 APPROACHES TO THE SELECTION OF EXCIPIENTS FOR DENTAL GEL WITH CETYLPYRIDINIUM CHLORIDE

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The aim of the study was to determine the excipients influence on the characteristics of gels with cetylpyridinium chloride and to select the dental gel formulation gelation agents promising for the development of dental gel compositions. Hereby, the properties of the active pharmaceutical ingredient, characteristics of the specific gelation agents, as well as their influence on stability, biopharmaceutical and application properties of gels, were taken into account.

Materials and methods. In this study, polymers with various gelation mechanisms were considered. Their compatibility with cetylpyridinium chloride as well as storing kinetic and colloid kinds of stability, pH of aqueous solutions, spreadability and textural properties, a penetration ability by the agar diffusion method, an osmotic activity and rheological properties of the gels, were examined. For a complex evaluation of gel compositions study results, a desirability function was used.

Results. Stable homogenous dental gels with cetylpyridinium chloride can be obtained by using 25% poloxamer 407 and 5.0% high molecular weight chitosan as the basis.

The addition of poloxamer 188 to high molecular weight chitosan gels can produce stable systems with improved textural characteristics as well as increase their osmotic activity. Agar and low molecular weight chitosan addition significantly decrease, whereas poloxamer 188 and various molecular weight polyethylene glycol increase the osmotic activity of 25% poloxamer 407 gels which are also characterized by a high penetration ability.

Conclusion. A complex evaluation of biopharmaceutical, physicochemical and application properties of the gels made it possible to establish that combinations of poloxamer 407 with polyvinylpyrrolidone, agar, and low molecular weight chitosan, can be recommended as a base for a dental gel with cetylpyridinium chloride.

Keywords: cetylpyridinium chloride; dental gel; composition; excipients; biopharmaceutical properties; chitosan; poloxamer; desirability function

Abbreviations: PP – pharmaceutical preparation; DF – dosage form; CMC – carboxymethylcellulose; PVP – polyvinylpyrrolidone; PEG – polyethylene glycol; FDA – Food and Drug Administration (U.S.)

PODХОДЫ К ВЫБОРУ ВСПОМОГАТЕЛЬНЫХ ВЕЩЕСТВ ДЛЯ ГЕЛЯ СТОМАТОЛОГИЧЕСКОГО С ЦЕТИЛПИРИДИНИЯ ХЛОРИДОМ

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INTRODUCTION

Currently, oral cavity diseases are ones of the most common. Periodontal diseases can be distinguished among them. Periodontium is a complex of tissues that form supporting apparatus of teeth; frequent symptoms of periodontal diseases are inflammations, primarily or secondarily associated with the growth of the infectious microorganisms [1, 2].

Dental gels are ones of the dosage forms (DFs) used for the local treatment of periodontal diseases.

The pharmaceutical preparations (PPs) in such DFs, registered in Russia, belong to local anesthetic, anti-septic, antimicrobial, non-steroidal anti-inflammatory agents. In such compositions, antimicrobial components are metronidazole, chlorhexidine digluconate, cetylpyridinium chloride, cetalkonium chloride, benzalkonium chloride and their combinations [3].

Cetylpyridinium chloride is one of the most common antimicrobial preparations prescribed for inflammatory infections of the oral cavity [4]. Its therapeutic concentration safety was confirmed by the clinical data and proved by FDA [5–7].

Among the DFs with cetylpyridinium chloride for the oral cavity, sprays and lozenges are prevalent [3, 8, 9]. In dental gels, 0.1% cetylpyridinium chloride is presented only in combination with lidocaine hydrochloride in local anesthetic preparations prescribed for children in cutting of the teeth [3, 9].

Currently, a large number of studies on dental gels with synthetic and natural substances development, including those with antimicrobial properties, are known [10–20]. There are investigations on the study of local adhesive DFs with cetylpyridinium chloride [9, 21–25].

But to date, there is no submitted research on the development of dental gels which contains only cetylpyridinium chloride as an active pharmaceutical ingredient. Therefore, the development of such a PP is relevant [9]. DFs for the local use in the oral cavity contain from 0.05 to 0.50% cetylpyridinium chloride [3]. The developed gel will contain one active pharmaceutical ingredient. For this reason, the choice of the maximum therapeutic concentration (0.50%) for this DF is appropriate.

When developing a gel composition, the base choice which will affect the biopharmaceutical properties of the DF, including its penetration ability and osmotic activity, is very important. The prolongation of gel presence on mucosa can be achieved by including mucoadhesive polymers as well as their combinations, in the gel composition. It is important to consider this fact in the pharmaceutical development of this DF [26–29].

