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Two compartmental fractional derivative model with general fractional derivative

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Abstract

This study presents a new two compartmental model with, recently defined General fractional derivative. We review that concept of General fractional derivative and use the kernel function that generalizes the classical Caputo derivative in a mathematically consistent way. Next we use this model to study the release of antibiotic gentamicin in poly (vinyl alcohol)/gentamicin(PVA/Gent) hydrogel aimed for wound dressing in medical treatment of deep chronical wounds. The PVA/Gent hydrogel was prepared by physical cross linking of poly (vinyl alcohol) dispersion using freezing–thawing method, and then was swollen in gentamicin solution at 37 °C during 48 h. The concentration of released gentamicin was determined using a high-performance liquid chromatography coupled with mass spectrometer. The advantage of this model is the existence of new parameters in the definition of fractional derivative, as compared with classical fractional compartmental models. The model proposed here in the special case reduces to the classical (integer order) linear two compartmental model as well as classical fractional order two compartmental model since it has more parameters that are determined from the experimental results.

Keywords Fractional kinetics · General fractional derivative · Gentamicin · Hydrogel

Introduction

Selecting appropriate models is a crucial step in capturing complex biological and physiological phenomena. Any choice of a model structure implies a simplified view of the interaction among the various elements that may characterise a dynamical system. In pharmacokinetics, a popular choice is that of compartmental models, due to their implicit simplicity and ease of understanding in relation to the mass balance equations and assumptions for uniform distribution, homogeneous transient times and immediate response to drug bolus administration [1]. Numerous works and decades of research have tailored their applicability for optimal drug delivery assist devices in several domains of medical applications, e.g., diabetes [2], cancer [3, 4], anaesthesia [5, 6], immune deficiency, leukaemia [7] and hormonal treatment [8].

Fractional-order models are found to be more adequate for compartmental analysis in many cases [9–11] especially when in a process under consideration memory effects are pronounced [12]. Interested reader can find detailed references regarding fractional calculus (FC) and fractional-order models in [12–16]. The application of fractional calculus of Riemann–Liouville and Caputo type in pharmacokinetics and diffusion is presented in [17] and in our papers [7, 18–20].

The latest developments and trends in the application of fractional calculus (FC) in biomedicine and biology are provided by Ionescu et al. [21]. Nature has often showed to follow rather simple rules that lead to the emergence of complex phenomena as a result. Of these, the paper addressed the properties in respiratory lung tissue, whose natural solutions arise from the midst of FC in the form of

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non-integer differ-integral solutions and non-integer parametric models. Diffusion of substances in human body, e.g., drug diffusion, is also a phenomena well known to be captured with such mathematical models. FC has been employed in neuroscience to characterize the generation of action potentials and spiking patters but also in characterizing bio-systems (e.g., vegetable tissues). Despite the natural complexity, biological systems belong as well to this class of systems, where FC has offered parsimonious yet accurate models.

Recently there is new type of fractional derivative that is intensively studied, named General fractional derivative. It is defined so that basic properties of integer order derivatives are retained. We stress that the basic requirement proposed in General fractional derivative is that it takes nonlocality in time but that resulting equations modelling the process can not to be represented as differential equations or systems of differential equations of integer order only. Thus, General fractional calculus is a branch of mathematical analysis of the integral and integro-differential operators that are generalizations of integrals and derivatives of integer order for which the generalization of the fundamental theorems of the calculus are satisfied [22]. More details on this fascinating topic are presented in [23–28]. Novelty of the compartmental system that we formulate in the next Section, is the use, for the first time, of General fractional derivatives in pharmacokinetics. Our analysis will be similar to the one presented in the context of viscoelasticity [29].

