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METHODOLOGICAL APPROACHES TO THE DESIGN OF SOLID DOSAGE FORMS OF NOOTROPIC ACTION ON THE BASIS OF PLANT RAW MATERIALS

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Обґрунтувано загальну методологію створення твердих лікарських форм з рослинної сировини на прикладі сухого екстракту та подрібнених коренів з кореневищами шоломниці байкальської та встановлення їх стабільності у процесі зберігання.

Мета. *Визначити загальні методологічні підходи до розробки твердих лікарських форм з рослинною сировиною - Scutellaria baicalensis.*

Матеріали та методи. *Стабільність розроблених препаратів вивчали методом тривалого зберігання при температурі (25±2) °С, та відносній вологості повітря 60±5 %. Показники якості контролювали протягом (0, 3, 6, 9, 12, 18, 22, 24, 27 міс).*

Результати. *Відповідно до запропонованого методологічного підходу, першим етапом дослідження було вивчення сучасного стану фітопрепаратів з створенням ноотропних та седативних ефектів.*

Встановлено фактори, які можуть впливати як на саму речовину, так і на якість готової лікарської форми. Досліджено природні джерела мінеральних комплексів (макро- та мікроелементи (МЕ)). Вивчено поглинання вологи та її вплив на фізико-хімічну стабільність та технологічну поведінку при підготовці лікарського засобу. Застосовували групу біорелевантних середовищ, що дозволяють моделювати поведінку, розчинення і адсорбцію препаратів у шлунково-кишковому тракті пацієнта.

Висновки. *Розроблено методичний підхід до приготування препаратів на основі нативної рослинної сировини та сухого екстракту (Scutellaria baicalensis). Вивчено термін зберігання таблеток і капсул і було визначено, що таблетки і капсули стабільні протягом 2 років зберігання при температурі зберігання 15-25 °С; оптимальні пакувальні матеріали - полівінілхлоридна плівка і алюмінієва фольга, набита лакована*

Ключові слова: *Шлемник байкальський, методологічні підходи, рослини, біорелевантність, ноотропн препаратиі, технологічні, фармако-технологічні, таблетки, капсули*

1. Introduction

Social danger of the central nervous system diseases determines the relevance of the search and development of new psychotropic drugs [1]. This problem has received special attention recently due to the appearance in the environment of many negative factors (excess information, extra noise, vibration, electromagnetic and radioactive radiation, chemical pollution, etc.), which causes the violation of physiological functions of the body, especially mental disorders [2]. Mental activity is disturbed not only with the extreme stress of excitement, but also with its relative insufficiency, which is possible during fatigue, intoxication [3]. For the correction and treatment of central nervous system diseases are used nootropic drugs. Therefore, the creation of effective and safe drugs in this area of action is an urgent problem.

The presence of a wide range of biological compounds in the Scutellaria baicalensis, which have a diverse pharmacological activity, and good tolerability, justifies the feasibility of studying the preparations of this plant as potential nootropic agents [4]. Today in the world, there are two directions of phytopreparations design: the use of native medicinal raw materials for the preparation of drugs and the receipt of extractions from medicinal plant raw materials (tinctures, extracts) with their subsequent introduction into the finished medicines. Both directions require the use of a certain methodological approach.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The methodology of developing rational composition and technology of dosage forms depends on the choice of dosage form. To create solid medicinal preparations on the basis of plant material, it was necessary to investigate the qualitative composition of the active substance, conduct a series of physico-chemical and pharmaco-technological studies in order to justify the choice of auxiliary substances and the method of obtaining.

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

The methodological guidelines of the criteria for the development of the Likarskih forms have accumulated widespread vicarities during the development of the various drugs. Different authors use these studies in the development of new drugs [5]. The methodology for the development of the rational composition and technology of the medicinal product depends on the purpose of treatment and the chosen dosage form [6–8].

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

According to literary data, there are no general approaches to preparations based on vegetable raw materials. Therefore, a methodological approach to the crea-

tion of a rational technology and the composition of solid medicinal preparations based on vegetable substances is relevant.

