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DEVELOPMENT OF COMPOSITE GEL "DENTATRYHIN"

The choice of gelling agent has been proved by means of structural and mechanical, physical and chemical studies. For this it was selected a range of modern gelling agents most commonly used in the development of dental gel (the carbomer of the mark "934", sodium alginate and hydroxyethylcellulose), and the experimental models with and selected active compounds (triclosan, aminocaproic acid, lavender oil) were studied. It is established that the sample of gel with the the carbomer of the mark "934" at a concentration of 0,8 % had the best structural and mechanical, physical and chemical properties and consumer characteristics. On the background of thermographic studies the absence of chemical interaction between the components of a new combined dental gel for the treatment of gingivitis was proved.

Key words: dentistry, gel, triclosan, aminocaproic acid, lavender oil, physico-chemical properties, structural and mechanical properties.

STATEMENT OF THE PROBLEM

In today's pharmaceutical and dental practice pressing an actual issue is the creation of new effective drugs for treatment acute and chronic mouth inflammation. One of such kind of diseases is gingivitis. Gingivitis is the inflammation of the gums' mucous membrane. According to the statistics, gingivitis is the most common disease of the mouth, and mainly children, adolescents and those aged older than 30 years suffer from it compared to other periodontal diseases [2, 14, 23].

The main method of treatment and prevention of gingivitis is the meticulous oral hygiene with ordinary toothbrushes and toothpastes, but there are special gels and ointments that reduce inflammation of the gums. Regarding local treatment, it is to reduce edema, anesthesia of the gums' mucous membrane, prevention secondary infection [2, 14].

Local treatment of various forms of gingivitis is aimed to eliminate the causes that give rise to the symptoms of the disease, to eliminate secondary effects and complications (the elimination of inflammation, the stable circulation's renew, occlusion, enhancing local immunity, etc.).

To develop a new combined dental tool for gingivitis pharmacotherapy was selected such kind of dosage form as gel [3, 7, 9, 12, 13]. The main advantages of gels are the prolonged action of active substances, simple technology, the convenience and comfort of the use, the water structures inside the gel allowing you to input chemically incompatible substances into its composition; namely gels have the ability to stay on treated parts of the body that are treated (as solid) and they are effective in applications.

Gels also distribute well and are absorbed in the mucosa, what causes the high bioavailability of active substances and the prolonged effect [4].

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

The primary challenge in developing a new drug is effective and correct selection of non-hazardous active substances and adjutants, and creation of high-quality technology for getting pharmaceutical drugs (PD).

As an active ingredient for the developing dental gel, we have chosen triclosan - a well-known antibacterial agent of broad spectrum, which has anti-inflammatory properties, effects gram-positive and gram-negative flora as well as fungal microorganisms [16, 20, 22]. The optimal concentration of triclosan 0,5 % was chosen by us on the background of microbiological studies at the Department of Biotechnology under the pharmacy supervisor Doctor of Pharmacy Strylets O. P. [10]. Effective concentrations of other active gel ingredients such as aminocaproic acid – 5,0 % and lavender oil – 0,5 % were chosen by the conducted biological research at the laboratory of the problem morphological studies at Ukrainian National

Academy of Pharmacy under the supervision of the prof. Maloshtan L. M. [11].

TAGGING THE PARTS OF GENERAL PROBLEM NOT RESOLVED IN THE PAST

To create a new PD it is necessary to apply the general rules and methods of pharmaceutical development taking into account the individual physical, chemical and technological properties of active substances and adjuvants. Also, when developing LP, great attention should be paid to pharmaceutical manufacturing processibility which includes: the least number of stages of the technological process, using a small amount of process equipment, identifying critical factors and their parameters as well as the cooking process should be energy efficient [8].

It is known that the technology of the gel consists of several processes: manufacturing the base, getting solutions of drugs and putting them into the base and so on. The primary objective in the development of the gel is the selection and justification the concentration of gelling agent to create the stable gel base with satisfactory consumer, technology, etc. properties [8].

FORMATION ARTICLE`S PURPOSES

The aim of our work is to study the composition of the original drug "Dentaryhin" in the form of gel with a set of active substances - triclosan, aminocaproic acid, lavender oil.

THE MAIN MATERIAL OF THE RESEARCH

As-prepared gel samples, in which the active substances were put in selected concentrations, were selected as the objects of study [16, 20, 22]. A number of adjuvants (gelling agents of different origin nature, hydrophilic non-aqueous solvents, etc.) were also used during this experiment.