Materials and methods

The main idea of the General fractional calculus is the definition of a general fractional integral $I^t_{(M)}$ and General fractional derivative $D^t_{(K)}$ as

$$I^t_{(M)}[\tau]f(\tau) = \int_0^t M(t-\tau)f(\tau)d\tau,$$
$$D^t_{(K)}[\tau]f(\tau) = \frac{d}{dt}\int_0^t K(t-\tau)f(\tau)d\tau, \quad (1)$$

where the kernels, M and K satisfy certain properties, i.e., they are associated in the sense of Sonin. The general fractional derivative of the Caputo type with the kernel K is

$${}^C D^t_{(K)}f(\tau) = \int_0^t K(t-\tau)f^{(1)}(\tau)d\tau, \quad (1a)$$

We state two conditions that the kernels in (1),(1a) must satisfy:

$$M(t), K(t) \in C_{-1,0}(0,\infty), \quad \int_0^t M(t-\tau)K(\tau)d\tau = 1, \quad (2)$$

where

$$C_{a,b}(0,\infty) = \{f(t) : f(t) = t^p Y(t), \ t>0, \ a<p<b, \ Y(t) \in C[0,\infty)\}. \quad (3)$$

Note that the Riemann–Liouville kernels [13]

$$M(t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad K(t) = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}, \quad (3a)$$

where $0<\alpha<1$ and Γ is the Euler Gamma function, satisfy (2), (3) and that, in this case (1) becomes fractional integral and Caputo fractional derivative.

There are many kernels that satisfy (2), (3) as shown in [22]. We mention two of them. In [26] the following kernels are proposed

$$M(t) = \left[\frac{t^{-\beta}}{\Gamma(1-\beta)} + \frac{t^{\alpha-\beta}}{\Gamma(\alpha-\beta+1)}\right]H(t),$$
$$K(t) = \left[t^{\beta-1}E_{\alpha,\beta}(-t^\alpha)\right]H(t), \quad t\in(0,\infty), \ \beta\geq 0, \ 0<\alpha\leq\beta,$$

where H is the Heaviside step function and $E_{\alpha,\beta}(t) = \sum_{k=0}^{\infty}\frac{t^k}{\Gamma(k\alpha+\beta)}$, $\alpha>0$, $\beta\geq 0$, is a two parameter Mittag-Lefler function [30]. In our analysis in this paper we shall use the following kernels that are presented in [23] and are generalization of (3a)

$$M(s) = \lambda^\alpha + \frac{\alpha}{\Gamma(1-\alpha)}\int_t^\infty \frac{\exp(-\lambda u)}{u^{1+\alpha}}du, \quad K(t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)}\exp(-\lambda t). \quad (3b)$$

where $\lambda\geq 0$ and we replaced α in [23] with $1-\alpha$. Therefore the general fractional derivative of the Caputo type that we use in this work is given, see (1a)

$${}^C D^{\alpha,\lambda}f(t) = {}^C D^t_{(K)}f[\tau] = \frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{\exp(-\lambda\tau)}{\tau^\alpha}f^{(1)}(t-\tau)d\tau \quad (4)$$

The proof the M and K used in (4) satisfy $(2)_2$ is given in [23].

Our aim in this work is to formulate generalized two compartmental model for pharmacokinetics with General fractional derivative defined by (4) and to apply this generalization to a specific problem of release of gentamicin in poly(vinyl alcohol)/gentamicin (PVA/Gent) hydrogel. Namely, chronic wound healing and care is a major area of medical and biomaterials science research, as frequent and persistent infections (often caused by multidrug-resistant

(microbial strains) and ever-rising numbers of antibiotic resistant bacterial strains have become a serious concern in modern times. Here, we synthesized novel PVA/Gent hydrogel with embedded gentamicin for wound treatments with long-term controlled release of gentamicin in the wound locally, without systemic antibiotic administration.

Consider the classical two compartmental model of pharmacokinetics, see Fig. 1, with different volumes of compartments [31]

$$\begin{aligned}\frac{dQ_1}{dt} &= -k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right)+f_1(t),\\ \frac{dQ_2}{dt} &= k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right),\end{aligned} \tag{5}$$

where Q_i, $i = 1, 2$ is the mass of the substance (gentamicin in our case) in the compartments **1** and **2**, respectively, V_i, $i = 1, 2$ are volumes of compartments **1** and **2,** k is a constant depending on the diffusion coefficient, D, hydrogel area through which diffusion takes place, A, and hydrogel thickness, δ, and f_1 is the supply of drug—in the compartment **1**. The dimension of k is [cm^3/s].

