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ТҰЖЫРЫМ

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RHEOLOGICAL STUDIES OF SEMISOLID MEDICINES

Жұмсақ дәрілік заттардың құрамын әзірлеу сатысында реологиялық зерттеулердің орны ерекше, себебі көмекші заттар мен олардың концентрацияларының тұтқырлы- пластикалық қасиеттеріне әсерін анықтауға мүмкіндік береді.

Материалдар мен әдістер: Әртүрлі құрылымдық тасымалдаушы белсенді заттар негізінде жасалған «Левомеколь» мазі, «Эспол » мазі, «Синтомицин» линименті, «Троксерутин» гелі зерттелді. Жүйенің реологиялық қасиеттерін (құрылымдық-механикалық) реовискозиметрі «Rheolab QC» (Anton Paar, Австрия) қондырғысы арқылы 20 ^{0}С температурада зерттелді.

Талдаулармен нәтижелер: Зерттеліп отырған жұмсақ дәрілік түрдің механикалық құрылымы анықталып, нәтижесінде жылжу жылдамдығының орын ауыстыруына байланысты құрылымдық тұтқырлығының, гистерезистің петлясының көлемінің өзгеруіне алып келеді, механикалық құрылымдық жүйесінің тұрақтылығын сипаттайды және тиксотропты жағдайы белгіленген.Әр жұмсақ дәрілік формасының ағу шегі, гистерезис петлясыныңауданы анықталды. Графикалық және кестедегі мәліметтер арқылы жүйенің құрылымдық тұтқырлықтың, жылжу жылдамдығына тәуелділігі анықталды, тікелей (жылжу жылдамдығы артады), және кері жүрісінде (жылжу жылдамдығы баяулайды).

Қорытынды: Жасалған зерттеулер жұмсақ дәрілік заттарды әзірлеу сатыларында тұрақтылықтарын болжау мақсатында экструзионды және тұтынушылық қабілеттерін, тұтқырлы – пластикалық қасиеттерін бағалалауға мүмкіндік береді.

Негізгі сөздер: *реологиялық қасиеттері, жұмсақ дәрілік қалып, құрылымдық тұтқырлық, жылжу жылдамдығы, механикалық құрылымдық, тиксотропия.*

RESUME

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RHEOLOGICAL STUDIES OF SEMISOLID MEDICINES

Rheological study of semi-solid dosage forms are required during the design composition, that allows to estimate the influence of excipients and their concentration on the visco-plastic properties, as well as to determine the technological parameters of the production process.

Material and methods. The objects of the rheological properties study of of semi-solid dosage forms were used ointment “Levomekol”, ointment “Espoli”, liniment “Chloromycetin”, gel “Troxerutin” made on various suitable vehicles of active substances. Rheological properties (structural and mechanical) were studied by using rheoviscosimeter «Rheolab QC» (Anton Paar, Austria) at 20°C.

Results and discussion. The results of the data were plotted transverse strain versus shear rate, which allows us to estimate the visco – plastic properties of semi-solid dosage forms, the type of flow and thixotropic properties that shows the mechanical stability of structured systems. For each semi-solid dosage form was determined liquid limit, defined the square of the hysteretic loops. From tabular and graphical data presents the variation of plastic viscosity on the shear rate in the forward (shear rate increases) and reverse way (shear rate decreases).

Conclusions. The studies assist to assess the visco-plastic properties of semi-solid dosage forms in the development phase for prediction their stability, extrusion capacity and consumer properties.

Key words: *rheological properties, semisolid medicines, structural viscosity, shear rate, shear stress, thixotropy.*

УДК 615.014.22:615.454.1:615.282

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COMPOSITION AND FORMULATION DEVELOPMENT OF ANTIFUNGAL SEMISOLID DOSAGE FORM

The aim of our work was elaboration of antifungal gel with Tee tree oil as an active ingredient. The obtained rheological properties give validation for using concentration as 1% of carbomer as a basis. Propylene glycol as a non aqueous solution due to its osmotic activity and penetrative properties had been chosen. Osmotic activity and pH correlate with requirements for medical application dermatological semi-solid medicine for treatment micosis. Technology for gel’s manufacture had been proposed.

Key words: *semisolid dosage form, technology, antifungal activity, rhehological properties, carbomer.*

Introduction

Nowadays, ointments are not only well-tried forms of non-prescription drugs but they also present a dominating group of prescription drugs. Pharmaceutical preparations for conditions treatment such as rashes, skin irritation, stings, fungal infections etc. are normally supplied in the form of cream or ointment, as this provides the effective means of delivering the active ingredient directly to the required area. Dissemination of fungal infections is one of the problems for society at the moment. Their treatment and prevention is an important goal of medicine [1, 2].

