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RESEARCH ON THE DEVELOPMENT OF THE COMPOSITION OF COMPLEX ACTION DENTAL FILMS WITH CALCIUM HYDROXYAPATITE

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The aim. *Development of the composition of dental films for remineralization, treatment and prevention of dental hyperesthesia, prevention of the formation of microbial biofilms, elimination of pathogenic microflora.*
Methods*. Determination of crystallographic characteristics, uniformity of particle distribution and their ability to aggregation was carried out by microscopy, viscosity – by rotational viscometer, pH-potentiometrically. The tensile strength of the films, the ability to stretch and lengthen, the strength of the bioadhesive bond were investigated by a texture analyzer, the thickness of the films – by calipers. Antimicrobial activity was determined by the disk-diffusion method and by the effectiveness of antimicrobial preservatives.*
Results*. The choice of CHA concentration (10 %) was based on the analysis of literature sources. Structural-mechanical and organoleptic studies established the feasibility of using a combined system with the inclusion of purified water, glycerin and macrogol 400. The study of sedimentation and aggregation stability of the samples showed a uniform distribution of particles in samples from PVA, HEC, HPC. Films from Sodium Alginate, PVP, Na-CMC and HPMC were excluded from the work due to unsatisfactory properties. Structural-mechanical and physico-chemical properties allowed us to choose 5 % PVA as the film former, and 4 % glycerin as the plasticizer. The concentrations of API (metronidazole and chlorhexidine) were selected based on antimicrobial activity and preservative effect.*
Conclusions*. As APIs, CHA – a remineralizing, anti-caries agent, metronidazole and chlorhexidine – antimicrobial components were selected. The introduction of CHA is rational in a complex dispersion medium, metronidazole as a suspension with glycerin, chlorhexidine as a 20 % solution. The composition of the film base was substantiated. The concentrations of metronidazole and chlorhexidine bigluconate were determined. The developed drug met the specifications of the MQC*
Keywords*: dental films, hydroxyapatite, hyperesthesia, dental diseases, metronidazole, chlorhexidine*

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1 Introduction

Despite the development of the dental field, the prevalence of diseases of the hard tissues of the teeth does not decrease but increases at a progressive pace [1]. In recent years, an extremely common phenomenon that accompanies many dental diseases is tooth hypersensitivity or hyperesthesia, which is manifested by pain, discomfort and leads to a deterioration in the patient's quality of life [2]. Enamel hypersensitivity is associated with impaired mineralization. Insufficient mineralization of the enamel defect brings the stimulus closer to the tooth pulp. Pain sensations arise due to irritation of the pulp, which is rich in nerve endings. Hyperesthesia manifests itself as short-term pain that occurs because of the action of thermal, chemical and mechanical stimuli on the exposed surface of the dentin of the tooth, which is exposed when the integrity of the enamel is violated. The dentin tubules containing nerve endings become open and an external factor leads to the development of a pain symptom. The mechanism of the occurrence of a pain symptom is complex and affects various structures and components of the tooth [3].

The etiology of hyperesthesia is complex and multifactorial, with the main causes being caries, gingival recession, periodontitis, non-carious lesions, and congenital and acquired enamel defects [4]. Dental caries remains the most common chronic bacterial disease, despite significant progress in its diagnosis and treatment [5]. According to The Global Burden of Disease, 2.3 billion people worldwide suffer from caries of permanent teeth, and more than 530 million children have caries of primary teeth [6, 7]. If left untreated, caries can spread to the dental pulp, cause dental abscesses, significant pain, and eventually even lead to tooth loss [5]. Caries develops due to the action of acids on the enamel surface, which are formed as a result of the vital activity of bacteria in dental biofilm (dental plaque). Bacteria metabolize sugar from food or drinks, forming acid that causes enamel demineralization – the loss of calcium and phosphorus. In addition, plaque can cause gum inflammation, known as gingivitis. Studies have also shown that severe periodontal (gum) disease affects about 10 % of the world's population [7]. Thus, controlling microbial biofilm on

the surface of teeth is key to preventing caries and periodontal tissue diseases. Congenital enamel defects are undifferentiated tooth tissues: lamellae, tufts, spindles. As the human body matures and ages, they turn into cracks, which become the initial pathways for irritants to penetrate through the enamel to the pulp, resulting in increased enamel sensitivity. Acquired defects include non-carious tooth lesions, including erosions, wedge-shaped defects, pathological tooth abrasion, and necrosis [4]. The development of aesthetic dentistry using composite materials, adhesive systems, vital tooth whitening, modern methods of orthodontic and periodontal treatment, and professional and personal hygiene products increase the frequency of hyperesthesia and make the issue of treatment and prevention of dentin hypersensitivity one of the most relevant [8].

Thus, we see that the prevention of many dental pathologies is measures aimed at restoring the processes of mineralization of hard dental tissues and normalizing phosphorus-calcium metabolism in the body and removing pathogenic microorganisms that cause oral diseases. To solve this, gels, varnishes, rinses, toothpastes are prescribed, the main components of which are remineralizing mixtures. Special sealants can also be used to close dentinal tubules [9]. The use of these agents leads to a decrease in the volume of dentin micropores by increasing the mineralization of hard tissues [9, 10]. However, many substances that are part of dental preparations cannot provide a long-term therapeutic and prophylactic effect due to their low ability to penetrate hard tooth tissues. In addition, some of the above dosage forms (for example, gels, pastes, rinses) have limited bioavailability, since they are quickly washed away by saliva, which requires frequent use over a long period of time to achieve the desired effect [11].

Typically, the active components of remineralization agents are calcium, phosphorus, and fluorine compounds. However, the effect of fluoride-containing drugs is short-lived and requires repeated courses. This increases the risk of developing intoxication with fluoride compounds, which, in turn, can lead to darkening of tooth enamel and pathology of the bone and central nervous system. Therefore, the use of fluoride drugs is not recommended for children and pregnant women. Another disadvantage of using fluoride drugs is the risk of developing fluorosis [12].

