



**STUDY OF THE STABILITY AND DETERMINATION OF
THE SHELF LIFE OF A COMBINED INFUSION SOLUTION
BASED ON L-ARGININE HYDROCHLORIDE**

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ABSTRACT

In the field of pharmacy, it is essential for any pharmaceutical product to undergo comprehensive stability testing. This is a critical step before a product can be approved and made available to the public. The purpose of these tests is to ensure that the product's quality, safety, and efficacy remain consistent throughout its entire shelf life. This article details a stability study and the subsequent shelf-life determination for an investigational drug, a hepatoprotective infusion solution known as "Gepaton."

INTRODUCTION.

A drug's quality, therapeutic efficacy, and safety are directly dependent on its stability. This refers to its ability to maintain its defined properties within the limits established by regulatory documentation over a specified period, and under designated storage and transportation conditions. The results of stability testing are crucial. They guide the determination of the drug's shelf life, the selection of the most suitable packaging materials, and the establishment of correct storage conditions [1] All of these details are officially documented in the regulatory dossier (RD), provided in the instructions for use, and printed directly on the product's packaging. Because drug stability isn't routinely tested as part of state-level quality control, it's especially important to have a rigorous documentary review of the data submitted by applicants. A medication's shelf life is determined by real-world testing. This involves storing the drug for a specific period under controlled conditions and in the exact packaging specified by regulatory documents. The shelf life can be adjusted as more data becomes available, allowing for both extensions and reductions as needed[1].

Stability studies are carried out in accordance with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan and international guidelines such as ICH Q1A(R2) "Stability Testing of New Drug Substances and Products", which regulate the selection of storage conditions and analytical procedures for quality assessment [2, 3].



Stability testing gives necessary data on the effect of such factors as temperature, light, humidity, etc. on the medicinal product quality. The results of these studies help to select suitable primary and secondary packaging and to determine storage conditions and shelf life for the product[4].

To determine the shelf life of a product, identify optimal storage conditions and ensure the preservation of its quality characteristics over long periods of storage, it is necessary to evaluate its stability [5, 6].

LITERATURE REVIEW AND METHODOLOGY

Stability testing for the combined infusion solution "Gepaton" was conducted using two primary methods: a long-term stability study under natural storage conditions and an accelerated aging study as outlined in temporary guideline I-42-2-82. The stringent packaging requirements for this and other medical products are due to the necessity of safeguarding their stability and efficacy against various environmental factors, such as temperature, light, and humidity. Based on these aspects, suitable packaging materials were chosen for the infusion and transfusion solutions. Specifically, glass vials (GOST 10782-85, GOST 19808-86), rubber stoppers (TU 38-006-269-95 or TU 9467-019-00152164-2004), and aluminum-plastic caps (Flip Off) were used for this purpose. The research was conducted using laboratory samples of the "Gepaton" infusion solution. The drug's active ingredients are L-arginine hydrochloride, L-glutamic acid, L-metionin, riboxin, nicotinamide. The stability study was conducted based on the established specifications for the drug (Table 1).

Table 1

Specification for the "Gepaton" Infusion Solution

Parameters	Standards	Methods
Appearance	A clear, colorless or greenish-yellow solution.	Visual
Identity Arginine Glutamic Acid Methionine Nicotinamide Riboxin Sodium Ions Chlorides	The retention times of the substances in the drug's chromatogram must correspond to the retention times of the respective substances in the standard sample (SS) solution's chromatogram. Chemical reaction for sodium A white, curdy precipitate should form.	HPLC Uz. St.Ph., 2.2.29 Uz. St.Ph, 2.3.1 Chemical reaction Uz. St.Ph, 2.3.1 Chemical reaction
Clarity	The preparation must be clear.	Uz. St.Ph, 2.2.1



Coloration	The color of the preparation must not be more intense than the color of the Y ₇ or GY ₇ reference solutions.	Eur.Ph., B.Ph., USP. Uz.St.Ph 2.2.2
pH	4,5-6,8	Uz.St.Ph, 2.2.3., potentiometric
Fill Volume	The volume of the solution must not be less than the nominal volume stated on the label. The maximum volumes must be 51 ml, 102 ml, and 204 ml.	Uz.St.Ph, 2.9.17
Particulate Matter 1. Visible Particles	There must be no visible particles.	Uz.St.Ph 2.9.20., EuPh. 2.9.20, GPM 42 Uz- 0006-3341-2023
2. Sub-visible Particles	For 50 ml and 100 ml vials: The number of particles of ≥ 25 microns must not exceed 600 per vial. The number of particles of ≥ 10 microns must not exceed 6,000 per vial.	Uz.St.Ph 2.9.19., EuPh. 2.9.19, GPM 42 Uz-0005- 3340-2023
Foreign Matter Individual Foreign Substance Total Foreign Matter	Not to exceed 0.6% Not to exceed 1.5%	HPLC, Uz.St.Ph. 2.2.29
Osmolality	400-525 mOsmol/kg	Uz.St.Ph 2.2.35, Cryoscopic
Quantitative Analysis: L-arginine L-glutamic acid L-methionine Riboxin Nicotinamide Sodium chloride	9,75-11,93 mg/ml 8,24-10,08 mg/ml 1,35-1,65 mg/ml 1,8-2,2 mg/ml 0,225-0,275 mg/ml 8,1-9,9 mg/ml	HPLC, Uz.St.Ph 2.2.29 HPLC, Uz.St.Ph 2.2.29, Titration Titration

Long-term stability studies were conducted to determine the drug's properties under natural conditions. The samples were stored in a laboratory at a temperature of 25±2°C with real-time monitoring and were assessed every six months. A stability study was conducted using the accelerated aging method to test the drug under stress conditions. The experiment was performed at 60°C in an HS 32 AS thermostat, following temporary guideline I-42-2-82. Samples were analyzed every 11.5 days, a period equivalent to six months of natural storage, for a total study duration of 46 days.

