

Methodological Aspects of Development of Gels for Treating Inflammatory Dental Diseases

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Abstract

Introduction: Inflammatory periodontal diseases take one of the first places among dental diseases; they are prevalent in various age groups and tend to grow steadily. The highest morbidity rate is found at the age from 15 to 44, that is 64-98% of the population. For the rational pathogenetic therapy, multiagent medications affecting different parts of the pathological process in a multiple way should be developed. **Materials and Methods:** In the work, marketing and economic research methods are used to ground social and medical practicability of developing new dental products for local treatment. **Results and Discussions:** With reference to the analysis of the Ukrainian market, it was found out that a dominant position in the range of dental gels, presented at the national pharmaceutical market is held by imported preparations. Methodological approaches to developing semisolid dosage form for treating inflammatory periodontal and oral mucosa diseases were summarized. **Conclusions:** Methodological approaches to developing medicine in gel dosage form for treating inflammatory periodontal and oral mucosa diseases were developed. With reference to the proposed methodology for developing gel for applying in dental practice, we theoretically and experimentally grounded the structure and rational technology of new combination preparations “Aloe-Dental” and “Dentatrin” in the form of gels.

Key words: Gel, inflammatory dental diseases, pharmaceutical development

INTRODUCTION

Inflammatory periodontal diseases take one of the first places among dental diseases; they are prevalent in various age groups and tend to grow steadily. The highest morbidity rate is found at the age from 15 to 44, that is 64-98% of the population.^[1-3]

The reasons for increasing morbidity of various types of inflammatory dental diseases are delayed diagnosis, refractory course of processes, and considerable difficulties of stable remission due to the close relation of the periodontal inflammatory diseases.^[3-6]

Inflammatory processes in the gums and periodontal tissues lead to teeth loss and pockets of chronic infection in the mouth, reduced reactivity of the host, microbial sensitization, and development of allergic disorders. It should be noted that this chronic inflammation processes do not cause only local inflammation but also affect the overall health. Significant changes in the dentition of patients

cause social, general medical, and economic aspects of the problem.^[7-11]

One of the directions to solve the problem is developing rational medications for complex therapy of gingivitis, periodontitis, and periodontosis. The medical treatment tactics for dental diseases should be based on the knowledge of anatomical and histological structure of periodontal complex of the tissues, structural and functional properties of the components of the parodont, and etiological factors causing various clinical forms of the disease. Furthermore, the manner of the disease course, its degree and severity of damage, and the pathological process extension must be considered.^[12-15]

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For the rational pathogenetic therapy, multiagent medications affecting different parts of the pathological process in a multiple way should be developed.^[14,15] Rational dosage forms for dental medications are films and gels that provide medication prolonged contact with mucous membranes, equable and protracted flow of medication to the periodontium.^[16,17] Over recent years, gels are gaining increasing popularity among soft dosage forms^[18-21] because they have a number of advantages as compared to other dosage forms. Gel form is safe for the skin and easy to use. Furthermore, gel bases evenly spread on the surface of the wound or the mucous membrane, forming a protective film, and do not prevent the release of medications. They have a cooling effect when applied to the skin due to the evaporation of water. In addition, some hydrophilic gels due to the high osmotic activity can absorb significant amounts of extracellular exudates in case of a purulent pathology without making a negative impact on the dehydration of the skin or mucosa cells on long-term contact. They are easily applied and absorbed into the skin without leaving oily sheen on it, more fully and evenly release medications, have cooling, moisturizing, and softening effects, are affordable, etc. Thus, the problem of treating periodontal disease is relevant and solved by applying combination therapy, which includes the use of long-acting medications with multifactor influence on the processes occurring in the periodontal complex of the tissues.

The objective of the work is to determine the main components of the process of developing semisolid dosage in gel form for applying in dental practice and to ground and develop methodical approaches to their development.

MATERIALS AND METHODS

In the work, marketing and economic research methods are used to ground social and medical practicability of developing new dental products for local treatment.

RESULTS AND DISCUSSIONS

Developing new medications is a consistent, thorough, quite long, and time-consuming process, which consists of two major stages:

Stage 1: Conducting marketing analysis of the current pharmaceutical market regarding medications used to treat the selected nosology. This stage consists of several components:

- Analysis of modern approaches and methods of the selected nosology treatment,
- Analysis of the existing arsenal of pharmaceuticals available at the market for the pharmacotherapy of a specific disease,
- Analysis of characteristics (average wholesale price of preparations, price index; liquidity ratio; and availability

indicator) of the medicines, used to treat the selected nosology.

