An Approach to Modeling Protein Release from Lipid Implants

Rumiana Blagoeva*, Assen Nedev

Institute of Mechanics, Bulgarian Academy of Science
4 Acad. G. Bonchev Str., 1113 Sofia, Bulgaria
E-mail: rumiana.blagoeva@abv.bg

**Corresponding author*

Received: February 04, 2011 **Accepted: March 22, 2011**

Published: May 20, 2011

Abstract: *A new approach to modeling protein release kinetics from lipid implants is presented. The recently offered model for prediction of protein transfer out of the lipid implant simultaneously with two water soluble excipients release is improved. Appropriate expressions for concentrations dependent diffusion coefficients are introduced taking into account the initial and current implant porosity. A numerical scheme for solving the arisen highly nonlinear model problem is also developed on the basis of Finite Element (FE) domain approximation and time difference scheme. The new approach and created software are validated using available experimental data for protein release, under different initial content of the drug release modifier. A good correspondence is obtained and a numerical simulation of the effect of the initial implant porosity on drug release profiles is performed.*

Keywords: *Protein release, Diffusion, Lipid implants, Porosity change, FE approach, Difference scheme.*

Introduction

Sustained release systems for pharmaceutical proteins can be regarded as innovative pharmaco-therapies, since they offer the possibility to deliver this type of bioactive agents to their target sites reducing the administration frequency and enhancing their *in vivo* stability. Non-degradable lipid implants particularly, are reliable alternative of parenteral drug delivery systems for protein controlled release. These systems are based on the embedding of protein ingredients into a lipid matrix [4-8].

Recently a mathematical model for description of the simultaneous diffusion of multiple compounds (drug-interferon α-2a (INF-α) and water soluble excipients: release modifier – polyethylene glycol (PEG); drug stabilizer – hydroxypropyl-β-cyclodextrin (HP-β-CD)) in tristearin based implants was presented introducing the effect of matrix porosity [8]. According to the authors, "the increase in porosity at a particular position at a particular time point is calculated based on the knowledge of INF-α, PEG and HP-β-CD lost at this position at this time point", but there is a lack of mathematical description of the porosity concentrations dependence in the paper. The proposed linear dependence between the diffusivity of each compound and the current porosity (introducing a critical diffusion parameter as a linear coefficient) supposes in advance that the values of the diffusivities should be different (much smaller, because the porosity varies from 2% up to 25%, for example [5]) from the corresponding diffusion parameters. The estimation of the drug (INF-α) diffusion parameter in [8] is approximately equal to the value of the drug diffusivity used for explanation of one and the same experimental data with the proposed model and the classical diffusion theory, respectively [4].

The aim of the present study is to improve the above model offering a new approach to a more accurate and reliable quantitative prediction of protein drug release from lipid implants. Explicit mathematical expressions for concentrations dependent diffusion coefficients of different compounds are presented within each considered element of the domain, taking into account the current porosity increasing in time. A FE approach to solving the arisen highly non-linear model problem is also introduced, and noncommercial software is created. The developed model is validated using experimental data for INF-α/HP-β-CD and PEG release, under different initial PEG loading. The INF-α critical diffusion parameter is evaluated for three levels of PEG content fitting the new approach with experimental data. Numerical simulation of the effect of initial implant porosity on the protein drug release kinetics is performed.

Statement of the model problem

The release of IFN-α/HP-β-CD from a cylindrical lipid implant of radius R and height $2H$, containing PEG ($10\% \div 40\%$), is considered. It is assumed that: (1) the controlling mechanism of protein release kinetics is the simultaneous diffusion of IFN-α, HP-β-CD and PEG upon contact with biological fluid or water; (2) the initially slight porosity of the lipid matrix steadily increases due to IFN-α/HP-β-CD and PEG release from the implant; (3) the diffusion coefficients of the dissolved ingredients within the implant are directly related to the matrix porosity which is dependent on their concentrations; (4) water penetration into the implant (much faster than the subsequent protein diffusion), as well as matrix swelling and dissolution, are negligible; (5) full liberation of each compound is realized; (6) perfect sink conditions are maintained [8].

