Mathematical Model of Gentamicin Sulfate Release from a Bioactive Textile Material as a Transdermal System Under *In Vitro* Conditions

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ABSTRACT: A mathematical model was developed to estimate the release of gentamicin sulfate from a bioactive textile material as a transdermal system for wound dressing. The gentamicin sulfate released from the antibiotic/chitosan hydrogel complexes was measured *in vitro* by the Franz diffusion cell technique. The diffusive transport of gentamicin sulfate through three connected compartments, that is, chitosan hydrogel, membrane, and solution, was considered by the formulation of a model based on Fick's second law. Initially, the total amount of gentamicin sulfate was placed within an already swollen chitosan hydrogel. The value of the diffusivity coefficient of the drug through the chitosan hydrogel was calculated for every initial amount of the active substance. For the initial concentration of gentamicin sulfate, which was lower than 2.81×10^4 μg/mL, the diffusion coefficient was approximately constant. A higher amount of gentamicin sulfate in the hydrogel reduced its own transport as a consequence of an increase in the intensity of the interaction field between the molecules of gentamicin sulfate. The model provides the possibility of optimizing the process of drug release by ensuring a compromise between a higher value of the diffusivity coefficient and a desirable amount of gentamicin sulfate and a constant concentration within the solution over 48 h. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 1424–1430, 2010

Key words: biomaterials; diffusion; drug delivery systems; hydrogels

INTRODUCTION

The controlled release of drugs from a bioactive textile material as a transdermal system for wound dressing has been examined from many points of view during the past decades.[1–6]

Through a combination of the unique protective characteristics of textile materials with their potential features, such as supersorbents, and their ability to create storage for medicine with different therapeutic effects, biomaterials with certain traits could be produced. Through association and the connection of different scientific fields, including practical medicine, pharmacy, pharmacology, physical chemistry (e.g., chemistry of polymers, chemistry of colloids), and textile technology, the multifunctional aspects of these materials can be achieved.[1–4]

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Antimicrobial biotextile materials are especially interesting for wound dressing and healing. Amplification of their actions may be attained with special antibiotics or a combination of materials. In previous research, we showed that an antimicrobial biomedical textile material based on polyacrylonitrile fibers and nonwoven textile showed considerable activity against different strains of bacteria.[7–11] An antimicrobial textile material could consist of a nonwoven textile base, composed of polypropylene (PP)/viscose, a natural polymer carrier, and an antimicrobially active substance. The polymer carrier was usually in the form of a hydrogel.

The regulation of drug release from a polymer hydrogel matrix is important from the perspective of the rate and the delivered amount of active substance to its final destination (injury/wound) with prolonged time of effectiveness.[12–15] Aminoglycoside antibiotics are therapeutically important for the treatment of numerous infections.[14,16]

The application of natural polymers for such purposes attracts great attention because of their excellent biocompatibility and biodegradability. Chitosan is one widely used polymer because it is

hypoallergenic and possesses some extraordinary features, such as biodegradability, nontoxicity, and excellent biocompatibility.

The release of a drug from a polymer matrix has multistage characteristics. Such a complex physiological–chemical process has been divided into the following stages:

- Diffusion of water molecules or physiological solution in a polymer carrier of active substance and swelling.
- Breaking up primary and secondary bonds of the drug and polymer matrix.
- Diffusion of the drug from a polymer hydrogel through a membrane to the physiological solution (water, buffer).

Mathematical modeling plays an important role in the optimization of hydrogel network design by identification of the key parameters and the molecule release mechanisms. Several mechanisms have been elucidated to describe molecule release from polymer hydrogel systems, including diffusion, swelling, and chemically controlled release. Diffusion-controlled release is the most widely applicable mechanism for describing drug release from hydrogels. Fick's law of diffusion, with either constant or variable diffusion coefficients, is commonly used to model diffusion-controlled release.[15,17,18] Drug diffusion within highly swollen hydrogels is also best described by Fick's law of diffusion or Maxwell–Stefan equations.[19]

