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Ophthalmic drug delivery system based on the complex of gellan and ofloxacin

G.S. Tatykhanova^{1,2*}, V.O. Aseyev³,
M. Vamvakaki⁴, V.V. Khutoryanskiy^{5,6},
S.E. Kudaibergenov¹

¹Institute of Polymer Materials and
Technology, Almaty, Kazakhstan

²Satbayev University, Almaty, Kazakhstan

³University of Helsinki, Finland

⁴University of Crete, Greece

⁵Reading School of Pharmacy,
University of Reading, UK

⁶Al-Farabi Kazakh National University,
Almaty, Kazakhstan

*E-mail: gulnur-ts81@yandex.kz

Complex formation between a natural polysaccharide – gellan and an antimicrobial drug – ofloxacin was studied in aqueous solution. Conductimetric and potentiometric titration curves revealed that gellan and ofloxacin forms a water-soluble complex of composition 2:1 mol/mol stabilized by ionic and hydrogen bonds. The formation of the gellan-ofloxacin complex was confirmed by FTIR spectroscopy, dynamic light scattering, zeta-potential and thermogravimetric analysis. The average hydrodynamic size of the complex was found 307±5 nm and its zeta-potential was negative and equal to -15 mV. Thin films of the gellan-ofloxacin complex, gelled in 0.3 wt.% of CaCl₂, were used to study the release kinetics of ofloxacin in distilled water and phosphate buffer. The drug release kinetics evaluated by UV-Vis spectroscopy at $\lambda_{\text{max}} = 289$ nm and calculated by the Ritger-Peppas model correspond to non-Fickian diffusion in distilled water and Case II transport (zero-order kinetics) in phosphate buffer. The cumulative release of ofloxacin from the gellan-ofloxacin films was equal to 96±2% and 36±2% in phosphate buffer and distilled water, respectively. It is expected that the gellan-ofloxacin complex is able to form *in situ* gel on the surface of the eye and to prolong the drug residence time in the tear fluid.

Keywords: gellan; ofloxacin; complexation; drug delivery.

Геллан және офлоксацин кешеніне негізделген офтальмологиялық дәрі-дәрмектерді жеткізу жүйесі

Г.С. Татыханова^{1,2*}, В.О. Асеев³,
М. Вамвакаки⁴, В.В. Хуторянский^{5,6},
С.Е. Кудайбергенов¹

¹Полимерлік материалдар және
технологиялар институты,
Алматы, Қазақстан

²Сәтбаев Университеті,
Алматы, Қазақстан

³Хельсинки Университеті, Финляндия

⁴Крит Университеті, Грекия

⁵Рединг қаласының фармацевтикалық
мектебі, Рединг Университеті,
Ұлыбритания

⁶Әл-Фараби атындағы Қазақ ұлттық
университеті, Алматы, Қазақстан

*E-mail: gulnur-ts81@yandex.kz

Табиғи полисахарид – геллан мен микробқа қарсы препарат – офлоксациннің сулы ерітінділерінің арасындағы кешеннің түзілуі зерттелді. Кондуктометрлік және pH-метрлік титрлеу қисықтарының нәтижелері бойынша геллан офлоксацинмен иондық және сутектік байланыстар арқылы 2:1 моль/моль қатынаста кешен түзетіндігі анықталды. Кешеннің орташа гидродинамикалық өлшемі 307±5 нм, дзета-потенциалы теріс, яғни -15 мВ тең. Геллан-офлоксацин кешенінің түзілетінін ИК-Фурье спектроскопия, динамикалы жарықты шашыратқыш, дзета-потенциал және термогравиметриялық анализдермен расталды. Геллан-офлоксациннің өте жұқа пленкасы 0,3% CaCl₂ ерітіндісінің қатысында алынып, су және фосфат буферінің ерітіндісіне пленкадан офлоксациннің шығу кинетикасы зерттелді. Дәрілік заттың шығу кинетикасы УК-көрінетін спектроскопиясында $\lambda_{\text{макс}} = 289$ нм толқын ұзындығында анықталып, Ритгер-Пеппас моделімен есептелді. Суда және фосфат буферінің ерітіндісінде дәрілік заттың шығу кинетикасы Фик заңына бағынбайды және аномальды (II жағдайда) диффузия байқалады. Геллан-офлоксацин пленкасынан офлоксациннің кумулятивті босап шығуы фосфат буферінде 96±2%, ал дистилденген суда 36±2% тең болды. Зерттеулерден күтетін нәтиже, геллан-офлоксацин кешені көз жасымен әрекеттескенде *in situ* гель түзіп, дәрілік заттың әсер ету мерзімін ұзартады.

