

ANNOTATION

of the dissertation for the degree of Doctor of Philosophy (PhD) in the specialty
8D07105 – «Chemical Technology of Organic Substances»

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on the topic: «Development of new iodine-containing polymer compositions
based on poly(2-oxazolines) for application in medicine»

Relevance of the research topic. Of particular interest to researchers over the past five years is the direction of creating effective antimicrobial agents due to the risk of the spread of viruses and microbes in public places and transport, as well as the resistance of microorganisms to most antibiotics. Iodine has antimicrobial and antiseptic properties and simultaneously affects all organs of microbial cells. Exposure to iodine leads to rapid destruction of membranes and cytoplasm, and complex formation with polymeric carriers not only increases the solubility of iodine, but also promotes its prolonged release and a decrease in the equilibrium concentration in the free form. Complexes of iodine with polymers (iodophors) exhibit bactericidal, fungicidal and virucidal activities. According to the literature data, complexes of iodine with many water-soluble polymers, such as polyvinyl alcohol, starch, polyvinylpyrrolidone (PVP), chitosan, polyethylene glycol (PEG), and cyclodextrins, have been studied. Currently, povidone-iodine is widely used as an antimicrobial agent for external use and for disinfecting the surfaces of various devices.

Poly(2-oxazolines) are a class of polymers with biocompatibility, cyto- and hemocompatibility, and non-immunogenicity. Some poly(2-oxazolines), such as poly(2-methyl-2-oxazoline) (PMOZ), poly(2-ethyl-2-oxazoline) (PEOZ) and poly(2-propyl-2-oxazoline) (PPOZ) and poly(2-isopropyl-2-oxazoline) (PiPOZ) are soluble in water. Poly(2-oxazolines) have a carbonyl group and an amide bond in their structure resembling PVP and are potential alternatives to PVP and PEG in many biomedical applications. At the same time, as far as is known, there are currently no studies in the literature on iodophors based on poly(2-oxazolines).

At the Department of the Chemistry and Technology of Organic Substances, Natural Compounds and Polymers of KazNU named after al-Farabi has been successfully conducting research on the study of polymer complex formation for many years, which were reflected in numerous publications in high-ranking journals. Previously, in the department was conducted research on the study of complex formation of homo- and copolymers of vinyl ether of monoethanolamine with iodine. Based on the scientific results of the department new mucoadhesive film materials based on chitosan and PEOZ and hydrogels based on pentaerythritol tetraacrylate, trimethylolpropane triacrylate, pentaerythritol tetrakis(3-mercaptopropionate) and poly(ethylene glycol) diacrylate were created for vaginal drug delivery.

This dissertation work is a continuation of the research work of the department and is aimed at creating new iodine-containing compositions based on poly(2-oxazolines) with antimicrobial properties for the treatment of vaginal infections.

The purpose of the dissertation research is the study of new complexes of iodine with poly(2-oxazolines) to create new iodine-containing polymer compositions with antimicrobial properties for use in medicine and the development of their production technology.

Tasks:

1) synthesis of PMOZ, PPOZ, study of complex formation of polyalkyloxazolines (PAOZ) with iodine, comparative characterization of iodophors based on PVP and PAOZ by various physicochemical methods;

2) creation of iodine-containing polymer hydrogel compositions based on PEOZ, study of their physicochemical characteristics, antimicrobial properties *in vitro*, mucoadhesive properties *in vivo*, local irritant effect on animals to determine the possibility of using them as vaginal dosage forms;

3) development of technology for obtaining iodine-containing hydrogel polymer compositions based on PEOZ: calculation of the material balance of production, basic technological equipment and economic justification.

Research methods: UV spectroscopy, ¹H NMR spectroscopy, Fourier transform IR spectroscopy, dynamic light scattering method, isothermal calorimetry, horizontal diffusion system method (Ussing Chamber), viscometry, microbiological studies, and *in vivo* studies on rabbits.

The main provisions submitted for defense:

1. PMOZ, PEOZ and PPOZ form complexes with iodine at a molar ratio of [polymer]:[iodine] equal to 1:1, 5:1 and 10:1, characterized by the presence of a bathochromic shift in the UV spectra and a change in optical density, a decrease in the characteristic viscosity and an increase in the Huggins's constant of iodophor solutions, a decrease in the hydrodynamic radius of PEOZ macromolecules from 7.6 nm to 4.8 nm, and the formation of a monomolecular complex of PEOZ with iodine at a [polymer]:[iodine] molar ratio of 2:1.

2. PEOZ is characterized by a greater ability to complex formation with iodine compared to PVP, which is confirmed by the higher value of the binding constant of iodine with PEOZ (30% higher) and the value of the partition coefficient of iodine (for iodophor PEOZ - 1.47 and iodophor PVP - 1.1). At the same time, both iodophors exhibit similar antimicrobial activity against strains of *Staphylococcus aureus* and *Candida albicans*.

