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DEVELOPMENT AND VALIDATION OF METHODS OF ANALYSIS OF ACTIVE SUBSTANCES IN EMULGEL WITH THICK EXTRACT OF TANACETUM PARTHENIUM

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Introduction

It is known that inflammatory diseases of the muscular and skeletal systems are one of the most common pathologies affecting bones, joints, muscles, and connective tissue. These disorders can lead to loss of working capacity, deterioration of the quality of life, and disability [1]. Today, for the treatment of the above-mentioned pathology, soft drugs containing active pharmaceutical ingredients of the NSAIDs group are used. These drugs are not recommended to be used for more than 14 days because with long-term use on large areas of the skin, they can cause systemic side effects [2]. Herbal preparations are practically devoid of these disadvantages, can be used for a long time and do not cause addiction [3].

Therefore, the composition and technology of a soft medicinal product in the form of emulgel with a thick extract of the tanacetum parthenium (TETP) of the Asteraceae family was developed. Previous studies have confirmed its high content of phenolic substances of the hydroxycinnamic acid class, namely 3,5-dicaffeoylquinic, 4,5-dicaffeoylquinic and chlorogenic acids, sesquiterpene lactones. Among the flavonoids, the presence of apigenin-7-glucoside and kaempferol was discovered [4,5]. This range of biologically active substances provides high anti-inflammatory, antibacterial and analgesic effects. They were confirmed by pharmacological studies [6,7].

An important stage of pharmaceutical development is working out methods of quality control (MQC) of active substances in the composition of the drug being developed in order to create a MQC project. Analytical methods must correctly, accurately and with an acceptable level of reliability (95%) determine the composition of the medicinal product and control the quality and influence of various factors in the process of manufacturing the drug. Thus, the development of analytical methods, testing and evaluation of validation parameters is an important part of the life cycle of the drug.

The objective of this article is to develop methods for determining active pharmaceutical ingredients (APIs) in the emulgel composition. The planning of the study on standardizing the quality of the studied drug included the development of a test for the identification and methods of determining the quantitative content of API; validation studies of methods of quantitative determination in accordance with the requirements of the general article of SPhU (State Pharmacopoeia of Ukraine) 2.4, 5.3.N.2 "Validation of analytical methods and tests".

Materials and methods

Obtaining an emulgel. In the production of the emulgel, a thick extract tanacetum parthenium (TETP) was used, which is standardized according to the requirements of SPhU. First, the solution of TETP is carried out in a portion of purified water in a ratio of 1:20 while stirring at low revolutions (60 rpm) of the stirrer to prevent air from entering the solution, the phenylethyl alcohol is added.

100,0 g of a ready-made emulgel contain (in grams)

TETP	3,0 g
Sunflower oil	30,0 g
Sepiplus 400	4,0 g
Phenethyl alcohol	1,0 g
Purified water	up to 100,0

Identification of API in the emulgel for the presence of hydroxycinnamic acids. With the identification purpose, we selected and worked out the unified pharmacopoeial method [8] during the analysis of the studied finished dosage form. The research was carried out by the method of thin-layer chromatography (TLC).

Test solution. 2 g of emulgel was heated in a water bath with 30 ml of *methanol P* to precipitate the gelling agent. The resulting solution was filtered into a 50 ml volumetric flask, the filter was washed twice (10 ml each) with *methanol P,* the filtrate was cooled and brought up to the mark with the same solvent and mixed. An aliquot (1 ml) was placed in a round-bottomed flask and 10 ml of methanol P was added. It was filtered. Evaporated to a dry residue. The dry residue was dissolved in 2 ml of methanol P. A mixture of reagents was used as a mobile phase: *anhydrous formic acid P - purified water P - methyl ethyl ketone P - ethyl acetate P* (10:10:30:50). Detection was carried out after spraying with a solution of 10 g/l *aminoethyl ether of diphenylboronic acid P* in *methanol P* and 50 g/l *macrogol* 400 P in *methanol* P. Determination of the qualitative composition of hydroxycinnamic acids was carried out after 30 minutes by color in daylight and by their fluorescence in filtered UV - light at 365 nm. A solution of caffeic and chlorogenic acids was used as a comparison solution.

