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Diffusion models of gentamicin released in poly(vinyl alcohol)/chitosan hydrogel

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Abstract: This study presents comparison of our recently formulated two compartmental model with General fractional derivative (GFD) and Korsmeyer–Peppas, Makoid–Banakar and Kopcha diffusion models. We have used our GFD model to study the release of gentamicin in poly (vinyl alcohol)/chitosan/gentamicin (PVA/CHI/Gent) hydrogel aimed for wound dressing in medical treatment of deep chronical wounds. The PVA/CHI/Gent hydrogel was prepared by physical cross linking of poly(vinyl alcohol)/chitosan dispersion using freezing-thawing method, and then was swollen for 48 h in gentamicin solution, at 37 °C. Different physicochemical (FTIR, SEM), mechanical and biological (cytotoxicity, antibacterial activity) properties have been determined. The concentration of released gentamicin was determined using a high-performance liquid chromatography (HPLC) coupled with mass spectrometry (MS). The ratio between concentration of released gentamicin and initial concentration of gentamicin in the hydrogel was monitored for the prolonged time period in order to obtain gentamicin release profile. It was proven that our novel diffusion GFD model better fitted to experimental data then other models, and enabled the determination of diffusion coefficient precisely for the entire time period.

Keywords: drug release; diffusion; pharmacokinetics; cytotoxicity; antibacterial activity; mechanical properties.

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INTRODUCTION

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,[5–7] immune deficiency, leukaemia[8] and hormonal treatment.[9] In this work we made an attempt to employ results of fractional derivative model, recently formulated[10,11] for the study of drug release from hydrogel aimed for deep chronic wounds. Along with being a physical barrier for bacterial colonization, wound dressings often need to contain an antibacterial agent for active infection protection, which would be released gradually to maintain wound sterility.[12–14] Generally, profiles of drug release from hydrogel matrices usually exhibit quick initial release – the so-called "burst release" effect, followed by a longer period of gradual release that eventually levels off as a plateau reaching 80–100 % release efficiency.[15–17] There are several diffusion models used for evaluating the drug release profiles from hydrogel carriers, among which the most widespread are Korsmeyer–Peppas,[18] Makoid–Banakar,[19] Kopcha,[20] as well as the early-time approximations[21,22]

The aim of this work was to synthesize and characterize poly(vinyl alcohol)/ /chitosan/gentamicin (PVA/CHI/Gent) hydrogel aimed for wound dressing and to predict the drug release behaviour using our two compartmental diffusion GFD model, as well as to compare GFD model with Korsmeyer–Peppas, Makoid– –Banakar and Kopcha diffusion models.

EXPERIMENTAL

Materials

The following chemicals were utilized for preparation of PVA/CHI/Gent hydrogel: poly(vinyl alcohol) powder (fully hydrolysed, *Mw*, 70–100 kDa, Sigma Aldrich), chitosan powder (*Mw*, 190–310 kDa, deacetylation degree 75–85 %, Sigma Aldrich) and gentamicin sulfate solution (50 mg/ml in dH_2O, Sigma Aldrich). All solvents used for gentamicin release measurements were HPLC grade from J.T. Baker, USA, or Sigma Aldrich, gentamicin sulphate (50 mg/ml, Sigma Aldrich). Deionized water was obtained by passing the distilled water through a GenPure ultrapure water system (TKA, Germany). For antibacterial properties evaluation, monobasic (Centrohem, Serbia) and dibasic (Sigma Aldrich) potassium phosphates were used. Cell culture suspensions for cytotoxicity tests were prepared using MTT tetrazolium salt, EDTA, fetal calf serum and antibiotic–antimycotic solution (Sigma Aldrich).

