https://10.31489/2025FEB3/79-88

UDC 615.322:579.61 Received: 25.05.2025 | Accepted: 15.07.2025 | Published online: 30 September 2025

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Pharmaceutical development and standardization of *Salvia stepposa* tablets

In response to the growing threat of antimicrobial resistance, plant-derived compounds are increasingly being explored as safe and effective alternatives to conventional antibiotics. This study focused on the development of solid oral dosage forms based on a dry extract of *Salvia stepposa* (MVSHS-40), rich in phenolic acids and flavonoids with proven antimicrobial and anti-inflammatory activity. The extract was obtained using microwave-assisted extraction (MAE) with 40 % ethanol, yielding up to 6 % rosmarinic acid as the dominant bioactive compound, along with caffeic and p-coumaric acids, and flavonoids such as apigenin, naringenin, and luteolin. The tablets were formulated by direct compression using microcrystalline cellulose, EMDEX, citric acid, and calcium stearate, with some variants incorporating essential oils. Out of more than 30 experimental variants, five optimized compositions were selected. Physicochemical and pharmacopeial evaluations confirmed excellent disintegration times (<12 minutes), dissolution rates (>79 %), uniform mass, high mechanical strength (≥107 N), and minimal friability (≥99.99 %). HPLC-UV/MS analysis quantified 3.046 mg of rosmarinic acid per tablet. Comparative analysis revealed a 5.5-fold increase in active content over commercial *Salvia officinalis* tablets while avoiding thujone-related safety concerns. Stability studies over 18 months demonstrated sustained integrity of pharmacological properties. The resulting MVSHS-40 tablets meet all quality specifications and represent a safe, stable, and effective herbal formulation with potential applications in the prevention and treatment of upper respiratory tract infections.

Keywords: *Salvia stepposa*, microwave-assisted extraction, rosmarinic acid, phenolic compounds, HPLC-MS/MS, phytopharmaceuticals.

Introduction

Amid the growing problem of microbial antibiotic resistance, there is an urgent need to find new, effective, and safe medicinal agents. Plant-derived bioactive compounds are attracting increasing attention due to their low toxicity and ability to inhibit the growth of pathogenic and opportunistic microorganisms [1]. In particular, herbal extracts have become a promising source of natural antimicrobial agents with a broad spectrum of activity and high bioavailability. Steppe sage (*Salvia stepposa*) is a plant known for its high content of phenolic compounds and flavonoids, which exhibit pronounced antimicrobial activity [2]. In recent studies, thin-layer chromatography (TLC) and high-performance liquid chromatography coupled with mass spectrometric detection (HPLC-MS/MS) were used to identify key components of sage extracts, among which rosmarinic acid was dominant [3], accounting for up to 6 % of the extract mass. Additionally, the extracts contained caffeic and p-coumaric acids, as well as flavonoids such as naringenin, apigenin, and luteolin. The antimicrobial activity of these extracts was confirmed through testing on bacterial strains (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*) and fungi of the genus *Candida albicans* [4]. The results showed significant inhibition of microbial growth, indicating the potential use of steppe sage extracts as natural antimicrobial agents.

Solid oral dosage forms, particularly tablets, dominate modern pharmaceutical production due to their versatility, cost-efficiency, and ease of administration [5]. Among them, tablets provide a targeted delivery system for the treatment of upper respiratory tract infections. The goal of this research was to develop a tablet formulation based on a dry extract of *Salvia stepposa* (MVSHS-40), recognized for its anti-inflammatory and antibacterial activity.

Experimental

Plant material. The wild species *Salvia stepposa* Des. -Schost (syn. *Salvia dumetorum*), native to the flora of Kazakhstan, was collected during field expeditions in the Karaganda region (Republic of Kazakhstan) at coordinates N 49°88898’; E 73°15569’, during its budding and flowering stages in July–August 2024.

