СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

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Development of methods for analysis of the amount of flavonoids and their stability study in the combined dental gel

An important aspect in the pharmaceutical development of dental medicines is to provide them with a prolonged therapeutic effect while reducing the side effects of drug substances and the possibility of long-term use. This can be achieved by using active components of plant origin.

Aim. To develop methods for analyzing biologically active substances in the composition of a new combined dental gel.

Materials and methods. The study object was a dental gel containing "Phytodent" complex tincture (PJSC "CPP Chervona zirka", Ukraine). Based on the analysis of the composition of the tincture it was proposed to carry out standardization by the amount of biologically active substances, namely flavonoids. Identification was carried out by TLC, while the quantitative determination by absorption spectrophotometry, the ultraviolet and visible method by the reaction with aluminum chloride using the standard method calculated with reference to rutin and the absorbance measurement at 406 nm.

Results and discussion. As a result of the research, the methods for the analysis of flavonoids in the composition of the new combined gel have been developed. The spectrophotometric method developed is characterized by specificity, accuracy, precision and linearity with r = 0.9998. One of the important issues when using components of plant origin is their stability both during preparation and storage. Using the method developed the stability of flavonoids has been studied depending on pH changes of the carbomer-based dental gel.

Conclusions. It has been determined that the methods developed are easily reproducible and allow to identifying and quantifying flavonoids in the dental gel. It has been found that a stable content of flavonoids is characteristic of the carbomer-based gel neutralized to pH values from 5.0 to 6.0.

***Key words**: dental gel; flavonoids; spectrophotometry; stability; pH*

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Розробка методик аналізу суми флавоноїдів і вивчення їх стабільності в комбінованому дентальному гелі

Важливим аспектом фармацевтичної розробки дентальних препаратів є надання їм тривалого терапевтичного ефекту за одночасного зменшення побічних ефектів лікарських речовин та можливості тривалого застосування. Цього можна досягти, використовуючи активні компоненти рослинного походження.

Мета дослідження. Дослідження присвячено розробці методів аналізу біологічно активних речовин у складі нового комбінованого дентального гелю.

Матеріали та методи. Об'єктом дослідження був дентальний гель, до складу якого входила комплексна настойка «Фітодент» (ПАТ «ХФЗ «Червона зірка»», Україна). Виходячи з аналізу складу настойки, було запропоновано проводити стандартизацію за сумою біологічно активних речовин, а саме флавоноїдів. Ідентифікацію проводили за допомогою ТШХ, а кількісне визначення – за допомогою абсорбційної спектрофотометрії в УФ і видимих ділянках спектра шляхом реакції з хлоридом алюмінію та вимірюванням поглинання за 406 нм стандартним методом з використанням рутину як стандарту.

Результати та їх обговорення. У результаті досліджень було розроблено методики аналізу флавоноїдів у складі нового комбінованого гелю. Розроблений спектрофотометричний метод характеризується специфічністю, точністю, прецизійністю і лінійністю з r = 0,9998. Одним із важливих питань використання компонентів рослинного походження є їхня стійкість як під час приготування, так і під час зберігання. За допомогою розробленого методу вивчали стабільність флавоноїдів залежно від змін pH дентального гелю на основі карбомеру.

Висновки. Виявлено, що розроблені методи легко відтворюються і дозволяють ідентифікувати та кількісно визначати флавоноїди в дентальному гелі. Виявлено, що стабільний вміст флавоноїдів характерний для гелю на основі карбомеру, нейтралізованого до значень pH від 5,0 до 6,0.

***Ключові слова**: дентальний гель; флавоноїди; спектрофотометрія; стабільність; pH*

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Разработка методик анализа суммы флавоноидов и изучение их стабильности в комбинированном дентальном геле

Важным аспектом фармацевтической разработки стоматологических препаратов является обеспечение пролонгированного терапевтического эффекта при одновременном снижении побочных эффектов лекарственных веществ и возможности длительного применения. Этого можно добиться, используя активные компоненты растительного происхождения.

Цель исследования. Наше исследование посвящено разработке методов анализа биологически активных веществ в составе нового комбинированного стоматологического геля.

Материалы и методы. Объектом исследования являлся стоматологический гель, в состав которого входила комплексная настойка «Фитодент» (ЧАО «ХФЗ «Красная звезда»», Украина). Исходя из анализа состава настойки, было предложено проводить стандартизацию по сумме биологически активных веществ, а именно флавоноидов. Идентификацию проводили с помощью ТСХ, а количественное определение – с помощью метода абсорбционной спектрофотометрии в УФ и видимых участках спектра по реакции с хлоридом алюминия стандартным методом в отношении рутина и измерении оптической плотности при 406 нм.

Результаты и их обсуждение. В результате исследований были разработаны методики анализа флавоноидов в составе нового комбинированного геля. Разработанный спектрофотометрический метод характеризуется специфичностью, точностью, прецизионностью и линейностью с r = 0,9998. Одним из важных вопросов при использовании компонентов растительного происхождения является их стабильность как при приготовлении, так и при хранении. С помощью разработанной методики изучали стабильность флавоноидов в зависимости от изменения pH стоматологического геля на основе карбомера.

