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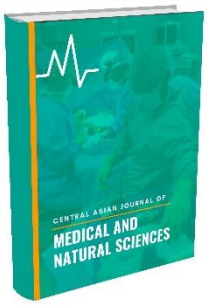

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EVALUATION OF THE EFFECT OF PROLONGATION IN EYE DRUG FILMS

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ABSTRACT: The work is devoted to the assessment of prolongation in eye drug films. It is shown that the use of prolonged polymer forms of medicines in the treatment of various, including ophthalmic, diseases contributes to increasing the effectiveness and reducing the level of negative effects of the drug on healthy organs.

KEYWORDS: Evaluation, effect of prolongation, eye drug films, medicine.

INTRODUCTION

Prolongation of the action of drugs in the body is one of the ways to maintain the therapeutic concentration of drugs in the body for a long time.

There are many methods of prolongation of the action of drugs, the main principles of which include the creation of a "depot" in the body of a drug that releases a constantly dosed therapeutic concentration of the drug for a long time.

The need to prolong the action of low-molecular drugs is determined by the nature of the disease, the frequency and duration of their introduction into the body. Not all forms of low-molecular-weight medicines need to prolong their action in the body. Medicines that require prolongation of their action in the body include:

- low-molecular drugs used in the treatment of chronic diseases that require frequent medication for a long time; (diabetes, tuberculosis, etc.)
- unstable and unstable forms of low-molecular drugs with high toxicity at high doses of administration;
- medicines with a small therapeutic range of action, in order to increase their selectivity of action;

- local medications, the spread of which throughout the body is not desirable because of the possibility of side effects;
- medicines-bioregulators introduced into the body constantly, in small doses.

Creation of prolonged forms of medicines can be carried out in two ways: 1) Creation of polymer forms of medicines with "own" biological activity. The biological activity of this class of polymers occurs only at the polymer level and depends on their composition, structure, and molecular parameters. The mechanism of action of polymers by their own biological activity is not related to their decomposition, but is caused by the properties of macromolecules, in particular, with cooperative polymer-polymer reactions of the medicinal polymer and biopolymers of the body. This mechanism is not possible for low-molecular drugs. Medicinal polymers with " own " activity are as diverse as low-molecular-weight drugs. This class includes biopolymers such as enzymes, hormones, heparin, neutral polymers such as blood substitutes dextran, polyglucin, polyvinylpyrrolidone, polyvinyl alcohol, polycations such as ionene polymers, polyanions such as poly-(I), poly-(C), [1] DEAE – dextran, dextran sulfate, chitosan sulfate, ascorbathitosan, [2] carboxymethylchitosan [3] and other polymers with "own" activity – chitosan, [4] polymer n-oxides, polymer polyphenols – kagocel, celagrip, etc. [5]

The second group of medicinal polymers produced by the synthesis of polymer forms of medicines by chemical, physical and chemical combination of low-molecular drugs with a polymer matrix. In this group, more or less biologically inert polymers and low-molecular biologically active or high-molecular medicinal compounds are used as polymers.

Transport of the second group of medicinal polymers in the body, their interaction with biomembranes, pharmacokinetics, and a number of other properties differ from the corresponding properties of a low-molecular drug attached to the polymer matrix.

The aim of the research was to compare and identify differences in changes in therapeutic concentrations of low-molecular and polymer forms of antiviral drugs in the form of eye drug films (GLP) and to study the kinetics of the release of the active principle from GLP.

Currently, many drugs and various methods of their delivery to the eye tissue are used in ophthalmological practice for the prevention and treatment of diseases of various etiologies. The vast majority of drugs are administered by traditional instillation in the case of the dosage form in the form of solutions.

MATERIALS AND METHODS

We have developed and mastered the production of a polymer form of an interferon inducer with antiviral activity "celagrip" with the chemical name sodium salt 2,3-diethoxy–6–O–carboxymethyl-(1→4)–β–D–oxyglucose–diethoxygossipolate–2–ethoxy-(1→4)–β–D–oxyglucose–diethoxygossipolate–2–O–carboxymethyl-(1→4) – β – d glucose -2,6 – o – dicarboxymethyl-(1→4)–B–d glucose suppresses the growth and development of a wide range of viruses – influenza, SARS, herpes, etc.. When creating bio – soluble GLP with antiviral activity, the substance "Celagrip" and purified carboxymethylcellulose (CMC) were used as a polymer matrix. To study the kinetic parameters of the release of the substance Celagrip from the CMC polymer matrix, a UV – spectrometric analysis method was used on the Specord-210 device. The electronic spectrum of the substance at its concentration of 0.01% is characterized by the presence of an intense absorption maximum at 245±5 nm. By changing the concentration of the substance in the solution, calibration graphs were constructed. The change in the concentration of the substance in aqueous

solutions of polymer forms of GLP in time was carried out as follows: in 100 ml of saline solution, an exact GLP suspension was placed at 37 °C and samples of the solution were taken at certain intervals and the optical density was measured on a spectrophotometer. The concentration of the substance in the solution was calculated using the calibration schedule. The measurements were performed until the change in the optical density of the solution stopped over time.

