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Research Article

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Rationale for the choice of the gelling agent, physical and chemical properties of the gel with a complex of essential oils

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ABSTRACT

For topical treatment of respiratory diseases complex of essential oils, namely ginger (Olei Zingiber officinale), clary (Olei Salvia sclarea), marjoram (Olei Majarana hortensis) and tea tree (Olei Melaleuca alternifolia) were selected as active substances [1, 2]. Choice of gelling agent and rational technology of introduction of active substances and excipients was justified. It was studied the impact of the solution with complex of essential oils on the structural and mechanical (structural viscosity, shear stress, the type of flow), physical and chemical (colloidal stability, pH) properties of the gel system in order to justify the selection of optimal gelling agent, as to ensure the stability of the drug within 24 months. The study of structural and mechanical properties of the developed samples was performed on a rotary viscometer Brookfield DV-II + PRO (USA), spindle SC4-21. According to the results of the study the optimal gelling agent, which ensures the creation of a stable gel base with essential oils complex, was selected [3].

Key words: hydrogel, essential oils of ginger, clary, marjoram, tea tree, pH, colloidal stability, rheological parameters.

INTRODUCTION

Inflammation of the upper respiratory tract is the most common disease among people of all ages. According to epidemiological studies and opinion polls of different countries of Europe colds are the most common reason for seeking medical help to the pharmacy and purchase OTC drugs [4].

For effective treatment of respiratory diseases, in particular rhinitis, the choice of dosage form and route of administration of the drug into the organism is very important. Transdermal therapeutic systems can significantly increase the concentration of the active ingredient directly at the site of application, namely the mucous nasal cavity, which distinguishes them from the liquid dosage forms. Rational dosage form is a gel that has the properties of solids and liquids, that`s why it is effective in form of application [5-7].

The processes of absorption and release of active substances are largely dependent on the media type, physical, chemical, structural and mechanical properties of both active substances and excipients, pH and solubility of drugs in base [8, 9].

Using biological and microbiological testing concentration of selected active substances of developed drug was grounded, namely essential oils of ginger (1%), clary (1%), marjoram (0.5%) and tea tree oil (0.5%) [10, 14]. As solubilizer Cremophor RH 40 and the solvent ethanol 96% were selected. This technology is most often used for administration of hydrophobic substances in hydrophilic medium. It is proved that the complex of essential oils with selected concentrations have expressed therapeutic effect, namely anti-inflammatory and antimicrobial. By means of microbiological tests complex of preservatives with sodium benzoate and nipagin with concentration of 0.25% and

0.1% respectively was selected. This concentration provides microbiological purity for 24 months in the selected container - aluminum tubes with internal lacquer finish of type Paclac with bouchon [15].

The purpose of this study is to justify the selection of optimal gelling agent and rational technology of introduction of active substances and excipients in selected gel base.

EXPERIMENTAL SECTION

The objects of study were the following examples of gelling agents:
- Hydroxyethylcellulose (ERh, p. 2102-2103, monography Hydroxyethylcellulose) - cellulose ether and ethylene oxide, molecular degree of substitution of 2.5. It represents a non-ionic, water-soluble polymer, which exhibits thickening effect; at high concentrations forms a film; provides a protective colloid effect. It can be used to prepare solutions with a wide range of viscosities [16];

- Xanthan gum (EPh, p. 1323-1325, monography Xanthan Gum) - is a natural polysaccharide microbiological origin, obtained by using hydrocarbon fermentation culture Xanthomonas Camprestris [16];

- «Structure XL» (Hydroxypropyl Starch Phosphate) - modified corn starch, derived from waxy hydroxypropyl corn starch. This substance has non-ionic nature. White powder, soluble in hot and cold water, which forms a colloidal solution, practically insoluble in acetone, toluene and alcohol [16-18];

- Carbomer of brand Ultrez-10 NF (SPU, p. 215; EPh, p. 814; USP p. 2426-2428, monography Carbomer) - a synthetic high molecular weight polymers of acrylic acid cross-stitched by allyl ether of sucrose or pentaerythritol. It is well dispersed in water to form viscous dispersions; effectively and easily keeps releasing active ingredients; has a low pH (due to the presence in the initial product 56-68% of end carboxyl groups). For properties of gelling egent it is necessary to convert the acid form to alkaline. After neutralizing the aqueous dispersion of carbomer by neutralizing agents (solutions of alkali metal hydroxide, organic amines, ammonia solution) transparent, colorless gel system is formed.