In this article, we show a mathematical model of gentamicin sulfate release from a biomedical complex of a nonwoven textile, chitosan hydrogel, and gentamicin sulfate. Also, the transdermal diffusion of gentamicin sulfate (through artificial skin–membrane) was observed *in vitro* by the Franz diffusion cell technique. The mathematical model was developed to connect the initial concentration of gentamicin sulfate in chitosan with the concentration in the physiological solution by determination of the diffusion coefficient of the drug in hydrogel (D_H). The simple mathematical concept with the possibility of analytical solving was formulated with Fick's second law for three connected compartments (the hydrogel, membrane, and physiological solution). It was used to predicted the drug-release profiles within the compartments. Deeper insight into the complex phenomenon of drug release was possible through the connection of the calculated diffusivity coefficient of the drug in the hydrogel and the experimental conditions. The subject of this article is the optimization of the *in vitro* transdermal diffusion with the proposed mathematical model of the release of gentamicin sulfate from the chitosan hydrogel.

EXPERIMENTAL

Bioactive textile materials have characteristics of composite materials; these include

1. A nonwoven textile base.
2. A polymer carrier of an active antimicrobial substance.
3. An active substance, in this case, the drug gentamicin sulfate.

1. Nonwoven textile material

The textile material used in the design of this transdermal system had all of the necessary features of a certified material for medical use; that is, it was hygroscopic, it possessed air and moisture permeability; and it had appeal and flexibility and was comfortable when in contact with a wound surface or skin. Furthermore, it possessed little shrinkage and had a nontraumatic nature, sterilization ability, and possible application for polymeric composition.

The nonwoven textile base presented the inertial medical textile material consisting of a mixture of PP and viscose fibers thermally bonded (Table I).

2. Polymer carrier of the active substance

The polysaccharide [poly-(D-glucosamine)] chitosan was the product of the deacetylation of chitin with a degree of deacetylation of 78–82% purity for biomedical use. We received the chitosan from Sigma-Aldrich (St. Louis, MO) with a molecular weight of 200,000. Chitosan gels were prepared at 1–2 wt/wt % concentrations in a diluted acetic acid solution (20 wt/wt %, pH 5).

3. Active substance

The active substance was the aminoglycoside antibiotic gentamicin sulfate (Galenika-Pharma Generi CSBV).

Procedure of the formation of the antimicrobial textile material

Gentamicin was immobilized onto a polymer matrix of chitosan, as a polymer carrier, at a desirable concentration; this was spread on the surface of a nonwoven textile foundation by means of adhesion.

TABLE I
Characteristics of the Nonwoven Textile Materials

Raw composition	PP 50%/viscose 50%
Linear density	1.7/1.7 dtex
Surface mass	84 g/m^2
Thickness	0.90 mm
Increase in length under a maximal stress of 40 N/50 mm	20%
Sterilization	Dry procedure with gaseous ethylene oxide

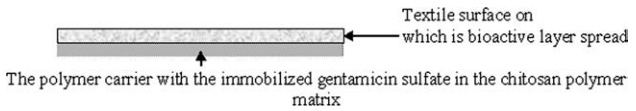


Figure 1 Scheme of the bioactive textile material.

Gentamicin sulfate was incorporated into the formulations at a 2 wt/wt % concentration.

The procedure of formation of this antimicrobial textile material was developed at the Faculty of Technology and Metallurgy in Belgrade under the project Development of Biomedical Textile Material and Products of Programmed Characteristics (Fig. 1).[11]

The bioactive layer of the bandage included the polymer carrier with the immobilized gentamicin sulfate in the chitosan polymer matrix. The concentrations of the active substance in the polymer matrix on the nonwoven textile material were

- 0.09 mg/cm^2 and 0.10 mg/cm^2 or 2.81×10^4 μg/mL and 3.12×10^4 μg/mL.
- 0.90 mg/cm^2 and 1.00 mg/cm^2 or 2.81×10^5 μg/mL and 3.12×10^5 μg/mL.

