FORMULATION THERMORESPONSIVE NANOCOMPOSITE HYDROGEL WITH EMBEDDED PLGA NANOPARTICLES CONTAINING CYTOTOXIC AGENT

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Application of chemotherapeutic agents still remains one of the principal approaches in anticancer therapy. Majority of chemotherapeutic compounds are not characterized by well biodistribution due to their poor water solubility. Additionally, rapid clearance and non-specificity determines the necessity of their application in high doses, which results in serious side and toxic effects. One of the ways to reduce such effects is development of novel drug delivery systems [1,2].

Local chemotherapy maintains high concentration of active substance in the target region and provides its extended release, which minimizes severity of systemic toxicity and side effects [3,4].

Hydrogel is widely used as a drug delivery system, due to its physical, chemical, and biological properties it is compatible with biological tissues [2,4]. However traditional hydrogel is not characterized by injectability and it requires surgical implantation. Considering these limitations stimuli responsive injectable hydrogels has gained a tremendous interest [5].

Among the stimuli responsive materials great attention is attributed to the development of injectable temperature sensitive (37°C) hydrogels. At room temperature thermo-sensitive hydrogel is a solution, it can be delivered to the targeted area by injection and at body temperature it is transformed into a gel. In addition to this, the structural-mechanical properties of in-situ hydrogel provides its flexibility in accordance with the target tissue.

Research trends are currently focused on the incorporation of different nanoparticulate systems into the hydrogel network so as to obtain nanocomposite hydrogel. By combination of hydrogel and polymer nanoparticles it is possible to achieve dual effect of each individual component [4,6]. As a result, in-situ depot is formed, which releases active substance locally and avoids systemic toxic action. This is promising approach especially for post-surgical therapy when high dose of cytotoxic agent might be applied [5]. By localizing the active ingredient in the injured zone systemic adverse effects is minimized. Therefore, the aim of this manuscript is to develop thermosensitive hydrogel containing PLGA nanoparticles enriched cytotoxic extract from Erysimum contractum Somm. etLevier.

Material and methods. Biodegradable polymer PLGA, Poly(D,L-Lactide-co-Glycolide, (LA:GA 50:50, MW 7000-17000), polyvinyl alcohol (PVA, Mowiol 8-88, MW 13 000-23 000), sodium alginate, poloxamer 407 was purchased from Sigma-Aldrich (Munich,Germany). Acetone was provided by Tbilisi State Medical University. Freeze-dried extract from Erysimum contractum Somm. Et Levier was obtained from Neopharmi LTD, Tbilisi, Goergia.

Chemical composition and cytotoxic activity of crude extracto f Erysimum contractum Somm. Et Levier is provided by Dali Beridze [7-9].

Preparation of PLGA NPs. The NPs were prepared by modified emulsification-solvent diffusion method. All experiments of NPs formulation were performed at room temperature. More briefly, 50 mg of PLGA and 5 mg of extract is dissolved in 2 ml of acetone. The organic phase is poured into 5 ml of aqueous phase containing 2.5% surfactant (polyvinyl alcohol) and stirred on the magnetic stirrer at 2500 rpm for 3 hr. Organic phase is removed at room temperature by stirring on magnetic stirrer. The obtained nanoparticles are washed three times with distilled water and collected at 15 000 g for 15 min.

Preparation of pure in-situ hydrogel. Poloxamer 407 based in-situ hydrogel is prepared by cold method. More briefly, 15% (w/w) of poloxamer 407 is dispersed into distilled water and placed at 4^0C until the polymer is completely dissolved. To insure mucoadhesive properties of the formulation 1% sodium alginate is added to poloxamer 407 solution (15% (w/w)) under magnetic stirrer to achieve homogenous solution. Resulting homogenous mixture was maintained at 37^0Cfor sol-to-gel transition.