5. Formulation of goals (tasks) of Article.

To find out general methodological approaches for the design of solid dosage forms with plant material of Scutellaria baicalensis.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

The development of each new drug should occur directly through a consistently planned methodological approach, taking into account the chosen dosage form. We have offered to develop two dosage forms containing medicinal plant material and a dry extract of the Scutellaria baicalensis – tablets and capsules. The stability of the developed formulations was studied by the method of prolonged storage at a temperature (25±2) °C, and relative humidity of air 60±5 %. Quality indices were monitored during all period of the study (0, 3, 6, 9, 12, 18, 22, 24, 27 months).

In accordance with the proposed methodological approach, the first stage of the research was the study of the current state of phytopreparations with nootropic and sedative effects creation. It was necessary to conduct an analysis on the creation of herbal preparations and the peculiarities of technological methods for their production.

Expansion of the range of modern effective and safe medicines can be achieved by introducing into the pharmaceutical industry new original medicines based on natural raw materials.

Due to the transition of domestic pharmaceutical production to the rules of Good Manufacturing Practice (GMP), get stricter the requirements for the practice of cultivation and quality of medicinal plant materials. Ukraine has adopted "Good Agricultural and Collection Practices" (GACP) of medicinal plants, which is one of the good practices of GxP, which form the system of quality assurance of pharmaceutical production and complies with the current legislation of Ukraine. The principles of GACP are recommended for both the agricultural production of medicinal plants and their collection in nature. This guideline contains detailed requirements and recommendations in a specific area of activity – cultivation and harvesting of raw material of plant origin.

The next stage of the research was the marketing research of the market of nootropic drugs by studying the market segment of nootropics of plant origin in order to substantiate the expediency of developing and introducing into the industrial production of solid pharmaceutical products in the form of tablets and capsules of this direction of action.

In order to ensure the effectiveness of the developed medicines, it is necessary to establish factors that may affect both the substance itself and the quality of the finished dosage form. It was also necessary to determine the indicators of standardization and pharmacological activity of drugs.

Specificity of plants is that they are able to synthesize a huge number of various chemical compounds belonging to different classes. But it is important that therapeutic properties possess only those that have physiological (biological) activity [9].

Therefore, no less important is the study of medicinal plants for natural sources of mineral complexes (macro- and trace elements (TE)). There is a correlation between the accumulation of certain groups of BAS in plants and the concentration of TE in them.

The therapeutic effect of TE can increase the activity of the main active ingredient of medicinal plants. It is known that macro- and TE play a significant role in the life of organisms. They can act as activators of processes, acting on enzymes and genetic apparatus of cells. Enrichment of medicinal plants and medicinal plant raw materials with TE is usually carried out in the process of cultivation [10].

Of great importance is the method of obtaining both substance and finished product. Drying of extracts can be carried out in spray, sublimation dryers (without condensation) and in a vacuum-drying cabinet (through the condensation stage). We used a spray dryer to obtain dry extract.

Determination of the kinetics of moisture absorption of plant material substances, both dry extracts and native raw material, is an important criterion for further choice of auxiliary substances and technology for the manufacture of solid dosage forms. The value of moisture content and moisture absorption kinetics affects both physical and chemical stability and technological behavior when receiving a drug. In the dry extract of Scutellaria baicalensis, the complex of organic substances is present dominated by flavonoid glucuronides salts and carbohydrates, which create the conditions for increasing hygroscopicity.

Forecasted evaluation of bioavailability is one of the important stages in the process of developing the technology of drugs. One of the most important characteristics of medicinal substances is solubility. The study of solubility is used to predict bioavailability in vitro. For preparations from native raw materials, the expression of bioavailability in the gastrointestinal tract is very relevant. However, the use of classical pharmacopoeial buffer solutions in vitro does not always adequately reflects their behavior in vivo. As a way out of this problem, a group of biorelevant media was developed that allow modelling the behavior, dissolution and adsorption of drugs in the gastrointestinal tract of a patient. Biorelevant media are buffer solutions with the addition of natural surfactants that are as close as possible to the internal fluids of the human body in terms of chemical composition and physical and chemical properties, such as pH, osmolarity, buffer capacity, surface tension.

We have proposed studying the solubility of the sum of biologically active substances - flavanoids in the powder of the roots and rhizomes of the Scutellaria in biorelevant media FaSSIF and FeSSIF with pH 6.5 and 6.8.

The general methodological approach to the development of medicinal products with nootropic action on the basis of plant material is shown in Fig.1, 2.

