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QUANTITATIVE DETERMINATION OF GLYCINE IN A COMBINED LOZENGE DOSAGE FORM BY FORMOL TITRATION

Actuality. *Glycine is a biologically active amino acid widely used in combined medicinal products with anxiolytic and neuroprotective effects. The need for patient-friendly dosage forms, particularly for elderly patients and individuals with swallowing difficulties, has led to increased interest in oromucosal formulations, including lozenges. At the same time, small-scale and pharmacy-based manufacturing requires simple, reliable, and cost-effective analytical methods for routine quality control.*

The aim of the study *was to develop and validate a formol titration method for the quantitative determination of glycine in a combined medicinal product in the form of lozenges in accordance with the requirements of the State Pharmacopoeia of Ukraine and current regulatory standards.*

Materials and methods. *The formol titration method described in the United States Pharmacopeia and the British Pharmacopoeia monographs "Glycine Irrigation Solution" was adapted for the quantitative determination of glycine in a new combined medicinal product in the form of lozenges manufactured on a small scale, taking into account the specific dosage form and the presence of excipients. Validation was performed in accordance with ICH guidelines and the State Pharmacopoeia of Ukraine. Linearity, accuracy, and precision were evaluated in the concentration range of 80–120% of the nominal glycine content.*

Research results. *The proposed method demonstrated good linearity (r = 0.9997) within the studied concentration range. Accuracy and precision met the established acceptance criteria, with a relative standard deviation of 0.38%. Both statistical and practical insignificance of systematic error were confirmed.*

Conclusion. *The developed formol titration method is simple, validated, and economically feasible for routine quantitative determination of glycine in combined lozenges, particularly under conditions of small-scale pharmacy-based manufacturing.*

Key words: *glycine, lozenges, small-scale manufacturing, titrimetric analysis, validation.*

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КІЛЬКІСНЕ ВИЗНАЧЕННЯ ГЛІЦИНУ В КОМБІНОВАНОМУ ЛІКАРСЬКОМУ ЗАСОБІ У ФОРМІ ЛЬОДЯНИКІВ МЕТОДОМ ФОРМОЛЬНОГО ТИТРУВАННЯ

Актуальність. *Гліцин є біологічно активною амінокислотою, яка широко застосовується у складі комбінованих лікарських засобів з анксіолітичним і нейропротекторним ефектами. Потреба у зручних для пацієнта лікарських формах, зокрема для осіб літнього віку та пацієнтів із порушеннями ковтання, зумовила зростання інтересу до оромукозальних форм, включно з льодяниками. Водночас малосерійне й аптечне виробництво потребує простих, надійних та економічно доцільних аналітичних методів для рутинного контролю якості.*

Мета дослідження *полягала в розробленні та валідації методики формольного титрування для кількісного визначення гліцину в комбінованому лікарському засобі у формі льодяників відповідно до вимог Державної фармакопеї України та чинних нормативних стандартів.*

Матеріали та методи. *Метод формольного титрування, описаний у монографіях Фармакопеї США та Британської фармакопеї «Гліцину іригаційний розчин», було адаптовано для кількісного визначення гліцину в новому комбінованому лікарському засобі у формі льодяників малосерійного виробництва з урахуванням специфіки лікарської форми та наявності допоміжних речовин. Валідацію проводили відповідно до настанов МОЗ України / ICH та вимог Державної фармакопеї України. Оцінювали лінійність, правильність та прецизійність у діапазоні концентрацій 80–120 % від номінального вмісту гліцину.*

Результати дослідження. *Запропонована методика продемонструвала добру лінійність (r = 0,9997) у досліджуваному діапазоні концентрацій. Показники правильності та прецизійності відповідали встановленим критеріям прийнятності, відносне стандартне відхилення становило 0,38 %. Підтверджено як статистичну, так і практичну незначущість систематичної похибки.*