RESULTS AND DISCUSSION

The selected initial samples-the substance "Celagrip" and the polymer matrix-CMC significantly differed in the values of their molecular weights.

When the molecular weight of the substance M=10-15x103, the molecular weight of the polymer matrix was 104. Due to the low molecular weight values, the substances formed from its film were brittle, had no mechanical strength, and quickly dissolved in both water and saline solution. Films formed from solutions of polymer-polymer compositions of CMC: substances with a thickness of 75±5 microns had sufficiently high strength values-37±2 kgf/cm2 and tensile elongation-5±0.1 %.

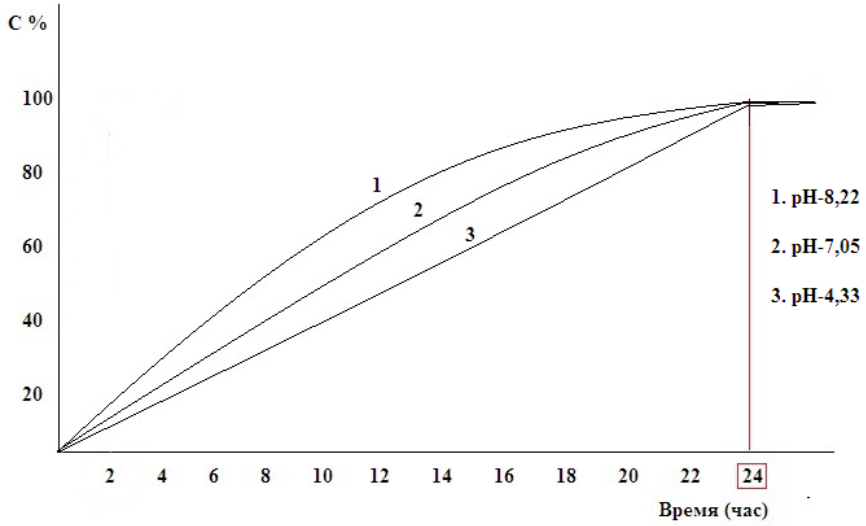


Figure 1. *Kinetics of release of the substance Celagrip from the polymer matrix at different pH values over time.*

As can be seen from figure 1, the rate of release of the substance from the polymer matrix decreases with a decrease in the pH values in the initial na-CMC film-forming solution.

When the PH value of the CMC solution is equal to 8.22, the release rate of the substance is the highest and the necessary level of prolongation effect is not provided. In addition, the obtained GLP due to the detection of alkalinity in the solution, contact with the eyeball irritates it and the swollen fraction is quickly removed by lacrimal fluid, which also negatively affects the effect of prolongation.

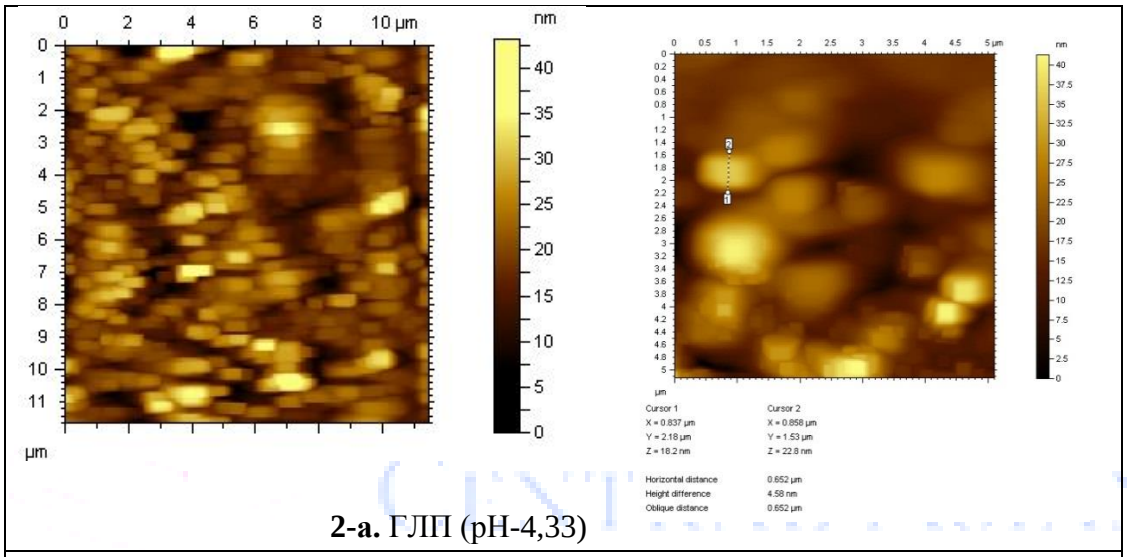
When the PH value of the GLP solution is equal to 4.33, the acidic environment created as a result of its swelling and dissolution in the lacrimal fluid contributes to rapid withdrawal from the eye due to the irritating effect.

