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GAS CHROMATOGRAPHIC DETERMINATION OF METHYLSULFONYLMETHANE IN AN ANTI-ARTHRITIC COMBINED PHARMACEUTICAL PRODUCT

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Methylsulfonylmethane is a pharmacologically active compound that is widely used in mono- and combined pharmaceutical preparations to maintain the functional state of the musculoskeletal system. The development of promising anti-arthritic drugs requires proper analytical support, particularly the use of validated methods suitable for routine quality control in accordance with modern pharmaceutical requirements.

The aim. *The aim of the study was to develop and validate methods for the quantitative determination of methylsulfonylmethane in a combined medicinal product using gas chromatography with mass-selective detection (GC-MS) and flame ionization detection (GC-FID), and to compare their validation characteristics.*

Materials and methods*. The object of the study was a combined medicinal product in the form of a powder containing methylsulfonylmethane, glucosamine sulfate, chondroitin sulfate sodium and excipients. The study was conducted using Shimadzu GC/MS GCMS-QP2020 EI and Shimadzu GC-2010 Plus AF gas chromatographs with a flame ionization detector using capillary columns of type 5MS and the external standard method. The validation of the methods was carried out in accordance with the requirements of the State Pharmacopoeia of Ukraine and ICH Q2(R1) recommendations.*

Results. T*wo methods for the identification and quantitative determination of methylsulfonylmethane by gas chromatography were developed. The retention time of MSM by the GC-MS method was 9.157 min in the reference solution and 9.163 min in the test solution, and by the GC-FID method – 8.456 and 8.442 min, respectively. The validation characteristics of the methods were confirmed in the range of 80–120% of the nominal content (0.32–0.48 mg/ml) with correlation coefficients r > 0.9981. The relative standard deviations did not exceed 0.42%, and the total analytical uncertainty met the pharmacopoeial acceptance criteria*

Conclusions. *The proposed methods are accurate, reproducible and suitable for routine quality control of combination medicinal products containing methylsulfonylmethane*

Keywords: *methylsulfonylmethane, gas chromatography, GC-MS, GC-FID, validation of analytical methods, pharmaceutical analysis, combination medicinal product, quality control, quantification*

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1. Introduction

Methylsulfonylmethane (MSM, $(CH_3)_2SO_2$, M.w. 94.1) – is a naturally occurring organosulfur compound known by various names, including dimethylsulfone, methylsulfone, sulfonylbismethane, organic sulfur, or crystalline dimethyl sulfoxide [1]. Methylsulfonylmethane contains 34% sulfur, which is the fourth most abundant element after calcium, phosphorus, and potassium, and is present in relatively high amounts in hair, nails, skin, and cartilage [2]. The chondrogenic and anti-inflammatory effects of MSM characterize the compound's benefits in treating a variety of pathological conditions, from arthritis and other inflammatory disorders to improving wound healing and increasing energy and metabolism [3].

The MSM market is global in scope and is represented by a wide range of pharmaceutical products in the form of powders, capsules, tablets, solutions and oral gels (softgel). Such a representation of release forms provides ease, speed, flexibility of application and allows adapting products to the needs of different consumer groups. In terms of application, the leading place in the market is occupied by products with MSM [4] to support joint health, which is due to the high prevalence of degenerative diseases of the musculoskeletal system [5], age-related changes in cartilage tissue and increased physical activity in different age groups of the population [6].

It is believed that the effect of MSM on the human body is associated with its ability to act as a sulfur donor and promote the synthesis of sulfur-containing amino acids, including methionine, cysteine and taurine [7].

The presence of clinical studies on the anti-inflammatory, chondroprotective and immunomodulatory activity of MSM supports not only its commercial attractiveness, but also the functional feasibility of its use in pharmaceutical preparations. Taken together, these factors define methylsulfonylmethane as a strategically important ingredient for the further development of pharmaceutical portfolios.

A promising drug has been proposed as an anti-arthritic combined medicinal product of MSM with glucos-

amine and chondroitin sodium sulfate [8]. Despite the availability of pharmacopoeial methods for the quantitative determination of MSM, most of them are focused on the analysis of single-component dosage forms using an internal standard, which complicates sample preparation and increases the risk of additional sources of analytical error. This makes it advisable to develop simplified, selective and reproducible methods suitable for routine quality control of combination drugs [9]. Considering the volatility of methylsulfonylmethane, its quantitative content in the substance and finished single-component medicinal products is determined by gas chromatography using an internal standard of diethylene glycol methyl ether [10, 11]. The same approach is used in combinations of compounds of glucosamine hydrochloride and chondroitin sulfate, using helium as the mobile phase [12, 13] or gaseous nitrogen [14] with flame ionization detection. At the same time, there are no validated methods using the external standard method for multicomponent medicinal products in powder form.