Висновки. *Розроблена методика формольного титрування є простою у виконанні, валідованою та економічно доцільною для рутинного кількісного визначення гліцину в комбінованих льодяниках, зокрема, в умовах малосерійного аптечного виробництва.*

Ключові слова: *гліцин, льодяники, малосерійне виробництво, титриметричний аналіз, валідація.*

Introduction. Actuality. Glycine (NH_2-CH_2-COOH, 75.067 g/mol) is an amino acid that plays an important role in the formation of the tertiary structure of proteins, regulation of gene expression, and neurotransmission. In the central nervous system, glycine functions as an inhibitory neurotransmitter, participating in the modulation of neuronal excitability, nociceptive transmission, and control of motor functions (Mizzi, 2025; Saifudinova, 2025).

In addition to its neurotransmitter activity, glycine affects protein activity and conformation, stimulates the synthesis of collagen and growth hormone, promotes tissue regeneration, supports muscle tone, and slows down processes of muscle degeneration. Its anti-inflammatory and cytoprotective effects have also been demonstrated, including the ability to reduce tissue damage during radiation therapy (Aguayo-Cerón, 2023).

In recent years, stress-induced disorders have remained one of the most prevalent medical and social problems in Ukraine and are increasingly reported in clinical practice, requiring personalized approaches to pharmacotherapy. At the same time, recent pharmaceutical literature emphasizes the need to adapt dosage forms to the needs of geriatric patients, particularly through the use of formulations that do not require active swallowing and allow for dose individualization (Deviatkina, 2021; Comoglu, 2025).

Lozenges represent a promising dosage form for use in elderly patients, as they do not require swallowing and dissolve slowly in the oral cavity. This is of particular importance for patients who frequently experience dysphagia, reduced salivation, and impaired swallowing reflex. Contemporary review studies confirm that lozenges ensure better patient adherence to therapy and may be considered an alternative to tablets and capsules in patients with difficulties in oral administration (Kulkarni, 2022).

In countries with a well-developed practice of pharmaceutical compounding, particularly in the United States, lozenges are widely used in pharmacy settings both for individual prescriptions and for small-scale manufacturing. Recent reviews in pharmaceutical technology emphasize that lozenges are a technologically accessible dosage form that allows variation of the active pharmaceutical ingredient dose according to the clinical needs of individual patients, which is especially relevant in geriatric practice (Porwal, 2025).

Within this concept, compressed lozenges containing glycine (100 mg) and magnesium citrate (250 mg) with anxiolytic and neuroprotective effects have been developed (Yakovenko, 2021).

Ensuring the quality of medicinal products requires reliable methods for the quantitative determination of active pharmaceutical ingredients throughout the entire lifecycle of the product, particularly under conditions of small-scale pharmacy-based manufacturing. In this regard, the development and validation of a selective and reproducible method for the determination of glycine in combined dosage forms is a relevant task.

The aim of research. To develop and validate a formol titration method for the quantitative determination of glycine in a combined medicinal product in the form of lozenges in accordance with the requirements of the State Pharmacopoeia of Ukraine and current regulatory standards.

Materials and methods of research. The study was aimed at the development of a titrimetric method for the quantitative determination of glycine in a medicinal product.

Method for the determination of glycine in the medicinal product. Thirty lozenges were dissolved in 500.0 mL of purified water R under constant stirring; if necessary, the solution was heated to 40 °C. An aliquot of 25.0 mL of the obtained solution was transferred to a suitable vessel, and 10.0 mL of formaldehyde solution R, previously adjusted to pH 9.0, was added, followed by 0.25 mL of an indicator mixture prepared by dissolving 75 mg of phenolphthalein R and 25 mg of thymol blue R in 100 mL of 50% ethanol. The resulting solution was titrated with 0.1 M sodium hydroxide solution until the color changed from yellow to violet.

1ml of 0.1 M sodium hydroxide solution is equivalent to 7.507 mg of $C_2H_5NO_2$.