The study of the *quantitative* content of phenolic components in the emulgel was carried out according to the content of the amount of hydroxycinnamic acids and the amount of flavonoids. To assess the content of active substances in the emulgel, the method of spectrophotometry was chosen using the method of specific absorption index. The use of this method is based on the application of unified pharmacopoeial methods for determining the amount of basic biologically active

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substances in terms of a standard substance. The methods of analysis were developed and checked for correctness and reliability on the used samples of TETP, samples of the model mixture and experimental samples of the finished dosage form. To evaluate the validation characteristics, we used the limits of the amount of hydroxycinnamic acids converted to chlorogenic acid, from 0.27% to 0.33% and the amount of flavonoids, converted to hyperoside, from 0.025% to 0.035%.

Quantitative determination of the amount of hydroxycinnamic acids converted to chlorogenic acid. According to the method of SPhU "Nettles leaves" [9], the optical density of the tested solution was measured immediately at a wavelength of 525 nm, using a compensating solution as a comparison solution.

The starting solution. 2 g of emulgel was heated in a water bath with 30 ml of ethanol (50% v/v) P to precipitate the gelling agent, filtered into a 100 ml volumetric flask, the filter was washed twice (10 ml each) with ethanol (50% v/v) P, the filtrate cooled and brought to the mark with the same solvent and mixed.

Test solution. 2.0 ml of the original solution was placed in a 10 ml volumetric flask. Further research was carried out according to the methodology given in the monograph "The nettle leaves".

The content of the amount of hydroxycinnamic acids converted to chlorogenic acid (in percent) in the emulgel was calculated according to the formula:

$$x(\%) = \frac{A \cdot 1000}{m \cdot 188}$$

where: A is the optical density of the tested solution;

188 – specific index of absorption of chlorogenic acid;

m is the weight of the test sample in g.

Quantification of the amount of flavonoids converted to hyperoside. According to the method given in the monograph of the SPhU "Hawthorn leaves and flowers N", the optical density of the tested solution was measured 30 minutes after preparation at a wavelength of 410 nm [9].

Test solution. 2 g of emulgel was heated in a water bath with 30 ml of ethanol (70% v/v) P to precipitate the gelling agent, filtered into a 50 (100) ml volumetric flask, the filter was washed twice (10 ml each) with ethanol (70% v/v) P, the filtrate was cooled and brought to the mark with the same solvent and mixed. Further research was carried out according to the methodology described in the monograph "Hawthorn leaves and flowers N" [9].

The content of flavonoids converted to hyperoside in the emulgel was calculated as a percentage according to the formulas:

$$x(\%) = \frac{A \cdot 50 \cdot 25}{m \cdot 5 \cdot 405} = \frac{A \cdot 0{,}617}{m}$$

where: A is the optical density of the tested solution;

t is the weight of the test sample, in g;

405 – specific absorption rate of hyperoside;

Results and discussion

The main active component of the emulgel being developed is a thick extract of tanacetum parthenium, the content of biologically active substances of which is characterized by the presence of mainly hydroxycinnamic acids and flavonoids. Given the fact that hydroxycinnamic acids are one of the main chemical markers of tanacetum parthenium, it was decided to identify emulgel based on their presence [5]. Identification was carried out by the method of thin-layer chromatography on experimental samples of the dosage form. In the course of the study, the influence of the chromatography conditions on the final result was evaluated (the influence of the type of stationary phase, the saturation of the chamber, the application volume, the distance from the start line to the finish line, the influence of the developer, the stability of the application solutions). The obtained results were evaluated by comparing the R_f, obtained when applying the test solutions and reference solutions. When studying the reproducibility of the technique, R_f values were calculated for the caffeic and chlorogenic acid marker zones when tested on one TLC plate, on different plates and on different days, by different analysts. The metrological characteristics of R_f, values are equal for the zones of caffeic acid R_f, = 0.87±0.02, chlorogenic acid R_f, = 0.45±0.025.

Based on the results of the study, the most optimal conditions for TLC analysis were determined for the purpose of identifying marker substances of hydroxycinnamic acids. Fig. 1 shows the sequence of zones on the chromatograms of the comparison solution and the test solution. The chromatogram of the tested solution should show zonic acid and chlorogenic acid. In addition, other zones may also be detected on the chromatogram of the tested solution. During the validation studies of the method of quantitative determination of BAC (biologically active compounds) in the emulgel composition, the following metrological characteristics were checked: specificity, linearity, correctness, precision and intra-laboratory precision. Taking into account the regulated requirements for the content of the group of biologically active substances, and the peculiarities of spectrophotometric determination by the method of specific absorption index, the criteria were calculated acceptability of analytical methods. According to the requirements of SPhU 2.0.5.3.N.2 "Validation of analytical methods and tests" for quantitative determination, the maximum permissible total uncertainty of the analysis method is: $\max\Delta_{AS}$, % ≤ 0.32•10% = 3.2%.