Synthesis of PVA/CHI/Gent hydrogel

PVA colloid dispersion was prepared by dissolving PVA powder in hot distilled water at 90 °C for 2 h, under magnetic stirring. Chitosan was dissolved in 2 vol. % CH_3COOH under constant stirring at room temperature. After cooling of PVA, the CHI dispersion was added dropwise and the final dispersions (containing 10 wt. % PVA and 0.5 wt. % CHI) were homo-

genized by mixing at room temperature for 2–3 h. Further, the PVA/CHI hydrogels were prepared by physical cross linking of PVA/CHI dispersion using freezing–thawing method in 5 cycles. One cycle consisted of 16 h freezing at –18 °C followed by 8 h thawing at 4 °C. Finally, the hydrogels were swollen in 5.0 mg/ml gentamicin solution at 37 °C during 48 h.

Physicochemical and mechanical characterization

Field-emission scanning electron microscopy (FE-SEM) was carried out on Mira3 XMU FEG-SEM (Tescan, Czech Rep.), operated at 7 kV, with SE detector. Fourier-transform infrared spectroscopy (FTIR) was carried out using the Nicolet iS10 FTIR spectrometer (Thermo Fisher Scientific, USA) between 4000 and 400 cm^{-1}. Tensile test of PVA, PVA/CHI and PVA/CHI/Gent films was performed at texture analyzer (Shimadzu, Japan) with load cell of 5 kN and test speed of 1 mm/min. The tensile strength (σ_{TS}) was determined as maximum on stress- strain curve, while Young's modulus of elasticity (E) was calculated as the slope of elastic part of stress–strain curve with Trapezium X software (Shimadzu, Japan). Specimens were prepared by cutting the films in long stripes (15×50) mm^2. All measurements were performed in triplicates.

Gentamicin release studies

For the drug release assay, PVA/CHI/Gent hydrogel was immersed in deionized water and kept at 37 °C. Detailed experimental procedure is provided in the Supplementary material to this paper.

Evaluation of antibacterial properties

Antibacterial properties of PVA/CHI/Gent hydrogels were evaluated by quantitatively monitoring changes in the viable number of bacterial cells in suspensions that allowed for the direct contact with the material. In order to provide meaningful comparisons, tests were also run simultanously on PVA, PVA/CHI and PVA/Gent. Two bacterial strains were used; *Staphylococcus aureus* TL (culture collection FTM, University of Belgrade, Serbia) and *Escherichia coli* ATCC 25922 (American Type Culture Collection). Detailed experimental procedure is provided in the Supplementary material.

Cytotoxicity

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test and dye exclusion test (DET) were employed to evaluate the toxicity of PVA, PVA/Gent, PVA/CHI and PVA/CHI/Gent hydrogels. Two fibroblast cell lines were used, a human (MRC-5) and a mice (L929) cell line. The experimental procedures for preparing cell cultures, MTT and DET tests are explained in the Supplementary material.

RESULTS AND DISCUSSION

Scanning electron microscopy (SEM)

The microphotographs of PVA/CHI (Fig. 1a) and PVA/CHI/Gent hydrogels (Fig. 1b) revealed three-dimensional network structures with interconnected micropores evenly distributed through the hydrogels, suggesting that antibiotic has no influence on the hydrogels structure, confirming its homogeneous distribution through the polymer matrix.

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra for PVA/CHI and PVA/CHI/Gent hydrogels are represented in Fig. 2.