Түйін сөздер: геллан; офлоксацин; комплекс түзу; дәрі-дәрмекті босату.

Лекарственная офтальмологическая форма на основе комплекса геллан-офлоксацин

Г.С. Татыханова^{1,2*}, В.О. Асеев³,
М. Вамвакаки⁴, В.В. Хуторянский^{5,6},
С.Е. Кудайбергенов¹

¹Институт полимерных материалов и
технологий, Алматы, Казахстан

²Университет Сатбаева,
Алматы, Казахстан

³Университет Хельсинки, Финляндия

⁴Университет Крит, Греция

⁵Редингская школа фармации,
Университет Рединга, Великобритания

⁶Казахский национальный университет
им. аль-Фараби, Алматы, Казахстан

*E-mail: gulnur-ts81@yandex.kz

Комплексообразование между природным полисахаридом – гелланом и антимикробным препаратом – офлоксацином изучено в водном растворе. Кривые кондуктометрического и pH-метрического титрования показали, что геллан образует с офлоксацином водорастворимый комплекс состава 2:1 моль/моль, стабилизированный ионными взаимодействиями и водородными связями. Среднегидродинамический размер комплекса составляет 307±5 нм, а его дзета-потенциал отрицателен и равен -15 мВ. Образование комплекса геллан-офлоксацин подтверждено данными ИК-Фурье спектроскопии, динамического светорассеяния, дзета-потенциала и термогравиметрического анализа. Тонкая пленка геллан-офлоксацин, приготовленная в 0,3% растворе CaCl₂ была использована для изучения кинетики выхода офлоксацина в воду и фосфатный буфер. Кинетика выхода лекарства, изученная методом УФ-видимой спектроскопии при $\lambda_{\text{макс}} = 289$ нм и вычисленная по модели Ритгера-Пеппаса, в воду и фосфатный буфер соответствует нефиковской и аномальной (случай II) диффузии. Кумулятивное высвобождение офлоксацина из пленок геллан-офлоксацин соответственно равно 96±2% и 36±2% в фосфатном буфере и дистиллированной воде. Ожидается, что комплекс геллан-офлоксацин способен образовывать *in situ* гель в слезной жидкости и пролонгировать время удержания лекарства.

Ключевые слова: геллан; офлоксацин; комплексообразование; высвобождение лекарства.



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Ophthalmic drug delivery system based on the complex of gellan and ofloxacin

G.S. Tatykhanova^{1,2*} , V.O. Aseyev³ , M. Vamvakaki⁴ , V.V. Khutoryanskiy^{5,6} ,
S.E. Kudaibergenov¹ 

¹Institute of Polymer Materials and Technology, microdistrict "Atyrau 1" 3/1, 050019 Almaty, Kazakhstan

²Satbayev University, Satpaev str. 22a, 050013 Almaty, Kazakhstan

³University of Helsinki, Yliopistonkatu 4, 00100 Helsinki, Finland

⁴University of Crete, Heraklion 700 13, Greece

⁵Reading School of Pharmacy, University of Reading, Whiteknights RG6 6APUK, Reading, UK

⁶Al-Farabi Kazakh National University, al-Farabi av. 71, 050040 Almaty, Kazakhstan

*E-mail: gulnur-ts81@yandex.kz

1. Introduction

Over the past few decades, microbial polysaccharides have attracted the attention of researchers due to their advantageous physicochemical properties. Currently, one of the most widely studied and comprehensively described member of this group is gellan – a linear polymer consisting of a tetrasaccharide repeating unit of 1,3-linked β -D-glucose, 1,4-linked β -D-glucuronic acid, 1,4-linked β -D-glucose, and 1,4-linked α -L-rhamnose produced by *Sphingomonas elodea* [1]. The fermentative production and manufacturing of gellan at industrial scale is described in many reviews [2,3].

Due to its unique structure and beneficial properties, gellan is currently described as a potent multifunctional additive for various pharmaceutical products. Its specific gelling properties in different media has led to the development of controlled release formulations based on gellan. Various formulations have been studied including oral, ophthalmic, nasal and other [4, 5]. A recent report [4] suggests that gellan-based materials can also be used in regenerative medicine, dentistry or gene delivery. Gellan gum-based hydrogels exhibit excellent *in vivo* and *in vitro* biocompatibility [6], tunable physical mechanical and injectable properties [7-9] for application in the regeneration of cartilage [7,8], tissue engineering [10], cell encapsulation [11], nucleus pulposus regeneration [12]. Recent progress in the design of multifunctional hydrogels based on gellan gum in the context of biomedical engineering and regenerative medicine is discussed and summarized in recent reviews [4,13-15].