Our generalization of (5) is obtained when we replace the first derivative on the left hand side of (5) by two GFC given by (4). Therefore, we consider the following system, as generalization of (5)

$$\begin{aligned}\left[a\,{}^{C}D^{\alpha,\lambda_1}+b\,{}^{C}D^{\beta,\lambda_2}\right]\,Q_1(t) &= -k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right)+f_1(t),\\ \left[a\,{}^{C}D^{\alpha,\lambda_1}+b\,{}^{C}D^{\beta,\lambda_2}\right]\,Q_2(t) &= k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right),\end{aligned} \tag{6}$$

where again, Q_i,V_i $i = 1,2$ denote the mass of drug and volume of the compartment i, respectively, and the derivatives ${}^{C}D^{\alpha,\lambda_1}(\cdot)$ and ${}^{C}D^{\beta,\lambda_2}(\cdot)$ are given by (4). The parameters a and b are given as $a = T^{\alpha-1}$, $b = T^{\beta-1}$ where T is the characteristic time of the compartment, in [s]. Basically we are replacing the first derivatives $\frac{d}{dt}(\cdot)$ in (5) by linear combination of two general fractional derivatives of different orders $a{}^{C}D^{\alpha,\lambda_1}(\cdot)+b{}^{C}D^{\beta,\lambda_2}(\cdot)$. Note that for $\lambda_i = 0, i = 1, 2,\ \alpha = 1, \beta = 1$ the system (6) reduces to (5). Note that in (6) we used two fractional derivatives of different order in the same way as in [18].

We discuss now the relation of the model proposed here, Eqs. (6) with the standard models with Riemann–Liouville or Caputo fractional derivatives, as used in [7] and [21], for example. By setting $\lambda_1 = \lambda_2 = 0, b = 0$ in (6) we obtain the model Eqs. (41)–(44) in [21]. However by setting $\lambda_1 \neq 0, \lambda_2 = 0, b = 0$ we obtain a model in which Q_1 decreases more quickly than in the case when classical Caputo derivative is used. This may be important in some problems, see Eq. (11) in [7]. Also we stress that the model (6) has six parameters that have to be determined from experimental data. Such generality may not be needed in all application. Actually in the example that we treat in detail here, this is the case. However in some applications, presence of additional parameters b, β, λ_2 may be crucial for obtaining solution.

Explicit form of the system of integro-differential equations that we will solve in this work, follows from (6) and reads

$$\begin{aligned}&a\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_a\tau)}{\tau^\alpha}Q_1^{(1)}(t-\tau)d\tau+b\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_b\tau)}{\tau^\alpha}Q_1^{(1)}(t-\tau)d\tau\\ &\quad=-k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right)+f_1(t),\\ &a\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_a\tau)}{\tau^\alpha}Q_2^{(1)}(t-\tau)d\tau+b\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_b\tau)}{\tau^\alpha}Q_2^{(1)}(t-\tau)d\tau\\ &\quad=k\left(\frac{Q_1(t)}{V_1}-\frac{Q_2(t)}{V_2}\right),\end{aligned} \tag{7}$$

In [32] the so-called pseudo diffusion coefficient is introduced that has dimension [cm^2/s$^\beta$]. This corresponds to the special case when $a = 0$ and when both equations are divided by b. The initial conditions corresponding to (7) are

$$Q_1(0) = Q_0, \quad Q_2(0) = 0. \tag{8}$$

Further, note that for the case when $V_2 \to \infty$ the system (7) becomes

$$\begin{aligned}&a\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_a\tau)}{\tau^\alpha}Q_1^{(1)}(t-\tau)d\tau+b\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_b\tau)}{\tau^\alpha}Q_1^{(1)}(t-\tau)d\tau\\ &\quad=-k\frac{Q_1(t)}{V_1}+f_1(t),\\ &a\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_a\tau)}{\tau^\alpha}Q_2^{(1)}(t-\tau)d\tau+b\,\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{\exp(-\lambda_b\tau)}{\tau^\alpha}Q_2^{(1)}(t-\tau)d\tau\\ &\quad=k\frac{Q_1(t)}{V_1},\end{aligned} \tag{9}$$