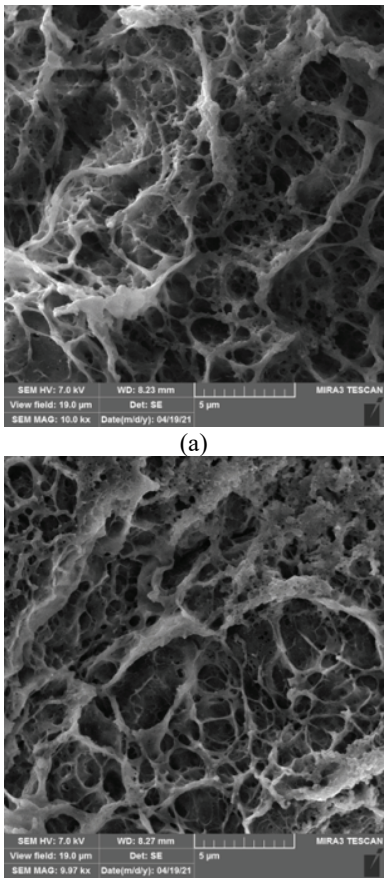
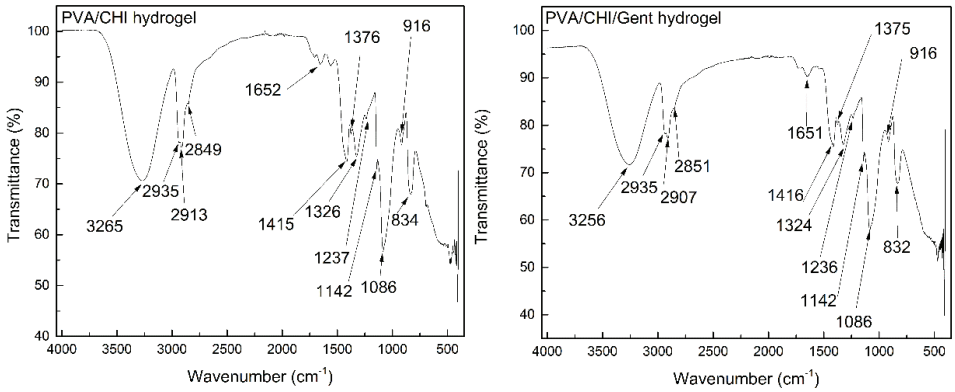


Fig. 1. SEM micrographs of PVA/CHI (a) and PVA/ /CHI/Gent (b) hydrogels.

The broad band observed at around 3260 cm^{-1} can be assigned to the stretching vibration of O–H participating in hydrogen bonding interactions.[17,23] In comparison to the FTIR spectra of pure PVA hydrogel (data not shown), the shifting of this band to the lower wavenumbers indicated the interaction between hydrogen bonded –OH groups in PVA matrix and water molecules, along with hydrogen bond cross-linking between PVA hydroxyl groups and $–NH_2$ and –OH groups from gentamicin and chitosan. Bands at 2935 cm^{-1} and at around 2910 cm^{-1} can be assigned to the asymmetric stretching of CH_2 and symmetric stretching of C–H of the alkyl groups,[24] suggesting trans zigzag conformation of the polymers' hydrocarbon chains. The band at around 1650 cm^{-1} suggested the stretching of carbonyl bonds (C═O), most probably originated from the residue after hydrolysis of polyvinyl acetate during PVA production.[17,24] The bands that appear at 1415 and 1416 cm^{-1} can be assigned to the –OH in plane coupling with C–H wagging in CH_2.[17,25] In the case of PVA/CHI hydrogel (Fig. 1a), detected

bands at 1237 and 1326 cm^{-1} can be assigned to the C–H wagging, while band detected at 1376 cm^{-1} can be assigned to the $–CH_2$ wagging.[25] Almost the same bands' position for PVA/CHI/Gent hydrogel can be observed (Fig. 2b). Bands corresponding to symmetric stretching of C–O at 1142 cm^{-1} for both hydrogels, pointed to crystalline sequence of PVA.[26,28] Bands detected at 1086, 916 and around 833 cm^{-1}, can be assigned to the C–O stretching in secondary alcohols (C–O–H),[25,27] rocking of CH_2 vibration and C–C stretching in atactic form of PVA,[23,24] respectively. Band at around 2850 cm^{-1}, represented the C–H stretching in chitosan structure.[25]

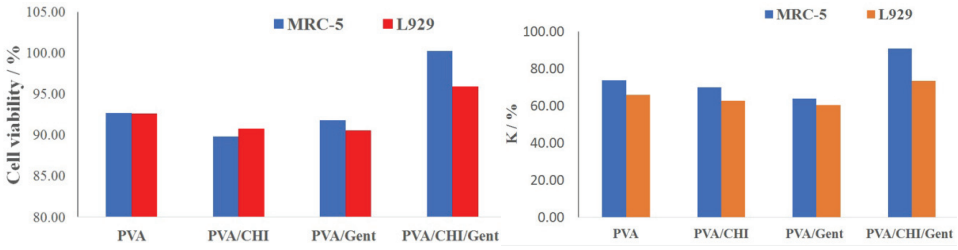


(a) (b)

Fig. 2. FTIR spectra of PVA/CHI (a) and PVA/CHI/Gent (b) hydrogels.