Calcium phosphates are an effective alternative to fluoride, providing high penetration into the hard tissues of the tooth [13]. Calcium phosphates used in dental products and materials include: hydroxyapatite – $Ca_{10}(PO_4)_6(OH)_2$ or $Ca_5(PO_4)_3OH$; fluorapatite – $Ca_{10}(PO_4)_6F_2$; amorphous calcium phosphates – $Ca_xH_y(PO_4)_z{\cdot}nH_2O$, n=3–4,5; dicalcium phosphate dehydrate (brushite) – $CaHPO_4{\cdot}2H_2O$; dicalcium phosphate anhydrous (monetite) – $CaHPO_4$; tetracalcium phosphate (hilgenstockite) – $Ca_4(PO_4)_2O$; α-tricalcium phosphate – α-$Ca_3(PO_4)_2$, β-tricalcium phosphate – β-$Ca_3(PO_4)_2$); octacalcium phosphate – $Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$; monocalcium phosphate monohydrate – $Ca(HPO_4)_2{\cdot}H_2O$; monocalcium phosphate anhydrous – $Ca(H_2PO_4)_2$ [14]. Among the calcium phosphates used in dentistry, the most important role is played by hydroxyapatite and fluorapatite, which are characterized by the highest chemical stability and very low solubility. Given the maximum affinity of calcium hydroxyapatite (CHA) to the chemical composition of tooth tissues (about 97 % of tooth enamel and 70 % of dentin consists of an inorganic matrix, which is mainly CHA [14]) and the highest ionic ratio Ca/P [15] (Table 1), we chose it as the active substance for remineralization and reduction of tooth sensitivity in these studies.

Table 1

Composition of mineral components of tooth enamel and dentin compared to hydroxyapatite

Component	Enamel	Dentin	Hydroxyapatite
Ca^{2+}, wt. %	37.6	40.3	39.6
P^{5+}, wt. %	18.3	18.6	18.5
Ca/P, wt. %	1.59	1.67	1.67

When using and selecting CHA in a dental product, the structure of enamel and dentin should be considered. The inorganic component of enamel consists of hydroxyapatite crystals, which are densely packed and organized into enamel prisms. These basic structural and functional units of enamel are thin bundles with a thickness of 3 to 6 microns, passing through the entire enamel, while in dentin, hydroxyapatite crystals have the appearance of flattened hexagonal prisms or plates with dimensions of 3−3.5×20−60 nm. They are much smaller than hydroxyapatite crystals in enamel. The diameter of dentinal tubules should also be considered, which has a size of 2−3 microns to 0.5−1 microns (decreasing in the direction from the pulp end to the dentino-enamel boundary). Due to the large number of tubules that penetrate dentin, it is characterized by high permeability. This is of clinical importance, as it ensures a rapid response of the pulp to dentin damage. In the presence of caries, dentinal tubules become pathways for the spread of microorganisms [16]. Reducing the size of hydroxyapatite to nano- and microstructures significantly increased its activity. This is due to the ability to penetrate the microscopic spaces between the enamel prisms, seal the dentinal tubules, integrate into the crystal lattice and stimulate the formation of new hydroxyapatite crystals of tooth enamel [13].

In the therapeutic practice of treating dental diseases of infectious etiology, such as pulpitis, periodontitis and periodontal disease, timely selection of antimicrobial drugs is critically important. Today, in world medical practice, the pharmacological industry offers more than 2000 types of such drugs. About 600 molecules have been described in detail, and about 120–160 drugs are used in practice, depending on the indications. For the treatment of infectious dental diseases, substances from different groups are used, including antiseptics, synthetic antibacterial agents, antibiotics and their combinations, such as chlorhexidine, hydrogen peroxide, metronidazole, miramistin, acyclovir, gentamicin, lincomycin, etc. [17, 18].

A rational dosage form for the treatment of dental diseases is local drug delivery systems with prolonged release – dental drug films [19, 20]. Films are matrix-type

delivery systems in which medicinal substances are evenly distributed throughout the polymer film, and the release of the drug through the film occurs by diffusion and/or dissolution or erosion of the matrix. The advantages of dental films compared to traditional dosage forms, in addition to prolonged action, are ease of administration, good fixation and adhesion, dosage accuracy, minimal pain during application or its absence depending on the site of application, the ability to control the size and shape of the film according to the size of the site of application, compact storage, minimal or no side effects [21].

The aim of the study. Development of the composition of dental films with complex action with calcium hydroxyapatite for remineralization of tooth enamel, treatment and prevention of dental hyperesthesia, prevention of the formation of microbial biofilms, elimination of pathogenic microflora.

2. Research planning (methodology)

The therapeutic efficacy of topical preparations, in particular dental films, is determined by many interrelated factors, among which the key ones are the activity of active ingredients and their interaction with the film-forming solution. Therefore, the main task in the development of a new drug is the selection of effective and safe active pharmaceutical ingredients (API), which would maximally contribute to the prevention and treatment of dental diseases. In addition, an important aspect in the development of films is the justification of the choice of a film-forming agent - the API matrix. Only the optimal combination of active ingredients with the matrix provides the necessary therapeutic effect, proper technological and consumer characteristics of the drug, and allows you to regulate the release and bioavailability of the API [22].

In accordance with the goal and objectives of the study, the methodology for the development of dental films of complex action included the following stages:

1. Selection and justification of API based on analysis and generalization of data from scientific publications of domestic and foreign authors.

2. Justification of the method of introducing active substances into the dosage form and selection of dispersion medium based on the study of their physicochemical characteristics.

3. Selection and justification of the film-forming agent based on the study of the physicochemical and structural-mechanical indicators of the polymer base and films.

4. Selection of the concentration of antimicrobial components based on microbiological properties.

5. Evaluation of the physicochemical, structural-mechanical and microbiological indicators of the developed films, which are related to their consumer, technological and biopharmaceutical properties.

3. Materials and methods

The objects of the study were:

1. API: micronized calcium hydroxyapatite (CHA) under the trade name “Kalident Powder 100” (Kalichem, Italy), metronidazole (Thermo Fisher Scientific, USA), chlorhexidine bigluconate (in the form of a 20 % solution) (Sigma-Aldrich, Steinheim, Germany).

2. Dispersion media: purified water (main solvent for the film-forming polymer), ethyl alcohol 96 %, polysorbate 80 (Carl Roth GmbH, Roth, Germany), glycerin (Chem-Lab Nv, Belgium), polyethylene oxide-400 (macrogol 400, Sigma-Aldrich, Germany), propylene glycol (PG, Sigma-Aldrich, Germany), sunflower oil, vaseline oil (Hansen & Rosenthal KG, Humburg, Germany).

3. Film formers: Sodium Alginate (Carl Roth GmbH+Co, Germany), polyvinylpyrrolidone (PVP, Sigma-Aldrich, USA), polyvinyl alcohol (PVA, Sigma-Aldrich, USA), sodium carboxymethylcellulose (Na-CMC, Sigma-Aldrich, Finland), hydroxypropylmethylcellulose (HPMC, Sigma-Aldrich, USA), hydroxyethylcellulose (HEC, Sigma-Aldrich, USA), hydroxypropylcellulose (HPC, Alfa Aesar GmbH & Co, Germany).