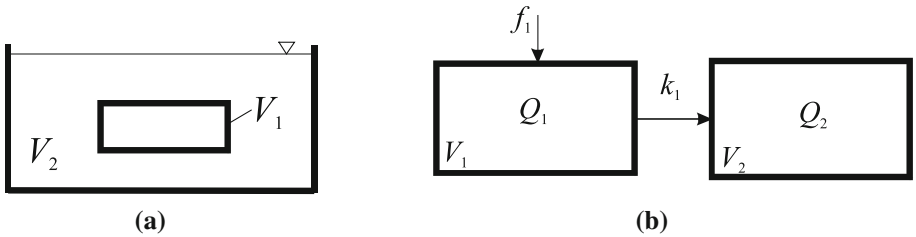

Fig. 1 Two compartmental simplified model of gentamicin release: **a** physical system, **b** mathematical model

System (9) represents the generalized two compartmental model with GFD for radioactive decay.

Solution of the system (7), (8)

We use the Laplace transform method in solving (7), (8). The Laplace transform of an exponentially bounded function f is defined as

$$[Lf(t)](s) = \hat{f}(s) = \int_0^\infty f(t)\exp(-st)dt, \tag{10}$$

where $s \in C$ is complex number. It is known that

$$L[\frac{t^{\alpha-1}}{\Gamma(\alpha)}\exp(-\lambda t)](s) = \frac{1}{(s+\lambda)^\alpha}, \quad \lambda \geq 0, \quad 0 \leq \alpha \leq 1.$$

Using expression for the Laplace transform of the first derivative applied to $Q_1^{(1)}$, i.e., $L[Q_1^{(1)}](s) = s\hat{Q}_1(s) - Q_1(0)$ we obtain

$$L\left[\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{\exp(-\lambda u)}{u^\alpha} Q_1^{(\alpha)}(t-u)du\right] = \frac{s}{(s+\lambda_1)^\alpha}\hat{Q}_1(s) - \frac{1}{(s+\lambda_1)^\alpha}Q_1(0). \tag{11}$$

Further, since in our experiments no mass is added, we have $f_1 = 0$. Therefore, the Laplace transform of the system (7) is

$$\left[a\frac{s}{(s+\lambda_1)^\alpha} + b\frac{s}{(s+\lambda_2)^\beta}\right]\hat{Q}_1(s) = -k[\frac{\hat{Q}_1(s)}{V_1} - \frac{\hat{Q}_2(s)}{V_2}] + \left[a\frac{1}{(s+\lambda_1)^\alpha} + b\frac{1}{(s+\lambda_2)^\beta}\right]Q_1(0)$$
$$\left[a\frac{s}{(s+\lambda_1)^\alpha} + b\frac{s}{(s+\lambda_2)^\beta}\right]\hat{Q}_2(s) = k[\frac{\hat{Q}_1(s)}{V_1} - \frac{\hat{Q}_2(s)}{V_2}]. \tag{12}$$

Note that (12) leads to

$$[\hat{Q}_1(s) + \hat{Q}_2(s)] = \frac{Q_1(0)}{s}, \tag{13}$$

or by taking the inverse Laplace transform

$$Q_1(t) + Q_2(t) = Q_1(0), \quad t \geq 0. \tag{14}$$

Equation (14) represents the conservation of mass law. Therefore we shall determine Q_2 from (12) and then Q_1 from (14). Also by using the Initial and Final Value Theorems [33], we have

$$\lim_{s\to\infty} s\hat{Q}_1(s) = Q_1(0), \quad \lim_{s\to 0} s\hat{Q}_1(s) = Q_1(\infty) = Q_1(0)\frac{V_1}{V_1+V_2}. \tag{15}$$