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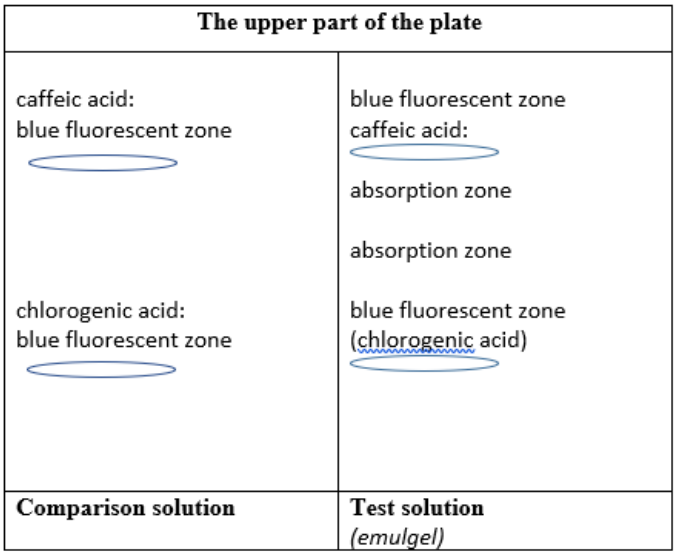

Fig. 1 The sequence of zones on the chromatograms of the comparison solution and the test solution.

The criterion of insignificance compared to the maximum permissible uncertainty of the analysis results (Δ_{AS}): $\Delta_{AS}\% \leq \max\Delta_{AS}$, %•0,32 = 3,2%•0,32 = 1,024%.

Quantitative determination of the amount of hydroxycinnamic acids

The calculation of uncertainty of sample preparation (Δ_{sp}), uncertainty of the final analytical operation (Δ_{FAO}) and total uncertainty of the analysis method ($\Delta_{AS}\%$) п was carried out in accordance with the requirements of SPhU 2.1. [10] (table 1).

Table 1 Calculation of the uncertainty of the method of determining the amount of hydroxycinnamic acids in the dosage form – emulgel

Sample preparation operation	Value	Uncertainty, (Δ),%
Test solution		
Weight (m)	2000 mg	0,010
Bringing to volume	100 ml	0,12
Aliquot	1 ml	0,54
Bringing to volume	10 ml	0,50
Total sample preparation uncertainty Δsp%		**0,90**
Uncertainty of the final analytical operation		**0,52**
Δ_{FAO} *(spectrophotometry, standard method)*		
Total uncertainty of the analysis method $\Delta_{AS}\%$		**1,03**
$\Delta_{AS}\% = \sqrt{(\Delta sp\%)^2+(\Delta_{FAO}\%)^2}$		

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Thus, the calculated total uncertainty of the analysis method Δ_{AS}% is less than max Δ_{AS} (1,03% < max Δ_{AS}=1,024%), which meets the requirements for this parameter. Therefore, the uncertainty of sample preparation and analysis as a whole should ensure sufficient measurement accuracy.

At the first stage of the study, model mixtures were used. For their preparation, standardized TETP and a placebo mixture were used, the composition of which corresponds to medicine.

The parameters of the linearity of the method of spectrophotometric determination of the amount of hydroxycinnamic acids (HCA) converted to chlorogenic acid of the model mixture of emulgel were studied in the range from 1 to 5 mg, which corresponds to the range of application of the method for analysis in medicinal form from 60% to 140% of the nominal content of the active substance. The determination was made at five concentration points: 60.00%, 80.00%, 100.00%, 120.00%, 140.00%. Each determination was performed three times randomly. The correlation coefficient was r=1,0000, RSD_{range}=29,28. The calibration graph of the method is shown in fig. 2. The obtained linearity characteristics are shown in table 2.