Gellan-based systems for the sustained delivery of ophthalmic drugs are of great interest because the sol-gel transition of gellan in response to mono- (Na^+ , K^+) and bivalent (Ca^{2+} , Mg^{2+}) cations present in tear fluid makes it suitable for ophthalmic formulations as a thickening or gelling component [14, 16]. Gellan is nontoxic and not harmful for human organisms and is therefore widely used as a viscosifying additive in the food industry [17]. The most popular ocular formulation based on gellan is Timoptic XE[®] which is administered topically to the eye and increases the drug bioavailability by 3-4 times, while it considerably decreases the unfavorable effect in comparison with the standard solution of timolol [18,19]. The systems consisting of the model drug Gatifloxacin (0.3%) and gellan or a mixture of gellan-sodium alginate-carboxymethylcellulose exhibit mucoadhesive properties. *In vivo* experiments on ocular delivery demonstrated that the drug retention was exceeding 12 h [20]. Combination of a Gerlite[®]:alginate containing matrix also shows the prolonged effect *in vivo*. The rheological measurements showed that such mixtures exhibit pseudoplastic character after contact with tear liquids [21]. The viscosity of a microemulsion system containing terbinafine hydrochloride in combination with mucin confirms the interaction of gellan and mucin justifying the possibility of adhesion to biosurfaces [22]. Gellan gum and its methacrylated derivatives were tested as *in situ* gelling mucoadhesive formulations of pilocarpine [23]. A recent review [24] highlights the stimuli-responsive *in-situ* gelling systems based on gellan gum studied using *in vivo* models for glaucoma and various ocular infections. In spite of the wide applications of gellan-drug combinations in medicine,

pharmacy and biotechnology, the application of novel eye drops of prolonged action based on gellan and ofloxacin in ophthalmology was not described in the literature yet. Only one information that we have found is ofloxacin loaded gellan/poly(vinyl alcohol) nanofibers possessing gastroretentive/mucoadhesive drug delivery potential [25].

The present communication describes the complexation of gellan with ofloxacin to develop prolonged dosage eye drops by the immobilization of the antibacterial drug – ofloxacin within a matrix of biocompatible and biodegradable natural polymer – gellan in the form of thin film. It is expected that the eye drops consisting of gellan and ofloxacin will form a thin gel-like film on the eye surface due to the presence of inorganic ions in tear fluid and will provide delivery of ofloxacin for a definite time.

2. Experiment

2.1 Materials

Commercial low acyl gellan with the molecular weight in the range of $(1-5) \cdot 10^5$ Da was purchased from “Zhejiang DSM Zhongken Biotechnology Co., Ltd.”, China, and used without further purification. Antimicrobial drug – ofloxacin purchased from Sigma-Aldrich (UK) was used as received. Reagent grade phosphate buffer with pH 7.4 was purchased from Sigma-Aldrich (UK).

2.2 Methods

FTIR spectra of samples were recorded using Carry 660 (Agilent, USA) using dried samples. The thermal characteristics of samples were determined using TGA «Labsys EVO» Setaram (France). The average hydrodynamic sizes and ζ -potentials were measured using Malvern Zetasizer Nano ZS90 (UK). Absorption spectra were registered by UV-Vis spectroscopy (Specord 210 plus BU, Germany). Conductimetric and pH-metric titrations were carried out on Modular conductivity meter 856 Conductivity Module Metrohm and Automatic Titrator 905 Titrando Metrohm (Switzerland). Mini-magnetic stirrer IKA Topolino (Germany) was used for gentle stirring of the solution (around of 50 rpm) in order not to damage the hydrogel film.

2.3 Preparation of gellan-ofloxacin films

Gellan-ofloxacin films were prepared by mixing of a 10 mL 10^{-3} mol·L⁻¹ gellan solution and 5 mL 10^{-3} mol·L⁻¹ ofloxacin (2:1 mol/mol) and adding 1 mL 0.3 wt.% CaCl₂ to this mixture to achieve a uniform dispersion and gelation. Casting of the fluid gel into Petri dishes and allowing it to stand at room temperature and afterwards drying for 24 h, leads to the formation of an insoluble in water gellan-ofloxacin flexible film. Circular pieces of each film, 4.0 ± 0.2 mm in diameter and 0.5 ± 0.1 mm thick, were cut with a cork borer and were used for drug delivery studies. Each piece of weighed film was approximately equal to 10 ± 1 mg.