Dissolution studies

Skin penetration and gentamicin sulfate released from the antibiotic–polymer complexes were measured *in vitro* by the Franz diffusion cell technique. The gentamicin sulfate release was studied in 500 mL of phosphate-buffered saline at pH 7.4 and 37°C in a mild shaking environment (75–100 rpm). Aliquots of 3 mL were assayed for gentamicin sulfate at time points of 0, 0.25, 0.5, 0, 75, 1, 2, 3, 4, 5, 6, 12, and 24 h. For assessment of the quantity of gentamicin sulfate released, a high-performance liquid chromatography method was used. An apparatus with a paddle was used for this examination. The container was filled with a certain amount of fluid as a solution, and it was thermally isolated to a temperature of 37 ± 0.5°C.

Phenomenological background of the model

The process of gentamicin sulfate release from the chitosan hydrogel through the membrane to the physiological solution was considered for various amounts of drug initially stored in the hydrogel. The hydrogel swelling was much faster than the transport of gentamicin sulfate. It was finished after 5 min, whereas the transport of the drug was considered complete at 48 h. Initially, the total amount of the drug was placed within an already swollen hydrogel. The slow release of the drug through the hydrogel and the membrane to the solution and the slow removal of the part of the physiological solution ensured an approximately constant drug concentration within the physiological solution over 48 h. The release of gentamicin sulfate was considered by observation of the changes of the concentration of gentamicin sulfate in the physiological solution as a function of time, as shown in Figure 2.

The measured concentration of gentamicin sulfate in the solution reached a constant value after 30 min for all initial concentrations of the drug in the hydrogel. An interesting phenomenon was discovered When the initial concentration (C_0) of the drug in the hydrogel increased up to $C_0 = 2.81 \times 10^4$ μg/mL, the corresponding equilibrium concentration (C_{RS}) in solution also increased up to $C_{RS} = 37.8$ μg/mL. However, the highest initial concentration of drug, that is, $C_0 = 3.12 \times 10^4$ μg/mL, ensured a lower value of the equilibrium concentration of the drug in the solution, that is, $C_{RS} = 30.4$ μg/mL. Such a phenomenon pointed to an increase in the resistance effect for drug transport through the hydrogel matrix; this indicated a decrease in the diffusion coefficient. In accordance with the fact that the optimum experimental conditions included that the maximum concentration of the drug in the solution was ensured, we recommend using a value of the initial concentration of the drug in the chitosan hydrogel equal to $C_0 = 2.81 \times 10^4$ μg/mL.

For further consideration of this phenomenon, we formulated a mathematical model. It offered the possibility of determining the values of D_H of gentamicin sulfate and the concentration profiles for all of the experimental conditions.

Model development

For the development of the mathematical model, we considered the transport of gentamicin sulfate through three connected compartments: the polymer carrier in the form of the hydrogel (H), the membrane (M), and the solution (R; Fig. 3).

The balance equation for each compartment was formulated with Fick's second law, presented in

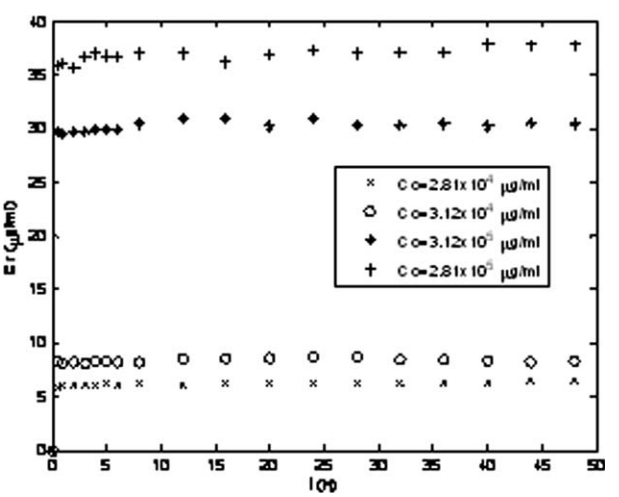


Figure 2 Release of gentamicin sulfate as a function of time.

