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Gentamicin Release from Hydroxyapatite-based Bioceramic Coating on Titanium

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Abstract: Novel antibacterial bioceramic hydroxyapatite/poly(vinyl alcohol)/chitosan/gentamicin (HAP/PVA/CS/Gent) coating on titanium substrate was successfully produced for bone tissues implants, to enable a drug delivery directly at the infection site and avoid the systemic antibiotic administration in the case of post-operative hospital infections. This study represents novel two compartmental model with General fractional derivative of distributed order used to investigate the release of gentamicin in surrounding tissue. The gentamicin release profile was represented as time dependence of ratio between mass of released gentamicin, determined by high-performance liquid chromatography (HPLC), and initial mass of gentamicin in the coating. It has been proved that proposed a two compartmental model with General fractional derivative of distributed order exhibited excellent agreement between experimental values and calculated values from the model, and enabled the determination of gentamicin diffusion coefficient in entire time period.

Keywords: Coatings, Bioceramics, Hydroxyapatite, Titanium, Gentamicin, Diffusion, Modeling

1. Introduction

Compartmental models are often used in pharmacokinetics to describe the response to drug bolus administration (Copot et al., 2017). Numerous works have proved their applicability for optimal drug delivery assist devices in different medical treatments, e.g. diabetes, cancer, anaesthesia, immune deficiency, leukaemia and hormonal treatment (Churilov et al., 2009; Copot & Ionescu, 2014; Drexler et al., 2011; C. M. Ionescu et al., 2017; Kiss et al., 2013; Kovács et al., 2011; Popović et al., 2015). Fractional-order models are found to be more adequate for compartmental analysis in many cases (Atanackovic et al., 2025; Dokoumetzidis et al., 2010; Dokoumetzidis & MacHeras, 2009; C. Ionescu et al., 2017; Miskovic-Stankovic et al., 2023; Mišković-Stanković et al., 2024, 2025; Mišković-Stanković & Atanackovic, 2024; Miskovic-Stankovic & Atanackovic, 2023; Popović et al., 2010, 2011, 2015; Rajšić et al., 2022; Sopasakis et al., 2018; Verotta, 2010) where fractional calculus (FC) was applied in pharmacokinetics and drug diffusion in biological systems.

The rapid aging of the world's population undoubtedly leads to a growing need for orthopaedic interventions. In order to be suitable for implantation, biomaterials have to meet numerous requirements, including biocompatibility, bioactivity, as well as good mechanical and antibacterial properties (Fiume et al., 2021). Titanium (Ti) is still the most commonly used metallic material in reconstruction surgery

due to its good mechanical properties and biocompatibility, as well as its corrosion resistance (Kaur & Singh, 2019). In order to improve biocompatibility, bioactivity and to prevent bacterial biofilm formation, titanium surface should be modified (Chouirfa et al., 2019; Stepanovska et al., 2020). For metallic implants´ surface modification, hydroxyapatite (HAP) is very often the material of choice due to its similarity to the mineral part of the natural bone tissue. On the other side, HAP is brittle, having poor mechanical strength (Mahanty & Shikha, 2022). Synthetic and/or natural polymers, like poly(vinyl alcohol) (PVA), and chitosan (CS) are often used in production of HAP-based composites with the aim to provide good adhesion and improve the mechanical properties of the coatings (Abdulghani & Mitchell, 2019; Mahanty & Shikha, 2022; Raut et al., 2020).

In the field of orthopaedic and trauma surgery, possible infections of the surgical site can cause serious complications. With the aim to overcome this issue, a great number of antibiotics are applied in the medical treatment of bacterial infections. Sometimes, it is required to apply a high local concentration of antibiotics to prevent the biofilm formation, e.g. after orthopaedic surgery. Significant reduction of colonized bacteria on the bone and implant surfaces (methicillin-sensitive S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA)) could be achieved by employing the antibiotic-coated implants (Masters et al., 2019) since the antibiotic-loaded implants' surface coatings enable a delivery of high concentrations drugs directly at the infection site, reducing the possibility of side effects, which may occur during systemic antibiotic administration.