It is known that the quality of semi-solid preparations depends on numerous factors such as: chemical properties of the used components, order of their addition and even the applied technique of production [3, 4].

The aim of this research paper was to check the possibility of obtaining an effective form of a topical drug through the usage of tea tree oil as a modern active ingredient along with quantitative change of auxiliary substances.

Materials and methods

During making the work technical, physical and chemical, structural and mechanical methods of research have been used, which allow to estimate samples of raw materials and finished products [5, 6].

The pH evaluated according to EPh 6.0 2.3.3. p 24. 2.5 grams of gel (accurately weighed) was put into a beaker, added 50 ml of purified water and dissolved while stirring during 10 minutes. Then the pH of the resulting water dispersion has determined by potentiometry (pH-150 МИ).

Structural and mechanical (rheological) properties of the samples were determined by using rotational viscometer «Rheolab QC», Anton Paar company (Germany), with coaxial cylinders C-CC27/SS/QC-LTD. (EPh 6.0 *2.2.10. p 27*) Temperature control of samples was carried out by the thermostat. The sample of cream with a mass 17,0 (± 0,5) g was put in a container of outside fixed cylinder. The temperature desired while the experiment was set by the thermostat, after this by using the software the necessary conditions of the experiment (gradient shear rate, the number of experience points at the flow curve and length of the measurement at each point of the curve) installed. The device allows to measure shear stress in the range of 0.5 – $3.0 \cdot 10^4$ Pa, shear rate from 0.1 to 4000 s^{-1}, the viscosity – 1 – 10^9 mPa·s. Measurements were carried out at the temperature of 20±2°C and 37±2°C.

The osmotic activity was determined by the method of dialysis through a semipermeable membrane. A sample of the gel (10.0 g) was applied at the surface area of the semipermeable membrane of 1808 mm^2 as uniform layer. Thereafter, the internal cylinder with the test sample was placed to dialysis chamber. Previously, the calculated amount of water purified (50±0,5 ml) has been poured into dialysis chamber.

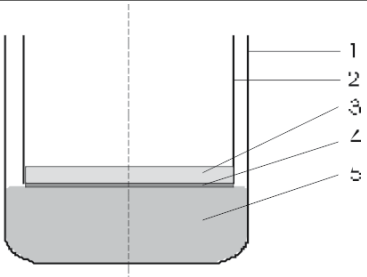

Fig. 1 – dialyser:

1. Dialysis chamber;
2. Internal cylinder;
3. Sample of the gel;
4. Semi permeable membrane;
5. Water purified.

The cylinder's mass measurement was carried out through regular intervals (1 hour). Periodically, the volume of water in the dialysis chamber was reduced to the score. The amount of absorbed water has been determined by the difference between the primary and obtained results. The experiment has been carried out at 36°C (skin temperature) for modeling the conditions of application of this medicine, which is achieved by the thermostat TC-80M-2. The scales Sartorius accurate within 0.01 g has been used.

For determination of ointment uniformity each of four samples of gel 20 – 30 mg were put on a slide, covered with another slide and pressed for forming a spot with diameter about 2 cm. These samples were examined by naked eye (the distance was approximately 30 sm from the eye). The sample is considered to be homogeneous if debris and signs of physical instability (phase separation) are not detected in all four samples visible particles. If one of the samples did not pass the test, the study is carried out on an additional eight samples. In this case, all eight additional samples must pass the test.

For carring out the test determination of the colloidal stability the laboratory centrifuge MPW-210 by company «Mechanika precyzyjna» (Poland) has been used with a set of tubes, mercury thermometer with an interval of temperatures from 0 till 100°C with 1°C as a value of division, also a stopwatch and a water bath. The tubes were filled to 2/3 of the volume (approximately 9 g) with samples (the mass of tubes with medicine should not differ more than 0.02 g), and weighed to within 0.01 g. Then the tubes were put in the water bath with a temperature 42,5±2,5°C for 20 minutes, then wiped dry from the outer sides and placed in the nests of centrifuge. Centrifuge for 5 minutes with 6000 rpm (relative centrifugal force becomes approximately 5000 g). The sample is considered stable if after centrifugation in tubes did not observe any changes. If in one tube at least separation or sedimentation of the sample were observed, the analysis carried out again with new batches. If the second test detected at least one tube with a separation, the sample would be considered unstable.

