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DEVELOPMENT OF THE COMPOSITION OF THE GEL BASE FOR TREATING TELOGEN EFFLUVIUM

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Key words: telogen effluvium; nettle juice; gels; bases; preservatives; hydrophilic non-aqueous solvents

The article presents the study results of developing the optimal composition for the base of the mask-gel for treating telogen effluvium. The effect of the preservative potassium sorbate in different concentrations (from 0.1% to 0.3%) on the pH and structural-mechanical properties of gels has shown that its 0.2% content provides pH 5 to the base, and it corresponds to the skin surface acid-alkaline physiological range; the structural viscosity and thixotropy, the mechanical stability (MS) value (1.04) and the high K_d rate (63.48) corresponding to the optimal technological and consumer properties of the gel base have been determined. The results of the biopharmaceutical and rheological studies have confirmed that the base with 5% glycerin has the best ability to retain moisture in the composition, possesses the insignificant osmotic effect, and is characterized with proper viscosity compared to other hydrophilic non-aqueous solvents (HNS) such as propylene glycol, the HNS mixture in the ratio of 1:1. Therefore, the gel base of the following composition: sodium alginate – 1.0 g; carbopol (Ultrez 10) – 1.0 g; glycerin – 5.0; potassium sorbate – 0.2; purified water – up to 100.0 g has the optimal properties.

Telogen effluvium (TE) – excessive hair loss in the telogen phase – occupies up to 8% of cases among dermatological diseases and is the most common form of diffuse alopecia in women of the reproductive age [3, 4]. Induced factors of TE development are insufficient dietary intake of nutrients, pathology of the digestive and the endocrine systems, acute and chronic infectious diseases, stress, toxic effects of drugs, postpartum period, etc. Despite the wide range of health and beauty products intended to stimulate hair growth the amount of drugs indicated for TE treatment is limited at the pharmaceutical market [8]. Therefore, development of new effective medicines for TE therapy is a topical problem of the pharmaceutical science.

In order to create new medicines the method of obtaining the nettle juice from its fresh aerial parts was tested previously under laboratory conditions [7]. Biologically active substances (BAS) of the nettle juice (organic and phenolcarboxylic acids, carotenoids, chlorophylls, flavonoids, organically bound silicon, etc.) improve the blood circulation in the skin capillary system, stimulate metabolism and trophic processes, reveal regenerating and growth-stimulating properties of the hair follicle cells [11].

To provide the proper BAS penetration and the ease of the nettle juice application the rational dosage form is the mask-gel. This is due to several advantages of gels compared to fatty or emulsion bases, namely gels provide deep BAS penetration through the skin structure, easily applied and distributed on its surface, do not smear and do not leave oily sheen on the hair, simple to prepare [1, 5].

The previous studies of the rheological properties of combined bases with carbopol and sodium alginate in different ratios allowed us to propose the gel base containing carbopol (Ultrez 10) – 1.0 g, sodium alginate – 1.0 g, potassium sorbate – 0.2 g, purified water – up to 100.0 g. Potassium sorbate has functions of a preservative and a thickener (carbopol neutralizer) [6]. The studies conducted at the Microbiology, Virology and Immunology Department of the Ivano-Frankivsk National Medical University confirmed the efficacy of potassium sorbate as an antimicrobial preservative in the concentrations of 0.1%, 0.2% and 0.3% in the composition of the base selected. The next important task in substantiation of the optimal composition of the gel base was to study the effect of potassium sorbate at various concentrations on the pH and the rheological properties of the experimental samples.

Hydrophilic non-aqueous solvents (HNS) – glycerin, propylene glycol, sorbitol, polyethylene glycol 400, etc., are the necessary excipients of gel bases. HNS solubilize natural high molecular substances (sodium alginate, gums, etc.) and significantly accelerate their swelling, promote solubility of hydrophobic BAS (chlorophyll, carotenoids), prevent evaporation of water during the technological process and the drug application, provide the BAS even release and their deeper penetration through the skin structures. However, the HNS concentration in the gel formulations should not exceed 10% since these substances in higher amount cause formation of the unpleasant sticky film on the skin surface, osmotic processes and skin dehydration [1, 5].