Due to the numerous advantages, e.g. uniform composition and thickness of the deposited coatings, the possibility of deposition on substrates of complex geometries that can be found in orthopaedics, low degree of environmental pollution, as well as room temperature processing, which is crucial for deposition of bioceramic coatings containing thermo labile antibacterial agents, we have chosen electrophoretic deposition (EPD) for the production of biocomposite coatings (Stevanović, Djošić, Janković, Kojić, et al., 2020; Stevanović, Djošić, Janković, Nešović, et al., 2020; Stevanović et al., 2018, 2021). The drug release behaviour is a major parameter that could influence both antibacterial activity and biocompatibility, therefore antibiotic release measurements are an integral part of the in vitro characterizations of drug-loaded materials.

In this work we made attempt to incorporate gentamicin in hydroxyapatite/poly(vinyl alcohol)/chitosan/gentamicin (HAP/PVA/CS/Gent) coating on titanium aimed for bone tissues implant, in order to enable a drug delivery directly at the infection site and avoid the systemic antibiotic administration. The advantages of HAP/PVA/CS/Gent coating produced by EPD from four-component aqueous suspension are environmentally friendly product consisting of medical approved components deposited in one step without additional fabrication and uniform coating thickness, We employed novel FC model to study the release of gentamicin from HAP/PVA/CS/Gent coating..

2. Materials and Methods

2.1. Materials

Hydroxyapatite powder (particles<200 nm particle size, Sigma-Aldrich), chitosan powder (medium molecular weight 190-310 kDa, deacetylation degree 75-85%, Sigma-Aldrich), poly(vinyl alcohol) (medium molecular weight 89-98 kDa, 99% hydrolyzed, Sigma-Aldrich), and aqueous gentamicin sulphate solution (concentration 50 mg/ml, Sigma-Aldrich) were used. Titanium plates, Ti (99.7% purity, Sigma-Aldrich), were mechanically polished before EPD (grit emery paper) and ultrasonicated (15 min in acetone and 15 min in ethanol).

2.2. Electrophoretic deposition

EPD was performed in aqueous suspension consisting of hydroxyapatite (1.0 wt%), chitosan (0.05 wt%), poly(vinyl alcohol) (0.1 wt%) and gentamicin sulphate (0.1 wt%). Cathodic EPD process was performed on the titanium plate (dimensions 1 cm x 1 cm) using constant voltage method according to the procedure we have published earlier (Stevanović, Djošić, Janković, Nešović, et al., 2020). The coating thickness was 3.1 μm.

2.3. Gentamicin release

For the gentamicin release measurements, the HAP/PVA/CS/Gent coating on titanium 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 (Stevanović et al., 2021)[31].

3. Results and Discussion

3.1. Mathematical model

We shall use General fractional calculus to formulate mathematical model in order to describe release of gentamicin in the experiments described in Section 2.3. We recall some basic notation of the general fractional calculus and then we define a distributed order general fractional derivative. It will be used in two compartmental system to describe the mass exchange.

The basic idea of the General fractional calculus is the definition of a General fractional integral $\boldsymbol{I}^{t}_{(M)}$ and General fractional derivative $\boldsymbol{D}^{t}_{(K)}$ 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 follows the classical definition and reads

$$ {}_0^C D_{(K)}^t f(\tau) = \int_0^t K(t-\tau) f^{(1)}(\tau) d\tau, \quad (2) $$

The kernels in Eq. (1) and Eq. (2) satisfy

$$ M(t), K(t) \in C_{-1,0}(0,\infty), \ \int_0^t M(t-\tau)K(\tau)d\tau = 1, \quad (3) $$

where

$$ C_{a,b}(0,\infty) = \{f(t): \ f(t) = t^p Y(t), \quad t > 0, \\ a < p < b, \quad Y(t) \in C[0,\infty)\}. \quad (4) $$

Note that the Riemann-Liouville kernels (Atanackovic et al., 2014), (Podlubny, 1999)

$$ M(t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)}, \quad K(t) = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}, \quad (5) $$

where $0 < \alpha < 1$ and Γ is the Euler Gamma function, satisfy Eq. (1) and Eq. (3) and that, in this case Eq. $(1)_1$ and Eq. (2) become fractional integral and fractional Caputo derivative in the usual sense.

