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PHARMACOTECHNICAL AND STRUCTURAL-MECHANICAL CHARACTERIZATION OF HYDROGELS WITH THIENOFLOGIN

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Introduction

Inflammatory lesions of the musculoskeletal system are an urgent problem in modern rheumatology and traumatology. Among the most frequently reported complaints to physicians are pain and swelling in the affected area, which lead to impaired mobility and, in general, to a significant deterioration in patients' quality of life [1].

According to the recommendations of the European League Against Rheumatism (EULAR), the most commonly used drugs for the therapy of pain syndrome in bone and joint diseases are non-steroidal anti-inflammatory drugs (NSAIDs), which are effective due to their anti-inflammatory and analgesic effects, but also have certain side effects, including gastrointestinal disorders and negative effects on kidney and liver function, especially in the case of prolonged treatment of chronic forms of the pathology [2]. This has prompted the scientific community to develop local analgesic and anti-inflammatory agents based on NSAIDs in the form of ointments, creams, gels, sprays, or patches, whose use improves compliance and reduces systemic side effects [3, 4].

It is known that the concentration of NSAIDs in topical drug formulations is often 100 times lower than in their oral forms, which suggests their low bioavailability. However, recent studies indicate that NSAIDs, when applied repeatedly to the affected area in optimal pharmaceutical forms, can provide pain relief without accompanying side effects, without accumulating high concentrations in the blood plasma [5]. By overcoming the protective barrier, NSAIDs can reach deeper layers of the skin and muscles, accumulate to effective concentrations, and thus provide the necessary therapeutic efficacy [6, 7, 8].

Some authors have reported data on successful clinical trials of a ketoprofen patch at a dose of 100 mg, which remains in the affected tissues for 24 hours, provides a therapeutic effect, is well tolerated, and does not cause adverse effects. The efficacy of controlled delivery of NSAIDs (diclofenac epolamine) in the form of a topical patch is also known [9, 10].

A number of studies have reported the development of topical pharmaceutical formulations aimed at improving joint function in osteoarthritis, where gel bases served as delivery systems for active pharmaceutical ingredients (APIs) into tissues. Liang F, Zheng Y, et al. presented data on the treatment of arthritis using a gel formulation based on extracellular vesicles derived from the alga Spirulina platensis, which affects cartilage metabolic processes and exhibits antioxidant properties at mildly acidic pH [11, 12].

The use of botulinum neurotoxin A (BoNT/A), which inhibits the release of acetylcholine at neuromuscular synapses, is also known, and it is proposed in a more convenient, safer, non-invasive formulation with the possibility of transdermal delivery, unlike the injectable form of the drug. Studies published by de Faro Silva R, Barreto AS et al. [13] present data on the results of clinical studies of a nanoencapsulated hydrogel with active particles of the oil of the plant *Caryocar coriaceum*, which demonstrated a reduction in pain, swelling, and locking of the knee joint, improvement in the patient's quality of life, together with the absence of cytotoxicity and irritant effects on human skin [14].

The above indicates the relevance of searching for new active pharmaceutical ingredients (APIs) and developing topical pharmaceutical formulations based on them with anti-inflammatory and analgesic effects.

At the National University of Pharmacy (NUPh), at the Institute of Organic Synthesis, Prof. S. V. Vlasov synthesized a new pharmaceutical substance — the methyl ester of 5-methyl-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (Thienoflogin), which, according to the results of pharmacological activity screening, exhibited analgesic and anti-inflammatory effects, for which a draft quality control specification was developed. Preliminary studies by Prof. Vlasov et al. established that Thienoflogin, in terms of anti-inflammatory activity in the carrageenan-induced edema model and analgesic activity in the acetic acid-induced writhing model in mice, was superior to the reference drug [15,16].

A significant share of the pharmaceutical market for topical agents with combined analgesic and anti-inflammatory effects is occupied by foreign products, whereas domestic agents with similar activity are limited. This motivates contemporary Ukrainian researchers and manufacturers to pursue the development of modern, effective, and accessible pharmaceutical formulations for the local treatment of inflammatory lesions of the musculoskeletal system.

