Development of the Composition and Technology of a New Dental Gel with Anti-Inflammatory and Antimicrobial Action

S.M. Adekenov*, A.N. Zhabayeva, Kh.I. Itzhanova, A.S. Amirzhanova, Zh.R. Shaimerdenova

JSC «International Research and Production Holding «Phytochemistry», 100009, M. Gazaliev str. 4, Karaganda, Republic of Kazakhstan

Abstract

The development of a dental gel that meets modern requirements for the effectiveness and safety of a medicinal product is a serious scientific study related to the selection of active and auxiliary substances, providing the necessary biopharmaceutical and rheological properties of the gel composition, standardizing the quality of the dosage form. The article presents the results of a study on the development of the composition and technology of the soft dosage form of the new dental gel «Matripin-Dent» using pharmacologically active ingredients of the sum of flavonoids from *Populus balsamifera* L. buds (pinostrobin, pinocembrin, chrysin, techtochrysin) and the sum of terpenoids from *Matricaria chamomilla* L. (bisabolol oxides A and B, chamazulene). Three bases are selected: fat, gel, and multicomponent. According to the results of pharmacological studies, the optimal composition is a gel base containing polyethylene oxide 1500 and 400. The rheological index of the gel base confirms its thixotropic properties, good spreadability, the ability of the obtained gel to extrude from the tube, and stability. The indicators of control and critical points of the technological process are determined and a technological scheme for the production of dental gel is developed.

1. Introduction

The modern range of drugs used in dental practice is quite diverse. Drugs used in dentistry belong to various pharmacotherapeutic groups, characterized by the nature of the active substances and the dosage form [1]. There are some dental products on the pharmaceutical market of the Republic of Kazakhstan, such as: Denta-met® (Russia), Kamistad® (Germany), Calgel® (Poland), Metrogyl Denta® (India), Cholisal® (Poland) and Asepta® (Russia), the active ingredients in which are synthetic substances.

In the treatment of diseases of the teeth, gums, and mucous membranes of the oral cavity, drugs are used in the form of lozenges, films, solutions, sprays for topical applications, as well as liniments, gels and ointments. However, the effectiveness of pharmacotherapy of various diseases depends on the choice of the dosage form used [2, 3]. To relieve symptoms of inflammatory periodontal diseases, the main indications for the use of drugs are gingivitis, periodontitis, stomatitis, cheilitis, glossitis, increased sensitivity of the teeth, prophylaxis of gingival inflammation. In the treatment of the above-mentioned diseases, significant progress in the provision of dental care was achieved thanks to the use of prolonged dosage forms of the application action in the form of gels with high efficiency, a wide range of therapeutic effects and no side effects, unlike synthetic antibacterial preparations [4–8].

An integral part of the development and production of soft dosage forms is the determination and evaluation of the rheological characteristics of gels, which depend on the concentration and stability of surface-active materials. The base of the dental gel should ensure uniform distribution of the drug on the gums, high bioavailability of the active substances [9–11].

*Corresponding author. E-mail: info@phyto.kz

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Given the relevance of creating and organizing the production of modern drugs based on biologically active plant substances for the treatment of periodontal disease, JSC «International Research and Production Holding «Phytochemistry» (Kara-ganda, Kazakhstan) together with LLP «Karaganda Pharmaceutical Plant» (Karaganda, Kazakhstan) developed a new drug «Matripin-Dent», which has pronounced anti-inflammatory and antimicrobial activities [12].

The work aimed to develop the composition and technology of a new dental gel.

2. Materials and methods

When choosing auxiliary components for the development of a soft dosage form, the following factors were guided by: the gel components should be compatible, not cause irritation, contribute to the maximum release of active components, ensure ease of application and packability of the gel. For this, gel samples were prepared on hydrophilic and hydrophobic bases. The following pharmacologically active components were used: extractives of *Populus balsamifera* L. and *Matricaria chamomilla* L., as well as auxiliary ingredients for flavorings menthol, indifferent bases polyethylene glycol-400, polyethylene glycol-1500, beeswax, sunflower oil, glycerin, arespol.

