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## STUDY OF STRESS DEGRADATION AND DETERMINATION OF THE STABILITY OF THE SUBSTANCE AND INJECTION SOLUTION OF SODIUM 2-((4-AMINO-5-THIOPHEN-2-YLMETHYL)-4H-1,2,4-TRIAZOL-3-YL)THIO)ACETATE

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**Research goal.** The aim of the work was to investigate stress degradation and determine the stability of the substance and injection solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate (API) to determine storage conditions and establish shelf life.

**Research materials.** The substance API was synthesized earlier. The chromatographic system used was Agilent 1260 Infinity HPLC, equipped with a diode array detector and a single quadrupole mass spectrometric detector Agilent 6120. Software was OpenLAB CDS.

**Methods, research results, and their discussion.** The stability determination procedure of the substance and injection solution involves maintaining the dosage forms at a temperature higher than the average storage temperature and constant monitoring of the quantitative content of the active substance during storage. Investigation of stress-induced thermal degradation was conducted in a dry heat oven. Additionally, samples of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate with hydrogen peroxide, 0.1 M alkali, and 0.1 M acid were kept at room temperature for 4 days. The influence of ultraviolet (UV) irradiation on the substance and solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate was also investigated. HPLC system was used to monitor the quantitative content of the active substance. It has been established that the shelf life of substance API and a 1% solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate is at least 2 years. Hydrogen peroxide and ultraviolet radiation have the greatest impact on sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate, so it is recommended to store the observed objects in conditions free from solar radiation.

**Key words:** 1,2,4-triazoles, active pharmaceutical ingredient, shelf life, stress degradation, parenteral dosage form.

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### ДОСЛІДЖЕННЯ СТРЕСОВОЇ ДЕГРАДАЦІЇ І ВИЗНАЧЕННЯ СТАБІЛЬНОСТІ СУБСТАНЦІЇ ТА ІН'ЕКЦІЙНОГО РОЗЧИНУ НАТРІЙ 2-((4-АМІНО-5-ТІОФЕН-2-ІЛМЕТИЛ)-4H-1,2,4-ТРИАЗОЛ-3-ІЛ)ТІО)АЦЕТАТУ

Запорізький державний медико-фармацевтичний університет, Запоріжжя, Україна

Процедура визначення стабільності субстанції та ін'екційного розчину включає утримання лікарських форм у разі температури, вищої за середню температуру зберігання, та в процесі зберігання постійний контроль кількісного вмісту діючої речовини. Дослідження стресової термічної деградації проводилось у сухожаровій шафі, крім того, зразки натрій 2-((4-аміно-5-тіофен-2-ілметил)-4H-1,2,4-тріазол-3-іл)тіо)ацетату (АФІ) з  $H_2O_2$ , 0.1 М луку і 0.1 М кислотою тримали за кімнатної температури протягом 4 днів. Також досліджено вплив ультрафіолетового випромінювання на субстанцію і розчин АФІ. Для контролю кількісного вмісту діючої речовини використали систему Agilent 1260 Infinity HPLC, діодно-матричний детектор та одноквадрупольний мас-спектрометричний детектор Agilent 6120 з іонізацією в електроспрее.

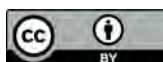
**Ключові слова:** 1,2,4-тріазоли, активний фармацевтичний інгредієнт, термін придатності, стресова деградація, парентеральна лікарська форма.

**Introduction.** In the modern world, derivatives of 1,2,4-triazole-3-thione have attracted significant attention from researchers, as they exhibit various biological properties, and scientists, in turn, are interested in the search for new biologically active compounds [1–6]. One example of creating active pharmaceutical ingredients (API) and dosage forms based on derivatives of 1,2,4-triazole-3-thione is sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate, for which experimental evidence

of actoprotective and stress-protective action has been confirmed [7]. Previous studies have analyzed the patterns of maintaining API and possible technological impurities, such as 2-(thiophen-2-yl)acetohydrazide, potassium 2-(2-(thiophen-2-yl)acetyl)hydrazine-1-carbodithioate, and 4-amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione, under reversed-phase chromatography conditions. Special attention was paid during the research to studying the influence of the eluent composition on the characteristics of analyte retention. Additionally, within the scope of investigating the thermodynamic functions of chromatographic retention of API sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate and its impurities [8], it was possible to theoretically and

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practically consider the thermodynamic process of transferring API and their impurities from the mobile phase to the stationary phase, study the dependency of the retention of the aforementioned compounds on temperature, and based on the obtained data, improve the methodology of quantitative determination of API sodium 2-((4-amino-5-thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate using high-performance liquid chromatography. Isotonicity determination of the potential dosage form based on API was also carried out [9], during which, based on the experimental data obtained, depression of the crystallization temperature and calculations were conducted to establish and scientifically justify the final composition for the preparation of an isotonic 1% aqueous solution of sodium 2-((4-amino-5-thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate for parenteral application.