Cytotoxicity

Fig. 3a and b display the results of cytotoxicity towards MRC-5 and L929 cells, based on the MTT test and the DET test, respectively.



(a) (b)

Fig. 3. Cytotoxicity of PVA, PVA/Gent, PVA/CHI and PVA/CHI/Gent hydrogels towards MRC-5 and L929 cell lines based on (a) MTT test and (b) DET test results.

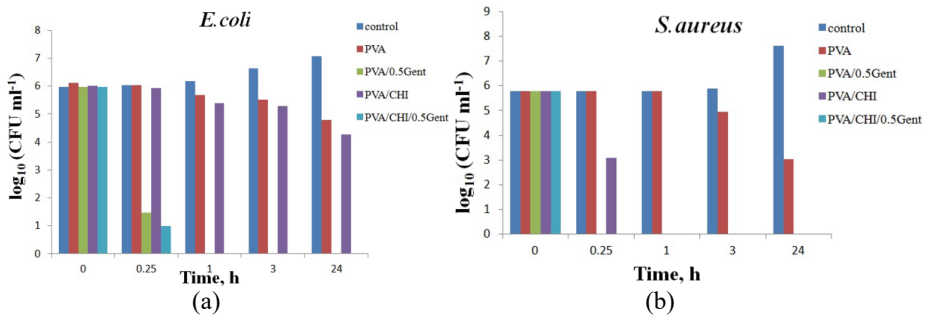
The MTT test is based on the reduction of a water-soluble monotetrazolium salt to a violet-blue water-insoluble formazan. Only metabolically active cells are able to reduce the MTT salt that passes through the cell membrane and the inner

mitochondrial membrane into coloured formazan, thus providing insight into the metabolic activity of the cell.[29] Based on the material cytotoxicity scale proposed by Sjogren *et al.*[30] (S, cell viability >90 % – non-cytotoxic, 60–90 % – mildly cytotoxic, 30–60 % – moderately cytotoxic, ≤30 % – cytotoxic), according to which PVA, PVA/Gent, PVA/CHI and PVA/CHI/Gent could be considered as non-toxic materials and therefore are suitable for future *in vivo* testing. Trypan blue DET test is an efficient and simple method that is based on cell staining after their mixing with the solution of a dye. PVA/CHI/Gent hydrogel with active component did not provoke the inhibition of growth neither in the case of MRC-5 (91.11 %) nor for L929 (73.59 %), which is still within acceptable cytotoxicity limits. Slight drop in survival rate was attributed to the antibiotic presence similar to the recent study[31] that described high concentrations of gentamicin (250–270 μg/mL), that were reached during the immersion of the antibiotic containing films, affected osteoblastic proliferation (MC3T3-E1 cells).

Antibacterial activity

The results obtained by examining the kinetics of antibacterial activity against *Escherichia coli* ATCC25922 and *Staphylococcus aureus* TL are shown in Fig. 4a and b, respectively. In the case of Gram-negative *E. coli*, PVA/Gent and PVA/CHI/Gent hydrogels show a bactericidal effect, since the reduction of the number of viable bacterial colonies was more than three orders of magnitude after only 15 min of incubation. After 1 h of inoculation, a sterile environment was achieved since there were no longer any alive *E. coli* cell present. For the Gram-positive *Staphylococcus aureus*, the absence of any living cells was observed after only 15 min. Interestingly, chitosan in PVA/CHI hydrogel exhibited bactericidal effect against *S. aureus*, because even after 15 min of incubation the number of living cells decreased by almost three orders of magnitude, and after 1 h it was established that there were no more living cells of *S. aureus* present.