There are many kernels that satisfy Eq. (2) and Eq. (3) as shown in (Tarasov, 2021). To study the mass exchange in pharmacokinetics, in our earlier paper (Miskovic-Stankovic et al., 2023) we used Eq. (5), while in (Miskovic-Stankovic et al., 2023) the following kernels are used

$$ M(s) = \lambda^\alpha + \frac{\alpha}{\Gamma(1-\alpha)} \int_t^\infty \frac{exp(-\lambda u)}{u^{1+\alpha}} du, \\ K(t) = \frac{t^{\alpha-1}}{\Gamma(\alpha)} exp(-\lambda t). \quad (6) $$

where $\lambda = const. \geq 0$. Therefore, the general fractional derivative of the Caputo type that we use as a basis for our analysis is

$$ {}_0^C D^{\alpha,\lambda} f(t) = {}^C D_{(K)}^t f[\tau] \\ = \frac{1}{\Gamma(1-\alpha)} \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{exp(-\lambda\tau)}{\tau^\alpha} f^{(1)}(t-\tau) d\tau, \quad (7) $$

where $0 \leq \alpha \leq 1$. The proof that *M* and *K* used in Eq. (6) satisfy Eq. (3) is given in (Samko & Cardoso, 2003). Using Eq. (7) we define *distributed* order General fractional derivative as

$$ {}_0^C DC_t^{\alpha,\lambda} f(t) = \int_0^1 \varphi(\alpha) {}_0^C D_t^\alpha f(t) d\alpha. \quad (8) $$

In Eq. (8) the weight function $\varphi(\alpha)$, $\alpha \in [0,1]$ denote a weighting function that has must have dimension $dim\, \varphi(\alpha) = [dim\, t]^\alpha$ to obtain dimensional homogeneity of Eq. (8). The simplest form of such function, that we shall use in Eq. (8) is $\varphi(\alpha) = \psi(\alpha) a^\alpha$ where a is the characteristic time and $\psi(\alpha), \alpha \in [0,1]$ is a dimensionless function. In the analysis that follows we take $\psi(\alpha) = 1$. Then Eq. (8) becomes

$$ {}_0^C D_t^{\alpha,\lambda} f(t) = \int_0^1 a^\alpha {}_0^C D_t^\alpha f(t) d\alpha. \quad (9) $$

We shall use Eq. (9) to define kinetics of a two compartmental model of pharmacokinetics (Fig. 1). Recall that the classical two compartmental model of pharmacokinetics, with different volumes of compartments is described as, see (Rescigno, 2003)

$$ \frac{1}{V_1} \frac{dm_1}{dt} = -k \left(\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}\right) + f_1(t), \\ \frac{1}{V_2} \frac{dm_2}{dt} = k \left(\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}\right) + f_2(t), \quad (10) $$

where m_i, $i = 1,2$ is the gentamicin mass in 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. The dimension of k is [cm^2/s]. Also, we assume that in compartments **1** and **2** we have supply $f_i, i = 1,2$. The Eq. (10) may be written in the form when on the left and side we have $\frac{dm1}{dt}$ and $\frac{dm2}{dt}$ instead of $\frac{1}{V_1}\frac{dm1}{dt}$ and $\frac{1}{V_2}\frac{dm_2}{dt}$, see (Rescigno, 2003). In this case coefficient k may be different in each of Eq. (10) and they represent transport activity of the substances that can be approximated by concentration and the rate of change of concentration. We propose the generalization of Eq. (10) in which we replace first derivatives on the left-hand side by Distributed order general fractional derivative Eq. (9). Then we obtain

$$ \frac{1}{V_1} b^{\beta C} D^{\beta,\Lambda} m_1(t) + \frac{1}{V_1} {}^C D^{\alpha,\lambda} m_1(t) \\ = -k \left(\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}\right) + f_1(t), \\ \frac{1}{V_2} b^{\beta C} {}_0 D_t^{\beta,\Lambda} m_2(t) + \frac{1}{V_2} {}_0^{\bar{C}} D_t^{\alpha,\lambda} m_2(t) \\ = k \left(\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}\right) + f_2(t), \quad (11) $$