One of the most important indicators of the quality of medicines is the shelf life. During the period of storage, there should be no negative changes in the physical, chemical, pharmacological and consumer characteristics of the drug. Stability of a medicinal

product and its quality are closely linked. The criterion of stability is preservation of the drug`s quality. Reduction of the amount of biologically active substance confirms the instability of the drug. Shelf life - the period during which a drug must fully maintain therapeutic activity, harmlessness, meet the conditions of regulatory documentation. Shelf life and stability are closely related. Stability studies are conducted starting from the earliest phases of pharmaceutical development. We have conducted a study of obtained tablets and capsules for 27 months, where we evaluated the indicators at set intervals (3.6, 9, 12, 18, 22, 24, 27). The preparations were stored in the contour-cell package on the basis of PVC film and aluminum foil.

The results are shown in Table 1 and Table 2. Studies show that, according to all quality indicators, the drugs development meet the requirements of regulatory documentation.

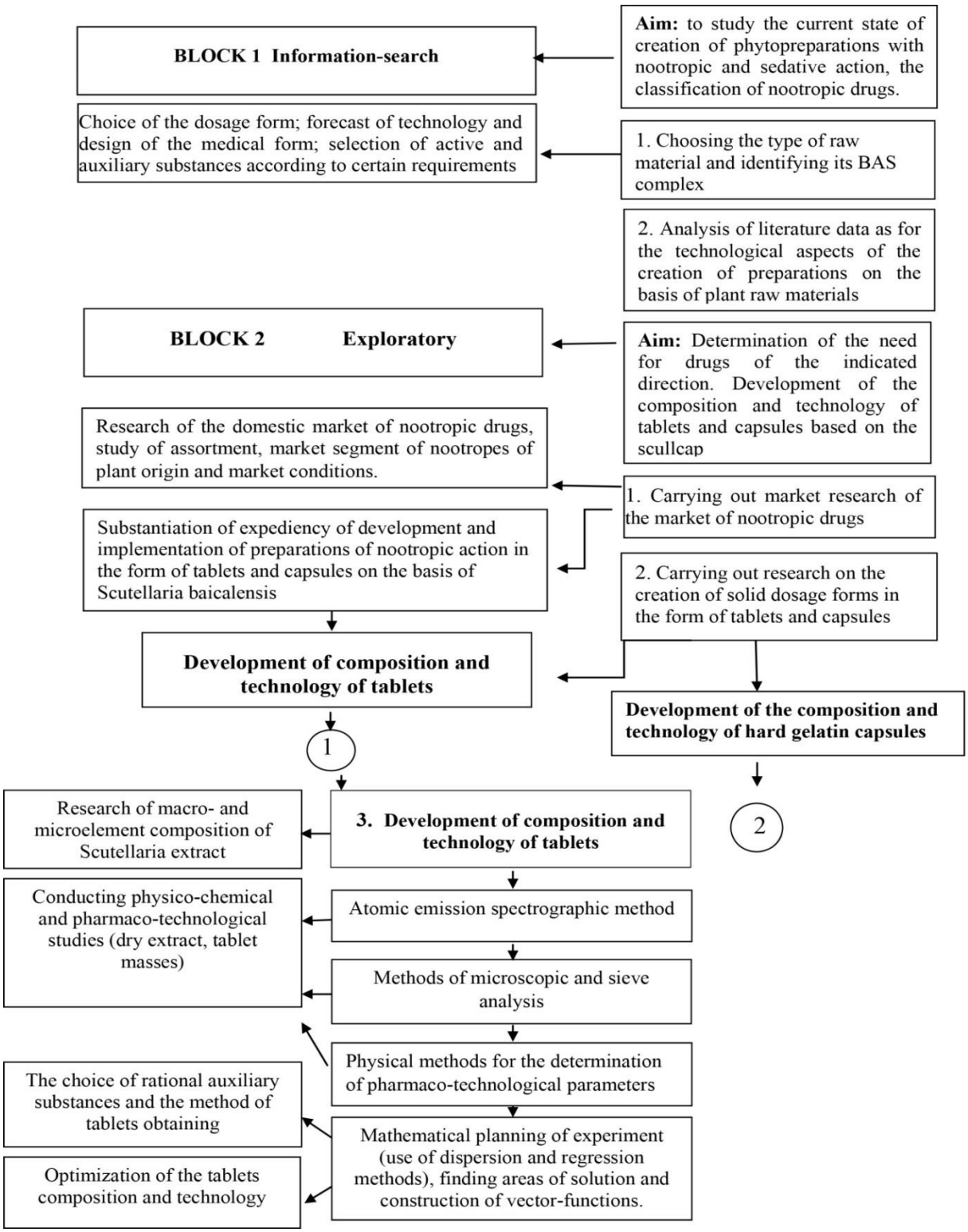

Fig. 1. Methodological approach to the creation of drugs with nootropic action on the basis of plant material