Considering the above mentioned it is essential to study the effect of potassium sorbate in different concentrations and HNS on the physical and chemical, rheological and biopharmaceutical properties of the mask-gel base to develop its optimal composition.

Materials and Methods

The first stage of the experiment was preparation of 5 bases with the different concentrations of potassium sorbate – 0.10%, 0.15%, 0.20%, 0.25%, and 0.30%. The rheological studies of the experimental samples (structural viscosity, degree of thixotropy, mechanical stability, the coefficient of dynamic liquefaction) were carried out at the temperature of 20°C on a Brookfield viscometer, type HB DV-II PRO, SC4-21 spindle with the chamber volume of 8.3 ml. The value of the mechanical stability (MS) of the experimental bases was determined as the ratio of the structure strength border value before destruction (τ_1) to the structure strength border value after destruction (τ_2) [1, 9]:

$$MS = \tau_1 / \tau_2 \quad (1)$$

To study the extrusive properties of the bases the coefficient of dynamic liquefaction was calculated by the formula:

$$K_d = \frac{(\eta_{18.6} - \eta_{93.0}) \cdot 100\%}{\eta_{18.6}}, \quad (2)$$

where: $\eta_{18.6}$ – is the base viscosity at the shear rate 18.6 s^{-1}; $\eta_{93.0}$ – is the base viscosity at the shear rate 93.0 s^{-1} [9].

The pH measuring was performed potentiometrically in 10% aqueous solution of gels using the universal pH-meter EB-74 at 20ºC (SPhU, II-nd ed., art.2.2.3) [2].

After selecting the potassium sorbate optimal concentration 4 batches of bases were prepared: base 1 – without HNS; base 2 – with 5% glycerin; base 3 – with 5% propylene glycol; base 4 – with 5% the HNS mixture (1:1). For these samples the pH value, the water-retention capacity, the rheological properties, the osmotic activity were studied.

The water-retention capacity of the gels was studied using the weight express method by infrared rays drying on the hygrometer of BT-500 torsion scales [1, 2]. For this purpose 0.2 g of the sample base was weighed, and the electric lamp below the balance was turned on. In the process of drying due to the moisture evaporation the balancer deviated from zero, so it was regularly adjusted to the zero level again. The end of drying was considered to be the balancer position when it remained at the zero point regardless of the subsequent drying. The study was conducted for 25 min. The water-retention capacity was determined by the formula:

$$u = (G_{moist} - G_{dry})/G_{moist} \cdot 100\%, \quad (3)$$

where: G_{moist} – is the base weight before drying, g; G_{dry} – is the dried base weight, g.

The osmotic activity of the samples was studied by the method of dialysis through the semipermeable cellophane membrane. The mass of the dialyzer inner cylinder with the weighed quantity of the base of 10.0 g was measured every hour. The amount of liquid absorbed by the sample was expressed as a percentage of the weight of the test sample [1, 5].

Results and Discussion

The results of measurement of the structural viscosity for the bases with the different potassium sorbate content, their MS, the coefficient of dynamic liquefaction and pH are presented in Table.

As can be seen from Tab., there is a direct correlation between the increase of the structural viscosity of the bases and the increase of potassium sorbate concentration. The preservative content of 0.3% thickened base 5 to the value of 10250 mPa·s, which exceeded the optimum parameters for the gel viscosity – 2000-10000 mPa·s at 20 rpm [5].

All samples had MS values from 1.051 to 1.081, i.e. they were close to optimum (1.0); for base 3 (0.20% potassium sorbate) MS was characterized by the best indicator – 1.04. The appropriate MS values indicate the gel ability to withstand the mechanical stress during preparation and storage. The coefficient of dynamic liquefaction was characterized by high values for bases 3-5 and was 63.48; 63.53; 63.90, respectively. The high values of K_d indicate the convenience of applying the gels, better dilution and distribution of active ingredients in the base while stirring.

The important drug quality parameter is pH. The human skin surface is slightly acidic with pH in the range of 4.5-5.5. Such physiological parameters prevent the growth of pathogenic microorganisms and maintain the viability of the beneficial microflora on the skin surface [5]. Thus, medicines should be characterized by pH values within the physiological range. As can be seen from Table, base 3 had the optimal pH value (5.0±0.04), while bases 2 and 4 were close to optimum (4.5±0.05 and 5.6±0.06).