In addition, glps with a pH value of 4.33 do not have the necessary transparency and may have a negative effect on vision.

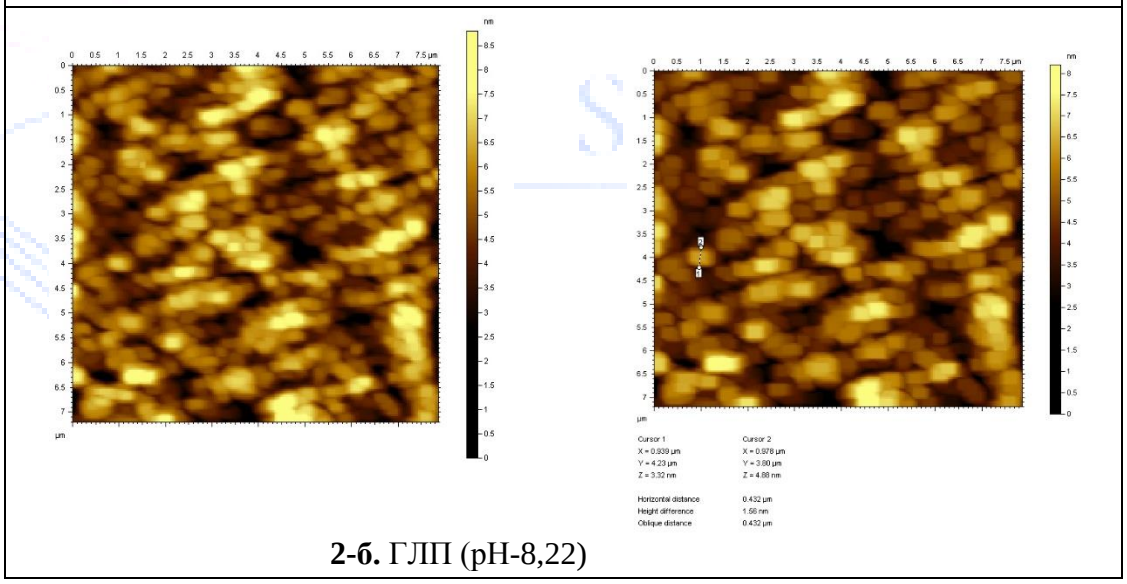
The manifestation of GLP turbidity is explained by the presence of macro - and micro-gel particles in CMC solutions that are suspended in the solution and create a certain roughness and turbidity during the formation of films.

The most acceptable for the effect of prolongation, absence of irritating effect and transparency of the film is the film 3 (Fig.1) obtained from a polymer - polymer mixture solution.