The aim of this study was to develop and validate methods for the quantitative determination of methylsulfonylmethane in a combination medicinal product by gas chromatography with mass-selective and flame ionization detection, as well as to compare their validation characteristics.

2. Research planning (methodology)

The study is aimed at developing and validating a selective, precise, and reproducible method for the quantitative determination of methylsulfonylmethane in a combination medicinal product.

When choosing an analytical approach, consider the physicochemical properties of methylsulfonylmethane, its volatility and thermal stability, as well as the presence of excipients and concomitant active pharmaceutical ingredients in the composition of the medicinal product, which can potentially affect the selectivity of the determination.

Select conditions for determining MSM by gas chromatography with two types of detection – mass-selective (GC/MS) and flame ionization (GC-FID) for a comprehensive assessment of the possibility of identification and quantification, to determine the maximum uncertainties of the analysis methods and to establish acceptance criteria.

Validate analytical methods in accordance with the requirements of the State Pharmacopoeia of Ukraine and ICH Q2(R1) recommendations, assessing validation characteristics such as robustness, selectivity, linearity, precision, limit of detection (LOD), and limit of quantification (LOQ).

3. Materials and research methods

Experimental studies were conducted in the second half of 2025 at the Materials, Substances and Products Research Department of the Transcarpathian Research Expert Forensic Center of the Ministry of Internal Affairs of Ukraine.

3. 1. Materials

The object of the study was a promising drug in the form of a powder in a sachet, the components of which are listed in Table 1.

Table 1

Composition of the studied medicinal product

Substance	Contents	Manufacturer	Batch used in the study, quantitative content of the API
Glucosamine sulfate	1500 mg	Shandong Xiwang Sugar Industry, China	XWAC003, 99.97%
Chondroitin sodium sulfate	500 mg	Bioiberica, s.a.u. R.M. Barcelona, Spain	F0932, 105.00%
Methylsulfonylmethane	400 mg	Shijiazhuang Jirong Pharmaceutical, China	101-1303006, 100.05%
Sodium hyaluronate	30 mg	Nippon Rica, Japan	5992-143, 96.40%
Ascorbic acid	80 mg	SD LUWEI Pharmaceutical,Co. Ltd, China	201404197, 99.63%
Sorbitol	1000 mg	Evonic Industries, Germany	2111240201, 99.93%
Citric acid	490 mg	Shandong Ensing Industry Co., Ltd, China	3MT2504023, 99.90%
Total	4000 mg	–	–

All active pharmaceutical ingredients and excipients were of pharmacopoeial quality, in accordance with the manufacturer's quality certificates and the requirements of the current pharmacopoeias (USP, EP). To prepare the reference solution, methylsulfonylmethane of pharmacopoeial quality (series 101-1303006, manufacturer Shijiazhuang Jirong Pharmaceutical (China), purity 100.05%), which meets the requirements of the USP monograph "Methylsulfonylmethane", was used.

3. 2. Equipment

The research was carried out on a Shimadzu GC-2010 Plus AF gas chromatograph with a flame ionization detector (Japan) and a Shimadzu GC/MS GCMS-QP2020 EI gas chromatograph with mass-selective detection (Japan). Sample portions were weighed on an AXIS analytical balance (Poland). Sample preparation was carried out using class A measuring vessels and reagents that meet the requirements of EP/SPhU. A Kraft & Dele KD500 ultrasonic bath (Poland) was used to dissolve the samples.

3. 3. Procedure

Solvent: methanol for chromatography.

Test solution. An amount of the test substance equivalent to 20.0 mg of methylsulfonylmethane is placed in a 50.0 ml volumetric flask, shaken with 20 ml of methanol for chromatography in an ultrasonic bath at room temperature for 10 minutes, the volume of the solution is brought to the mark with the same solvent. The mixture is filtered, discarding the first 5 ml of the filtrate.

Reference solution. 20.0 mg of methylsulfonylmethane is dissolved in 20 ml of methanol for chromatography and the volume of the solution is adjusted to 50.0 ml with the same solvent.