In the development of quality control methodologies for pharmaceutical substances, one of the important and key stages is the investigation of accelerated stress degradation of API in substances and various dosage forms. This research allows predicting the impact of the environment on the pharmaceutical substance and enables the development of storage conditions. Moreover, the investigation of stress degradation of API is necessary to confirm the selectivity of analysis methodologies in the presence of various degradation products. Additionally, determining the stability and establishing the shelf life of the substance and dosage form is very important, as every developed pharmaceutical preparation, besides specific storage conditions, must be maximally effective and safe for application. Ignoring storage rules and expiry dates of medicines can lead to changes in their composition, resulting in side effects, loss of effectiveness, and in some cases, improperly stored medicines can become a source of toxins or other harmful substances.

**The aim of the work** involves stress degradation investigation and stability determination of the substance and 1% aqueous injection solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate to determine storage conditions, establish shelf life, and sensitivity to external environmental factors.

**Research materials.** The research object is sodium 2-((4-amino-5-thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate, which has experimentally proven act- and stress-protective effects. The substance was synthesized at the Department of Toxicological and Inorganic Chemistry of Zaporizhzhia State Medical University by Doctor of Pharmacy A.A. Safonov.

Reagents and solvents – CH<sub>3</sub>CN for HPLC classification Super Gradient (Avantor Performance Materials Poland S.A., Poland), HCOOH “For analysis” (98%) (Appli-Chem GmbH, Germany), 3% solution of H<sub>2</sub>O<sub>2</sub> (PC VIOLA LLC, Ukraine), 0.1 M solution of NaOH, 0.1 M solution of HCl, high-quality purified water (Q<sub>3</sub>, 18 MΩ, 25 °C). For the preparation of high-quality purified water used Direct Q 3UV (Millipore, Molsheim, France).

During the investigation of the UV radiation influence, a fluorescent ultraviolet lamp YF UV-9W was used (with a long-wave ultraviolet range and a maximum emission wavelength of 365 nm).

The quantitative content of API was monitored using a patented high-performance liquid chromatography (HPLC)

method [10] (priority belongs to Zaporizhzhia State Medical University). The chromatographic system used was Agilent 1260 Infinity HPLC, equipped with a diode array detector and a single quadrupole mass spectrometric detector Agilent 6120. The column used was Zorbax SB-C18; 30 mm x 4.6 mm; 1.8 μm. The mobile phase consisted of water (0.1% formic acid) and acetonitrile (0.1% formic acid) (75:25). The flow rate of the eluent was 0.4 μL/min. The wavelength of the diode array detector was set at 232 nm. Mass spectrometry was performed in scanning mode within the range of m/z 100–2000. The injection volume was 0.5 μL for accelerated degradation and 2 μL for stability investigation using accelerated aging method. The flow rate of the drying gas (nitrogen) was set to 10 L/min, and the gas pressure was 55 psi.

The working solutions were prepared according to the requirements of the State Pharmacopoeia of Ukraine, section “Reagents” [11].

#### **Methods, research results, and their discussion.**

During the investigation of stress degradation, samples of the API sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate were collected daily over a period of 4 days of exposure to each stress factor. These samples were prepared for injection and analyzed using HPLC. The percentage content was determined based on the OpenLab CDS Software report using the signal from the diode array detector at a wavelength of 232 nm [10].

*Degradation under laboratory conditions:* substance and a 1% aqueous solution of the API were stored at room temperature under laboratory conditions [12].

*Thermal degradation:* substance and a 1% aqueous solution of the API were stored in a dry heat oven at a temperature of 70°C [12].

*Oxidative degradation:* 10 mg of the API substance was dissolved in 1 mL of 3% H<sub>2</sub>O<sub>2</sub>, and the influence of the oxidizing agent was investigated [12].

*Alkaline and acid hydrolysis:* to study the influence of an alkaline or acidic environment, 10 mg of the API substance was separately dissolved in 1 mL of 0.1 M NaOH and in 1 mL of 0.1 M HCl [12].

*Ultraviolet degradation:* substance and a 1% aqueous solution of the API were subjected to UV radiation [12]. The samples were mixed at intervals of 4 hours during the study.

