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DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF PREPARATION OF A SUSPENSION WITH ADAPALENE FOR THE TREATMENT OF ACNE TAKING INTO ACCOUNT THE BIOPHARMACEUTICAL FACTORS

Marina Buryak, Liubov Bodnar, Natalia Shtuchna, Svitlana Oliinyk, Kateryna Semchenko, Liliia Vyshnevska

The aim *of the research is the development of the suspension with adapalene for use in the symptomatic block of complex acne therapy composition and technology of preparation.*
Materials and methods. *The objects of the study were suspension samples, which included active pharmaceutical ingredients (adapalene, hyaluronic acid, liquid aloe extract and zinc oxide), and purified water.*
Results*. Hyaluronic acid was determined as the optimal stabilizer and its concentration was selected using the resuspension method, at which the suspension is a stable system. It was established that the samples, which include adapalene, zinc oxide, liquid aloe extract, hyaluronic acid and purified water, have satisfactory physical and chemical properties.*
Conducted rheological studies showed that due to the potentiation of associative thickening, optimal rheological indicators of the suspension, which affect both the extrusion and consumption properties of the developed suspension, were obtained.
The quantitative content of adapalene in the developed suspension was confirmed by the method of alkalimetry. The completeness and speed of release of adapalene from the suspension was confirmed by the method of dialysis through a semipermeable membrane.
Conclusions*. An extemporaneous suspension, based on adapalene, zinc oxide and liquid aloe extract, with the addition of a stabilizer – hyaluronic acid, was developed. The proposed suspension has satisfying consumer, physical and chemical properties, and meets the quality requirements established for suspensions*
Keywords*: suspension, adapalene, hyaluronic acid, liquid aloe extract, zinc oxide, composition, technology of preparation, acne*

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1. Introduction

Acne is one of the most common dermatological diseases in children, adolescents, and young adults, which not only causes pain, cosmetic defects, and a decrease in the quality of life, but can also lead to the development of depression and suicidal behavior [1]. This is a skin disease caused by inflammation of the sebaceous glands. It usually manifests itself in the form of pimples, blackheads, comedones, and scars. Modern acne therapy is strictly regulated: the most widespread are the international guidelines of the American Academy of Dermatology (AAD) [2], the National Institute for Health and Care Excellence (NICE) [3], as well as domestic standards, but the tendency to a long course and recurrence (sometimes insufficient effectiveness of standard therapy) justifies the search for ways to increase the effectiveness of treatment. Therefore, the issue of acne treatment remains relevant [1].

In 2021, experts from the National Institute for Health and Care Excellence in the United Kingdom published a guideline on the treatment of acne in primary and specialist care settings. This document reviews in detail aspects of topical and systemic pharmacotherapy, including the use of antibacterial agents and retinoids. Particular attention is paid to third-generation retinoids, in particular adapalene, which is recommended for its long-term pharmacological effect [4]. Adapalene is a chemically stable, retinoid-like compound. Studies of the biochemical and pharmacological profile of adapalene have shown that it is a modulator of the processes of cellular differentiation, keratinization and inflammation, which are involved in the development of various pathological skin conditions. It has a rapid and potent anti-inflammatory and anti-comedogenic effect. It penetrates deep into the pores, cleanses them and prevents the formation of new acne. Adapalene quickly heals wounds and restores the skin's natural texture and tone. Adapalene is stable to light and oxygen. Light stability means that it will not lose its effectiveness when exposed to sunlight [5].

Zinc oxide was introduced into the composition of the suspension for the treatment of acne due to its anti-inflammatory and antioxidant effects, which promotes skin regeneration and wound healing. Zinc also regulates the work of the sebaceous glands, which reduces the risk of new rashes [6].

To enhance the anti-inflammatory, antibacterial and antioxidant effect, liquid aloe extract was introduced into the composition of the drug under development [7].

Hyaluronic acid plays a key role in the treatment of acne due to its multifaceted properties: it effectively retains moisture, providing the necessary level of skin hydration; has an anti-inflammatory effect, which helps reduce redness and swelling characteristic of acne; stimulates rapid cell regeneration, restoration of damaged skin areas and reduces the likelihood of scarring. In combination with retinoids, its effectiveness increases markedly, improving the results of therapy [8].

On the pharmaceutical market of Ukraine there are 4 prescription drugs with adapalene ("Effezel", "Effezel forte", "Deriva water gel", "Deriva C", "Belacne duo"), which are used to treat acne vulgaris with comedones, papules and pustules. These medicines of foreign production (France, India, Croatia) are limited in the range of dosage forms and are produced only in the form of gels. Taking into account the lack of drugs with adapalene of domestic production on the pharmaceutical market, this segment of medicines is not available to the general population of Ukraine due to their high cost (from 458.30 to 679.40 UAH, gel "Deriva C" 15.0 g, from 602.80 to 758.90 UAH, gel "Belacne duo" 15.0 g, from 1,738.17 to 2,006.80 UAH, gel "Effezel forte" 30.0 g) [9].

The range of cosmetics containing adapalene is also represented by foreign-made products (mainly India) in the form of gels ("Eleneon-A acne gel with 0.1 % adapalene", "Perolight-A acne gel with benzoyl peroxide and adapalene", "Eleklin-A acne gel with clindamycin and adapalene"), which are recommended to reduce acne (acne vulgaris) and promote rapid acne healing [9].