The model equations describing the simultaneous IFN-α, HP-β-CD and PEG diffusion in a cylindrical implant corresponding to the domain $\Omega \subset R^2$ (a quarter of the axial cross-section due to the symmetry) are as follows:

$$\frac{\partial c_1}{\partial t} = div(D_{1,cr}\varepsilon(c_1,c_2,c_3)gradc_1) \text{ in } \Omega\times(0, t_f], \quad (1)$$

$$\frac{\partial c_2}{\partial t} = div(D_{2,cr}\varepsilon(c_1,c_2,c_3)gradc_2) \text{ in } \Omega\times(0, t_f], \quad (2)$$

$$\frac{\partial c_3}{\partial t} = div(D_{3,cr}\varepsilon(c_1,c_2,c_3)gradc_3) \text{ in } \Omega\times(0, t_f], \quad (3)$$

where $c_1 = C_1 / c_{1in}$, $c_2 = C_2 / c_{2in}$ and $c_3 = C_3 / c_{3in}$ are the dimensionless concentrations of IFN-α, HP-β-CD and PEG in respect to the corresponding initial concentrations c_{1in}, c_{2in} and c_{3in}; $D_{1,cr}$, $D_{2,cr}$, $D_{3,cr}$ and $\varepsilon(c_1, c_2, c_3)$ are the character diffusion constants and concentrations dependent implant porosity; t and t_f are the time and the final moment under consideration.

The following relations concerning the effect of increasing porosity can be presented according to the model assumptions (2) and (3):

$$\bar{\varepsilon} = \frac{\bar{V}_{geom} - \bar{V}_{true}}{\bar{V}_{geom}}, \quad (4)$$

$$\bar{\varepsilon} - \varepsilon_o = \frac{\bar{V}_{true}(0) - \bar{V}_{true}(t)}{\bar{V}_{geom}} = \sum_{k=1}^{3} \frac{\Delta\bar{M}_k(t)}{\rho_k \bar{V}_{geom}} = \sum_{k=1}^{3} \frac{c_{kin} - \bar{C}_k(t)}{\rho_k} = \sum_{k=1}^{3} \frac{c_{kin}(1-\bar{c}_k(t))}{\rho_k}, \quad (5)$$

where $\overline{V}_{geom}$ and $\overline{V}_{true}$ are an effective volume connected with a representative sub domain of Ω which is assumed not to be changed in time and the corresponding volume not containing pore space (decreasing in time); $\overline{\varepsilon}$, $\varepsilon_0, \rho_1, \rho_2, \rho_3$ are the considered sub domain porosity, the initial implant porosity and the density of IFN-α, HP-β-CD and PEG respectively; $\Delta\overline{M}_k$ and $\overline{c}_k(t) = \dfrac{\overline{C}_k(t)}{c_{kin}}$ are the decrease of the mass of k^{th} diffusing compound in the period (0, t) within the considered domain and the corresponding average current dimensionless concentration.

For our future considerations the current porosity is referred to each discrete element of Ω as a function of the average element concentrations as follows:

$$\overline{\varepsilon}(c_1, c_2, c_3) = \varepsilon_0 + \frac{c_{1in}}{\rho_1}(1-\overline{c}_1) + \frac{c_{2in}}{\rho_2}(1-\overline{c}_2) + \frac{c_{3in}}{\rho_3}(1-\overline{c}_3), \tag{6}$$

The above equations are posed under the following initial and boundary conditions:

$$c_1(x, y, 0) = 1, \quad 0 \le x \le R, \quad 0 \le y \le H \tag{7}$$

$$c_2(x, y, 0) = 1, \quad 0 \le x \le R, \quad 0 \le y \le H \tag{8}$$

$$c_3(x, y, 0) = 1, \quad 0 \le x \le R, \quad 0 \le y \le H \tag{9}$$

$$c_1(x, y, t) = 0, \quad 0 < t \le t_f, \; x = R, \; 0 \le y \le H \text{ or } 0 \le x \le R, \; y = H \tag{10}$$

$$c_2(x, y, t) = 0, \quad 0 < t \le t_f, \; x = R, \; 0 \le y \le H \text{ or } 0 \le x \le R, \; y = H \tag{11}$$

$$c_3(x, y, t) = 0, \quad 0 < t \le t_f, \; x = R, \; 0 \le y \le H \text{ or } 0 \le x \le R, \; y = H \tag{12}$$

The fractional drug release of the three ingredients is expressed as follows:

$$R_i(t) = 1 - \frac{1}{S}\int_{\Omega} c_i dv, \quad i = 1, 2, 3, \tag{13}$$

where S is the area of the axial cross-sectional domain Ω.