For determination of thermal stability 6 glass tubes of 15 mm diameter and 150 mm height were taken. Test tubes were filled with 8-10 ml of sample and put in a thermostat TS-80M-2

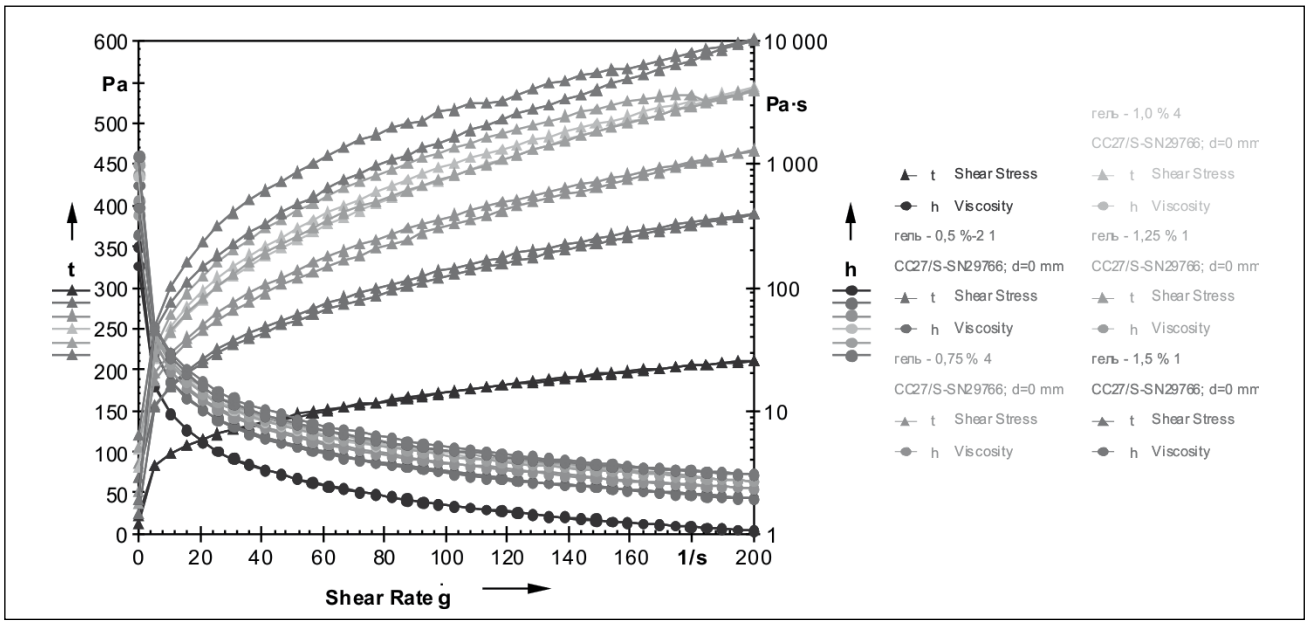

Fig. 2 – Flow curves of gel bases (with a different concentrations of carbomer) at 25°C

with the temperature 42,5±2,50°C for 7 days. Thereafter the samples were transferred for 7 days to refrigerator with the temperature 6±2°C and then for 3 days they were kept at the room temperature. Stability was determined visually, if there was no stratification in the tubes, then the sample could be considered stable.

Results and discussion

Rheological studies were applied under two different temparutres 25°C and 37°C to choose the optimal concentration of carbomer needed for perfect preparation and application of our gel. Different concentrations (0.25→1.5) gave different curves of viscosity and flowabilty shown below.

According to the results of measuring, rheograms of shear stress ( ) dependence on the shear gradient (Dr) have been built (Fig. 2, 3) in which the yield limit, the type of flow and the presence of thixotropic properties were determined.

As we can see in Figure 2, which shows the dependence of gel properties on the carbomer gels concentration, all samples have non-Newtonian type of flow: while increasing of shear rate, the curves of shear stress gradually increases. Flow curves of samples also indicate that their flowing doesn't begin immediately, but only after a certain applied shear needed to break it's elemental structure. Due to the decreasing of shear, the samples viscosity is gradually restored. This confirms the plastic-viscous and thixotropic properties of examined gels.

In the rheograms descending and ascending curves form a hysteresis loops (except the base of 0,25% carbomer concentration), that confirms thixotropic properties of examined systems. Upon analyzing the hysteresis loops, it can be concluded that the samples with the 1,25 and 1,5% concentration of carbomer have sufficient thixotropic properties, evidenced by the large surface area. The presence of thixotropic properties of the samples indicates the convenience and easiness of their application to skin, their packaging, and their extrusion from tubes.