Linearity study. Aliquots of the medicinal product solution corresponding to 80, 85, 90, 95, 100, 105, 110, 115, and 120% of the nominal glycine content (150 mg) were used to construct the calibration curve.

Determination of glycine in the substance. A quantity of 0.150 g of glycine was dissolved in 25 mL of water R, and the procedure was then carried out as described for the medicinal product, starting from the step "10.0 mL of formaldehyde solution R is added…"

Placebo solution analysis. To assess the influence of excipients, a placebo solution containing 0.563 g of magnesium citrate, 0.203 g of isomalt, 0.1125 g of copovidone, and 0.023 g of glyceryl behenate dissolved in 25 mL of purified water R was prepared. Further analysis was performed according to the procedure described for the medicinal product.

The pH of the formaldehyde solution R was adjusted to pH 9.0 using an ADWA AD1030 pH meter equipped with an AD1131B pH electrode (ADWA, Hungary).

Preparation of indicator solutions and standardization of the 0.1 M sodium hydroxide were carried out in accordance with the methods of the State Pharmacopoeia of

Ukraine (SPhU, 2nd ed., Vol. 1, 2015). For each sample, three parallel titrations were performed using a 25.0 mL burette with a graduation of 0.05 mL (Chykalova, 2016). The obtained data were subjected to statistical processing using Microsoft Excel software. Validation of the proposed method was performed in accordance with the requirements of the State Pharmacopoeia of Ukraine, section 5.3.N.2 "Validation of analytical procedures and tests" (SPhU, 2nd ed., Suppl. 7, Vol. 2, 2024).

All chemical reagents and solvents were purchased from commercial suppliers and complied with the purity requirements of the State Pharmacopoeia of Ukraine. Previously qualified laboratory glassware conforming to ISO Class A standards was applied throughout the analysis.

Research results and their discussion. According to international standards and pharmacopoeial requirements, lozenges are classified as oromucosal medicinal products. In terms of appearance, the investigated lozenges represent a solid dosage form containing the active pharmaceutical ingredients glycine and magnesium citrate and are intended for administration in the oral cavity to achieve a systemic effect. Therefore, during the development of a method for the quantitative determination of glycine in the studied medicinal product, the requirements of current legislation, international quality standards, and the general monographs of the State Pharmacopoeia of Ukraine "Oromucosal medicinal products" and "Sublingual and buccal tablets", as well as the provisions of the ICH Q8 (R2) guideline, were taken into account (SPhU, 2nd ed., Vol. 1, 2015; ICH guideline Q8 (R2), 2017).

In accordance with the requirements of the International Council for Harmonisation (ICH), the recommendations of the European Directorate for the Quality of Medicines and HealthCare (EDQM), the United States Pharmacopeia, and the World Health Organization, a method for the quantitative determination of an active pharmaceutical ingredient in a medicinal product may be approved only after its validation (EDQM, 2015; USP 40, 2024; WHO, 2006).

The scientific literature describes numerous spectrophotometric methods for the determination of amino acids containing an amino group, which are based on their interaction with various chromogenic reagents. In particular, reactions with ninhydrin, 2,4,6-trinitrobenzene, and o-phthalaldehyde in the presence of 2-mercaptoethanol have been reported (Lohoyda, 2014).

A separate group comprises spectrophotometric methods based on the formation of colored reaction products between amino acids and electron-acceptor reagents, such as chloranil (tetrachloroquinone), fluoranil (tetrafluoroquinone), 1,2,4-trihydroxyanthraquinone, p-benzoquinone, and the sodium salt of 1,2-naphthoquinone-4-sulfonic acid (Al-Sulimany, 1973).

In addition, a high-performance liquid chromatography method has been proposed for the determination of glycine in combined medicinal products using a Hypersil ODS-C18 column (5 μm, 4.6 × 250 mm), a mobile phase consisting of an aqueous solution of Bu_4NHSO_4 (3.4 g/L) and 0.05% trifluoroacetic acid, with detection at 220 nm (Kucherenko, 2020).