Выводы. Установлено, что разработанные методы легко воспроизводимы и позволяют идентифицировать и количественно определять флавоноиды в стоматологическом геле. Установлено, что стабильное содержание флавоноидов характерно для геля на основе карбомера, нейтрализованного до значений pH от 5,0 до 6,0.

Ключевые слова: *стоматологический гель; флавоноиды; спектрофотометрия; стабильность; pH*

Introduction. One of the promising areas of pharmaceutical science is the development of new medicines for the treatment of various diseases. Along with the search for new synthetic molecules, much attention is paid to the development of combined preparations, which combine the action of active pharmaceutical ingredients (API) of synthetic origin with herbal components. This combination often helps to increase the therapeutic effect and reduce possible side effects [1]. This approach is often used in the treatment of dental diseases; it allows extending the range of action on the pathogenesis of diseases.

In the complex therapy of various dental pathologies, medicinal plants are widely used; it is associated with their high efficiency, safety, minimal side effects and allergic reactions. Herbal components are characterized by a wide spectrum of action: they exhibit antimicrobial, anti-inflammatory, analgesic, immunomodulating, hemostatic and wound healing effects, and also have a positive effect on metabolic processes, improve microcirculation, normalize homeostasis, and increase the protective properties of tissues and the body as a whole. At the same time, some of them are not inferior to synthetic agents in the effectiveness of the therapeutic effect [2-8].

In addition to the native medicinal plant raw material, tinctures and extracts are often used in dental preparations. In dental practice, an alcohol solution of chlorophyllipt, an alcohol tincture of calendula and propolis, "Phytodent" tincture, an alcohol solution "Stomatophyt" used in the local treatment of inflammatory diseases of the oral mucosa and periodontium are known. However, the constant use of alcohol solutions can lead to thinning and dryness of the oral mucosa, which, ultimately, on the contrary, will increase the inflammatory process in the gums. Therefore, the transfer of an alcohol tincture into a gel form will reduce its irritating and dehydrating effect and provide this drug with an adhesive and prolonging effect [9-11].

For the treatment and prevention of infectious and inflammatory diseases of the parodentium, oral mucosa, as well as for adaptation to removable dentures, we are developing a combined dental gel under the name "Cholident", which includes APIs of both natural and synthetic origin, such as 80 % choline salicylate (Basf Pharma, Switzerland), lidocaine hydrochloride (Societa Italiana Medicinali Scandicci, Italy) and the herbal medicine "Phytodent" tincture (PJSC "CPP Chervona zirka", Ukraine) in the form of a complex tincture based on seven types of the medicinal plant material: calamus rhizome (*Acorus calamus* L.); marigold flowers (*Calendula officinalis* L.); nettle leaves (*Urtica dioica* L.); chamomile flowers (*Chamomilla recutita* L.); sophora Japanese fruit (*Sophora japonica* L.); celandine herb (*Chelidonium majus* L.); rose hips fruits (*Rosa majalis Herrm.*) [12]. As a gelling agent a carbomer of Polacril® 40P brand (Amedeo Brasca & C. Srl, Italy) approved for application in oral medicinal products and capable of forming a high-quality gel in the presence of an alcohol tincture was used [13]. OraRez® W-100L16 (BOAI, China) was added in the gel composition as a mucosal adhesive; it contributed to increasing the gel retention time in the oral mucosa and, thus, improving its therapeutic efficacy [14].

During the experimental studies the rheological, biopharmaceutical and adhesive properties of the combined

gel were studied, and its antimicrobial and specific activity was proven [15]. However, it is known that in the pharmaceutical development of new medicines, one of the necessary steps is standardization of the finished product.

The aim of this work was to develop methods for analyzing one of the components of the gel, namely "Phytodent" tincture as part of a combined dental preparation.

Materials and methods. The study objects were the experimental samples of the new combined dental gel "Cholident".

Reagents meeting the requirements of the State Pharmacopoeia of Ukraine (SPhU) [16] harmonized with the European Pharmacopoeia [17] were used. The identification of flavonoids in the gel was carried out using the method of thin layer chromatography (TLC). To apply the samples to the plates, a GAMAG Linomat 5 sample applicator equipped with a 100 µl syringe was used. The components studied were separated on silica gel plates (HPTLC Silica gel 60 F 254) in the system of *acetic acid R – formic acid anhydrous R – water R – ethyl acetate R (11 : 11 : 27 : 100)*.The results were evaluated using a CAMAG TLC Visualizer 2 in UV light at a wavelength of 366 nm.

The quantitative determination of flavonoids in the gel was carried out by absorption spectrophotometry, the ultraviolet and visible method [16-17] based on the complexation reaction with aluminum chloride. UV spectra were recorded on a Specord 200 Analityk Jena spectrophotometer (Germany).

TLC

Test solution. Place 2.5 g of the gel in a 50 ml volumetric flask, add 40 ml of *methanol R* and treat on an ultrasonic bath for 5 min, dilute to the volume with the same solvent and filter through a blue ribbon filter, discarding the first portions of the filtrate. Evaporate 40 ml of the filtered solution to dryness under reduced pressure; dissolve the residue in 1 ml of *methanol R*.