Finite element approach to solving the model problem

The numerical solution of the nonlinear initial boundary value problem (1-10) is sought in a FE form:

$$\tilde{c}_k(x, y, t) = \sum_{p=1}^{M} N_p(x, y) c_{kp}(t) \quad \text{or} \quad \tilde{c}_k(x, y, t) = \mathbf{C}_k^T(t)\mathbf{N}(x, y), \; k = 1, 2, 3, \tag{14}$$

where N_p, $p = 1, \ldots, M$ are the shape interpolation functions corresponding to the current FE discretization of the domain Ω, and c_{1p}, c_{2p}, c_{3p}, $p = 1, \ldots, M$ are the nodal values of the water and drug concentrations, respectively; $\mathbf{C}_1, \mathbf{C}_2, \mathbf{C}_3, \mathbf{N}$ are vectors with elements $c_{1p}, c_{2p}, c_{3p}, N_p$. The upper notation $(\cdot)^{\mathrm{T}}$ means a vector transposition.

Applying the semi-discrete Galerkin method to equations (1)-(3), as it is done in [1, 2], the equivalent initial matrix problem for the vector functions $\mathbf{C}_1, \mathbf{C}_2, \mathbf{C}_3$ is obtained:

$$\frac{d[\mathbf{CM}\,\mathbf{C}_1]}{dt} + \mathbf{ST1}\mathbf{C}_1 = \mathbf{0} \tag{15}$$

$$\frac{d[\mathbf{CM}\,\mathbf{C}_2]}{dt} + \mathbf{ST2}\,\mathbf{C}_2 = \mathbf{0} \tag{16}$$

$$\frac{d[\mathbf{CM}\,\mathbf{C}_3]}{dt} + \mathbf{ST2}\,\mathbf{C}_3 = \mathbf{0} \tag{17}$$

$$\mathbf{C}_1 = \mathbf{I}, \quad \mathbf{C}_2 = \mathbf{I}, \quad \mathbf{C}_3 = \mathbf{I}, \tag{18}$$

where **CM**, **ST1**, **ST2**, **ST3** are FE matrices generated under the chosen FE mesh as follows:

$$\mathbf{CM} = \int_{\Omega_t} \mathbf{NN}dv, \qquad \mathbf{ST1} = \int_{\Omega_t} D_{1cr}\,\bar{\varepsilon}\,(\mathbf{C}_1,\mathbf{C}_2,\mathbf{C}_3)\nabla\mathbf{N}\nabla\mathbf{N}dv,$$
$$\mathbf{ST2} = \int_{\Omega_t} D_{2cr}\,\bar{\varepsilon}(\mathbf{C}_1,\mathbf{C}_2,\mathbf{C}_3)\nabla\mathbf{N}\nabla\mathbf{N}dv, \quad \mathbf{ST3} = \int_{\Omega_t} D_{3cr}\,\bar{\varepsilon}\,(\mathbf{C}_1,\mathbf{C}_2,\mathbf{C}_3)\nabla\mathbf{N}\nabla\mathbf{N}dv \tag{19}$$

The unit vector is denoted with **I**.

