ANNOTATION

of the dissertation for the degree of Doctor of Philosophy (PhD) in the specialty 6D072100 – «Chemical Technology of Organic Substances»

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On the topic: «Development of hydrogel forms of antiseptic and antibacterial disinfectants»

The relevance of the problem. According to the world's leading virologists and epidemiologists, most likely the epidemiological crisis "Covid-19", which the world faced in 2020, was far from the last, moreover, such outbreaks of viral infection can acquire a seasonal character. The current reality shows the correctness of such assumptions.

In this regard, the issue of developing adequate protection measures is of particular relevance. This circumstance highlights the need to expand the range of preventive means to protect the population from new threats, including including a set of sanitary and hygienic and anti-epidemic measures aimed at preventing infectious diseases in general.

To date, the leading disinfection method is chemical, based on the use of DS, which are based on active active substances - biocides or disinfectants, which actually determine the antimicrobial activity of DS.

The purpose of the thesis research

The purpose of the dissertation research is to create hydrogel forms of the broad-acting antiseptic chlorhexidine bigluconate and the antibiotic gentamicin using poly-N-vinylpyrrolidone, gellan as gel-forming polymers, as well as hybrid thermosensitive pH-dependent copolymers based on N,N-dimethylacrylamide and acrylic acid.

Research objectives:

- investigation of the basic laws of the synthesis of polymer hydrogels in the process of radiation three-dimensional polymerization of N-vinylpyrrolidone in the presence of a crosslinking agent and the physico-chemical properties of the crosslinking polymers formed in this case;
- development of laboratory technology for the production of hydrogel ointments and dressings based on poly-N-vinylpyrrolidone containing the antiseptic chlorhexidine bigluconate;
- the study of phase transitions in aqueous solutions of gellan under the action of additives of low molecular weight salts, the study of the physico-chemical properties of the hydrogels formed at the same time, the development of antiseptic ointments based on them
- synthesis and investigation of the physico-chemical properties of hybrid thermosensitive pH-dependent copolymers of linear and crosslinked structure of N,N-dimethylacrylamide (DMA) and acrylic acid (AA) and the creation of a hydrogel form of the broad-spectrum antibiotic gentamicin on their basis;
- biomedical investigation of the obtained hydrogel forms of chlorhexidine bigluconate and gentamicin

Research methods: Fourier transform infrared spectroscopy, UV and visible spectroscopy, elemental analysis, turbidimetry, gravimetry, deformation and mechanical testing of hydrogels, scanning electron microscopy, rotational viscometry, rheology.

Objects of research: hydrogels based on poly-N-vinylpyrrolidone, gellan and copolymers N,N-dimethylacrylamide and acrylic acid;

Subject of research: radiation three-dimensional polymerization of VP; physico-chemical properties and structural parameters of hydrogels formed in the processes of three-dimensional polymerization of VP and radiation crosslinking of PVP; gelation in aqueous solutions of gellan under the action of additives of low molecular weight salts; stimulus-sensitive behavior of water-soluble and water-swelling copolymers DMA-AA; biomedical properties of hydrogel ointments and dressings based on PVP, gellan and DMA-AA copolymer containing CH or gentamicin.

The main provisions submitted for protection:

- antiseptic hydrogel ointments and dressings containing 0.05 wt.% chlorhexidine bigluconate (CH) with anti-inflammatory and wound healing activity can be obtained on the basis of crosslinked PVP formed during three-dimensional radiation polymerization of the VP monomer in the presence of CA or by radiation crosslinking of poly-N-vinylpyrrolidone macromolecules;

- antiseptic hydrogel ointments with pronounced antifungal and antibacterial activity, containing 0.05 wt.% chlorhexidine bigluconate and 20 wt. % sodium thiosulfate can be obtained on the basis of gellan hydrogel formed during the phase transition in its aqueous solution under the influence of additives CH and sodium thiosulfate;

- the presence of water-soluble and water-swelling copolymers of ionic and hydrophobic components in the structure determines their sensitivity to the effects of both temperature and pH of the medium, which is manifested in their ability to phase transitions when exposed to these two parameters; the cross-linked copolymer DMA-AA can be used to create an antibacterial hydrogel form of gentamicin, an antibiotic with a wide spectrum of action.