For samples with the 0,5%, 0,75% and 1% concentration of Carbomer thixotropic properties are not satisfactory, which requires addition of non-aqueous solvents. Thus, the thixotropic properties of Carbopol gel are expressed to a greater extent with increasing of gelling agent concentration.

At low shear rates, the structure collapses and ointments fully restored (in this case, the system has the highest viscosity). With increasing shear rate, destruction of the structure begins to dominate the ointment restoration, and the viscosity decreases. At high shear rates, the structure is completely destroyed and the system begins to flow.

Measurements of rheological parameters at 25°C were conducted for studying the gels characteristics during stirring, packaging and extrusion capacity inorder to derive the conclusion about technological properties of the gels.

As it is presented at the fig 2, 0,5 to 1,5% concentration of gelling agent is possible for application in the semi-solid medicine manufacture. In terms of mechanical stability, the 1% concentration of gelling agent is optimal, because MS=1 (Table 1).

Table 1 – **Mechanical stabilty of gel bases**

Concentration of carbomer 940	MS of gel basis
0,25%	0.8
0,5%	0.9
0,75%	1.05
1,0%	1.00
1,25%	1.05
1,5%	1.50

Measurements of the rheological parameters at 37°C have been conducted to study gels characteristics while application to skin and validate it's consumer properties. The dependence of shear stress upon the versus shear rate shows that at 37°C, gels have a non-Newtonian flow type that provides spreadability on the skin.

As can be concluded from the viscosity values, temperature slightly reduces the gels' viscosity. At high rotational speeds, a sharp decrease of viscosity occurs, and then reduction is gradual, which indicates that the system is structured. Thus, this gel will spread but not flow of the skin. So, consumer properties within the range of used concentrations of Carbopol and temperatures remain sufficient.

Non aqueous solutions don't have a great influence on the osmotic activity of carbomer gel. Three different non aqueous solutions represented different osmotic activity with variable concentrations during five hours of study (fig 4). The concentration of non aqueous solutions was the same – 10%. All samples did not have high osmotic activity. Macrogol 400

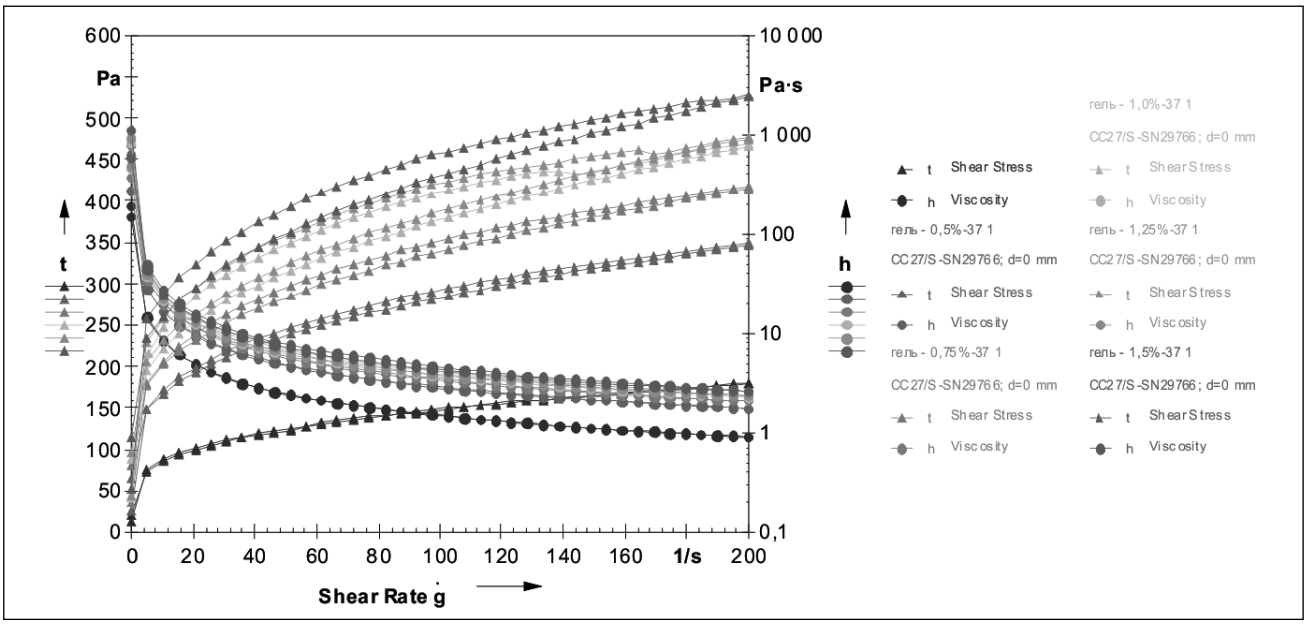

Fig. 3 – Flow curves of gel bases (with a different concentration of carbomer) at 37°C