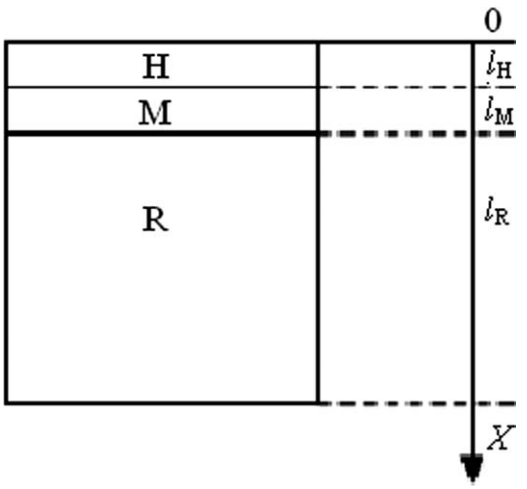


Figure 3 Scheme of the compartments.

Descartes coordinate system. This was in accordance with fact that the radii (R's) of both the hydrogel matrix and the membrane compartments were much higher than the width of the compartments, that is, l_H and $l_M - l_H$ (where l_H is the width of the already swollen hydrogel and $l_M - l_H$ is the width of the membrane; Fig. 3). The balance equation for the already swollen hydrogel compartment is expressed as

$$\frac{\partial C_H(x,t)}{\partial t} = D_H \frac{\partial^2 C_H(x,t)}{\partial x^2} \tag{1}$$

where $C_H(x,t)$ is the local concentration of gentamicin sulfate in the hydrogel compartment expressed per swollen hydrogel volume, t is the time, and x is a spatial coordinate ($0 \le x \le l_H$).

The balance equation for the membrane compartment is expressed as

$$\frac{\partial C_M(x^*,t)}{\partial t} = D_M \frac{\partial^2 C_M(x^*t)}{\partial x^{*2}} \tag{2}$$

where $C_M(x^*,t)$ is the local concentration of gentamicin sulfate in the membrane compartment expressed per membrane volume, D_M is the diffusion coefficient of the drug in the membrane, and $x^* = x - l_H$ is a spatial coordinate ($0 \le x^* \le l_M$).

The balance equation for the solution compartment is expressed as

$$V_R \frac{\partial C_R(t)}{\partial t} = [-D_M \frac{\partial^2 C_M(x^*,t)}{\partial x^{*2}}]/_{x^*=I_M-I_H} R^2\pi - kC_R(t) \tag{3}$$

where $C_R(t)$ is the concentration of gentamicin sulfate in the solution compartment expressed per solution volume, V_R is the solution volume, $R_2\pi$ is the contact surface between the membrane and the solution, and k is the specific rate of solution removal. It is experimentally determined as $k = Q^*/V_R$ (where Q^* is the average flow rate of solution removal). The first term of the right-hand side of eq. (3) represents the drug input, whereas the second represents the drug output.

One solves model eqs. (1)–(3) analytically, starting from the boundary conditions:

1. At $t = 0$, for $x = 0$, $C_H(0,0) = C_{\max}$, where $C_{\max}$ is the maximum local concentration of the drug in the hydrogel.
2. At $t = 0$, the total initial amount of the drug placed within the already swollen hydrogel (m_T) is experimentally obtained. It should satisfy
$$m_T = R^2\pi \int_0^{l_H} C_H(x,0)dx$$
3. At every t, for $x = 0$, the drug concentration profile has the maximum values, that is
$$\frac{\partial C_H(x,t)}{\partial x}/_{x=0} = 0$$
4. At every t, for the boundary between the hydrogel compartment and the membrane compartment [$x = l_H$, from eq. (1), and $x^* = 0$, from eq. (2)], the concentrations of the drug should satisfy the condition $C_M(0,t) = \alpha(t)C_H(l_H,t)$. The suitable form of the function $\alpha(t)$ could be $\alpha(t) = \sin(bt)$ (where $\alpha(t)$ is the drug concentration ratio in the hydrogel/membrane interface and b is a model parameter that is determined during the fitting procedure). The proposed functional form is suitable to satisfy both conditions:
   a. At $t = 0$, the parameter $\alpha(0) = 0$ and the concentration of drug $C_M(0,0) = 0$.
   b. The parameter $\alpha(t)$ increases with time.
5. At $t = 0$, for $l_H \ge x^* \ge l_M$, the concentration of the drug is $C_M(x^*,0) = 0$.According to the boundary conditions, the following analytical solution for the drug concentration profile within each compartment is formulated. For the hydrogel compartment, it is expressed as:
$$C_H(x,t) = C_{\max} e^{-\lambda_H^2 t} \cos\left(\sqrt{\frac{\lambda_H^2}{D_H}}x\right) \tag{4}$$
where λ_H^2 is the specific rate of the concentration decrease.

