_{31}=-6.8E+17	G_{32}=5.7E+23	G_{33}=-1.2	G_{34} =-1.1E+6	G_{35}=2.2E+7	G_{36}=401.4
	G_{40} =8.5E+25	G_{41}=3.9E+15	G_{42}=3.3E+21	G_{43}=0.007	G_{44}=6227.94	G_{45}=-1.3E+5	G_{46}=-2.3
	G_{50}=-3.7E+23	G_{51}=-1.7E+13	G_{52}=-1.4E+19	G_{53}=-0.3E-4	G_{54}=-26.8	G_{55}=536.9	G_{56}=1.2E-12
	G_{60}=9.9E+7	G_{61} =6.4E+10	G_{62} =0.7E-40	–	–	–	–
52	H_{10}=-H_{20} =-4.6E+14	H_{11} =-H_{21} =-7.8E+15	H_{12} =-H_{22} =-6.7E+22	H_{13} =-H_{23} =-0.14	H_{14} =-H_{24} =7.4E+6	H_{15} =-H_{25} =-1.5E+8	H_{16} =-H_{26} =-2734.9
	H_{30} =7.8E+12	H_{31}=1.3E +14	H_{32}=1.2E +21	H_{33}=0.24E-2	H_{34}=1.3E+5	H_{35}=2.5E+6	H_{36} =-47.2
	H_{40}=-6.8E+10	H_{41}=-1.2E+12	H_{42}=9.95E+18	H_{43}=0.2E-4	H_{44}=-1097.5	H_{45} =21950	H_{46} =0.4
	H_{50} =3.9E+8	H_{51} =6.6E+9	H_{52}=-5.7E+16	H_{53}=1.2E-7	H_{54} =6.3	H_{55} =-126.2	H_{56}=-0.2E-2
	H_{60} =9.7E+7	H_{61} =1.6E+9	H_{62}=-1.4E+16	H_{63}=-3.1E-8	H_{64}=-0.03	H_{65}=0.54	H_{66}=1.2E-15
53	B_{10} =-B_{20} =6.3E+13	B_{11} =-B_{21} =1.1E+15	B_{12}=-B_{22} =-9.2E+21	B_{13} =-B_{23} =-0.02	B_{14}=-B_{24} =-1596.8	B_{15}=-B_{25} =3.5E+5	B_{16} =-B_{26} =6.5
	B_{30}=55.3E+7	B_{31} =9.1E+8	B_{32}=-7.9E+15	B_{33}=-1.7E-8	B_{34} =-31.6	B_{35} =631.4	B_{36} =0.01
	B_{40} =-9.3E+9	B_{41}=-1.6E+11	B_{42}=1.4E+18	B_{43}=0.3E-5	B_{44} =5493.4	B_{45}=-1.1E+5	B_{46} =-2.03
	B_{50} =1.1E+12	B_{51}=1.8E+13	B_{52}=-1.6E+20	B_{53}=-0.3E-3	B_{54}=-6.4E+5	B_{55}=1.3E+7	B_{56} =236.01
	B_{60}=-4.8E+8	B_{61}=-8.3E+9	B_{62}=7.1E+16	B_{63}= -1.5E-7	B_{64} = 0.13	B_{65}=−2.72	B_{66}=-6.1E-15
54	N_{10}=-2.6E+20	N_{11}=-4.5E+21	N_{12}=-3.9E+28	N_{13}=83420.4	N_{14}=1.5E+18	N_{15}=-2.9E+19	N_{16}=-5.5E+14
	N_{20}= -4.5E+18	N_{21}= -7.7E+19	N_{22}=6.7E+26	N_{23}=1438.3	N_{24}=2.6E+16	N_{25}=-5.1E+17	N_{26}=-9.4E+12
	N_{30}=-2.2E+14	N_{31}=-2.8E+15	N_{32}=3.3E+22	N_{33} =0.1	N_{34}=1.3E+12	N_{35}=-2.5E+13	N_{36}=-4.7E+8
	N_{40}=9.7E+11	N_{41}=1.7E+14	N_{42}=-1.4E+20	N_{43}=-0.3E-3	N_{44}=5.4E+9	N_{45}=1.1E+11	N_{46}=-2.02E+6
	N_{50}=3.3E+9	N_{51}=-5.7E+10	N_{52}=4.96E+17	N_{53}=0.1E-5	N_{54}=1.9E+7	N_{55}=-3.8E+8	N_{56}=-6948.8
	N_{60}=1.9E+14	N_{61}=3.3E+15	N_{62}=-2.8E+22	N_{63}=−0.1	N_{64}=−53913.5	N_{65}=1.1E+6	N_{66}=2.4E-9
55	F_{10}=-F_{20} =-2.6E+20	F_{11}=-F_{21} =-4.5E+21	F_{12}=-F_{22} =-3.9E+28	F_{13}=-F_{23} =83420.4	F_{14}= -F_{24} =2.9E+25	F_{15}= -F_{25} =-5.9E+26	F_{16}=-F_{26} =-1.1E+22
	F_{30}=-4.5E+18	F_{31}=-7.7E+19	F_{32}=6.7E+26	F_{33}=1438.3	F_{34}=5.1E+23	F_{35}=-1.02E+25	F_{36}=-1.9E+20
	F_{40}=3.9E+16	F_{41}=6.7E+17	F_{42}=-5.8E+24	F_{43}=-12.4	F_{44}=-4.4E+21	F_{45}=8.8E+22	F_{46}=1.6E+18
	F_{50}=−2.2E+14	F_{51}=-3.8E+15	F_{52}=3.3E+22	F_{53}=0.1	F_{54}=2.5E+19	F_{55}=-5.1E+20	F_{56}=-4.9E+15
	F_{60}=9.7E+11	F_{61}=1.7E+13	F_{62}=-1.4E+20	F_{63}=-0.3E-3	F_{64}=-1.1E+17	F_{65}=2.2E+18	F_{66}=4.3E+13
	F_{70}=-3.3E+9	F_{71}=-5.7E+10	F_{72}=4.9E+17	F_{73}=0.10E-5	F_{74}=3.8E+14	F_{75}=-7.5E+15	F_{76}=-1.4E+11
	F_{80}=3.8E+21	F_{81}=6.5E+22	F_{82}=-5.6E+29	F_{83}=-1.2E+6	F_{84}=-1.1E+12	F_{85}=2.2E+13	F_{86}=3.99E+8