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Development of a target quality profile for capsules containing a dry extract of *Salvia sclarea* L. grown in Tajikistan

Aim. To work out the concept of scientific research on the pharmaceutical development of capsules based on the substance of a dry extract of *Salvia sclarea* L. (clary sage) grown in Tajikistan by developing a target drug quality profile.

Materials and methods. During the research, methods of a systematic approach, scientific analysis, comparison, analogy, and generalization of information on the pharmaceutical development of herbal medicines were used. Tabular and schematic tools for visual presentation of the data obtained were also applied.

Results. The pharmacological studies of a dry extract of *Salvia sclarea* L. grown in Tajikistan using the "elevated plus maze" test indicate the prospects of its use as an active substance of a moderate anxiolytic action in the dose of 300 mg/kg. The results obtained served as the basis for developing a target quality profile for capsules containing a dry extract as the first stage of the pharmaceutical development, implementing the programmable quality concept "Quality by Design". When developing the target quality profile for capsules, a set of complementary provisions, recommendations, and methods of the State Pharmacopoeia of Ukraine and the Eurasian Economic Union concerning the issues of technological, chemical, and microbiological requirements for the development of pharmaceutical products was analyzed.

Conclusions. Thus, the development of a target quality profile for capsules containing a dry extract of *Salvia sclarea* L. will make it possible to rationally use material resources and implement the programmable quality concept.

Keywords: *Salvia sclarea* L.; clary sage; dry extract; anxiolytic activity; target drug quality profile; technology of solid dosage forms.

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Розробка цільового профілю якості капсул із вмістом сухого екстракту *Salvia sclarea* L., вирощеної в Таджикистані

Мета наукового дослідження – розробити цільовий профіль якості капсул на основі субстанції сухого екстракту *Salvia sclarea* L. (шавлії мускатної), вирощеної в Таджикистані.

Матеріали та методи. Під час виконання досліджень використовували метод системного підходу, наукового аналізу, порівняння, аналогії та узагальнення відомостей про фармацевтичну розробку лікарських рослинних засобів. Також застосовували табличні та схематичні засоби наочної презентації отриманих даних.

Результати досліджень. Проведені фармакологічні дослідження сухого екстракту шавлії мускатної, вирощеної в Таджикистані за допомогою тесту «припіднятий хрестоподібний лабіринт», доводять перспективність його використання як активної субстанції помірної анксіолітичної дії в дозі 300 мг/кг. Отримані результати стали основою цільового профілю якості капсул із вмістом сухого екстракту як першого етапу фармацевтичної розробки, реалізуючи концепцію програмованої якості «Quality by Design». Розробляючи цільовий профіль якості капсул, проаналізували комплекс взаємодоповняльних положень, рекомендацій та методик Державної фармакопеї України та Євразійського економічного союзу щодо питань технологічних, хімічних та мікробіологічних вимог до розробки фармацевтичних препаратів.

Висновки. Отже, розробка цільового профілю якості капсул із вмістом сухого екстракту шавлії мускатної дозволить раціонально використовувати матеріальні ресурси й реалізувати концепцію програмованої якості.

Ключові слова: *Salvia sclarea* L.; шавлія мускатна; сухий екстракт; анксіолітична активність; цільовий профіль якості препарату; технологія твердих лікарських форм.

Statement of the problem. In the modern world, in conditions of excessive, intense, and inadequately prolonged stress exposure to various external factors, a human body needs therapeutic or prophylactic agents with a protective neurotropic or neuroprotective effect. Stress, especially chronic stress, is reasonably considered one of the main factors in the development of many pathologies [1]. Psychoemotional stress and constant fatigue lead to the development of various symptoms that force people to seek medical aid. During the period of stress, there are adaptive changes at the physiological, mental and behavioral levels. An increase in the level of emotional tension in the modern world, combined with concomitant negative factors, has brought cardiovascular diseases, in particular, strokes, myocardial infarction, coronary sclerosis, atherosclerotic cardiosclerosis, etc. to the first place among the causes of death [1].