For the membrane compartment, it is expressed as

$$C_M(x^*,t) = V(x^*,t) + W(x^*,t) \tag{5}$$

where the function $V(x^*,t)$ is the basic solution and is expressed as

$$V(x^*,t) = C_{\max} e^{-\lambda_H^2 t} \sin(bt) \cos\left(\sqrt{\frac{\lambda_H^2}{D_H}}\, l_H\right) \cos(ax^*)$$

where a is the characteristic spatial frequency, the function $W(x^*,t)$ represents the contribution of the spatial harmonics and is expressed as

$$W(x^*,t)=\sum_{k=1}^{\infty} I\left\{\begin{array}{l}\xi be^{-Qt}\left[\dfrac{e^{Qt}}{Q^2+b^2}\left(Q\cos(bt)+b\sin(bt)-\dfrac{A}{Q^2+b^2}\right)\right]-\\ D_M\xi a^2e^{-Qt}\left[\dfrac{e^{Qt}}{Q^2+b^2}\left(Q\sin(bt)-b\cos(bt)-\dfrac{b}{Q^2+b^2}\right)\right]\end{array}\right\}\sin\left(\frac{k\pi}{2}\frac{x^*}{l_M-l_H}\right)$$

where the constants are

$$Q=D_M\left(\frac{k\pi}{2(l_M-l_H)}\right)^2$$

$$\xi=C_{\max}\cos\left(\sqrt{\frac{\lambda_H^2}{D_H}}\ l_H\right)$$

$$I=\frac{1}{2}\left[\frac{1}{\theta_1}(1-\cos(\theta_1(l_M-l_H)))+\frac{1}{\theta_2}(1-\cos(\theta_2(l_M-l_H)))\right]$$

$$\theta_1=\frac{k\pi}{2(l_M-l_H)}+a$$

$$\theta_2=\frac{k\pi}{2(l_M-l_H)}-a$$

where I is characteristic length for drug transport through membrane and θ_1 and θ_2 are the minimum and the maximum effective special harmonics of frequency. For the solution compartment, it is expressed as

$$C_R(t)=Ae^{-kt}\left\{\frac{b}{\chi^2+b^2}-\frac{e^{-\chi t}}{\chi^2+b^2}[\chi\sin(bt)+b\cos(bt)]\right\} \quad (6)$$

where A and χ are constants and are expressed as

$$A=C_{\max}\cos\left(\sqrt{\frac{\lambda_H^2}{D_H}}l_H\right)\cos(a(l_M-l_H))\frac{D_M}{V_R}R^2\pi a$$

$$\chi=\lambda_H^2-k.$$

The model parameters are determined in accordance with the following procedure. The choice of the value of parameter b of 0.01 h^{-1} should be small enough to ensure the dumping of the oscillatory trend of the solution given by eq. (6), which corresponded to our experimental observations. The value of D_M is approximately the same as the value obtained in water, which was in accordance with our experimental conditions, that is, high membrane permeability. The value of the diffusion coefficient in a water solution is 0.036–0.072 cm^2/h.[12,16] C_{max} is introduced as a slightly higher value than the average initial concentration of the drug within the already swollen hydrogel. The total initial amount of gentamicin sulfate within hydrogel was calculated as $m_T = C_0V_H$ (where V_H is the volume of the already swollen hydrogel matrix). The values of the model parameters introduced in the balance equation for further calculation of D_H and the parameter λ_H^2 are shown in Table II. The optimum values of both D_H and the parameter λ_H^2 should satisfy condition 2.