The chromatography conditions are given in Table 2.

Table 2

Conditions for determining methylsulfonylmethane in a medicinal product by gas chromatography

Chromatographic system	
Instrument	
Shimadzu GC- 2010 Plus AF	Shimadzu GC/MS GCMS-QP2020 EI
Detector	
Flame ionization	mass detector, electron impact ionization
Column	
capillary column RXI-5MS (USA), length – 30 m, diameter – 0.25 mm, phase – 0.25 μm	capillary column HP-5MS (USA), length – 30 m, diameter – 0.25 mm, phase – 0.25 μm
Temperature	
– column: 40°*C*, *h*old 5 min., heating – 10°C/min., T_{fin} = 280°C; – injector: 250°C; – detector: 300°*C*	– column: 40°*C*, hold 5 min., heating – 10°C/min., T_{fin} = 280°C; – injector: 250°*C*; – detector: interface temperature: T = 280°*C*; – Ion source temperature: T = 200°*C*
→	Ionization energy: 70eV
Carrier gas: helium	
Flow rate: 1.5 mL/min	
Injector volume: 1 μL	
Injector type: Split	
Split ratio 40:1	

The choice of capillary columns of the 5MS type was due to their versatility, thermal stability and ability to provide effective separation of low molecular weight sulfur-containing organic compounds, in particular sulfones. The use of a non-polar stationary phase allowed to minimize the influence of matrix components of the combined medicinal product and to provide reproducible values of the retention time of methylsulfonylmethane with different types of detection.

3. 4. Validation of analytical methodology

The validation of the method was carried out for analysis by the standard method under conditions of conventional (non-vapor phase) chromatography according to the requirements of the general article of the SPhU 5.3.N.2. "Validation of analytical methods and tests" [15, 16]. To prepare MSM solutions at a concentration of 80.0–120% of the nominal, samples of the model mixture of 0.16 g, 0.17 g, 0.18 g, 0.19 g, 0.20 g, 0.21 g, 0.22 g, 0.23 g and 0.24 g were taken and dissolved in 10 ml of methanol for chromatography and the volume of the solution was brought to 50.0 ml with the same solvent. Then 1 μl of each solution was introduced into the gas chromatograph and analyzed under optimized conditions. The data were used to construct a curve of the peak area versus concentration.

The test solution and the reference solution were chromatographed alternately, obtaining 5 chromatograms of each solution.

For each solution, the average peak area values and the content of the test substance in the composition of the medicinal product were calculated.

The total uncertainty of sample preparation was calculated taking into account the requirements of the SPhU [15].

3. 5. Statistical data processing

Statistical data processing was carried out in accordance with the requirements of SPhU 5.3.N.1. "Statistical analysis of chemical experiment results" using Microsoft Excel software [15]. To process the obtained results, the calculation of the mean value, standard deviation of the mean result and relative standard deviation (RSD) were used. Additional methods of mathematical statistics were not used, since the study was analytical in nature.

4. Research results

The starting point for the development of all validation criteria is to determine the maximum uncertainty of the analysis method and establish acceptance criteria [15]. For this purpose, 5 chromatograms of the reference solution (Fig. 1, 4), the test solution (Fig. 2, 5) and placebo solutions (Fig. 3, 6) were obtained. The peak areas obtained as a result of the studies are given in Tables 3, 4.

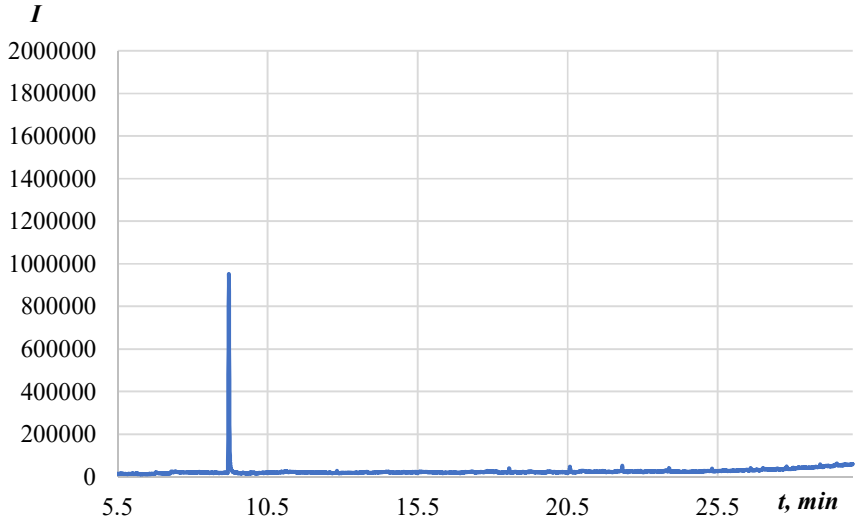

Fig. 1. Typical GC/MS chromatogram of a reference solution

Table 3

Peak areas of the test solution and reference solution obtained during quantitative determination by GC/MS