Preparation of nanocomposite hydrogel. Extract loaded PLGA nanoparticles are incorporated into the thermosensitive hydrogel. Varied concentration of nanoparticles (0.5; 1; 2; 5; 8%) are incorporated into the hydrogel. Therefore, influence of nanoparticle concentration on hydrogel gelation time and temperature was evaluated. Three different ways are used to incorporate nanoparticles into the hydrogel, more briefly dispersion of freeze-dried nanoparticles into obtained hydrogel, dispersion of freeze dried nanoparticles into precursor solution of hydrogel, incorporation of gel forming agents into nanoparticle suspension.

Fourier infrared spectroscopy. Fourier-infrared spectroscopy is used to identify the characteristic functional groups of a nanocomposite hydrogel and to establish a possible interaction between the constituent components of the composition. Spectra was performed in the range from 4000 to 500 cm^{-1}. Experiment was carried out with a FTIR spectrometer IR Spirit, shimadzu.

Scanning electron microscopy. Scanning electron microscopy was used to observe the surface morphology of nanocomposite hydrogel. Prior to experiment the samples were coated with an ultrathin layer of gold by high-vacuum metallization (SEM–JEOL JSM-7001F).

Rheology. Viscoelastic properties of nanocomposite hydrogel was observed by rotational viscometer LVDV-1T. 10 ml of the sample was placed into a removable sample chamber equipped with a temperature probe. Spindle 2 was used. Data were collected at 37^0C, the temperature was maintained constant. The measurement of the samples was performed triplicate.

Release study. Release study was performed in PBS pH 7.4 and RPMI 1640 medium supplemented with 10% fetal bovine serum in order to mimic the biological environment. Franz diffusion cell apparatus was used to evaluate drug release kinetic from nanocomposite hydrogel. Semipermeable membrane is placed between donor and acceptor. Nanocomposite containing 1 mg phenolic compound is placed into the donor compartment of the Franz diffusion cell. The samples were withdrawn from acceptor compartment at predetermined time intervals over 72 h (1, 2, 5, 20, 28, 48, 56, 72 h). After sampling the volume was replaced with an equal volume of fresh medium. The amount of released phenolic compounds was measured at a wavelength of 425 nm using UV-vis spectrophotometer.

The hen's egg test. In order to evaluate irritating effect of nanocomposite hydrogel was tested on fertilized chicken egg model. The eggs were incubated for 7-10 days at 37 °C. Prerequisite for the

Table 1. Ifluence of nanoparticles concentrations on gelation time and temperature of hydrogel

Formulation №	Poloxamer 407 (% w/w)	Sodium alginate (% w/w)	Polymeric nanoparticles (% w/w)	Gel forming temperature (^{0}C)	Gel forming time (min)	pH
F1	15	1	0,5	36.6	10	7.36
F2	15	1	1	36.6	10	7.41
F3	15	1	2	36.8	10	7.4
F4	15	1	5	30.0	12	7.39
F5	15	1	8	38.5	18	7.35

start of the experiment is the formation of blood vessels. In order to perform the experiment, shell of the egg is removed on a certain area. Care was taken when removing the eggshell to ensure that the inner membrane is not injured. Research object were placed on the chorioallantoic membrane. The following samples were tested: phosphate buffered saline (pH 7.4) as negative control, 0.1N NaOH as positive control, and nanocomposite hydrogel as test sample. Since samples were placed on the vascular membrane of egg, the samples were monitoring up to 12 h. Following toxic effect were evaluated at a different time (0, 1, 2, 4, 8,12): hemorrhage, thrombosis, hemolysis. Each sample was tested in three independent experiments with at least 6 hen's egg.

Results and discussion. *Formulation of PLGA NPs and characterization*

In our previous study PLGA nanoparticles were fabricated loaded with extract (from Erysimum contractum Somm. etLevier). Dynamic light scattering was used to characterize particle size, polydispersity index and surface charge, results were around 232±3.25 nm, 0.18±0.004 and 5.1±0.45 mV, respectively.

Influence of PLGA NPs on gel forming process of nanocomposite hydrogel.