The results of measuring the rheological properties of the bases with the different potassium sorbate content are presented in Fig. 1 and 2. When studying the dependence of the structural viscosity of gels on the shear rate gradient it was determined that the structural viscosity of the experimental samples decreased with the shear rate increase (Fig. 1). However, for the sample with the preservative lowest concentration (0.10%) this dependence was less clearly observed. Such correlation is typical for systems with a plastic flow and characterizes gels as the structured dispersed systems, in which

Table

The study results of pH and rheological properties of the bases with the different potassium sorbate content

Indicator	Base 1 (0.10% conc.)	Base 2 (0.15% conc.)	Base 3 (0.20% conc.)	Base 4 (0.25% conc.)	Base 5 (0.30% conc.)
η, mPa·s (20 rpm, 20°C)	4750±40	6298±60	6907±55	8502±70	10250±50
MS	1.051	1.074	1.040	1.081	1.053
K_d	58.95	62.22	63.48	63.53	63.90
pH	4.2±0.06	4.5±0.05	5.0±0.04	5.6±0.06	6.2±0.04

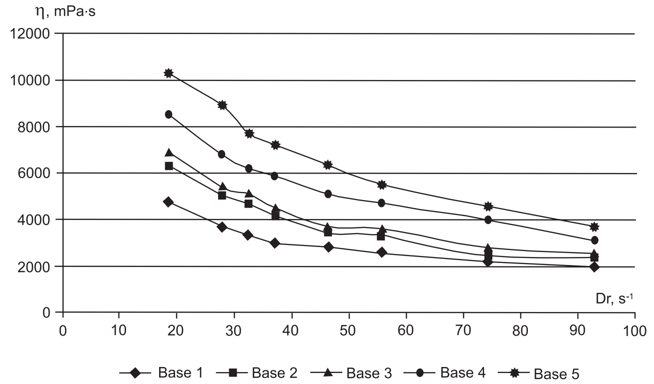

Fig. 1. The dependence of the structural viscosity of the bases with the different potassium sorbate concentration on the shear rate.

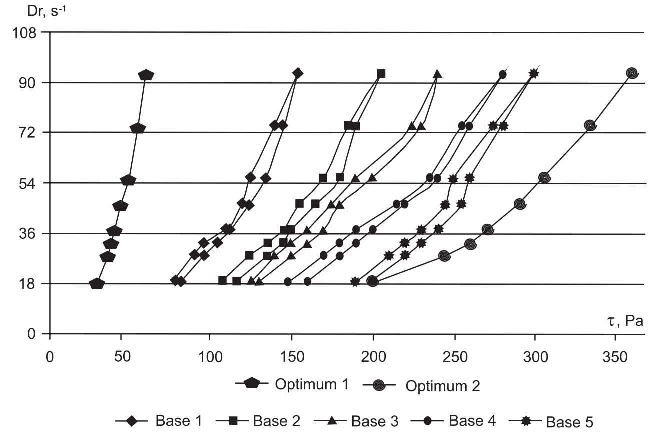

Fig. 2. Rheograms of the gel bases containing different concentrations of potassium sorbate.

rheological properties will be strongly retained while adding BAS.

The study of the "shear rate – shear stress" dependence (Fig. 2) showed that all samples were characterized by the plastic flow type with a certain thixotropy since there were the slight hysteresis loops of the ascending and descending curves. The increase of the rheological parameters of the bases was observed due to the increase of the potassium sorbate concentration; base 5 was beyond the rheological optimum.

Thus, based on the rheological tests performed and the pH measurement it was found that base 3 with 0.20% potassium sorbate possessed the optimal properties; the parameters of base 4 (0.25% potassium sorbate) were close to optimum.

The next stage of the experiment was to study the effect of 5.0% HNS (glycerin, propylene glycol, their mixture – 1:1) on the water-retention capacity of the bases when drying with IR-radiation. According to the results of the experiment (Fig. 3) when introducing HNS the gels lost moisture slower and in a smaller amount compared to base 1 (sample without HNS). The water-retention capacity was the highest for base 2 (glycerin), the lowest – in base 3 (propylene glycol), average – in base 4 (the HNS mixture).