Although it is very well known, from the literature, that chitosan possesses good antibacterial properties,[32] it was obvious that in this case its initial concen-



(a) (b)

Fig. 4. Antibacterial activity of PVA, PVA/Gent, PVA/CHI and PVA/CHI/Gent hydrogels against: a) *Escherichia coli* and b) *Staphylococcus aureus*.

tration was too low to cause any effect on the tested *E. coli* strain. For the tested *S. aureus* (Fig 4b) sudden drop in the viable cells, only 1 h of post-incubation, agrees well with the documented[33] increased antibacterial effect of chitosan in the slightly acidic conditions.

Gentamicin release study and diffusion models

Mathematical properties as well as application of fractional derivatives of Riemann–Liouville and Caputo type are presented in the literature.[34–37] Especially in Petráš[38] and Carvalho,[39] application of fractional calculus in biological systems is discussed. Here we recall the central result for the two compartmental model of drug diffusion, GFD model, presented by Miskovic-Stankovic.[10,11] The amount of released gentamicin is determined from the following formula:

$$m_2(t) = m_1(0)\frac{k}{2\pi V_1}\int_{x_0-i\infty}^{x_0+i\infty} \frac{\exp(x_0+ip)t/(x_0+ip)}{a\dfrac{x_0+ip}{(x_0+ip+\lambda_1)^{\alpha}} + b\dfrac{x_0+ip}{(x_0+ip+\lambda_2)^{\beta}} + k\left(\dfrac{1}{V_1}+\dfrac{1}{V_2}\right)}\mathrm{d}p \quad (1)$$

with $x_0 \geq 0$. Also:

$$m_1(t) = m_1(0) - m_2(t) \quad (2)$$

Parameters in the model are determined by least square method, *i.e.*, the sum squared residuals between measured and calculated values of m_2 at five measured points, Z, is minimized. Therefore, Z is given as:

$$Z(\alpha,\beta,\lambda_1,\lambda_2,a,b,k) = \sum_{j=1}^{5}\left(m_2(t_j) - m_{2\text{measured}}(t_j)\right)^2 \quad (3)$$

where $m_2(t_j)$ are values determined from Eq. (1) and $m_{2\text{measured}}(t_j)$ are measured values at time instant t_j.

The measured values of mass m_2 are divided by initial, total mass of gentamicin that in our experiments is $m_1(0) = 2.4551$ mg. Thus, we define relative mass of the gentamicin in hydrogel, q_1, and relative mass of released gentamicin in deionized water surrounding hydrogel, q_2, as:

$$q_1(t) = \frac{m_1(t)}{m_1(0)}; q_2(t) = \frac{m_2(t)}{m_1(0)} \quad (4)$$

We determined the parameters in Eq. (1), denoted as α^*, β^*, λ_1^*, λ_2^*, a^*, b^*, k^*) from the condition given by Eq. (2). Thus, the optimal values α^*, β^*, λ_1^*, λ_2^*, a^*, b^*, k^*) satisfy:

$$\min_{(\alpha,\beta,\lambda_1,\lambda_2,a,b,k)} Z(\alpha,\beta,\lambda_1,\lambda_2,a,b,k) = Z(\alpha^*,\beta^*,\lambda_1^*,\lambda_2^*,a^*,b^*,k^*) \quad (5)$$

In the minimization process we observed the restrictions that follow from the formulation of the model:

$$0 < \alpha \leqslant 1,\ 0 < \beta \leqslant 1,\ \lambda_1 \geqslant 0,\ \ \lambda_2 \geqslant 0,\ a \geqslant 0,\ b \geqslant 0,\ k \geqslant 0 \qquad (6)$$

Experiments were performed with $V_1 = 254.5$ mm^3, $V_2 = 1000$ mm^3 and the area over which diffusion takes place $A = 2.40$ cm^2. Condition given by Eq. (5) with Z given by Eq. (3) leads to $\alpha = 1$, $\beta = 0.001$, $\lambda_1 = 8.7\times10^{-7}$ s^{-1}, $\lambda_2 = 6.7562$ s^{-1}, $a = 0.000898$ s, $b = 0.037720$ s$^{-0.999}$, $k = 0.005193$ cm^4/day.