Rheological studies of the test samples were carried out at a temperature of 22.8 °C using «ViscoQC 300-H» (Austria) rotation viscosimeter. The test samples of the bases in an amount of 250 g were placed in a chamber with a volume of 300 ml, the spindle was lowered into it and the viscosity readings were measured.

The choice of the optimal concentration of active substances of *Populus balsamifera* L. extract and *Matricaria chamomilla* L. extract, which provide sufficient anti-inflammatory, antimicrobial, wound-healing effects, was based on previous studies [13].

3. Results and discussion

At the first stage of the study, screening of the bases capable of providing the maximum therapeutic effect in the dosage form was carried out.

The main active substances of *Populus balsamifera* L. extract are flavonoids – pinostrobin (1), pinocembrin (2), chrysin (3), techtochrysin (4), which are characterized by anti-inflammatory and antioxidant activity. Pharmacologically active compounds of the carbon dioxide extract of *Matricaria chamomilla* L. – bisabololoxides A (5) and B (6), chamazulene (7), determine the antimicrobial properties of the developed gel.

When developing the composition and technology of the gel with extracts of *Populus balsamifera* L. and *Matricaria chamomilla* L., model compositions were made. The compositions of model samples per 100 g of mass are presented in Table 1.

The study of model mixtures of dental gel for periodontal diseases of inflammatory and inflammatory-destructive nature showed that a dental gel based on polyethylene oxide-1500 and polyethylene glycol-400 has an antibacterial, anti-inflammatory and regenerating effect, reduces the duration of treatment of periodontal disease and oral mucosa to 5–7 days [12].

Gels based on a mixture of polyethylene oxides have several advantages over hydrophobic ointments. When applied to the skin, they form smooth films, absorb skin excretory and secretory products, are well distributed on the skin surface, have a cooling effect due to the presence of menthol, do not violate the physiological functions of the skin, do not cause allergic reactions and irritating effects, have a pleasant appearance.
To determine the choice of the optimal structure former, a study was made of the effect of polymer concentration on the effective viscosity of the composition on water-soluble and fat-soluble substrates.

Rheological parameters have a direct impact on the quality, stability of the finished dosage form, the release of drugs from the ointment base, the convenience and ease of application, packability, and extrusion from tubes [14].

The parameters of the rheological indicators on a lipophilic and hydrophobic basis are presented in Table 2.

Analysis of the data presented in Fig. 1 shows the presence of upward curves, that is, the destruction of the dental gel system. The test samples had satisfactory spreadability. The results of determining the effective viscosity of the shear rate are shown in Table 3.

![Fig. 1. Rheogram of the flow of gel samples of a dental product.](image-url)
Based on the obtained rheogram, one can assume good spreadability, the ability of the obtained gel to be squeezed out of the tube, and the stability of the developed gel based on pharmacologically active compounds of *Populus balsamifera* L. and *Matricaria chamomilla* L.

To study the thixotropic properties, the curves of the kinetics of gel deformation with a polyethylene oxide base were constructed in the coordinates: shear rate and shear stress in the range of variation of flow velocity gradients from small to large and from large to small. An analysis of the effective viscosity rheogram shown in Fig. 2 shows the presence of ascending (system failure) and descending (system recovery) curves and an increase in the hysteresis loop, which indicates an increasing depth of structure formation in the polyethylene oxide-400:polyethylene oxide-1500 system and confirms the thixotropic properties of the dental gel.

As a result of biological and rheological studies, the composition of the dental gel «Matrinpin-Dent» was developed (Table 4) with the active ingredient of *Populus balsamifera* L. and *Matricaria chamomilla* L. extractives.

The technological scheme for the production of dental products in the form of a gel is shown in Scheme, which includes the preparatory stage and the actual process of manufacturing a gel with extractive substances of *Populus balsamifera* L. and *Matricaria chamomilla* L. extractives.

4. The preparation technology of the developed dental gel “Matrinpin-Dent”

The preparatory phase of gel production includes the manufacture of disinfectant solutions, weighing of the initial and auxiliary ingredients, the preparation of production premises, equipment, personnel, as well as the preparation of containers for filling the gel.