The specific outflow of solution k was experimentally determined, that is, $k = 1\ h^{-1}$. The optimum value of the model parameter λ_H^2 should be lower than the value of model parameter k to ensure an approximately constant concentration of drug in the solution over the 48-h time period. The model parameter a was determined by comparison of the experimental data of the drug concentration in the solution with the model predictions calculated with eq. (6).

RESULTS

The model presented here describes the influence of various amounts of gentamicin sulfate initially placed in a chitosan hydrogel on the process of drug release. The release of gentamicin sulfate was attended by measurement of the concentration in the solution as a function of time (Fig. 4). The predicted values of the concentration of gentamicin sulfate in the solution, calculated with eq. (6) were fitted with the experimental data by nonlinear least-squares regression with minimization of the squared magnitude of the residuals of the gentamicin sulfate concentrations. The optimum model parameters obtained by this fitting procedure that enabled the best agreement with the experimental data are shown in Table III. The optimum value of parameter a was the same for all experimental conditions and was $a = 10\ cm^{-1}$. As shown in Figure 4, the model predicted values for the dimensionless cell concentration profile correlated well with the experimental data with a relative error of 10%.

TABLE II
Measured Parameters of the Model

C_0 (μg/mL)	C_{max} (μg/mL)	m_T (μg)	D_M (cm^2/h)
2.81×10^4	2.83×10^4	1.76×10^3	0.072
3.12×10^4	3.13×10^4	1.96×10^3	0.072
2.81×10^5	2.83×10^5	17.66×10^3	0.072
3.12×10^5	3.13×10^5	19.62×10^3	0.072

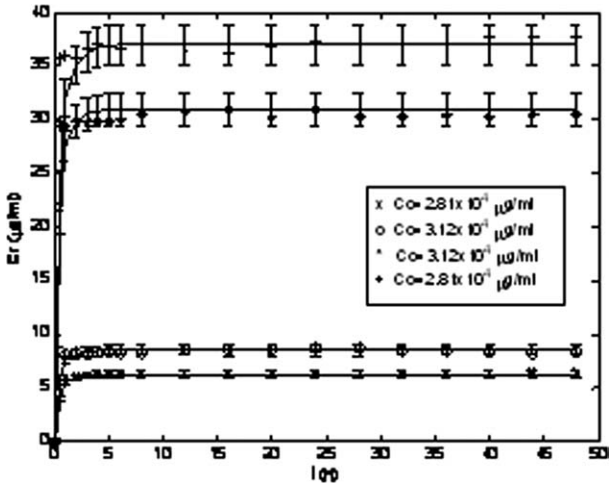
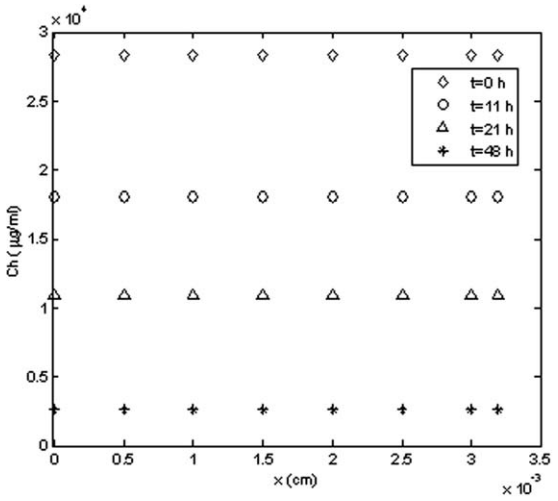
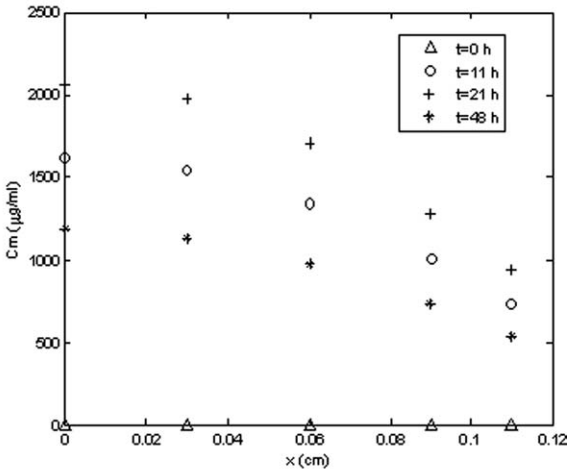