On the EU pharmaceutical market, the entire range of drugs with adapalene belongs to prescription type ("Adapalene/Benzoyl peroxide 0.1 %/ 2.5 % gel", "Differin cream", "Differin gel", "Epiduo 0.1 %/2.5 % gel") and is presented in the form of creams, gels or lotions for external use. The cost of Adapalene gel 0.3 % for external use is about 77 US dollars per 45.0 g, depending on the pharmacy. However the cost of Differin cream 0.1 %, which is most often prescribed by doctors, is about USD 567 for 45.0 g [10].

Therefore, the creation of new dosage forms for external use, including in a pharmacy, which includes adapalene, can have significant advantages, not only therapeutic, but also financial, due to the reduction of development costs and risks.

The value of the suspension as a dosage form lies in the fact that water-insoluble medicinal substances introduced into their composition have a higher degree of dispersion than in the smallest powders, and therefore show their therapeutic effect faster and more fully. When the substance is crushed, the surface area increases, therefore, the area of contact with the surface of tissues and organs also increases. By changing the size of the particles of the medicinal substance contained in the suspension, it is possible to obtain long-acting drugs. And the use of corrective substances allows you to improve the consumer properties of the drug: to mask the unpleasant taste and smell. In addition, the enveloping effect of a number of medicinal substances is most fully manifested when they are used in the form of suspensions. The advantages of suspensions also include the possibility of simultaneous use of both soluble and insoluble medicinal substances in this medium [11, 12].

According to the results of the analysis of the assortment of the EU pharmaceutical market, it was determined that the drug "Differin" is presented in 3 dosage forms - cream, gel and lotion for external use. The safety and efficacy of daily use of "Differin" gel for the treatment of acne vulgaris were evaluated in one 12-week multicenter controlled clinical study, conducted with a total of 653 people aged 12 to 52 years with mild to moderate acne vulgaris. The main results of the clinical study of the effectiveness of the use of "Differin" gel at the 12th week were 21 % (IGA Success Rate) [13].

A similar study was conducted with "Differin" lotion, applied once daily for the treatment of acne vulgaris. Results were evaluated in two 12-week, multicenter, controlled clinical trials of similar design, comparing "Differin" lotion to vehicle lotion in patients with acne. In Study 1, 1,075 subjects were randomized to "Differin" lotion or vehicle. The mean age of these subjects was 16.7 years, and 53.1 % were female. At baseline, subjects had 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. Most subjects (91.0 %) had a baseline IGA score of "Moderate." The primary efficacy outcome of the clinical trial at week 12 was 26.3 % (IGA Success Rate). Therefore, the liquid dosage form ("Differin" lotion) compared to the soft dosage form ("Differin" gel) was found to be more effective according to clinical studies [13].

Given the results of the above clinical studies, ease of use, uniform distribution of the active substance throughout the volume of the drug, the possibility of introducing both water-soluble and water-insoluble active pharmaceutical ingredients (API) or excipients into the composition, a suspension was chosen as the dosage form. In addition, the manufacture of adapalene suspension in pharmacy production conditions will significantly reduce the cost of the finished product on the pharmaceutical market and make it available to all segments of the population.

The aim of the study. Development of the composition and technology for manufacturing adapalene suspension for use in the symptomatic block of complex acne therapy.

2. Research planning (methodology)

Planning an experiment is an integral part of the statistical component of research. The implementation of the planned experiment was carried out according to the developed scheme. Conducting research on the development of the suspension composition can be divided into three stages. At the first stage, the selection of excipients was carried out, at the second - the optimal parameters of the technological process were established, at the third - the quality control of the studied samples was carried out (Fig. 1). The second and third stages are characterized by the parallel conduct of certain studies [14].

Thus, it is planned to establish the dependence of the output data on the input variables and establish the advantage of one of the quality variables. According to the experimental scheme, the input qualitative variables were the substances used to stabilize the suspensions, and the quantitative ones were the concentrations of stabilizers. The constant input data are the active pharmaceutical ingredient (API), other excipients and their concentrations [14].

The predicted impact of the qualitative and quantitative input variables on the main quality indicators of the suspensions is shown in Fig. 2.

The reliability of the predicted data (n=3) using the example of the influence of quantitative input variables was established using regression analysis (Fig. 3).