The following non-linear matrix equations are obtained after integration of (13)-(15) by using a two-point time difference scheme:

$$\begin{aligned} \mathbf{A1}_{n+1}\,\mathbf{C}_1^{n+1} &= \mathbf{B1}_n\,\mathbf{C}_1^n \\ \mathbf{A2}_{n+1}\,\mathbf{C}_2^{n+1} &= \mathbf{B2}_n\,\mathbf{C}_2^n, \\ \mathbf{A3}_{n+1}\,\mathbf{C}_2^{n+1} &= \mathbf{B3}_n\,\mathbf{C}_3^n \end{aligned} \tag{20}$$

where
$$\begin{aligned} \mathbf{A1}_{n+1} &= \mathbf{CM} + 0.5\Delta_{n+1}\mathbf{ST1}_{n+1}, \quad \mathbf{B1}_n = \mathbf{CM} - 0.5\Delta_{n+1}\mathbf{ST1}_n \\ \mathbf{A2}_{n+1} &= \mathbf{CM} + 0.5\Delta_{n+1}\mathbf{ST2}_{n+1}, \quad \mathbf{B2}_n = \mathbf{CM} - 0.5\Delta_{n+1}\mathbf{ST2}_n \\ \mathbf{A3}_{n+1} &= \mathbf{CM} + 0.5\Delta_{n+1}\mathbf{ST3}_{n+1}, \quad \mathbf{B3}_n = \mathbf{CM} - 0.5\Delta_{n+1}\mathbf{ST3}_n \end{aligned}$$

The lower index of the FE matrices and the upper one of the vectors corresponds to the considered time level under the introduced time difference mesh.

In order to avoid equations nonlinearity, the following predictor-corrector scheme is proposed:

$$\begin{aligned} \mathbf{A1}_n\,\tilde{\mathbf{C}}_1^{n+1} &= \mathbf{B1}_n\,\mathbf{C}_1^n + \mathbf{O}(\Delta_{n+1}^2) \\ \mathbf{A2}_n\,\tilde{\mathbf{C}}_2^{n+1} &= \mathbf{B2}_n\,\mathbf{C}_2^n + \mathbf{O}(\Delta_{n+1}^2) \\ \mathbf{A3}_n\,\tilde{\mathbf{C}}_3^{n+1} &= \mathbf{B3}_n\,\mathbf{C}_3^n + \mathbf{O}(\Delta_{n+1}^2) \end{aligned} \tag{21}$$

$$\begin{aligned} \mathbf{A1}_{n+1}^*\,\mathbf{C}_1^{n+1} &= \mathbf{B1}_n\,\mathbf{C}_1^n + \mathbf{O}(\Delta_{n+1}^3) \\ \mathbf{A2}_{n+1}^*\,\mathbf{C}_2^{n+1} &= \mathbf{B2}_n\,\mathbf{C}_2^n + \mathbf{O}(\Delta_{n+1}^3) \\ \mathbf{A3}_{n+1}^*\,\mathbf{C}_3^{n+1} &= \mathbf{B3}_n\,\mathbf{C}_3^n + \mathbf{O}(\Delta_{n+1}^3), \end{aligned} \tag{22}$$

where $\mathbf{A1}_{n+1}^*$, $\mathbf{A2}_{n+1}^*$, $\mathbf{A3}_{n+1}^*$ are evaluated at the obtained from (21) predictor solutions $\tilde{\mathbf{C}}_1^{n+1}$, $\tilde{\mathbf{C}}_2^{n+1}$, $\tilde{\mathbf{C}}_3^{n+1}$. The notation $\mathbf{O}(\Delta_{n+1}^3)$ means a second order accuracy of the numerical scheme.

The scheme correctness is investigated and the following sufficient condition for its initial stability is derived:

$$\tilde{\Delta}_{n+1} \le \frac{1}{\max(1, D_{2cr}/D_{1cr}, D_{3cr}/D_{1cr})\max(c_{1in}/\rho_1, c_{2in}/\rho_2, c_{3in}/\rho_3)}, \tag{23}$$

where $\widetilde{\Delta}_{n+1}$ is the dimensionless time step under the introduced dimensionless variables $T = \frac{tD_{1cr}}{R^2}$, $X = \frac{x}{R}$, $Y = \frac{y}{R}$.

Numerical results

In order to validate the proposed approach (including the explicit relations between the current porosity and FE concentrations as well as the numerical scheme and noncommercial program) two numerical examples for the release of IFN-α/ HP-β-CD (1:3) and PEG from cylindrical tristearin-based implants with sizes of R = 0.25 cm and $2H$ = 0.23 cm and weight 50mg are performed. The real time step used when calculating is approximately 14 minutes, which satisfies the initial stability condition (23).