The mechanical stirrer MM-1000 of the company BioSan (Latvia) was used while getting bases. Structural and mechanical tests were performed at 20 rev / min on the viscometer Brookfield DV-II + PRO with rotary spindle SC 4-21 (the USA). Experiments were carried out at the temperature of 15-25 ° C (according to the SPU). The rheological parameter such as the mechanical stability (MS) was determined as the ratio of the tensile strength to the destruction of (τ1) to the value of the tensile strength after the destruction (τ2) [16]. pH level of the researching samples was determined potentiometrically (SPU 1.2 and 2.2.3) with "pH Meter Metrohm 744" (Germany).

Derivatographic analysis of substances was performed by the SPU method, appendix 1, paragraph 2.2.34 on the derivatograph Q-1500D with platinum-rhodium thermocouple by heating the samples in the ceramic crucibles from 15 to 5000 °C in air. The device simultaneously recorded curves T – the temperature change, TG – the mass change, DTG – the differential curve of the mass change, DTA – the differential heating curve. Such following conditions as average weight of the sample specimens ranged from 0,2 to 0,5 g, temperature range - 20 to 500 °C, heating rate - 5 °C/min, sensitivity shooting TG curve was - 2 mg/mm, DTG – 200 mV, DTA – 200 mV, paper speed – 5 m/min were chosen for getting derivatograms [5, 15].

RESULTS AND DISCUSSION

It is known that structural and mechanical studies are mandatory in the development of any drugs or pharmaceutical product in a soft form (ointment, cream, gel) [1, 6, 18, 19, 21].

Choosing the main adjuvant component of the gelling agent was on the first phase of this experiment. To select the gelling agent we conducted a number of structural and mechanical studies of experimental models with the base of gelling agent that are often used in the development of dental local action drugs, such as the carbomer of the mark "934", sodium alginate and hydroxyethylcellulose (HETS). These gelling agents meet the requirements for local action drugs; they have moderate osmotic activity, good adhesive properties, and other properties. Gel bases were prepared according to generally accepted techniques [1, 6, 18, 19, 21]. Triclosan and lavender oil are alcohol-soluble substances, so they are first dissolved in ethanol and then are added to the same gel bases while stirring. There were added aqueous acid solution and sorbitol of aminokapronoic acid (10,0 %) as a substance with moderate osmotic effect [7, 6] into the gel bases.

The results of physicochemical and structural-mechanical studies are presented in the Table 1.

Table 1

COMPARATIVE CHARACTERISTICS OF PHYSICOCHEMICAL SAMPLES PROPERTIES WITH DIFFERENT GELLING AGENTS

Sample №, gelling agent's name and its concentration	Structural viscosity, η, mPa · sec at 20 rev/min	MS	pH
№ 1(with HETS – 2,0 %)	13000	1,94	7,60 ± 0,11
№ 2 (with the carbomer of the mark «934» – 0,5 %)	3,500	1,00	6,55 ± 0,10
№ 3(with sodium alginate – 2,0 %)	600	1,15	8,10 ± 0,08

According to the experimental data from further studies samples № 1 and № 2 were removed

from the samples. Sample number 1 (based on HETS), despite the high structural viscosity values in the future can stratify because the calculated value of MC is almost two times higher than normal [1]. Sample number 2 (based on sodium alginate) had a very liquid consistency and respectively poor consumer properties (increasing the concentration of gelling agent is not rational).

The samples with a base of the the carbomer are noted to have satisfactory consumer, physicochemical, structural-mechanical properties. In addition, it is known from literature that the the carbomer of the mark "934" has different stability properties, high purity, ability to form transparent gels, which makes it a promising ingredient in the composition of dental gels for local application [3, 4, 7, 9, 13,]. In the next step we have produced samples with different concentration of chosen gelling agent – the carbomer of the mark "934", the data are presented in Table 2.

Table 2

COMPARATIVE CHARACTERISTICS OF PHYSICOCHEMICAL SAMPLES PROPERTIES OF SAMPLES CARBOMER OF THE MARK "934"

Sample №, gelling agent's name and its concentration	Structural viscosity, η, mPa · sec at 20 rev / min	MS	pH
№ 2,1 (with concentration – 0,4 %)	700	1,06	6,75 ± 0,06
№ 2,2 (with concentration – 0,5 %)	3,500	1,00	6,55 ± 0,10
№ 2,3 (with concentration – 0,6 %)	5,500	1,01	6,75 ± 0,12
№ 2,4 (with concentration – 0,7 %)	7,000	1,05	6,70 ± 0,09
№ 2,5 (with concentration – 0,8 %)	10300	1,02	6,76 ± 0,11
№ 2,6 (with concentration – 0,9 %)	14900	1,18	6,69 ± 0,10

As seen from the obtained results, for further research (choosing technology, stability study) the best example is a sample with a concentration of the carbomer of the mark "934" – 0,8 %. This sample had a satisfactory structural-mechanical, physicochemical and consumer properties (half-transparent, homogeneous gel mass without additives and with a specific smell and taste).