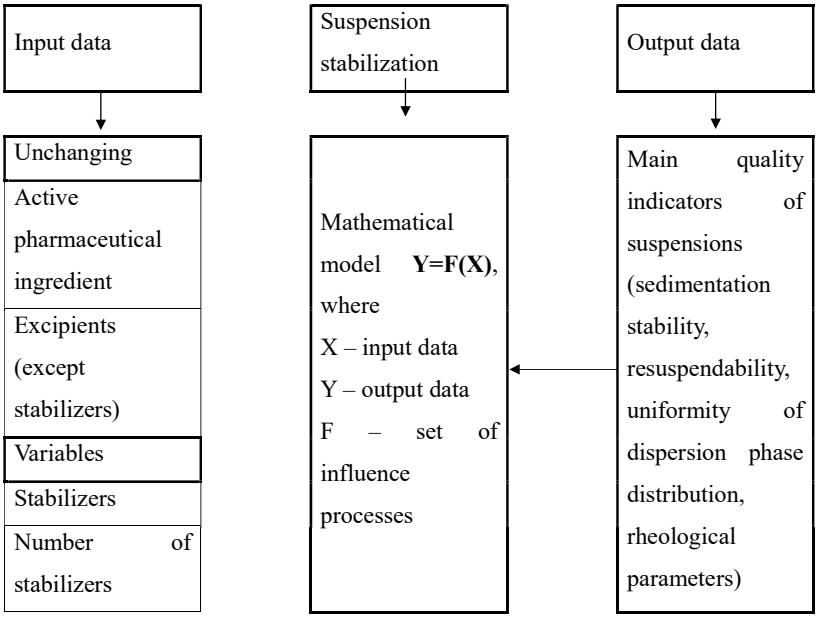


Fig. 1 Mathematical model of the planned experiment

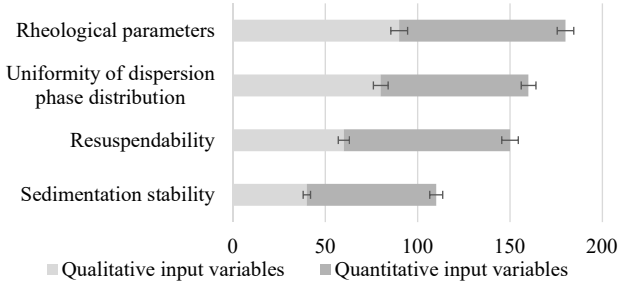


Fig. 2. Forecasting the impact of input variables on output data, %

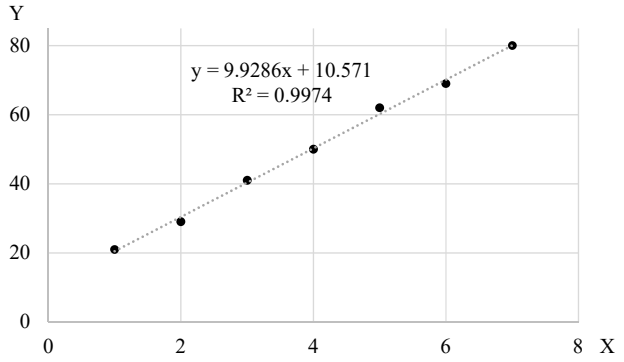


Fig. 3. Linear regression equation of the planned experiment

The obtained level of approximation (R^2=0.9974) indicates the reliability of the data and the reproducibility of the planned experiment.

3. Materials and methods

The object of the study were samples of extemporaneous suspension with adapalene (CAS N 106685-40-9) and zinc oxide (CAS N1314-13-2), liquid aloe extract, prepared by dispersion method using various stabilizers. Sedimentation stability and resuspendability were studied for all suspension samples. Microscopic analysis was performed to determine the particle size and homogeneity of the dispersed phase distribution.

To prepare samples of aqueous suspensions with adapalene, the most used stabilizers in the pharmaceutical industry were employed: hyaluronic acid (CAS No. 9067-32-7), carbopol (Carbopol 940, Synthalen K) (SPhU 1.1, p. 215), and propylene glycol (SPhU 2.0, Vol. 2, p. 563; CAS No. 57-55-6) at various concentrations. The concentration of stabilizers was selected based on literature data [15, 16]. Solutions of hyaluronic acid, carbopol, and propylene glycol were prepared separately in different concentrations and added to the suspension with a mass fraction of adapalene of 0.1 % [5, 8].

The stability of the proposed suspension samples with stabilizers was determined by a known method [17].

Description (SPhU 2.0, p. 2.2.2). The appearance and colour were determined by examining a drop of suspension applied to a glass slide or a sheet of white paper [18].

Determination of resuspendability. Containers with suspension samples with different stabilizers and different storage periods were shaken and the number of shakings required to restore the homogeneity of the suspension was counted. If the stability of the suspensions is impaired, they should reproduce a uniform distribution of particles throughout the volume after 24 h of storage when shaken for 15–20 seconds, after 3 days of storage – for 40–60 seconds.

Determination of aggregative stability. The aggregative stability of the developed suspension samples with stabilizers was determined according to the standard method [17]. 50 cm^3 of the suspension was poured into cylinders with a ground cork, tightly corked and their contents were thoroughly mixed for 5 min (by shaking). Then the cylinders were lined up and left alone. After certain time intervals (t), the volumes (V) of sedimentation sediments were measured until they stopped changing.

Excipients: purified water, hyaluronic acid, propylene glycol, carbopol – viscosity regulators.

The particle size of the suspension samples was determined using a Granum laboratory microscope with a Toupcam UCMOS video camera. Magnification – ×10. Software for obtaining microphotographs – ToupView 4.10 from ToupTek.

The pH was determined potentiometrically using a pH-150 MI pH meter [18].

The study of rheological parameters was carried out according to the standard pharmacopoeial method on a rotational viscometer with coaxial cylinders Reotest-2 at temperatures of 20±2 °C and 37±2 °C [15].

Identification of adapalene. Method of identification of the substance: 0.1 g of the adapalene substance is placed in a test tube and dissolved in 5 ml of 96 % ethanol, 5–6 drops of concentrated sodium hydroxide solution are added, and the release of carbon dioxide bubbles is observed.