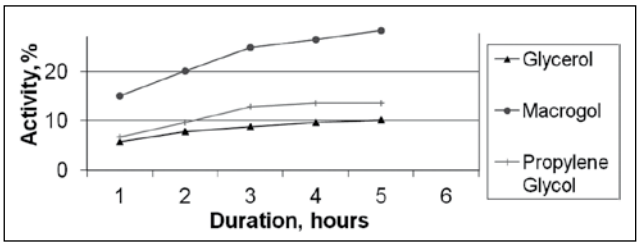

Fig. 4 – Graph showing osmotic activity of gel bases with non aqueous solutions

showed a relatively high osmotic activity with a concentration starting with 15% reaching 28% which is not suitable for applying on skin infected by mycosis. While, glycerol showed a low osmotic activity with an initial concentration of 5% reaching a final one of 10% which is not enough for medical efficiency.

Concerning propylene glycol a medium osmotic activity was shown by an initial concentration of 7% reaching a final one of 13%. The osmotic activity of propylene glycol and glycerol is similar. Macrogol can't be used due to it's high osmotic activity and glycerol can't be applied because of it's viscousity and unsuitable consumer properties (sticky). Depending on the above results the suitable non aqueous solution needed for preparing our antifungal gel would be propylene glycol, which has a medium osmotic activity and a high penetrative ability correlating with the parameters needed to treat skin mycosis.

The rheological properties of glycerol, propylene glycol, and macrogol were studied under 25°C (maximal temperature of storage for semisolid medicines) and 37°C (skin temperature) to choose the optimal non aqueous solutions needed for preparing antifungal gel. These results are shown in the following curves.

As we can see from the pictures 5 and 6, the non-aqueous solvents added improves the thixotropic properties of the 1% Carbopol gel. However, there is no significant difference between the curves of shear stress and shear rate and hysteresis loops for various non-aqueous solvents.