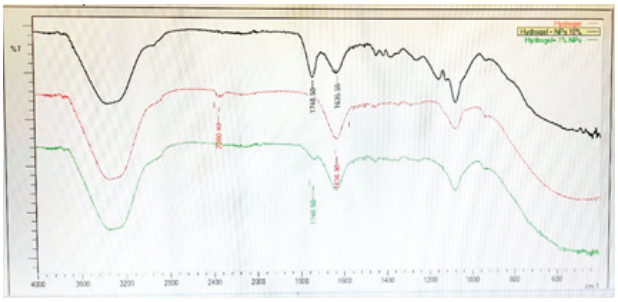
In order to incorporate nanoparticles into the thermosensitive hydrogel following approached were used: dispersion of freeze dried nanoparticles into obtained hydrogel, dispersion of freeze dried nanoparticles into precursor solution of hydrogel, incorporation of gel forming agents into nanoparticle suspension.

It has been experimentally established that the powder of nanoparticles is not homogeneously distributed neither in formed hydrogel, nor in hydrogel precursor solution. In both case formation of separate aggregates was observed. Therefore, for the formation of nanocomposite hydrogels, it is preferable to incorporate gel-forming substances into the nanoparticle suspension. As a result, the degree of particle distribution is not changed, the formation of aggregates is not observed. Thus, in order to obtain a nanocomposite hydrogel, a gel-forming substance was added to the nanoparticles suspension of different concentrations (PLGA nanoparticles). Therefore, we estimated the influence of nanoparticles concentrations (0,5; 1; 2; 5; 8) on gelation time and temperature. The results are presented in Table 1.

The results in Table 1summarizes that the concentration of nanoparticles affects the gel forming process, in particular, increasing the particle concentration resulted in increased gelling time and temperature. This can be explained by the fact, that increased number of nanoparticles prevent the cross-linking of the polymer chains. Therefore, the optimum concentration of nanoparticles in hydrogels (which does not dramatically alter the gelation time and temperature) is 5%. Also the concentration of nanoparticles does not change the pH significantly.

Fourier infrared spectroscopy

Possible intramolecular interaction between thermo-sensitive hydrogel and nanoparticles was evaluated by Fourier infrared spectroscopy. The FTIR infrared spectra of pure hydrogel and nanocomposite hydrogel is given below.



Spectrum 1. Infrared spectrum of pure hydrogel and nanocomposite hydrogel

The presence of nanoparticles in the nanocomposite hydrogel is confirmed by the characteristic absorption peak of PLGA at a wavelength of 1748 cm $^{-1}$ which corresponds to the carbonyl group. It should be noted that the concentration of nanoparticles affects its visualization in the hydrogel using infrared spectroscopy as well. As can be seen from the spectrum (№1), this peak is observed only in the nanocomposite hydrogel, where the nanoparticle concentration is 5%.

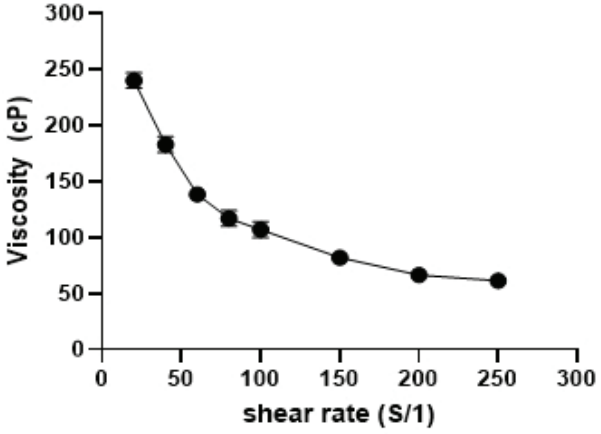
With low nanoparticle concentration (1-2%) the visualization of PLGA characteristic absorption peak could not be observed by this method. Therefore, 5% suspension of nanoparticles was found to be the optimal concentration that did not alter gel forming process. Also, it gives the possibility to assess the nature of the particle-hydrogel possible interaction by FTIR. Additionally, it was observed, that the characteristic absorption peaks of pure hydrogel is maintained in the nanocomposite hydrogel as well. Which indicates that there is no direct chemical interaction between the pure hydrogel and the nanoparticles. It proves that gelation is the result of physical interaction between the polymer chains of gel forming agents.