Despite the high analytical sensitivity and diversity of spectrophotometric methods, their application for the quantitative determination of glycine in combined medicinal products is limited. This is due to the presence of excipients that may interact with chromogenic reagents, forming additional colored products and causing overlapping absorption spectra, which complicates the selective determination of glycine. Moreover, spectrophotometric and chromatographic methods often require harsh reaction conditions, time-consuming sample preparation, or the use of toxic reagents, which restricts their suitability for routine quality control, particularly under conditions of small-scale manufacturing.

One of the methods for the quantitative determination of aliphatic amino acids is alkalimetry. Its disadvantages include non-equivalent titrant consumption in aqueous media, which is associated with the amphoteric properties of amino acids and the presence of an amino group. To improve the sensitivity and accuracy of the determination, formaldehyde solution is used, which binds the amino group to form a methylene derivative and prevents the formation of an internal salt.

The quantitative determination of glycine in the investigated lozenges was performed using a pharmacopoeial approach in accordance with the monographs of the United States Pharmacopeia and the British Pharmacopoeia "Glycine Irrigation Solution" (USP 40, 2024; British Pharmacopoeia, Vol. III, 2020, 710–711), adapted to the dosage form and its composition.

At the first stage, an appropriate aliquot of the glycine solution was selected for titrimetric analysis; the theoretical titrant volume was 19.98 mL (79.92% of the nominal burette volume of 25.0 mL), which complies with the recommendations of the State Pharmacopoeia of Ukraine for titration procedures (SPhU, 2nd ed., Suppl. 7, Vol. 2, 2024).

Prior to the analysis of the medicinal product, titration of the placebo solution was performed. The volume of titrant consumed did not exceed 0.05 mL, indicating the absence of interference from excipients in the titration results. In addition, analysis of the glycine substance was performed, and the determined content was 99.5%, which was consistent with the

manufacturer's certificate of analysis. The obtained results confirmed the selectivity of the method and its suitability for the quantitative determination of glycine in the investigated medicinal product and justified the feasibility of further evaluation of its validation characteristics.

To assess the reproducibility of the results during the linearity study, three aliquots were analyzed at each concentration level in the range of 80% to 120% of the nominal glycine content (150 mg) with a step of 5%. For each concentration, the mean titrant volume was applied for calculations. As a result, a set of nine points was obtained and processed separately using the least-squares linear regression method (Fig.).

As can be seen from the linearity parameters (Table 1), the requirements for simultaneous statistical insignificance of the parameters $|1 - b| = 0.009253$ and $a = -0.0964$ are not met. However, the analytical procedure complies with the criteria of practical acceptability for linearity. For informational purposes, the limit of detection and the limit of quantification were calculated. These values do not exceed the acceptance criteria and therefore do not significantly affect the quantitative determination of glycine in the test sample.

As shown in Table 2, the requirements for lack of statistically significant systematic error ($0.7140 \leq 1.89$) and practical insignificance of systematic error ($0.44 \leq 1.0667$) are fulfilled, confirming that the