### Table 3
Dependence of viscosity on shear rate and shear stress

| # | Shear rate, rpm | Sample 1          | Sample 2          | Sample 3          |
|---|---------------|--------------------|--------------------|--------------------|
|   |               | Dynamic link, MPa·s | Effective viscosity, % | Dynamic link, MPa·s | Effective viscosity, % | Dynamic link, MPa·s | Effective viscosity, % |
| 1 | 10.0          | 106567             | 24.90              | 143733             | 33.50              | 109700             | 25.63              |
| 2 | 15.6          | 76727              | 27.97              | 99127              | 37.63              | 83403              | 30.40              |
| 3 | 21.1          | 62200              | 30.67              | 77347              | 38.13              | 68827              | 33.93              |
| 4 | 26.7          | 53117              | 33.13              | 62240              | 38.83              | 59900              | 37.37              |
| 5 | 32.2          | 46653              | 35.10              | 53077              | 39.93              | 53520              | 40.27              |
| 6 | 37.8          | 41817              | 36.93              | 48043              | 42.47              | 48497              | 42.83              |
| 7 | 43.3          | 37983              | 38.43              | 44503              | 45.03              | 44570              | 45.10              |
| 8 | 48.9          | 34950              | 39.93              | 42040              | 48.03              | 41340              | 47.23              |
| 9 | 54.4          | 32423              | 41.20              | 40013              | 50.03              | 38533              | 48.97              |
| 10| 60.0          | 30273              | 42.43              | 36053              | 50.53              | 36340              | 50.93              |

### Table 4
The composition of the dental gel “Matrinpin-Dent”

| Name of ingredients | Gel base, g |
|---------------------|-------------|
| Extractives of *Populus balsamifera* L. | 5.0         |
| Extractives of *Matricaria chamomilla* L. | 1.0         |
| Menthol             | 0.1         |
| Polyethylene glycol–400 | 69.9          |
| Polyethylene glycol–1500 | 24.0          |
| Total               | 100.00      |

Fig. 2. Rheogram of the effective viscosity of the dental product.
The technological process for the production of dental gel “Matripin-Dent” consists of the melt of the base, the introduction of medicinal substances into the base, the homogenization of the prepared gel, packaging in tubes of 30 g, marking, and packaging in a secondary container.

The gel was prepared as follows: the calculated amount of polyethylene oxide powder-1500 was introduced into the production capacity of the reactor. A weighed amount of polyethylene glycol-400 was added to the molten base. The ingredients were thoroughly mixed using a high-speed homogenizer stirrer, the stirrer speed was 50 rpm, the duration of the mixing process was 10 min. The sum of flavonoids of *Populus balsamifera* L. and the sum of terpenoids of *Matricaria chamomilla* L. were introduced into the molten base. The gel was homogenized for 20 min. After the set homogenization time, a sample was taken for analysis. Upon reaching uniformity and particle size less than 100 µm, the gel was unloaded and sent to the packaging stage in the filling and capping monoblock of the brand “Master”.

The packaging of the finished dosage form of the Matripin-Dent dental gel was carried out in labeled aluminum tubes of 30 g each. Tubes were corked with screw-on plastic caps type 1.1-40 TU 64-2-269-78. After the packaging step, packing control was carried out. The melting of the base of a mixture of polyethylene oxides of grades 400 and 1500 in the ratio (7: 3) to a temperature of 55 °C is a critical point in the process of preparing the gel. A control point in the process of preparing a dental gel is considered to be the stage of preparation of the premises, equipment, personnel, the technological stage of the process of weighing the ingredients, melting the base, introducing the active ingredients into the base, mixing, determining the uniformity of the obtained gel and packing the mass into aluminum tubes.

In the production process according to the developed technology, a dental gel was obtained, which has a pleasant appearance, without mechanical impurities, with a greenish tint, a specific odor, is easily applied when used, tightly adhering to the gum surface, dries quickly, forming a film, is stable during storage.