As you know, the important biopharmaceutical parameter that significantly affects the gel pharmacokinetics is the nature of gelling agent. The main requirements for gel bases include compatibility with active ingredients, chemical and pharmacological indifference, necessary structural-mechanical properties that allow raising the therapeutic effect of active substances and maximizing their release [3, 4]. Based on the chemical structure each substance has a typical thermal index. Thus, we can investigate the properties of individual substances and combinations with thermograms.

To study the temperature properties of the gel "Dentatryhin", structural properties and the compatibility of active substances and adjuvant in the developing gel we conducted derivatograpfic analysis.

Thermographic studies were conducted at the Department of Physics, Pharmacy, under the supervisor Prof. Timanyuka V. A.

There are derivatograms of triclosan, aminocaproic acid and gel developed "Dentatryhin" on fig. 1, 2, 3 and 4.

As shown in Fig.1 triclosan substance begins to decompose at 40 °C. The decay takes place in two stages: at 100 ° C with a mass loss of 4,5 % and at a temperature of 250–335 °C with the loss of 34 % by weight. Full triclosan decay was observed at 340 °C.

Fig. 2 shows derivatogram of a sample aminocaproic acid substance. From the above thermogram, we can see that the substance is stable at the temperature of 190 ° C and thermal reaction is not observed. In the temperature range from 190 to 250 °C, the mass loss is 24 %.

The maximum speed of the decay occurs at the temperature of 210 °C and it is accompanied by endothermic reaction. At the temperatures above 250 °C DTG is unstable due to the investigated sample evaporation with foam.

Lavender oil thermogram shows that disintegration begins at 40 °C (Fig. 2). The top speed of disintegration is observed when heated to 120 °C, weight loss of the sample mass is 74 %.

The mass exuding in the gel sample begins with a temperature of 30 °C (Fig. 4). Maximum speed of the developed gel decay that is accompanied by endothermic reaction is observed at the temperature of 124 °C (Fig. 4). The mass loss at the temperature of 134 °C is 82 % of the sample mass.

Thus, in the result of the thermo gravimetric analysis of active substances and the gel it was found out that thermal sample` effects are of similar nature, which may indicate a lack of chemical interaction.

It is also proved that the development of technology dental gel phase – "gel preparing" - should be carried out at the temperature below 30 °C.

So, as a result of the conducted studies, the gel rational basis was selected, the temperature