Example 1. The drug (INF-α) diffusion parameter is evaluated for three different levels of initial PEG content, fitting the model with available experimental data [4, 8] under $\varepsilon_0 = 0.02$ [5], $D_{2cr} = 1.1\times10^{-7}\ \mathrm{cm^2\cdot s^{-1}}$, $D_{3cr} = 1.7\times10^{-7}\ \mathrm{cm^2\cdot s^{-1}}$, $c_{1in} = 0.028\ \mathrm{g\cdot cm^{-3}}$, $c_{2in} = 0.084\,\mathrm{g\cdot cm^{-3}}$, $c_{3in} = 0.056\ \mathrm{g\cdot cm^{-3}}, 0.112\ \mathrm{g\cdot cm^{-3}}, 0.224\ \mathrm{g\cdot cm^{-3}}$ for 5%, 10%, 20% PEG, respectively [8], assuming the value of the average protein density 1.4 g·cm^{-3} [3]. The obtained values of D_{1cr} are $1.4\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$, $4.5\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$ and $4.8\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$ for 5%, 10% and 20% PEG, respectively. Fig. 1 and Fig. 2 show the fit of the proposed model to the experimental value for the considered levels of PEG.

The numerical results for INF-α release ($R_1(t)$), corresponding to the obtained in [8] value of the drug diffusion parameter $D_{1cr} = 5.9\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$ for 10% PEG are presented in Fig. 1 (profile 2). It is obvious that the experimental data are in better correspondence with the profile 1 in Fig. 1 (corresponding to our estimation) than with the profile 2.

In order to illustrate the advantages of the proposed approach in respect to the classical diffusion theory the drug diffusivity is also estimated for the three levels of PEG: $D_{1class} = 2.5\times10^{-9}\mathrm{cm^2\cdot s^{-1}}$, $D_{1class} = 0.75\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$, $D_{1class} = 1.5\times10^{-8}\mathrm{cm^2\cdot s^{-1}}$. The obtained profiles (dashed lines) show not enough good agreement with the experimental data.

Fig. 3 represents the comparison of the numerical results for PEG as an important release modifier ($R_3(t)$) with the available experimental data [8], using the obtained value of the drug diffusion parameter.

It is established an initial burst release (up to the first or second day) for each of the two compounds followed by a sustained liberation (within a period of at least 20 days). The numerical results obtained by using the proposed approach are in very good correspondence with the experimental data. The superior fitting of the model release profiles is observed after the 7th day for IFN-α and after the 4th day for PEG.

Example 2. Numerical simulation of IFN-α release and implant porosity change is performed for different values of the initial implant porosity ε_0 at 10% PEG using the obtained value for D_{1cr}.

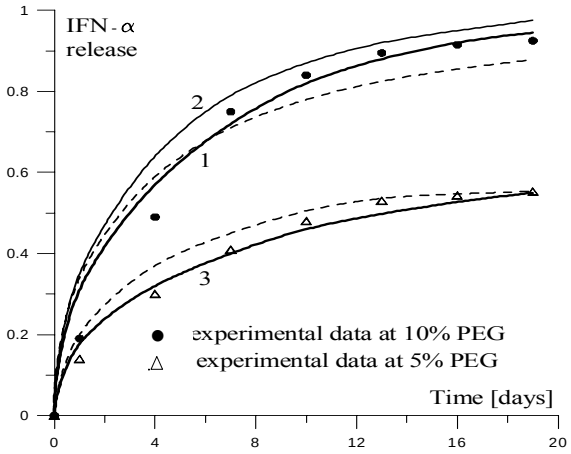


Fig. 1 Numerical results of IFN-α release compared with experimental data at 10% IFN-α/HP-β-CD and two levels of initial PEG loading: profile 1 – new model results for 10% PEG at $D_{1cr} = 4.5\times10^{-8}\,\mathrm{cm}^2\cdot\mathrm{s}^{-1}$; profile 2 – new model results for 10% PEG at $D_{1cr} = 5.9\times10^{-8}\,\mathrm{cm}^2\cdot\mathrm{s}^{-1}$; profile 3 – new model results for 5% PEG at $D_{1cr} = 1.4\times10^{-8}\,\mathrm{cm}^2\cdot\mathrm{s}^{-1}$; dashed profiles – classical diffusion results for 5% and 10% PEG