4. Model samples of film mass with film formers (Table 2).

5. Model samples based on PVA with different concentrations of glycerin (2 %, 4 %, 6 %, 8 %, 10 %).

6. PVA-based model samples with different concentrations of metronidazole and chlorhexidine (with equal concentrations of each from 0.01 to 0.05 mg/cm^2).

The production of experimental samples of medicinal films was carried out by the irrigation method in stages.

Stage 1. Preparation of film-forming polymer solutions.

Half the amount of purified water was measured and one of the polymers was added depending on the model sample: Sodium Alginate, PVP, Na-CMC and HPC swelled at room temperature, PVA was heated to a temperature of 80–90 °C, HPMC and HEC – 50–60 °C. Stirred and left until the polymer was completely dissolved and a homogeneous system was formed.

Stage 2. Obtaining a CHA suspension in a dispersed medium.

In another container, CHA was measured, glycerin and macrogol 400 were added alternately and mixed (ground manually) until a homogeneous pasty mass was formed. After that, the other part of purified water was added and thoroughly mixed using an Ultra-Turrax IKA T18 homogenizer (Staufen, Germany) at 6000 rpm for 5 min until a white suspension was formed.

Stage 3. Mixing mixtures and deaeration.

The CHA suspension was added to the formed polymer base and mixed on an Ultra-Turrax IKA T18 homogenizer (Staufen, Germany) at 10,000 rpm for 5 min until a homogeneous, viscous white mass was formed.

Stage 4. Pouring the mass and drying.

The mass (20 g) was poured into Petri dishes and dried in a drying oven at a temperature of 50 °C for approximately 7–8 hours until a film was formed that could be easily separated from the substrate.

The crystallographic characteristics of the particles were determined by optical microscopy (Article 2.9.37 of the State Federal University of Chemistry and Technology [23]) using a Konus Academy microscope (Italy) equipped with a DLT-Cam Basic 2MP camera and a microscope with a Krüss MBL-2100 eyepiece

micrometer (Germany). The obtained images were processed using DLT-Cam Viewer software.

The viscosity of the model film mass samples was measured using a Fungilab Alpha series rotational viscometer (Fungilab, Barcelona, Spain). Equal amounts (50±0.01 g) of samples were analyzed using an L4 spindle at a shear rate of 60 rpm. The measurements were performed at room temperature (Article 2.2.8 SPhU [24]).

The uniformity of the distribution of suspension particles in the casting mass and the ability to aggregate were investigated by microscopic analysis using a Nikon DS-Fi1 optical microscope (Japan) with a camera connected to a computer.

The pH was determined potentiometrically using a Thermo Scientific™ Orion™ Versastar Advanced Electrochemistry Meter (Beverly, USA) pH meter (Article 2.2.3 SPhU [25]).

The tensile strength of the films and their ability to stretch were investigated using a texture analyzer TA.XT.plus (Stable Micro Systems Ltd, Godalming, Surrey, UK). For this, the film sample was placed between two plates with a hole in the middle, which allows only a small section of the film to be left open, through which a spherical probe (HDP/FSR) is pushed to study its elasticity and ability to stretch. During the test, the maximum force of the sample to break (tensile strength) is recorded. The tensile strength (elongation) of the film was also carried out using a texture analyzer TA.XT.plus (Stable Micro Systems Ltd, Godalming, Surrey, UK). For this, a film sample 10 mm wide was fixed in the device, gripping its edges from both ends using an A/TG probe. Then, a tensile force was applied to it, which gradually increased until the film broke (torn). The mechanical property directly measured during the tensile test is the ultimate tensile strength (maximum force) of the film.

To measure the strength of the bioadhesive bond, a TA.XT.plus texture analyzer (Stable Micro Systems Ltd, Godalming, Surrey, UK) was used. For this purpose, the film sample was placed between two plates of a mucoadhesive probe (A/MUC) with a hole in the middle (10 mm), which allows only a small area of the film to be left open. The open part of the film was pre-moistened with a small amount (100 µl) of artificial saliva solution (pH=6.5), the hydration time was 10 min. Then, the P/0.5R nozzle was pressed with a force of 5 N for 60 s against the hydrated film, after which the probe was detached from the sample, measuring its adhesive ability.

The thickness of the films in five different places was measured with an electronic digital caliper DIN 862 (Vogel Germany GmbH & Co. KG, Kevelaer, Germany) and the average value was calculated.

To determine the degradation time of the films in saliva, a study of their solubility time was conducted (Article 2.9.3 SPhU [23]). For this, the film sample was placed in a liquid medium, which was a solution of artificial saliva with pH=6.5 (static conditions). The experimental temperature of 37.0±1.0 °C was maintained using a TS-80M-2 thermostat.

According to the SPhU article "Oromucous preparations" ([26]), the tests were performed for the following: Homogeneity of dosage units (Article 2.9.40 SPhU [27]), Homogeneity of content (Article 2.9.6 SPhU [24]), and Homogeneity of mass (Article 2.9.5 SPhU [24]).

The antimicrobial activity of the samples was determined in in vitro experiments by the generally accepted agar diffusion method in microbiology (disco-diffusion method). The activity of the studied samples was assessed on standard test strains of microorganisms: gram-positive microorganism *Staphylococcus aureus* ATCC 25293, gram-negative cultures *Proteus vulgaris* ATCC 4636, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, yeast-like fungus *Candida albicans* ATCC 885-653 [28]. An 18–24-hour culture of microorganisms was used in the work, the microbial load was 1×10^7 CFU/ml. Mueller-Hinton agar (for bacterial cultures) and Sabour agar (for fungi) were used for the studies. 10 ml of melted medium was added to Petri dishes, after the agar solidified, 0.1 ml of the prepared culture of each test strain was sown on the surface. Model samples of films with CHA and different concentrations of antimicrobial active substances in the form of disks with a diameter of 6 mm were laid out on the surface of the seeded medium. Petri dishes were kept for 30–40 min at room temperature and placed in a thermostat for 18–24 hours. The results were recorded by measuring the zone of inhibition of the growth of microorganisms, including the diameter of the disks. Measurements were made with an accuracy of 1 mm, while focusing on the complete absence of visible growth.