RESULTS AND THEIR DISCUSSION.

Analysis of parameters of drug specification confirmed that all indicators were within the specified standards, including: description, identity, clarity, color, foreign



matterparticulate matter. The results for pH, osmolality, and quantitative analysis are presented in Tables 2 and 3.

Table 2

Results of the Long-Term Stability Study of the "Gepaton" Drug

Samples	Storage duration (months)	Parameters/Standards						
		pH (4,0-5,5)	Osmolality 361-447 mOsmol/kg	Quantitative analysis				
				L-arginine 9,75-11,93 mg/ml	L-glutamic acid 8,24-10,08 mg/ml	L-methionine 1,35-1,65 mg/ml	Riboxin 1,8-2,2 mg/ml	Nicotinamide 0,225-0,275 mg/ml
Initial Sample	6	5,8	460	11,70	9,02	1,39	2,123	0,235
№1	6	6,0	467	11,70	8,95	1,42	2,134	0,245
№2	6	6,2	466	11,65	9,02	1,45	2,125	0,237
№3	6	5,9	460	10,98	8,93	1,38	2,132	0,243
№4	6	6,1	465	10,86	8,99	1,39	2,121	0,240
№5	6	5,8	460	11,30	9,00	1,41	2,127	0,240
Initial Sample	12	5,8	455	11,71	9,02	1,38	2,120	0,234
№1	12	6,1	465	11,65	9,00	1,40	2,136	0,246
№2	12	6,1	470	11,60	9,01	1,46	2,130	0,241
№3	12	6,0	460	11,00	8,95	1,40	2,131	0,243
№4	12	6,1	460	10,85	9,00	1,40	2,126	0,239
№5	12	5,7	465	11,30	8,95	1,41	2,125	0,239
Initial Sample	18	5,9	455	11,71	9,01	1,39	2,125	0,235
№1	18	6,1	465	11,64	9,02	1,41	2,134	0,246
№2	18	6,2	465	11,62	9,01	1,44	2,130	0,236
№3	18	6,0	470	10,95	9,00	1,39	2,131	0,244
№4	18	6,2	460	10,90	8,95	1,39	2,131	0,238
№5	18	5,9	460	11,25	9,00	1,40	2,127	0,238
Initial Sample	24	5,9	460	11,70	9,01	1,41	2,143	0,234
№1	24	6,1	470	11,65	9,02	1,39	2,124	0,244
№2	24	6,0	465	11,65	9,00	1,42	2,115	0,240
№3	24	6,0	465	11,00	9,00	1,40	2,102	0,242
№4	24	6,2	460	10,95	8,95	1,38	2,121	0,241
№5	24	6,0	465	11,15	9,00	1,40	2,127	0,240

Table 3



Results of the Accelerated Aging Stability Study of the "Gepaton" Drug

Samples	Storage duration (days)	Parameters/Standards						
		pH (4,0-5,5)	Osmolality 361-447 mOsmol/kg	Quantitative analysis				
				L-arginine 9,75-11,93 mg/ml	L-glutamic acid 8,24-10,08 mg/ml	L-methionine 1,35-1,65 mg/ml	Riboxin 1,8-2,2 mg/ml	Nicotinamide 0,225-0,275 mg/ml
Initial Sample	11,5	5,8	460	11,70	9,02	1,39	2,123	0,235
№1	11,5	6,0	467	11,70	8,95	1,42	2,134	0,245
№2	11,5	6,2	466	11,65	9,02	1,45	2,125	0,237
№3	11,5	5,9	460	10,98	8,93	1,38	2,132	0,243
№4	11,5	6,1	465	10,86	8,99	1,39	2,121	0,240
№5	11,5	5,8	460	11,30	9,00	1,41	2,127	0,240
Initial Sample	23	5,8	455	11,71	9,02	1,38	2,120	0,234
№1	23	6,1	465	11,65	9,00	1,40	2,136	0,246
№2	23	6,1	470	11,60	9,01	1,46	2,130	0,241
№3	23	6,0	460	11,00	8,95	1,40	2,131	0,243
№4	23	6,1	460	10,85	9,00	1,40	2,126	0,239
№5	23	5,7	465	11,30	8,95	1,41	2,125	0,239
Initial Sample	34,5	5,9	455	11,71	9,01	1,39	2,125	0,235
№1	34,5	6,1	465	11,64	9,02	1,41	2,134	0,246
№2	34,5	6,2	465	11,62	9,01	1,44	2,130	0,236
№3	34,5	6,0	470	10,95	9,00	1,39	2,131	0,244
№4	34,5	6,2	460	10,90	8,95	1,39	2,131	0,238
№5	34,5	5,9	460	11,25	9,00	1,40	2,127	0,238
Initial Sample	46	5,9	460	11,70	9,01	1,41	2,143	0,234
№1	46	6,1	470	11,65	9,02	1,39	2,124	0,244
№2	46	6,0	465	11,65	9,00	1,42	2,115	0,240
№3	46	6,0	465	11,00	9,00	1,40	2,102	0,242
№4	46	6,2	460	10,95	8,95	1,38	2,121	0,241
№5	46	6,0	465	11,15	9,00	1,40	2,127	0,240

CONCLUSION.

The studies described above showed that the manufacturing technology, composition, and packaging of the Gepaton infusion solution ensured its stability for 2



years under both natural and accelerated aging conditions. Based on these findings, the shelf life of this drug was established as 2 years.

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