–	Peak areas (S and S_{st}) for chromatograms No.				
	1	2	3	4	5
Test solution	1844912	1829775	1839102	1832668	1841958
Reference solution	1892345	1873210	1886789	1879654	1875767

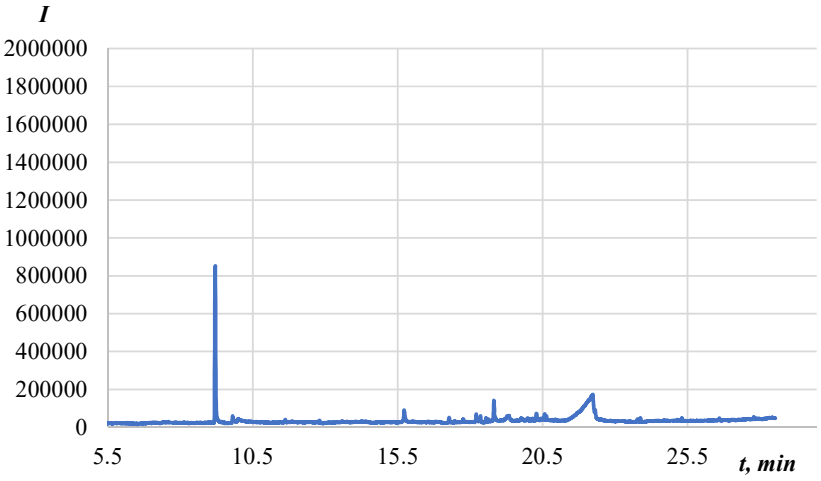

Fig. 2. Typical GC/MS chromatogram of the test solution

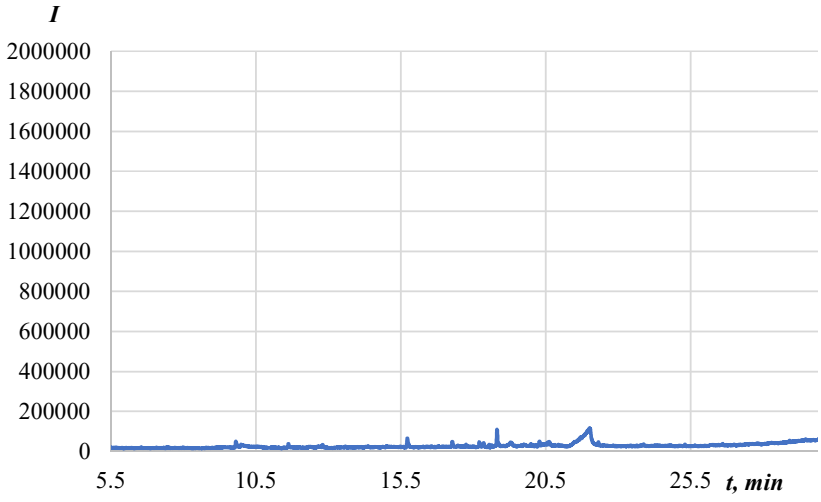

Fig. 3. Typical GC/MS chromatogram of a placebo solution

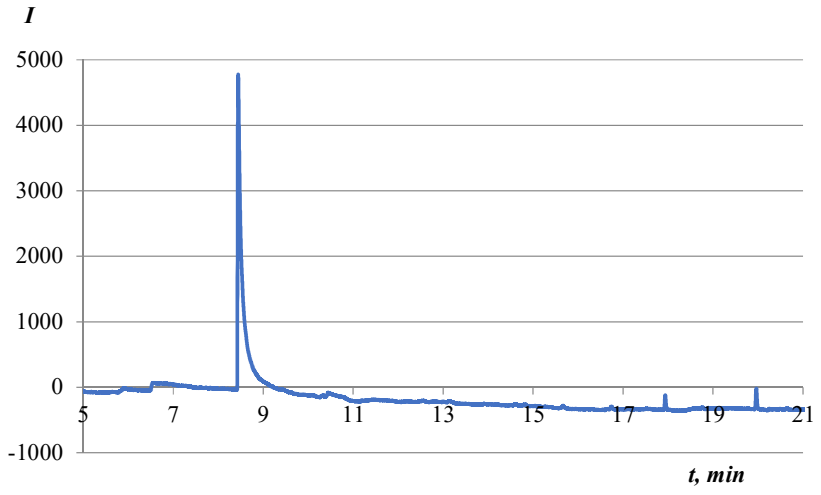

Fig. 4. Typical GC-FID chromatogram of the reference solution

The relative standard deviations of the peak areas for the test solution are 0.40%, for the reference solution – 0.42%, which indicates the high precision of the GC/MS method under repeatability conditions.

The data in Table 4 demonstrate low values of relative standard deviation (test solution – 0.35%, reference solution – 0.38%). Comparative analysis of the results obtained using mass-selective and flame ionization detection indicates comparable precision of both methods within the limits of repeatability. At the same time, the use of GC/MS provides additional identification reliability due to the mass spectral characteristics of the analyte, which is especially important at the stages of drug development and validation, while GC/MS can be recommended for routine quantitative quality control.