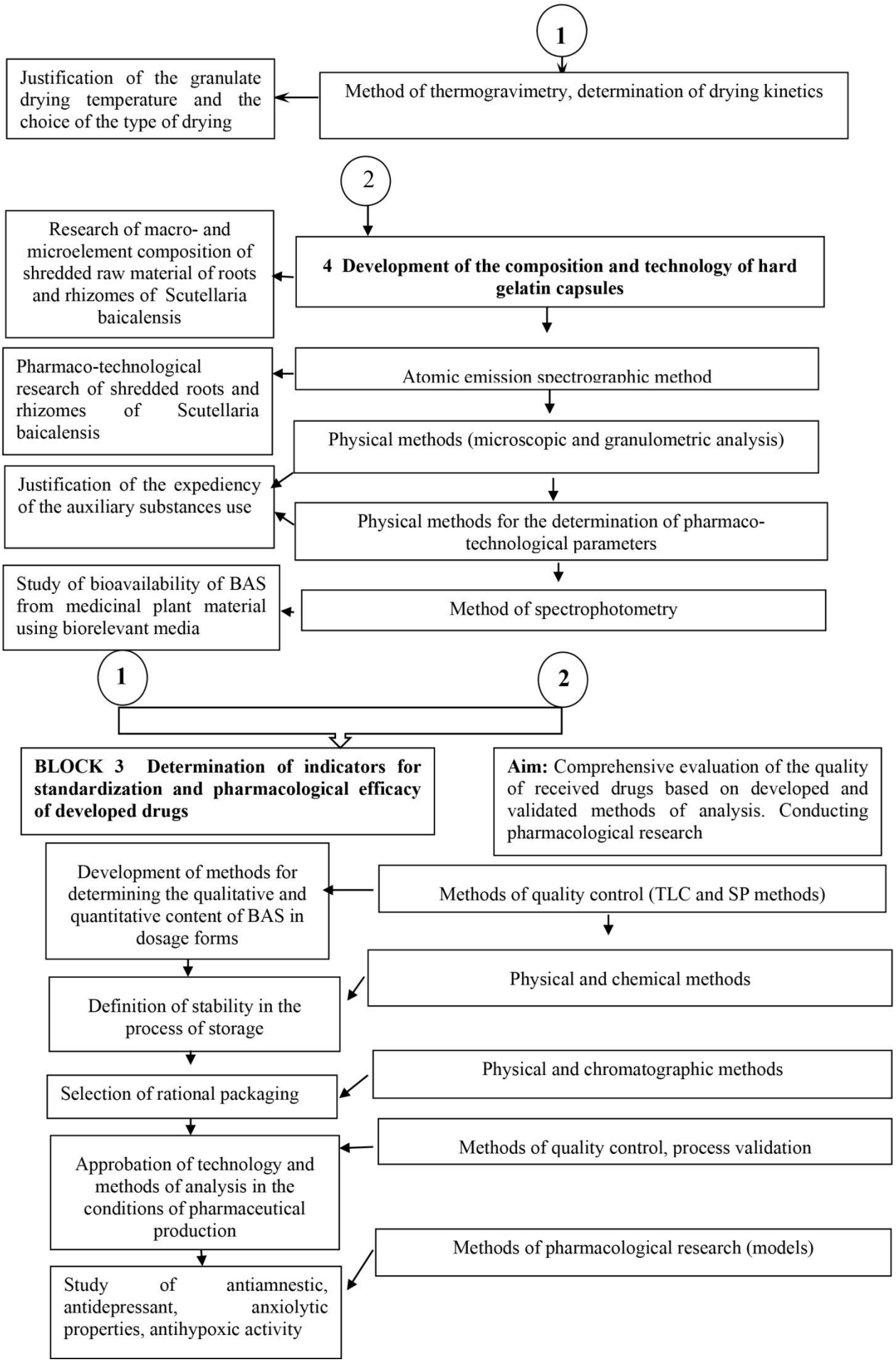

Fig. 2. Methodological approach to the creation of drugs with nootropic action on the basis of plant material