Reference solution. Dissolve 5.0 mg of *rutin R* in 10 ml of *methanol R*.

In parallel, under the same conditions, the test solution of "Phytodent" tincture was prepared. To do it, 5 ml of tincture was evaporated to dryness under reduced pressure, and the residue was dissolved in 1 ml of *methanol R.*

TLC procedure. On a TLC plate with F_{254} silica gel *R* of a 5 × 10 cm layer, apply 2 µl of the reference solution, 3 µl of the test solution of the tincture and 3 µl of the test solution of the gel as 6 mm strips. Place the plate with the samples applied in a chamber with a mixture of solvents: *acetic acid R – formic acid anhydrous R – water R – ethyl acetate R (11 : 11 : 27 : 100)*. When the front of the solvents passes 8 cm from the start line, remove the plate, dry in the air for 30 min, spray with the solution of 10 g/l of *diphenylboric acid* of *aminoethyl ether R* in *methanol R*, then spray with the solution of 50 g/l of *macrogol 400 R* in *methanol R*, dry in the air for 30 min and examine in UV light at a wavelength of 366 nm.

The sequence of zones in the chromatogram of the test solution and the reference solution should correspond to the zones given in Tab. 1.

Table 1

The sequence of zones in the chromatograms of the test solution and the reference solution

Top of the plate	
	A blue fluorescent zone
	An yellowish-blue fluorescent zone
Rutin: a yellowish-brown fluorescent zone	An yellowish-brown fluorescent zone (rutin)
	An yellow fluorescent zone
Reference solution	*Test solution*

Spectrophotometry

Test solution. Place 5.0 g (accurate weight) of the gel in a beaker, add 5 ml of *ethanol R* and heat on a water bath with constant stirring for 10 min to precipitate the carbomer. Filter the resulting solution into a 25 ml volumetric flask. In a glass add another 5 ml of *ethanol R* and repeat the procedure. Wash the filter with two 5 ml portions of *ethanol R* and dilute the solution to the volume with the same solvent and mix thoroughly.

Transfer 5 ml of the filtered solution into a 25 ml volumetric flask, add 1 ml of *aluminum chloride R*, dilute to the volume with *5 % acetic acid* in *methanol*, mix thoroughly and leave in a dark place for 30 min.

Blank solution. Transfer 5 ml of the filtered solution into a 25 ml volumetric flask, dilute to the volume with *5 % acetic acid* in *methanol*, mix thoroughly and leave in a dark place for 30 min.

Reference solution. Place 50.0 mg (accurate weight) of the *rutin standard* in a 100 ml volumetric flask, dissolve in 60 ml of *ethanol R* and dilute the solution to the volume with the same solvent, mix thoroughly. Transfer 5 ml of the resulting solution into a 25 ml volumetric flask, dilute to the volume with *ethanol R* and mix thoroughly.

Transfer 5 ml of the resulting solution into a 25 ml volumetric flask, add 1 ml of *aluminum chloride R*, dilute to the volume with *5 % acetic acid* in *methanol*, mix thoroughly and leave in a dark place for 30 min.

Blank solution. Transfer 5 ml of the *rutin standard* solution into a 25 ml volumetric flask, dilute to the volume with *5 % acetic acid* in *methanol*, mix thoroughly and leave in a dark place for 30 min.

The absorbance of the resulting solutions was measured at a wavelength of 406 ± 5 nm.

The quantitative content of flavonoids (%) calculated with reference to rutin was determined by the formula:

$$X, \% = \frac{A \cdot m_{st} \cdot V_{2st} \cdot V_{4st} \cdot V_1 \cdot V_3 \cdot P}{A_{st} \cdot V_{1st} \cdot V_{3st} \cdot V_{5st} \cdot m \cdot V_2} = \frac{A \cdot m_{st} \cdot P}{A_{st} \cdot m \cdot 20},$$

where: A – is the absorbance of the test solution; A_{st} – is the absorbance of the reference solution; m_{st} – is the weight of the rutin standard sample, g; m – is the sample weight of the gel, g; P – is the quantitative content of the main active substance in the rutin standard sample, %.

Validation

Validation of the method developed was carried out in accordance with the recommendations of ICH [18],

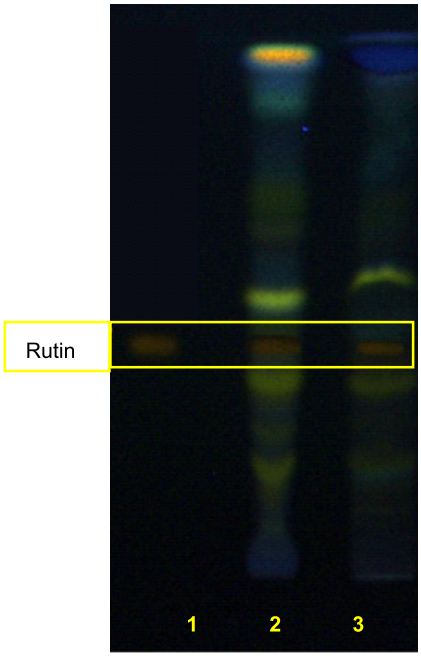

Fig. 1. The chromatogram of the test solution (3), tincture solution (2) and reference solution (1)

the requirements of the monograph 5.3.N.2 of the SPhU [16], as well as according to the standard procedure of validation for quantitative methods using an external standard by studying its linearity, accuracy and precision.