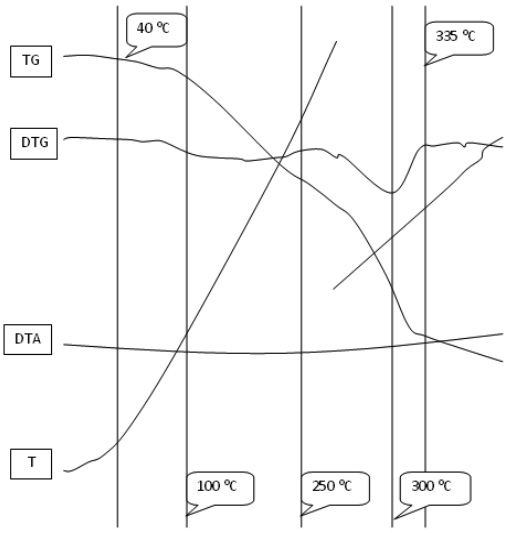

Fig. 1. *Triclosan derivatogram*

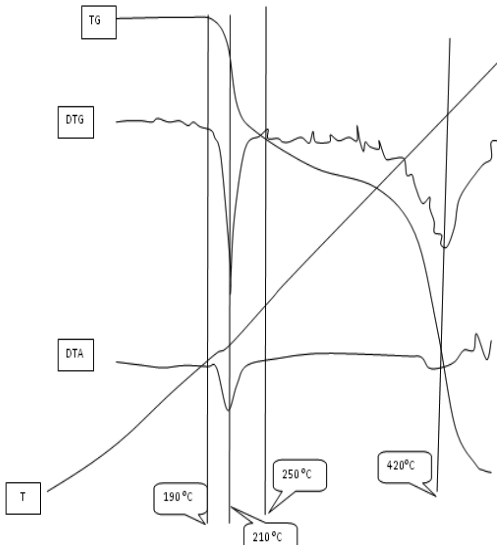

Fig. 2. *Aminocaproic acid derivatogram*

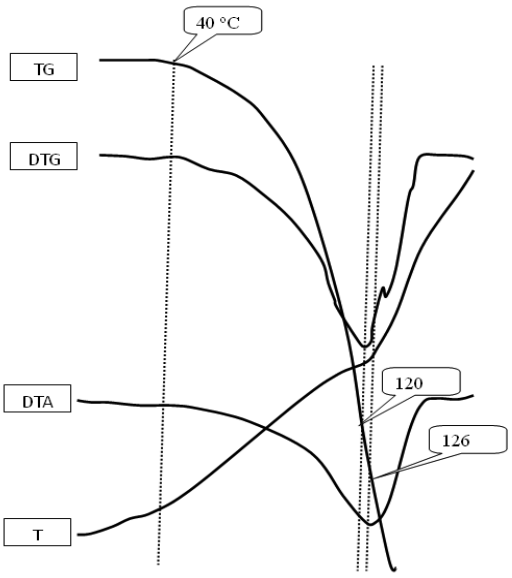

Fig. 3. *Lavender oil derivatogram*

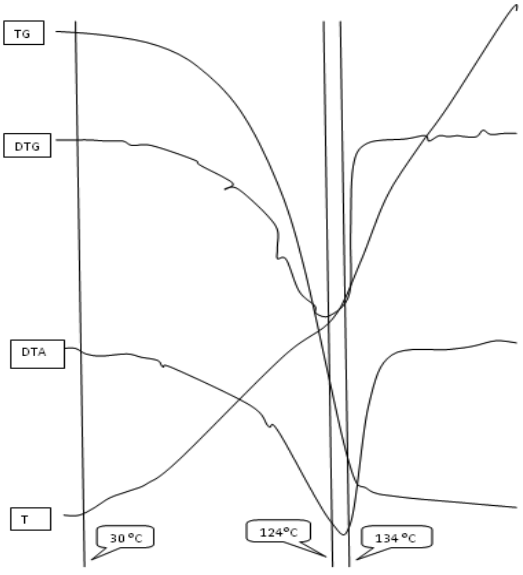

Fig. 4. *The sample developed gel "Dentatryhin" derivatogram*

mode of introducing active substances was proved, and the absence of chemical interaction between the adjutants and active substances was confirmed.

CONCLUSIONS AND PROSPECTS FOR FURTER RESEARCH

1. Using conducted structural-mechanical and physicochemical studies the properties of gels samples with complex active compounds (triclosan, aminocaproic acid and lavender oil) with different gelling agents (HETS, sodium alginate, the carbomer of the mark "934") in the composition study of the combined dental gel were investigated.

2. It is established that it is rational to use the the carbomer of the mark "934" at a concentration of 0,8 % as a gelling agent. This gel sample has satisfactory consumption, technological, structural–mechanical properties.

3. The lack of interaction between the components of a new combined gel with triclosan, aminocaproic acid and lavender oil to treat gingivitis (derivatographic method) is confirmed. The obtained data will be used to establish the tempera-

ture modes of the gel "Dentatryhin" manufacturing technological process.

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РОЗРОБКА СКЛАДУ КОМБІНОВАНОГО ГЕЛЮ «ДЕНТАТРИГІН»

Обґрунтовано за допомогою структурно-механічних та фізико-хімічних досліджень вибір гелеутворювача. Для цього обрано низку сучасних гелеутворювачів, які найчастіше використовуються при розробці стоматологічних гелів (карбомер марки «934 Р», натрію альгінат та гідроксіетилцеллюлоза), та досліджено експериментальні зразки з ними і обраними активними речовинами (триклозан, амінокапронова кислота та лавандова олія). Встановлено, що зразок гелю з карбомером марки «934 Р» в концентрації 0,8 % мав найкращі структурно-механічні, фізико-хімічні властивості та споживчі характеристики. На підставі проведених термографічних досліджень доведено відсутність хімічної взаємодії між компонентами нового комбінованого стоматологічного гелю для лікування гінгівітів.

Ключові слова: стоматологія, гель, триклозан, амінокапронова кислота, лавандова олія, фізико-хімічні властивості, структурно-механічні властивості.

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РАЗРАБОТКА СОСТАВА КОМБИНИРОВАННОГО ГЕЛЯ «ДЕНТАТРИГИН»

Обоснован, с помощью структурно механических и физико-химических исследований, выбор гелеобразователя. Для этого выбран ряд современных гелеобразователей, которые чаще всего используются при разработке стоматологических гелей (карбомер марки «934 Р», натрия альгинат и гидроксиэтилцеллюлоза), и исследованы экспериментальные образцы с ними и выбранными активными веществами (триклозан, аминокапроновая кислота и лавандовое масло). Установлено, что образец геля с карбомером марки «934 Р» в концентрации 0,8 % имел лучшие структурно-механические, физико-химические свойства и потребительские характеристики. На основании проведенных термографических исследований доказано отсутствие химического взаимодействия между компонентами нового комбинированного стоматологического геля для лечения гингивитов.

Ключевые слова: стоматология, гель, триклозан, аминокапроновая кислота, лавандовое масло, физико-химические свойства, структурно-механические свойства

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