2.4 Evaluation of release rate of ofloxacin from gellan-ofloxacin films

The release rate of ofloxacin from the gellan-ofloxacin films was studied as follows. Small pieces of gellan-ofloxacin films ($d = 4.0 \pm 0.2$ mm, $h = 0.5 \pm 0.1$ mm) were placed in glass vials at room temperature ($25 \pm 1^\circ\text{C}$) and soaked in either 8 mL distilled water or phosphate buffer under gentle stirring (around of 50 rpm) in order not to damage the hydrogel film [26]. From time to time 2 mL of the solution were taken to measure the absorbance of ofloxacin at 289 nm. These experiments were performed under sink conditions and to keep the volume of the solution constant, the 2 mL solution taken for UV-Vis measurement were compensated by adding 2 mL of distilled water or phosphate buffer, respectively [25]. The accumulative release was calculated by formula [27]:

$$\begin{aligned} \text{Cumulative percentage release, \%} &= \\ &= \frac{\text{Volume of sample withdrawn, mL}}{\text{Bath volume, mL}} \cdot P_{t-1} + P_t, \end{aligned}$$

where P_t is the percentage release at time t ; P_{t-1} is the percentage release previous to “ t ”

and the results were shown as mean \pm SD. The cumulative release of ofloxacin is the total amount (in percentage) of ofloxacin released from the gel matrix during the full time of experiments until the full or partly release of drug will be reached.

3. Results and Discussion

Addition of an aqueous solution of ofloxacin to an aqueous solution of gellan leads to the decrease in the electrical conductivity and pH of the system due to the formation of both ionic and hydrogen bonds between the two components (Figure 1). Partial neutralization of glucuronic acid of gellan by tertiary amine groups of ofloxacin and formation of hydrogen bonds with participation of carboxylic groups of drug and polymer chain is responsible for sharp decrease in conductivity and gradually decrease the pH of the solution. After formation of gellan-ofloxacin complex of definite composition, the excess of drug molecules significantly increases the conductivity and slightly decreases pH of the system. Such phenomenon is usually specific for interpolymers or polymer-drug complexes stabilized by ionic and hydrogen bonds or both [28,29]

The composition of gellan-ofloxacin determined from the minimum and the bend in the conductimetric and pH-metric titration curves was approximately equal to [gellan]:[ofloxacin] = 2:1 mol/mol. Taking into account that the molar composition of gellan-ofloxacin determined by the conductimetric and pH-metric titration curves is close to 2:1 mol/mol, the speculative structure of the complex can be represented as shown in Figure 2.

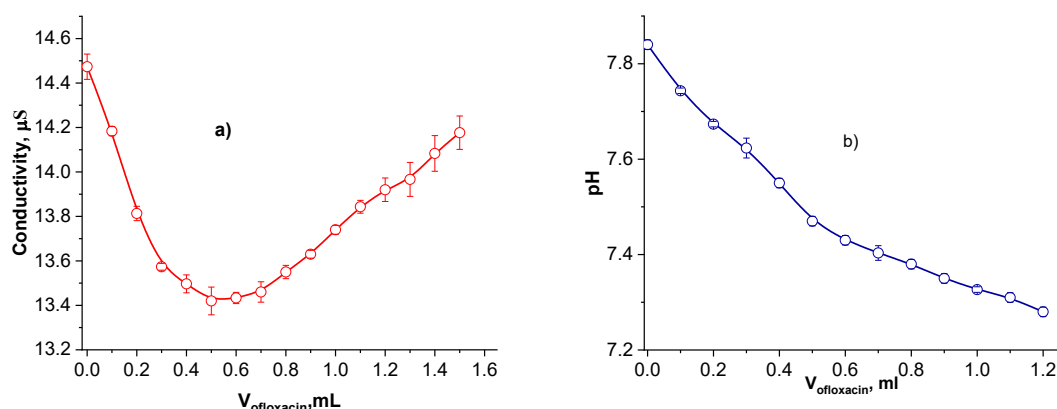


Figure 1 – Conductimetric (a) and pH-metric (b) titration curves of gellan with ofloxacin. [Gellan] = $1 \cdot 10^{-4}$ mol·L⁻¹, [Ofloxacin] = $1 \cdot 10^{-3}$ mol·L⁻¹. The volume of gellan solution used for the titration is 10 mL.