The main results of the study:

1 The formation of polymer hydrogels in the process of radiation three dimensional radical polymerization of N-vinylpyrrolidone (VP) using N,N'-methylene bis-acrylamide (BAA) as a crosslinking agent (CA) was in detail studied. It is shown that an increase in the radiation dose and the concentration of the crosslinking agent in the initial monomer mixture (IMM) is accompanied by an increase in the yield of the gel fraction and the modulus of elasticity of the formed gels, the equilibrium degree of swelling in the water of which decreases. For the first time, for hydrogels formed during radiation crosslinking polymerization of VP in the presence of CA (BAA), based on data on the modulus of elasticity of meshes and sol-gel analysis, the structural parameter of polymer meshes M_C was calculated, which is the value of the average molecular weight between the crosslinking nodes of a polymer hydrogel. It is shown that an increase in the radiation dose or the

concentration of the crosslinking agent in the IMM is accompanied by an increase in the crosslinking density of the formed polymer meshes, which is expressed in a decrease in the values of M_C. A comparison of the values of the structural parameter M_C, performed on the basis of experimental data, and M_C, calculated theoretically taking into account only the concentration of CA in the IMM, shows that the formation of a cross-linked structure of PVP is carried out not only with the participation of double suspended bonds of CA BAA, but also with the participation of PVP macroradicals formed in the process of radiation irradiation of the reaction mixture. It was also found that water has an activating effect on N-vinylpyrrolidone molecules, which causes the phenomenon of an abnormal acceleration of the three-dimensional radical polymerization of this monomer when diluted with IMM with water, accompanied by a corresponding increase in the yield of the gel fraction.

2 For the first time, a laboratory technology was developed for the production of hydrogel ointments and dressings based on poly-N-vinylpyrrolidone containing the antiseptic chlorhexidine bigluconate, for which a complex of biomedical studies was performed. At the same time, radiation crosslinking of poly-N-vinylpyrrolidone macromolecules was used to obtain hydrogel dressings, which makes it possible to combine two operations in one technological stage: the formation of a finished product (hydrogel dressing) and its sterilization. As a result of studies conducted in "in vivo" conditions, it was found that the obtained hydrogel ointments and dressings have pronounced anti-inflammatory and anti-burn activities.

3 The formation of hydrogels during phase transitions in aqueous solutions of gellan under the action of additives of chlorhexidine bigluconate and sodium thiosulfate was studied for the first time. It has been shown that in the presence of CH, the formation of gellan gel proceeds at a higher rate and yield than in the presence of sodium thiosulfate, which is obviously due to the multicharging of CH and its organic nature, which cause a more pronounced deterioration in the thermodynamic quality of water as a solvent. The physicochemical properties of the hydrogels formed in this process have been studied, hydrogel ointment compositions have been developed on their basis, for which rheological properties have been studied.

4 For the first time, on the basis of gellan hydrogel formed during the phase transition of its aqueous solution under the action of CH and sodium thiosulfate additives, a laboratory technology for the production of antiseptic hydrogel ointments has been developed, for which rheological properties have been studied. It is shown that hydrogel ointments have the parameters of non-Newtonian liquids characterized by pronounced thixotropic properties due to the destruction and restoration of the three-dimensional structure in the process of viscous flow. For antiseptic hydrogel ointments containing CH and sodium thiosulfate, as a result of the conducted biomedical studies, their pronounced antifungal and antibacterial activity has been established.

5 Hybrid thermosensitive pH-dependent copolymers of linear and mesh structure based on N,N-dimethylacrylamide (DMA) and acrylic acid (AA) have been obtained. It was found that the obtained copolymers (CPL) are simultaneously sensitive to changes in pH and temperature of the surrounding solution. At the same

time, for their aqueous solutions, the phase separation temperature naturally increases with an increase in the pH of the medium. For DMA-AA network CPL, a thermally induced continuous flow is observed, the parameters of which are regulated by a change in the composition of the CPL and the pH of the medium. For the first time for hybrid hydrogels of CPL DMA-AA, it was shown that the curves of the temperature dependence of their relative volume can have a complex form, including the stages of swelling and contraction, due to the competition of oppositely directed effects of ionic and hydrophobic components in the structure of the obtained polymer hydrogels.