where, $0 \leq \alpha, \beta \leq 1$ and $m_i, V_i, i = 1,2$ denote the mass of drug and volume of the compartment i, respectively. The derivatives ${}_0^C D_t^{\beta,\Lambda}(\cdot)$ and ${}_0^C D_t^{\alpha,\lambda}(\cdot)$ is given by Eq. (7) and Eq. (9) and a and b are constants having the dimension of time to the exponent $-1+\alpha$ and $-1+\beta$, respectively. Note that in (Miskovic-Stankovic et al., 2023) we used model of the type Eq. (11) with weighting functions in Eq. (8) taken as

$$ \varphi(\alpha) = a\delta(\alpha - \alpha_1), \quad (12) $$

where $\alpha_1$is a constant, and δ denotes Dirac distribution.

We formulate now a mathematical model for the gentamicin release in antibacterial hydroxyapatite-based bioceramic coating on titanium surface. The physical system is shown in Fig. 1a, while the corresponding two compartmental model is shown in Fig. 1b.

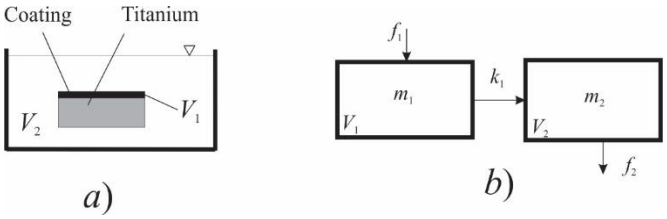

Figure 1. Two compartmental simplified model of gentamicin release: a) physical system, b) mathematical model.

We write the system Eq. (11) is in expanded form as

$$\frac{1}{V_1} b^{\beta} \frac{1}{\Gamma(1-\beta)} \int_0^t \frac{exp(-\Lambda\tau)}{\tau^{\beta}} m_1^{(1)}(t-\tau)d\tau + \frac{1}{V_1}\int_0^1 a^{\alpha} [\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{exp(-\lambda\tau)}{\tau^{\alpha}} m_1^{(1)}(t-\tau)d\tau]\, d\alpha = -k_1 (\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}) + f_1(t),$$

$$\frac{1}{V_2} b^{\beta} \frac{1}{\Gamma(1-\beta)} \int_0^t \frac{exp(-\Lambda\tau)}{\tau^{\beta}} m^{(1)}(t-\tau)d\tau + \frac{1}{V_2}\int_0^1 a^{\alpha} [\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{exp(-\lambda\tau)}{\tau^{\alpha}} m_2^{(1)}(t-\tau)d\tau]\, d\alpha = k_2 (\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}) + f_2(t).$$

In the analysis that follows we shall take $k_1 V_1 = k_2 V_2 = k$ to preserve the mass conservation equation that. Also we multiply Eq. $(11)_{1,2}$ with V_1 and V_2 respectively, to obtain the form of presented in (Rescigno, 2003).

$$b^{\beta} \frac{1}{\Gamma(1-\beta)} \int_0^t \frac{exp(-\Lambda\tau)}{\tau^{\beta}} m_1^{(1)}(t-\tau)d\tau + \frac{1}{V_1}\int_0^1 a^{\alpha} [\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{exp(-\lambda\tau)}{\tau^{\alpha}} m_1^{(1)}(t-\tau)d\tau]\, d\alpha = -k (\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}) + f_1(t),$$

$$\frac{1}{V_2} b^{\beta} \frac{1}{\Gamma(1-\beta)} \int_0^t \frac{exp(-\Lambda\tau)}{\tau^{\beta}} m^{(1)}(t-\tau)d\tau + \frac{1}{V_2}\int_0^1 a^{\alpha} [\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{exp(-\lambda\tau)}{\tau^{\alpha}} m_2^{(1)}(t-\tau)d\tau]\, d\alpha = k_2 (\frac{m_1(t)}{V_1} - \frac{m_2(t)}{V_2}) + f_2(t). \quad (13)$$

To Eq. (13) we adjoin the following initial conditions that are used in our experiments

$$m_1(0) = m_0, \quad m_2(0) = 0. \quad (14)$$

System Eq. (13) represents the generalized two compartmental model with GFD that we shall use in this work.