It is common knowledge that the characteristics of active pharmaceutical ingredients can impact the physicochemical and technological properties of a gel base. This fact is especially important for cetylpyridinium chloride, which, as a cationic compound, can affect the conformation of gelation agents molecules, sensitive to the presence of ions in the system [9, 27, 30].

The possibility of the chemical interaction between cetylpyridinium chloride and acids should be also taken into account. The problem of combining cetylpyridinium chloride and acidic compounds in one DF is complex and depends on the type of the DF, its aggregate state, the presence of stabilization agents, the method of substances introduction and, in particular, the degree of substitution of acid groups in cellulose derivatives gelling agents [9, 23, 25, 31].
Hence, the selection of excipients for dental gel base is a complex problem that should be solved by determining biopharmaceutical, physicochemical and technological characteristics of a gel base with the consideration of special aspects of this DF administration.

THE AIM of the study was to determine the excipients influence on the characteristics of gels with cetylpyridinium chloride, and to select the dental gel formulation gelation agents promising for the development of the dental gel composition.

The research objectives included the selection of compatible with cetylpyridinium chloride gelation agents and viscosity modifying agents, the selection of their concentrations, the investigation of physicochemical and biopharmaceutical properties of the gel compositions, their complex evaluation and the excipients selection for the dental gel.

MATERIALS AND METHODS

The cetylpyridinium chloride substance (“Diam”, Russia) and the excipients – acid-soluble high molecular weight chitosan (ZAO «Bioprogress», Russia), aqua-soluble low molecular weight chitosan (ZAO «Bioprogress», Russia), polyvinlypyrolidone (PVP) (Plasdone K 29/32, ISP Pharmaceuticals, Switzerland), agar (Agar 900, Qixiang, China), poloxamer 407 (Kolliphor P 407, BASF, Germany), poloxamer 188 (Kolliphor P 188, BASF, Germany), polyethylene glycol 300 (PEG 300) (Polyethylene glycol 300, Merck, USA), polyethylene glycol 6000 (PEG 6000) (NORCHEM-008, Russia), glycerine (NevaReaktiv®, Russia), carbomer (Carbopol® 974 P NF, IMCD, Netherlands), sodium alginate (FOODALRA®, 500, FOODCHEM, Russia), iota carageenan (Benvisco, USA), xanthan gum (NOW® FOODS, USA), methylcellulose (Methocel® A15, DOV chemical company limited, USA), carboxymethylcellulose (CMC) (Akucell® AF 2785, Akzo Nobel, Netherlands), acacia gum (Instantgum® BA, CNI, France) – were used.

N-tris hydroxyethylaminomethane (trometamol) (NevaReaktiv®, Russia) was used to obtain carbomer gel and hydrochloric acid for chitosan gel (Lenareaktiv, Russia). A 10% Cetylpyridinium chloride aqueous solution was introduced in the gels.

The storing stability was examined by gels exposure infilled to the top orange glass jars (BTC-20-27,5-OS-1 type) at the room temperature for 6 months. The storing stability was examined by centrifugation of the gel samples at 6000 rpm for 15 min. The kinetic stability was determined. The colloid stability was determined by centrifugation of the gel samples at 6000 rpm for 5 min after their freezing and thawing [33]. The colloid stability coefficient ($K_c$) was calculated as the ratio of the phase height released after centrifugation to the total height of the gel sample in the centrifuge tube. For the colloid stable gels, the value of $K_c$ should be equal to 0.0.

The spreadability and textural properties were determined by estimation of the gel sample (0.5 g) distribution between the glass plates with a force of 0.5 kg [34].

The penetration ability was studied by the agar diffusion method according to the developed methods [20] based on the classic approach to the biopharmaceutical characteristics of semi-solid dosage forms [33].

The determination of the osmotic activity was carried out by the Kruvchinsky equilibrium dialysis method through a semipermeable membrane with a pore diameter of 12–14 kDa («Orange Scientific», Belgium) [35]. A 0.9% aqueous solution of Sodium chloride was used as a dialysis liquid.

The dynamic viscosity was examined on Brookfield DV-II+PRO programmable viscometer (Brookfield Engineering Laboratories, Inc., ClWA) subject to OFS. 1.2.1.0015.15 “Viscosity” [36]. The sample viscosity in the range of shear rates from 10 to 200 s$^{-1}$ and from 200 to 10 s$^{-1}$ was determined. The torque values ranged from 30 to 80%.