The corresponding diffusion coefficient, D, is calculated as follows. The shape of the hydrogel is cylinder with diameter 9 mm and the height (thickness) 4 mm. The area of the diffusion is calculated to be $A = 2.4$ cm^2. Therefore, diffusion coefficient is $D = k/A = 2.50\times10^{-8}$ cm^2 s^{-1}.

The obtained data (GFD model) were compared to several theoretical models in order to elucidate the diffusion parameters and to quantitatively compare gentamicin release behavior. The models applied were Makoid–Banakar,[19] Korsmeyer–Peppas[18] and Kopcha,[20] described by Eqs. (7)–(9), respectively.

$$C_t / C_0 = k_{\mathrm{MB}} t^n \exp(-ct) \qquad (7)$$

$$C_t / C_0 = k_{\mathrm{KP}} t^n \qquad (8)$$

$$C_t / C_0 = At^{1/2} + Bt \qquad (9)$$

where C_t is the concentration of gentamicin released from hydrogel at time, t; C_0 is the initial concentration of gentamicin inside the hydrogel; k_{MB} is the Makoid–Banakar constant; c is the Makoid–Banakar parameter; k_{KP} is the Korsmeyer–Peppas constant; n – coefficient which describes release transport mechanism, ($n < 0.5$ – Fickian diffusion, $n > 0.5$ – non-Fickian/anomalous diffusion, $n = 1$ – Case II transport,[18] A and B – Kopcha's constants which depend on the dominant transport phenomenon during release. The models are depicted along with experimental profiles in Fig. 5 for Makoid–Banakar (Fig. 5a), Korsmeyer–Peppas (Fig. 5b) and Kopcha (Fig. 5c) models compared to GFD model. It should be noted that $m_2(t)$ in our GFD model Eq. (1) is proportional to the concentration C_t, while $m_1(0)$ is proportional to the concentration, C_0. Gentamicin release profiles verified the initial burst release effect of gentamicin from the hydrogel, *i.e.*, 70 % 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. The calculated parameters and the fit quality evaluated using minimization of square residual, Z, for different models are listed in Table I.

It can be observed that GFD model provided the lowest value of Z, *i.e.*, notably better correlation with the experimental data in respect to the other models. The time exponent n is an indication of the dominant diffusion mechanism and, as its values were less than 0.5 (Table I), it can be concluded that the

release of gentamicin from hydrogel conformed to the Fickian diffusion behavior[18] and was governed mainly by the concentration gradient of released gentamicin. This was also proved by Kopcha model, as the absolute values of the parameter *A* were higher compared to *B*, indicating that the predominant driving force for the release is the diffusion, and not the polymer matrix relaxation.[40]

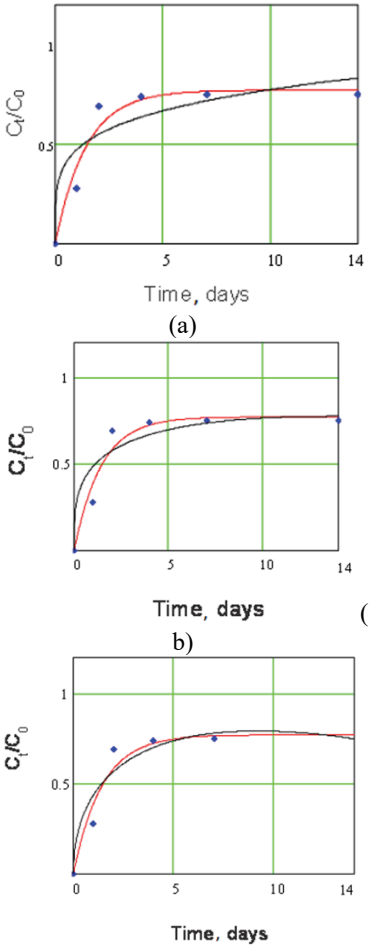


Fig. 5. Comparison between: a) Korsmeyer–Peppas (black line) and GFD model (red line), b) Makoid–Banakar (black line) and GFD model (red line) and c) Kopcha (black line) and GFD model (red line); ● experimental points.