Microwave-assisted extraction (MAE). MAE of *Salvia stepposa* Des.-Schost leaves was performed according to the methods described in the literature [6]. For MAE of *Salvia stepposa*, a 40 % hydroalcoholic

solution was used as the extracting solvent. Air-dried *Salvia* leaves weighing 20 g were placed into a 500 ml round-bottom flask, and 200 ml of the solvent was added, maintaining a solid-to-liquid ratio of 1:10 (mw%: vw%). The flask containing the material was placed into a domestic microwave oven operating at a frequency of 2.45 GHz and connected to a reflux condenser to condense vapors. Extraction was performed four times until a nearly clear solution was obtained, with microwave irradiation lasting 4 minutes at a power of 300 W. The exposure was carried out in 10-second cycles with 1-minute intervals to prevent overheating and boiling of the solvent. The temperature of the mixture was monitored every minute using an IR-T1 CONDTROL infrared thermometer. The obtained extracts were concentrated under vacuum on a Labtech IR-1LT rotary evaporator to preserve the bioactive compounds without degradation. Subsequently, the dry extract was obtained by vacuum drying at temperatures not exceeding 40 °C, ensuring the preservation of thermolabile components and producing a stable powder suitable for further use in pharmaceutical formulations.

High-Performance Liquid Chromatography. The analysis of rosmarinic acid in the tablets was performed using high-performance liquid chromatography (HPLC) combined with ultraviolet (UV) detection and real-time tandem mass spectrometry (ESI-MS/MS) according to the methodology [7]. The analysis was carried out on an Agilent 1260 Infinity HPLC system (Agilent Technologies, USA) equipped with a G1311C 1260 Pump VL (four-channel pump), G1329B 1260 ALS autosampler, G1316A 1260 TCC column thermostat, G1314C 1260 VWD VL+ variable wavelength detector, and a G6130A Quadrupole LC-MS/MS mass spectrometer. The system was operated using ChemStation software under Windows NT.

Chromatographic separation was performed on a reversed-phase Zorbax Eclipse Plus C18 column (150 mm × 4.6 mm, 3.5 μm, Agilent Technologies, USA). A gradient elution system was used with mobile phase A (2.5 % formic acid in water) and mobile phase B (2.5 % formic acid in acetonitrile). The gradient profile was as follows: 0.00 min—3 % B, 7.00 min—20 % B, 7.10 min—30 % B, 27.00 min—40 % B, 35.00 min—50 % B, 35.10 min—20 % B, 40.00 min—3 % B. The flow rate was 0.4 mL/min, and the column temperature was maintained at 30 °C. Tablets and standard of rosmarinic acid were dissolved in a 1:1 (v/v) mixture of acetonitrile and purified water. The injection volume was 20 μL for tablet and standard solutions. The eluent passed through the UV detector before reaching the mass spectrometry interface. UV detection wavelengths were set at 280 nm and 360 nm.

Mass spectrometric detection with electrospray ionization was performed in negative mode with the following optimized parameters: capillary temperature 350 °C; drying gas N_2 at 8 L/min; nebulizer pressure 45 psi. Data collection was carried out using the multiple reaction monitoring (MRM) method, which tracks specific mass transitions during the corresponding retention time windows.

Quantitative determination of rosmarinic acid was performed using the Agilent 1260 Infinity HPLC system.

The percentage of rosmarinic acid (X) in tablets containing dry extract of *Salvia stepposa* leaves was calculated using the formula:

$$X = \frac{S_1 \cdot m_0 \cdot 1 \cdot P \cdot 100}{S_0 \cdot m_1 \cdot 1.100}, \quad (1)$$

where:

S_1 — peak area of rosmarinic acid;

m_0 — mass of the standard sample of rosmarinic acid, g;

m_1 — mass of tablets containing dry extract of *Salvia stepposa* leaves, g;

P — content of rosmarinic acid in the standard sample, expressed as a percentage. Rosmarinic acid (molecular formula $C_{18}H_{16}O_8$), CAS — 20283-92-5, purity 98 % (Sigma-Aldrich, USA).

Methods of standardization of tablets [8, 9].

Description. According to the State Pharmacopoeia of the Republic of Kazakhstan (SPRK), Vol. 1, p. 550, general monograph "Tablets" and Pharmacopoeia of the Eurasian Economic Union (EAEU) 2.1.6.0.

Average tablet mass. The average mass of tablets was determined in accordance with SPRK Vol. I, 2.9.5 and EAEU Pharmacopoeia 2.1.9.5.

Disintegration. The disintegration test was performed according to SPRK Vol. I, 2.9.1 and EAEU Pharmacopoeia 2.1.9.1 using a Julabo disintegration tester (Germany).