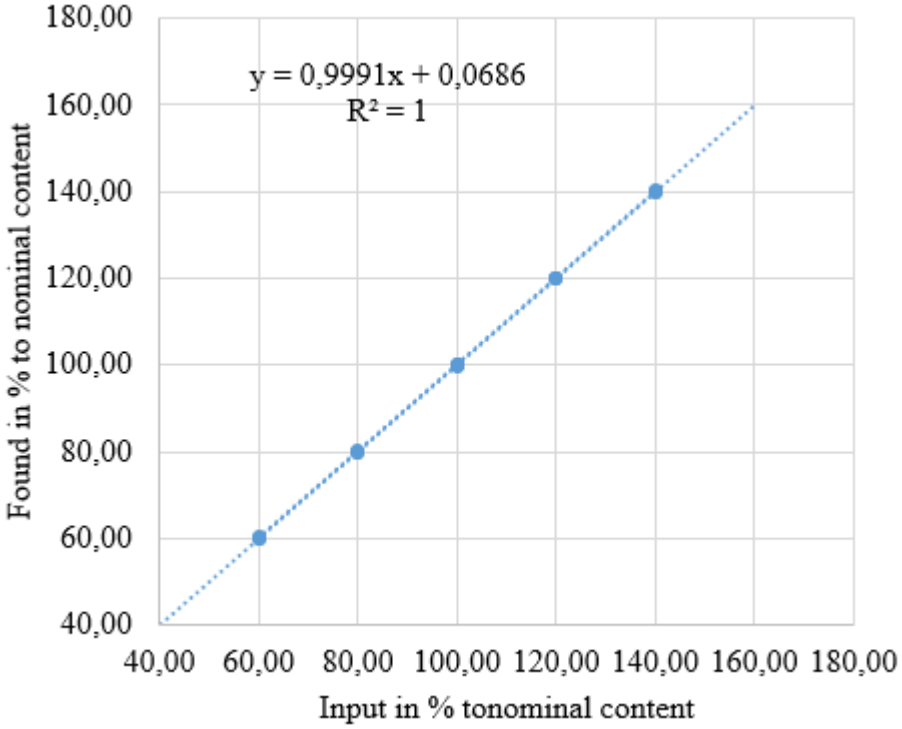

Fig. 2 Graph of the linearity of the dependence of the method of determining the amount of HCA by the spectrophotometric method of the absorption index in the composition of model emulgel mixtures.

Table 2. Linearity parameters of the method of determining the amount of HCA by the spectrophotometric method of the absorption index in the composition of model emulgel mixtures.

Parameter	Result	Admission criterium 90,0% - 110,0%, n=5
Range of application	1 – 5 мг/г	-
Regression equation	У = 0,9991x + 0,0686	-
Slope (b ± Sb)	0,9991 ± 0,0012	-
Interception a	0,0686	1) ≤2,3534*Sa/√3=0,98; 2) if not performed ≤2,30
Sa	± 0,1299	-
The standard error of the mean value of the regression line S0	0,14	≤1,36
Correlation index R	1,0000	≥0,9957
Limit of detection	0,45 mg/mg	
Limit of quantification	1,3 mg/mg	

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The second stage of the study of the validation parameters of the quantitative determination method was carried out on model samples of the finished emulgel dosage form.

An experimental series of emulgel was analyzed by the additive method, i.e. by adding known concentrations of chlorogenic acid SS (standard sample) (0.5 mg, 0.75 mg, 1.0 mg, 1.25 mg and 1.5 mg) to a previously analyzed emulgel sample. This procedure was repeated three times for each concentration. The calibration line is shown in fig. 3.

The results of the determination are shown in table 3.