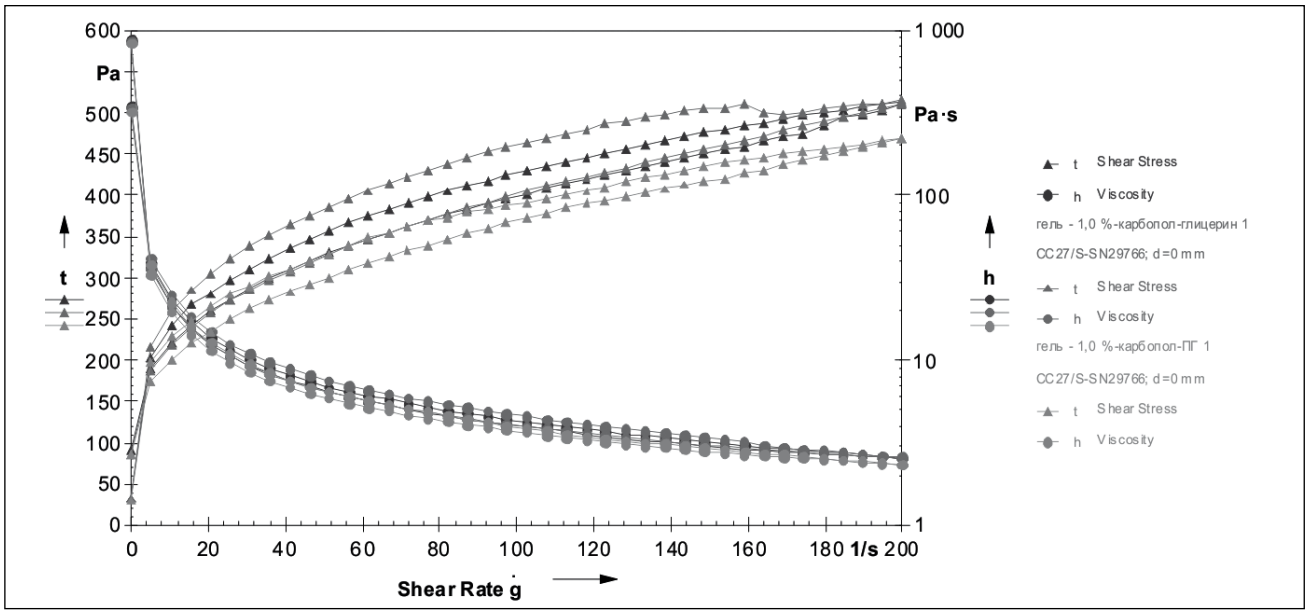

Fig. 5 – Flow curves of gels with different non aqueous solutions at 25°C

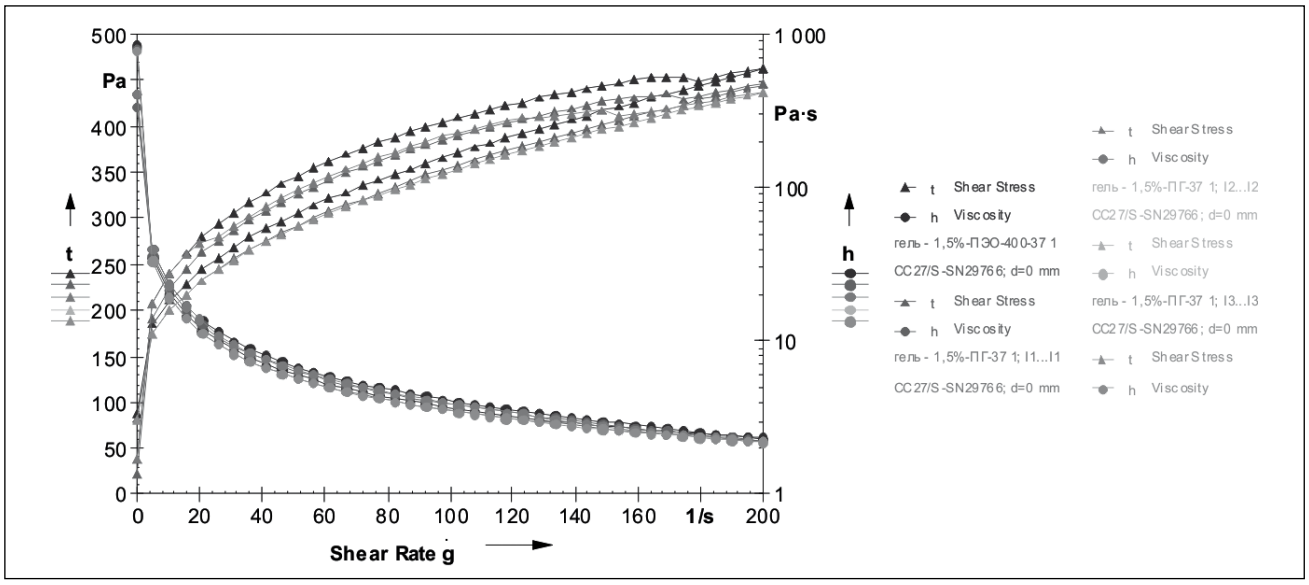

Fig. 6 – Flow curves of gels with different non aqueous solutions at 37°C

Thus, in a concentration of 10% addition of non-aqueous solvent affects the rheological parameters of the carbomer gel. But, the type of these solvents is not related to this rheological effect.

Development of fungal infection occurs in a neutral or weakly alkaline medium. The most favorable pH value for them is 6 – 6.7. It must be emphasized that the pH of healthy human skin is 5.5 (acidic environment is not conducive to fungi), which is one of the factors of protection of human skin against fungal infection. Excessive sweating, especially in closed areas of the skin, the evaporation of sweat from which is difficult, as well as some diseases are accompanied by a shift of skin pH to the alkaline side, which makes it more vulnerable in the face of fungal diseases and contributes to the development of fungal infections. Furthermore, stability of the gel and the absorption of drugs depends on pH level which also influences on gel's activity against living tissues.

The results shown above gave suitable pH values when essential oil included. (Table 2) So our active ingredient doesn't affect the pH of the gel and provides treatment for skin mycosis, where level of pH shifts due to fungal infection.

Table 2 – **Results of pH test for antifungal gel**

pH / Composition	pH with Glycerol	pH with propylene glycol	pH with macrogol
Gel without essential oil	6,38	5,61	5,49
Gel with essential oil	6,12	5,6	5,57

The examined samples of the gel have shown no visible particles, no debris and no signs of physical instability (phase separation). So, the gel is uniform.

By visual examination after thermal stability test, no bundles were observed in the test tubes. The gel is stable.

By visual examination after colloidal stability test, neither sedimentation nor separation was observed in the test tubes. The gel is stable.

