

## ANNOTATION

of 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: "Creation of new biodegradable materials for drug delivery"

**Relevance of the research topic.** In recent years, interest in biodegradable materials has increased significantly. In biomedicine, biodegradable polymeric materials are used for the development of therapeutic devices, including temporary implants and 3D scaffolds for tissue engineering. The use of biodegradable polymeric materials for pharmacological applications, such as delivery devices for controlled/prolonged drug release, has been further developed. Biodegradable implantable polymers as matrices for various drugs can bypass the need for surgery to remove the implant, and also reduce the likelihood of a chronic immune response; in addition, the versatility of polymeric materials makes it possible to control drug release using the specific characteristics of polymers. Biodegradable polymers can be synthesized in various ways but one of the most modern and versatile methods is the thiol-ene "click" reaction. These reactions imply mild synthesis conditions, high yields and, for this reason, are quite an attractive synthetic tool. Speaking about the prolonged release of drugs, one of the most promising and widespread is the use of mucoadhesion principle in the development of dosage forms. Adhesion to mucosal covering epithelial tissues is of interest to the pharmaceutical industry in terms of improving localized drug delivery. Localization is necessary to maintain the required therapeutic concentration of the drug, since with traditional delivery methods, significant amounts of the drug can be lost on the way to the target organ. When using mucoadhesive polymers, the residence time of drugs on the mucous membranes can be significantly increased which ensures their steady release at a given target site.

The development of new polymer dosage forms with mucoadhesive and biodegradable properties is one of scientific directions of Department of Chemistry and Technology of Organic Substances, Natural Compounds and Polymers of al-Farabi KazNU. Earlier, department developed various polymeric materials for biomedical purposes based on 2-hydroxyethyl methacrylate and 2-hydroxyethyl acrylate, which have mucoadhesive properties, these materials were tested as buccal dosage forms. It is worth noting development of hydrogel materials based on polyvinyl alcohol and 4-mercaptophenylboronic acid, which are capable of degradation in glutathione. Also ocular dosage forms based on chitosan and poly(2-ethyl-2-oxazoline) exhibiting mucoadhesive properties, etc. were obtained at the department.

This work is a continuation of these studies and is devoted to the development of new biodegradable materials with mucoadhesive properties for drug delivery.

### **Purpose of the work**

Creation of new biodegradable materials based on pentaerythritol tetraacrylate (PETA), trimethylol propane triacrylate (TMPTA), pentaerythritol tetrakis(3-

mercaptopropionate) (PEMP) and poly(ethylene glycol) diacrylate (PEGDA) for use as drug delivery systems.

#### **Tasks:**

1. Synthesis of biodegradable mucoadhesive polymeric materials based on pentaerythritol tetraacrylate, trimethylol propane triacrylate, pentaerythritol tetrakis(3-mercaptopropionate) and poly(ethylene glycol) diacrylate for drug delivery;
2. Study of the physicochemical and mechanical properties of the obtained polymeric materials;
3. Study of the obtained gels as biodegradable and mucoadhesive materials for drug delivery;
4. Developing hydrogel dosage forms with clindamycin phosphate and clotrimazole and studying their release profiles;
5. Evaluation of the antibacterial and antifungal properties of the obtained hydrogel dosage forms;
6. Development of several technological aspects for preparation of gel dosage forms (development of a basic technological scheme, calculation of the material balance of production).

#### **Research methods**

A number of modern methods of research and analysis were used in the work: Fourier transform IR spectroscopy, RAMAN, UV spectroscopy, thermogravimetric analysis, scanning electron microscopy, atomic force microscopy, gravimetry, mechanical analysis, elemental analysis, microbiological tests, research of biodegradation and mucoadhesive properties of gels.

#### **Scientific novelty and main results of the study**

For the first time, gels based on PETA-PEMP, TMPTA-PEMP, PEGDA-PEMP were obtained by thiol-ene "click" chemistry method. Using sol-gel analysis methods, it was established that gel formation process depends on composition of the initial monomer mixture (IMM), the stoichiometric composition of IMM in terms of thiol and acrylate functional groups increases gel fraction yield.