For complex evaluations of gel compositions, a desirability function was used [37].

The results of parallel measurements were processed according to GPM 1.1.0013.15 “Statistical processing of the results of a chemical experiment” [36].

RESULTS AND DISCUSSIONS

Selection of compatible excipients

At the first stage, the compatibility of cetylpyridinium chloride with widely used in dental gels excipients, was studied [3, 10, 12–15, 17–19, 27]. The calculated amounts of a 10% aqueous solution of cetylpyridinium chloride were added to gels or excipients aqueous solutions until its 0.5% concentrations in the samples. The obtained systems were described immediately and after 30 days of storage. The mixtures of cetylpyridinium chloride with 1.0% carbomer, 2.0% iota carrageenan, 8.0% acacia gum, 2.0% methylcellulose, 4.0% carboxymethylcellulose, 6.0% high molecular weight chitosan, 4.0% low molecular weight chitosan, 20.0% poloxamer 407, 15.0% poloxamer 188, 1.0% agar, 3.0% xanthan gum, 1.0% sodium alginate, 20.0% PVP, 10.0% PEG 300, 5.0% PEG 6000 and 40.0 glycerol were studied.

It has been established that heterogeneous systems are formed at the addition of a cetylpyridinium chloride solution to carbomer, iota carrageenan, cellulose derivatives, xanthan gum gels, and acacia gum solutions. There were various kinds of a residue structure of these systems – from the white adhesive mass in carrageenan gels to a fine precipitate in methylcellulose gels.
Homogeneous systems with no changes in the appearance were formed with chitosans, poloxamers, PVP, agar, PEG 400 and 6000 and glycerol. High molecular weight chitosan and poloxamer 407 were selected as a base gelation agent with the properties of their aqueous systems taken into account.

Poloxamer 407 is a non-ionic polymer of a synthetic origin. It is used as a gelation agent, a viscosity modifying agent, emulsifier and solubilizer (HLB value 18–23) in liquid and semi-solid DF technologies. Thermoreversible properties of poloxamer 407 are its technology features. Gelation mechanism is connected with a micelles formation and association, as the temperature rises [38, 39].

Chitosan is a chemically modified gelation agent of the natural origin with known antiseptics and wound healing activities. The characteristics of chitosan molecules depend on their molecular weight. Gelation mechanism is connected with ionization and changes in molecular conformation at the interaction with acid solutions [29, 40, 41].

Chitosans, poloxamers, agar, PVP and PEG of various molecular weight have mucoadhesive properties which are developed differently [26, 28, 29, 39]. Mucoadhesive properties are the aim of a separate research in the framework of a dental gel with cetylpyridinium chloride pharmaceutical development, and are not considered in this work.

**Excipients influence on gel with cetylpyridinium chloride characteristics**

At the next stage, the working concentration of gelation agents was chosen. For this textural, biopharmaceutical and physicochemical properties of 20.0–30.0% poloxamer 407 and 2.0–6.0% high molecular weight chitosan gels were investigated [20]. According to their properties, complex evaluation gels of 25.0% poloxamer 407 and 5.0%, chitosan were chosen for a further study.

To develop a composition that meets the requirements for dental gels, taking into account the characteristics of their use and the properties of the active substance, combinations of the main gelation agents with compatible excipients were made up. Their stability, pH, penetration ability, osmotic activity, spreadability, and textural properties, as well as organoleptic characteristics, were studied. Fifteen compositions of dental gels were selected for the investigation (Table 1).

Appearance, a storing stability, kinetic and colloidal stabilities were determined for gels compositions (Table 2).

It has been established, that compositions 2, 3 and 5 with high molecular weight chitosan as a base gelation agent, separated into two phases after 6 months of storage. The gels separation can be explained by the significant difference between the molecular weight of the base gelation agent — high molecular weight chitosan (200 kDa) and viscosity modifying agents — low molecular weight chitosan (1–30 kDa), PEG 300 and 6000 as well as the absence of synergism during gelation. The gels formation was due to simple physical molecules intertwining of high molecular weight chitosan and the excipients. This did not provide stability of the systems, and further on, the gels separated into two phases — the lower one contained mainly high molecular weight chitosan, and the upper lighter phase contained viscosity modifying agents.

At the same time, by combining high molecular weight chitosan with poloxamer 188 (ratio 5:10 and 4:20) and PVP (5.0 : 1.5), stable homogeneous systems were obtained. However, composition 6 showed a change in consistency towards its density. For these reasons, 2, 3, 5 and 6 gels were excluded from the further study.