3. The interaction of PAOZ PMOZ, PEOZ, and PPOZ with iodine increases with an increase in the electron-donating properties of the alkyl substituent in the series -CH₃ < -C₂H₅ < -C₃H₇ and is characterized by an increase in the values of the iodine partition coefficient in iodophor systems and Huggins's constants.

The main results of the study and the rationale for the novelty and importance of the results obtained:

1. PMOZ and PPOZ were synthesized by chemical modification of commercially available PEOZ, their structure was studied by IR, NMR spectroscopy and hydrodynamic properties. For the first time, the complex formation of PMOZ, PEOZ, PPOZ with iodine was studied in comparison with PVP, and the main patterns of intermolecular interaction with iodine were established using various modern physicochemical methods of analysis, such as isothermal calorimetry,

dynamic light scattering, capillary viscometry, UV spectroscopy, and distribution in a horizontal diffusion cell. It has been established that with an increase in the concentration of iodine in the complex, more intense coloring occurs, aggregation of the complexes, which manifests itself in a low intrinsic viscosity and a decrease in the hydrodynamic radius of PEOZ from 7.6 to 4.8 nm. It was established for the first time by the method of dynamic light scattering and isothermal calorimetry that PEOZ and iodine are characterized by monomolecular binding. Titration isotherms show the two-phase behavior of polymers in iodine solution, consisting of conformational changes in macromolecules and subsequent aggregation of complexes with iodine. For the first time in this work, the horizontal diffusion cell method was used to study the complex formation of polymers with iodine. The study of the binding ability of PMOZ, PEOZ, PPOZ in a horizontal diffusion cell showed that poly(2-oxazolines) exhibit a greater ability to bind iodine, while the binding ability depends on the structure of poly(2-oxazolines).

2. For the first time, hydrogel polymeric compositions based on PEOZ complexes with iodine were created and *in vitro* antimicrobial properties, adhesive, *in vivo* locally irritating properties of the vaginal environment were studied. It has been established that the content of PEOZ in the hydrogel composition improves rheological characteristics and promotes prolonged release of iodine. The optimal concentration of carbopol in the compositions is 1,25 %. Iodophors based on PEOZ have greater antiviral and fungicidal activity compared to iodine. At the same time, hydrogel compositions do not irritate the vaginal environment of female experimental rabbits and are retained in the vagina for 48 hours.

3. For the first time, a basic technological scheme to produce hydrogel compositions based on carbopol and a complex of PEOZ with iodine was developed, a laboratory procedure to produce hydrogel dosage forms was developed, the material balance of production was calculated for 1000 pieces of products per year, the productivity of the main equipment and main economic indicators of production. It is established that the cost of manufactured products, payback period and profitability are 12,369.25 tenge, 2.9 years and 23.9 %, respectively.

Theoretical and practical significance of the results

The established basic patterns of complex formation of poly(2-oxazolines) with iodine can be used to develop new iodine-containing polymer compositions based on polyoxazolines with antimicrobial properties. The obtained iodine-containing hydrogel polymeric compositions based on PEOZ can be recommended as antimicrobial mucoadhesive preparations for a wide range of applications (local, buccal, vaginal, etc.).

Compliance with the directions of development of science or government programs (projects)

The dissertation work was carried out within the framework of the grant funding program of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan AP08052780 «Development of technology for obtaining new vaginal dosage forms based on hydrophilic polymers» 2020-2022.

Publications

As a result of the research, within the framework of the dissertation work, 6 scientific papers were published in co-authorship, including 1 article in the international peer-reviewed journal «European Polymer Journal» (Q1, percentile 90%), 1 review article in the Review Journal of Chemistry (new title Reviews and Advances in Chemistry, Pleiades Publishing, Ltd., distributed by Springer Nature), 1 article in the journal «Chemical Journal of Kazakhstan», included in the list of journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan, as well as materials and abstracts of 3 reports at international scientific conferences.

Description of the contribution of the doctoral student to the preparation of each publication

The doctoral student was directly involved in obtaining experimental data, processing, and interpreting experimental results for the preparation of the article «Polymeric iodophors with poly(2-ethyl-2-oxazoline) and poly(N-vinylpyrrolidone): optical, hydrodynamic, thermodynamic, and antimicrobial properties» in «European Polymer Journal» (2022, vol. 165, no. 15, P. 111005 - 111015, Q1).

The doctoral student was directly involved in obtaining experimental data, processing, and interpreting the results obtained for the design of the article «Obtaining and studying the physicochemical properties of hydrogel ointments based on the complex of poly(2-ethyl-2-oxazoline) with iodine and carbopol» in the journal «Chemical Journal of Kazakhstan» (2022, 4(80), pp. 26-36).

The doctoral student was directly involved in the collection of literature and data processing and the design of the review article «Polymeric Iodophors: Preparation, Properties, and Biomedical Applications» in the «Review Journal of Chemistry» (2020, vol. 10, no. 1, pp. 40–57) (new title Reviews and Advances in Chemistry, Pleiades Publishing, Ltd., distributed by Springer Nature).

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