Transferring the method to the identification of adapalene in a dosage form: 10.0 g of the suspension is mixed with 10 ml of 96 % ethanol, filtered into a test tube using a piece of long-fiber cotton wool moistened with purified water, 0.5–1 ml of concentrated sodium hydroxide solution is added, and the release of carbon dioxide bubbles is observed. Since the amount of adapalene in the test sample is smaller, compared to the previously described method, the reaction is less violent, but it certainly has a visual effect [19].

Quantitative determination of adapalene. Before quantitative determination of adapalene in dosage form, it is advisable to develop and validate the method directly for the substance.

Method: 0.1000 g of the substance (accurate weight) is placed in a 50 ml volumetric flask, dissolved in 10 ml of 96 % ethanol, made up to the mark with purified water, mixed, and the resulting solution is transferred to a 100 ml conical flask, which is more convenient for titration. Titrate with 0.1 M sodium hydroxide solution, using phenolphthalein as an indicator. The end point of the titration is recorded by the colour of the solution in a pale pink colour [19].

The content of adapalene in the substance (C, %) in terms of dry matter is calculated by the formula (1):

$$C, \% = \frac{V_{\text{NaOH}} \cdot T \cdot K \cdot 100 \cdot 100}{m_S * \left(100 - \%_{weig.}\right)}, \quad (1)$$

where V_{NaOH} – volume of 0.1 M sodium hydroxide solution used for titration, ml;

T – titrant titer for the test substance (0.04125 g/ml);

K – correction factor of 0.1 M sodium hydroxide solution (1.0000);

m_s – mass of adapalene substance sample, g;

$\%_{weig.}$ – weight loss during drying of adapalene substance (0.1 %).

Transfer of the method to the quantitative determination of adapalene in a dosage form: 10.0 g of the suspension is mixed with 10 ml of 96 % ethanol, filtered into a 50 ml volumetric flask, filtered into a test tube using a piece of long-fiber cotton wool moistened with purified water, the volume is brought to the mark with purified water, the resulting solution is transferred to a 100 ml conical flask, which is more convenient for titration. Titrate with 0.1 M sodium hydroxide solution, using phenolphthalein as an indicator. The end point of the titration is fixed by the colour of the solution in a pale pink colour. In parallel, a control experiment is carried out [19].

The content of adapalene in the suspension (X, g) in terms of dry matter is calculated by the formula (2):

$$X, \text{g} = \frac{\left(V_{\text{NaOH}_{m.e.}} - V_{\text{NaOH}_{c.e.}}\right) \cdot T \cdot K \cdot 100}{m_S * \left(100 - \%_{weig.}\right)}, \quad (2)$$

where $V_{\text{NaOH}_{m.e.}}$ – volume of 0.1 M sodium hydroxide solution used for titration in the main experiment, ml;

$V_{\text{NaOH}_{c.e.}}$ – volume of 0.1 M sodium hydroxide solution used for titration in the control experiment, ml;

T – titer of the titrant for the test substance (0.04125 g/ml);

K – correction factor of 0.1 M sodium hydroxide solution (1.0000);

m_s – mass of adapalene suspension sample, g;

$\%_{weig.}$ – weight loss during drying of adapalene substance (0.1 %).

The rate and completeness of adapalene release from the dosage form was determined by dialysis through a semipermeable membrane. The kinetic properties of the suspension were studied using a dialysis film made of cellulose derivatives with a pore size of 45 μm at a temperature of (37±0.5) °C. Considering the solubility of adapalene, 96 % ethanol was chosen as the dialysis medium. Sampling with subsequent renewal of the sampled volume was carried out every half hour for 8 h [11].

Statistical processing of the conducted studies was carried out according to the requirements of the SPhU [18]. Software: Excel 2021, StatisticKingdom.

4. Research results

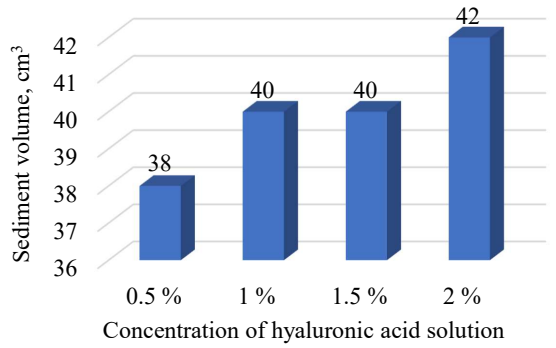
Considering that the main task in developing the composition and technology of the suspension is to ensure stability, which is achieved by stabilizers and surfactants, the selection of excipients was the first stage of research. For evaluation, the aggregative and sedimentation stability of the suspension, as well as its resuspendability were studied [11].

According to the experimental data obtained, diagrams were constructed (Fig. 4), which allowed us to clearly compare the stability of stabilized suspensions for three days.

Based on the results obtained (Fig. 4), for further stability studies, stabilizers were selected in concentrations that provided the greatest stability of suspension samples, namely: hyaluronic acid – 2.0 %, carbopol – 2.0 %, propylene glycol – 2 %. To construct kinetic sedimentation curves $V=f(t)$, the average values of five stability measurements of stabilized suspensions were taken (Fig. 5).

As can be seen from Fig. 5, the suspension samples stabilized with a propylene glycol solution formed sediments with a volume of up to 38 cm^3 within 24 hours. In the suspensions stabilized with hyaluronic acid and carbopol, insignificant changes in the suspension volume were observed only after 3 days – 48 and 43 cm^3, respectively.