Evaluation of hydrogel appearance

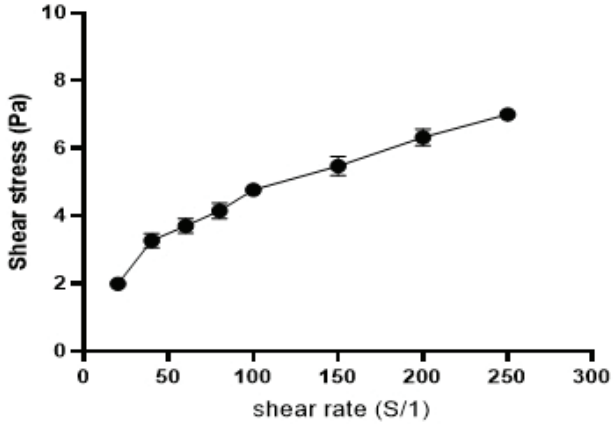
Purity and homogeneity of nanocomposite hydrogel was assessed with naked eye. By incorporating nanoparticles into the pure hydrogel, the composition becomes whitish opaque. The purity of each prepared sample was checked visually on a white and black background. The absence of microparticles in the composition was not observed.

Evaluation of rheological properties of nanocomposite hydrogel

Viscosity is one of the most significant parameters of in-situ hydrogel. After gel formation at body temperature, the nanocomposite hydrogel must have desired rheological properties, which is necessary for maintaining it on the site of injection, prevent leakage of the composition from the tissue to ensure drug diffusion prolongation. To that aim, the rheological properties of the resulting nanocomposite hydrogel was assessed.



RheogramN1. Share rate Vs Viscosity



RheogramN2. Share rate Vs Share stress

The correlation between share rate and share stress, as well as share rate and viscosity are shown on N1 and N2 rheograms, respectively.

As seen from N1 and N2 rheograms, an increase of share rate viscosity of nanocomposite decreases, while tension of displacement increases. Due to such characteristics nanocomposite hydrogel belongs to pseudo plastic systems when viscosity decreases at the increase of share rate. This is conditioned by the fact, that at the increase of share rate the components of a liquid move towards applied force. For pseudo plastic liquids the change of viscosity induced by share stress is not time depended, because the structure of pseudo plastic liquids are not characterized by the ability to restore their initial structure. And this determines deformation ability of a nanocomposite and its plasticity. It can be seen from the rheograms (rheogram №1-2) that the nanocomposite hydrogel retains the rheological characteristics of pseudoplastic fluids.

Evaluate morphology of nanocomposite hydrogel

The shape, distribution, and aggregation tendency of embedded PLGA nanoparticles in hydrogel was assessed by scanning electron microscope. The results are presented by microscopic images №3-4. As SEM photos demonstrates nanoparticles appear to be dispersed in polymeric matrix, with relatively uniform distribution. As it is observed gelation step did not influence on nanoparticle structure as well.

As can be seen from the microscope images (Fig. 1-2), the sphere-shaped polymer nanoparticles are homogeneously distributed, no aggregation take place. In general, the tendency of nanoparticles to aggregate is considered a significant disadvantage of the nano system due to their small size, large surface area, and increased surface activity. Though by incorporating them in hydrogels, the possibility of aggregation is minimized.