The total uncertainty of sample preparation of the proposed methods is

$$\Delta Sp,\ r = \sqrt{\left(0.2^2 + 1^2\right) + \left(0.23^2 + 0.17^2\right)} = 1.06 \le \max \Delta As = 1.6\%.$$

Total uncertainty of the final analytical operation:

– for GC/MS method

$$\Delta FAO,\ r = \sqrt{0.38^2 + 0.40^2} = 0.55 \le \max \Delta As = 1.6\%;$$

– for GC-FID method

$$\Delta FAO,\ r = \sqrt{0.33^2 + 0.36^2} = 0.49 \le \max \Delta As = 1.6\%.$$

The total uncertainty of the determination of methylsulfonylmethane by GC in the composition of the medicinal product is:

– for GC/MS method

$$\Delta As,\ r = \sqrt{1.06^2 + 0.55^2} = 1.19 \le \max \Delta As = 1.6\%;$$

– for GC-FID method

$$\Delta As,\ r = \sqrt{1.06^2 + 0.49^2} = 1.17 \le \max \Delta As = 1.6\%.$$

As can be seen, the total uncertainty of the proposed GC methods for quantitative determination of the finished medicinal product by the standard method corresponds to the recommendations of the general article SPhU 5.3.N.2 “Validation of analytical methods and tests” [15] and ICH Q2(R1) [17], which confirms the reliability and reproducibility of the proposed methods.