To assess the activity of the samples, the following generally accepted characteristics were used: the absence of zones of inhibition of the growth of microorganisms, as well as a zone of inhibition with a diameter of up to 10 mm, indicate that the microorganism is not sensitive to the sample; zones of inhibition of growth with a diameter of 10–15 mm indicate low sensitivity of the culture; zones of inhibition of growth with a diameter of 15–25 mm are considered an indicator of the sensitivity of microorganisms to the sample under study; zones of inhibition of growth, the diameter of which exceeds 25 mm, indicate high sensitivity of microorganisms to the sample under study [28, 29].

The effectiveness of antimicrobial preservatives was tested according to the SPhU method (Article 5.1.3 of the SPhU [27]). The following media were used: soy-casein agar, Sabouraud-dextrose agar; solutions: buffer solution with sodium chloride and peptone pH=7.0, containing 50 g/l polysorbate-80, 5 g/l lecithin, 1 g/l histidine hydrochloride; test cultures of microorganisms: *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404.

According to the requirements of SPhU, the sterility of the nutrient media, solvent, growth properties of the nutrient media (soy-casein nutrient medium – for growing bacteria and Sabouraud-dextrose medium without the addition of antibiotics – for growing fungi) and the suitability of the method for determining the total number of viable cells were checked. The nutrient media corresponded to the growth properties and withstood the

sterility test, and the test microorganisms corresponded to the taxonomic characteristics – the morphology of the colonies on the media and the morphology of the cells under microscopy were typical for the corresponding strain. The suitability of the method for determining the total number of viable microorganisms was checked for the tested samples of the preparation diluted 1:10 with a solvent buffer solution with sodium chloride and peptone pH=7.0 with 5 % polysorbate-80, 0.5 % lecithin and 0.1 % histidine hydrochloride.

The criterion for assessing the effectiveness of a preservative in a dosage form is the reduction in the number of viable cells of test microorganisms in the preparation over a certain period after its contamination. In accordance with the requirements of the SPhU for oromucosal preparations, the logarithm of the decrease in the number of viable bacterial cells after 14 days should be at least three, after 28 days the number of viable bacterial cells should not increase; the logarithm of the decrease in the number of viable fungal cells after 14 days should be at least one, in the future the number of viable fungal cells should not increase.

All experiments were performed in five replicates. The results of the studies are presented as the mean value±standard deviation. Statistical analysis was performed using the Student's t-test. The value $p<0.05$ was taken as the level of significance [27].

4. Results

In our studies, we focused on the use of micronized calcium hydroxyapatite under the trade name "Kalident Powder 100" (Kalichem, Italy), the particles of which have a size and rod-like morphology resembling that of natural enamel. CHA in this form has a high affinity for binding to substances due to the increased surface area, which can improve remineralization and reduce sensitivity. Accordingly, this leads to densification and restoration of the enamel surface and a decrease in tooth sensitivity.

CHA is also believed to be an effective anti-caries agent through its effect on biofilms. CHA particles are small enough to directly interact with the bacterial membrane and, due to their adhesive ability to plaque particles with their subsequent removal, act as an anti-caries agent [30]. The latter fact is important given the goal of the work to create a dental product with a complex effect with an impact on enamel remineralization and the causes of hyperesthesia, in particular periodontitis and caries.

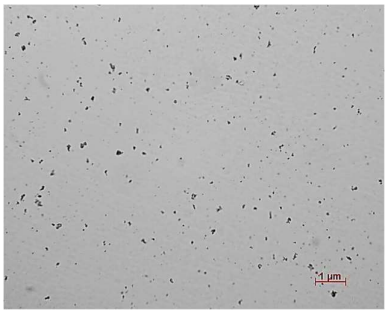
The choice of CHA concentration was based on an analysis of literature sources, which showed that dental products containing 10 % CHA demonstrated similar remineralizing potential as fluoridated ones and can be used as an effective alternative to fluoride-containing products [13, 30].

The next stage of the work was the justification of the antimicrobial component of the dental product. It is recommended to include substances that affect the reproduction and vital activity of microorganisms in the composition of combined antimicrobial drugs, having different mechanisms and directions of therapeutic action [31]. Also, given the growing trend towards the formation of antibiotic resistance and the corresponding decrease in the effectiveness of the use of antimicrobial drugs, the use of antiseptic drugs or in combination with antibacterial drugs is relevant [17, 32]. We focused on substances with antiseptic action – chlorhexidine and with antibacterial action – metronidazole. They are widely used in various dental products both individually and in combination [17, 18]. Thus, the concentrations of metronidazole and chlorhexidine gluconate in the dental gels "Metronidazole Denta" (LLC "Arpimed", Armenia), "Dentagel" (PrJSC "Fitopharm", Ukraine), "Metrogil Denta" (Unique Pharmaceutical Laboratories, India), etc. are 10 mg/g and 2.5 mg/g, respectively [33], the concentrations of these substances in dental films are 0.01–0.03 mg/cm^2, in scientific works of domestic authors there are concentrations of 0.08 mg/cm^2 and 0.15 mg/cm^2 [19, 20]. Considering the potential impact of CHA on microbial biofilms in the oral cavity [13, 30], we focused on concentrations of 0.01–0.05 mg/cm^2, the final choice of the concentration of antimicrobial agents was determined in microbiological studies of model film samples.

Since hydroxyapatite is a poorly soluble substance [14], the first stage of experimental studies was devoted to the justification of the optimal method of its introduction into the composition of the dental film. Studies of the physicochemical characteristics of CHA "Kalident Powder 100", which were carried out by optical microscopy, showed that the substance is a finely dispersed powder capable of agglomeration, agglomerates are different in volume, their surface is heterogeneous, porous, the linear size is in the range from 1 to 100 microns. The results of the dispersion analysis by size indicate its polydispersity and the possibility of obtaining a dispersion with small particles. Therefore, at the next stage, the crystallographic characteristics of CHA were determined upon the addition of aqueous and non-aqueous solvents that are permitted for use in oral medicinal products: purified water, ethyl alcohol 96 %, polysorbate 80, glycerin, polyethylene oxide-400 (macrogol 400), propylene glycol (PG), sunflower oil, and vaseline oil. According to the degree of influence of liquids on the homogeneity of the distribution of particles of "Kalident Powder 100", solvents can be differentiated as follows: glycerin>macrogol 400>polysorbate 80>purified water>ethyl alcohol 96 %>PG>sunflower oil>vaseline oil. The addition of solvents such as purified water, glycerin, ethanol 96 %, macrogol 400, polysorbate 80 contributes to the formation of sols with a decrease in the linear size of particles from 7 to 0.01 μm and uniform distribution in the field of view of the microscope [34].