The substantiation of the HNS content was also performed according to the results of determination of their effect on the osmotic properties of the gel bases. When comparing the experimental samples with the HNS con-

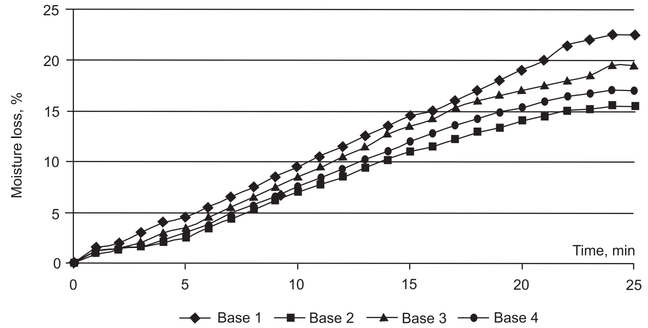

Fig. 3. The study of the water-retention capacity of the bases: base 1 – without HNS; base 2 – with glycerin; base 3 – with propylene glycol; base 4 – with the HNS mixture (1:1).

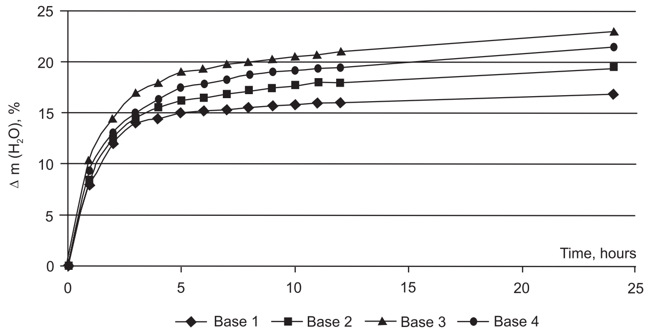

Fig. 4. Kinetics of water adsorption of the bases of the test samples.

tent and control (base 1 – without HNS) it was found that gels had the low osmotic activity (Fig. 4).

The ability of the bases with HNS to adsorb water through the semipermeable membrane was the highest in base 3 (propylene glycol), the lowest – in base 2 (glycerin), average – in base 4 (the HNS mixture). Thus, the reference sample absorbed approximately 14% of water for the first four hours, while sample 2 – 15.5%, sample 3 – 18%, sample 4 – 16.5%.

Thus, the results obtained in studying the water-retention capacity and the osmotic action of the samples indicate that base 2 will not significantly change its composition in the process of preparation and application of a drug, and it will not overdry the skin during prolonged mask-gel local application.

In order to determine the HNS impact on the rheological properties of the gels their viscosity parameters were studied (Fig. 5).

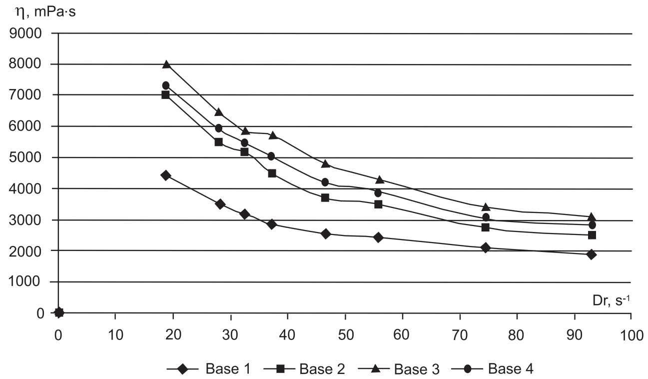

Fig. 5. The dependence of the structural viscosity of the bases on the shear rate: base 1 – without HNS; base 2 – with glycerin; base 3 – with propylene glycol; base 4 – with the HNS mixture (1:1).

The introduction of HNS greatly increased the structural and mechanical properties of the test samples: the η value (at 20°C, 20 rpm) for base 1 was 4400 mPa·s, for base 2 – 7000 mPa·s, for base 3 – 8000 mPa·s, and for base 4 – 7300 mPa·s. Propylene glycol thickened the base the most intensively, glycerin and the HNS mixture had the similar rheological parameters of the bases.