Analysis of recent research and publications. Medicinal products derived from the medicinal plant raw material of *Valerianaceae, Paeoniaceae, Hypericaceae, Passifloraceae, Polemoniaceae, and Lamiaceae* families, which have a pronounced neurotropic effect, mainly the sedative activity, are widely known [2, 3]. At the same time, the analysis of the results of numerous scientific studies of the medicinal plant raw material conducted to expand the range of medicinal products with a sedative and anxiolytic activity shows that the greatest attention is paid to the representatives of the *Lamiaceae* family. *Salvia* L. is one of the largest genera of the *Lamiaceae* family, accounting for about 900 species. The most studied medicinal plant is *Salvia officinalis* L. (medicinal sage). *Salvia officinalis* leaves contain essential oil (up to 2.5 %), as well as di- and triterpenes, phenylpropanoids, caffeic acid derivatives, including rosemarinic and lithospermic acids, flavonoids, tannins, etc. [5, 6]. Flavonoids, in most cases flavones, can interact with various zones of GABA-α receptors and, as a result, affect their functioning. Neurotropic properties expressed in varying degrees are found in the following flavones – hispidulin, apigenin, chrysoeriol, luteolin, scutellarein, baicalin, baicalein, etc. Flavones interact with GABA-α receptors, as do benzodiazepines, which are among the most commonly used medicinal products [3-7].

Identification of aspects of the problem unsolved previously. In addition to the pharmacopoeial species, *Salvia sclarea* L. (clary sage), which grows in Tajikistan, is also of scientific interest [13, 14]. Due to favorable climatic conditions, the chemical composition of wild medicinal herbs in Tajikistan is very diverse and promising as a source of pharmacologically active substances.

Objective statement of the article. The Department of Pharmaceutical Technology and Pharmacology of the Tajik National University develops hard gelatin capsules containing a dry extract of *Salvia sclarea* L. The technology was developed for the production of a dry extract of clary sage (DECS) using the method of percolation and extraction with 70 % ethanol. In the studies on the standardization of DECS it was determined that the quantitative content of the total amount of flavonoids was at least 13.0 % calculated with reference to apigenin, and the quantitative content of the total amount of hydroxycinnamic acids was not less than 1.2 % calculated with reference to rosmarinic acid.

The aim of this work was to study the anxiolytic activity (anxiety reduction) of DECS and the design of a target quality profile for hard gelatin capsules with its content.

Presentation of the main material of the research. The anxiolytic activity of DECS was studied at the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy (Kharkiv, Ukraine). The screening search for the pharmacological activity of DECS was performed on white outbred female rats weighing 200 ± 20 g. Animals were kept in a separate room with controlled microclimate parameters. Animals were on a balanced diet (granulated feed TU.U 15.7-2123600159-001:2007) with free access to food and water. The animal care was carried out by standard laboratory operations, all stages of the study were carried out in accordance with Directive 2010/63/EU of the European Parliament and the Council dated September 22, 2010, on the protection of animals used for scientific purposes [8, 9].

Before the beginning of the experiment, animals underwent acclimatization for 14 days. During the acclimatization period, there was a daily examination of each animal (behavior and general physiological state were assessed),

and all animals were examined to identify possible cases of morbidity or mortality [10].

Each stage of the study was reproduced according to the following design: 24 animals were divided equally into 4 experimental groups:

- negative control (NC) / positive control (PC);
- animals administered DECS in the dose of 100 mg/kg;
- animals administered DECS in the dose of 200 mg/kg;
- animals administered DECS in the dose of 300 mg/kg.

Before conducting experimental tests, animals were injected with a suspension of the test substance in purified water daily on an empty stomach for 5 days. The NC group of animals received an adequate amount of the solvent. On day 5, permissive tests were performed on each group of animals regarding the last injection.

The results obtained were processed by descriptive statistics tools with an assessment of the distribution normality expressed as an arithmetic mean (M) and a standard error of the mean (SEM). The experimental groups were compared using parametric analysis methods (ANOVA, Tukey HSD test). The significance of the differences was determined by the level of significance $P<0.05$. Statistical processing was carried out using the basic software package MS Excel 2007 and IBM SPSS Statistics 22 [11].

The "elevated plus maze" (EPM) test was used to screen the anxiolytic activity of DECS, which was the basis for studying the effect of the intervention on the animal anxiety. The EPM test was conducted in the appropriate laboratory unit, where the following indicators were recorded within 5 minutes: the duration of staying in the open arm (including in the center of the unit), the duration of staying in the closed arm and the total number of crossings between the arms. The test was performed 1 hour after the last administration of the test sample [12].