Dissolution. The dissolution test was carried out in accordance with SPRK Vol. I, 2.9.3 and EAEU Pharmacopoeia 2.1.9.3.

 ISSN 3080-6836 (Print) ISSN 3080-6844 (Online)

Friability. Tablet friability was evaluated according to SPRK Vol. I, 2.9.7 and EAEU Pharmacopoeia 2.1.9.6 using an AE-1 friability tester (Charles Isch AG).

Tablet crushing resistance. The crushing resistance was determined according to SPRK Vol. I, 2.9.8 and EAEU Pharmacopoeia 2.1.9.7 using an HC 6.2 hardness tester (Kraemer Elektronik GmbH).

Microbiological purity. Testing was carried out according to SP RK Vol. I, 2.6.12, SPRK Vol. I, 2.6.13, SPRK Vol. I, 5.1.4 (category 3B), and EAEU Pharmacopoeia 2.3.1.4.

Loss on drying. Determination of loss on drying was performed according to SPRK Vol. I, 2.2.32 "Loss on Drying" and EAEU Pharmacopoeia 2.1.2.31.

Results and Discussion

Excipients play a vital role in tablet formulation, influencing tablet integrity, disintegration, drug release, and stability. Moisture content was tightly controlled to improve flowability and compressibility.

Five optimal compositions were identified from over 30 experimental variants (Table 1). MVSHS-40 served as the active pharmaceutical ingredient (API). Excipients included microcrystalline cellulose (MCC 105) as a binder and disintegrant, EMDEX (dextrates) as a filler, citric acid for pH stabilization, and calcium stearate as a lubricant. Peppermint and eucalyptus oils were included in selected formulations to enhance organoleptic properties.

Table 1

Optimized formulations for MVSHS-40 tablets (per tablet, mg)

Component	F1	F2	F3	F4	F5
Dry extract MVSHS-40	50.0	50.0	50.0	50.0	50.0
MCC 105	75.0	75.0	75.0	75.0	75.0
EMDEX	–	593	589.5	589	587.5
Citric acid	28.0	28.0	28.0	28.0	28.0
Calcium stearate	–	4.0	7.5	7.5	7.5
Lactose monohydrate	589.5	–	–	–	–
Peppermint oil	–	–	–	–	1.5
Eucalyptus oil	–	–	–	0.5	0.5
Tablet weight (mg)	750.0	750.0	750.0	750.0	750.0

The use of EMDEX improved flow and compressibility. Inadequate tablet ejection observed with 4 mg calcium stearate prompted an increase to 7.5 mg. MCC enhanced water absorption and disintegration, while essential oils improved flavor.

The tablets were evaluated for mass uniformity, disintegration, dissolution, mechanical strength, and friability, complying with SPRK standards. Formulation 5 was deemed optimal.

Table 2

Quality evaluation of MVSHS-40 tablets

Test	Requirement	F1	F2	F3	F4	F5
Appearance	Conforms	✓	✓	✓	✓	✓
Avg. weight variation	±5 %	0.002	0.004	0.002	0.003	0.003
Mass uniformity	±10 %	3	4	4	2	5
Disintegration time	≤15 min	13:00	12:35	12:55	12:45	11:47
Dissolution (45 min)	≥75 %	72 %	81 %	80 %	79 %	79 %
Crushing strength (N)	≥50 N	151.8	139.5	142.1	135.4	107.2
Friability	≥97 %	99.994	99.995	99.993	99.994	99.991

Bulk and tapped density, flow rate, compressibility, and ejection force were evaluated (Table 3).

Table 3

Physico-technological properties of MVSHS-40 tablet blend

Property	Value
Bulk density (g/cm³)	0.53 ± 0.01
Tapped density (g/cm³)	0.75 ± 0.02
Flow rate (g/s)	3.1 ± 0.1
Compressibility (kg)	8.5 ± 0.21
Compression index (%)	3.97
Ejection force (kg/cm²)	270.0 ± 8.0

The blend exhibited good flow and compressibility, suitable for direct compression.