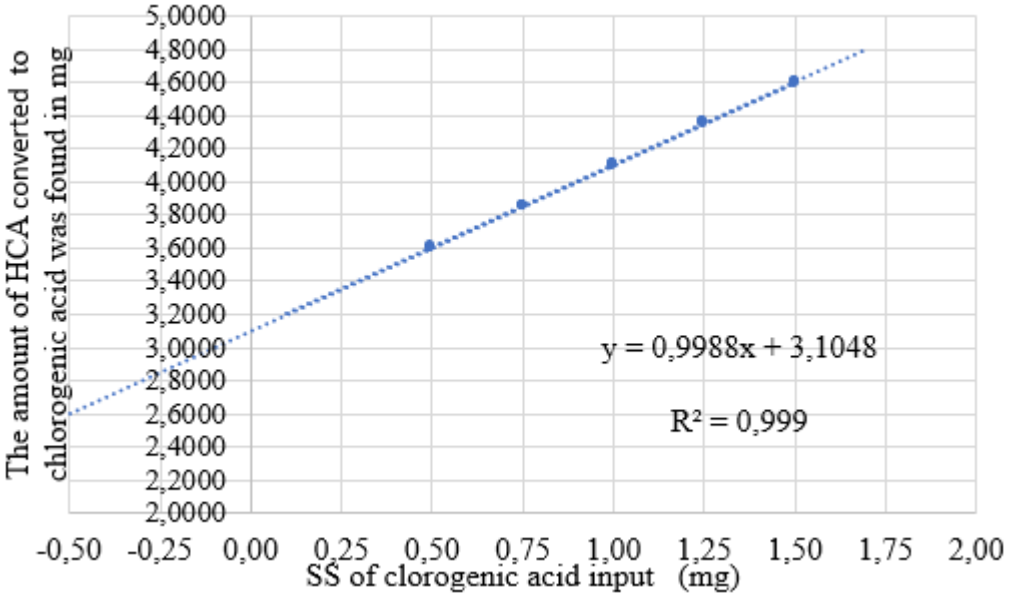

Fig. 3. The schedule for determining the amount of HCA in the composition of the emulgel converted chlorogenic acid by the additive method

Table 3. Results of studying the reproducibility of the methodology in the analysis of the finished dosage form

n	HCA sum content in a sample (mg)	Amount of SS CA added (mg)	Found HCA converted to CA (mg/g)	The determined content of the additive, (mg)	Percentage of reproducibility %	% RSD	Uncertainty ε, %
1	3,1	0,5	3,60	0,4957	99,15	0,72	0,92
			3,60	0,5077	101,54		
			3,60	0,5037	100,74		
2	3,1	0,75	3,85	0,7497	99,96		
			3,85	0,7577	101,03		
			3,85	0,7524	100,32		
3	3,1	1,0	4,10	1,0104	101,04		
			4,10	0,9984	99,84		
			4,10	1,0064	100,64		
4	3,1	1,25	4,35	1,2497	99,98		
			4,35	1,2617	100,94		
			4,35	1,2657	101,26		
5	3,1	1,5	4,60	1,4904	99,36		
			4,60	1,4997	99,98		
			4,60	1,5037	100,25		
Average value					100,40		
critical value for results' convergence Δ_{As},%=10,00·0,32=3,2						3,2	

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systematic error *δ*	0,40
uncertainty criterion of systematic error 1) δ≤maxδ,%=0,32×maxΔAs=1,0 2) if not met 1), then *δ*≤2,3	corresponds
general conclusion about the methodology	correct

It was indicated that the content of the sum of hydroxycinnamic acids converted to chlorogenic acid in the tested emulgel dosage form is within 3.1048±0.75 mg (RSD=0.72%, ε=0.92%). Our studies revealed a recovery percentage of 99.48 - 101.32% (100.40% ± 0.92%), which indicates that the developed method was accurate, selective, fast and economical.

Quantitative determination of the amount of flavonoids

The results of the uncertainty assessment of the tested analysis method were carried out in accordance with the requirements of SPhU 2.1. [10] (table 4)

Table 4. Calculation of the uncertainty of the method determining the content of the flavonoids amount converted to hyperoside in the dosage form - emulgel

Sample preparation operation	Value	Uncertainty, (Δ),%
Test solution		
Weight of raw materials	2 000 mg	0,01
Bringing to volume	100 ml	0,12
An aliquot	5ml	0,69
Bringing to volume	25 ml	0,23
Complete uncertainty of sample preparation Δsp%		0,74
*Uncertainty of the final analytical operation $Δ_{FAO}$ (spectrophotometry)**		0,52
Complete uncertainty of the method of analysis $Δ_{AS}$% $Δ_{AS}\% = \sqrt{(Δsp\%)^2+(Δ_{FAO}\%)^2}$		0,90

The calculated total uncertainty of the analysis method $Δ_{AS}$% less than max$Δ_{AS}$(0,90% < max$Δ_{AS}$=2,048%), which meets the requirements of this parameter. Therefore, the uncertainty of sample preparation and analysis as a whole should ensure sufficient measurement accuracy.

The parameters of the linearity of the method of spectrophotometric determination of the amount of flavonoids in terms of hyperoside of the model mixture of emulgel were studied in the range from 0.5 mg to 1.2 mg, which corresponds to the range of application of the method for analysis in medicinal form from 60% to 140% of the nominal content of the active substance. The determination was made at five concentration points: 60.00%, 80.00%, 100.00%, 120.00%, 140.00%. Each determination was performed three times randomly. The correlation coefficient was r=0.9997, RSD_{range}=29,28. The calibration graph of the method is shown in fig. 4. The obtained linearity characteristics are shown in the table 5.