Figure 4 Experimental data of the concentration of gentamicin sulfate in the solution and model predictions as a function of time.



a) typical profile of change of concentration in hydrogel



b) typical profile of change of concentration in the membrane

Figure 5 Profile predictions of the concentration of gentamicin sulfate in the (a) hydrogel (Ch) and (b) membrane (Cm) for $C_0 = 2.81 \times 10^4$ µg/mL.

DISCUSSION

The results indicate that the calculated values of D_M for gentamicin sulfate were approximately the same, that is, $D_H = 0.030 \pm 0.01$ cm^2/h for the initial concentration of drug in hydrogel up to $C_0 = 2.81 \times 10^4$ µg/mL, as is shown in Table III. However, for the highest initial concentration ($C_0 = 3.12 \times 10^4$ µg/mL), the corresponding value of D_M was 1.18 times lower, that is, $D_H = 0.024 \pm 0.01$ cm^2/h. This indicated that a higher amount of gentamicin sulfate in chitosan ($C_0 > 2.81 \times 10^4$ µg/mL) induced an additional resistance effect for its own mass transport. This represented the consequence of an increase in the intensity of the interaction field between the molecules of gentamicin sulfate. Gentamicin sulfate has a tendency to form aggregates at higher concencrations.[14] The drug diffusion coefficients decreased as a result of steric hindrance. The bonded molecules of gentamicin sulfate filled the pores of the chitosan hydrogel and represented a barrier for transport of the unbounded molecules from the hydrogel to the membrane.

The predicted profiles of gentamicin sulfate in the hydrogel and the membrane were calculated with eqs. (4) and (5). The profiles of the drug in the hydrogel showed approximately the same trend, regardless of the value of the initial concentration. On that basis, we show one representative prediction profile in the hydrogel for $C_0 = 2.81 \times 10^4$ µg/mL in Figure 5(a). The model prediction of the concentration profile of gentamicin sulfate in the hydrogel indicated a homogeneous distribution. However, the concentration profile of gentamicin sulfate in the membrane decreased significantly compared to the hydrogel. This is shown in Figure 5(b). The obtained results represent the consequence of the corresponding values of the diffusion coefficients. The value of D_H for gentamicin sulfate was 2.4 times lower than that of D_M.

TABLE III
Calculated Parameters of the Model

C_0 (µg/mL)	λ_H (h^{-1})	D_H (cm^2/h)
2.81×10^4	$(5 \pm 1) \times 10^{-2}$	0.031 ± 0.01
3.12×10^4	$(4 \pm 1) \times 10^{-2}$	0.030 ± 0.01
2.81×10^5	$(3 \pm 1) \times 10^{-2}$	0.030 ± 0.01
3.12×10^5	$(2 \pm 1) \times 10^{-2}$	0.024 ± 0.01

The mathematical model through the analytical solutions of material balances for the three compartments, that is, the hydrogel, the membrane, and the solution, provided an opportunity to connect the

initial concentration of the drug within the hydrogel and D_H. The constant concentration within the solution over 48 h was obtained for all values of the initial concentration of gentamicin sulfate in the hydrogel from 2.81×10^4 to 3.12×10^5.

The results of this study point to some important cause–consequence relationships between the initial concentrations of gentamicin sulfate in the chitosan hydrogel and the corresponding value of the diffusion coefficients. For the initial concentration of gentamicin sulfate, lower than 2.81×10^4 μg/mL, the diffusion coefficient was constant. However, for the higher initial concentration of gentamicin sulfate, the diffusion coefficient decreased approximately 1.18 times. The higher amount of gentamicin sulfate in the hydrogel reduced its own transport as a consequence of the increased intensity of the interaction between the molecules of gentamicin sulfate.