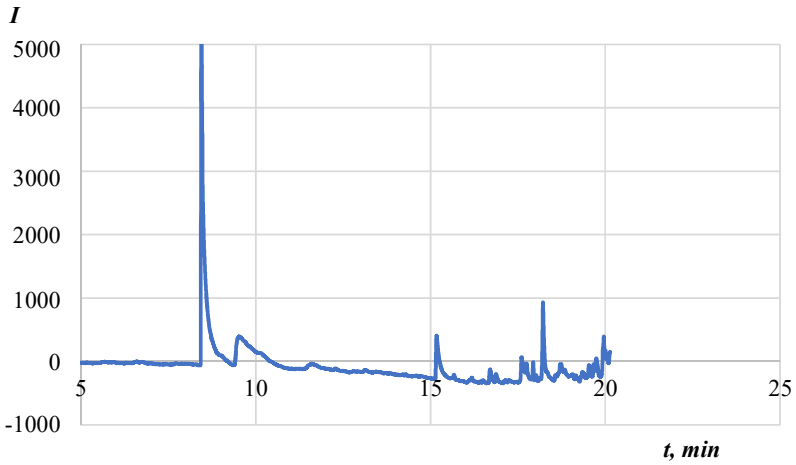

Fig. 5. Typical GC-FID chromatogram of the test solution

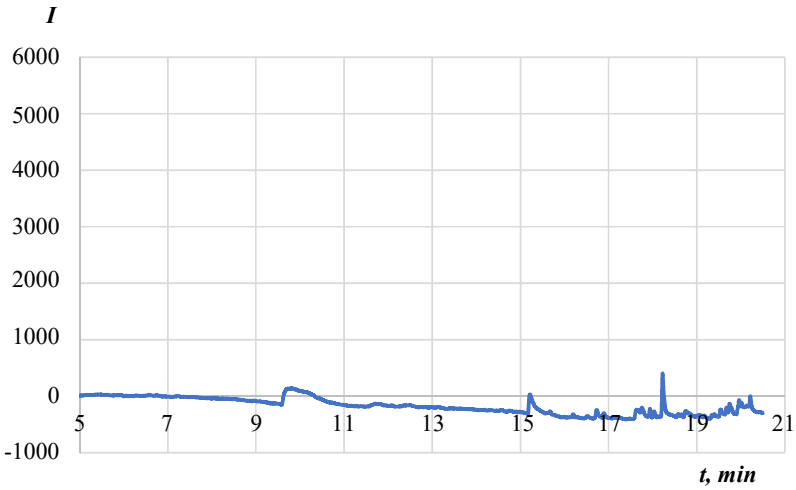

Fig. 6. Typical GC-FID chromatogram of a placebo solution

One of the validation characteristics that was determined before the start of other validation studies was the stability check of the test solution and the reference solution (Table 5), which is a component of the robustness assessment, since a change in the analyte concentration in the solutions can affect the reliability of the results obtained [18, 19].

To confirm the specificity of the analytical method and the identification of analytes of the substances being determined, chromatograms obtained from the following solutions were compared:

– reference solution (Fig. 1, 4);
– test solution (Fig. 2, 5);
– placebo solution (Fig. 3, 6).

There are no additional peaks in the chromatograms of the placebo solution, the retention times of which would coincide with the retention times of the target peak of MSM. This confirms the specificity of the method and the absence of the influence of excipients on the determination of the active pharmaceutical ingredient in the studied medicinal product.

Linearity for the studied method was studied for 9 concentrations of MSM solutions, which covered the range from 80% to 120% of the nominal content of the active pharmaceutical ingredient in the model mixture (Fig. 7).

The methods demonstrated linearity in the concentration range of 0.32–0.48 mg/mL (corresponding to 80–120% of the nominal concentration) with correlation coefficients $r > 0.9981$ regardless of detection.

The limit of detection

$$LOD = 3.3 \times S_a / b,$$

and the limit of quantification

$$LOQ = 10 \times S_a / b,$$

were calculated as information on how much the range of application of the method exceeds its maximum capabilities ("safety margin" of the method).

Table 4

Peak areas of the test solution and reference solution obtained during quantitative determination by GC-FID method

–	Peak areas (S and S_{st}) for chromatograms No.				
	1	2	3	4	5
Test solution	32160	32340	32210	32310	32240
Reference solution	32230	32410	32300	32370	32275

Table 5

Results of stability study of the test solution and the reference solution

Chromatogram	MSM Area	"Found / Entered"	Deviation from 100%
GC/MS			
Test solution, freshly prepared	1837483	–	–
Test solution, 24 h	1826485	99.40	|–0.6|
GC-FID			
Test solution, freshly prepared	32272		
Test solution, 24 h	32158	99.65	|–0.35|
|GC/MS			
Test solution, freshly prepared	1881553	–	–
Test solution, 24 h	1879649	99.89	|–0.11|
GC-FID			
Test solution, freshly prepared	32317		
Test solution, 24 h	32264	99.87	|–0.13|
Requirement:			≤ 5%
Conclusion:			Corresponds