Also, from (15) we obtain

$$\lim_{s\to 0} s\hat{Q}_2(s) = Q_2(\infty) = Q_1(0)\frac{V_2}{V_1+V_2}. \tag{16}$$

Therefore the limiting concentrations, in each compartment $c_i = \frac{Q_i}{V_i}, i = 1, 2$ are equal

$$c_1(\infty) = c_2(\infty) = \frac{Q_1(\infty)}{V_1} = \frac{Q_2(\infty)}{V_2} = \frac{Q_1(0)}{V_1+V_2},$$

since we have Fick's model of diffusion. The parameters in the model $\alpha, \beta, \lambda_1, \lambda_2, a, b$ will be determined from the measured values preformed at several time instants, t_j, j = 1, 2,…6.

Experimental

Synthesis of PVA/Gent hydrogel

The following chemicals were utilized for preparation of PVA/Gent hydrogel: poly(vinyl alcohol) powder (fully hydrolyzed, Mw = 70–100 kDa; Sigma Aldrich, USA) and gentamicin sulfate solution (50 mg/ml in dH_2O, Sigma Aldrich, USA). All solvents used for gentamicin release measurements were HPLC grade from J.T. Baker, USA or Sigma-Aldrich, USA. Deionized water was obtained by passing the distilled water through a GenPure ultrapure water system (TKA, Germany)0.10 wt% PVA colloid dispersion was prepared by dissolving PVA powder in hot distilled water at 90 °C for 2 h, under magnetic stirring. The PVA hydrogels were obtained by physical cross linking of PVA dispersion using freezing–thawing method in 5 cycles. One cycle consisted of freezing for 16 h at 18 °C, followed by thawing for 8 h at 4 °C. Thus obtained hydrogels were cut into discs with diameters, d, of 10 mm and thicknesses, δ, of 4 mm. Then, the hydrogels were swollen in 5.0 mg/ml gentamicin solution at 37 °C during 48 h.

Gentamicin release profiles

For the drug release assay, PVA/Gent hydrogel was immersed in deionized water and kept at 37 °C. The concentration of released gentamicin was determined using a high-performance liquid chromatography (HPLC) (Thermo Fisher Scientific, USA) coupled with ion trap (LCQ Advantage, Thermo Fisher Scientific) as a mass spectrometer (MS), according to procedure we have published earlier [34]. Gentamicin mass spectrum was recorded in the

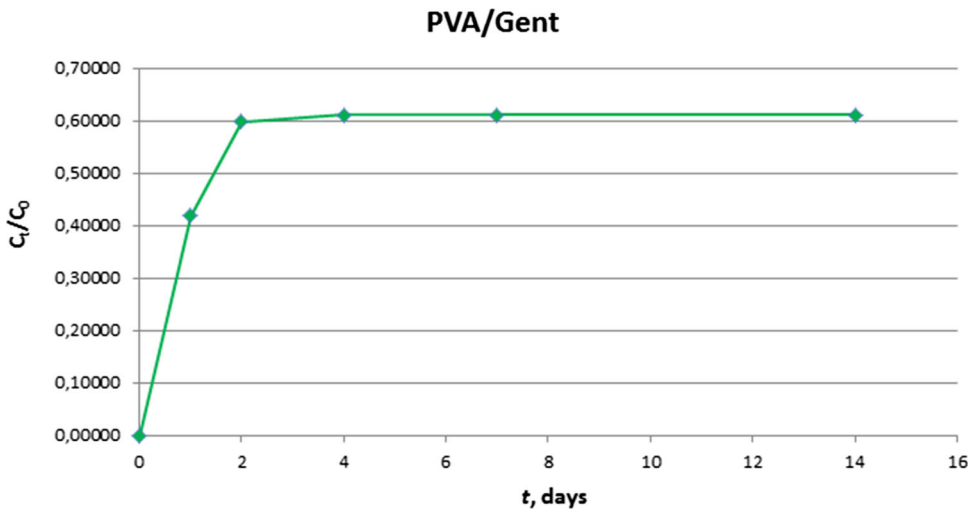

Fig. 2 Increase in concentration of released gentamicin from PVA/Gent hydrogel, c_t, with time during 14 days in deionized water at 37 °C (experimental data)