Previous studies have established that the greatest influence on the distribution of CHA powder throughout the volume of the sample with satisfactory shape and size indicators had three-component mixtures – water:glycerin:macrogol 400 (1:1:1) and water:glycerin:polysorbate-80 (1:1:1). This contributed to obtaining a more homogeneous suspension due to the disintegration of agglomerates into smaller particles compared to the systems of the studied powder with monosolvents and two-component mixtures [34]. Fig. 1 shows examples of

micrographs comparing the distribution of the substance "Kalident Powder 100" in three-component mixtures of liquids compared to purified water as the main solvent for obtaining films. These results are important in the development, since the use of these solvents will provide an increased surface area of the substance, i.e. high affinity for binding to substances, which, in turn, can improve remineralization and reduce tooth sensitivity, and a decrease in particle size will ensure interaction with the bacterial membrane and enhance the effect on biofilms [13].



a

b

c

Fig. 1. Micrographs of the substance "Kalident Powder 100" in three-component mixtures compared to purified water: *a* – purified water; *b* – water:glycerin:macrogol 400; *c* – water:glycerin:polysorbate-80

Also, the obtained results of determining the characteristics of the CHA mixture in three-component mixtures of liquids allow predicting the same speed of movement of powder particles and the absence of their adhesion during penetration between the layers of the film-forming agent. Thus, the feasibility of using combined systems with the inclusion of purified water, polysorbate 80, glycerin and macrogol 400 was established to improve the properties of the substance "Kalident Powder 100" when it is introduced into the composition of the medicinal product in the form of a dental film.

The next stage of our research was the selection of a rational film-forming agent in the composition of the film being developed. The following polymers were selected as film-forming agents approved for use in the oral cavity: Sodium Alginate, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), sodium carboxymethylcellulose (Na-CMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC).

In the first experimental compositions of dental films, selected combinations of solvents were used as a dispersion medium (Fig. 1, *b*, *c*). However, films containing polysorbate 80 had a characteristic unpleasant odor and bitter taste, which, in turn, makes it impossible to use this drug in the oral cavity for a long time. This was the basis for excluding the sample containing polysorbate 80 from further studies. The concentration of CHA in the initial film mass for pouring was selected, focusing on the concentration of the substance in the finished film after drying of about 10 %. The concentration of film formers was selected based on their viscous and film-forming properties, as well as the ability of the formed systems to pour. Thus, in further studies, samples obtained on the basis of the film mass were used, the composition of which is given in Table 2.

Table 2

Composition of film mass samples with CHA and various film formers

Components	Sample number / Quantity, wt. %						
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7
Glycerin	2.0						
Macrogol 400	2.0						
Sodium alginate	2.0						
PVP		5.0					
PVA			5.0				
Na-CMC				2.0			
HPMC					5.0		
HEC						3.0	
HPC							2.0
Purified water	up to 100.0						

Since the resulting mass for pouring is a suspension, the next stage of our research was the study of its sedimentation and aggregation stability. It is known that suspensions must be stable, that is, the dispersed phase must be in a suspended state for a long time and must be easily resuspended (restored) when shaken (in our case, when stirred, since the formed system is viscous). The ability to resuspend was good in all samples, but the sedimentation time was different - the systems stratified: sample No. 2 – after 5 min, No. 5 – after 15 min, No. 1 – after 3 h, No. 3 – after 5 h, samples No. 4, No. 6 and No. 7 were stable after 24 h of storage.

It should also be noted that the stability of the systems of multicomponent mixtures CHA was also controlled at the previous stages of solvent selection. Microscopic studies of CHA mixtures with water, glycerin, polysorbate 80, and macrogol 400 in various combinations showed the invariance of their crystallographic parameters during 24 hours of observation.

The differences in sedimentation time of samples No. 1–7 can be explained by the different viscosity of the formed systems. The results shown in Table 3 confirm the relationship between sedimentation time and viscosity of the pouring mass – less viscous systems had a greater ability to sediment and, as a result, worse sedimentation stability.

Further, for all samples, the uniformity of the distribution of suspension particles in the casting mass and the ability to aggregate were investigated using microscopic analysis. The results are presented in Fig. 2.

The results shown in Fig. 2 showed that samples No. 1, No. 2, No. 4 and No. 5 have a greater ability to aggregate CHA particles in the casting mass, which can negatively affect the uniformity (quality) of the film. Greater uniformity of particle distribution is characteristic of samples No. 3, No. 6 and No. 7.

Table 3 also shows the results of determining the pH of the samples, the value of which is important for dental products. It is known that the pH of dental products should correspond to the pH of the oral cavity, the value of which depends on many factors and can vary from 5.5 to 8.0. Based on the results, only samples No. 1 and No. 4 do not correspond to the required pH range, which can lead to a deterioration in the condition of the tissues of the oral cavity, affect its microflora and lead to irritation of the mucous membranes. Therefore, these samples were excluded from further research.