The chemical composition of PETA-PEMP, TMPTA-PEMP, and PEGDA-PEMP gels was determined by IR-, Raman-spectroscopy and elemental analysis for S content. The presence of ester groups in the composition of gels that have not reacted with C=C bonds has been established. Raman spectroscopy spectra show peaks characteristic for S-S, S-H groups. The results of elemental analysis showed that with an increase of PEGDA content in the IMM, the sulfur content decreases in the composition of the gels.

For the first time, the thermal characteristics of gels based on PETA-PEMP and TMPTA-PEMP were studied by TGA. It has been established that PETA-PEMP and TMPTA-PEMP samples demonstrate thermal stability, the onset of decomposition is observed at temperatures above 345–360 °C. The mechanical characteristics of gels based on PEGDA-PEMP have been studied for the first time. For the stoichiometric composition of IMM by functional groups, an improvement in the mechanical properties of PEGDA-PEMP gels was observed. The morphological features of PETA-PEMP, TMPTA-PEMP, PEGDA-PEMP gels have been studied

by scanning electron microscopy and atomic force microscopy. It is shown that decrease in the porosity of PETA-PEMP, TMPTA-PEMP, and PEGDA-PEMP polymer networks is characteristic for samples with stoichiometric composition of IMM by functional groups.

The biodegradation properties of gels based on PETA-PEMP and TMPTA-PEMP in solutions of porcine liver esterase (PLE) have been studied for the first time. The presence of esterase slowed down the rate of polymer degradation. For the first time, the biodegradability of gels based on PEGDA-PEMP in a solution of artificial vaginal fluid (AVF) was studied; it was found that polymer samples do not degrade for three weeks. For the obtained PETA-PEMP, TMPTA-PEMP and PEGDA-PEMP gels, their biodegradation in a hydrogen peroxide solution was studied for the first time, it was shown that all gels degrade passing through the swelling stage as a result of oxidative destruction of sulfide bonds with the formation of sulfoxide, sulfone and even sulfate groups, as well as hydrolytic destruction of ester groups. The biodegradation of gels depends on the concentration of hydrogen peroxide solutions and the composition of the gels themselves.

Mucoadhesive properties of gels based on PEGDA-PEMP in relation to the mucous surface of the vaginal tissues of the ewe have been studied for the first time. It was shown that with an increase in the thiol PEMP component the mucoadhesiveness of polymeric materials improves, which is associated with formation of disulfide bonds between SH groups of cysteine of mucous tissues and sulfide groups of PEGDA-PEMP gel.

Hydrogel dosage forms based on PEGDA-PEMP with antimicrobial agents clindamycin phosphate and clotrimazole were obtained for the first time. The process of loading a drug substance (DS) into a PEGDA-PEMP hydrogel matrix and the rate of drug release from it were studied. It was found that the nature of the release of clindamycin phosphate from the polymer matrix is prolonged. At the same time, an increase in the hydrophilic component in the composition of PEGDA-PEMP gels increases the amount of clindamycin phosphate loaded into the polymer network, which is probably associated with the formation of hydrogen bonds between the polymer and the drug substance, as well as with the water solubility of the drug. It was determined that the composition of the PEGDA-PEMP gels does not affect the amount of the hydrophobic drug clotrimazole loaded and released from the gel dosage form (DF). PEGDA-PEMP gels with clotrimazole demonstrate prolonged release of the drug from the polymer matrix.

For the first time, the antimicrobial properties of resulting DF against *Staphylococcus aureus* and *Candida albicans* were studied. It has been established that PEGDA-PEMP with clindamycin phosphate have good antimicrobial properties, depending on the degree of drug loading in the DF, which is associated with gel composition. The antifungal activity of PEGDA-PEMP with clotrimazole is less pronounced than the antimicrobial properties of PEGDA-PEMP with clindamycin phosphate and does not depend on the composition of the gels.