All samples were prepared using electronic scales laboratory CERTUS Balance CBA-300-0, 005 (Taiwan), pH indicators of samples were determined by potentiometric method on ionomer pH -150 MI from firm " Measuring Equipment" (Russia), colloidal stability - using laboratory centrifuge MPW -210 from firm «Mechanika precyzyjna» (Poland). Rheological studies of experimental samples were conducted using viscometer of rotary type. Method of determining the effective structural viscosity was as follows: sample weight (8.3) was placed in a cell viscometer and chosen spindle SC4-21 was lowered into it, which was resulted in the rotation, starting with low velocity of deformation, fixing such indicatirs of viscometer: η (mPa · s), Dr (s^{-1}), τ (Pa). By the results of the study ascending and descending curves of hysteresis loops (rheogram) were built and parameters of mechanical stability (MS) were calculated [3].

RESULTS AND DISCUSSION

Samples of gels were prepared by conventional techniques: they were homogenized at room temperature at medium revs mixer (40-60 ver / min), it is in terms of data destruction gel system, in case of increasing of revs occurs airing [3]:

hydroxyethylcellulose (sample № 1) - powder of gelling agent was added to a portion of purified water, which is part of the recipe (20-25%) and left for 2 hours for swelling. Then the remaining water was added and heated to 80-90 °C until dissolution. As a result transparent, colorless, odorless, non-sticky gels were obtained [19];

- Gels with Xanthan gum (sample № 2) - gel bases were prepared from previous soaking gum powder in purified water at room temperature: ½ of calculated amount of purified water was measured out according to the recipe, the required amount of xanthan was added, then composition was stirred and left for a while (an hour) for swelling. Then the rest of the water was added to obtain a gel - transparent mass of pale yellow, odorless [20];

- Gels with «Structura XL» (sample № 3) - powder of gelling agent was added to purified water at low revs mixer at room temperature. As a result, colorless, translucent gels of varying consistency were immediately formed . The pH of the gel bases was 7,2 ± 0,3 [21];

- Carbomer gels with of brand Ultrez-10 NF (sample № 4) - required quantity of gelling agent was added to ¾ of purified water and left for 30 minutes until the swelling of carbomer powder. Neutralizer (trometamol) was added to a pH of 6.5 - 7.0 and treated with homogeneous transparent gel base with satisfactory consumer properties [22-25]. In the prepared gel samples a solution of essential oils was added. The results of the data are presented in table 1.

Table 1 The investigated samples gels with a complex of essential oils (n = 5)

№	Name of gelling agent	Samples			
		№1	№2	№3	№4
1.	Hydroxyethylcellulose	1,0	-	-	-
2.	Xanthan gum	-	1,0	-	-
3.	«Structura XL»	-	-	1,0	-
4.	Carbomer Ultrez-10 NF	-	-	-	1,0
5.	Trometamol	-	-	-	1,0
6.	Methylparaben	0,1	0,1	0,1	0,1
7.	Sodium benzoate	0,5	0,5	0,5	0,5
8.	E. o. of clary	1,00	1,00	1,00	1,00
9.	E. o. of ginger	1,00	1,00	1,00	1,00
10.	E. o. of marjoram	0,5	0,5	0,5	0,5
11.	E. o. of tea tree	0,5	0,5	0,5	0,5
12.	Ethanol 96 %	10,0	10,0	10,0	10,0
13.	Cremophor RH 40	1,00	1,0	1,0	1,0
14.	Purified Water	Up to 100,0			

The next stage of the experiment consists of studying the rheological properties which are essential in the development of soft dosage forms [3]. If during the structural and mechanical investigations other conditions are not specified, data of rheological indicators was measured at 20 rev / min and at temperature (20 ± 2) °C [17]. For a more complete study of gel samples indicators of they mechanical stability (MS) were calculated. The value of MS is defined as the ratio of the tensile strength of the structure to destruction (τ1) to the value of tensile strength after destruction (τ2) using the formula:

As comparator drug (sample № 5) was chosen "Pinosol" from manufacturer JSC «Zentiva» Czech Republic. As pharmacologically active ingredients this drug contains: pine oil, eucalyptus oil, menthol, thymol and tocopherol acetate. As excipients it contains: butylhydroxyanisol, labrafil M, white wax, petrolatum white. The results of the data are presented in table 2:

Table 2The results of study of the samples gels with a complex of essential oils

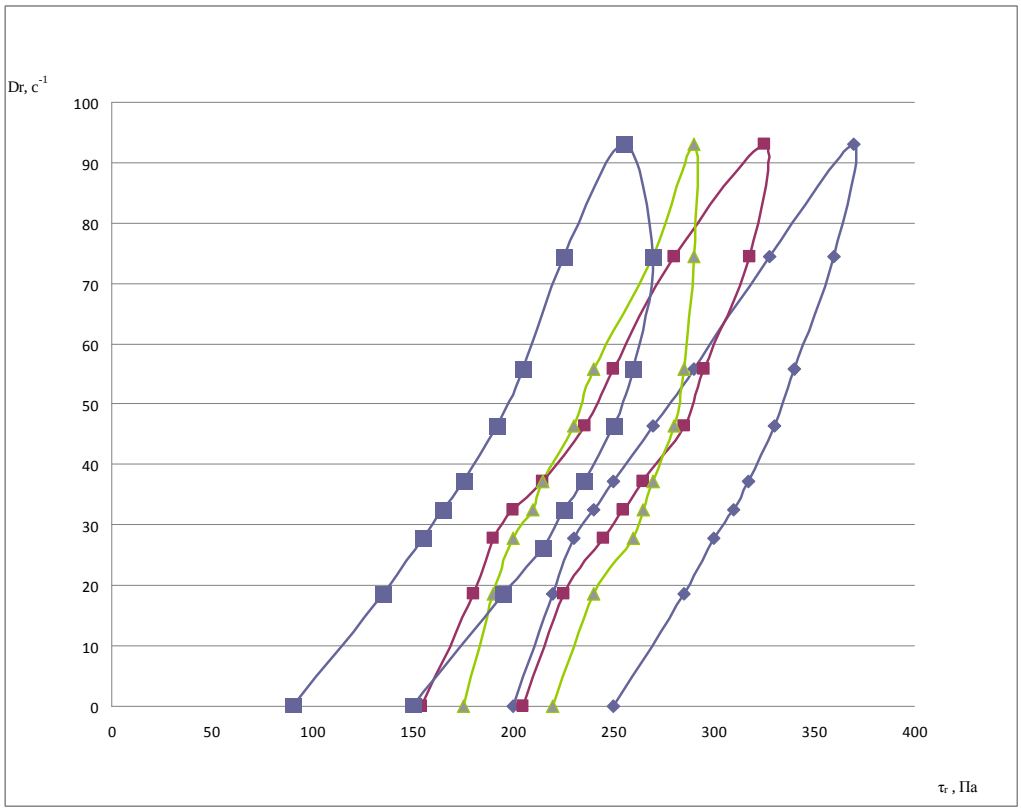
№	Characteristics	Number of sample				
		№1	№2	№3	№4	№5
1.	Appearance	Gel transparent of white color	Gel transparent of white color	Gel transparent of white color	Gel transparent of white color	Ointment of white color
2.	pH of 10 % solution	7,6±0,2	7,5±0,3	6,5±0,2	6,5±0,2	5,1±0,1
3.	Structural viscosity η (mPa·s)	7000	1800	3800	13000	3300
4.	Colloid stability, (at 6000 ver / min)	-	-	+	+	+
5.	Mechanical stability (MC)	1,66	1,52	1,32	1,17	1,27

According to the results of experimental data samples №№ 1, 2 with hydroxyethylcellulose and xanthan gum as a base were excluded, because in 5-10 minutes under the influence of complex of active substances gel structure was distroyed. Sample № 3 on the basis of «Structura XL» does not correspond to the requirements of gels by rheological parameters, because it was rare, while increasing the concentration of gelling agent become sticky and had unsatisfactory properties. Comparator drug "Pinosol" satisfies the structural, mechanical and consumer properties (slight smearing, extrusion properties). The value of the selected sample MS (№ 4) is close to the optimum value, comparator drug "Pinosol" also had a close value.

Thus, for further research sample № 4 on the basis of carbomer (neutralizer - trometamol) has been selected. It satisfies consumer, physical, chemical, structural and mechanical properties.
We studied the effect of selected compounds on rheological parameters of gel system with carbomer:

- Sample № 1 - gel base;
- Sample № 2 - gel base + preservative;
- Sample № 3 gel base + preservative + essential oils + Cremophor RH 40;
- Sample № 4 - gel base + preservative + essential oils + Cremophor RH 40+ ethanol 96%.

Rheograms, which were obtained (Pic. 1) show, that introduction of active substances (complex of essential oils) and excipients (Cremophor RH 40, ethanol 96%) did not change type of flow and was characterized as plastic [].



Picture 1. **Rheogram of gels: 1 - gel base; 2 - gel base + preservative; 3 - gel base + preservative + essential oils + Cremophor RH 40; 4 - gel base + preservative + essential oils + Cremophor RH 40 + ethanol 96%.**

Under reducing of shear stress structural viscosity was restored. "Bottom-up" curves of hysteresis loops showed a reduction of structural viscosity after the destruction of the gel structure, and "descending" curves reflected the optimal equilibrium, in which there were systems after the destruction. It was observed that the addition of essential oils complex reducted rheological parameters and it was also noticed, that rational technology is the introduction of sample № 4: first - Cremophor RH 40, then - ethanol 96%. Its system is more structured, that due to the addition of first solubilizers.