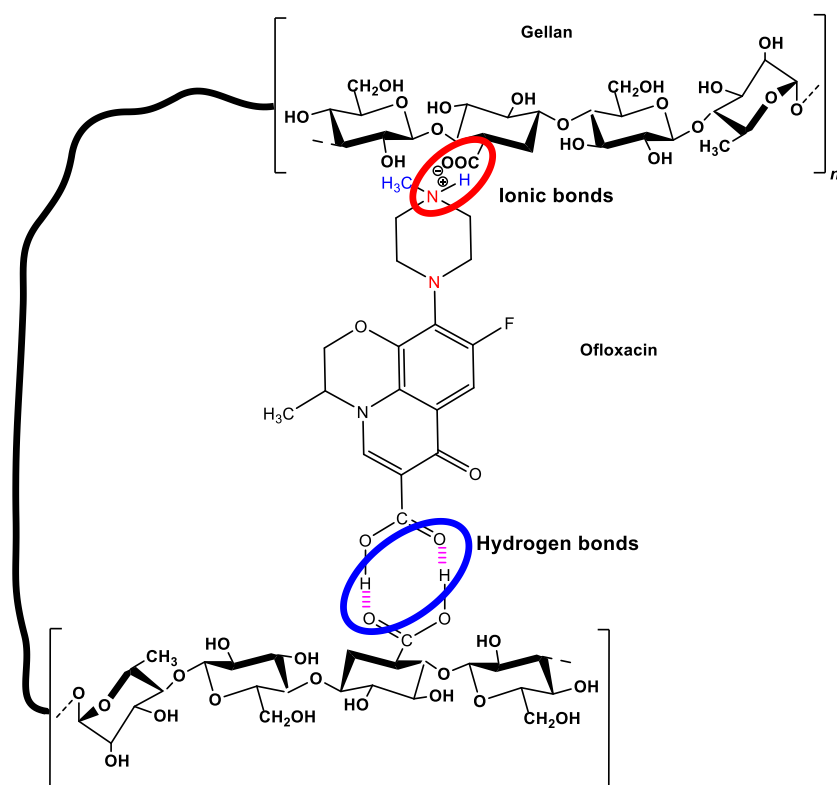


Figure 2 – Schematic representation of the intra-macromolecular gellan-ofloxacin complex of composition 2:1 mol/mol

It should be noted that ofloxacin can be involved into both intra-macromolecular and inter-macromolecular complexation with both hydroxyl and carboxyl groups of gellan. Formation of a gellan-ofloxacin complex of composition 2:1 mol/mol is also confirmed by DLS measurements (Table 1).

The minimal values of average hydrodynamic size and zeta-potential of the complex gellan-ofloxacin confirm the composition of 2:1 mol/mol. The negative charges of gellan,

ofloxacin and the complex particles is due to the presence of carboxylic groups in the structure of all substances. The minimum value of zeta-potential (– 14.9 mV) in case of the gellan-ofloxacin complex 2:1 mol/mol is probably related to the partial neutralization of the carboxylic groups of gellan by the amine groups of ofloxacin and the involvement of the carboxylic groups of gellan and ofloxacin in the formation of hydrogen bonds as schematically shown in Figure 2.

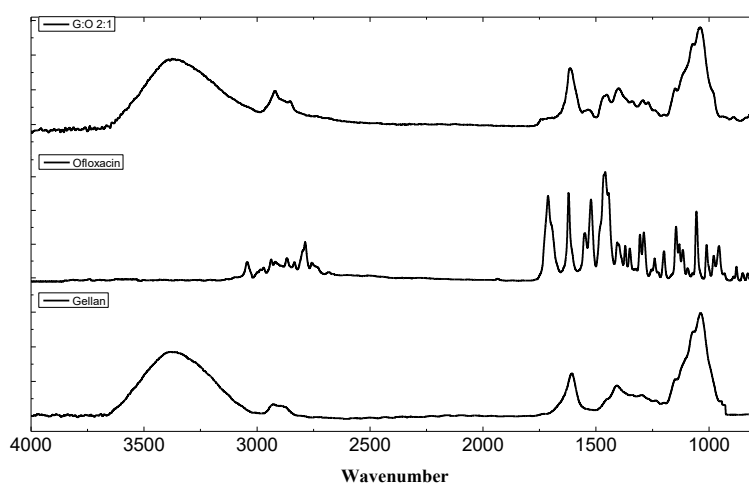
Table 1 – The average hydrodynamic size and zeta-potential of gellan, ofloxacin and a mixture of gellan-ofloxacin of different composition