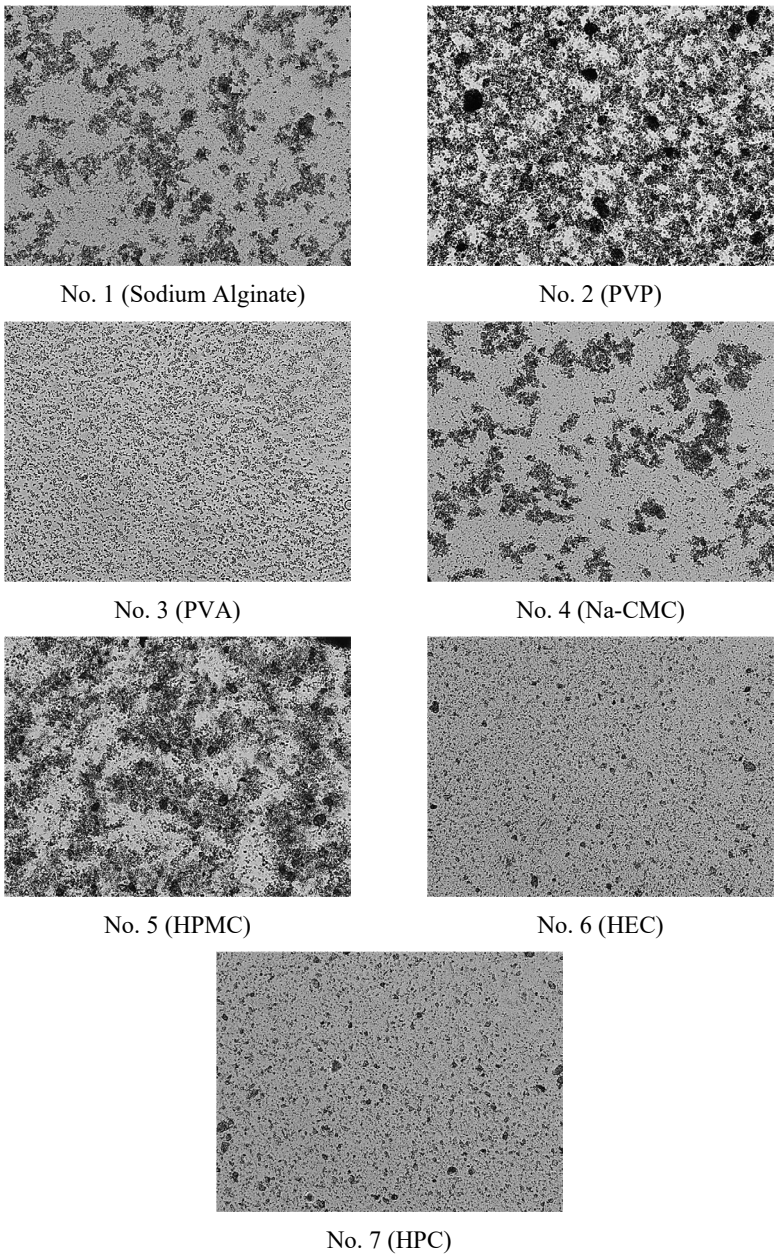


Fig. 2. Microscopic analysis of the mass for pouring samples (magnification ×1000)

Table 3

Sedimentation time, viscosity and pH of the mass for casting dental film samples with CHA

Sample (film former)	Sedimentation time, min	Viscosity, mPa·s	pH
#1 (Sodium Alginate)	180	1254±3	9.177±0.010
#2 (PVP)	5	640±10	7.039±0.032
#3 (PVA)	300	964±5	7.501±0.006
#4 (Na-CMC)	–*	1346±2	8.517±0.038
#5 (HPMC)	15	667±7	7.375±0.052
#6 (HEC)	–*	1003±5	7.300±0.019
#7 (HPC)	–*	1402±2	7.546±0.013

*Note: * – no sedimentation within 24 hours.*

Other samples (No. 2, No. 3, No. 5–7) were cast into molds and dried using the technology described above. However, the PVP-based films (sample No. 2) exhibited excessive adhesive properties to the surface – they were very sticky and did not separate from the substrate, and the HPMC-based films (sample No. 5) were very brittle in appearance and cracked. Therefore, these samples were also not used in further experiments. Samples No. 3, No. 6 and No. 7 showed positive organoleptic properties – they were white in color, uniform in appearance and elastic and plastic to the touch.

Further, the structural and mechanical properties of dental film samples No. 3, No. 6, and No. 7 based on PVA, HEC, and HPC were determined according to the following indicators: thickness, tensile strength, tensile ability, tensile strength (elongation), the results of which are given in Table 4.

Table 4

Indicators of structural and mechanical properties of dental film samples with CHA

Sample	Thickness, μm	Tensile strength, N	Tensile strength, mm	Elongation, N/mm
No. 3 (PVA)	200±5	16.604±0.835	5.163±0.116	1.795±0.095
No. 6 (HEC)	190±3	10.401±0.250	6.568±0.205	0.735±0.035
No. 7 (HPC)	150±5	3.275±0.092	5.774±0.120	0.265±0.012

As can be seen from the results given in Table 4, the model sample No. 7 based on HPC had the smallest thickness and tensile strength index. Samples No. 3 and No. 6 practically did not differ in thickness, the highest tensile strength was possessed by sample No. 3 based on PVA, films based on HEC (No. 6) also had sufficient resistance to tearing. The values of the films in terms of the tensile strength index, which correlates with the elasticity index, practically did not differ, all three samples had good elasticity. The results of determining the tensile strength of the films during stretching (elongation) fully correlate with the results of the test to determine the tensile strength of the films. The most durable and plastic was also the sample based on PVA (No. 3), which exceeded samples No. 6 and No. 7 in this indicator by 2.4 and 6.8 times, respectively. Considering the results obtained, we can conclude that film samples No. 3 and No. 6 combine high strength and elasticity.

In the development of dental polymer films, an important stage is the determination of adhesion characteristics. As can be seen from the results (Table 5), the best adhesion ability, almost 2 times greater than that of other samples, is possessed by the film based on HEC (sample No. 6). Samples based on PVA (No. 3) and HPC (No. 7) have similar results.

Table 5

Adhesion characteristics of dental film samples with CHA

Sample	Peak force (adhesive ability), N	Adhesion work, N·sec
No. 3 (PVA)	3.30±0.15	0.34±0.03
No. 6 (HEC)	6.84±0.56	0.65±0.05
No. 7 (HPC)	3.17±0.16	0.29±0.02

To determine the degradation time of the films in saliva and to establish the presence of a prolongation of the effect, we conducted a study of their solubility time in an artificial saliva solution and exposure at a temperature of 37.0±1.0 °C. The analysis results, presented in Table 6, showed that the shortest dissolution time (about 3.8 h) was for the film sample based on HEC (No. 6). The dissolution time of the films based on PVA (No. 3) and HPC (No. 7) was practically the same and was about 7.6 h and 7.8 h, respectively, which indicates their more prolonged effect than that of sample No. 6. This ability will allow them to be in the oral cavity for a longer time and have longer contact with the hard tissues of the tooth.

Therefore, considering the results of studies of the physicochemical and structural-mechanical properties of the bases, sample No. 3 with the following composition was selected for further work: PVA – 5 %, glycerin – 2 %, macrogol 400 – 2 %.

Table 6

Dissolution time of dental film samples with CHA

Sample	Time, min
No. 3 (PVA)	457.5±7.5
No. 6 (HEC)	227.5±8.5
No. 7 (HPC)	470±3.5

To establish the rational amount of glycerin as a plasticizer in the film composition, as well as considering its further use for the introduction of metronidazole in the form of a suspension with glycerin, film samples were made with its different amount – 4 %, 6 %, 8 %, 10 %. The appearance and thickness of the obtained films are presented in Fig. 3 and in Table 7.