When measuring the pH value it was found that introduction of HNS slightly altered the acid-alkaline properties of the gels. Thus, the pH value for sample 1 was 4.64±0.40; for other bases with HNS pH it was approximately the same – within 5.00±0.04.

CONCLUSIONS

1. It has been found that the content of the preservative potassium sorbate from 0.1% to 0.3% significantly affects the pH and the rheological properties of the gel bases. The content of 0.2% of the preservative in the base composition provides pH 5.0, which corresponds to the skin surface acid-alkaline physiological range. Moreover, the structural viscosity and thixotropy, the MS value (1.04) close to optimum and the high K_d rate (63.48) characterize the gel base as a base possessing good technological and consumer properties.

2. According to the biopharmaceutical and rheological studies it has been confirmed that the base with 5% glycerin has the best ability to retain moisture in the composition, possesses the insignificant osmotic effect, and is characterized with proper viscosity compared to other HNS (propylene glycol, the HNS mixture in the ratio of 1:1).

3. Therefore, according to the pH values, rheological and biopharmaceutical studies the gel base of the following composition: sodium alginate – 1.0 g; carbopol (Ultrez 10) – 1.0 g; glycerin – 5.0; potassium sorbate – 0.2; purified water – up to 100.0 g has the optimal properties.

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ОПРАЦЮВАННЯ СКЛАДУ ОСНОВИ ГЕЛЮ, ПРИЗНАЧЕНОГО ДЛЯ ЛІКУВАННЯ ТЕЛОГЕНОВОЇ АЛОПЕЦІЇ

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***Ключові слова**: телогенова алопеція; сік кропиви; гелі; основи; консерванти; гідрофільні неводні розчинники*

Представлені результати дослідження з опрацювання оптимального складу основи гель-маски для лікування телогенової алопеції. Визначення впливу консерванту калію сорбату в різних концентраціях (від 0,1% до 0,3%) на pH та структурно-механічні властивості гелів показало, що його 0,2% вміст забезпечує основі: pH 5, яке характерне кислотно-лужному балансу поверхі шкіри; структурну в'язкість і тиксотропію, значення МС – 1,04 та показник K_d – 63,48, що відповідають її оптимальним технологічним та споживчим властивостям. За результатами біофармацевтичних та реологічних властивостей підтверджено, що основа з 5% гліцерину в порівнянні з іншими ГНР (пропіленгліколь, суміш ГНР 1:1) володіє найкращою здатністю утримувати вологу в своєму складі, чинить незначну осмотичну дію, характеризується належною в'язкістю. Отже, оптимальними властивостями володіє гелева основа складу: натрію альгінат – 1,0; карбопол – 1,0; гліцерин – 5,0; калію сорбат – 0,2; вода очищена – до 100,0.

РАЗРАБОТКА СОСТАВА ОСНОВЫ ГЕЛЯ, ПРЕДНАЗНАЧЕННОГО ДЛЯ ЛЕЧЕНИЯ ТЕЛОГЕНОВОЙ АЛОПЕЦИИ

М.И.Федоровская, Н.П.Половко

Ключевые слова*: телогеновая алопеция; сок крапивы; гели; основы; консерванты; гидрофильные неводные растворители*

Представлены результаты исследования по разработке оптимального состава основы гель-маски для лечения телогеновой алопеции. Определение влияния консерванта сорбата калия в различных концентрациях (от 0,1% до 0,3%) на pH и структурно-механические свойства гелей показало, что его 0,2% содержание обеспечивает основе: pH 5, что характерно кислотно-щелочному балансу поверхности кожи; структурную вязкость и тиксотропию, значение МС – 1,04 и показатель K_d – 63,48, соответствующие ее оптимальным технологическим и потребительским свойствам. Результатами биофармацевтических и реологических свойств подтверждено, что основа с 5% глицерина в сравнении с другими ГНР (пропиленгликоль, смесь ГНР 1:1) обладает лучшей способностью удерживать влагу в своем составе, имеет незначительное осмотическое действие, характеризуется надлежащей вязкостью. Следовательно, оптимальными свойствами обладает гелевая основа: натрия альгинат – 1,0; карбопол – 1,0; глицерин – 5,0; калия сорбат – 0,2; вода очищенная – до 100,0.