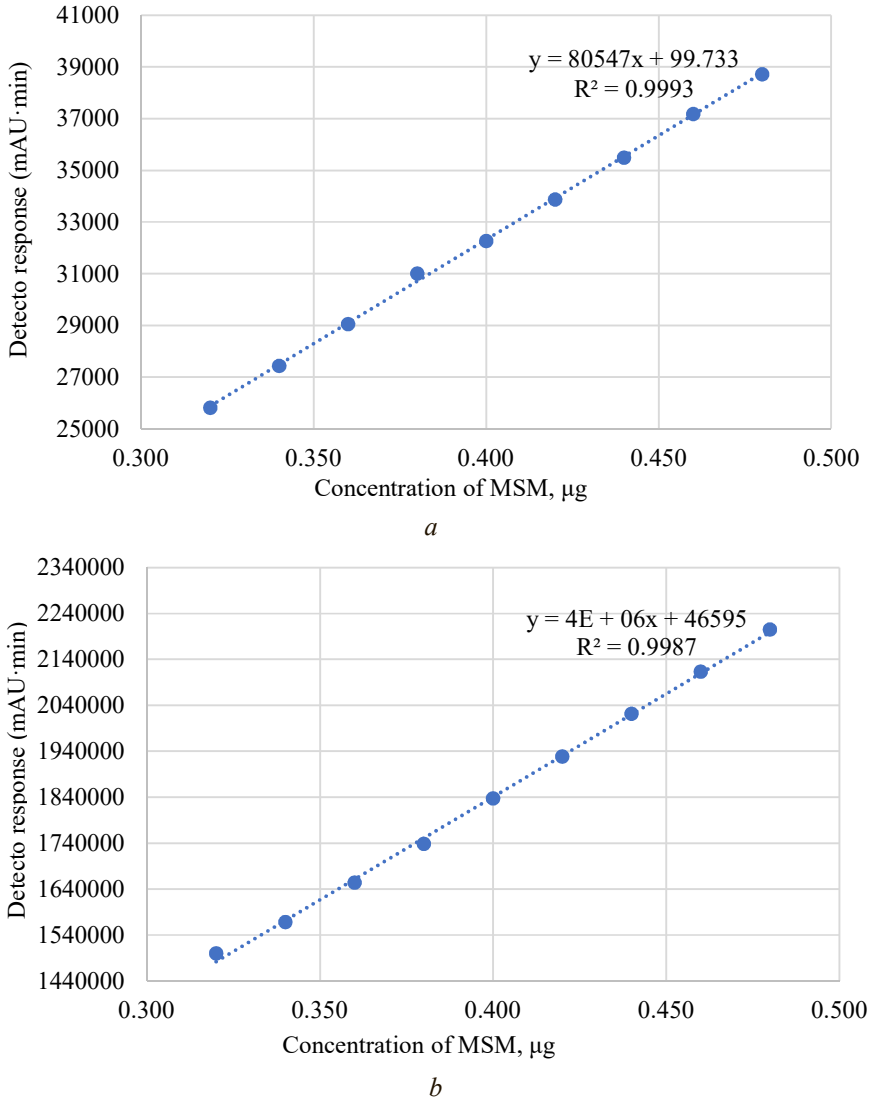

Fig. 7. Graph of the dependence of the device response on the concentration of MSM in model solutions by the methods: *a* – GC/MS; *b* – GC-FID

The LOD of MSM according to the proposed methods is 0.013%, 0.0088% and the LOQ is 0.04% and 0.026% for GC/MS and GC-FID, respectively. That is, the obtained LOD and LOQ values are significantly lower than the proposed concentration of MSM in the test solution.

5. Discussion of research results

MSM is a pharmacopoeial substance, according to the monographs of the United States Pharmacopeia "Methylsulfonylmethane" [10], "Methylsulfonylmethane Tablets" [11], "Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets" [12] and "Glucosamine and Methylsulfonylmethane Tablets" [13], the identification and quantification of the API is carried out by gas chromatography with flame ionization detection using an internal standard. Using a capillary column 30 m × 0.53 mm, with a film thickness of 5 µm, phase G2. The injection volume is 1 µl of the test solution 0.4 mg/ml methylsulfonylmethane, prepared by dissolving the sample in methanol (up to 1.0 L) and adding the internal standard diethylene glycol methyl ether (0.6 ml). Carrier gas – helium, column temperature – 120°C, detector and injection temperature – 250°C. Flow rate – 5 ml/min and Split 2:1 injection mode.

The linearity, precision and detection limits obtained in the work are consistent with the data given in modern publications on gas chromatographic analysis of MSM [20, 21]. At the same time, the proposed methods do not significantly affect sample preparation and do not require the use of an internal standard. This is especially important for the analysis of combined dosage forms, where the number of potential interferents increases significantly.

The presented study proposes an alternative approach to the quantitative determination of MSM in the composition of a combined medicinal product using the external standard method and two types of detection – mass-selective and flame ionization. This allowed not only to optimize the analysis procedure, but also to comprehensively assess the analytical capabilities of each method depending on the tasks.

To obtain the most complete information about the structure of MSM, the method of gas chromatography with mass selective detection (GC/MS) was used. Detection was performed with a mass detector, in the ionization mode.

Under the conditions of analysis by the GC/MS method, the retention time of MSM was 9.157 ± 0.06 min ($n = 5$, $P = 0.95$). For a solution of the test sample with a similar concentration of MSM, the chromatographic peak was recorded at 9.163 min (Fig. 2).