The result of thoroughly conducted market analysis is the conclusion of the practicability and prospects of the development of new pharmaceutical products. Furthermore, at this stage, the future object of research (active substance or complex of substances with pharmacological activity/activities aimed directly or indirectly at the pathological lines of the selected disease) is experimentally selected. Based on physicochemical and pharmacotechnological properties of active substances and the selected nosology treatment effectiveness, the dosage form is selected.

We have conducted the market analysis of the assortment of gels applied in dental practice, according to the State Register of Pharmaceutical Products of Ukraine and the ATC classification system. The objects of the research were gels that demonstrate various pharmacological properties and are used for various diseases. For this purpose, the method of secondary marketing information has been applied. That is, the study used the trade name of medications, presented in the State Register of Pharmaceutical Products of Ukraine as of November 2016. According to the information of the State Expert Center of the Ministry of Health of Ukraine (11.01.2016), 10 trade names of pharmaceuticals which do not take into account all dosage forms and 11 trade names which provide such dosage forms applied in therapeutic dentistry are registered in Ukraine. An important characteristic of the market segment to be researched is the absolute dominance of imported medications. First of all, one pharmaceuticals' trade name of national production (without taking into account the dosage forms) accounts for 4 imported preparations. The ratio between imported pharmaceuticals and the ones of national production is 73%: 27% [Figure 1].

It was found out that all pharmaceuticals' trade names have the status of over-the-counter (OTC) medicine. It seems logical, considering the peculiarities of the pathological process in the mouth cavity, and the possibility of pharmacotherapy for patients on an outpatient basis.

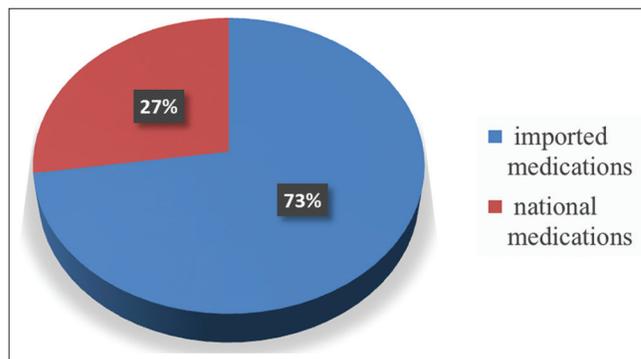


Figure 1: The ratio of national and imported medications represented at the pharmaceutical market of Ukraine and applied for treating inflammatory dental diseases

The dominance of preparations of Indian production in the range of OTC medications in Ukraine seems quite traditional for the segment. Thus, pharmaceutical products of Indian manufacturers make 50.0% of the range of pharmaceuticals being researched.

These are medications of such manufacturers as “Synmedic Laboratories” (4 preparations) and “Unique Pharmaceuticals Laboratories” (1 pharmaceutical product trade name). Pharmaceutical companies from the EU (“Legacy Pharmaceuticals Switzerland GmbH,” Switzerland and “Pharmaceutical Works Polfa,” Poland) represent only one pharmaceutical product trade name each. The national range of medications applied for treating gingivitis includes the products of such manufacturers as Pharmaceutical company “Health” and PJSC “Phytopharm.”

Next step of our research was analysis of the International Nonproprietary Names preparations composition. The results of the analysis show that 100% of medicine researched belongs to the group of combined preparations. Conventionally, all the preparations were divided into two groups. The first group is formed by preparations having in their composition two active pharmaceutical ingredients (APIs). The second group consists of combination medications that contain 3 or more APIs. It was found out that most of the preparations (9 trade names which do not take into account dosage forms) are represented in the first group (2 APIs). Thus, 55% of the preparations in this group are a combination of metronidazole and chlorhexidine bigluconate [Figure 2] which is recommended by clinical protocols for the treatment of inflammatory dental diseases.

Combination medications containing metronidazole + chlorhexidine bigluconate are represented by Indian manufacturers (5 trade names which do not take into account dosage forms, which is 54.0% of the whole range of preparations being researched) and by National Pharmaceutical Company PJSC “Phytopharm.”