6 For CPL DMA-AA hydrogels containing the antibiotic gentamicin, biomedical tests were performed using the bacteria GP (*Staphylococcus aureus* ATCC 6538-p) and GN (*E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 9027)). It was found that antibiotics diffuse well into the environment from hydrogel carriers, suppressing the growth of test microorganisms and creating a lysis zone around the carrier with antibiotics, which indicates a well-expressed ability of hydrogels to deliver drugs.

Tests of hydrogel ointments based on PVP and gellan for antiseptic and disinfection treatment have been carried out in medical institutions. It has been shown that hydrogel ointments, creating a protective film on the surface of equipment or rigid furniture for a long time (at least three days), are active in infections of bacterial, viral, fungal etiology. When used for antiseptic treatment of the hands of medical personnel, unlike other antiseptic agents, hydrogel ointments based on gellan with chlorhexidine biglucanate and sodium thiosulfate do not cause dry skin of the hands and any allergic reactions. The obtained test results indicate the high efficiency and prospects of practical use of hydrogel ointments containing HCG in medical institutions as antiseptic and disinfectants.

Substantiation of the novelty and importance of the results obtained.

Results 1-6 are characterized by novelty and significance, since they were obtained for the first time and are aimed at realizing the main goal of the dissertation work on the creation of hydrogel forms of the broad-acting antiseptic chlorhexidine bigluconate and the antibiotic gentamicin using polymers of various nature.

Theoretical significance of the results. The results of the study of the physico-chemical behavior of DMA-AA copolymers of linear and mesh structure and phase transitions with their participation induced by the influence of temperature and pH of the medium make a significant contribution to the development of theoretical ideas about the features of macromolecular design and functioning of stimulus-sensitive polymers.

Practical significance of the results.

The hydrogel ointments and dressings based on PVP and gellan obtained in the work can be recommended as effective antiseptic, antibacterial, disinfectants and wound healing agents.

Compliance of the work with priority areas of scientific development or government programs.

The work was carried out within the framework of the Targeted Scientific and Technical Program BR05236419 "Creation of functionalized organic substances and

materials with a wide range of possible highly effective practical applications (2018-2020), funded by the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan.

The author's personal contribution consists in the direct execution of the experimental part of the work, participation in the analysis, discussion and interpretation of the experimental data obtained.

The structure and scope of the dissertation. The dissertation is presented on 124 pages of typewritten text and includes an introduction, 3 sections, conclusion, 20 tables, 54 figures and a list of used sources from 183 titles.

Approbation of the work. The main results of the dissertation were reported and discussed at the III International Scientific and Practical Conference "Research and Development in promising scientific fields" (Novosibirsk, Russia, 2018), at the International Scientific Conference of Students and Young Scientists "FARABI ALEMI" (Almaty, Kazakhstan, 2018), at the Uzbek-Kazakh Symposium "Modern Problems Polymer Sciences", (Tashkent, Uzbekistan, 2020), at the International Symposium "Science, Education, Innovation: Global Trends and Regional Aspects", dedicated to the 80th anniversary of the birth of Academician E.E. Ergozhin (G. Almaty, Kazakhstan, 2021), at the 22nd International Conference on Science and Technology Russia-Korea-CIS (Moscow, Russia, 2022).

Publications.

1 Myltykbaeva Zh.K., Kairbekov Zh., Asanov M.K., Kovaleva G.G. Studies of the effectiveness of the disinfectant "Zhusan Formin" // KBTU Khabarshysy. - 2018, Vol. 15, Issue 1., pp. 53-59.

2 Myltykbaeva Zh.K., Asanov M.K., Kovaleva G.G. Evaluation of the effectiveness and safety of the disinfectant “Zhusan Mega" // Bulletin of KazNITU. 2019 No3 pp.53-58.

3 Kovaleva G.G., Myltykbaeva Zh.K., Asanov M.K. Smile M, Turegeldieva G., Smile M// Effectiveness of a disinfectant containing amines and chlorine on spore-forming microorganisms // Bulletin of PSU, Chemical and Biological series, - 2019. - No. 2. - pp. 19-27.

4 U. Nakan, SH. Bieerkehazhi, B. Tolkyn, Grigoriy A. Mun, Assanov M., Merey E. Nursultanov, Raikhan K. Rakhmetullayeva, K.Toshtay, El-Sayed Negim and A. Ydyrys. Synthesis, Characterization and Antibacterial Application of Copolymers Based on N,N-Dimethyl Acrylamide and Acrylic Acid. Materials 2021, 14, 6191, P 1-12. , Q2 (Wos and Scopus), IF=3,748 (WoS); Percentile 55 (Scopus), https://doi.org/10.3390/ma14206191.