| Composition of gellan-ofloxacin, mol/mol | Average hydrodynamic size, nm | Zeta-potential, mV |
|--|-------------------------------|--------------------|
| 4:1 | 336±5 | -43.0±2 |
| 2:1 | 307±5 | -15.0±1 |
| 1:1 | 315±5 | -40.0±2 |
| 1:2 | 338±4 | -21.0±5 |
| 1:4 | 370±2 | -25.0±5 |
| Gellan | 605±10 | -41.0±2 |
| Ofloxacin | 187±3 | 1.0±3 |

The FTIR spectra of dry gellan, ofloxacin and the complex of gellan-ofloxacin (2:1 mol/mol) are shown in Figure 3 together with the identification of some characteristic bands (Table 2).

As revealed from the FTIR spectra, the intensive peak at 1712 cm⁻¹ disappears in the complex of gellan-ofloxacin because

of the hydrogen bonding of the carboxylic groups of ofloxacin with the hydroxyl or carboxyl groups of gellan. In addition, the C-N stretching vibration of ofloxacin at 1549 and 1522 cm⁻¹ are shifted to 1537 cm⁻¹ confirming the involvement of the amine groups of ofloxacin in the formation of ionic bonds.

**Figure 3** – FTIR spectra of dry gellan, ofloxacin and the gellan-ofloxacin complex of composition 2:1 mol/mol**Table 2** – Identification of the characteristic bands of gellan, ofloxacin and the gellan-ofloxacin complex (2:1 mol/mol)

| | | Wavenumber, cm ⁻¹ | Band assignments |
|--------|------------|--|--------------------------------|
| Gellan | Ofloxacin | Gellan-ofloxacin complex (2:1 mol/mol) | |
| 3369 | - | 3376 | OH stretching |
| 2928 | 3044-2786 | 2920, 2857 | CH stretching |
| - | 1712 | - | C=O stretching of COOH groups |
| 1607 | 1621 | 1615 | COO ⁻ stretching |
| - | 1549, 1522 | 1537 | C-N stretching |
| | 1459 | 1453 | C-C stretching in benzene ring |
| 1408 | 1406 | 1399 | CH deformation |
| 1037 | - | 1039 | C-O-C stretching |

DTA curves of the individual components and the complex are shown in Figure 4. Decomposition of the gellan backbone takes place between 200 and 300°C. The sharpest weight loss is observed at 249°C that coincides well with the literature [16] which reports the thermal decomposition of ofloxacin at 243°C. In the case of the gellan-ofloxacin complex (2:1 mol/mol) the decomposition peaks of the individual components (gellan and ofloxacin) fully disappear demonstrating a weight loss for the complex at 338 and 379°C. This is related to the formation of the gellan-ofloxacin complex as the sole compound.

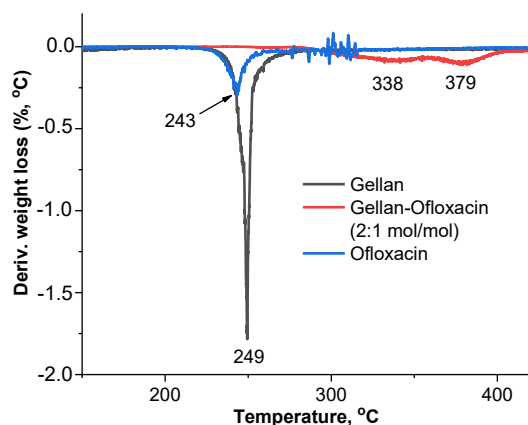


Figure 4 – DTA curves of gellan, ofloxacin and the gellan-ofloxacin (2:1 mol/mol) complex

The release kinetics of ofloxacin from the gellan-ofloxacin thin films, gelled by addition of 0.3 wt.% CaCl_2 , were evaluated using UV-Vis spectroscopy by detecting the time dependent absorption spectra of ofloxacin at $\lambda = 289 \text{ nm}$ in distilled water and phosphate buffer at room temperature (Figure 5).