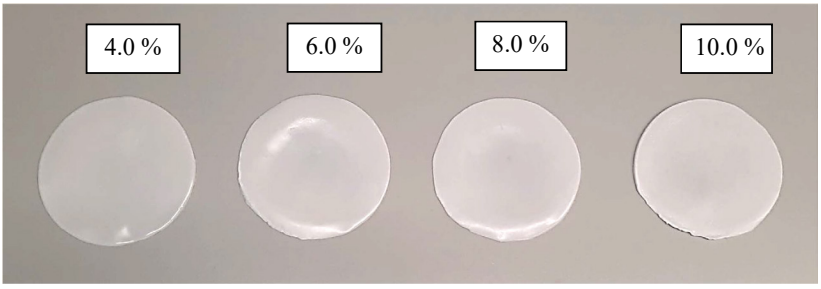


Fig. 3. Appearance of PVA-based films with different amounts of glycerin

Table 7

Thickness of PVA-based films with different amounts of glycerin

Amount of glycerin in the film	Thickness, μm
2.0 %	200±5
4.0 %	220±5
6.0 %	260±8
8.0 %	298±6
10.0 %	313±10

In appearance (Fig. 4), all samples were white, elastic, with a uniform shiny surface. The thickness of the films (Table 7) increased with increasing glycerin in the composition, which can be explained by its ability to retain water.

In addition, for all samples of films with different amounts of glycerin, their structural and mechanical properties were investigated, namely their strength and elasticity and adhesion. The results are presented in Table 8.

According to the results (Table 8), the strength, elasticity and adhesive characteristics of the films increase with an increase in the glycerin content from 2.0 % to 8.0 %. Further increase in the amount of glycerin is irrational.

In addition, the effect of the amount of glycerin on the solubility of the films was also studied. The results shown in Table 9 show that an increase in its amount in

the composition of the films leads to a decrease in their solubility time.

Table 8

Indicators of structural, mechanical and adhesive properties of samples of PVA-based films with different amounts of glycerol

Amount of glycerin in the film	Tensile strength, N	Tensile strength, mm	Peak force (adhesive ability), N	Work of adhesion, N·sec
2.0 %	16.604±0.835	5.163±0.116	3.30±0.15	0.34±0.03
4.0 %	16.605±0.816	7.62±0.20	4.57±0.40	1.06±0.10
6.0 %	19.834±1.005	10.74±1.04	4.49±0.37	1.04±0.06
8.0 %	20.117±1.791	13.56±1.15	7.90±0.69	1.08±0.10
10.0 %	19.675±1.350	15.96±1.12	4.96±0.42	1.09±0.10

Table 9

Determination of dissolution time of PVA-based film samples with different amounts of glycerol

Amount of glycerin in the film	Time. min
2.0 %	457.5±7.5
4.0 %	370±10
6.0 %	275±3.5
8.0 %	245±2.5
10.0 %	180±10

Based on the study of structural-mechanical and adhesive properties and dissolution time of film samples, it was decided to stop at the composition of the film with a glycerin content of 4 %, which combines high structural-mechanical and adhesive properties and at the same time prolonged dissolution time. Thus, the following composition of the film base was selected: PVA – 5 %, glycerin – 4 %, macrogol 400 – 2 %. Considering the volume of the resulting mass for pouring and the application area, the quantitative composition of API and excipients per 1 cm^2 of a dental film weighing 40 mg is: CHA – 4 mg, PVA – 16 mg, glycerin – 12 mg, macrogol 400 – 6 mg.

The next series of experiments was devoted to the justification of the concentration of antimicrobial components. Metronidazole, which is poorly soluble in water, was added to the polymer base in the form of a suspension with glycerin together with chlorhexidine bigluconate, which is used as a 20 % solution, at the stage of mixing the mixtures and deaeration (concentrations from 0.01 to 0.05 mg/cm^2). The study of the sedimentation and aggregation stability of the resulting mass for pouring at different concentrations of substances showed acceptable characteristics for further studies: all samples were stable for 24 h of storage, stratification of the systems did not occur, with the selected injection technology, a uniform distribution of the API in the mass was observed, which was confirmed by microscopic analysis of the films (Fig. 4).

To select the concentration of metronidazole and chlorhexidine, we investigated the antimicrobial activity of film samples of the selected composition with equal concentrations of each component from 0.01 to 0.05 mg/cm^2 (Table 10).

The results of the conducted studies (Table 10) showed a slow increase in antimicrobial activity with increasing concentration of selected components and the presence of antimicrobial action of varying degrees for samples No. 3–5. *S. aureus*, *C. albicans* strains were sensitive even to sample No. 1 with the lowest concentration of components with an increase in growth inhibition zones: *S. aureus* to samples No. 1, 2 is low sensitive, to No. 3–5 – sensitive; *C. albicans* is low sensitive to samples No. 1–4, sensitive to No. 5. The *E. coli* strain is assessed as low sensitive to samples No. 2–5, strains *P. aeruginosa*, *P. vulgaris* – to samples No. 3–5. Thus, the promising concentrations of metronidazole and chlorhexidine in this development are 0.03–0.05 mg/cm^2. Considering the potential anticariogenic effect of CHA due to adhesion to the cells of microorganisms in the oral cavity with subsequent removal, in our development the minimum effective concentration of antimicrobial components will be considered sufficient.

The final choice of the concentration of antimicrobial components was carried out when checking the adequacy of their preservative action to ensure the microbiological purity of the films (Table 11). The presence of microorganisms in non-sterile preparations can cause a decrease or even inactivation of their therapeutic effect, therefore, at the stage of pharmaceutical development, it is necessary to prove that the antimicrobial activity of the drug itself provides adequate protection against undesirable effects that may result from microbial contamination of the drug or the multiplication of microorganisms in it during storage and use. In the event of insufficient preservative action of the samples of the selected composition, the necessary measure will be either to increase the concentration of antimicrobial components or to introduce preservatives into the film composition.

Fig. 4. Microscopic analysis of films with CHA and antimicrobial components (magnification ×1000)

The obtained data show that the film sample with metronidazole and chlorhexidine concentrations of 0.03 mg/cm^2 passes the microbiological test only for *S. aureus* bacteria, and the sample with concentrations of 0.04 mg/cm2 passes the microbiological test for *S. au-*

reus bacteria and *C. albicans* fungi. Sample No. 3 does not meet the SPhU requirements, because after 14 days of observation the logarithm of the decrease in the number of viable microorganisms of *P. aeruginosa* bacteria is less than 3.0, and the cells of *C. albicans* and *A. brasiliensis* fungi are less than 1; sample No. 4 does not meet the SPhU requirements, because after 14 days the logarithm of the decrease in the number of *P. aeruginosa* bacteria is less than 3.0, and the cells of *A. brasiliensis* fungi are less than 1. Sample No. 5 meets the SPhU requirements for all test cultures. Thus, the concentrations of metronidazole and chlorhexidine of 0.05 mg/cm^2 in sample No. 5 provide sufficient preservative effect for the appropriate microbiological purity of the films during storage and use and do not require the addition of preservatives.