Tablets were produced using direct compression. Weighing of MVSHS-40 and excipients was performed using MK-32.2 and ET-600P-E scales. All components were sieved through a PVS30 vibrosieve and mixed in an Airpac blender. Lubrication was performed by adding calcium stearate, followed by mixing for 5 minutes. Moisture content was controlled (5-6 %) using EVLAS-2M. Tablets were compressed using a rotary tablet press RTM-10 and then dedusted using an Elevating De-Duster.

Direct compression provided several advantages over wet granulation, including process simplicity, reduced equipment use, and lower labor and energy costs. The technological flowchart for the production of tablets with MVSH-40 by the direct compression method is presented in Figure 1.

 ISSN 3080-6836 (Print) ISSN 3080-6844 (Online)

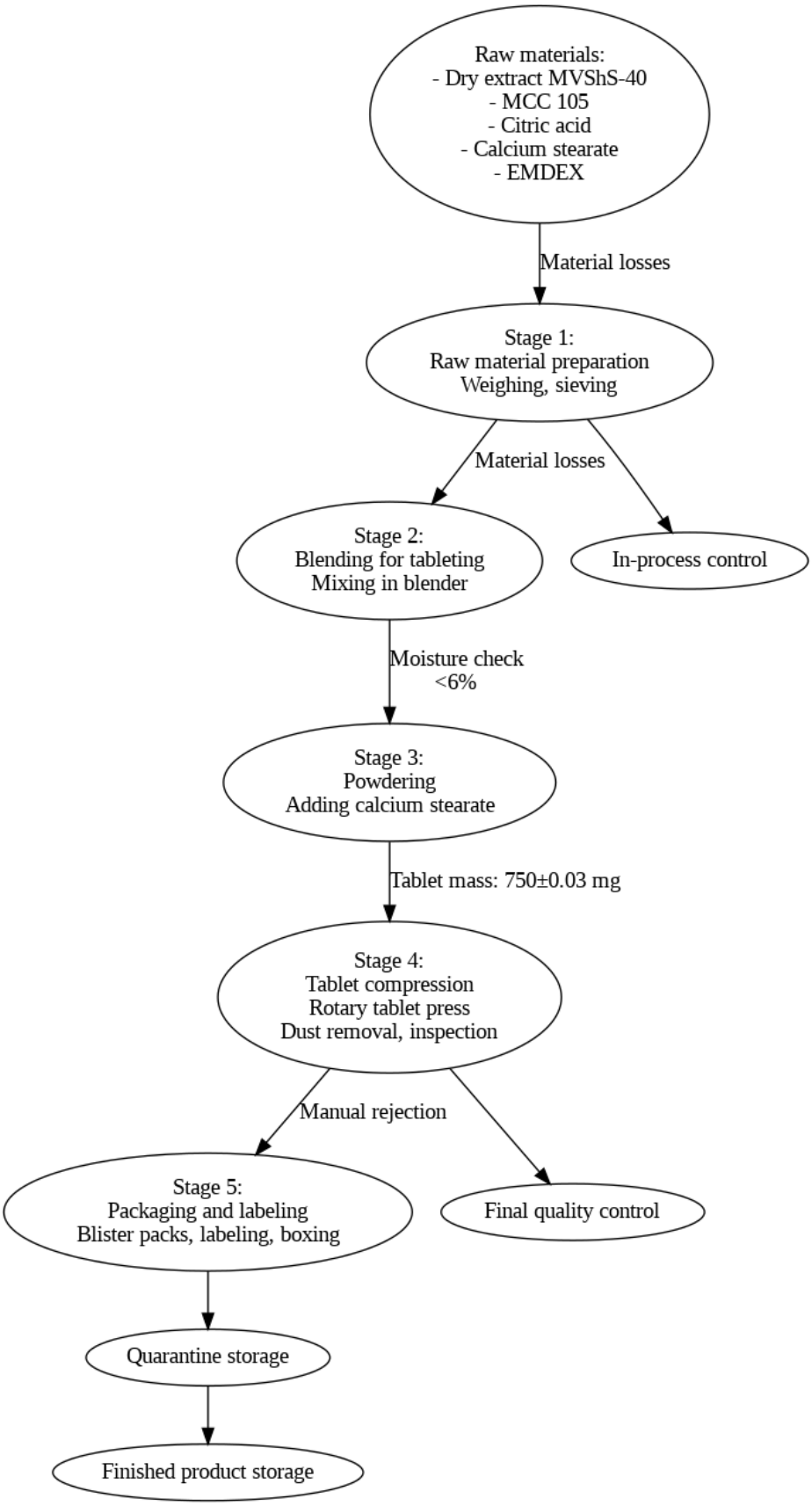
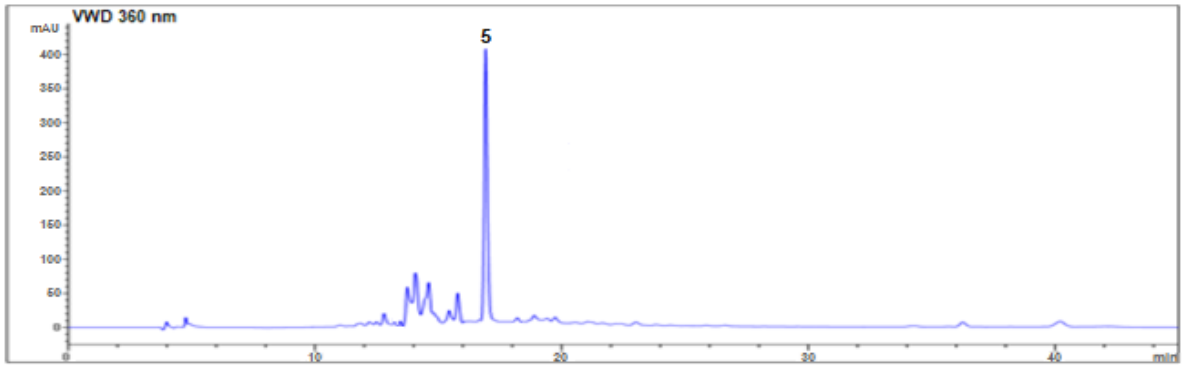
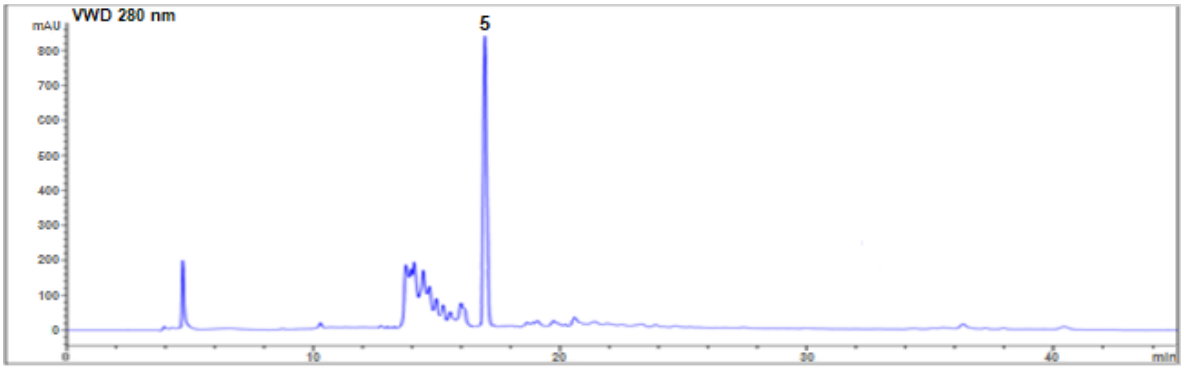