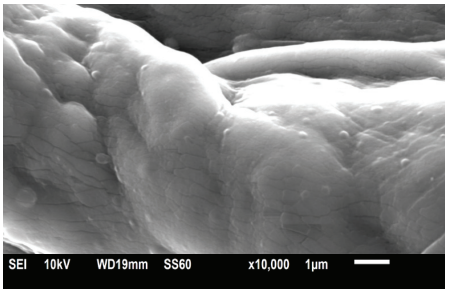


Fig. 1. Scanning electron microscopy of nanocomposite hydrogel

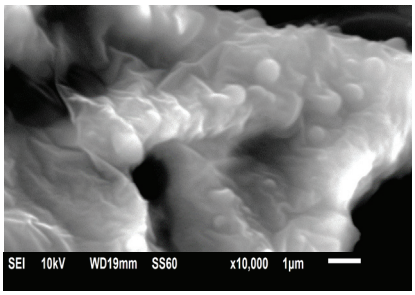
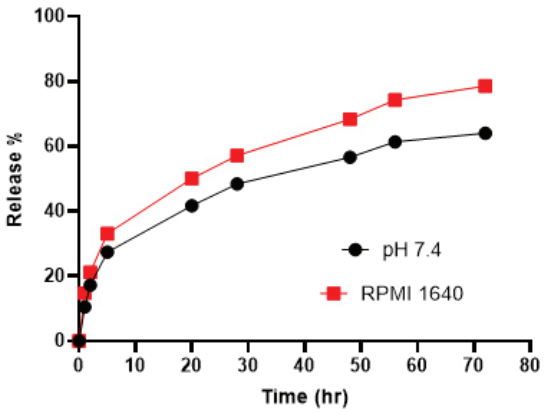


Fig. 2 . Scanning electron microscopy of nanocomposite hydrogel



Graph 1. Release study of extract from nanocomposite hydrogel (PBS (pH 7.4, RPMI 1640))

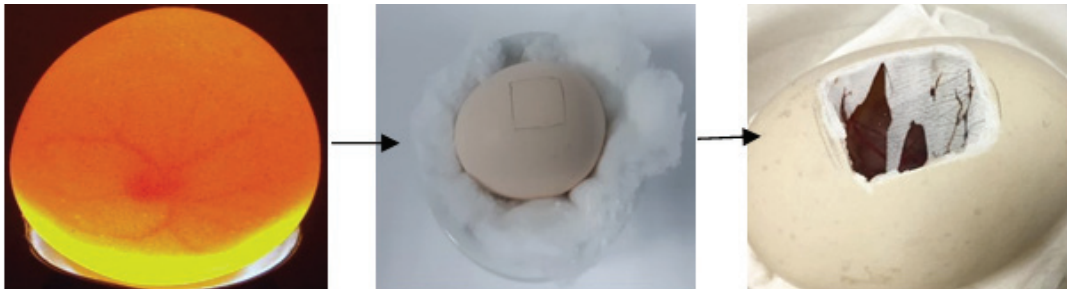


Fig.3 Preparation of egg for experiment

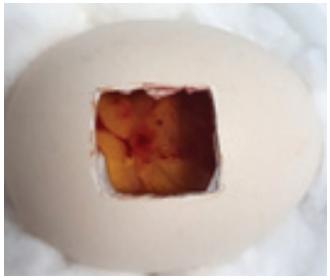


Fig. 4 Positive control

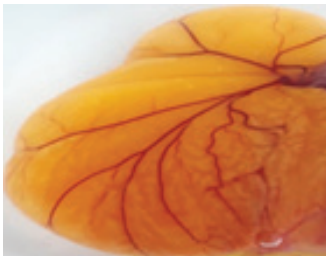


Fig. 5 Negative control

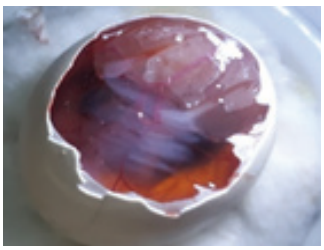


Fig.6 nanocomposite hydrogel

Release study

We studied the release dynamics of total flavonoids (calculated on quercetin) from Erysimum contractum Somm. etLevier extract. Phosphate buffer (pH 7.4) and RPMI 1640 were used as medium. The results of the release determination of the active substance from the nanocomposite hydrogel is shown on graph №1

The in-vitro release profile (Graph1) is biphasic in both, in the phosphate buffer and in RPMI 1640, respectively.

In the initial phase, during the first 5 h, 27% of the active substance from the nanocomposite hydrogel was released into the phosphate buffer and 33% into the RPMI 1640. However, the degree of release decreases during the remaining period of the experiment. At 72 h, 64% and 78% of the active substance (total flavonoids) were released into the phosphate buffer and RPMI 1640, respectively.