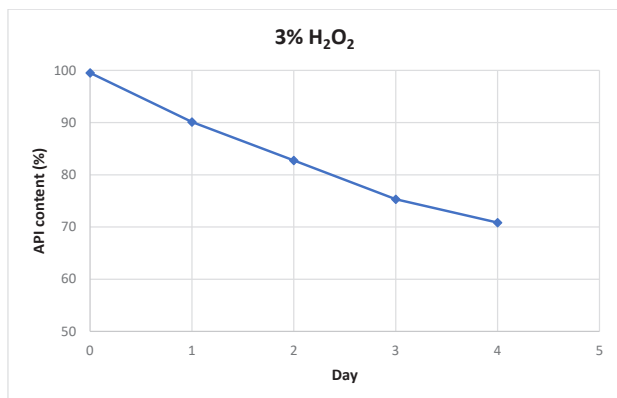
To prepare a 1% aqueous solution of the API for studying degradation under laboratory conditions, thermal and ultraviolet degradation, 10 mg of the API substance was dissolved in 1 mL of high-quality purified water. Similarly, for the investigation of the substance, 10 mg of the API substance was dissolved in 1 mL of high-quality purified water.

The results of determining the quantitative content of the API sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate after exposure to degradation factors are presented in Table 1. The quantity of the API in the substance and prepared solutions was taken as 100%.

*Degradation under laboratory conditions:* during storage of the 1% solution of the API at room temperature under laboratory conditions, the percentage of the main substance remained almost unchanged, with changes from the initial percentage content at the beginning of the experiment to its end being approximately 0.17%. Storage under laboratory conditions did not affect the substance.

**Thermal degradation:** under the influence of high temperature (70°C), the 1% solution of the API degraded by approximately 0.37%. Thermal degradation had almost no effect on the substance over 4 days (~0.1%).

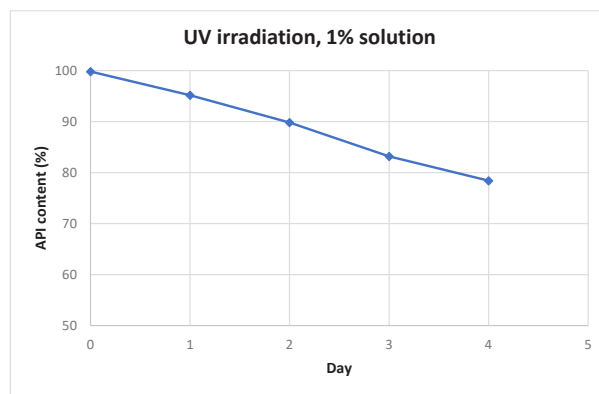
**Oxidative degradation:** the influence of 3% hydrogen peroxide over 4 days results in a decrease in the concentration of the API by approximately 30% (Figure 1).



**Fig. 1. The degradation curve of the API sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate under the influence of 3% hydrogen peroxide**

**Alkaline and acidic hydrolysis:** under the action of 0.1 M NaOH and 0.1 M HCl solutions, the quantitative content of the API remained substantially unchanged throughout the experiment (approximately ~0.1% in both cases).

**Ultraviolet degradation:** ultraviolet irradiation over 4 days leads to the decomposition of the 1% solution of the API by more than 20% (Figure 2). At the same time, the content of the API in the substance almost did not change during UV irradiation.



**Fig. 2. Degradation curve of the 1% solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate under ultraviolet irradiation**

Stability studies and determination of the shelf life of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate were conducted using the “accelerated aging” method, which involves exposing the test sample of the pharmaceutical formulation to a temperature higher than the average room temperature (~20°C). The substance API and the 1% solution (in 3 series each) were investigated under conditions of 40°C storage in a drying cabinet. Samples for analysis were taken every 60 days, prepared for injection, and analyzed using HPLC (3 series of 6 replicates each). Quantitative content control was performed based on the OpenLab CDS Software report using the signal from the diode array detector at a wavelength of 232 nm. The experiment lasted for six months, which corresponds to a shelf life of 2 years when storing the pharmaceutical formulation at room temperature.

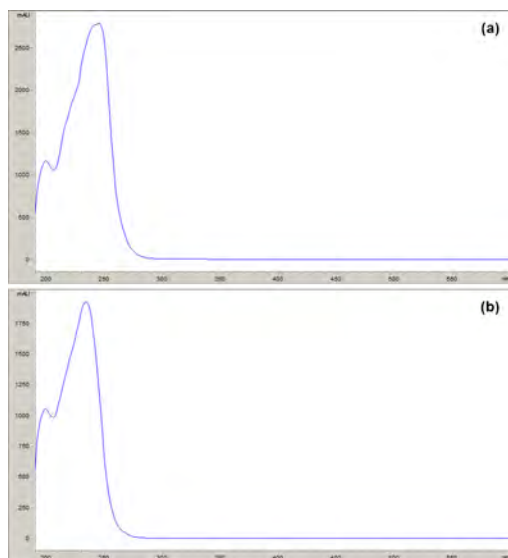
Preparation of a 1% solution of the API for the investigation was carried out by dissolving 100 mg of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate in 10 ml of high-quality purified water, while for the investigation of the API substance itself, 10 mg of the API substance was dissolved in 1 ml of high-quality purified water. Samples were stored in 10 ml ampoules made of NS-3 glass.