In the EPM test, a significant manifestation of activity was observed in only one dose of DECS – 300 mg/kg. Doses of 100 and 200 mg/kg did not lead to modification of the behavioral reactions of rats compared to the conditional norm of the negative control (Table 1). At the maximum dose, DECS led to a significant increase in time spent in the open arm by 69.3 % (66.7 s) compared to the control. In addition, the number of crossings between the arms increased by 42.4 %, but there was no statistically significant difference of this indicator ($p>0.05$) in NC.

The results of the study showed that DECS when administered intragastrically to rats for 5 days in the dose of 300 mg/kg had a moderate anxiolytic effect.

Taking into account the spectrum of the pharmacological activity of DECS, as well as the data of the scientific literature on the therapeutic use of plants of the genus *Salvia* L, it is rational to consider DECS as a pharmaceutical substance for the development of capsules for use in the complex treatment of cardiovascular diseases [2, 7].

Today, a risk-based approach is relevant for the pharmaceutical development and for building a quality assurance system. The use of the programmable quality approach, an integral part of which is the development of a target drug quality profile, will ensure the release of a quality product to the market. The concept of Quality by Design (QbD) or "programmable quality" is the most modern approach in the drug development. The strategy of the programmable quality is shown in Fig. Despite the fact that in the diagram all the stages are presented sequentially, they can go in parallel and be repeated many times [13, 14].

Table 1

BEHAVIORAL REACTIONS OF RATS IN THE EPM TEST AGAINST THE BACKGROUND OF THE ADMINISTRATION OF DECS, n=6, (M ± SEM)

Experimental Group	Time of staying in the closed arm, s	Time of staying y in the open arm, s	Number of crossings
NC	203.83 ± 7.71	96.17 ± 7.71	6.67 ± 0.36
DECS, 100 mg/kg	197.67 ± 9.14	102.33 ± 9.14	5.50 ± 0.39
DECS, 200 mg/kg	187.17 ± 5.60	112.83 ± 5.60	6.17 ± 0.36
DECS, 300 mg/kg	137.17 ± 3.55*	162.83 ± 3.55*	9.50 ± 0.31

Note: * – the differences are significant concerning the negative control ($p<0.05$).

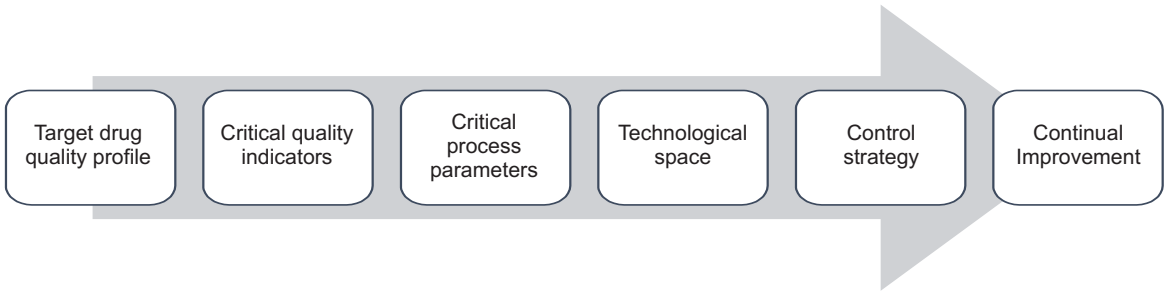

Fig. A schematic description of the main stages of QbD

This concept includes a set of complementary provisions and recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical Products (ICH): Q8 "Pharmaceutical Development", Q9 "Quality Risk Management", Q10 "Pharmaceutical Quality System". The ICH guidelines are not binding, but their application is the basis of an alternative approach to developing and manufacturing pharmaceutical products and is the key to ensuring the quality of medicines. The concept of QbD is described in Part II of Guideline Q8 (R2) "Pharmaceutical Development" [15-17].

In order to implement the approach of the programmable quality of a medicinal product and to build a methodological approach to the development of the capsule composition based on the DECS substance, a target quality profile for the capsules was developed by analyzing the regulatory documentation [17]. The target drug quality profile is a preliminary review of the characteristics of a medicinal product that must be achieved to gain the desired quality of the product, including in terms of its safety and efficacy. Typically, the target quality profile of a medicinal product at least includes information on the quality criteria of the drug product for such characteristics as appearance, activity, dosage, impurities, and microbiological purity, as well as the specification or acceptable limits that ensure the achievement of the target quality profile in terms of the patient's safety and efficacy.