Table 10

Results of antimicrobial activity of dental film samples

Sample (concentration of antimicrobial components, mg/cm^2)	Microorganism cultures				
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*P. vulgaris* ATCC 4636	*C. albicans* ATCC 885-653
	Diameters of zones of inhibition of growth of microorganisms, ($M\pm m$)*mm				
No. 1 (0,01)	13.1±0.2	8.9±0.5	9.0±0.4	8.6±0.2	10.5±0.5
No. 2 (0,02)	14.7±1.0	10.2±0.2	9.7±0.4	9.2±0.5	10.6±0.1
No. 3 (0,03)	15.1±0.7	12.0±0.9	10.6±0.1	10.0±0.9	10.6±0.5
No. 4 (0,04)	19.9±0.2	12.4±0.7	10.7±0.5	10.5±0.2	12.7±0.9
No. 5 (0,05)	21.3±0.9	13.3±0.5	11.5±0.5	10.7±1.0	14.2±0.2

Table 11

Indicators of the effectiveness of the preservative action of dental film samples with CHA

Sample (concentration of antimicrobial components, mg/cm^2)	lg reduction in the number of viable microorganisms, lg CFU/ml (SFU 2.3 requirements/results obtained)	
	14 days	28 days
Staphylococcus aureus ATCC 6538		
No. 3 (0.03)	3/3.13	NI/NV
No. 4 (0.04)	3/3.50	NI/NV
No. 5 (0.05)	3/3.50	NI/NV
Pseudomonas aeruginosa ATCC 9027		
No. 3 (0.03)	3/2.63	NI/NI
No. 4 (0.04)	3/2.50	NI/NV
No. 5 (0.05)	3/3.38	NI/NV
Candida albicans ATCC 10231		
No. 3 (0.03)	1/0.76	NI/NI
No. 4 (0.04)	1/1.12	NI/NV
No. 5 (0.05)	1/1.98	NI/NV
Aspergillus brasiliensis ATCC 16404		
No. 3 (0.03)	1/0.65	NI /1.9
No. 4 (0.04)	1/0.73	NI/NV
No. 5 (0.05)	1/NV	NI/NV

Note: NI – no increase in the number of microorganisms compared to the number of viable microorganisms at the previous control point; NV – no viable cells of microorganisms were detected in the experiment.

5. Discussion of research results

Based on the complex of studies conducted, the composition of dental films with complex action with CHA and antimicrobial components was substantiated (Table 12). The selected concentration of CHA at 10 % is standard in dental products to provide stimulation of remineralization and inhibition of demineralization, reduce symptoms of dentin hypersensitivity and effectively prevent caries, which is confirmed by a number of clinical studies [13, 30]; the selected concentrations of metronidazole and chlorhexidine bigluconate when used together with CHA in this development are effective for providing antimicrobial action and are lower compared to similar developments [19, 20].

The sequence of technological stages of film production is as follows: preparation of raw materials, preparation of API suspension, preparation of film-forming solution, preparation of film mass, pouring of film mass, drying of film mass, cutting of film, packaging of film.

Table 12

The composition of the developed dental films is complex with CHA and antimicrobial components

Substance	Quantitative composition, mg/cm^2
CHA	4.0
Metronidazole	0.05
Chlorhexidine bigluconate (20 % solution)	0.05
PVA	16.0
Glycerin	12.0
Macrogol 400	6.0
Purified water	residual amount

According to the developed composition and technology, 5 batches of the drug were manufactured and stored in different conditions (from +15 °C to +25 °C (room temperature), from +8 °C to +15 °C (cool place)) for compliance with the specifications of quality control methods: description, identification – CHA, metronidazole, chlorhexidine bigluconate, size, thickness, average mass, solubility, pH, tensile strength, tensile strength, uniformity of dosage units, uniformity of content, uniformity of mass, microbiological purity, quantitative determination – CHA, metronidazole, chlorhexidine bigluconate. The current results over 21 months showed compliance of the results with the acceptable norms of

the dental film specification indicators, which indicates the stability of the developed preparation during storage.

Practical significance. The conducted research will contribute to the introduction into pharmaceutical practice of new drugs effective for use in dental practice for remineralization of tooth enamel, elimination of tooth hypersensitivity, prevention of the formation of microbial biofilms, elimination of pathogenic microflora in the form of dental films based on a new substance for the domestic industry, calcium hydroxyapatite.

Study limitations. The results of the study were obtained on the basis of theoretical, physicochemical, structural-mechanical, and microbiological methods that guarantee the quality and stability of the developed drug, but do not allow assessing its effectiveness in real-world use due to the lack of use of clinical test strains in the analysis of antimicrobial properties and the lack of preclinical and clinical studies.

Prospects for further research. Processing the results of the last measurement studies to finally determine the shelf life of the developed drug and approve quality control methods.

6. Conclusions

Based on the analysis and generalization of data from scientific publications by domestic and foreign authors, calcium hydroxyapatite was selected as the active ingredients – a remineralizing, anti-caries agent, metronidazole and chlorhexidine bigluconate – antimicrobial components.

Based on physicochemical studies, the following were justified: the introduction of a poorly soluble substance of calcium hydroxyapatite in a combined dispersion medium with the inclusion of purified water, glycerin and macrogol 400, which ensures the improvement of the properties of the substance, the introduction of poorly soluble metronidazole in the form of a suspension with glycerin and chlorhexidine bigluconate as a 20 % solution.

Based on studies of the physicochemical and structural-mechanical indicators of the polymer base and samples of films based on them, the use of polyvinyl alcohol in an amount of 5 % and glycerin in an amount of 4 % as a film-forming solution was justified.

Based on the microbiological properties of the films, the concentrations of metronidazole and chlorhexidine bigluconate in this development were determined - 0.05 mg/cm^2 each.

The developed preparation of the following composition (mg/cm^2): CHA - 4 mg, metronidazole - 0.05 mg, chlorhexidine bigluconate – 0.05 mg, PVA – 16 mg, glycerin – 12 mg, macrogol 400 – 6 mg, purified water met the specifications of the MCQ at the beginning of production and during 21 months of observation (processing of the results of the last observation is ongoing).

Conflict of interest

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study, and its results presented in this article.

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Data availability

Manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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