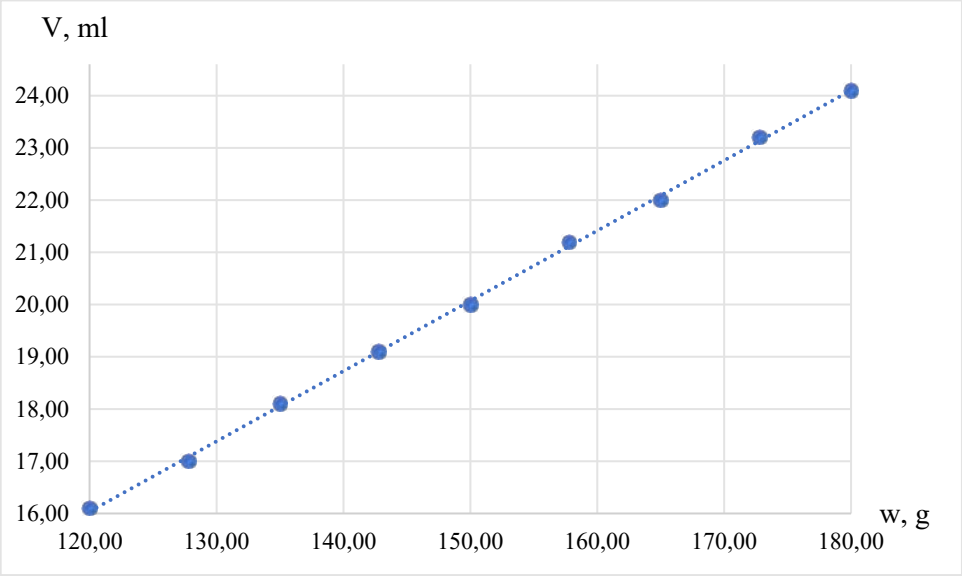

Fig. Graph of the linear relationship between the titrant volume and glycine content in the aliquot taken for analysis, presented in normalized coordinates

Table 1

Linearity parameters (Yi = a + b·X)

Parameter	Value	Standard deviation	Criterion of statistical insignificance	Criterion of practical acceptability	Conclusion
a	|0.2858|	1.0975	|a| ≤ 0.536		Complies
b	1.0093	0.0109			
|1 - b|	0.0093		|1 – b| ≤ 0.0054		does not comply
S_0	0.4216			≤ 0.536	Complies
r	0.9997			≥ 0.99894	Complies
r^2	0.9994			≥ 0.99789	Complies
Δ_{RL80}	0.5680			≤ 1.7066	Complies
Δ_{RL120}	0.6871			≤ 1.7066	Complies
Limit of detection (LOD)	3.6219			≤ 10% of nominal (≤ 15.0 mg)	Complies
Limit of quantification (LOQ)	complies			≤ 32% of nominal (≤ 48.0 mg)	Complies
Overall conclusion on the method					Complies

Table 2

Results of accuracy and precision studies

Added, % of glycine content (X, %)	Found, % of glycine content (Y, %)	Found as % of added (Zi = 100·Y/X)
80.00	80.58	100.72
85.00	84.88	99.86
90.00	90.58	100.65
95.00	95.39	100.41
100.00	100.09	100.09
105.00	105.90	100.85
110.00	110.10	100.09
115.00	115.91	100.79
120.00	120.61	100.51
Mean value of Z, %		100.44
Relative standard deviation (Sz, %)		0.3768
Relative confidence interval Δz% = t (95%, 8)·Sz		0.7140
Acceptance criterion for precision (ΔAs, %)		1.60
Lack of statistically significant systematic error $\delta \leq 1.89$		$0.7140 \leq 1.89$ Fulfilled
Practical insignificance of systematic error: $\delta \leq 1.0667$		$0.44 \leq 1.0667$ Fulfilled
Overall conclusion on precision and accuracy		Complies

proposed method meets the criteria for precision and accuracy.

The results of validation studies of the proposed titrimetric method for the determination of glycine in the experimental medicinal product manufactured on a small scale demonstrate good reproducibility and confirm the suitability of the method for pharmaceutical analysis.

Conclusions.

1. A formol titration method described in the United States Pharmacopeia and the British Pharmacopoeia monographs "Glycine Irrigation Solution" was adapted for the quantitative determination of glycine in a combined medicinal product in the form of lozenges.

2. Validation studies demonstrated compliance of the method with the requirements of the State Pharmacopoeia of Ukraine and ICH recommendations in terms of linearity, accuracy, and precision within the concentration range of 80–120% of the nominal glycine content.

3. The absence of statistically and practically significant systematic error and high reproducibility of quantitative determination results were confirmed.

4. The proposed method is simple to perform, cost-effective, and suitable for routine quality control of the combined medicinal product, particularly under conditions of small-scale pharmacy-based manufacturing.

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