Figure 1. Technological flowchart for the production of tablets with MVSH-40.

HPLC-UV analysis confirmed the presence of rosmarinic acid, quantified as 0.41 % (3.046 mg per tablet). Chromatograms showed clear identification peaks under multiple detection wavelengths (Fig. 2).



A



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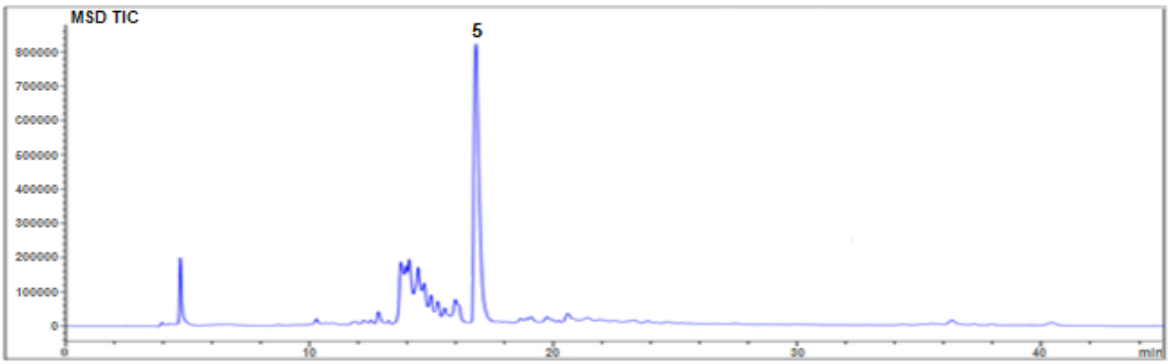

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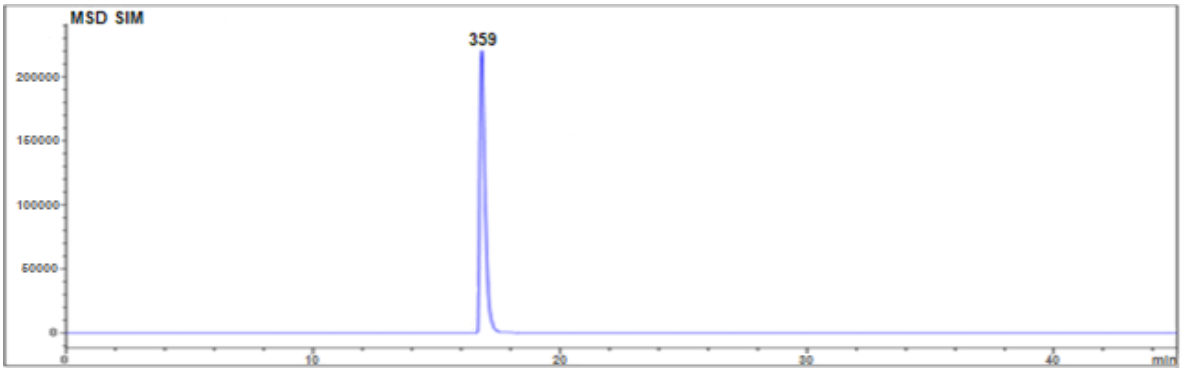

D

Figure 2. HPLC-UV chromatograms: A – 360 nm, B – 280 nm; HPLC-MS/MS: C – total ion chromatogram (TIC), and D – identification of rosmarinic acid in a tablets with steppe sage extract (SIM).

ISSN 3080-6836 (Print) ISSN 3080-6844 (Online)

A comparison with commercial *Salvia officinalis* tablets (Netherlands) highlighted key advantages of the MVSHS-40 tablets (Table 4).

Table 4

Comparative characteristics of Salvia-based tablets

Parameter	*Salvia officinalis*	*Salvia stepposa* (MVSHS-40)
Extract type	Dry	Dry
Active content	12.5 mg	50 mg
Essential oils	Sage essential oil	Eucalyptus, peppermint oils
Rosmarinic acid content	0.55 mg	3.046 mg
Safety concern	Contains thujone	Thujone-free

MVSHS-40 tablets offer significantly higher active content without the safety concerns associated with thujone.

Long-term stability studies were conducted over 18 months at 25±2 °C/60±5 % RH. Three production batches were evaluated at 0, 3, 6, 9, 12, and 18 months. No significant changes in physical or chemical parameters were observed, confirming product stability.

Quality specification was developed in compliance with EAEU and SPRK guidelines, encompassing organoleptic, physicochemical, microbiological, and assay parameters.