The gels with a poloxamer 407 base did not show any changes in properties.

For stable compositions, a pH value, spreadability and textural properties were determined (Table 3). Based on the analysis of the data obtained, it has been established that compositions 1 and 7 with high molecular weight chitosan and poloxamer 407 without viscosity modifying agents addition had equally low spreadability values. However, the textural properties of cationic high molecular weight chitosan with the addition of a non-ionic surfactant (poloxamer 188) forming different conformation micelles (compositions 4 and 15) were improved significantly. Sample 15 has the highest spreadability value of all the studied gels.

It is has been additionally noted that when spreading over the surface, this composition formed foam. At the same time, the addition of poloxamer 188, PVP, PEG 300 and 6000 as well as low molecular weight chitosan in poloxamer 407 based gels, has a slight effect on their spreadability. Hence, the introduction of excipients improving textural properties, is necessary for the main part of the obtained gels.

Poloxamer 407 based gels were characterized by a high penetration ability. Poloxamer 407 is known to be used as a penetrant in a semi-solid DF technology [38, 39]. To approximate the model to physiological conditions, the penetration ability was determined by thermostating the samples at 37°C. When choosing the experimental conditions, it was noted that the agar diffusion depth for poloxamer 407 gels at the room temperature was higher than at 37°C. The viscosity poloxamer 407 gels increasing at rising the temperature can explain this fact. Therefore, their agar diffusion was difficult.

When studying the penetrating ability of the gels based on chitosan, it was found out that the samples absorbed water and spread over the surface of the medium (compositions 1, 4, and 15). No diffusion into the agar can be explained by a high molecular weight of the base gelation agent.

The pH value of all examined samples is close to the physiological pH values of mixed saliva [42].

The results of the gels osmotic activity determinations are presented in Fig. 1.
Table 1 – Compositions of gels with cetylpyridinium chloride

| Composition number | CPC  | Chitosan h. | P 407 | Chitosan l. | PVP  | Agar 900 | P 188 | PEG 300 | PEG 6000 | Glycerol | 10% HCl | Purified water |
|--------------------|------|-------------|-------|-------------|------|----------|--------|---------|----------|----------|---------|----------------|
| 1                  | 0.5  | 5.0         | –     | –           | –    | –        | –      | –       | –        | 5.0      | to 100.0 |                |
| 2                  | 0.5  | 3.0         | 4.0   | –           | –    | –        | –      | –       | –        | 3.0      | to 100.0 |                |
| 3                  | 0.5  | 5.0         | –     | –           | –    | –        | 3.0    | –       | 7.0      | 5.0      | to 100.0 |                |
| 4                  | 0.5  | 5.0         | –     | –           | –    | 10.0     | –      | –       | –        | 5.0      | to 100.0 |                |
| 5                  | 0.5  | 5.0         | –     | –           | –    | 10.0     | –      | –       | 5.0      | to 100.0 |        |                |
| 6                  | 0.5  | 5.0         | –     | 1.5         | –    | –        | –      | –       | –        | 5.0      | to 100.0 |                |
| 7                  | 0.5  | –           | 25.0  | –           | –    | –        | –      | –       | –        | –        | to 100.0 |                |
| 8                  | 0.5  | –           | 25.0  | –           | –    | 10.0     | –      | –       | –        | –        | to 100.0 |                |
| 9                  | 0.5  | –           | 25.0  | –           | –    | 10.0     | –      | –       | –        | –        | to 100.0 |                |
| 10                 | 0.5  | –           | 25.0  | –           | –    | 10.0     | –      | –       | 7.0      | –        | –        | to 100.0       |
| 11                 | 0.5  | –           | 25.0  | –           | –    | 0.1      | –      | –       | –        | –        | –        | to 100.0       |
| 12                 | 0.5  | –           | 25.0  | 1.5         | –    | –        | –      | –       | –        | –        | –        | to 100.0       |
| 13                 | 0.5  | –           | 30.0  | 0.1         | –    | –        | –      | –       | –        | –        | –        | to 100.0       |
| 14                 | 0.5  | –           | 25.0  | 0.4         | –    | –        | –      | –       | –        | –        | –        | to 100.0       |
| 15                 | 0.5  | 4.0         | –     | 0.2         | –    | 20.0     | –      | –       | 4.0      | –        | –        | to 100.0       |

Note: CPC – cetylpyridinium chloride; chitosan h.– high molecular weight chitosan; P 407 – poloxamer 407; chitosan l.– low molecular weight chitosan; P 188 – poloxamer 188; 10% HCl – 10% hydrochloric acid solution.