One stage of pharmaceutical development is selecting an optimal dosage form to ensure maximum therapeutic effect with minimal side effects. A gel is a semi-solid system with a liquid dispersive medium, whose structural and mechanical properties are provided by gelling agents. The study of the structural and mechanical properties of hydrogels is an important stage in pharmaceutical development, enabling a sufficient release rate of APIs from the base, stability of the pharmaceutical preparation during storage, as well as effectiveness and ease of use [17].

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The aim of this study was to investigate the organoleptic, pharmacotechnical, and structural-mechanical properties of experimental Thienoflogin-containing hydrogel samples, as well as the effect of excipients on their rheological characteristics.

Materials and Methods. The objects of the study were experimental hydrogel samples with different concentrations of Aristoflex AVC, containing a dispersion of Thienoflogin in olive oil with the addition of polysorbate 80, and a dispersion of Thienoflogin in dimethyl sulfoxide.

The gel samples were prepared under laboratory conditions at 25 °C, with prior swelling of Aristoflex powder in purified water, followed by the addition of glycerin and the Thienoflogin substance in dry form as a suspension, as well as the dispersion of Thienoflogin in olive oil with the addition of polysorbate 80 and the dispersion of Thienoflogin in dimethyl sulfoxide, with a stirring rate of 100 rpm.

The appearance and homogeneity of the experimental samples were evaluated in accordance with the requirements of the State Pharmacopeia of Ukraine 2.0, Vol. 1, "Soft Pharmaceutical Dosage Forms for Topical Use" [18].

Colloidal stability was determined by centrifugation for 5 min at a rotational speed of 1000 s^{-1}. Thermostability was assessed using a thermostat (TS-80M-2, MIZ, Ukraine) at 42.5 ± 2.5 °C for 7 days. The pH of the model samples was measured potentiometrically in a 10% aqueous extract of the gel using a pH meter pH 150 MI (IT LLC, russia). Rheological studies were performed using a BROOKFIELD HB DV-II PRO viscometer (USA) over a shear rate range of 0.1 s^{-1} to 200 s^{-1} (spindle SC4-21 for a chamber with a volume of 8.3 ml) at 20 °C.

Based on the measurements of structural and mechanical parameters (shear stress, dynamic viscosity), flow rheograms were constructed in the coordinates "shear rate – shear stress," and the dependence of the structural viscosity on shear stress was investigated. The studies were conducted at 25 °C. The results were processed using software.

Results and Discussion

Contemporary advances in pharmaceutical technology indicate a shift in the concept of developing soft pharmaceutical formulations towards expanding the requirements for soft bases, which are now considered not only as systems for delivering active pharmaceutical ingredients (APIs) with regard to their physicochemical and biopharmaceutical properties, but also as providing new possibilities for controlled release, taking into account the characteristics of the pathological process at the site of application. The development of chemical technologies has opened new opportunities in the design of modern bases for soft pharmaceutical formulations by using excipients that combine multiple functions (structuring agents, gelling agents, stabilizers), thereby improving consumer properties, enhancing solubility and stability, and facilitating targeted drug delivery [19].

The rational combination of APIs with the base of soft pharmaceutical formulations largely influences the effectiveness of subsequent pharmacotherapy. Previous studies of Thienoflogin release kinetics using the diffusion method through a semipermeable membrane demonstrated the best results for the gel formulation.

The Ukrainian excipient market offers a wide range of polymers used as gelling agents, capable of forming homogeneous, semi-transparent, semi-solid systems in which 99 % of the liquid phase is absorbed by the polymer, thereby creating a three-dimensional network. APIs of various natures can be easily incorporated into such systems, making them excellent hydrophilic bases for viscoplastic pharmaceutical formulations [20].

However, the low solubility of Thienoflogin in water necessitated the study of hydrogels using excipients of different natures and properties, to determine the optimal hydrogel composition for the best Thienoflogin release and subsequent effective application. The composition of the studied samples is presented in Table 1.