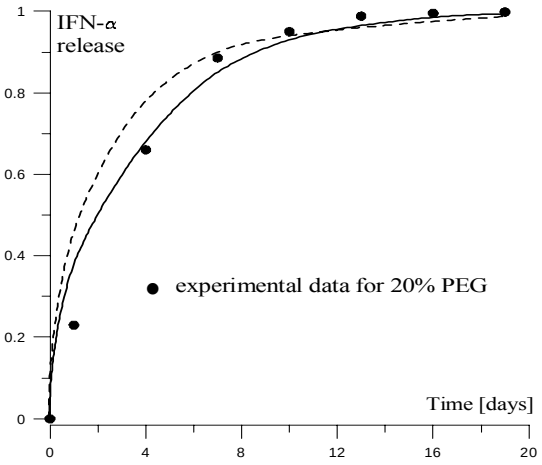


Fig. 2 Numerical results of IFN-α release compared with experimental data at 10% IFN-α/HP-β-CD and 20% initial PEG loading; continuous profile – new model results; dashed profile – classical diffusion results

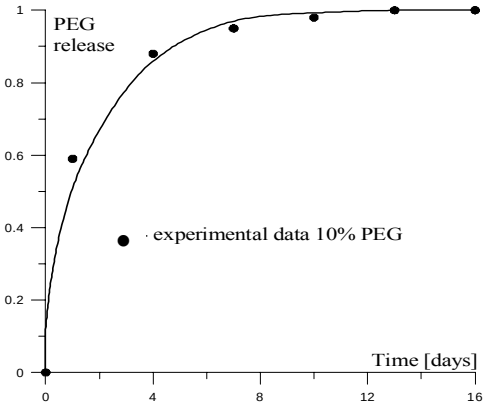
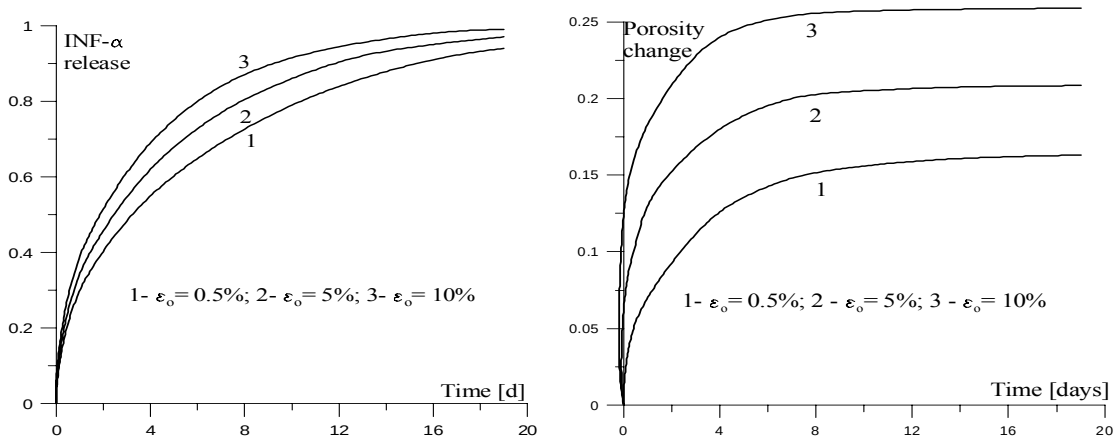


Fig. 3 Numerical results for $R_3(t)$ compared with the available experimental data for PEG release at 10% initial loading at the presence of 10% IFN-α/HP-β-CD

The numerical curves in Fig. 4b demonstrate that the porosity change reaches its steady state within the first week for each considered value of ε_0. This result explains the obtained significant effect of the initial porosity during the first week (e.g. 55% against 70% drug release at 4th day) (Fig. 4a).