Figure 1 – Dependence of the absorbed isotonic solution mass fraction on the time of gel dialysis
Note: A – compositions 1, 7, 8, 10, 12 and 15; B – compositions 4, 8, 11, 13 and 14

Figure 2 – Viscosity curves for compositions 7, 12 (A) and 11, 14 (B) at 20°C
### Table 2 – Stability of gel samples with cetylpyridinium chloride

| Composition number | Samples appearance after receipt | Samples appearance after 6 month of storage |
|--------------------|----------------------------------|--------------------------------------------|
|                    | Appearance                        | $H_s$ $K_c$                                 | Appearance                        | $H_s$ $K_c$ |
| 1                  | Slightly opalescent homogeneous dense yellowish non-flowing mass | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 2                  | Opalescent homogeneous dense light brown non-flowing mass         | 0.0 0.0                                     | Separation into a clear liquid and strongly opalescent gel phases, approximately equal in volume | 0.4 0.6 |
| 3                  | Opalescent homogeneous dense whitish flowing mass                 | 0.0 0.0                                     | Separation into a clear liquid (about 30% in volume) and strongly opalescent gel phases | 0.3 0.5 |
| 4                  | Strongly opalescent yellowish flowing mass                        | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 5                  | Strongly opalescent dense yellowish non-flowing mass              | 0.0 0.0                                     | Separation into a clear liquid and strongly opalescent gel phases, approximately equal in volume | 0.3 0.4 |
| 6                  | Strongly opalescent dense yellowish non-flowing mass              | 0.0 0.0                                     | Strongly opalescent jelly-like mass | 0.0 0.0 |
| 7                  | Clear homogeneous dense colorless non-flowing mass                | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 8                  | Clear homogeneous dense colorless non-flowing mass                | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 9                  | Clear homogeneous dense colorless non-flowing mass with foam on the surface | 0.0 0.0                                     | Clear homogeneous dense colorless non-flowing mass | 0.0 0.0 |
| 10                 | Clear homogeneous dense colorless non-flowing mass*               | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 11                 | Slightly opalescent homogeneous dense colorless non-flowing mass  | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 12                 | Strongly opalescent homogeneous dense colorless non-flowing mass*| 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 13                 | Strongly opalescent homogeneous dense yellowish non-flowing mass  | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 14                 | Opalescent homogeneous light brown non-flowing mass with a light texture | 0.0 0.0                                     | No changes                        | 0.0 0.0 |
| 15                 | Slightly opalescent homogeneous dense yellowish non-flowing mass with air bubbles in volume and foam on the surface | 0.0 0.0                                     | No changes                        | 0.0 0.0 |

Note: *Gel acquires a liquid consistency under cooling

### Table 3 – Characteristics of gel samples with cetylpyridinium chloride

| Parameter                        | Composition number |
|----------------------------------|--------------------|
|                                  | 1 4 7 8 9 10 11 12 13 14 15 |
| pH value of 5.0% aqueous gel solutions | 5.4±0.05 5.3±0.04 6.4±0.05 6.2±0.05 6.1±0.04 6.2±0.05 6.3±0.04 6.1±0.05 5.2±0.05 5.5±0.05 5.3±0.05 |
| Agar diffusion depth, mm         | – – 13.9±0.4 14.1±0.7 14.6±0.5 12.6±0.5 15.0±0.9 12.6±0.5 14.8±0.9 15.0±0.6 – |
| Spreadability, cm                | 3.3±0.3 3.8±0.4 2.7±0.3 2.6±0.2 3.1±0.3 2.6±0.4 3.1±0.2 3.0±0.3 2.9±0.3 3.0±0.4 5.0±0.3 |
It has been established that samples 1, 4 and 14 with high molecular weight chitosan, its combination with poloxamer 188 (5:10) and a composition of poloxamer 407 and low molecular weight chitosan (25:0.4) have the lowest osmotic activity value (less than 50% per first exposition hour). At the same time, 20% of poloxamer 188 addition in chitosan gel significantly increased its osmotic activity.

The additions of agar (sample 11), as well as low molecular weight chitosan (sample 14) significantly reduce the osmotic activity of 25% poloxamer gels.