For the following composition of the gel technology of preparation and compiled technological scheme of the gel was developed with essential oils in industrial environments. The composition of the gel includes: active substance: Tea tree oil and adjuvants: Carbomer 940 – a gelling agent, methyl paraben and propyl paraben, as preservatives, propylene glycol, as non-aqueous solvent, hydrogenated castor oil as a solubilizer, 10% ammonium hydroxide, as neutralizer, and water-solvent. Excipients provide necessary physical-chemical properties. On the basis of physico-chemical and technological studies, we developed a technology of the manufacture of the gel, which is provided for a specific procedure and temperature introduction of ingredients.

For manufacturing process of antifungal gel we can recommend the following main steps: swelling of carbomer 940 in purified water, preparing solutions of preservatives, preparing solutions of active substances, neutralization of Carbomer, mixing, homogenizationpackin and marking.

Conclusions

The composition and technology of gels with antifungal activity had been proposed.

The concentration of carbomer as 1% had been chosen. Propylene glycol as a suitable non aqueous solution had been provided.

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Т Ұ Ж Ы Р Ы М

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АНТИФУНГАЛЬДІ БЕЛСЕНДІЛІК ҚАСИЕТІ ИЕ ЖҰМСАҚ МАЙЛЫ ДӘРІЛІК ҚАЛЫПТЫҢ ҚҰРАМЫН ЖӘНЕ ТЕХНОЛОГИЯСЫН ЖАСАУ

Біздің жұмысымыздың мақсаты эфир майларын белсенді ингредиент ретінде пайдаланып антифунгальді гель жасау болып табылады. Карбомердің 1% концентрациясын негізгі зат ретінде қолдану оның реологиялық қасиетінің ие болуына байланысты қолданады. Антифунгальді ауруларды емдеуде жұмсақ дәрілік қалыпты медициналық талаптар бойынша осмотикалық белсенділігіне және pH ортасына байланысты таңдалып алынады. Карбомерді негізгі зат ретінде алынып гелдің технологиялық өндірісі жасалынып, ұсынылды.

Материалдар мен әдістер: Термотұрақтылығын аңықтау үшін 6 дана шыны түтіктері, диаметірі 15 мм, биіктігі 150 мм. алынды. Түтікшелер 8-10 мл толтырылып, түтікшелерді 7 күнге, ТС – 80М-2 Термостатына 42,5±2,500С температурасына қойылды. Содан кейін зерттеу үлгілері 7 күнге 6±200С тоңазытқышқа қоылды. Тұрақтылығы сыртқы келбетімен анықталды, егер де түтікшеде қатпарлану болмаса, онда ол тұрақты деп есептелінеді.

Талқылаумен нәтижелері: Гельдік композицияның құрамымен даярлау технологиясы, сонымен қатар өндірістегі технологиялық схемалар даярланды. Гельді даярлауда өндірістік жағдайдағы майлар пайдаланылды. Гельдің құрамына кіретін белсенді заттар гелтдің физико-химиялық қасиеттерін толықтай қанағаттандырады. Физико-химиялық және технологиялық зерттеулер негізінде белгіленген сатылыр мен берілген температура жағдайында геьдің дайындау технологиясы әзірленді.

Қорытынды: Антифунгальды белсенділікке арналған гельдің құрамы мен технологиясы әзірленді. Гель түзуші – карбомердің керекті концентрациясы -1% анықталды.

Негізгі сөздер: *жұмсақ дәрілік қалып, технология, антифунгальді белсінділігі, реологиялық қасиеттер, карбомер.*

Р Е З Ю М Е

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РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ МЯГКОЙ ЛЕКАРСТВЕННОЙ ФОРМЫ С ПРОТИВОГРИБКОВОЙ АКТИВНОСТЬЮ

Целью нашей работы была разработка противогрибкового геля с эфирными маслами в качестве активного ингредиента. Полученные реологические свойства позволяют подтвердить использование карбомера как основы в концентрации 1%. Осмотическая активность и pH коррелируют с требованиями для медицинского применения мягких лекарственных форм для лечения грибковых заболеваний. Была предложена технология производства геля.

Материал и методы. Для определения термостабильности были взяты 6 стеклянных трубок, диаметром 15 мм и высотой 150 мм. Пробирки были заполнены 8-10 мл пробы и поставлены в термостат ТС-80М-2, при температуре 42,5±2,50^{0}С в течение 7 дней. После этого образцы были переданы на 7 дней в холодильник при температуре 6±20^{0}С, а затем в течение 3 дней они хранились при комнатной температуре. Устойчивость определялась визуально, если нет расслоения в пробирках, то проба может считаться стабильной.