The results shows that the release of the active substance from the nanocomposite hydrogel has a prolonged nature, due to the existence of two barriers, on the one hand polymer nanoparticles and on the other hand, hydrogel.

However, the release of the active substance in the RPMI 1640 is faster than in phosphate buffer. This is due to the fact that the cell culture area contains amino acids, as well as it's enriched with calf embryonic serum (10%). Which we used to simulate the biological environment.

Evaluation irritation potential of nanocomposite hydrogel

To evaluate irritation potential of nanocomposite hydrogel a hen's egg model was used to simulate a complex biological environment. The fertilized hen's eggs were placed at thermostat (37^0C -37.5^0C), the experiment was performed after 7 days of incubation when the formation of blood vessels was visible. In the process of conducting the experiment: outer and inner shell of the eggs were carefully removed. The experiment was performed on chorioallantoic membrane. The following samples were placed on chorioallantoic membrane: phosphate buffered saline (pH 7.4) as negative control, 0.1N NaOH as positive control, and nanocomposite hydrogel as test sample. Toxic effects such as hemorrhage, thrombosis, hemolysis, were evaluated at a different time period (0, 1, 2, 4, 8,12). The process of conducting the experiment is shown in Figs 3-6.

The experiment clearly shows that the application of positive control (0.1 N NaOH) on the vascular membrane of the egg reveals vascular damage: hemolysis, thrombosis, hemorrhage. None of the above lesions were observed with negative control and nanocomposite hydrogels. It should be noted that the listed lesions were monitored only for 12 h. Based on a performed experiment, we can conclude that the nano composition is biocompatible as it does not cause various damage to blood vessels.

Conclusion. In this study combination of hydrogel and nanoparticles lead to formulation of nanocomposite hydrogel. Different concentration of PLGA nanoparticles were incorporated into the pure hydrogel. Influence of nanoparticle concentration on gelation time and temperature was evaluated. Combination of 5% PLGA nanoparticles did not influence negatively on the gelation conditions of hydrogel, also, nanocomposite hydrogel maintains the rheological characteristics of pseudoplastic fluids. In the nanocomposite hydrogel polymeric nanoparticles are physically embedded with pure hydrogel. Incorporation of PLGA nanoparticles into the hydrogel, revealed sustained release kinetic of flavonoid-rich extract. Additionally, no irritation effect was observed on the hen's egg model. Thus, formulated nanocomposite hydrogel embedded PLGA nanoparticles could be considered a promising thermo sensitive system for drug delivery of cytotoxic extract. Further experiments are planned by authors to established dose related cytotoxicity of the formulation.

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SUMMARY

FORMULATION THERMORESPONSIVE NANOCOMPOSITE HYDROGELWITH EMBEDDED PLGA NANOPARTICLES CONTAINING CYTOTOXIC AGENT

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The aim of the study was to develop and characterize the nanocomposite in-situ hydrogel as local drug delivery system of cytotoxic agent. In-situ hydrogel consisting of 15% thermosensitive (Poloxamer 407) and 1% mucoadhesive (sodium alginate) polymers was selected as the optimal formulation by the conducted studies.

The influence of nanoparticle concentration on gelation time and temperature has been experimentally established. As a result, the optimum concentration of nanoparticles (5%) is selected, which does not alter the gel forming process. The resulting nanocomposite hydrogel was characterized through Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), rotational viscometer (LVDV-1T). FT-IR spectra confirmed the PLGA nanoparticles presence within the hydrogel matrix through the absorption peak located at 1750 cm^{-1}. SEM images allowed observing the nanoparticles to be homogenously dispersed. The release pattern of the active substance from the nanocomposite hydrogel is following: at 72 h, 64% and 78% of the active substance were released into the phosphate buffer and cell culture area, respectively. Irritation test on hen's egg model revealed that formulated nanocomposite hydrogel did not show damage of vascular system.

Keywords: nanocomposite, thermosensitive hydrogel, PLGA nanoparticles.