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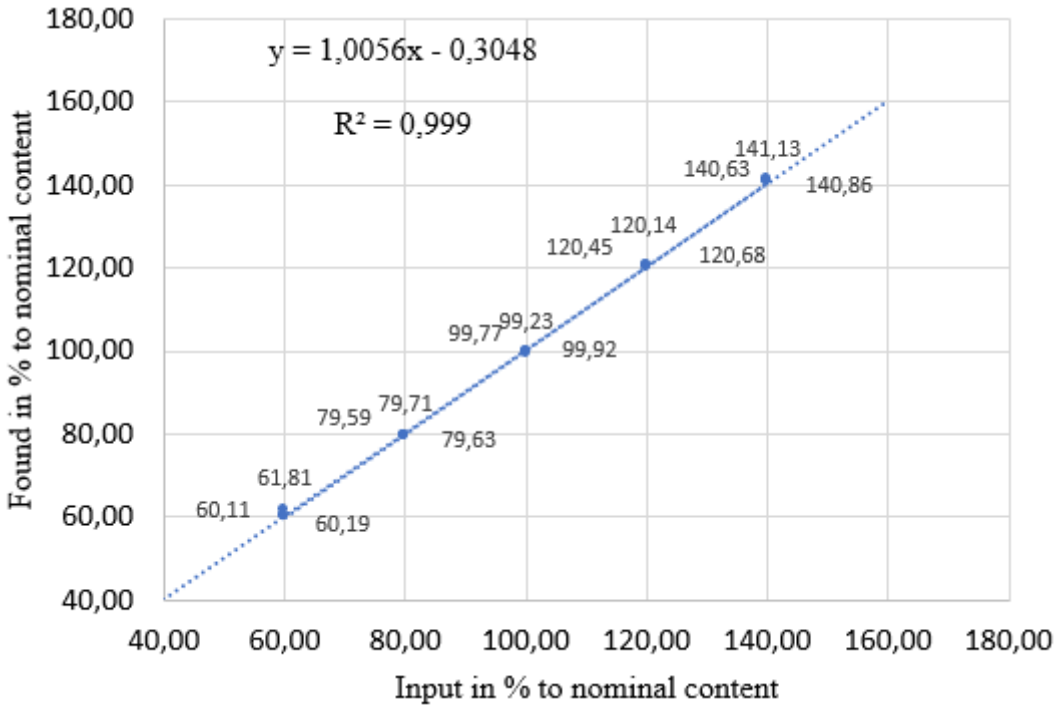

Fig. 4. Graph of the linearity of the method determining the amount of flavonoids in the composition of model mixtures of the tested emulgel dosage form.

Table 5. Study of the linearity of the method of determining the amount of flavonoids in the composition of model mixtures of the tested emulgel dosage form.

Parameter	Result	Criteria for admissions 90,0% - 110,0%, n=5
Range of application	0,5 mg – 1,2 mg	-
Regression equation	У = 1,0056x - 0,3048	-
Slope (b ± Sb)	1,0056 ± 0,0062	-
Interception a	-0,3048	1) ≤2,3534*Sa/√3=0,98; 2) if not performed ≤2,30
Sa	± 0,6486	-
The standard error of the mean value of the regression line S0	0,68	≤1,36
Correlation index R	0,9997	≥0,9957
Limit of detection	0,21 mg/mg	
Limit of quantification	0,64 mg/mg	

Further, the validation parameters of the method were studied on laboratory samples of the finished emulgel dosage form. The experimental series of emulgel was analyzed by the additive method, that is, by adding known concentrations of SS hyperoside (0.4 mg, 0.6 mg, 0.8 mg, mg, 1.0 mg and 1.2 mg) respectively (50%, 75%, 100 %, 125% and 150%) to the previously analyzed emulgel sample. This procedure was repeated three times for each concentration. The calibration line is shown in fig. 5. The results of the determination are given in table. 6.