However, during further storage, in the samples stabilized with carbopol and propylene glycol for 14 days, the destruction of the system was observed with the formation of a white sediment or a dense gel mass (Table 1).



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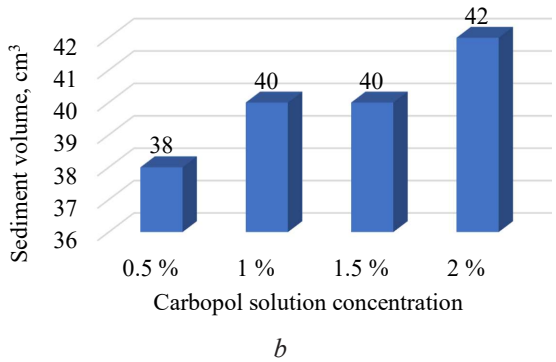

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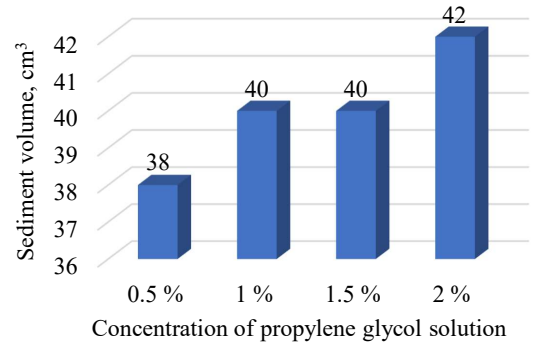


c

Fig. 4. Stability of the suspension after 3 days with stabilizers: *a* – hyaluronic acid; *b* – carbopol; *c* – propylene glycol

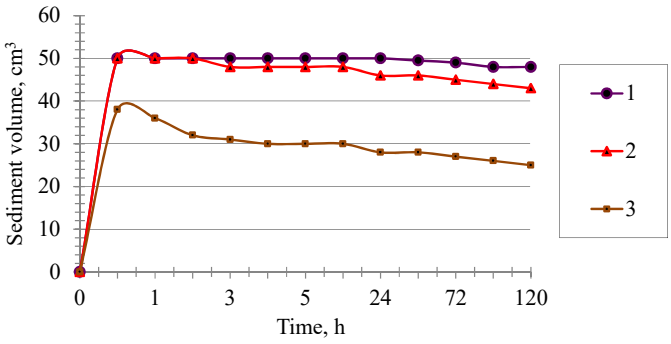


Fig. 5. Kinetic sedimentation curves of adapalene suspension samples with stabilizers: 1 – hyaluronic acid; 2 – carbopol; 3 – propylene glycol

To fully assess the stability of the developed suspension samples, we also studied their resuspendability. Resuspendability is the ability of a suspension with a precipitate after gentle shaking to form a system with a solid dispersed phase evenly distributed throughout the entire volume of the dispersion medium. In a well-resuspended suspension, the solid phase easily returns to its original state, while in a non-resuspended suspension, irreversible changes do not allow the solid phase to be evenly distributed throughout the entire volume of the liquid [12].

Table 1

Appearance of stabilized adapalene suspension samples during storage

Stabilizer	Observation period, days			
	1	7	14	30
Hyaluronic acid	The suspension is homogeneous after shaking			
Carbopol	The suspension is homogeneous after shaking		Formation of a dense gel precipitate	
Propylene glycol	The suspension is homogeneous after shaking		Formation of a dense gel precipitate	

For suspensions, resuspendability is an important characteristic that determines, along with aggregation stability, the possibility of its correct dosage. If a poorly resuspended precipitate forms in the suspension during the storage period, then such a suspension cannot be manufactured.

Traditionally, the resuspendability index of suspensions is estimated by the method according to which the number of shakings of the container with the suspension is determined, which is necessary to return it to its original state with a uniformly distributed solid dispersed phase (shaking is carried out manually). Although this method is not quantitative for determining the strength of the precipitate, it is most often used in pharmaceutical practice, because it sufficiently characterizes the suitability of suspensions for use as a finished drug.

For the convenience of classifying suspensions according to their ability to resuspend and for comparison by this indicator, all suspensions are conventionally divided into four groups. The first group includes easily resuspended suspensions that easily return to their original state with a uniform distribution of the solid phase, having performed less than five shaking. The second group includes suspensions that require from six to ten shaking for this. The third group includes those that require from eleven to two hundred shaking. Finally, the fourth group consists of suspensions that are practically not amenable to resuspension, that is, more than two hundred shaking [12].

In pharmaceutical practice, only suspensions of the 1st and 2nd groups can be used; suspensions of the 3rd and 4th groups have insufficient ability to resuspend, therefore they are unsuitable for practical use.

The number of shakings required for resuspension of suspensions after different storage periods was determined in suspensions with a mass fraction of adapalene of 0.1 % without stabilizer and with the addition of hyaluronic acid (Table 2).

As can be seen from the experimental data (Table 2), samples of unstabilized suspension deteriorate their resuspendability during storage. This indicates that the formed precipitate gradually hardens due to the for-

mation of a dense structure. Based on the data in the table, a sample of suspension stabilized with hyaluronic acid can be attributed to easily resuspended suspensions.