The rest of the preparations of the first group contain lidocaine hydrochloride monohydrate with blue chamomile

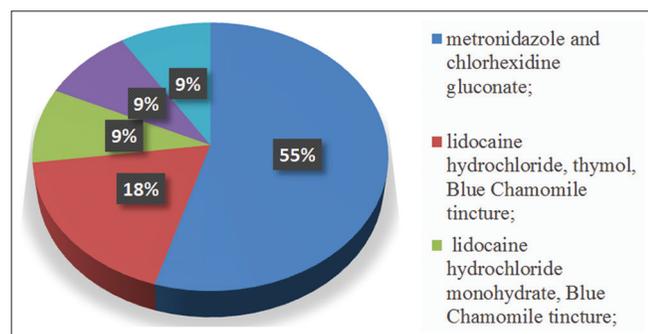


Figure 2: Analysis of the structure of pharmaceutical products available at the national pharmaceutical market applied for treating inflammatory dental diseases

tincture, choline salicylate with cetalkonium chloride, and deproteinized calf blood extract with polidocaine.

The preparations of the second group [Figure 2] include only two pharmaceuticals’ trade name. The composition of these preparations includes lidocaine hydrochloride monohydrate, blue chamomile tincture, and thymol.

That is, we have established that in the structure of the pharmaceuticals registered in Ukraine and recommended for the therapy for inflammatory dental diseases, there are no combination medications which include hemocorrectors, especially anticoagulants (aminocaproic acid).

Gels, which include active ingredients of strictly natural origin, are generally absent at the pharmaceutical market of Ukraine. Hence, necessity of expanding the range of gels’ domestic production from raw materials of natural origin was proved.

Stage 2: Pharmaceutical development of medicine: Nowadays, general methodical approach to pharmaceutical development is standardized by the ICH Guideline Q8 (R2: Pharmaceutical Development).^[22] The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.

The information and knowledge gained during pharmaceutical development are the basis for establishing of design properties space, specifications and production control, as well as risk management for quality.^[22,23]

While developing modern pharmaceutical products of different forms, including gels, there should be considered the main requirements applied to technical processes:

- Reproduction and reliability of technologies, excluding factors that can have a negative effect on the manufacturing process;
- Medicine producing process should be as less energy intensive as possible;
- The number of stages of production should be minimal, typical equipment should be used.

This systematic approach to the development of modern medicine means simultaneous keeping up with demands mentioned above that affect the quality of the end product.

The choice of the active substance

The active substance determines the pharmacological properties of pharmaceutical products, so the choice of the active substance and its quantitative content have to correspond the presumed aim, that is the instruction of usage. According to the guidance,^[22] the choice of the active substance and its concentration should be grounded experimentally or by reference to relevant scientific literature

sources. In particular, the concentration of substances with antimicrobial action should be experimentally defined. The compatibility of the active substance (active ingredients) with additives should be studied; in case of combination dosage form, the compatibility of active ingredients should be studied. The results of previous stability research are to be provided as supporting data.

Medications for the treatment of inflammatory periodontal diseases should meet a number of requirements such as antimicrobial activity, anti-inflammatory effect, ability to improve blood circulation and normalize metabolism, enhance tissue regeneration, prolonged effect, and comfortable applying for patients for a long time.^[24-26]

The choice of excipients

Medical pharmaceutical products consist not only of biologically active substances, which are the main carrier of therapeutic effect but also of a combination of excipients both organic and inorganic (preservatives, stabilizers, fillers, emulsifiers, etc.) as well. This combination should ensure not only the stability of the physicochemical properties of the medication during the course of its manufacture and storage but also the necessary conditions for releasing and absorbing the active substance which allows to develop effective and safe medicines. The composition of medical pharmaceutical products including the concentration of active substances should be justified not only theoretically but also experimentally, and the role of each additive should be explained.

Such key excipients in semisolid dosage forms (SDF) are: (a) antimicrobial preservatives; (b) antioxidants; (c) other substances including surfactants, solvents, complexing agents, substances that increase permeability, release modifiers, and sweeteners.^[23]

In a quite wide range of additives required for dental gels, the most important group of gel-forming bases should be pointed out.

According to a number of authors, hydrophilic gelling substances are most rational for making dental gels. These bases have high mucoadhesiveness that is the ability to cling to mucosa, providing the localization of the active preparation components effect on the one hand, and the extension of their pharmacological effect on the other. Hydrophilic gelling substances incorporate many medicinal agents quite easily and provide their desirable release. In addition, the use of hydrophilic bases within the required range allows regulating the biopharmaceutical and structural and mechanical properties of dental gels.^[27-32]

Cellulose derivatives are widely used as hydrophilic bases for dental products: Methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose,

and others. Gels formed by these compounding are compatible with many medicinal substances, do not cause irritation, can form homogeneous mixtures with the secrets of the mucous membranes, have adsorption properties absorbing exudates.