In order to determine the value of diffusion coefficient of gentamicin, the early time approximation (ETA) model was applied and compared to diffusion coefficient calculated from GFD model. For ETA, two equations were used, standard ETA, Eq. (10), and a modified ETA, Eq. (11), proposed by Ritger and Peppas.[21] According to Ritger and Peppas, the standard ETA is frequently misused, even though it only applies to very specific cases of swelling, and for spe-

cific geometries of thin films with very high aspect ratio (diameter divided by thickness; a thin film will typically have aspect ratio of the order of ~100, whereas for thick hydrogel discs it is closer to unity).[22] In these equations, C_t/C_0 denotes the fraction of released gentamicin at the time t, D is the diffusion coefficient of gentamicin during the release, t – the time of release, δ is the hydrogel thickness and r is the radius of the hydrogel disc:

$$C_t / C_0 = 4(\frac{Dt}{\pi\delta^2})^{1/2} \quad (10)$$

$$C_t / C_0 = 4(\frac{Dt}{\pi r^2})^{1/2} - \pi\frac{Dt}{\pi r^2} - \frac{\pi}{3}(\frac{Dt}{\pi r^2})^{3/2} + 4(\frac{Dt}{\pi\delta^2})^{1/2} - \\ -\frac{2r}{\delta}(8\frac{Dt}{\pi r^2} - 2\pi(\frac{Dt}{\pi r^2})^{3/2} - \frac{2\pi}{3}(\frac{Dt}{\pi r^2})^2) \quad (11)$$

TABLE I. Fitting parameters for different models of gentamicin release from PVA/CHI/Gent hydrogel; GFD – GFD model; KP – Krosmeyer–Peppas model; MB – Makoid–Banakar model; K – Kopcha model

Parameter	α	β	λ_1	λ_2	k cm^4/day	D cm^2 s^{-1}	a	b	Z
GFD	1	0.001	8.7×10^{-3}	6.7562	5.193×10^{-3}	2.5042×10^{-8}	8.9×10^{-4}	0.0377	0.02564
Parameter	k_{KP} / s^{-n}	n							Z
KP	0.4737	0.2137							0.07735
Parameter	k_{MB} / s^{-n}	n	c						Z
MB	0.4956	0.2736	0.01972						0.06284
Parameter	A / s$^{-1/2}$	B / s^{-1}							Z
K	0.52356	–0.08643							0.04353

The ETA models represent the dependence of the fraction of released gentamicin on the square root of the release time (Fig. 6), while diffusion coefficient, D, of gentamicin release was determined from the slope of initial linear part of the experimental curve.

The value of D calculated by the standard ETA (5.53×10^{-8} cm^2 s^{-1}) is two times greater than value of D calculated by modified ETA (2.57×10^{-8} cm^2 s^{-1}) and GFD model (2.50×10^{-8} cm^2 s^{-1}). This implied that GFD model enabled the determination of D considering the gentamicin diffusion through the thick hydrogel where ratio between hydrogel diameter and thickness was about 2. Moreover, while ETA model extends the predictability of release up to 60 % and modified ETA up to 80–90 %, GFD model predicted the gentamicin release in the entire time period.

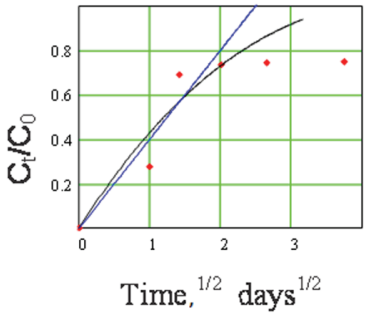


Fig. 6. Standard ETA (blue line) and modified ETA (black line) models, ◆ experimental points.

Mechanical properties

Fig. 7 shows stress–strain curves for the PVA, PVA/CHI and PVA/CHI/ /Gent films, while tensile strength, modulus of elasticity and the strain corresponding to tensile strength (maximum of curve, when geometrical weakening of material starts), ε_m, are presented in Table II.