3.2. Solution of the system Eq. (13) and Eq. (14)

We use the Laplace transform method in solving Eq. (13) and Eq. (14). The Laplace transform of an exponentially bounded function f is defined as

$$L[f(t)](s) = f(s) = \int_0^{\infty} f(t)\, exp(-st)dt. \quad (15)$$

Where $s \in C$ is a complex number. Since

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

where $0 \leq \alpha \leq 1$ and $L[m_1^{(1)}](s) = s\hat{m}_1(s) - m_1(0)$, we have

$$L[\frac{1}{\Gamma(1-\alpha)}\int_0^t \frac{exp(-\lambda u)}{u_s^{\alpha}} m_1^{(1)}(t-u)du] = \frac{1}{(s+\lambda)^{1-\alpha}} s\hat{m}_1(s) - \frac{1}{(s+\lambda)^{1-\alpha}} m_1(0) \quad (16)$$

Applying the Laplace transform to Eq. (7) and using Eq. (8) it follows

$$L[{}_0^C D_t^{\alpha,\lambda} m_1(t)](s) = a\int_0^1 [\frac{s}{[a(s+\lambda)]^{1-\alpha}} \hat{m}_1(s) - \frac{1}{[a(s+\lambda)]^{1-\alpha}} m_1(0)]\, d\alpha.$$

Let

$$K(s) = \int_0^1 \frac{d\alpha}{[a(s+\lambda)]^{1-\alpha}} = \frac{1-[a(s+\lambda)]^{-1}}{ln[a(s+\lambda)]} = \frac{a(s+\lambda)-1}{a(s+\lambda)\, ln[a(s+\lambda)]}, \quad (17)$$

so that

$$L[{}_0^C D_t^{\alpha,\lambda} m_1(t)](s) = aK(s)(s\hat{m}_1(s) - m_1(0)). \quad (18)$$

We now apply Laplace transform to Eq. (13) and Eq. (14) and obtain

$$[\frac{b}{[b(s+\Lambda)]^{1-\beta}} + aK(s)]\, [s\hat{m}_1(s) - m_1(0)] = -k (\frac{\hat{m}_1(s)}{V_1} - \frac{\hat{m}_2(s)}{V_2}) + f_1(s),$$

$$[\frac{b}{[b(s+\Lambda)]^{1-\beta}} + aK(s)]\, s\hat{m}_2(s) = k (\frac{\hat{m}_1(s)}{V_1} - \frac{\hat{m}_2(s)}{V_2}) + f_2(s), \quad (19)$$

By solving Eq. (19) we obtain the Laplace transform of m_1 and m_2 as

$$\hat{m}_2(s) = \frac{1}{V_1} \frac{k(m_1(0) + \frac{f_1(s)+f_2(s)}{aK(s)})}{s[\frac{bs}{[b(s+\Lambda)]^{1-\beta}} + asK(s) + k(\frac{1}{V_1} + \frac{1}{V_2})]}, \quad (20)$$

and

$$\hat{m}_1(s) = \frac{m_1(0)}{s} - \frac{f_1(s)+f_2(s)}{s[\frac{b}{[b(s+\Lambda)]^{1-\beta}} + aK(s)]} - \frac{1}{V_1} \times \frac{k(m_1(0) + \frac{f_1(s)+f_2(s)}{aK(s)})}{s[\frac{bs}{[b(s+\Lambda)]^{1-\beta}} + asK(s) + k(\frac{1}{V_1} + \frac{1}{V_2})]}. \quad (21)$$