Table 1

Results of stability study of tablets under the conditional name "Scutex" during storage

Description	Identification		Average weight	Weight uniformity	Disintegration	Solubility	Friability, %	Quantification	Expiration date	Conclusions
	The sum of flavonoids	Baicalin						The sum of flavonoids, in terms of baicalin, in grams		
Tablets of light yellow color, flat-cylindrical shape with a line and a facet. The diameter of the tablet (10.0±0.3) mm, height (3.2±0.4) mm. On the surface of the tablets, the presence of individual inclusions of white color is allowed	The UV absorption spectrum of solution prepared for quantification of flavonoids in the range from 220 to 400 nm must have absorption maxima at wavelengths (27±93) nm and (320±3) nm.	On a chromatogram of test solution, a spot of brown color should be detected on the value of R_f corresponding to the spot on the chromatogram of baicalin PRS .	From 0.304 g to 0,336	They must comply with the requirements of the SPU, 1 ed	No more than 15 minutes In water	No less than 75 % in 45 min	Not more than 1 %	Not less than 0.0135 g in one tablet	2 years	during storage
Corresponds	Corresponds	Corresponds	0.324	Corresponds	8	91.1	Corresponds	0.0209	3 months	Suitable
Corresponds	Corresponds	Corresponds	0.318	Corresponds	10	94.47	Corresponds	0.0205	6 months	Suitable
Corresponds	Corresponds	Corresponds	0.320	Corresponds	9	91.89	Corresponds	0.0212	9 months	Suitable
Corresponds	Corresponds	Corresponds	0.322	Corresponds	11	91.66	Corresponds	0.0210	1 year	Suitable
Corresponds	Corresponds	Corresponds	0.324	Corresponds	10	93.96	Corresponds	0.0209	18 months	Suitable
Corresponds	Corresponds	Corresponds	0.324	Corresponds	9	92.28	Corresponds	0.0210	22 months	Suitable
Corresponds	Corresponds	Corresponds	0.323	Corresponds	9	93.14	Corresponds	0.0209	2 years	Suitable
Corresponds	Corresponds	Corresponds	0.322	Corresponds	8	92.25	Corresponds	0.0209	27 months	Suitable

Table 2

Results of study of stability of capsules under the conditional name "Scutella" during storage

Description	Identification		Weight uniformity	Disintegration	Quantitative definition	Shelf-life	Conclusions
	Sum of flavonoids	Baicalin			The sum of flavonoids, in terms of baicalin, in grams		
Solid gelatin capsules number 1 with a cap of green color and a white body, containing a brownish-yellow powder.	The ultraviolet absorption spectrum of a solution prepared for quantification of flavonoids in the range from 220 to 400 nm must have absorption maxima at wavelengths (279±3) nm and (320±3) nm.	On a chromatogram of test solution, a brown spot should be found corresponding in the Rf value to spot on the chromatogram of baicalin PRS .	From 0.277 g to 0.332 g	No more than 30 minutes in water	Not less than 0.03 g in one capsule	2 years	during storage
Corresponds	Corresponds	Corresponds	Corresponds	11	0.067	3 months	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	10	0.065	6 months	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	12	0.063	9 months	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	12	0.063	1 year	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	11	0.066	18 months	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	13	0.062	22 months	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	10	0.064	2 years	Suitable
Corresponds	Corresponds	Corresponds	Corresponds	12	0.063	27 months	Suitable

7. Conclusions from the conducted research and prospects for further development of this field

1. The methodological approach to the preparation of drugs on the basis of native vegetable raw material and dry extract (Scutellaria baicalensis) has been developed. It is proposed:

– to study the macro- and microelement composition of plant material, which significantly influences the pharmacological activity of the prepared preparations;

– to study moisture absorption of both substances and the finished dosage form for determining the method of obtaining and determining the rational choice of packaging of the finished product;

– to study the solubility of the sum of biologically active substances – flavanoids in the powder of roots and rhizomes of the Scutellaria baicalensis in biorelevant media.

2. The shelf life of tablets and capsules has been studied and it was determined that tablets and capsules are stable for 2 years of storage at a storage temperature of 15–25 °C; optimal packaging materials – polyvinyl chloride film and aluminum foil printed lacquered.

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