We optimized the process of the release of gentamicin sulfate from the chitosan hydrogel by using an initial concentration of gentamicin sulfate equal to 2.81×10^4 μg/mL. This ensured the highest possible value of constant concentration in the solution and constant concentration within the solution over 48 h.

References

1. Oltarzhevskaya, N. D.; Krichevskii, G. E. Pharm Chem J 2005, 39, 42.
2. Kumar, R.; Philip, A. Tropical J Pharm Res 2007, 6, 633.
3. Petrulyte, S. Danish Med Bull 2008, 55, 72.
4. Wollina, U.; Heide, M.; Müller-Litz, W.; Obenauf, D.; Ash, J. In Textiles and the Skin; Elsner, P.; Hatch, K.; Wigger-Alberti, W., Eds.; Current Problems in Dermatology 31; Karger: Basel, Switzerland, 2003; p 82.
5. Knill, C. J.; Kennedy, J. F.; Mistry, J.; Miraftab, M.; Smart, G.; Groocock, M. R.; Williams, H. J. Carbohydr Polym 2004, 55, 65.
6. Dai, Y. N.; Li, P.; Zhang, J. P.; Wang, A. Q.; Wei, Q. J Biomed Mater Res Part B: Appl Biomater [Online] 2008, 86B, 493.
7. Skundric, P.; Simovic, L.; Kostic, M.; Medovic, A.; Milosevic, K.; Dimitrijevic, S. Presented at VII International Conference MEDTEX, Bolton, England, July 2007.
8. Skundric, P.; Medovic, A.; Simovic, L.; Dimitrijevic, S.; Kostic, M.; Janicijevic, M.; Milakovic, B. In Proceedings of the V International Conference MEDTEX, Lodz, Poland, 2005; p 24.
9. Skundric, P.; Medovic, A.; Kostic, M. AUTEX Res J 2002, 2, 78.
10. Skundric, P.; Medovic, A.; Simovic, L.; Dimitrijevic, S.; Kostic, M. Proceedings of the 5th World Textile Conference AUTEX, Portoroz, Slovenia, June 2005; Vol. 1, p 232.
11. Skundric, P.; Kostic, M.; Lukic, S.; Mihailidi, T.; Milosavljevic, S.; Stankovic, S.; Mihailovic, T.; Asanovic, K.; Dimitrijevic, S.; Siler-Marinkovic, M.; Lj, S.; Racin, M.; Popovic, K.; Medovic, A.; Simovic, L. J.; Janicijevic, M.; Simeunović, S.; Tasic, G.; Milakovic, B.; Uscumlic, G.; Hadzi-Djokic, J.; Stupar, M. Project: Development of the Biomedical Textile Materials and Products with Programmed Properties; TR 6713-B; Ministry of Science of the Republic Serbia, Belgrade, Serbia.
12. Krasko, M. Y.; Golenser, J.; Nyska, A.; Nyska, M.; Brin, Y. S.; Domb, A. J. J Controlled Rel 2007, 117, 90.
13. Chang, H. I.; Perrie, Y.; Coombes, A. G. A. J Controlled Rel 2006, 110, 414.
14. Singh, P. M.; Stefko, J.; Lumpkin, A. J. Rosenblatt Pharm Res 1995, 12, 1205.
15. Hariharan, D.; Peppas, N. A.; Bettini, R.; Colombo, P. Int J Pharm 1994, 112, 47.
16. Díez-Pena, E.; Frutos, G.; Frutos, P.; Barrales-Rienda, J. M. Chem Pharm Bull 2002, 50, 1201.
17. Amsden, B. Macromolecules 1998, 31, 8382.
18. Lin, C.-C.; Andrew, T. M. Adv Drug Delivery Rev 2006, 58, 1379.
19. Peppas, N. A.; Huang, Y.; Torres-Lugo, M.; Ward, J. H.; Zhang, J. Annu Rev Biomed Eng 2000, 2, 9.