Besides, cellulose derivatives and polyethylene oxide (PEO) are popular hydrophilic gelling substances.^[33,34] A variety of polymers of this group, which differ by their molecular mass and, consequently, their consistence that changes from liquid to waxy, allows developing various combinations of PEO to obtain bases with desired structural and mechanical properties. We know that PEO can interact with some medicinal substances to form various products interaction, followed by changes in physical and chemical properties, including increased solubility, and allows pharmaceuticals' biopharmaceutical characteristics modification.

It has been found out that high osmotic activity of PEO leads to a significant decrease in microbial cells activity due to their dehydration, which increases the antimicrobial effect of antiseptic and antibacterial medicines. In addition, PEO possess strong absorptivity for various products formed during inflammation, thus stopping its development and enhancing the pharmacotherapeutic effect of pharmaceuticals.

Nowadays, acrylic acid derivatives are quite popular - lightly cross-linked acrylic Carbopol copolymers that differ by a number of cross-links, and changing this number allows modifying specific properties of the formed gels without changing their molecular structure. Among the advantages of gels based on carbopol, there is thermal, chemical, and microbiological stability, high viscosity even at low concentrations of polymer, significant emulsifying and suspensive properties, compatibility with most medicines, a significant bioadhesion, providing high bioavailability and prolongation of pharmaceutical effects, etc.^[35-40] When planning the design of pharmaceutical preparations in the form of gels based on carbomers must be considered the different factors such as the type of carbomer, nature of the alkaline agent, and the ratio between the alkaline agent and carbomer, which influence on the pH and the rheological parameters of gels. The rheological parameters of gels based on carbomers little dependent on temperature; drugs remain gel-like consistency at high temperatures.

The properties of hydrophilic gelling substances described above allow developing dental gels of different pharmacotherapeutic effect.

Technological process

Using medical substances and additives with different physicochemical properties as part of pharmaceutical products require different processing methods (dissolution, dispersion, homogenization, etc.), which should be considered while organizing their producing to obtain a quality product.

The way of preparation – order of mixing ingredients, way of adding medical substances and additives to the base, – influences the effectiveness of SDF.^[41]

By applying appropriate technological methods (dissolving, suspending, and emulsifying), the medical substance can be reduced to a certain degree of dispersion: From coarse particles to ions and molecules, which in its turn affects its release from the dosage form and homogeneity of ointment.

Homogeneity is particularly important for SDF which have the form of a heterogeneous dispersed system. In the process of pharmaceutical development of SDF, it should be demonstrated that the composition of a medicinal product and the technology proposed provide homogeneity of active substances and (if necessary) additives distribution. Maintaining the homogeneity of SDF should be considered when reckoning storage conditions. Homogeneity, achieved by a process of homogenization, should be studied at the stage of development and confirmed with the results of the validation provided by the corresponding part of the registration dossier. Studies, conducted at the stage of development, can be used for preconditioning validation

protocols which are used for the full-scale processes of SDF homogenization while producing them.

Besides, the planned profile of the preparation which is being developed, it is necessary to specify medical and biological requirements, that is the requirements necessary for efficiency and safety.

Thus, basing on general approaches to pharmaceutical medications development, we have formulated development methodology for SDF in the form of gels for the treatment of inflammatory diseases of the oral cavity, selected as research objects based on pursuing the complex of marketing, physical, chemical, technological, biopharmaceutical, and economic researches, which ensure that the developed preparations meet modern requirements [Figure 3].

The developed approach we have used in the development of gels for treating inflammatory periodontal, oral mucosa, and gums disease.