When compiling the target quality profile for capsules based on the substance of DECS, when selecting critical indicators, the method of the preliminary hazard analysis (PHA) was used. It is based on the requirements of the State Pharmacopoeia of Ukraine, the GMP and the Pharmacopoeia of the Eurasian Economic Union for finished dosage forms, in particular for capsules [18]. According to this approach, the quality indicators and methods of their study were identified. They should be considered in the pharmaceutical development, according to the monograph.1.4.1.0005.15 "Capsules" of the Pharmacopoeia of the Eurasian Economic Union:

- appearance (the appearance of capsules is assessed visually);
- weight uniformity of the dosage form (private monograph.1.4.2.0009.15);
- uniformity of dosage (PM.1.4.2.008.18);
- disintegration (PM.1.4.2.0013.15);
- dissolution (PM.1.4.2.0014.15);
- microbiological purity (PM.1.2.4.0002.18)
- storage (PM.1.1.0010.18);
- packaging, labelling and storage of the medicinal product (PM.1.1.0025.18);
- shelf life of the medicinal product (PM.1.1.0009.18).

Thus, a preliminary target quality profile for hard gelatin capsules based on the DECS substance was compiled (Table 2). The dosage of the DECS substance was justified based on the results of the pharmacological preclinical studies presented.

Based on the theoretical knowledge of the methodology for the development of solid dosage forms, the analysis of the private monographs and the Pharmacopoeia of the Eurasian Economic Union on methods for studying the physicochemical and technological properties of the DECS substance and the capsular mass was carried out in a similar way. Thus, the necessary list of research methods in the development of the capsule composition includes:

- solubility of the DECS substance (PM.1.2.1.005.15);
- sieve analysis (PM.1.1.0015.15);
- optical microscopy (PM.1.2.1.0009.15);

Table 2

THE TARGET QUALITY PROFILE FOR CAPSULES BASED ON THE DECS SUBSTANCE

Quality parameter	Target value
ATC Classification System: – N drugs acting on the nervous system	Symptomatic treatment of cognitive disorders in elderly patients
Method of administration	Oral
Dosage form	Hard gelatin capsules
Dosage	300 mg
Packaging, labeling, storage	Polymer cans of type BP 10, storage at a temperature of 25 ± 2 °C, humidity 60 ± 5 %
Stability	2 years at a temperature not exceeding 25 °C
Uniformity of weight of the dosage form	300 mg or more: ± 7.5 %
Uniformity of dosage	Compliance with the requirements of private monograph.1.4.2.008.18
Disintegration	NMT 30 min
Dissolution	For 45 minutes of the experiment, at least 85 % of biologically active substances in terms of the main groups should pass into the solution
Assay of BAS	Tolerance ± 5 %
BAS Identification	TLC method, qualitative reactions
Microbiological quality	Compliance with the requirements of private monograph 1.2.4.0002.18

- crystallinity (PM.1.1.0018.15);
- loss on drying (PM.1.2.1.0010.15);
- hygroscopicity (Pharmacopoeia of the Eurasian Economic Union, monograph.2.3.6.0);
- degree of looseness of powders, angle of natural slope, determination of bulk volume (PM.1.4.2.0016.15).

When conducting the experimental studies, it is also necessary to use private monographs:

- determination of the water absorption coefficient and the plant raw material consumption coefficient (PM.1.5.3.0012.15);
- solubility of the substance (PM.1.2.1. 0005.15);
- spectrophotometry in the UV and visible regions (PM.1.2.1.1.0003.15);
- paper chromatography (PM.1.2.1.2.0002. 15);
- thin-layer chromatography (PM.1.2.1.2. 0003.15);
- validation of analytical methods (PM.1.1. 0012.15);
- statistical processing of the results of a chemical experiment (PM.1.1.0013.15).

Thus, the development of the target quality profile for capsules with the content of DECS and the design of a methodological approach to the development will make it possible to rationally use material resources and implement the programmable quality concept.

Conclusions. The development of the concept of scientific research on the pharmaceutical development of capsules based on the DECS substance by developing a target quality profile of the drug and a programmable quality strategy will ensure the proper quality of the future medicinal product. The pharmacological studies conducted using the "elevated plus maze" test showed that DECS when administered intragastrically to rats for 5 days in the dose of 300 mg/kg had a moderate anxiolytic effect.

Prospects for further research. The results of the pharmacological studies and the target quality profile for the capsules developed have formed the basis for the pharmaceutical development of hard gelatin capsules with the content of the DECS substance for use in the complex therapy of cardiovascular diseases.

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

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