Results and discussion. Standardization of multicomponent medicines has traditionally been a challenge. At the initial stage of our research, it was necessary to determine the class of biologically active compounds and select an active marker for standardizing the dosage form developed.

In order to select active markers, we identified biologically active substances (BAS) of the tincture by TLC using such standard samples as rutin, quercetin, isoquercetin, hyperoside and luteolin. The chroatogram obtained is shown in Fig. 1.

Based on the data obtained (Fig. 1) it was proposed to standardize BAS of "Phytodent" tincture in the test gel by the method of the flavonoid assessment using rutin as an active marker.

Table 2

The linearity parameters of the quantitative determination method

N	Parameter	Requirements	The value obtained	Criterion Fulfillment
1	|a|	≤ 2.6	0.4957	Satisfied
2	S_0	≤ 0.84	0.75	Satisfied
3	r	> 0.9981	0.9998	Satisfied

The next step was the development of the method for the quantitative analysis of the flavonoid content in the combined dental gel. It was based on the complexation reaction of flavonoids with aluminum chloride.

The spectra of the rutin standard and the gel were obtained. They are presented in Fig. 2.

The content of the total flavonoids in the gel analyzed was proposed to be determined taking into account the requirements to the content of this group of BAS in the tincture, the lower limit should be at least 0.01 % (10 mg/g of the gel).

The method for the quantitative analysis of flavonoids in the gel under study was validated. When validating its specificity, linearity, accuracy and precision were assessed.

During the validation it was proven that the sample preparation insignificantly affected the quantification result ($\Delta_{AS}\% \leq \max \Delta_{AS}$; $\max \Delta_{AS} = 6.4$ %; $\Delta_{AS}\% = 1.13$ %).

To assess specificity, a gel placebo was prepared and analyzed by the method developed. It was shown that the relative systematic error introduced by other active substances, as well as additional substances of the gel was insignificant ($\delta_{esx}\% \leq \max \Delta_{AS}$; $\max \Delta_{AS} = 6.4$ %; $\delta_{esx}\% = 1.88$ %).

To confirm linearity of the method, 5 model solutions were prepared, their concentrations varied uniformly within the application range: 50-250 % in increments of 50 %.

Characteristics and the curve of the linear dependence are given in Tab. 2 and in Fig. 3.

To determine accuracy and precision within the range of use of the analytical method, 5 test solutions were

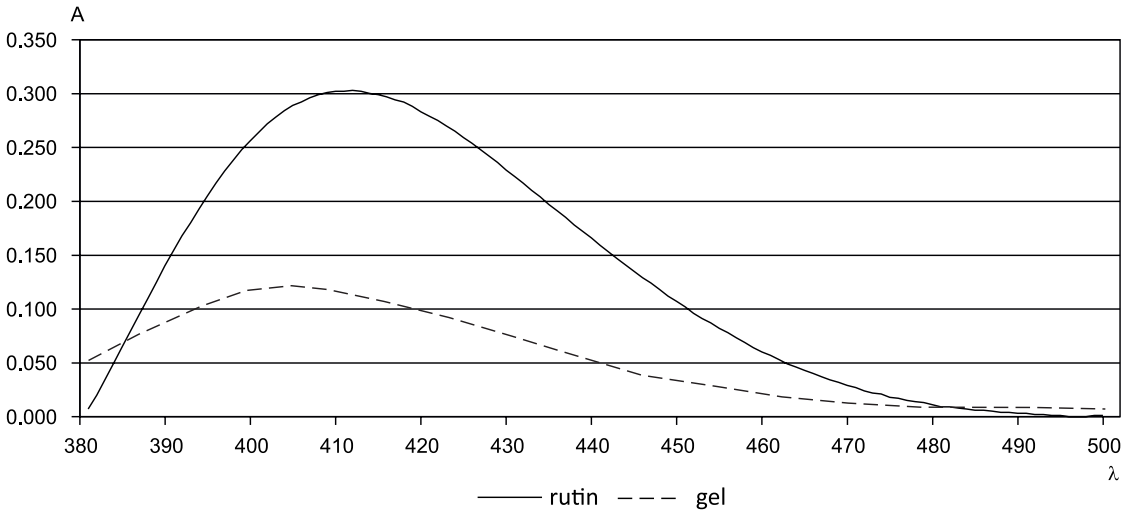

Fig. 2. The absorption spectrum of the rutin standard solution and the test solution