Note that from Eq. (19) we obtain the following conservation of mass law

$$m_1(t) + m_2(t) = m_1(0) + L^{-1}[\frac{f_1(s)+f_2(s)}{aK(s)}]. \quad (22)$$

In the special case when $f_1(t) = f_2(t) = 0$ i.e., there is no addition/loss of the mass in the compartments we have, as expected, conservation of mass law

$$m_1(t) + m_2(t) = m_1(0).$$

By using the Initial and Final Value Theorems (Brezinski, 2007), for the case $f_1(t) = f_2(t) = 0$ the following estimates are obtained from Eq. (20) and Eq. (21)

$$\lim_{s\to\infty} s\, \hat{m}_1(s) = m_1(0),$$

$$\lim_{s\to 0} s\, \hat{m}_1(s) = m(\infty) = m_1(0)\, \frac{V_1}{V_1 + V_2},$$

$$\lim_{s\to 0} s\hat{m}_2(s) = m_2(\infty) = m_1(0)\frac{V_2}{V_1+V_2}. \quad (23)$$

Therefore, limiting concentration in each compartment

$$c_i = \frac{m_i}{V_i}, i = 1,2,$$

are equal

$$c_1(\infty) = c_2(\infty) = \frac{m_1(\infty)}{V_1} = \frac{m_2(\infty)}{V_2} = \frac{m_1(0)}{V_1+V_2},$$

in accordance with Fick's model of diffusion.

3.3. Results

In this Section we present the results of numerical inversion of Eq. (20). Since in our experiments we have

$$f_1(t) = f_2(t) = 0,$$

so that

$$\hat{m_2}(s) = \frac{1}{V_1 s[\frac{bs}{[b(s+\Lambda)]^{1-\beta}} + asK(s) + k(\frac{1}{V_1}+\frac{1}{V_2})]}. \quad (24)$$

The *central equation of this work expressing the mass* of the released gentamicin is determined by Laplace transform inversion formula from the Eq. (24)

$$m_2(t) = m_1(0)\frac{k}{V_1}\frac{1}{2\pi} \times \int_{x_0-i\infty}^{x_0+i\infty} exp(x_0+ip)t\,(x_0+ip) \times \frac{b(x_0+ip)}{[b(x_0+ip+\lambda_1)]^{1-\beta}} + a(x_0+ip)K((x_0+ip)) + k(\frac{1}{V_1}+\frac{1}{V_2})]dp, \quad (25)$$

where $i = \sqrt{-1}$ is the imaginary unit and x_0 chosen so that all zeros in the denominator of Eq. (25) are with the real part less than x_0. In the equation Eq. (25) it is necessary that $x_0 > 0$.

Parameters in the model $a, k, \lambda, b, \beta, \Lambda$ are determined by least square method, i.e., the sum squared residuals Z between experimental and calculated from the model values of m_2 at five measured points, is *minimized*, that is

$$Z(a,k,\lambda,b,\beta,\Lambda) = \sum_{j=1}^{5}(m_2(t_j) - m_{2,\text{experimental}}(t_j))^2, (26)$$

where $m_2(t_j)$ are the values determined from Eq. (25) and $m_{2,\text{experimentaal}}(t_j)$ are the measured values at time instant t_j. The measured values are given in the Table 1.

The experimental values of mass m_2 are divided by initial, total mass of gentamicin that in our experiments is 163.52 mg. Thus, we define relative mass of the gentamicin in hydrogel, $m_{1,\text{rel}}$ and relative mass of released gentamicin in deionized water surrounding coating, $m_{2,\text{rel}}$ as

$$m_{1,\text{rel}}(t) = \frac{m_1(t)}{m_1(0)}, \quad m_{2,\text{rel}}(t) = \frac{m_2(t)}{m_1(0)}.$$

The values of $m_{1,\text{rel}}$ and $m_{2,\text{rel}}$ are represented in Table 1.

Table 1 Experimental values of $m_{2,\text{rel,exp}}$ and calculated according to Eq. (25) values of $m_{2,\text{rel}}$

***t*, days**	$m_{2,\text{rel,exp}}$	$m_{2,\text{rel}}$
0	0	0.00
1	0.22	0.222
2	0.30	0.287
7	0.32	0.316
14	0.31	0.317
21	0.31	0.318

The parameters in the model $(a^*, k^*, \lambda^*, b^*, \beta^*, \Lambda^*)$ are determined from the condition

$$\min_{(a,k,\lambda,b,\beta,\Lambda)} Z(a,k,\lambda,b,\beta,\Lambda) = Z(a^*,k^*,\lambda^*,b^*,\beta^*,\Lambda^*). \quad (27)$$