When developing “Aloe-Dental” gel plant extracts were used as APIs: Dense oak bark extract which has antimicrobial,

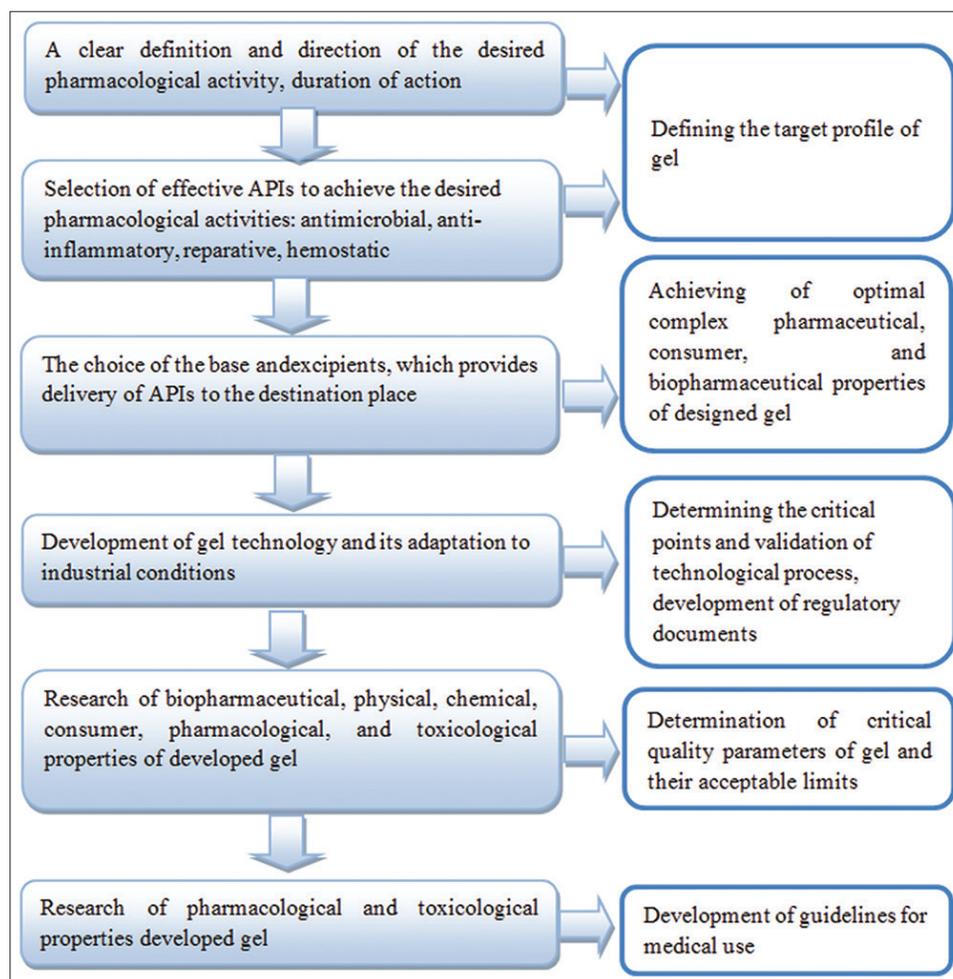


Figure 3: Methodological approaches of development of gels for treating inflammatory dental diseases

membrane stabilizing, anti-inflammatory properties,^[42,43] and dry aloe extract, which has strong antimicrobial properties and accelerates regeneration.^[44,45] The research of specific activity demonstrated that gel has strong periodontium protecting antimicrobial, anti-inflammatory, and reparative properties.

We have developed a co-formulated pharmaceutical product “Dentatryhin” of local action in the form of gel, which in a single dosage form contains both active ingredients of synthetic origin (triclosan and aminocaproic acid) and of natural origin (lavender oil), which can elicit the multifaceted range of these substances and influence progress of gingivitis of different types. By means of pharmaceutical and microbiological researches, its strong antimicrobial, anti-inflammatory, vessel-strengthening, and hemostatic effect was proved.^[46,47]

CONCLUSIONS

1. With reference to the analysis of the Ukrainian market, it was found out that a dominant position in the range of dental gels, presented at the national pharmaceutical market is held by imported preparations (73.0% of the total range being researched), mostly of Indian (50.0%) production. Given the unpredictable situation at the financial market and significant weakening of the state regulation mechanisms for the system of providing pharmaceutical supplies for the population, the mentioned characteristics of the market segment which has been researched has very negative social and economic consequences.
2. The main components of the SDF development process (choosing active ingredients, carrier-bases, technology, etc.) were summarized.
3. Methodological approaches to developing SDF in gel form for treating inflammatory periodontal and oral mucosa diseases were developed.
4. With reference to the proposed methodology for developing gentle medications for applying in dental practice, we theoretically and experimentally grounded the structure and rational technology of new combination preparations in the form of “Aloe-Dental” and “Dentatryhin” gels.

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