Table 5

Quality specification for tablets based on MVSH-40

Quality parameter	Specification (acceptable limits)	Test method references
Description	Tablets whole, uniform, light gray with light brown specks, homogeneous surface, bitter taste, characteristic aromatic odor.	EAEU Pharm. 2.1.6.0, SPRK Vol.1, p.550
Identification	Retention time of main peak in test solution chromatogram must match rosmarinic acid peak in standard chromatogram.	According to RD
Average mass / mass uniformity	±5 % individual tablet, ±10 % allowed deviations	EAEU Pharm. 2.1.9.5, SPRK Vol.1, 2.9.5
Disintegration	Not more than 15 minutes	EAEU Pharm. 2.1.9.1, SPRK Vol.1, 2.9.1
Dissolution	Not less than 75 % dissolved in 45 minutes	EAEU Pharm. 2.1.9.3, SPRK Vol.1, 2.9.3
Related substances (identified impurities)	Caffeic acid, cynaroside, p-coumaric acid, apigenin	According to RD
Friability	Not less than 97 %	EAEU Pharm. 2.1.9.6, SPRK Vol.1, 2.9.7
Tablet crushing strength	Not less than 50 N	EAEU Pharm. 2.1.9.7, SPRK Vol.1, 2.9.8
Microbiological purity	Category 3B. In 1.0 g: aerobic microorganisms ≤10*4, fungi ≤10*2, enterobacteria ≤10*2. No *Escherichia coli* in 1.0 g, *Salmonella* in 10.0 g, *Staphylococcus aureus* in 1.0 g allowed.	EAEU 2.3.1.4, SPRK Vol.1, 2.16.12, 2.16.13, 5.1.4
Loss on drying / Water content	Not more than 6.5 %	EAEU Pharm. 2.1.2.31, SPRK Vol.1, 2.2.32
Quantitative determination	Not less than 1.5 mg per tablet	According to RD
Packaging	Blister pack of polyvinyl chloride film and printed lacquered aluminum foil or heat-sealable packaging paper, 10 tablets per blister. 2, 3, or 5 blister packs per carton.	According to RD
Labeling	Label indicates name and content of active substances, expiry date, storage conditions, usage instructions.	According to RD
Transportation	According to GOST 17768-90E	GOST 17768-90E
Storage	In a place protected from light, at temperature not exceeding 25 °C	According to RD
Shelf life	18 months (observation period)	According to RD
Main pharmacological action	Anti-inflammatory, antimicrobial	According to RD

Conclusion

The development of tablets containing a dry extract MVSHS-40 of *Salvia stepposa* demonstrated promising results as a natural antimicrobial and anti-inflammatory agent suitable for pharmaceutical use. MAE using 40 % ethanol efficiently yielded a dry extract rich in bioactive compounds, including rosmarinic acid at 6 % of extract mass. The tablets, formulated by direct compression with optimized excipients, showed excellent physico-technological properties: uniform mass with variation within ±5 %, rapid disintegration times below 12 minutes, and dissolution rates above 79 % within 45 minutes, meeting pharmacopeial standards.

Quantitative HPLC-UV/MS analysis confirmed the presence of 3.046 mg of rosmarinic acid per 50 mg tablet of dry extract, significantly surpassing comparable commercial *Salvia officinalis* tablets (0.55 mg rosmarinic acid per tablet). Mechanical testing showed tablets had robust crushing strength (≥107 N) and low friability (≥99.99 %), ensuring integrity during handling and transport. Long-term stability studies over 18 months at controlled temperature and humidity demonstrated no significant changes in quality attributes, supporting product shelf life.

The absence of thujone, a toxic compound found in some *Salvia* species, further enhances the safety profile of MVSHS-40 tablets. Given their potent antimicrobial activity against key pathogens (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa,* and *Candida albicans*) and excellent pharmaceutical qualities, these tablets represent a viable natural alternative for upper respiratory tract infection treatments. This study confirms that MVSHS-40 tablets combine efficacy, safety, and stability, warranting further clinical evaluation and potential commercial production.

Funding

This research is funded by the Science Committee of the Ministry of Science and High Education of the Republic of Kazakhstan (Grant No. AP22785033) "Preclinical studies of a new drug based on steppe sage" 2024–2026 years.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Levaya Ya.K**. – Investigation, Methodology, Development of formulation and technology, Writing-review & Editing; **Atazhanova G.A**. – Conceptualization, Data curation; **Badekova K.Zh**. – Methodology, Plant material collection; **Ivasenko S.A**. – Data curation, HPLC-UV/MS.

Conflict of Interest

Authors declare no conflict of interest.