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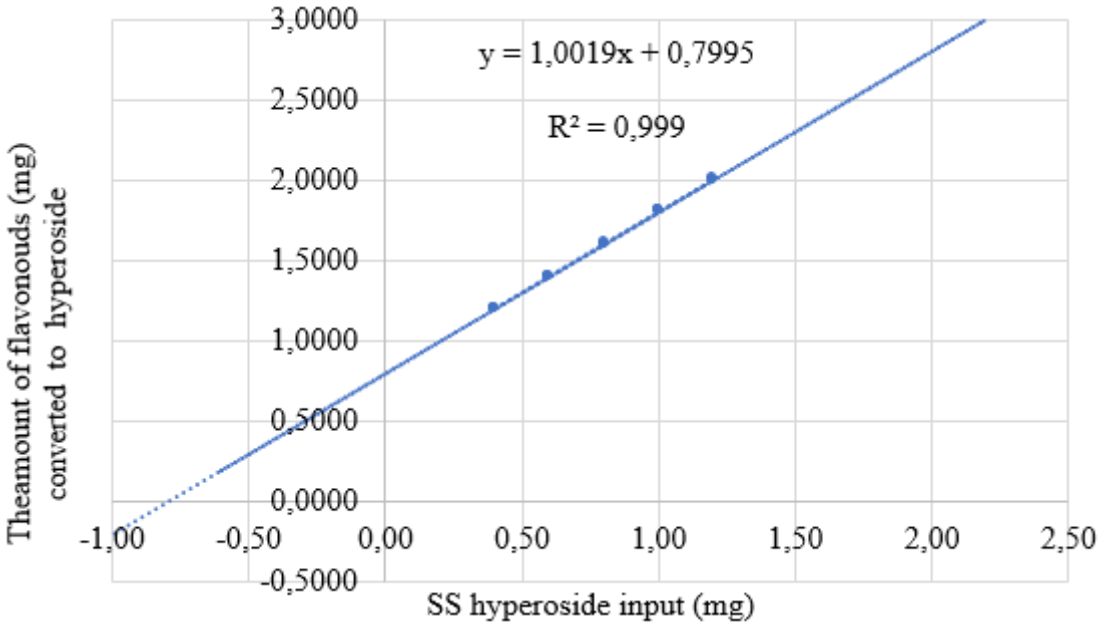

Fig. 5. Figure for determining the amount of flavonoids in the composition of the emulgel in terms of hyperoside by the additive method

Table 6. The results of studying the reproducibility of the technique in the analysis of the finished medicine

n	Flavonoids sum content in a sample (mg)	Amount of SS hyperosid added (mg)	Found flavonoid converted to hyperosid (mg/g)	The determined content of the SS additive, (mg)	Percentage of reproducibility %	% RSD	Uncertainty ε, %
1	0,8	0,40	1,20	0,3969	99,23	0,51	0,68
			1,20	0,3988	99,69		
			1,20	0,4009	100,23		
2	0,8	0,60	1,40	0,6009	100,15		
			1,40	0,6019	100,31		
			1,40	0,5988	99,79		
3	0,8	0,8	1,60	0,7988	99,85		
			1,60	0,8015	100,19		
			1,60	0,8037	100,46		
4	0,8	1,0	1,80	1,0031	100,31		
			1,80	1,0077	100,77		
			1,80	1,0093	100,93		
5	0,8	1,2	2,00	1,1954	99,61		
			2,00	1,1910	99,25		
			2,00	1,2065	100,54		
Average value					100,09		
critical value for results' convergence Δ_{As},%=10,00·0,32=3,2						3,2	
systematic error δ						0,09	
uncertainty criterion of systematic error 1) δ≤maxδ,%=0,32×maxΔAs=1,0 2) if not met 1), then δ≤2,3						corresponds	
general conclusion about the methodology						correct	

It was established that the content of flavonoids in terms of hyperoside in the tested emulgel dosage form is within 0.7995±0.29 mg (RSD=0.51%, ε=0.68%). Our studies revealed a recovery percentage of 99.58 - 100.60% (100.09% ± 0.51%), indicating that the

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developed method was accurate, selective, fast and economical.

Thus, the methods of quantitative determination of API according to such validation characteristics as specificity, linearity, correctness, precision and intra-laboratory precision meet the requirements of DPhU 2.4, 5.3.N.2

Conclusion

Methods for the identification of APIs in an emulgel based on tanacetum parthenium have been developed. Based on the results of the study, the most optimal conditions for TLC analysis were determined for the purpose of identifying marker substances of hydroxycinnamic acids.

A set of methods for quantitative determination of phenolic components in emulgel using spectrophotometry has been developed.