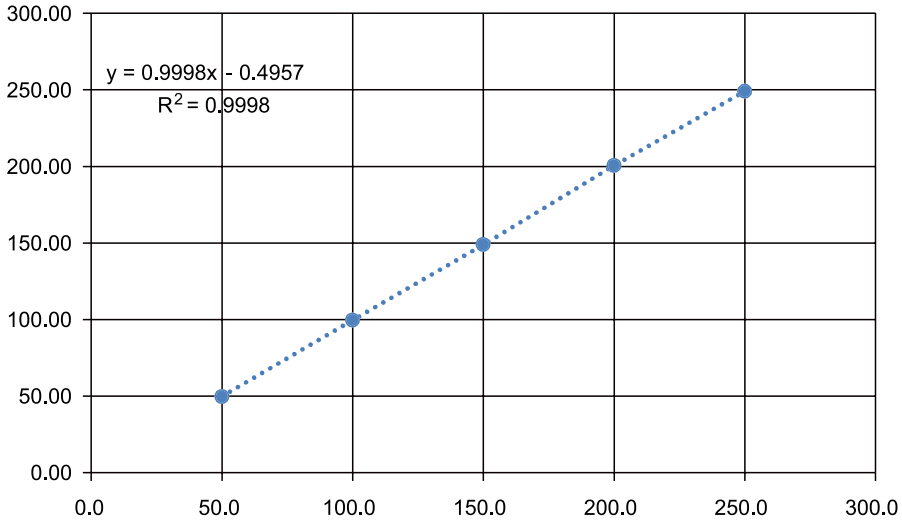

Fig. 3. The curve of the linear dependence of the optical density of rutin on the concentration in normalized coordinates

prepared in compliance with all stages of the analytical procedure. To determine intermediate precision, the results of the study of 6 tests of one sample by two analysts on different days during the same working week using different measuring glassware were used. The fulfillment of the criteria of accuracy, precision and intermediate precision in order to determine the amount of flavonoids calculated with reference to rutin in the gel under study are given in Tab. 3.

The method for spectrophotometric determination of the amount of flavonoids developed was successfully tested for the analysis of test batches of the new combined dental gel. The analysis of the amount of flavonoids in the experimental batches of the gel showed that the content of BAS in the gel was from 0.029 % to 0.11 % (according to the results of determination in 9 samples).

Dental medicines are required to meet the pH of the drug with the pH of the saliva (5.5-8.0) since this requirement has a significant effect on the health of the tissues of the oral cavity [19]. For gels based on carbomers the required pH can be created by neutralizing it with solutions of substances of a basic nature [20-22]. We used 10 % sodium hydroxide solution differing from other substances in this group by lower toxicity. In this regard, the method for the quantitative determination of the amount of flavonoids developed was used to study the dependence of the content of these BAS on the pH of the gel. The results are presented in Fig. 4.

The analysis of the data obtained showed (Fig. 4) that an increase in the pH value negatively affected the quantitative content of BAS in the gel. It may be associated with an increase in the amount of an alkaline agent in the medicine and possible processes of oxidation of these substances [23-24]. It should be noted that the gel developed neutralized in the pH range from 5 to 6 is characterized by the greatest stability in the quantitative content of flavonoids.

The method developed was also used for the preliminary assessment of the stability of the combined dental gel "Cholident" in the pH range of 5-6. The stability test was performed on the experimental gel samples, and the quantitative determination of the amount of flavonoids was carried out immediately after the gel preparation in 1, 3 and 6 months. The gels studied were stored at a temperature of 25 ± 2 °C and a relative humidity of 60 ± 5 %. The results are presented in Tab. 4.

The results presented in Tab. 4 showed that the quantitative content of the amount of flavonoids varied insignificantly during 6 months of the drug storage – the relative deviation was not more than 2.0 %, indicating a fairly stable content of biologically active substances in the gel developed. Changing the pH of the gel in the range

Table 3

The results of the evaluation of accuracy, precision and intermediate precision of the assay method

Parameter	Value	Criterion		Criterion Fulfillment
		Requirements to statistical insignificance	Requirements to practical insignificance	
$\lvert\bar{Z} - 100\rvert$	0.47	≤ 0.64 %	≤ 2.048 %	Satisfied
ΔZ	0.80	≤ 6.4 %		Satisfied
Δintra	1.92	≤ 6.4 %		Satisfied

Table 4

The results of the gel stability study during storage

Period, month	The content of flavonoids, mg/g gel			Deviation, %		
	pH of gel			*pH of gel*		
	5.0	5.5	6.0	5.0	5.5	6.0
0	20.62	20.92	20.84	–	–	–
1	20.58	20.91	20.76	0.22	0.08	0.38
3	20.42	20.73	20.59	0.98	0.92	1.22
6	20.28	20.58	20.50	1.68	1.63	1.61