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Salvia stepposa таблеткаларын фармацевтикалық әзірлеу және стандарттау

Антимикробтық төзімділіктің артуына байланысты, өсімдік текті қосылыстар дәстүрлі антибиотиктерге қауіпсіз және тиімді балама ретінде кеңінен зерттелуде. Бұл зерттеуде микробқа қарсы және қабынуға қарсы белсенділігі дәлелденген фенол қышқылдары мен флавоноидтарға бай *Salvia stepposa* құрғақ экстракт (MVSHS-40) негізінде қатты дәрілік форманы әзірлеу жүргізілді. Экстракт микротолқындық экстракция (MAE) әдісімен 40 % этанол қолданып алынған, бұл 6 %-ға дейін розмарин қышқылын бөліп шығаруға мүмкіндік берді. Таблеткалар микроцеллюлоза, EMDEX, лимон қышқылы және кальций стеараты қосылған және кейбір нұсқаларға эфир майлары енгізілген тікелей таблеткалау әдісі арқылы дайындалды. 30-дан астам эксперименталды нұсқаның ішінен 5 оңтайландырылған құрамы таңдалды. Физика-химиялық және фармакопеялық сынақтар таблеткалардың дисперсиялану уақыты 12 минуттан аз, ерігіштік көрсеткіші 79 %-дан жоғары, салмақтың біркелкілігі, жоғары механикалық беріктік (≥107 Н) және төмен сынғыштық (≥99.99 %) екенін растады. HPLC-UV/MS талдауы бойынша бір таблеткада 3.046 мг розмарин қышқылы бар екені анықталды. Саудаға арналған *Salvia officinalis* таблеткаларымен салыстырғанда, MVSHS-40 таблеткаларында белсенді заттың мөлшері 5,5 есе жоғары болып, туйонмен байланысты қауіпсіздік мәселелерінен сақталған. 18 ай бойы жүргізілген тұрақтылық зерттеулері препараттың фармакологиялық қасиеттерінің өзгермейтінін көрсетті. Алынған MVSHS-40 таблеткалары барлық сапа талаптарына сәйкес келеді және жоғарғы тыныс жолдарының инфекцияларының алдын алу және емдеу үшін қолдану мүмкіндігі бар қауіпсіз, тұрақты және тиімді өсімдік негізіндегі дәрілік форма.

Кілт сөздер: Salvia stepposa, микротолқынды экстракция, розмарин қышқылы, фенолды қосылыстар, HPLC-MS/MS, фитофармацевтика.

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Фармацевтическая разработка и стандартизация таблеток из *Salvia stepposa*

В связи с возрастающей угрозой антимикробной резистентности растительные соединения всё чаще рассматриваются как безопасная и эффективная альтернатива традиционным антибиотикам. В данном исследовании была проведена разработка твердой лекарственной формы на основе сухого экстракта *Salvia stepposa* (MVSHS-40), богатого фенольными кислотами и флавоноидами с доказанной антимикробной и противовоспалительной активностью. Экстракт получали методом микроволновой экстракции (MAE) с использованием 40 % этанола, что позволило выделить до 6 % розмариновой кислоты. Таблетки формировали методом прямого прессования с применением микрокристаллической целлюлозы, EMDEX, лимонной кислоты и кальция стеарата; в некоторых вариантах добавляли эфирные масла. Из более чем 30 экспериментальных вариантов было отобрано пять оптимизированных составов. Физико-химические и фармакопейные исследования подтвердили отличное время диспергирования (<12 минут), высокую скорость растворения (>79 %), однородность массы, высокую механическую прочность (≥107 Н) и минимальную ломкость (≥99,99 %). Анализ методом ВЭЖХ-УФ/МС показал содержание 3,046 мг розмариновой кислоты в одной таблетке. Сравнительный анализ выявил 5,5-кратное превышение содержания активного вещества по сравнению с коммерческими таблетками *Salvia officinalis* при отсутствии опасений, связанных с туйоном. Исследования стабильности в течение 18 месяцев продемонстрировали сохранение фармакологических свойств препарата. Полученные таблетки MVSHS-40 соответствуют всем требованиям качества и представляют собой безопасную, стабильную и эффективную фитопрепаративную форму с потенциалом применения для профилактики и лечения инфекций верхних дыхательных путей.

Ключевые слова: *Salvia stepposa,* микроволновая экстракция, розмариновая кислота, фенольные соединения, ВЭЖХ-МС/МС, фитофармацевтика.

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 ISSN 3080-6836 (Print) ISSN 3080-6844 (Online)