Table 1. Composition of the studied hydrogel samples, g

Sample number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Thienoflogin	0,12	0,12	0,12	0,12	0,12	0,12	0,12	0,12	0,12
Olive oil	-	3,7		-	3,7		-	3,7	
Polysorbate 80		2,2			2,2			2,2	
Aristoflex	1,0	1,0	1,0	1,5	1,5	1,5	2,0	2,0	2,0
Dimethyl sulfoxide			1,2			1,2			1,2
Glycerin	10,0	10,0	10,0	10,0	10,0	10,0	10,0	10,0	10,0
Water	up to 100,0								

The first stage of the study involved determining the organoleptic properties and pH values of the experimental samples. The results of the organoleptic analysis and the pH values are presented in Table 2. The results presented in Table 3.1 indicate that all experimental samples have a homogeneous consistency and are odorless, except for the samples containing dimethyl sulfoxide. Samples 7–9 are sticky to the touch, which may indicate good adhesion to the skin surface, whereas

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samples 1–3 exhibit low viscosity and a texture that does not correspond to satisfactory sensory properties (condition of the skin after application) and suggests an insufficient content of structuring agent. The results presented in Table 3.1 indicate that all experimental samples have a homogeneous consistency and are odorless, except for the samples containing dimethyl sulfoxide. Samples 7–9 are sticky to the touch, which may indicate good adhesion to the skin surface, whereas samples 1–3 exhibit low viscosity and a texture that does not correspond to satisfactory sensory properties (condition of the skin after application) and suggests an insufficient content of structuring agent.

Table 2. Organoleptic properties of the experimental samples

Sample number	*Organoleptic properties*	*pH*	Structural viscosity, Pa·s at 20 rpm
1	Homogeneous, semi-transparent, aqueous hydrogel, odorless, with a small number of air bubbles, light yellowish color, non-sticky.	5,4±0,09	1,41±0,07
2	Homogeneous, opaque, aqueous hydrogel, odorless, with a small number of air bubbles, light yellow color, non-sticky.	6,0±0,09	1,63±0,02
3	Homogeneous, semi-transparent, non-viscous hydrogel, yellowish-milky color, with a small number of air bubbles, slightly specific odor, non-sticky.	5,9±0,10	1,52±0,01
4	Homogeneous, semi-transparent, moderately viscous hydrogel, odorless, without air bubbles, light yellowish color, non-sticky.	5,5±0,08	2,35±0,10
5	Homogeneous, opaque, moderately viscous hydrogel, odorless, without air bubbles, light yellow color, non-sticky.	5,9±0,09	2,62±0,02
6	Homogeneous, semi-transparent, moderately viscous hydrogel, yellowish-milky color, without air bubbles, slightly specific odor, non-sticky.	6,0±0,09	2,35±0,15
7	Homogeneous, semi-transparent, viscous hydrogel, odorless, with a large number of air bubbles, light yellowish color, sticky.	5,4±0,10	2,82±0,11
8	Homogeneous, opaque, viscous hydrogel, odorless, with a large number of air bubbles, light yellow color, sticky.	6,1±0,09	2,98±0,03
9	Homogeneous, semi-transparent, viscous hydrogel, yellowish-milky color, with a large number of air bubbles, slightly specific odor, sticky.	6,1±0,09	2,78±0,10

Note. The number of repeated measurements of one sample is n=3

The pH measurement showed that all experimental hydrogel samples have a pH in the range of 5.4–6.1, which corresponds to the pH of the skin's hydro-lipid mantle. These results indicate that the hydrogel will not disrupt the metabolic processes of the skin.

Studies of the thermostability and colloidal stability of the experimental hydrogel samples showed that they are stable.

To assess the gel structure strength, thixotropy, and behavior under static and dynamic conditions, the rheological and structural-mechanical properties of the experimental hydrogel samples were studied, including viscosity and shear stress. The importance of these parameters is reflected in gel production factors, such as the mixing rate of the gel mass, the preparation temperature, and extrudability. Samples 4–9 were included in the study. Samples 1–3 were excluded because their consistency properties did not meet the requirements for the pharmaceutical formulation under development.

Based on the study of the structural and mechanical properties of the experimental samples, graphs of the dependence of dynamic viscosity on shear rate were constructed (Fig. 1), as well as complete rheograms showing the dependence of shear rate on shear stress at 25 °C (Fig. 2).

The presence of hysteresis loops on the flow rheograms indicates sufficient thixotropy of the studied samples, allowing the gel structure to gradually recover after disruption. As shown in Fig. 2, with increasing applied stress, the viscosity of the experimental samples decreases; however, upon removal of the external forces, the viscosity recovers, demonstrating the thixotropic properties of the hydrogels.