#### **Theoretical significance of the work**

For the first time, gels based on PETA-PEMP, TMPTA-PEMP, PEGDA-PEMP were obtained by thiol-ene "click" chemistry method, and the effect of IMM

composition on gel fraction yield, mechanical properties, porosity, mucoadhesive and biodegradable properties of the obtained polymeric materials was studied.

### **Practical significance of the study**

Development and synthesis of effective drug delivery systems are of vital importance for medicine and public health. This work shows that resulting gels can be proposed as promising biodegradable drug carriers due to their mucoadhesive and biodegradable properties.

### **The main provisions submitted for defense:**

1. Interaction in PETA-PEMP, TMPTA-PEMP, PEGDA-PEMP systems is accompanied by gelation as a result of thiol-ene "click" reactions. IMM composition affects gelation, swelling ability, and mechanical properties of the resulting systems.

2. The stoichiometric composition of IMM by functional groups for PETA-PEMP and PEGDA-PEMP systems increases the yield of the gel fraction, improves the mechanical properties, and reduces porosity of resulting polymer networks.

3. The mucoadhesive properties of hydrogels based on PEGDA-PEMP are improved as a result of an increase in the content of thiol groups in their composition.

4. Gels based on PETA-PEMP, TMPTA-PEMP, PEGDA-PEMP are biodegradable in hydrogen peroxide and hepatic esterase solutions, which may allow their use as drug delivery systems.

5. The most attractive dosage forms in terms of effectiveness is PEGDA-PEMP antibacterial system with clindamycin phosphate compared to PEGDA-PEMP antifungal system with clotrimazole. At the same time PEGDA-PEMP with clotrimazole demonstrates a higher prolongation of drug release.

### **Compliance with the directions of scientific development or state programs**

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, BR05236419 "Creating functionalized organic substances and materials with a wide range of possible highly effective practical applications" 2018-2020.

### **Publications**

As a result of research on the topic of the dissertation, 9 scientific papers were published in co-authorship, including 1 article in the international journal *Polymers of Advanced Technology* (Q2, percentile 75%), 1 article in the journal *Polymer Science, Part B* (Q3, percentile 37%), 1 article in the journal *Complex Use of Mineral Raw Materials*, which is included in the list of journals recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 1 useful model of the Republic of Kazakhstan, as well as materials and abstracts of 5 reports at international scientific conferences and symposiums.

### **Personal contribution of a doctoral student to the preparation of each article**

The doctoral student was directly involved in obtaining experimental data, processing and interpreting the experimental results for the preparation of article

«Synthesis of hydrolytically and oxidation-responsive networks using thiol-ene “click” chemistry with pentaerythritol tetrakis(3-mercaptopropionate) and tri/tetraacrylates» in journal *Polymers for Advanced Technologies* (2020, Vol. 32, №7, P. 1– 8. Q2).

The doctoral student was directly involved in the search for literature data, processing and writing for the preparation of article «Thiol-Ene “Click Reactions” as a Promising Approach to Polymer Materials» in journal *Polymer Science, Part B* (2022, Vol. 64, P. 1-16. Q3).

The doctoral student was directly involved in processing and interpreting the experimental results for the preparation of article «Synthesis and characterization of new biodegradable gels based on 2, 2'-(ethylenedioxy) diethanethiol and pentaerythritol triacrylate» in journal *Complex Use of Mineral Resources* (2022, Vol. 320, №1, P. 25-31).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting the experimental results for the preparation of the patent on useful model №5762 (Published in Bull. No. 29 dated 07/23/2021) on Method of production of degradable thiol-ene polymers based on pentaerythritol tetraacrylate (PETA) and pentaerythritol tetrakis (3-MERKAPTOPROPIONATA) (PEMP).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting the experimental results for the preparation of the materials and abstracts of 5 reports at international scientific conferences and symposiums.