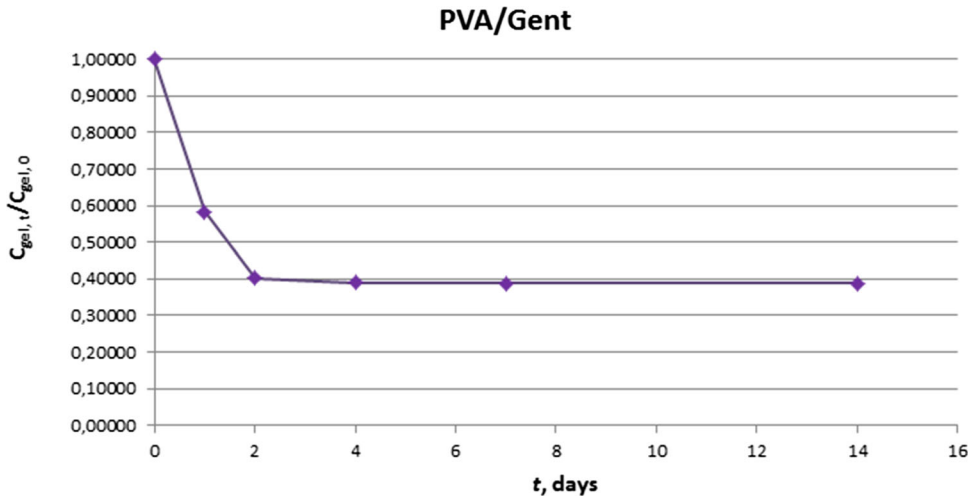

Fig. 3 Decrease in concentration of gentamicin remained in PVA/Gent hydrogel, $c_{gel,t}$, with time during 14 days in deionized water at 37 °C (experimental data)

m/z 50–1000 range, using the electrospray ionization technique. Gentamicin release was monitored for 14 days.

Results and discussion

The experimental cumulative gentamicin release profiles for PVA/Gent hydrogel are represented in Figs. 2 and 3 as an average of three samples, where c_o is the total concentration of released gentamicin, and c_t is the concentration of released gentamicin after certain time t, $c_{gel,t}$ is the concentration of gentamicin remained in hydrogel after certain time, t, and $c_{gel,0}$ is the initial concentration of gentamicin inside the hydrogel. Gentamicin release profiles verified the initial burst release effect of gentamicin from the hydrogel, i.e., 60% loaded antibiotic was released within first 48 h which could be very useful in preventing biofilm formation, followed by slow release of gentamicin in a later time period. This behavior is a consequence of gentamicin molecules entrapped in the cross linked PVA matrix.

Numerical results

In this Section we present the results of numerical inversion of (12). From (12) for we obtain

$$\hat{Q}_2(s) = Q_1(0)\frac{k}{V_1}\frac{1}{s\left[a\frac{s}{(s+\lambda_1)^{\alpha}} + b\frac{s}{(s+\lambda_2)^{\beta}} + k\left(\frac{1}{V_1}+\frac{1}{V_2}\right)\right]}. \tag{17a}$$

By using the argument principle, it can be easily shown that the function $\hat{Q}_2(s)$ does not have zeros with positive real part. Therefore

$$Q_2(t) = Q_1(0)\frac{k}{V_1}\frac{1}{2i\pi}\int_{x_0-i\infty}^{x_0+i\infty}\frac{\exp(x_0+ip)t}{(x_0+ip)\left[a\frac{(x_0+ip)}{(x_0+ip+\lambda_1)^{\alpha}}+b\frac{(x_0+ip)}{(x_0+ip+\lambda_2)^{\beta}}+k\left(\frac{1}{V_1}+\frac{1}{V_2}\right)\right]}d(x_0+ip). \quad (17b)$$