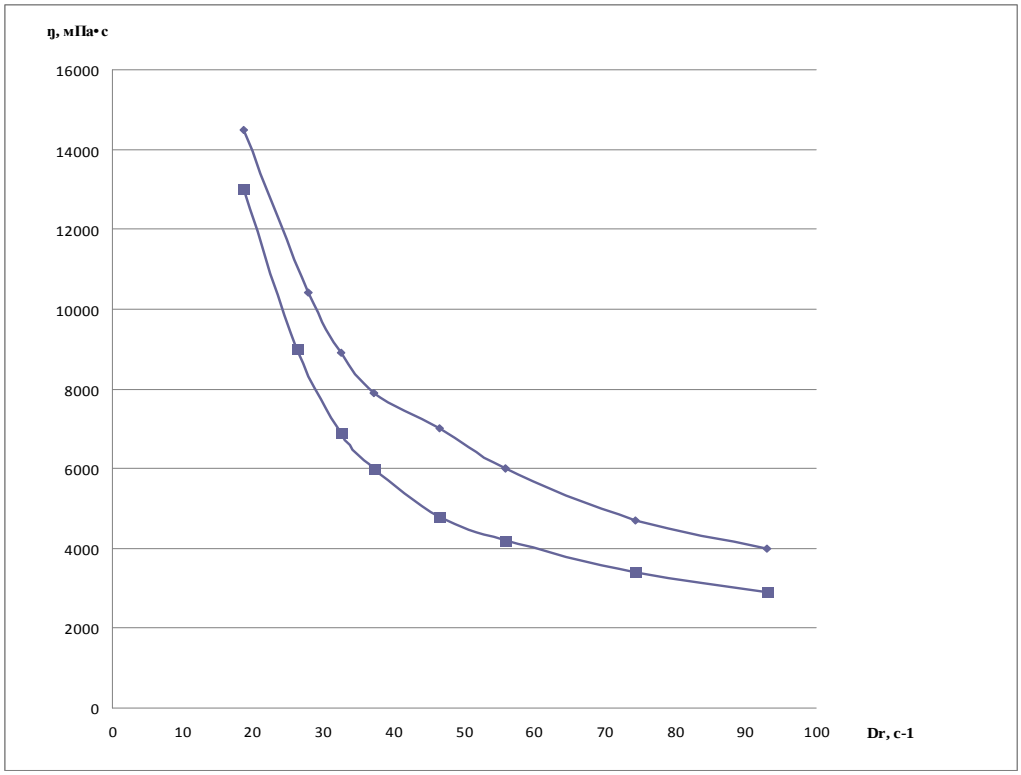
These data are confirmed in digital format and are presented in table 3:

Table 3 The results of studies of chosen gel

Number of sample	Components	η, mPa·s	MC
№ 1	Gel base + preservative + essential oils + Cremophor RH 40 + ethanol 96%	13000	1,17
№ 2	Gel base + preservative + essential oils + Cremophor RH 40	10600	1,22

The data table can be concluded that the two samples are satisfactory characteristics for gel system. However, for further research sample № 1 is selected, which had higher levels of viscosity and better mechanical stability value (MS), namely 13000 and 1.17, respectively.

The study of dependence of structural viscosity on shear rate gradient shows, that the structural viscosity of studied gels gradually decreased with increasing of shear rate gradient (Pic. 2).



Picture 2. Dependence of structural viscosity of gels shear rate: sample № 1, sample № 2

This dependence is also characteristic for systems with plastic flow and characterizes the type studied gels as structured dispersed systems, in which it is no interaction with the developed gel base after adding of active substances and excipients, that provides uniform and gradual applying to the skin and the mucous nasal cavity.

CONCLUSION

Based on the physical, chemical, structural and mechanical studies the choice of gelling agent, such as carbomer of brand Ultrez-10 NF, and rational technology of introduction of complex substances (pharmacologically active ingredients - essential oils of ginger, clary, marjoram and tea tree; excipients - Cremophor RH 40, ethanol 96%, preservatives complex) in a hydrophilic gel base were proved. Based on data research, it was proved, that the system has a plastic type of flow, that characterizes the studied gel as structured dispersed system, in which it is no interaction with the developed base after adding of active substances and excipients, that provides uniform and gradual applying. Therefore, we have developed a gel with a complex of essential oils for topical treatment of respiratory diseases, which has satisfactory structural and mechanical, technological and consumer characteristics.

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