As seen from Figure 6 the release kinetics of ofloxacin from the gellan-ofloxacin (2:1 mol/mol) thin films into distilled water and phosphate buffer is different. During 30-40 min, the

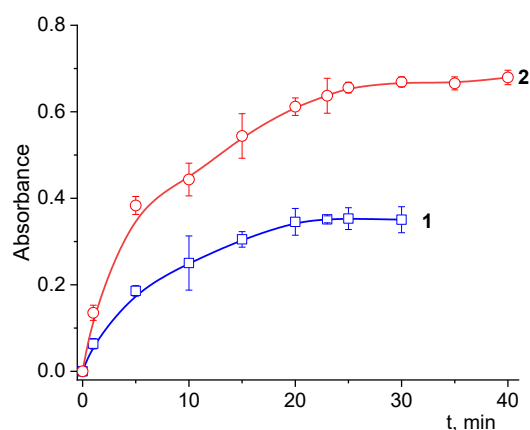


Figure 6 – Release kinetics of ofloxacin from the gellan-ofloxacin thin films, gelled by the addition of 0.3 wt.% CaCl_2 , into distilled water (1) and phosphate buffer (2) at $25 \pm 1^\circ\text{C}$

release of ofloxacin in phosphate buffer is 2 times faster compared to that in distilled water; this is related to the presence of inorganic ions in the buffer solution that reduce the strength of the polymer-drug ionic bonds. Calculation of the release kinetics using the Ritger-Peppas model [30] expressed as $A_t/A_\infty = kt^n$ (where A_t is the absorbance of ofloxacin at time t , A_∞ is the absorbance of ofloxacin at infinite time t_∞ , k is a structural/geometric constant for a gelled film, n is the release exponent representing the release mechanism) corresponds to non-Fickian diffusion ($n = 0.59$) in distilled water and Case II transport ($n = 0.95$) in phosphate buffer. The percentage release of ofloxacin into distilled water after 30 min and phosphate buffer after 40 min was leveled off at $\approx 12 \pm 1\%$ and $\approx 4 \pm 0.5\%$ respectively (Figure 7). The cumulative release of ofloxacin from the gellan-ofloxacin films calculated by procedure [27] is equal to $36 \pm 2\%$ and $96 \pm 2\%$ into distilled water and buffer solution respectively (Figure 8). In the case of distilled water, the release of ofloxacin may be influenced by the hydration and swelling of the gellan film, the penetration of water into the gel matrix

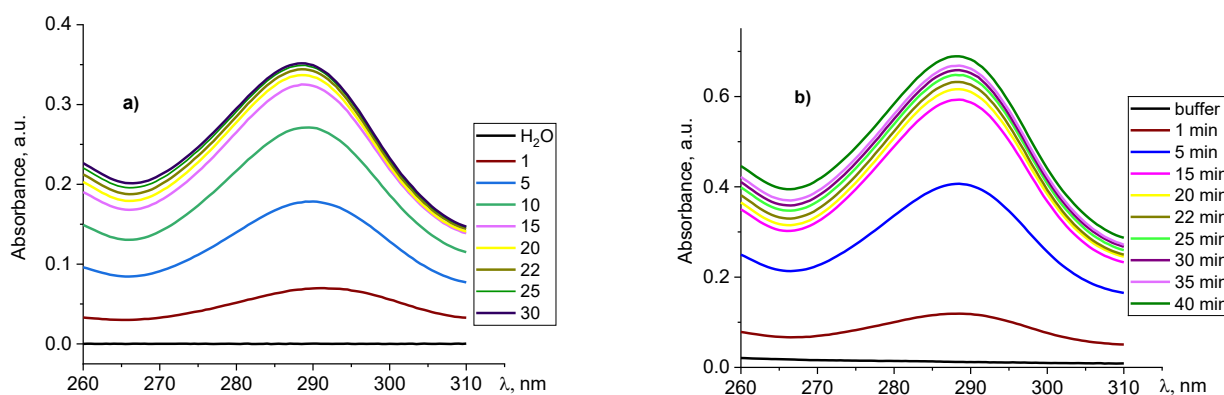


Figure 5 – Time-dependent absorbance of ofloxacin from the gellan-ofloxacin (2:1 mol/mol) thin films gelled by the addition of 0.3 wt.% CaCl_2 into distilled water (a) and phosphate buffer (b) at $25 \pm 1^\circ\text{C}$

resulting in the passive diffusion of ofloxacin from the gel matrix. The faster release of ofloxacin into the buffer solution was attributed to the destruction of the ionic bonds, formed between the carboxylic groups of gellan and the amine groups of ofloxacin, by the ionic species of the solution, which is accompanied by an enhanced diffusion of ofloxacin from the gel matrix.