Here $x_0 > 0$ is arbitrary. We used standard Mathcad program for the numerical inversion of (17b). In the evaluation of (17b) we used $Im\left[\hat{Q}_2(s)\right] = -Im\left[\hat{Q}_2(\overline{s})\right]$ so that

$$Q_2(t) = \lim_{P\to\infty} Q_1(0)\frac{k}{V_1}\frac{1}{\pi}Re\left[\int_0^P \frac{\exp(x_0+ip)t}{(x_0+ip)\left[a\frac{(x_0+ip)}{(x_0+ip+\lambda_1)^{\alpha}}+b\frac{(x_0+ip)}{(x_0+ip+\lambda_2)^{\beta}}+k\left(\frac{1}{V_1}+\frac{1}{V_2}\right)\right]}dp\right],$$

where we choose $P = 120$. Q_1 is determined from (14) as

$$Q_1(t) = Q_1(0) - Q_2(t) \quad (18)$$

The parameters in the model are determined so that the squared difference between measured and calculated values of Q_2 at five measured points is minimal. Thus, we defined

$$Z(\alpha,\beta,\lambda_1,\lambda_2,a,b) = \sum_{j=1}^{5}\left(Q_2(t_j) - Q_{2measured}(t_j)\right)^2 \quad (19a)$$

where $Q_2(t_j)$ are values determined from (17b) and $Q_{2measured}(t_j)$ are measured values at time instant t_j. The measured values are given in the Table 1.

The parameters in the model $(\alpha^*,\beta^*,\lambda_1^*,\lambda_2^*,a^*,b^*)$ are determined from the condition (19a) as

$$\min_{\alpha,\beta,\lambda_1,\lambda_2,a,b)} Z(\alpha,\beta,\lambda_1,\lambda_2,a,b) = Z(\alpha^*,\beta^*,\lambda_1^*,\lambda_2^*,a^*,b^*). \quad (19b)$$

In the minimization process we took into account restrictions

$$0<\alpha\le 1,\ 0<\beta\le 1,\ \lambda_1\ge 0,\ \lambda_2\ge 0,\ a\ge 0,\ b\ge 0.$$

In our experiments we have $V_1 = 254.5$ mm^3, $V_2 = 1000$ mm^3 and the area over which diffusion takes place is $A = 2.40$ cm^2. We also fixed $k = 0.02$ cm^3/day in (17b). The corresponding diffusion coefficient is calculated to be $D = 0.0333$ cm^2/day or $D = 3.85 \times 10^{-8}$ cm^2/s which is in accordance with the literature data for gentamicin release from different polymer matrices in the range of 7.2×10^{-5} to 1.6×10^{-9} cm^2/s^1 [35–39]. From (19b) we determined the following values of parameters for the model:

$$a = 0.0284s^{-0.0003},\ \alpha = 0.9997, b = 0.1038s^{-0.00072},\ \beta = 0.00028,\ \lambda_1 = 876\times 10^{-6},\ \lambda_2 = 6.75. \quad (20)$$

where we omitted stars for the optimal values. The value of Z for parameters given by (20) is

$$Z(\alpha^*,\beta^*,\lambda_1^*,\lambda_2^*,a^*,b^*) = 1.591\times 10^{-3}.$$

We also used the bootstrapping procedure to estimate the confidence intervals of obtained optimal coefficients. We used the centered Gaussian distribution with standard deviation equal to 1, in order to obtain resampling from initial data, with N = 100 samples. The probability that the obtained values of parameters are in the confidence intervals is 0.95. Intervals of confidence are shown in Table 2.

The Table 2 shows relatively large confidence intervals for parameters. This is due to relatively small number of measured points (6) and relatively large number of parameters (6). As is seen in Figs. 4 and 5, the agreement of experimental (points) and calculated (line) values is excellent due to presence of six parameters.