4. Conclusions

Thus, as a result of the studies, a selection of excipients was made, the composition and technology for the production of the new dental gel “Matripin-Dent” were developed. The best rheological properties were possessed by the gel base of prescription No. 1, including the sum of flavonoids
of *Populus balsamifera* L. buds 5%, the sum of terpenoids of *Matricaria chamomilla* L. 1%, menthol 0.1 g, auxiliary ingredients of a mixture of polymers of polyethylene oxide-400 and polyethylene oxide-1500 in the ratio (7: 3). The technological scheme for the production of dental gel based on the substance of the sum of flavonoids of *Populus balsamifera* L. and the sum of terpenoids of *Matricaria chamomilla* L. was developed. The control and critical points of the production processes of the dental gel “Matripin-Dent” were determined.

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**References**

[1]. J.I. Pattanshetti, I. Tiwari, G. Singh, F. Tazyeen, A.S. Parihar, N. Khare, *Journal of International Oral Health* 8 (2016) 296–301.

[2]. N.R. Shagalieva, V.A. Kurkin, E.V. Avdeeva, I.M. Baikirov, A.E. Scherbovskikh, *Fundamental studies [Fundamental Research]* 10 (2013) 1490–1494 (in Russ.).

[3]. V.L. Bagirova, N.B. Demina, N.A. Kulichenko, Ointments. Modern view of the dosage form, *Popular science journal “Farmatsiya” [Pharmacy]* 2 (2002) 24–26 (in Russ.).

[4]. B. Rescala, W. Rosalem, R.P. Teles, R.G. Fischer, A.D. Haffajee, S.S. Socransky, A. Gustafsson, C.M. Figueredo, *J. Periodontol.* 81 (2010) 1308–1316. DOI: 10.1902/jop.2010.090643

[5]. K. Bansal, M.K. Rawat, A. Jain, A. Rajput, T.P. Chaturvedi, S. Singh, *AAPS PharmSciTech* 10 (2009) 716–723. DOI: 10.1208/s12249-009-9260-z

[6]. S.K. Yellangi, J. Singh, F. Manvi, *International Journal of Pharma and Bio Sciences* 1 (2010) 1–9.

[7]. R. Patel, H. Patel, A. Baria, *Int. J. Drug Deliv. Technol.* 4 (2009) 42–45. DOI: 10.25528/ijddt.v4i11.8834

[8]. N. Sapna, K.L. Vandana, *J. Investig. Clin. Dent.* 2 (2011) 162–170. DOI: 10.1111/j.2041-1626.2011.00064.x

[9]. V. Yakovenko, D. Orlenko, L. Vyshnevska, *ScienceRise: Pharmaceutical Science* 5 (2019) 35–41. DOI: 10.15587/2519-4852.2019.182398

[10]. M.N.A. Rahman, O.A.J.A. Qader, S. Sukmasari, A.F. Ismail, A.A. Doolaan, *Journal of Pharmaceutical Sciences and Research* 9 (2017) 2633–2640.

[11]. C.M. Ofner, C.M. Klech-Gelotte, J. Swanbrick, J.C. Boylan (Eds.) (2002). Gels and jellies. Vol. 2. Encyclopedia of Pharmaceutical Technology. New York; Basel: Marcel Dekker, 1327–1344.

[12]. S.M. Adekenov, A.N. Zhabayeva, Kh.I. Itzhanova, N.G. Titova, *Protivoparadontoznoe sredstvo [Anti-periodontal drug]. Patent RK, no. 32653, 2018 (In Russ).*

[13]. A.N. Zhabayeva, N.G. Titova, Kh.I. Itzhanova, S.M. Adekenov, K.D. Altynbekov, 12th International Symposium on the Chemistry of Natural Compounds, Tashkent, 2017, p. 304.

[14]. Z.D. Khadzhieva, Zilfikarov I.N., E.A. Teunova, *Nauchnye vedomosti Belgorodskogo gosudarstvennogo universiteta. Seriya: Meditsina. Farmatsiya [Scientific statements of Belgorod State University. Series: Medicine. Pharmacy]* 22 (2010) 58–65 (in Russ.).