(a) (b)

Fig. 4 Effect of the initial implant porosity:
(a) INF-α release; (b) implant porosity increase

Conclusion

A new approach to modeling drug release kinetics from lipid implants is proposed describing simultaneous diffusion of INF-α (drug), HP-β-CD (stabilizer) and PEG (drug release modifier). Explicit mathematical expressions for the concentrations dependent diffusivities of the three compounds within each element of the domain are derived, taking into account the initial and current porosity.

A hybrid numerical scheme based on FE domain discretization and time difference method, as well as computational technique, was developed. Its validation was realized on the basis of available experimental data for INF-α / HP-β-CD and PEG under different levels of initial PEG loading. A detailed estimation of INF-α critical diffusion parameter in comparison with the drug diffusivity value is performed by fitting the new approach and the classical diffusion theory to the experimental data for 3 different PEG contents (5, 10 and 20%) using one and the same values of HP-β-CD and PEG diffusion parameters (much bigger than D_{1cr}) [8]. It is established a very good correspondence between the new model profiles and the experimental data. As the values of D_{1cr} for 10 and 20% PEG are very close (about 5% difference) the drug release profile for 20% PEG (as well as for 15% PEG) could be simulated with an admissible accuracy using the estimation of INF-α diffusion parameter obtained for 10% PEG in order to avoid an expensive experiment.

The presented numerical simulation of the protein release simultaneously with the current porosity increase illustrates the initial burst drug liberation for an initial implant porosity of the range of 0.5%÷10%.

The presented approach and the computational technique thereby proposed can be used as a fast and reliable simulation tool when designing a range of lipid implants for sustained drug delivery.

References

1. Blagoeva R., A. Nedev (2008). A Problem for Drug Release from 2D Polymeric Systems, Mech. Res. Comm., 35, 344-349.
2. Blagoeva R., A. Nedev (2009). Numerical Modeling of Drug Release from 2D HPMC-Matrices, Int. J. Bioautomation, 13, 19-26.
3. Fischer H., I. Polikarpov, A. Craievich (2004). Average Protein Density is a Molecular-weight-dependent Function, Protein Sci., 13(10), 2825-2828.
4. Herrmann S., G. Winter, S. Mohl, F. Siepmann, J. Siepmann (2007). Mechanisms Controlling Protein Release from Lipidic Implants: Effects of PEG Addition, J. Controlled Release, 118, 161-168.
5. Herrmann S. (2007). Lipidic Implants for Pharmaceutical Proteins: Mechanisms of Release and Development of Extruded Devices, Ph.D. Thesis.
6. Mohl S., G. Winter (2004). Continuous Release of rh-interferon α-2a from Triglyceride Matrices, J. Controlled Release, 97, 67-78.
7. Schulze S., G. Winter (2009). Lipid Extrudates as Novel Sustained Release System for Pharmaceutical Proteins, J. Controlled Release, 134, 177-185.
8. Siepmann F., S. Herrmann, G. Winter, J. Siepmann (2008). A Novel Mathematical Model Quantifying Drug Release from Lipid Implants, J. Controlled Release, 128, 233-240.

Assoc. Prof. Rumiana Blagoeva, Ph.D.
E-mail: rumiana.blagoeva@abv.bg

Rumiana Blagoeva received Ph.D. degree in the Institute of Mechanics, Bulgarian Academy of Sciences in 1997 with thesis: Numerical modeling of diffusion and sorption in porous media. Her field of research is numerical modelling of mass transport in composite materials. The current research interests are connected with modeling of drug release from different carriers (polymeric tablets, lipid implants and nanoparticles). She is a member of Union of scientists in Bulgaria and Union of mathematicians in Bulgaria.

Assoc. Prof. Assen Nedev, Ph.D.
E-mail: assennedev@abv.bg

Assen Nedev received Ph.D. degree in the Institute of Mechanics, Bulgarian Academy of Sciences in 1998. His field of current research interests is numerical modelling of contemporary controlled drug release systems (micro-implants and nanoparticles solutions).