Having in mind the clinical needs, several antibacterial and non-cytotoxic hydrogels based on poly(vinyl alcohol), chitosan and alginate with electrochemically synthesized silver nanoparticles (AgNPs) have also been developed by our group [40–43]. But, the advantage of presented poly(vinyl alcohol) hydrogel with embedded gentamicin is to avoid any non-desirable effect of silver nanoparticles to cell membrane in the live organism, as well as to enable the long-term controlled release of embedded gentamicin in the wound locally, without systemic antibiotic administration. Gentamicin release experimental profiles verified the initial burst release effect of gentamicin from the hydrogel, followed by slow release of gentamicin in a later time period. The novel General fractional derivative model was proposed to predict the release of gentamicin in poly(vinyl alcohol)/gentamicin hydrogel and proved excellent agreement between measured and calculated data, while gentamicin diffusion coefficient value was calculated to be in the expected interval for antibiotic release from hydrogel matrix, meaning that this model can be applied for different wound dressings. Consequently, the model is feasible in real-life situation because it could predict the life time of wound dressing, i.e., the time

Table 1 The measured values of Q_2 and corresponding values of Q_1

t [days]	$Q_{1\ measured} = 1 - Q_{2\ measured}$	$Q_{2\ measured}$
0	1	0
1	0.582	0.418
2	0.402	0.598
4	0.389	0.611
7	0.3884	0.6115
14	0.3880	0.612

Table 2 Confidence intervals for parameters of the model

a	β	λ_1	λ_2	a	b
[0.82,1.25]	[− 1.29, − 0.08]	[− 2.69,1.93]	[5.91,11.65]	[− 0.39,0.26]	[0.0034,0.335]

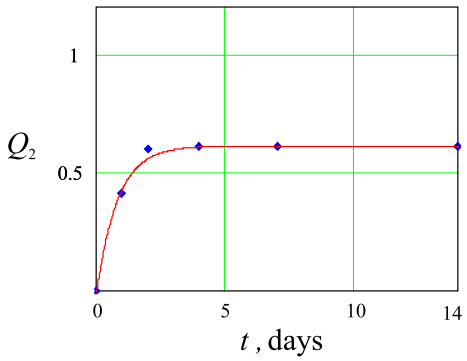

Fig. 4 Increase in concentration of released gentamicin from PVA/Gent hydrogel with time, obtained from (17b) (experimental-points, model-line)

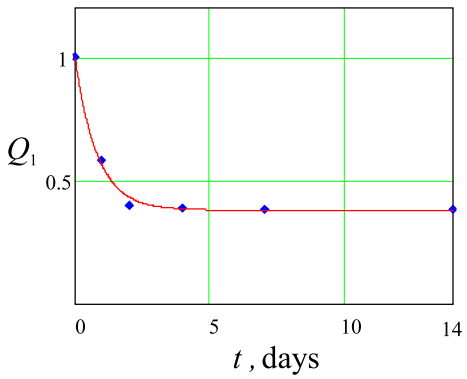

Fig. 5 Decrease in concentration of gentamicin remained in PVA/Gent hydrogel with time, obtained from (18) (experimental-points, model-line)

necessary to replace it, and can be implemented in clinical context.

Finally, we stress that our numerical results show rather large confidence intervals for parameters of the model. This is a consequence of the fact that we have only six measurements and rather large number of parameters, also equal to six. However, since our goal was to demonstrate the model (6) in its generality we did not include the results for $\lambda_1 \neq 0, \lambda_2 = 0, b = 0$ in (17a) that has smaller confidence intervals for parameters, but Z defined by (19b) is larger.

Conclusions

In this work we used General fractional derivative to formulate two compartmental system of pharmacokinetics. The novelty of the model was the use of General fractional derivative to predict the release of gentamicin in poly(vinyl alcohol)/gentamicin hydrogel aimed for wound dressing in medical treatment of deep chronic wounds. The results showed excellent agreement between experimental data and proposed model. Gentamicin release profile verified the initial burst release effect of gentamicin from the hydrogel, i.e., 60% loaded antibiotic was released within first 48 h which could be very useful in preventing biofilm formation, followed by slow release of gentamicin in a later time period.

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Author contributions VMS was responsible for hydrogel preparation and wrote the main manuscript text. MJ performed the numerical analysis. TMA formulated the mathematical model and prepared figures. All authors reviewed the manuscript.

Declarations

Competing interests The authors declare no competing interests.

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