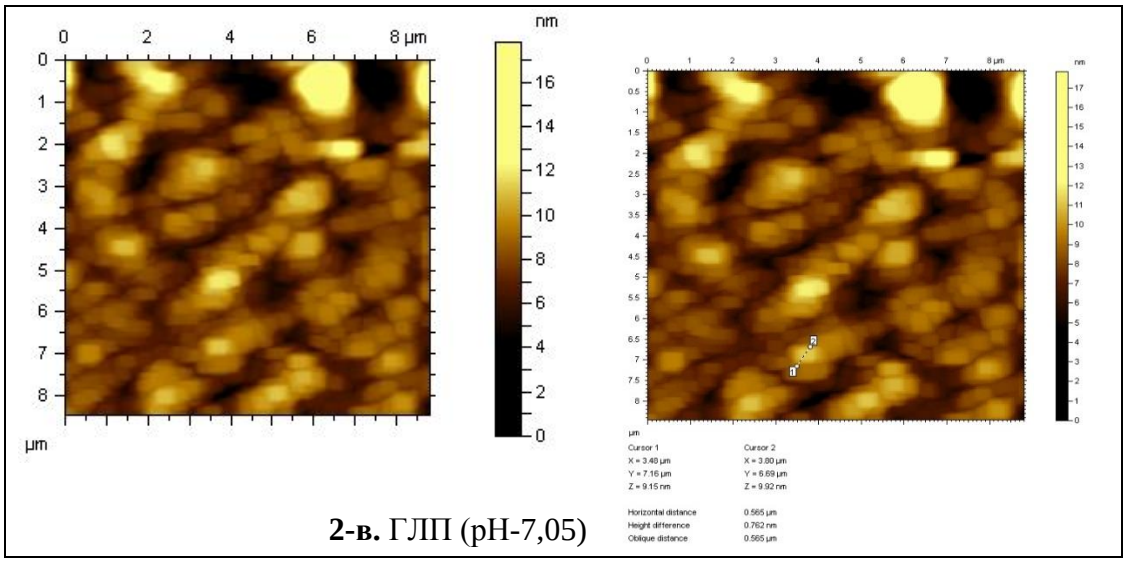
Figure 2.



2-а. ГЛП (pH-4,33)



2-б. ГЛП (pH-8,22)



2-в. ГЛП (pH-7,05)

Figure 2. *Shows images of the GLP surface obtained by Atomic force microscopy (Agilent 5500 AFM), which differ in the pH values of the initial solutions of the polymer matrix containing 20 % of the antiviral substance Celagrip.*

As can be seen from figure 2 - a, the highest surface roughness and therefore turbidity has a GLP with a pH value of the initial solution of the polymer matrix equal to 4.33.

In contrast to figure 2-a, a polymer matrix solution with a pH value of 8.22 was used to obtain sample 2-b.

Despite satisfactory physical and mechanical parameters and optical transparency, the resulting films, due to the alkalinity of the solution of this sample, irritated the eyeball and were subject to relatively rapid swelling and removal of tear fluid from the eye, which reduced the level of its prolongation effect.

Based on experimental studies, a sample of 2-b with a pH value of the initial solution of the film-forming matrix of 7.05 was selected as the prolonged form of GLP, which provides the necessary level of prolongation and does not irritate the eyeball during instillation and is optically transparent.

The therapeutic concentration of drugs in the body is the determining factor of their effectiveness.

Ideally, the longer the therapeutic concentration remains in the body over time, the higher the effect of treating the disease.

This effect is called a prolonging effect in pharmacology.

In practice, it is not possible to keep the therapeutic concentration of the drug in the body constant over time.

When the therapeutic concentration of the drug is introduced into the body, its concentration increases over time and falls with the maximum reached.

In practice, the rise and fall of therapeutic drug concentrations in the body should be within the range of certain effective therapeutic concentrations for each drug, depending on how they are obtained, administered to the body, and the nature of the drug.

In practice, it is difficult to control the timing of repeated drug administration within the upper and lower therapeutic concentrations. When a drug is introduced into the body, its therapeutic concentration first increases over time, then decreases. Often, the therapeutic concentration of the drug may exceed the

upper limit for some time, where the drug may have a negative effect on healthy organs and may be below the therapeutic concentration range, where the effectiveness of the drug will be insufficient.

When low-molecular-weight drugs are introduced into the body, the more frequent the interval of repeated drug doses until the disease is completely treated, the larger the area of the upper and lower critical concentrations, the lower the effect of treatment of the disease (Fig.3).

In the case of the creation of prolonged forms, even the same drugs, due to the reduction in the time of repeated doses, the area of the upper and lower critical concentrations decreases and increases the effectiveness of treatment of the disease.