Table 2

Comparative characteristics of resuspension of the studied samples of suspensions with adapalene

Research object	Stabilizer concentration (*w*), %	Shelf life, days								
		1	2	3	4	5	6	7	14	30
Suspension without stabilizer	–	1	2	3	3	3	3	3	3	3
Hyaluronic acid suspension	2 %	1	2	2	2	2	2	2	2	2

Note: 1 – first group; 2 – second group; 3 – third group.

The determination of the physicochemical parameters of the suspension sample was carried out according to the well-known SPhU methods (Table 3).

Table 3

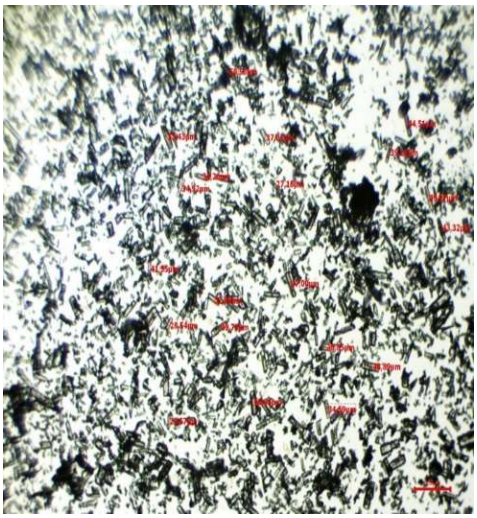
Physicochemical parameters of the suspension sample

No.	Sample	Density (g/cm^3)	Relative viscosity	Surface tension ($\times 10^{-3}$ N/m)	pH
1	Adapalene suspension	1.0056±0.0015	1.23±0.05	64.6±0.2	4.82±0.03

To determine the stability index of the suspension, we investigated the particle size of adapalene before grinding, after grinding in dry form and after grinding with a dispersion medium according to the Deryagin rule [20]. Grinding was carried out by grinding adapalene in a mortar. The results of the studies are shown in Fig. 6.

As can be seen from the results of the study (Fig. 6), the size of adapalene particles varies from 50 (sample a) to 2 (sample c) microns.

To establish the type of flow and determine the thixotropic properties, rheograms of the studied suspensions with selected active and auxiliary substances were constructed, in particular: sample No. 1 – adapalene+zinc oxide with water (base); sample No. 2 – base+hyaluronic acid, sample No. 3 – base+aloe extract, sample No. 4 – base+hyaluronic acid+aloe extract (Fig. 7). The determination was carried out by increasing the spindle rotation speed from 20 to 100 rpm and the subsequent decrease in the number of revolutions. During rheological studies, it was determined that all samples had a structured system and a pseudoplastic type of flow. It was noted that all samples had certain thixotropic properties, which ensure the presence of satisfactory extrusion properties of the developed product. It should be noted that the obtained parameters of the developed product were achieved primarily due to the potentiation of associative thickening and potentiation. It is known that during associative thickening, a gradual increase in these indicators occurs. In our case, optimal rheological indicators were obtained, which affected both the extrusion and consumer properties of the developed suspension [21]. Taking into account the results of the study, the optimal composition of the suspension was justified, which is given in Table 4.



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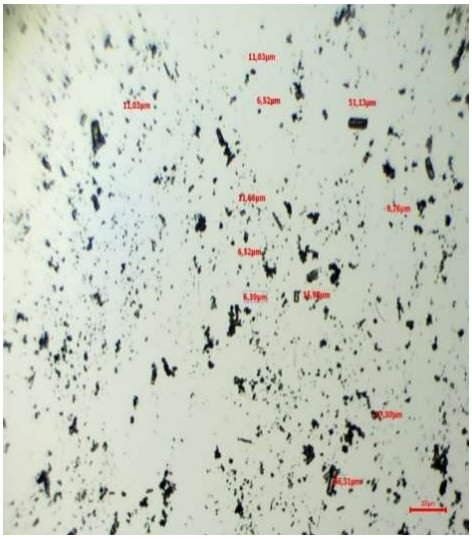

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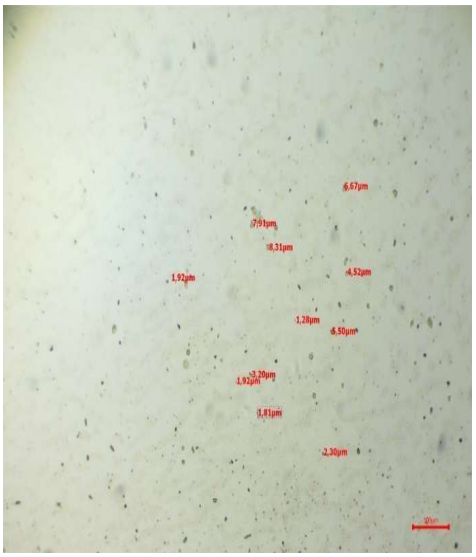

c

Fig. 6. Microscopy of adapalene powder: *a* – without grinding; *b* – after grinding; *c* – after grinding with water purified according to Deryagin's rule