In the minimization process we considered restrictions

$$a > 0,\ b > 0,\ k > 0,$$

since a and b have meaning of relaxation times and k is connected with diffusion coefficient. Also,

$$\lambda \geq 0, \Lambda \geq 0,$$

as this is required by the definition of General fractional derivative. Finally, since we are dealing with Fickian diffusion, the function $m_2(t), t \geq 0$ must be increasing. Since fractional derivative Eq. (7) for $\beta > 0$ has oscillatory, we must have

$$0 \leq \beta \leq 1.$$

Fitting parameters for GFD model of gentamicin release from HAP/PVA/CS/Gent coating are presented in Table 2.

Table 2. Fitting parameters for different models of gentamicin release from HAP/PVA/CS/Gent coating according to Eq. (27)

Parametar	GFD model
a	$7.7\text{x}10^{-5}$
b	0.1697
λ	$9.5\text{x}10^{-4}$
Λ	0.170
k (cm^3/day)	$2.04\text{x}10^{-5}$
D (cm^2 s^{-1})	$7.63\text{x}10^{-7}$
β	1
Z	0.000300

Finally, we determined the diffusion coefficient of gentamicin, *D*, from coefficient *k*. In Eq. (13) on the left-hand side, for Fick's interpretation of coefficient *k*, we used $k_1V_1 = k_2V_2 = k$, so $\overline{V_1} = k_1$. Diffusion coefficient *D*, may be then determined from k_1:

$$D = \frac{k/V_1}{A\times 24\times 3600} = 7.634 \times 10^{-7}\ \text{cm}^2/\text{s}. \qquad (28)$$

where A=1 cm^2 is the coating surface area. This value was calculated from our novel GFD model for entire time period of gentamicin release. The corresponding value of the square residual is $Z(a^*, k^*, \lambda^*, b^*, \beta^*, \Lambda^*) = 0.000300$.

4. Conclusion

The main results of our work are summarized as:

1. Novel antibacterial bioceramic HAP/PVA/CS/Gent coating on Ti substrate was successfully produced for bone tissues implants, in order to enable a drug delivery directly at the infection site and avoid the systemic antibiotic administration in the case of post-operative hospital infections.
2. Gentamicin release study indicated "burst" release effect in the first 48 h, with ~ 30% of total gentamicin released from the HAP/PVA/CS/Gent coating which is beneficial for the blockage of biofilm formation, followed by slow and steady release in the later time period.
3. We formulated novel two compartmental mathematical model to describe the release of gentamicin. It is based on General fractional derivative of distributed order and generalizes earlier models with fractional derivatives.
4. The experimental values corresponded very well with the model calculated values. In addition, we determined the value of the diffusion coefficient of gentamicin based on the model approximating the entire time period of the release.

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Otpuštanje gentamicina iz biokeramičke prevlake na bazi hidroksiapatita na titanu

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Apstrakt: Nova antibakterijska biokeramička hidroksiapatit/poli(vinil-alkohol)/hitozan/gentamicin (HAP/PVA/CS/Gent) prevlaka na titanu je uspešno dobijena za primenu u implantatima koštanog tkiva, da bi omogućila isporuku lekova direktno na mestu infekcije i da bi se izbegla sistemska administracija antibiotika u slučajevima postoperativne bolničke infekcije. Ovaj rad predstavlja novi dvokompartmentski model sa Generalnim frakcionim izvodom raspoređenog reda koji je korišćen za ispitivanje otpuštanja gentamicina u okolinu. Profil otpuštanja gentamicina je prikazan kao vremenska zavisnost odnosa mase otpuštenog gentamicina, odredjenog tečnom hromatografijom visoke performancije (HPLC), i početne mase gentamicina u prevlaci. Dokazano je da predloženi dvokompartmentski model sa Generalnim frakcionim izvodom raspoređenog reda pokazuje odlično slaganje sa eksperimentalnim vrednostima, i omogućava određivanje koeficijenta difuzije gentamicina u celom vremenskom periodu.

Ključne reči: Prevlake, biokeramika, hidroksiapatit, titan, gentamicin, difuzija, modelovanje