A method for identification and quantitative determination of MSM was proposed using the GC-FID method. The retention time of MSM in the analysis by the GC-FID method was 8.456 min ($n = 5$, $P = 0.95$) (Fig. 4), of the model mixture – 8.442 min (Fig. 5).

The absence of interfering peaks in the chromatograms of the placebo solution (Fig. 3, 6) confirms that excipients and concomitant active pharmaceutical ingredients do not affect the determination of MSM, which is fundamentally important for the analysis of combination drugs.

The quantitative content of MSM in the test mixture was calculated using the peak area of the test sample compared to the peak area of the reference solution, obtaining 5 chromatograms for each solution (Table 6).

The results obtained (Table 6) also confirm the feasibility of using the external standard method for the quantitative determination of MSM in the composition of the combined medicinal product without reducing the accuracy of the analysis.

Table 6

Results of quantitative determination of MSM in the study drug

Method	Peak area of the test solution	Peak area of the reference solution	MSM content in the powder	Content in % relative to the nominal
GC/MS	1837483 ± 0.40	1881553 ± 0.42	401.934 ± 1.13	100.48
GC-FID	32272 ± 0.35	32317 ± 0.38	401.546 ± 0.81	100.39

The use of two types of detection allowed a comprehensive assessment of the capabilities of gas chromatography for the analysis of MSM. The GC/MS method provides high specificity of identification due to mass spectral characteristics, which is especially important at the stages of drug development. In contrast, the GC-FID method is characterized by ease of implementation, high sensitivity and suitability for routine quantitative control.

Unlike the US Pharmacopoeia methods, which require the use of an internal standard and specific columns, the proposed approach does not require the introduction of additional standard substances, which reduces potential sources of analytical error.

Practical significance. The proposed methods can be used in quality control laboratories of pharmaceutical enterprises for routine quantitative determination of methylsulfonylmethane in the composition of combination drugs. The simplicity of sample preparation, the absence of an internal standard, and compliance with the requirements of SPhU and ICH Q2(R1) ensure the possibility of implementing the methods in pharmaceutical analysis.

Study limitations. The study was conducted on a model combination drug in the form of a powder for oral administration, which does not allow direct extrapolation of the results obtained to all possible dosage forms containing methylsulfonylmethane. In addition, the impact of intentional changes in chromatographic parameters was not assessed within the scope of the work.

Prospects for further research. They consist in expanding the application of the proposed methods for the analysis of other dosage forms and dosages, as well as in conducting interlaboratory validation to confirm the reproducibility of the results under different analytical conditions.

6. Conclusions

1. Two alternative methods for the quantitative determination of methylsulfonylmethane in a combination drug product by gas chromatography with mass-selective (GC/MS) and flame ionization (GC-FID) detection using an external standard method have been developed and validated.

2. The proposed methods demonstrated high selectivity for methylsulfonylmethane and the absence of influence of excipients and concomitant active pharmaceutical ingredients, which was confirmed by analysis of chromatograms of the placebo solution.

3. The validation characteristics of the methods meet the requirements of the State Pharmacopoeia of Ukraine and the recommendations of ICH Q2(R1): linearity in the range of 80–120% of the nominal concentration ($r > 0.9981$), high precision (RSD < 0.42%), sufficient sensitivity, as well as acceptable values of the limits of detection and quantification have been established.

4. The assessment of the total analytical uncertainty showed that the total uncertainty of the determination of methylsulfonylmethane for both methods does not exceed the permissible pharmacopoeial criteria, which confirms their reliability and reproducibility.

5. A comparative analysis of the methods demonstrated the feasibility of using GC/MS to confirm the identity of the analyte at the stages of drug development, while the GC-FID method is suitable for routine quantitative quality control of combination drugs.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

Authors' contributions

Andrii Koptielov: investigation, validation, formal analysis, writing – original draft, **Volodymyr Petruk:** conceptualization, investigation, software, resources, **Olena Bevz:** validation, formal analysis, writing – original draft, **Olha Rudakova:** methodology, resources, funding acquisition; **Oleksandr Kryvanych:** resources, data curation, visualization, funding acquisition; **Nataliia Bevz:** conceptualization, validation, data curation, writing – review & editing, supervision; **Yaroslav Studenyak:** investigation, data curation, writing – review & editing, project administration.

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