The osmotic activity increases with the increase of poloxamer 188 and 407 concentration (compositions 8 and 13). PEG 300 and 6000 (composition 10 and 9) introduction significantly increases the poloxamer 407 gels osmotic activity.

Meanwhile, sample 10 has the highest value of the osmotic activity: its mass increases more than twice for the first exposition hour.

**Compositions complex evaluation for the selection of dental gel base with cetylpyridinium chloride**

The following demands to the excipients selection were taken into account: the gel base should have a light spreadability and good textural properties, pH value close to the physiological condition, a low osmotic activity (to avoid the moisture loss by mucus membranes), a low penetration depth (to prevent the entry of local antiseptics into the bloodstream) and a neutral flavour [12–14, 27].

Harrington’s generalized desirability function can provide a complex evaluation of gels compositions [37]. Taking into account the above-listed requirements for dental gels, the following responses of the desirability function have been selected:

- **1.** $d_1$ – pH value of 5.0% aqueous gel solutions;
- **2.** $d_2$ – agar diffusion depth, mm;
- **3.** $d_3$ – osmotic activity per first exposition hour;
- **4.** $d_4$ – spreadability, cm;
- **5.** $d_5$ – textural properties;
- **6.** $d_6$ – flavour.

The characteristics of desirability function response variables are presented in Table 4.

Generalized desirability coefficient ($D$) was calculated by the formula (2):

$$D = \sqrt[d_1]{x_1} \times \sqrt[d_2]{x_2} \times \sqrt[d_3]{x_3} \times \sqrt[d_4]{x_4} \times \sqrt[d_5]{x_5} \times \sqrt[d_6]{x_6},$$ (2)

The results of the determination are presented in Table 5.

Based on the analysis, it was established that composition 12 with poloxamer 407 and PVP has a high generalized desirability coefficient value.
Meanwhile, compositions 7, 11 and 14 also had rather high $D$ values. Their bases contain 25% poloxamer and its combinations with agar and low molecular weight chitosan. These gels can be used as a base with the introduction of excipients that correct their properties.

When choosing excipients, their effect on the structural and mechanical properties of gels is of great importance.

That’s why at the next stage, rheological characteristics of compositions 7, 11 and 14 were determined. The viscosity curves are presented in Fig. 2.

It has been established that all studied samples had similar dynamic viscosity values in the range of shear rates from 30 to 200 s$^{-1}$. With an increase in the shear rate, the dynamic viscosity of all compositions decreased, which makes it possible to attribute it to systems with a pseudoplastic type of flow. It should be noted that all examined samples restored the viscosity after unloading, which allows predicting the retention of the structural and mechanical properties of these systems during their production and packaging.

CONCLUSION
Cetylpyridinium chloride forms stable homogeneous systems with chitosans, poloxamers, PVP, agar, PEG 300 and 6000. When studying the properties of gels containing these substances in different combinations, their influence on the properties of the resulting compositions was determined. Hence, it was found that poloxamer 188 addition to the high molecular weight chitosan (20:4) can obtain stable systems, as well as improve their spreadability and textural properties, and increase their osmotic activity. At the same time, a further stabilization is required by combinations of high molecular weight chitosan with PEG 300 and 6000, low molecular weight chitosan (in the ratio 5:3, 5:10 and 3:4, respectively) to prevent their separation.

Poloxamer 407 based gels were characterized by a high penetration ability. The studied excipients (poloxamer 188, agar, low molecular weight chitosan, PVP, PEG 300 and 6000) do not significantly impact on these characteristics. Additions of agar, as well as low molecular weight chitosan, significantly reduce the osmotic activity of 25% poloxamer gels, while poloxamer 188 and PEG of various molecular weight increase it. It should be noted that poloxamer 407 gels require the introduction of excipients that improve their texture properties.

The complex evaluation of gels biopharmaceutical, physicochemical and application properties established that combinations of poloxamer 407 with polyvinylpyrrolidone, agar, and low molecular weight chitosan can be recommended as a base for a dental gel with cetylpyridinium chloride. These systems were characterized by the pseudoplastic type of flow and restored the viscosity after an applied load of shear rates in the studied range.

The final composition selection can be made after studying mucoadhesive and antimicrobial properties of the developed dental gels, which will be discussed in the further research.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION
E.Yu. Zagorulko – determination of the aim and objectives of the study, planning of the experiments and interpretation of their results, selection of the desirability function responses and calculation of the generalized coefficient values, preparation of the article manuscript; A.S. Karavaeva – execution of the experimental work, statistical processing of the primary data, discussion of the research results.

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