It was found that samples 4–6 have lower viscosity than samples 7–9, which is associated with a higher content of gelling agent. However, their stickiness is uncomfortable, and therefore for further studies, hydrogel samples containing 1.5 % Aristoflex AVC were selected. Sample 5 exhibited slightly higher viscosity compared to samples 4 and 6, apparently due to the presence of Thienoflogin dispersion in Olive oil and an additional stabilizing agent, Polysorbate 80. Experimental samples 4–6 showed good consumer properties: they spread evenly on the skin surface and did not leave marks on clothing. These results allow for continued investigation of the obtained samples with respect to active pharmaceutical ingredient release and physicochemical stability during storage.

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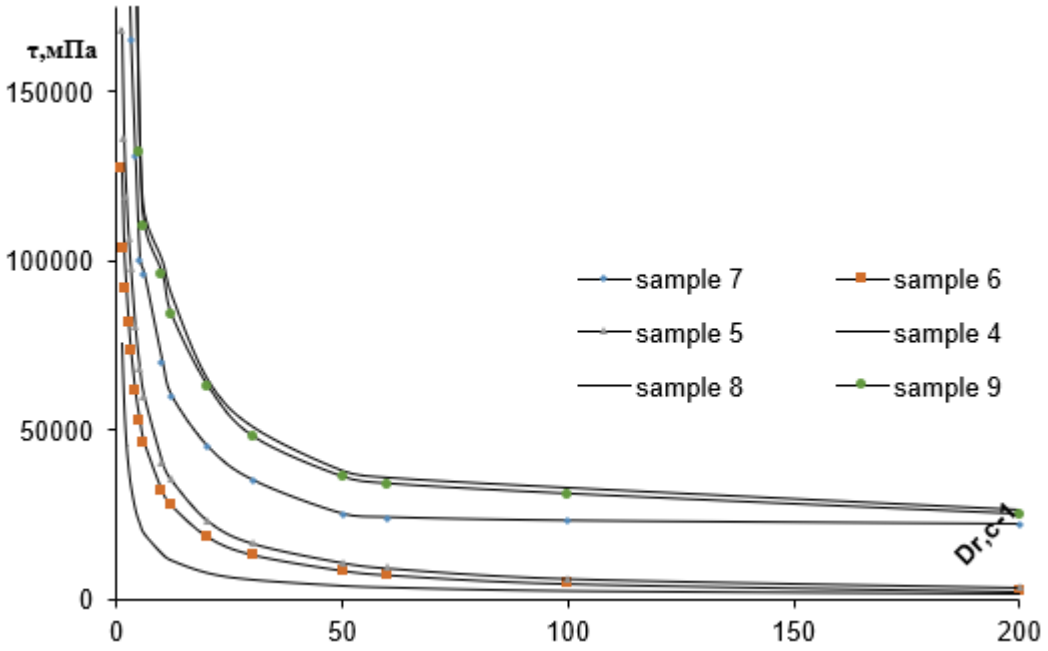

Fig. 1. Graphs of the dependence of dynamic viscosity on shear rate of the experimental samples (n=5, P=95 %)

Fig. 1 shows that dynamic viscosity decreases with increasing shear rate, indicating pseudoplastic behavior of the experimental samples and the disruption of the hydrogel's internal structure under applied stress.