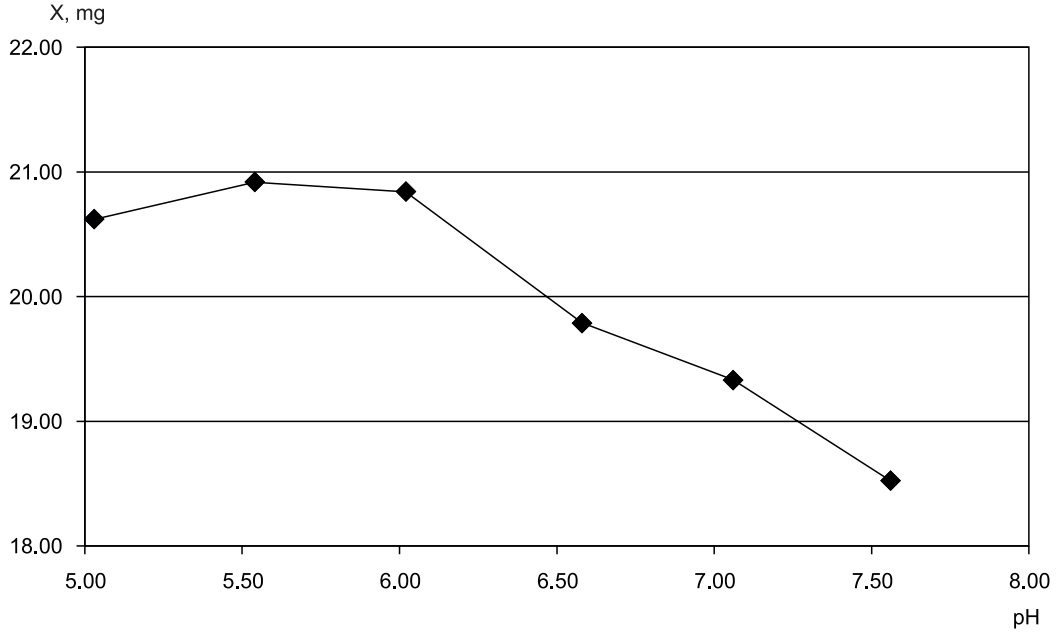

Fig. 4. The dependence of the quantitative content of flavonoids on the gel pH

from 5 to 6 did not significantly affect the stability of the medicine.

Conclusions and prospects of further research

1. As a result of the studies, the methods for analyzing the amount of flavonoids in the new combined gel under the name "Cholident" have been developed. The identification has been proposed to be carried out by TLC in the solvent system of *acetic acid R – formic acid anhydrous R – water R – ethyl acetate R (11 : 11 : 27 : 100).* A standard of rutin is recommended as a marker.

2. The quantitative determination of the amount of flavonoids in the gel has been proposed to be carried out by absorption spectrophotometry, the ultraviolet and visible method by the complexation reaction with aluminum chloride calculated with reference to rutin. For the quantification procedure, validation characteristics that met the criteria set have been studied.

3. The method developed for the spectrophotometric determination of the amount of flavonoids have been successfully tested for the analysis of test batches of the new combined dental gel. The amount of flavonoids identified in 9 samples of the gel developed ranges from 0.029 % to 0.11 % corresponding to the lower limit of the content of this group of biologically active substances in the tincture according to the specification of the medicine "Phytodent" (not less than 0.01 %).

4. The method developed has been used to assess the dependence of the quantitative content of the amount of flavonoids on the pH of the gel. As a result of the studies, it has been found that gels neutralized to pH values from 5.0 to 6.0 have the stable content of flavonoids.

5. The study of the chemical stability of flavonoids in the new dental gel showed a slight change in the quantitative content of the amount of flavonoids during storage of the gel for 6 months. Changing the pH of the gel in the range from 5.0 to 6.0 does not significantly affect the stability of the medicine.

Conflict of interests: authors have no conflict of interests to declare.

REFERENCES

1. Influence of aqueous extract of fenugreek seed powder on pharmacodyanamics and pharmacokinetics of gliclazide in rat and rabbits / S. Satyanarayana et al. *Therapy*. 2007. № 4 (4). P. 457–463. DOI: 10.1586/14750708.4.4.457.
2. Parasuraman S., Thing G. S., Dhanaraj S. A. Polyherbal formulation: Concept of Ayurveda. *Pharmacognosy Reviews*. 2014. Vol. 8, Iss. 16. P. 73–80. DOI: 10.4103/0973-7847.134229.
3. Current status of herbal drugs and their future perspectives / S. Z. Hasan et al. *Biological Forum – An International Journal.* 2009. Vol. 1, Iss. 1. P. 12–17. DOI: 10.1038/npre.2007.1176.1.
4. The Traditional Medicine and Modern Medicine from Natural Products / H. Yuan et al. *Molecules.* 2016. Vol. 21, Iss. 5. P. 559. DOI: https://doi.org/10.3390/molecules21050559.
5. Ishnava K. B. Role of herbal medicine in dental health. *Journal of Environmental Chemistry and Toxicology.* 2018. Vol. 2, Iss. 1. P. 28–29.
6. Periodontal disease and phytotherapy / M. S. Petkovic et al. *Journal of Oral Hygiene & Health.* 2015. Vol. 3, Iss. 1. P. 1–4. DOI: https://doi.org/10.4172/2332-0702.1000172.
7. Herbs in dentistry / J. B. Taheri et al. *International Dental Journal.* 2011. Vol. 61, Iss. 6. P. 287–296. DOI: https://doi.org/10.1111/j.1875-595X.2011.00064.x.
8. Emerging trends of herbal care in dentistry / G. Kumar et al. *Journal of Clinical and Diagnostic Research.* 2013. Vol. 7, Iss. 8. P. 1827–1829. DOI: https://doi.org/10.7860/jcdr/2013/6339.3282.