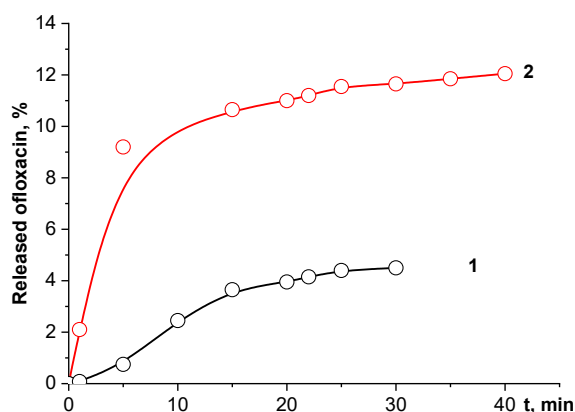


Figure 7 – Percentage of released ofloxacin into distilled water (1) and phosphate buffer (2) from the gellan-ofloxacin thin films, gelled by the addition of 0.3 wt.% CaCl_2 at $25\pm 1^\circ\text{C}$

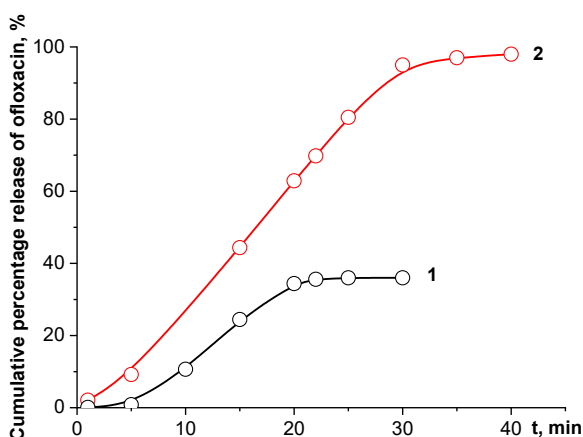


Figure 8 – Cumulative percentage release of ofloxacin from gellan gel matrix into distilled water (1) and phosphate buffer (2) from the gellan-ofloxacin thin films, gelled by the addition of 0.3 wt.% CaCl_2 at $25\pm 1^\circ\text{C}$

References (GOST)

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Authors [31] have studied *in vitro* release of covalently bounded and physically incorporated methylprednisolone (MP) from the gellan film and found that approximately 75% and 95% of MP is released into phosphate buffer at 32°C during 24 h. The gellan-MP films exhibited zero-order (or Case II transport) release kinetics with $n=0.93$. Since the gellan-MP film contains esterified MP, its release involves penetration of water into the matrix, swelling of the matrix, hydrolysis of the covalent ester bonds and diffusion of the drug through the matrix. The gellan film with physically entrapped methylprednisolone exhibited anomalous release kinetics with $n = 0.7$. The release mechanism of physically entrapped MP from the gellan gel matrix is explained by hydration and swelling of the network, penetration of water and diffusion of drug to the outer solution. The behavior of the gellan-ofloxacin system studied by us is also similar to the results of above authors.

4. Conclusion

A water-soluble gellan-ofloxacin complex of composition 2:1 mol/mol is stabilized by both ionic and hydrogen bonds, formed by the carboxylic, hydroxyl and amine groups of the two interacting components. The formation of the gellan-ofloxacin complex is confirmed by conductimetric and potentiometric titrations, DLS and zeta-potential measurements in addition to FTIR spectroscopy and TG analysis. The gellan-ofloxacin complex is gelled upon addition of 0.3 wt.% CaCl_2 and forms thin gel films. The release kinetics of ofloxacin from the gellan-ofloxacin complex were described by the Ritger-Peppas model ($A_t/A_\infty = kt^n$) and corresponds to non-Fickian diffusion ($n = 0.59$) in distilled water and Case II transport ($n = 0.95$) in phosphate buffer. The amount of cumulative ofloxacin release from the gellan-ofloxacin films was $96\pm 2\%$ in phosphate buffer and $36\pm 2\%$ in distilled water. To assess the effectiveness of the gellan-ofloxacin system as a sustainable drug delivery system, experiments, both *in vitro* and *in vivo*, should be carried out in tear fluids at various temperatures, and pH values of the medium.

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