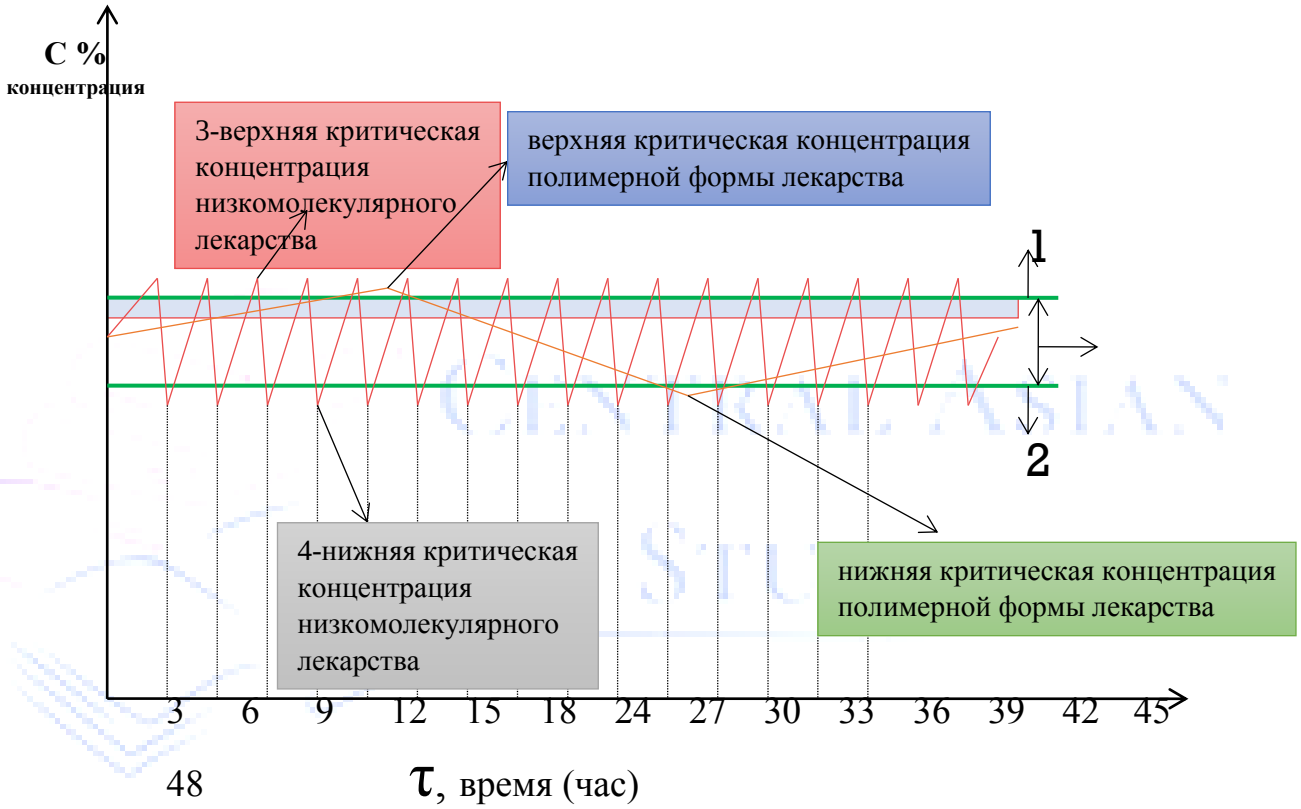


Figure-3. *Changes in the therapeutic concentration of low-molecular and polymer forms of drugs over time.*

Figure 3 shows the comparative values of changes in therapeutic concentrations of low-molecular and polymer forms of drugs over time.

As can be seen from figure 3, medicinal products of any form, including ophthalmic use, have therapeutic concentrations varying from the upper 1 and lower 2 concentrations. If the drug is introduced into the body above the upper 3 therapeutic concentration, they can have a negative effect on both the patient and healthy organs by increasing the level of toxicity. If the concentration of the drug decreases below the lower limit of 4 therapeutic concentration, the effect of the drug on the diseased organ is reduced to its complete loss. Thus, ideally, the change in the optimal concentration of the drug in the body should be within its upper 1 and lower 2 therapeutic concentrations. In real conditions, when a low-molecular drug is introduced into the body, its concentration increases over time above the upper critical therapeutic concentration-3, followed by a decrease in the concentration below the lower critical therapeutic

concentration-4. When the lower critical concentration is reached, the next dose of the drug is introduced into the body and the cycle is repeated until the diseased organ is completely cured.

Thus, the more stages of administration of low molecular weight drugs and number of cycles of its introduction to the complete cure of the patient's body the more square top and bottom critical therapeutic concentrations exceeding the range of optimal therapeutic concentrations of drugs, which characterize the effectiveness of the treatment of the disease.

CONCLUSIONS

In contrast to low-molecular drugs, when using prolonged polymer forms of drugs, the frequency of their instillation is significantly reduced and this reduction is directly dependent on the duration of preservation in the body of the therapeutic concentration of the polymer form of the drug in the body.

Consequently, the areas exceeding the upper and lower critical concentrations of the polymer prolonged form of the drug will be significantly less than when using a low-molecular-weight analog of the drug. Thus, the use of prolonged polymer forms of medicines in the treatment of various, including ophthalmic, diseases contributes to improving the effectiveness and reducing the level of negative effects of the drug on healthy organs.

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