Table 1

**The quantitative content of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate under different degradation conditions**

Degradation conditions	Experiment day				
	0	1	2	3	4
Laboratory conditions, substance	99.85	99.84	99.81	99.81	99.80
Laboratory conditions, 1% solution	99.51	99.45	99.37	99.37	99.34
Dry heat oven 70°C, substance	99.70	99.68	99.65	99.61	99.59
Dry heat oven 70°C, 1% solution	99.49	99.41	99.28	99.16	99.12
3% hydrogen peroxide	99.53	90.12	82.76	75.32	70.84
0.1 M NaOH solution	99.61	99.58	99.51	99.49	99.50
HCl 0.1 M solution	99.57	99.55	99.51	99.51	99.45
Impact of UV radiation, substance	99.35	99.34	99.12	99.11	99.09
Impact of UV radiation, 1% solution	99.81	95.16	89.82	83.19	78.41

The results of the investigation of the series of 1% aqueous solution of the API and the substance throughout the experiment are presented in Tables 2 and 3, as well as in Figure 3.



**Fig. 3. The absorption spectrum of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate in the UV region after storage at 40°C (spectrum corresponds to 60, 120, 180 days of storage, there were no significant changes); a – spectrum of 1% solution; b – spectrum of substance**

The shelf life (C) at the average storage temperature (~20°C) is directly proportional to the experimental shelf life (C<sub>e</sub>) at the elevated storage temperature (40°C) and has the following relationship:

$$C = C_e \times K$$

Conformity coefficient (K)  $t_{exp}^o - t_{stor}^o = 20^\circ\text{C}$  is 4.

The analysis using HPLC allowed establishing that during “accelerated aging” at a set temperature of 40°C, the 1% aqueous solution and the substance sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate remained unchanged in composition after 180 days of the experiment. For all investigated series, the pH level of the API solution and the visual condition also remained unchanged.

Determining the shelf life:

$$C = 180 \times 4 = 720 \text{ days } (\sim 2 \text{ years})$$

Thus, it has been established that after the completion of experimental storage under the influence of high temperature (40°C) using the “accelerated aging” method, the 1% aqueous solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate and its substance correspond to a shelf life of at least 2 years (in ampoules at room/nominal temperature of 20°C). Determination of the shelf life of the substance API and the 1% aqueous solution at normal storage temperature continues.

**Conclusions**

1. The influence of degrading factors such as temperature, hydrogen peroxide, sodium hydroxide, hydrochloric acid, and ultraviolet radiation on a 1% solution and sub-

Table 2

**Results of the analysis of the 1% solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate during the accelerated aging study**

Series	Experiment duration	Equivalent storage period	Quality indicators		
			pH	The quantitative content of the active substance per 1 ml	Appearance
A	60 days	240 days	7.0	0.01056	Transparent yellowish liquid
B			7.0	0.01082	
C			7.0	0.0110	
A	120 days	480 days	7.0	0.00991	Transparent yellowish liquid
B			7.0	0.00997	
C			7.0	0.01014	
A	180 days	720 days	7.1	0.00952	Transparent yellowish liquid
B			7.0	0.00943	
C			7.0	0.00963	

Table 3

**Results of the analysis of the substance sodium 2-((4-amino-5-(thiophene-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate during the accelerated aging study**

Series	Experiment duration	Equivalent storage period	Quality indicators		
			pH	The quantitative content of the active substance per 1 ml	Appearance
A	60 days	240 days	7.0	0.01023	Powder of yellowish color
B			7.0	0.01038	
C			7.0	0.01028	
A	120 days	480 days	7.0	0.00987	Powder of yellowish color
B			7.0	0.00991	
C			7.0	0.00984	
A	180 days	720 days	7.0	0.00960	Powder of yellowish color
B			7.0	0.00968	
C			7.0	0.00961	

stance of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate has been investigated.

2. It has been determined that hydrogen peroxide and ultraviolet radiation have the greatest impact on the sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate. Therefore, it is recommended to store the observed objects in conditions free from solar radiation.

3. Long-term exposure to high temperature was investigated for the 1% aqueous solution and the substance sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate. It was determined that the shelf life of the substance and the 1% aqueous solution of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate is at least 2 years.

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