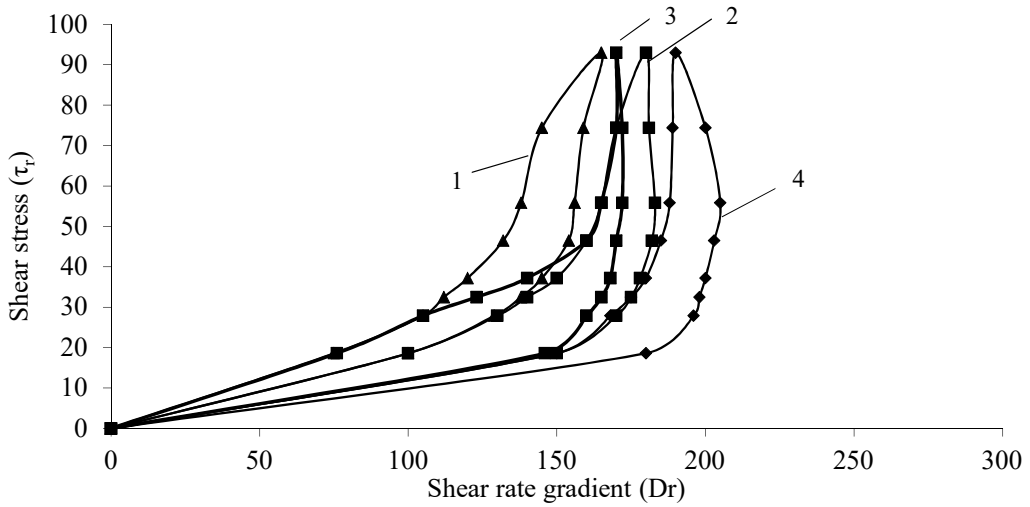

Fig. 7. Sample No. 1 (adapalene with zinc oxide and water (base)); sample No. 2 – base with hyaluronic acid; sample No. 3 – base with aloe extract; sample No. 4 – base with hyaluronic acid and aloe extract

Further work consisted in the selection and adaptation of methods for identification and quantitative determination of adapalene in the composition of the developed suspension.

Table 4

Composition and purpose of the components of the developed suspension

Component	Quantity, g	The aim
Adapalene	0.1	API
Zinc oxide	10.0	API
Hyaluronic acid	2.0	API, viscosity regulator, stabilizer
Aloe extract liquid	10.0	API
Purified water	up to 100.0	Excipient; solvent, aqueous phase

According to the data given in the European Pharmacopoeia, the identification of adapalene is carried out by infrared spectrophotometry by comparing the obtained spectrum with the spectrum of a standard pharmacopoeial sample, the quantitative determination of the substance is carried out by liquid chromatography [22]. The proposed methods are modern and effective, however, for the identification and quantitative determination of adapalene in pharmacy conditions, the search for alternative, more economically accessible methods are relevant [11].

Adapalene (6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid) is a derivative of naphthoic acid in its chemical structure (Fig. 8).

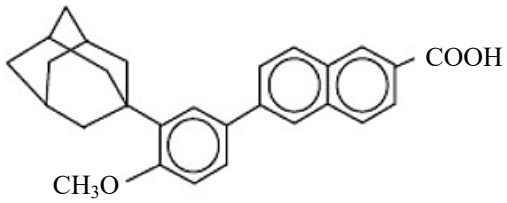

Fig. 8. Adapalene

Given the presence of a carboxyl group in the adapalene molecule, the substance can be identified by reaction with sodium hydroxide, and quantitative determination should be carried out by acid-base titration (alkalimetry) [22]. To confirm the reproducibility of the method, adapalene was quantitatively determined in the substance in the range from 80 to 120 % of the nominal weight and the results were statistically processed (Table 5).

Table 5

Metrological characteristics of alkalimetric titration of adapalene, (n=3, P=95 %)

No.	m_s, g	V_{NaOH}, ml	$C_{adapalene}$, %	Statistical data	
1	0.0801± ±0.0002	1.95±0.05	101.18± ±2.59	$\overline{x}$	101.184± ±2.11
2	0.0901± ±0.0003	2.20±0.05	100.82± ±2.29	S^2	0.091
3	0.1002± ±0.0002	2.45±0.05	100.96± ±2.06	$t_{critical}$	2.78
4	0.1098± ±0.0004	2.70±0.05	101.54± ±1.87	t_{actual}	1.97
5	0.1201± ±0.0003	2.95±0.05	101.42± ±1.72	$\overline{\varepsilon}$, %	0.263

The metrological characteristics of the obtained results indicate the reproducibility of the method, so alkalimetry can be used for the quantitative determination of adapalene.

The content of adapalene in 10.0 g of suspension should be 0.01 g, the permissible deviation is ±20 % [19]. In the studied suspension, the quantitative content of adapalene is 0.0103±0.0008 g, which indicates compliance with the established requirements.

To establish the speed and completeness of the release of adapalene from the developed suspension, the dialysis method was used through a semipermeable membrane. The study was carried out for 8 hours. The quantitative determination of adapalene in the selected dialysate was carried out using the developed alkalimetric method [11, 19].

According to the results of the study, a graph was constructed showing the dependence of the amount of

adapalene in the dialysate (C, %) on the time the suspension was in the experimental environment (Fig. 9).