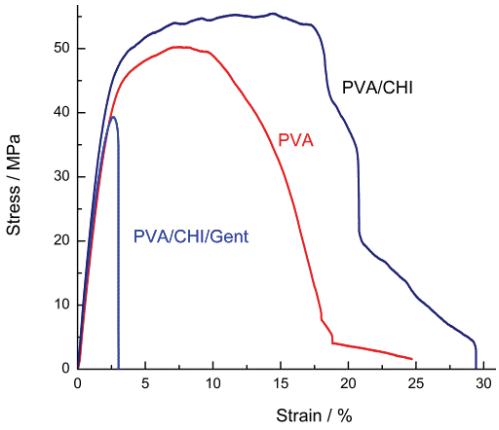


Fig. 7. Stress–strain curves from tensile test for PVA, PVA/CHI and PVA/CHI/ /Gent films.

TABLE II. Tensile strength (σ_{TS}), Young's modulus of elasticity (E) and tensile strain for maximum of tensile curves (ε_m)

Sample	σ_{TS} / MPa	*SD* / MPa	*E* / MPa	*SD* / MPa	ε_m / %	*SD* / %
PVA	47.25	4.3	1886.87	147	7.27	0.49
PVA/CHI	53.43	2.9	2223.67	211	13.31	1.57
PVA/CHI/Gent	36.50	4.0	1969.73	162	2.61	0.04

It could be seen that the tensile strength of PVA/CHI film increased by 13.1 %, Young's modulus by 18.0 % and tensile strain, ε_m, by 83.1 % compared to pure PVA film. This improvement in mechanical properties is a consequence of strong physical interactions and establishment of hydrogen bonds between PVA and CHI molecules.[41,42] By comparing the mechanical properties of the PVA/CHI and PVA/CHI/Gent films, a decrease by 31.7 %, in tensile strength with the

addition of gentamicin, is observed. Young's modulus of elasticity by 11.4 %, while the tensile strain was even five times smaller. Also, from the shape of tensile curves it could be seen that the addition of gentamicin leads to an increase in the brittleness of the films.

CONCLUSION

In the course of this work we have synthesized poly(vinyl alcohol)/chitosan/gentamicin (PVA/CHI/Gent) hydrogel, non-toxic towards MRC-5 and L929 cell lines and with strong antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. Diffusion mechanism of gentamicin release from PVA/CHI/Gent hydrogel was studied by comparison of novel two compartmental models with general fractional derivative (GFD) and Korsmeyer–Peppas, Makoid–Banakar and Kopcha diffusion models. GFD model fitted the experimental gentamicin release profile better than other models and enabled the determination of the diffusion coefficient of gentamicin in entire time period.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12722, or from the corresponding author on request.

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ИЗВОД

ДИФУЗИОНИ МОДЕЛИ ОТПУШТАЊА ГЕНТАМИЦИНА ИЗ ПОЛИ(ВИНИЛ АЛКОХОЛ)/ХИТОЗАН ХИДРОГЕЛА

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Ова студија представља поређење нашег недавно формулисаног дво-компартментског модела са општим фракционим изводима (GFD) и Корсмејер–Пепасовим, Макоид–Банакаровим и Копча моделима дифузије. Користили смо наш

GFD модел за проучавање отпуштања гентамицина из поли(винил алкохол)/хитозан/гентамицин (PVA/CHI/Gent) хидрогела намењеног за третман дубоких хроничних рана. PVA/CHI/Gent хидрогел је припремљен физичким умрежавањем дисперзије поли(винил алкохол)/хитозан методом замрзавања и одмрзавања, а затим је бубрен 48 h у раствору гентамицина, на 37 °C. Испитивана су физичко–хемијска (FTIR, SEM), механичка и биолошка (цитотоксичност, антибактеријска активност) својства. Концентрација отпуштеног гентамицина је одређена коришћењем течне хроматографије високих перформанси (HPLC) у комбинацији са масеном спектрометријом (MS). Однос између концентрације отпуштеног гентамицина и почетне концентрације гентамицина у хидрогелу је праћен током дужег временског периода. Доказано је да је наш, нови дифузиони, GFD модел боље усклађен са експерименталним подацима од других модела и омогућава прецизно одређивање коефицијента дифузије за цео временски период.

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