РЕЗЮМЕ

РАЗРАБОТКА ТЕРМОРЕАКТИВНОГО ГИДРОГЕЛЯ СО ВСТРОЕННЫМИ НАНОЧАСТИЦАМИ PLGA, СОДЕРЖАЩИМИ ЦИТОТОКСИЧЕСКИЙ АГЕНТ

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Целью исследования явилась разработка нанокомпозитного гидрогеля для местной доставки активного ингредиента.

В результате проведенных исследований в качестве оптимальной композиции выбран гидрогель, состоящий из 15% термочувствительных (полоксамер 407) и 1% мукоадгезивных (альгинат натрия) полимеров. Экспериментально установлено влияние концентрации наночастиц на время и температуру гелеобразования. В результате выбрана оптимальная концентрация наночастиц (5%), не влияющая на процесс гелеобразования. Полученный нанокомпозитный гидрогель охарактеризовали с помощью инфракрасной спектроскопии, сканирующей электронной микроскопии, ротационного вискозиметра (LVDV-1T). Спектры FT-IR подтвердили присутствие наночастиц PLGA в матрице гидрогеля по пику поглощения, расположенному при 1750 $см^{-1}$. Из нанокомпозитного гидрогеля спустя 72 часа в фосфатный буфер и зону культивирования клеток происходило Высвобождение активного вещества в количестве 64% и 78%, соответственно (RPMI 1640). Испытание на раздражение на модели куриного яйца показало, что составленный нанокомпозитный гидрогель не повреждает сосудистую систему.

რეზიუმე

თერმომგრძნობიარე ნანოკომპოზიციური ჰიდროგელის ფორმულაცია და ტექნოლოგია

[1]ლ.ებრალიძე, [1]ა.ცერცვაძე, [1]ლ.ბაკურიძე, [2]დ.ბერაშვილი, [1]ა.ბაკურიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]ფარმაციის ფაკულტეტი, ფარმაცევტული ტექნოლოგიის დეპარტამენტი; [2]ფარმაკოგნოზიისა და ფარმაცევტული ბოტანიკის მიმართულება, საქართველო

კვლევის მიზანს წარმოადგენდა ადგილობრივი მიწოდების ნანოკომპოზიციური in-situ ჰიდროგელის, როგორც მოქმედი ნივთიერების, ადგილობრივი მიწოდების სისტემის შემუშავება და დახასიათება.

ჩატარებული კვლევებით ოპტიმალურ კომპოზიციად შერჩეულია in-situ ჰიდროგელი,რომელიც შედგება 15% თერმომგრძნობიარე (პოლოქსამერ 407) და 1% მუკოადჰეზიური (ნატრიუმის ალგინატი) პოლიმერებისგან.

ექსპერიმენტში დადგენილია ნანონაწილაკების კონცენტრაციის გავლენა გელ-წარმოქმნის დროსა და ტემპერატურაზე. შედეგად შერჩეულია ნანონაწილაკების

ოპტიმალური კონცენტრაცია (5%), რომელიც არ არღვევს თერმომგრძნობიარე გელის ფორმირების პროცესს. მოწოდებული in-situ ჰიდროგელის გელწარმოქმნის ტემპერატურა არის 36.6^{0}C, ხოლო გელწარმოქმნის დრო 10 წთ. მოწოდებული ჰიდროგელი რეოლოგიური მახასიათებლებით შეესაბამება ფსევდოპლასტიკური სითხეების ვისკოელასტიკურ თვისებებს. ნანოკომპოზიციურ ჰიდროგელში შეფასებულია შემადგენელ კომპონენტებს შორის შესაძლო ურთიერთკავშირი ინფრაწითელი სპექტროსკოპიის გამოყენებით. დადგენილია, რომ ჰიდროგელსა და ნანონაწილაკებს შორის პირდაპირი ქიმიური კავშირი არ აღინიშნა. მიკროსკოპულად დადასტურებულია პოლიმერული ნანონაწილაკების ჰომოგენური განაწილება ჰიდროგელში. ნანოკომპოზიციური ჰიდროგელიდან მოქმედი ნივთიერების გამოთავისუფლების დინამიკა ორფაზური და გახანგრძლივებული ხასიათისაა. 72 სთ-ში ფოსფატურ ბუფერში და უჯრედული კულტურის არეში გამოთავისუფლდა მოქმედი ნივთიერების 64% და 78%, შესაბამისად.