Результаты и обсуждение. Разработан состав гелевой композиции и технология его приготовления, также составлены технологические схемы производства. Гель разработан с использованием масел в промышленных условиях. Входящие в состав геля вспомогательные вещества обеспечивают необходимые физико-химические свойства. На основе физико-химических и технологических исследований, разработана технология изготовления геля, которая предусматривает конкретный порядок и введение температуры.

Выводы. Разработаны оптимальный состав и технология геля с противогрибковой активностью. Определена оптимальная концентрация гелеобразователя – карбомера 1%.

Ключевые слова: *мягкая лекарственная форма, технология, противогрибковая активность, реологические свойства, карбомер.*

УДК 616.131-005.6

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СОВРЕМЕННАЯ СТРАТИФИКАЦИЯ СТЕПЕНИ ТЯЖЕСТИ ТРОМБОЭМБОЛИИ ЛЕГОЧНЫХ АРТЕРИЙ

Представленный обзор относительно венозных тромбоэмболий (ВТЭ) свидетельствует о трудности диагностики тромбоза глубоких вен (ТГВ) и тромбоэмболии легочных артерий (ТЭЛА) из-за отсутствия специфических проявлений заболевания. Необходимо оценить факторы риска в развитии ВТЭ и результаты инструментальных исследований для верификации диагноза ТГВ и ТЭЛА. При этом ультразвуковое исследование с компрессией является надежным и неинвазивным методом диагностики ТГВ. При подозрении на ТЭЛА уровень артериального давления, состояние правого желудочка по данным эхокардиографического исследования и биохимические маркеры повреждения миокарда, такие как тропонин и мозговой натриуретический пептид, являются надежными критериями в оценке степени тяжести заболевания. Кроме того, внедрение в клинику электронной шкалы тяжести состояния ТЭЛА является важным шагом для быстрой и оперативной оценки состояния больного и определения неотложной терапевтической тактики.

Ключевые слова: *тромбоэмболия легочных артерий, факторы риска.*

Тромбоэмболия легочных артерий (ТЭЛА) – довольно часто встречающееся заболевание в условиях сердечно-легочной реанимации, которое сопровождается развитием обратимой, но потенциально острой жизнеугрожающей недостаточности правого желудочка (НПЖ). Диагностика ТЭЛА очень сложная и часто пропускается из-за отсутствия специфических клинических симптомов. Однако ранняя диагностика является фундаментальной, так как немедленно начатое лечение высокоэффективно и спасает больных от смерти и инвалидизации [1].

ТЭЛА и тромбоз глубоких вен (ТГВ) нижних конечностей являются двумя клиническими проявлениями венозной тромбоэмболии (ВТЭ) и имеют общие предрасполагающие факторы. ТЭЛА в большинстве случаев является осложнением ТГВ. Установлено, что среди больных с проксимальным ТГВ приблизительно в 50% случаях выявляются признаки ТЭЛА при сканировании легких [2]. С другой стороны, у 70% больных с ТЭЛА выявляется ТГВ нижних конечностей при использовании чувствительных методов диагностики [3, 4]. Поэтому ТЭЛА и ТГВ считаются одной болезнью, названной ВТЭ, однако клинические проявления ТЭЛА отличается от симптоматики ТГВ. При этом риск развития смерти, связанной с ВТЭ болезнью у больных с острой или рецидивирующей ТЭЛА, гораздо выше по сравнению с больными, у которых имеется только ТГВ [5]. По данным проспективных когортных исследований, летальность от острой ТЭЛА колеблется от 7 до 11%. Частота повторных эпизодов заболевания примерно в три раза больше после ТЭЛА, по сравнению с больными, у которых были только проявления в виде ТГВ (около 60% после ТЭЛА, по сравнению с 20% после ТГВ) [6].

ТЭЛА может возникнуть у пациентов без каких-либо определенных предрасполагающих факторов, однако наличие одного или нескольких факторов, как правило, обнаруживается у больных с ТЭЛА. Следовательно, ТЭЛА в большинстве случаев является вторичным заболеванием. В то же время, согласно данным международного регистра кооперативный легочной эмболии (ICOPER), доля пациентов с идиопатической или неспровоцированной ТЭЛА составляет около 20% [7].

В настоящее время ВТЭ рассматривается как результат взаимодействия между собой двух групп факторов: факторов, связанных с состоянием пациента, и факторов окружающий среды [8]. Факторы, связанные с состоянием больного, как правило, являются постоянными, тогда как факторы окружающей среды (ФОС) чаще являются временными (табл. 1).