When conducting validation studies of the methodology for quantitative determination of the amount of HCA and the amount of flavonoids in the composition of the emulgel, the following metrological characteristics were checked: specificity, linearity, correctness, precision and intra-laboratory precision. Taking into account the regulated requirements for the content of the group of biologically active substances, and the peculiarities of spectrophotometric determination by the method of the specific absorption index, the criteria for the acceptability of the analytical technique were calculated.

Development and validation of methods of analysis of active substances in emulgel with thick extract of tanacetum parthenium

Velia M.I., Yevtifieieva O.A, Ruban O.A., Ponomarenko T.O.

Introduction. It is known that inflammatory diseases of the muscular and skeletal systems are one of the most common pathologies affecting bones, joints, muscles, and connective tissue. These disorders can lead to loss of working capacity, deterioration of the quality of life, and disability. For the treatment of the above-mentioned pathology, soft drugs containing active pharmaceutical ingredients of the NSAIDs group are used. These drugs are not recommended to be used for more than 14 days because with long-term use on large areas of the skin, they can cause systemic side effects. Herbal preparations are practically devoid of these disadvantages, can be used for a long time and do not cause addiction. Therefore, the composition and technology of a soft medicinal product in the form of emulgel with a thick extract of the tanacetum parthenium (TETP) of the Asteraceae family was developed. The range of biologically active substances of the tanacetum parthenium provides high anti-inflammatory, antibacterial and analgesic effects. The objective of this article is to develop methods for determining active pharmaceutical ingredients (APIs) in the emulgel composition. The planning of the study on standardizing the quality of the studied drug included the development of a test for the identification and methods of determining the quantitative content of API; validation studies of methods of quantitative determination in accordance with the requirements of the general article of SPhU (State Pharmacopoeia of Ukraine) 2.4, 5.3.N.2 "Validation of analytical methods and tests". **Material & methods.** Identification of API in the emulgel for the presence of hydroxycinnamic acids. With the identification purpose, we selected and worked out the unified pharmacopoeial method during the analysis of the studied finished dosage form. The research was carried out by the method of thin-layer chromatography (TLC). The study of the quantitative content of phenolic components in the emulgel was carried out according to the content of the amount of hydroxycinnamic acids and the amount of flavonoids.
Quantitative determination of the amount of hydroxycinnamic acids converted to chlorogenic acid. According to the method of SPhU “Nettles leaves", the optical density of the tested solution was measured immediately at a wavelength of 525 nm, using a compensating solution as a comparison solution. Quantification of the amount of flavonoids converted to hyperoside. According to the method given in the monograph of the SPhU "Hawthorn leaves and flowers N", the optical density of the tested solution was measured 30 minutes after preparation at a wavelength of 410 nm. **Results & discussion**. Based on the results of the study, the most optimal conditions for TLC analysis were determined for the purpose of identifying marker substances of hydroxycinnamic acids shows the sequence of zones on the chromatograms of the comparison solution and the test solution. The chromatogram of the tested solution should show zonic acid and chlorogenic acid. In addition, other zones may also be detected on the chromatogram of the tested solution. It was indicated that the content of the sum of hydroxycinnamic acids converted to chlorogenic acid in the tested emulgel dosage form is within 3.1048±0.75 mg (RSD=0.72%, ε=0.92%). Our studies revealed a recovery percentage of 99.48 - 101.32% (100.40% ± 0.92%), which indicates that the developed method was accurate, selective, fast and economical. It was established that the content of flavonoids in terms of hyperoside in the tested emulgel dosage form is within 0.7995±0.29 mg (RSD=0.51%, ε=0.68%). Our studies revealed a recovery percentage of 99.58 - 100.60% (100.09% ± 0.51%), indicating that the developed method was accurate, selective, fast and economical. **Conclusion**. Methods for the identification of APIs in an emulgel based on tanacetum parthenium have been developed. Based on the results of the study, the most optimal conditions for TLC analysis were determined for the purpose of identifying marker substances of hydroxycinnamic acids. A set of methods

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for quantitative determination of phenolic components in emulgel using spectrophotometry has been developed. When conducting validation studies of the methodology for quantitative determination of the amount of HCA and the amount of flavonoids in the composition of the emulgel, the following metrological characteristics were checked: specificity, linearity, correctness, precision and intra-laboratory precision. Taking into account the regulated requirements for the content of the group of biologically active substances, and the peculiarities of spectrophotometric determination by the method of the specific absorption index, the criteria for the acceptability of the analytical technique were calculated.
Keywords: validation, methods of analysis, emulgel, thick extract of Tanacetum parthenium

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