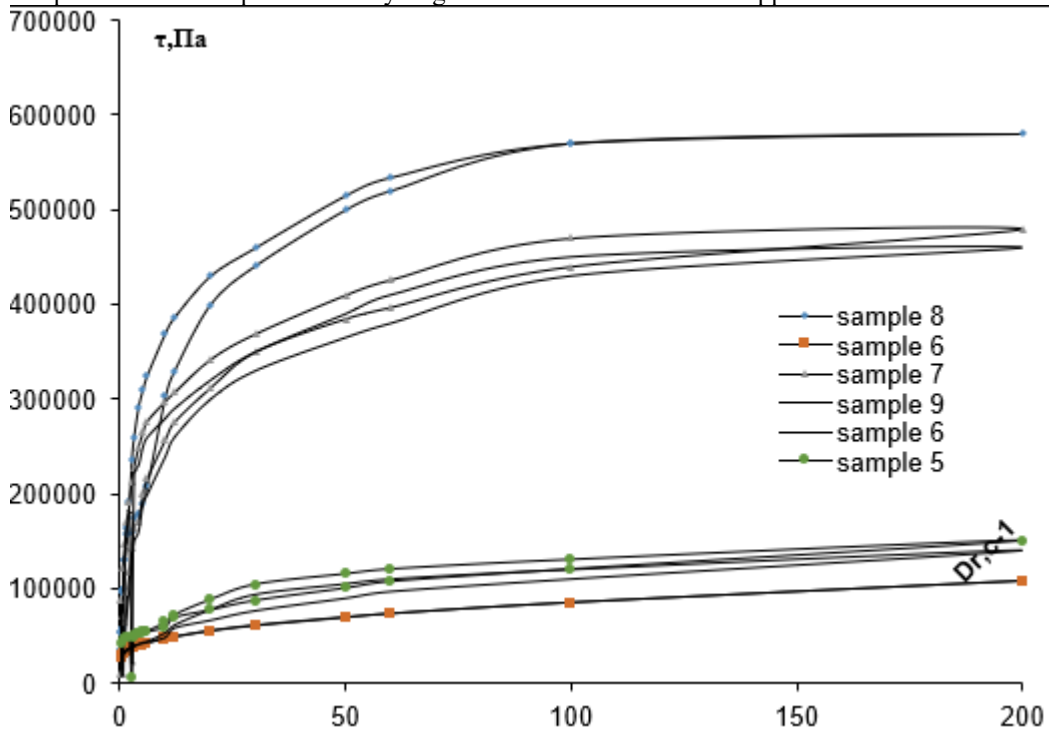

Fig. 2. Flow rheograms of experimental hydrogel samples 4–9 (n=5, P=95 %)

Conclusions

The organoleptic and rheological properties of hydrogels containing Thienoflogin were studied. It was established that the developed samples exhibit non-Newtonian flow behavior and moderate thixotropic properties.

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It was found that the Thienoflogin hydrogel based on the gelling agent Aristoflex AVC at a concentration of 1.5 % demonstrates satisfactory quality parameters and consumer characteristics.
Фінансування – відсутнє.
Подяки – відсутні.
Конфлікт інтересів – відсутній.

Pharmacotechnical and structural-mechanical characterization of hydrogels with thienoflogin
Natalya Rybak, Tetyana Kovalova
The aim of this study was to investigate the organoleptic, pharmacotechnical, and structural-mechanical properties of Thienoflogin-containing hydrogels, as well as the effect of excipients on their rheological characteristics. **Materials and Methods.** The objects of the study were experimental hydrogel samples with different concentrations of Aristoflex AVC, containing a dispersion of Thienoflogin in olive oil with the addition of polysorbate 80, and a dispersion of Thienoflogin in dimethyl sulfoxide. The appearance and homogeneity of the experimental samples were evaluated; colloidal stability and thermostability were assessed, and the pH of the model samples was measured. Based on measurements of structural and mechanical parameters (shear stress and dynamic viscosity), flow rheograms were constructed, and the dependence of structural viscosity on shear stress was investigated. **Results.** The rational combination of Thienoflogin with the gel formulation is supported by previous studies on release kinetics using the diffusion method across a semipermeable membrane. Hydrogels using excipients of different natures and properties were studied, and the optimal hydrogel composition with the best Thienoflogin release and its subsequent effective application was determined. The results of the research indicate that all experimental samples have homogeneous consistency, and their pH ranges from 5.4 to 6.1. The samples are thermostable and colloidally stable. Based on the study of the structural and mechanical properties of the experimental samples, graphs of the dependence of dynamic viscosity on shear rate were constructed. It was established that the dynamic viscosity decreases with increasing shear rate, indicating pseudoplastic behavior of the experimental samples and the disruption of the hydrogel's internal structure under applied stress. The presence of hysteresis loops on the flow rheograms indicates sufficient thixotropy of the studied samples, allowing the gel structure to gradually recover after disruption. Experimental samples were selected that showed good consumer properties: they spread evenly on the skin surface and did not leave marks on clothing. **Conclusions.** The organoleptic and rheological properties of hydrogels containing Thienoflogin were studied. It was established that the developed samples exhibit non-Newtonian flow behavior and moderate thixotropic properties. It was found that the Thienoflogin hydrogel based on the gelling agent Aristoflex AVC at a concentration of 1.5 % demonstrates satisfactory quality parameters and consumer characteristics.
Keywords: hydrogel, gelling agent, auxiliary substances, structural and mechanical properties, thixotropic properties.

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