მოწოდებული ნანოკომპოზიციური ჰიდროგელის ბიოთავსებადობა შეფასებულია კვერცხის მოდელზე. ჩატარებული ექსპერიმენტით დადადგენილია, რომ ის არ იწვევს სისხლძარღვების ისეთ დაზიანებებს, როგორიცაა სისხლძარღვთა ლიზისი, ჰემორაგია, თრომბოზი, ჰემოლიზი.

HEPATOPROTECTIVE EFFICIENCY OF G10 SUBSTANCE FROM ZHUZGUN PLANT IN EXPERIMENTAL TOXIC HEPATITIS

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The problem of hepatitis is one of the most significant in modern medicine, since millions of cases are registered annually and at the moment there is no tendency to reduce the incidence rate [3,19]. To attract attention to this problem all over the world, who announced the 28th of July the world Day of fight against hepatitis. It should be emphasized that close attention to the problem of hepatitis treatment is due not only to the increase in the incidence of hepatitis worldwide, but also to the increase in the mortality rate. In this regard, for practical health care, the task of finding new, effective treatments that can accelerate the rate of functional recovery of the liver or protect hepatocytes from the damaging effects of hepatotropic viruses and other pathogens remains urgent. The modern approach to adequate treatment of hepatitis involves the use of both synthetic drugs and herbal preparations that have a multi-sided positive effect [3,19].

The hepatoprotective properties of herbal preparations are closely studied by scientists in many countries [4,5,12,13]. The reason for this is their high biological activity, low toxicity and lower probability of side effects compared to drugs of synthetic origin. Biologically active substances of plants are close to the natural metabolites of the human body, they are well compatible with them. Many of them are necessary for normal life and can be used in complex pharmacotherapy of diseases of the hepatobiliary system. Plant objects can become an unlimited source for obtaining phytopreparations, including hepatoprotectors, which, ultimately, will lead to a reduction in the cost of production and release of drugs, and, consequently, to a decrease in its market price [1,14-16].

One of the most common etiological factors that cause pathology of the hepatobiliary system is the action of toxicants of various origins. Toxic liver damage is caused by an absolute increase in the body's contacts with hepatotoxic xenobiotics: household, industrial and agricultural chemicals. In addition, long-term and uncontrolled use of drugs, which is the cause of 40% of hepatitis in patients over 40 years of age, is of significant importance in the development of toxic liver damage [6,7,10,11,17]. At the same time, in most cases of drug-induced liver damage, withdrawal of the drug is sufficient to reverse the development of pathological changes [20]. However, when a long course of treatment with highly effective drugs with potential hepatotoxic effects is required, it is necessary to combine them with correctors of metabolic disorders [20], which may be plant-based hepatoprotectors.

One of the promising species in this direction is the Zhuzgun plants of the genus Calligonum L. of the Polygonaceae family. This genus includes about 150 species, most of which are distributed in the deserts of Central and Central Asia, from the Sahara Desert (North Africa) to Alashan and Ordos in China. On the territory of the Republic of Kazakhstan, this plant is found everywhere and includes about 80 species. In the laboratories of the L. N. Gumilyov Eurasian National University (Republic of Kazakhstan, Moscow, Russia). Nur-Sultan) from the Zhuzgun plant, the substance G10 was obtained on the basis of biologically active substances containing various classes of natural compounds: flavanoids, tannins, terpenoids, amino acids, carbohydrates, trace elements, essential oils, which made it possible to study it as a basis for creating a drug with a hepatoprotective effect [8].

The aim of this study is to study the hepatoprotective properties of the substance G10 obtained from the plant "Zhuzgun" on an experimental model of acute toxic hepatitis in rats and to determine its effectiveness in comparison with the official plant hepatoprotector "Karsil".