9. Mucoadhesive drug delivery system: an overview / B. M. Boddupalli et al. *Journal of Advanced Pharmaceutical Technology & Research.* 2010. Vol. 1, Iss. 4. P. 381–387. DOI: https://doi.org/10.4103/0110-5558.76436.
10. Pragati S., Ashok S., Kuldeep S. Recent advances in periodontal drug delivery systems. *International Journal of Drug Delivery.* 2009. Vol. 1, Iss. 1. P. 1–14. DOI: 10.5138/ijdd.2009.0975.0215.01001.
11. Kovalenko S. M., Khokhlenkova N. V., Azarenko J. M. Methodological Aspects of Development of Gels for Treating Inflammatory Dental Diseases. *Asian Journal of Pharmaceutics.* 2017. Vol. 11, Iss. 1. P. 129–135.
12. Production Phytodent®, tincture 100 ml. ATS A01A D11 UA/3681/01/01. URL: https://zvezda.kharkov.ua/en/catalog/fitodent-nastoyka-po-100-ml.html.
13. Ruban O. A., Maslii Yu. S. Research on the choice of rational concentration of the gel forming agent in the composition of dental gel. *Annals of Mechnikov Institute.* 2019. № 2. P. 29–33. DOI: https://doi.org/10.5281/zenodo.3265076.
14. Choice of Mucosal Adhesive in the Composition of a New Dental gel / Yu. Maslii et al. *Pharmakeftiki*. 2020. № 32 (1). P. 40–49. URL: https://bit.ly/3ssoUL6.
15. Maslii Yu. S., Ruban O. A. The study of biopharmaceutical and adhesive characteristics of a dental gel. *News of Pharmacy.* 2018. № 1 (93). P. 28–32. DOI: https://doi.org/10.24959/nphj.18.2188.
16. Державна Фармакопея України : у 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». 2-ге вид. Харків : ДП «Український науковий фармакопейний центр якості лікарських засобів». 2015. Т. 1. 1128 с.
17. European Pharmacopoeia / European Directorate for the Quality of Medicines & Health Care. 9-th ed. Strasbourg, 2017.
18. ICH harmonized tripartite guideline Q2 (R1). Validation of analytical procedures: text and methodology Q2 (R1). *Proceedings of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.* Geneva, Switzerland, 2005.
19. Baliga S., Muglikar S., Kale R. Salivary pH: A diagnostic biomarker. *Journal ofIndian Society of Periodontology*. 2013. Vol. 17, Iss. 4. P. 461–465. DOI: https://doi.org/10.4103/0972-124X.118317.
20. Panzade P., Puranik P. K. Carbopol Polymers: A Versatile Polymer for Pharmaceutical Applications. *Research Journal of Pharmacy and Technology.* 2010. № 3 (3). P. 672–675.
21. Viscoelastic properties and rheological characterization of carbomers / P. T. P. Kumara et al. *International Journal of Latest Research in Engineering and Technology.* 2015. Vol. 1, Iss. 6. P. 17–30. URL: http://www.ijlret.com/Papers/Vol-1-issue-6/4-A178.pdf.
22. Carbomers and their use in pharmaceutical technology / M. Rabisková et al. *Ceska a Slovenska farmacie.* 2004. Vol. 53, Iss. 6. P. 300–303.
23. Effect of pH on the chemical modification of quercetin and structurally related flavonoids characterized by optical (UV-visible and Raman) spectroscopy / Z. Jurasekova et al. *Physical Chemistry Chemical Physics.* 2014. Vol. 16, Iss. 25. P. 12802–12811. DOI: https://doi.org/10.1039/C4CP00864B.
24. Flavonoid oxidation in plants: from biochemical properties to physiological functions / L. Pourcel et al. *Trends in Plant Science.* 2007. Vol. 12, Iss. 1. P. 29–36. DOI: https://doi.org/10.1016/j.tplants.2006.11.006.