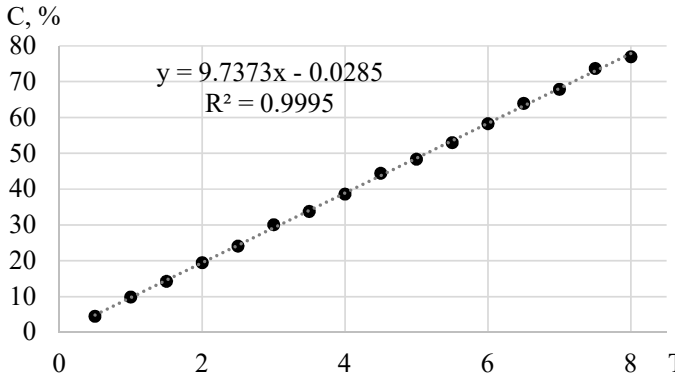

Fig. 9. Dynamics of adapalene release from the developed suspension

The obtained data indicate a gradual release of the active substance from the suspension and the content of adapalene in the dialysate at the level of 76.97 % after 8 hours.

5. Discussion of research result

The obtained results indicate the ability of all selected stabilizers (hyaluronic acid, carbopol, propylene glycol) at a concentration of 2 % to provide the greatest stability of suspension samples with adapalene, however, suspension samples stabilized with a propylene glycol solution formed precipitates within a day, and in suspension samples stabilized with carbopol and propylene glycol, destruction of the system with the formation of a white precipitate or dense gel mass was observed within 14 days. Therefore, the choice of stabilizer was confirmed by additional study of the resuspendability of the suspension with adapalene stabilized with 2 % hyaluronic acid. The results of the studies indicate the ability of the sample stabilized with hyaluronic acid with a precipitate after light shaking to form a system with a solid dispersed phase evenly distributed throughout the volume of the dispersion medium, and therefore its belonging to easily resuspended suspensions. The obtained results correlate with the literature data on the classification of suspensions according to their ability to resuspend and the determination of the resuspension index. This allows us to conclude that it is possible to obtain a stable suspension using hyaluronic acid [12].

According to the results of rheological studies of suspension samples with selected active and auxiliary substances, it was determined that all samples had a structured system and a pseudoplastic type of flow. In addition, the studied suspension samples had certain thixotropic properties, which were achieved due to the potentiation of associative thickening and potentiation and provide satisfactory extrusion properties of the developed product. The obtained data correlate with the literature data on the influence of body temperature on the properties of the dosage form and confirm the stability during external use [21].

Thus, the composition of the extemporaneous suspension for the treatment of acne was experimentally substantiated: adapalene 0.1 (API), zinc oxide 10.0 (API), hyaluronic acid 2.0 (API, stabilizer), aloe extract liquid 10.0 (API) and water purified to 100.0 (solvent).

The main physicochemical quality indicators of the developed suspension with adapalene were determined: density, relative viscosity, surface tension and pH. According to data published in the European Pharmacopoeia, the identification of the adapalene substance is carried out by infrared spectrophotometry, and quantitative determination is carried out by liquid chromatography [22]. However, the qualitative reaction with sodium hydroxide and quantitative determination by acid-base titration were determined as alternative and more economically accessible methods for identifying adapalene in the developed suspension in pharmacy conditions. The quantitative content of adapalene in 10.0 g of extemporaneous suspension is 0.0103±0.0008 g.

The method of dialysis through a semipermeable membrane determined the gradual release of API adapalene from the developed suspension (76.97 % after 8 hours). The obtained data correlate with the literature data on the rate and completeness of the release of the substance depending on the type of the selected dosage form, since the rate of release of active substances in vitro is influenced by the solubility of the substance, its particle size, rheological properties and solubility in the dialysis medium into which the substance is released [11]. The developed extemporaneous suspension with adapalene is a stable system, has satisfactory physicochemical, rheological and consumer characteristics, is convenient for use and meets the established requirements in terms of the quantitative content of adapalene.

Practical significance. The conducted research will contribute to the development and expansion of the range of extemporaneous medicines in Ukraine, as well as the introduction into production of liquid dosage forms with adapalene in the form of a suspension for complex acne therapy.

Study limitations. The planned study was fully implemented, the results obtained are predictable and reproducible. The selected methods in the planned study have no limitations. However, we will conduct additional studies related to the study of the shelf life of the developed suspension and the choice of primary packaging.

Prospects for further research. At the next stages of research, it would be advisable to study the *in vitro* biopharmaceutical profile for the developed suspension.

6. Conclusions

The composition of the suspension for the treatment of acne was developed: adapalene 0.1, zinc oxide 10.0, hyaluronic acid 2.0, aloe extract liquid 10.0 and water purified to 100.0. According to the results of studying the resuspendability index of the suspension, it was determined that the sample stabilized with hyaluronic acid at a concentration of 1.5 % belongs to easily resuspended suspensions, which characterizes the possibility of correct dosage of the dosage form. By microscopy, it

was established that depending on grinding in dry form and with the addition of an auxiliary liquid, the size of adapalene particles varies from 50 to 2 microns. According to the results of structural and mechanical studies, due to the potentiation of associative thickening and potentiation, optimal rheological indicators of all studied samples were obtained, which affect both the extrusion and consumer properties of the developed suspension. Methods for identifying and quantitatively determining adapalene in the composition of the developed suspension under the conditions of pharmacy production were adapted. The substance can be identified by reaction with sodium hydroxide, and quantitative determination is advisable to carry out by acid-base titration. By dialysis through a semipermeable membrane in a dialysis medium of ethanol 96 %, the gradual release of adapalene from the suspension was determined after 8 hours, the content was 76.97 %. The resulting suspension has satisfactory physicochemical and consumer characteristics, rheological properties, pH, stability and is convenient for use.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship, or other, that could influence the study and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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