5 Kim K.I., Mangazbaeva R.A., Asanov M.K., Ermukhambetova B.B., Alikulov A.J., Balabaeva A.M., Zezin A.A. Creation of antiseptic ointments based on gellan hydrogels and chlorhexidine bigluconate // Proceedings of the scientific and technical society "KAHAK". - 2023. - No. 2 (80). – pp. 48-73.

6 Myltykbaeva Zh.K., Asanov M.K., Kovaleva G.G. Production of disinfectants as a component of infectious safety // Materials of the III International Conference "Research and Development in promising scientific fields". - Novosibirsk, January 23, February 21, 2018 From-13-17 5 .

7 Asanov M.K. Myltykbayeva Zh.K., Evaluation of the effectiveness of the disinfectant "Zhusan Formin" // Collection of abstracts of the International scientific Conference of students and young scientists "Farabi alemi", Almaty, 2018. p. 274.

8 Asanov M.K., Mangazbaeva R.A., Ermukhambetova B.B., Alikulov A., Zezin A.A., Development of hydrogel antiseptic ointment based on poly-N-vinylpyrolidone // Proceedings of the Scientific and Technical Society "KAHAK", 2024, No. 1 (81). pp. 88-96. Almaty 2024.

Description of the doctoral student's contribution to the preparation of each publication.

1 Myltykbaeva Zh.K., Kairbekov Zh., Asanov M.K., Kovaleva G.G. Studies of the effectiveness of the disinfectant "Zhusan Formin" // KBTU Khabarshysy. - 2018, Vol. 15, Issue 1., pp. 53-59.

The applicant made the main contribution to the development of the composition and evaluation of the effectiveness of the applications of the disinfectant “Zhusan Mega”.

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The applicant made the main contribution to the development of the composition and evaluation of the effectiveness of the applications of the disinfectant “Zhusan Mega”, as well as to the preparation and writing of the draft and final version of this article.

3 Kovaleva G.G., Myltykbaeva Zh.K., Asanov M.K. Smile M, Turegeldieva G., Smile M// Effectiveness of a disinfectant containing amines and chlorine on spore-forming microorganisms // Bulletin of PSU, Chemical and Biological series, - 2019. - No. 2. - pp. 19-27.

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The applicant has completed the entire scope of work on the study of DMA and AA copolymerization. He synthesized and developed experimental samples of DMA-AA hydrogels containing gentamicin, as well as transferred them to biomedical tests. He took an active part in the discussion of the scientific results obtained, he also prepared the initial version of this article, corrected the articles in accordance with the comments received by the reviewers.

5 Kim K.I., Mangazbaeva R.A., Asanov M.K., Ermukhambetova B.B., Alikulov A.J., Balabaeva A.M., Zezin A.A. Creation of antiseptic ointments based

on gellan hydrogels and chlorhexidine bigluconate // Proceedings of the scientific and technical society "KAHAK". - 2023. - No. 2 (80). – pp. 48-73.

Аыsanov M.K. carried out research on the formation of gellan gel in aqueous solutions under the action of additives of low molecular weight salts of CH and sodium thiosulfate. He took part in the development of the technology of hydrogel ointments based on gellan containing CH.

6 Myltykbaeva Zh.K., Asanov M.K., Kovaleva G.G. Production of disinfectants as a component of infectious safety // Materials of the III International Conference "Research and Development in promising scientific fields". - Novosibirsk, January 23, February 21, 2018 From-13-17 5.

The applicant made the main contribution to the development of the composition and evaluation of the effectiveness of the disinfectant, as well as to the preparation and writing of the draft and final version of this article.

8 Asanov M.K., Mangazbaeva R.A., Ermukhambetova B.B., Alikulov A., Zezin A.A., Development of hydrogel antiseptic ointment based on poly-N-vinylpyrolidone // Proceedings of the Scientific and Technical Society "KAHAK", 2024, No. 1 (81). pp. 88-96. Almaty 2024.

Asanov M.K. carried out research on the formation of a PVP gel in the process of three-dimensional polymerization of a monomer in the presence of a crosslinking agent. He took part in the development of the technology of hydrogel ointments based on PVP containing CH.