REFERENCES

1. Satyanarayana, S., Kumar, K. E., Rajashekhar, J., Thomas, L., Rajanna, S., Rajanna, B. (2007). Influence of aqueous extract of fenugreek seed powder on pharmacodyanamics and pharmacokinetics of gliclazide in rat and rabbits *Therapy, 4,* 457–463. doi: 10.1586/14750708.4.4.457.
2. Parasuraman, S., Thing, G. S., Dhanaraj, S. A. (2014). Polyherbal formulation: Concept of Ayurveda. *Pharmacognosy Reviews*., *8 (16),* 73–80. DOI: 10.4103/0973-7847.134229.
3. Hasan, S. Z., Misra, V., Singh, S., Arora, G., Sharma, S. (2009). Current status of herbal drugs and their future perspectives. *Biol Forum Int J., 1,* 12–17. doi: 10.1038/npre.2007.1176.1.
4. Yuan, H., Ma, Q., Ye, L., Piao, G. (2016). The Traditional Medicine and Modern Medicine from Natural Products. *Molecules, 21 (5),* 559. doi: https://doi.org/10.3390/molecules21050559.
5. Ishnava, K. B. (2018). Role of herbal medicine in dental health. *J Environ Chem Toxicol., 2 (1),* 28–29.
6. Petkovic, M. S., Kesic, L. G., Kitic, D. V., Milašin, J. M., Obradovic, R. R., Bojovic, M. D., Simonovic, A. A. (2015). Periodontal disease and phytotherapy. *Org Hyg Health, 3*, 1–4. doi: https://doi.org/10.4172/2332-0702.1000172.
7. Taheri, J. B., Azimi, S., Rafieian, N., Akhavan Zanjani, H. (2011). Herbs in dentistry. *Int Dent J., 61*, 287–296. doi: https://doi.org/10.1111/j.1875-595X.2011.00064.x.
8. Kumar, G., Jalaluddin, M., Rout, P., Mohanty, R., Dileep, C. L. (2013). Emerging trends of herbal care in dentistry. *J Clin Diagn Res., 7,* 1827–1829. doi: https://doi.org/10.7860/jcdr/2013/6339.3282.
9. Boddupalli, B. M., Mohammed, Z. N. K., Nath, R. A., Banji, D. (2010). Mucoadhesive drug delivery system: an overview. *J. Adv. Pharm. Technol. Res., 1,* 381–387. doi: https://doi.org/10.4103/0110-5558.76436.
10. Pragati, S., Ashok, S., Kuldeep, S. (2009). Recent advances in periodontal drug delivery systems. *Int. J. Drug Deliv., 1,* 1–14. doi: 10.5138/ijdd.2009.0975.0215.01001.
11. Kovalenko, S. M., Khokhlenkova, N. V., Azarenko, J. M. (2017). Methodological Aspects of Development of Gels for Treating Inflammatory Dental Diseases. *Asian J. Pharm., 11,* 129–135.
12. Phytodent®, tincture 100 ml. Available at: https://zvezda.kharkov.ua/en/catalog/fitodent-nastoyka-po-100-ml.html
13. Ruban, O. A., Maslii, Yu. S. (2019). Research on the choice of rational concentration of the gel forming agent in the composition of dental gel. *Annals of Mechnikov Institute, 2,* 29–33. doi: https://doi.org/10.5281/zenodo.3265076.
14. Maslii, Yu., Ruban, O., Levachkova, Yu., Gureyeva, S., Kolisnyk, T. (2020). Choice of Mucosal Adhesive in the Composition of a New Dental gel. *Pharmakeftiki, 32 (1),* 40–49.
15. Maslii, Yu. S., Ruban, O. A. (2018). The study of biopharmaceutical and adhesive characteristics of a dental gel. *News of Pharmacy, 1,* 28–32. doi: https://doi.org/10.24959/nphj.18.2188.

16. DP "Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv". (2015). *Derzhavna Farmakopeia Ukrainy. (Vols. 1-3; Vol. 1).* (2nd ed.). Kharkiv: DP "Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv", 1128.
17. European Directorate for the Quality of Medicines & Health Care. (2017). *European Pharmacopoeia.* (9th ed.). Strasbourg.
18. ICH harmonized tripartite guideline Q2 (R1). Validation of analytical procedures: text and methodology Q2 (R1). *Proceedings of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*. Geneva, Switzerland, 2005.
19. Baliga, S., Muglikar, S., Kale, R. (2013). Salivary pH: A diagnostic biomarker. *Journal ofIndian Society of Periodontology, 17 (4),* 461–465. doi: https://doi.org/10.4103/0972-124X.118317.
20. Panzade, P., Puranik, P. K. (2010). Carbopol Polymers: A Versatile Polymer for Pharmaceutical Applications. *Research Journal of Pharmacy and Technology, 3 (3),* 672–675.
21. Kumara, P. T. P., Prakash N. K. S. C., Lokesh, P., Manral, K. (2015). Viscoelastic properties and rheological characterization of carbomers. *International Journal of Latest Research in Engineering and Technology, 1 (6),* 17–30. Available at: URL: http://www.ijlret.com/Papers/Vol-1-issue-6/4-A178.pdf.
22. Rabisková, M., Sedláková, M., Vitková, M., Kuna, M. (2004). Carbomers and their use in pharmaceutical technology. *Ceská a Slovenská farmacie, 53 (6),* 300–303.
23. Jurasekova, Z., Domingo, C., Garcia-Ramos, J. V., Sanchez-Cortes, S. (2014). Effect of pH on the chemical modification of quercetin and structurally related flavonoids characterized by optical (UV-visible and Raman) spectroscopy. *Physical Chemistry Chemical Physics, 16 (25),* 12802–12811. doi: https://doi.org/10.1039/C4CP00864B.
24. Pourcel, L., Routaboul, J. M., Cheynier, V., Lepiniec, L., Debeaujon, I. (2007). Flavonoid oxidation in plants: from biochemical properties to physiological functions. *Trends in Plant Science, 12 (1),* 29–36. doi: https://doi.org/10.1016/j.tplants.2006.11.006.

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