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STABILITY OF THE NEW TABLET FORM OF ANTIBACTERIAL ACTION

The stability of the new tableted dosage form with antibacterial action on the basis of the FS-1 substance is investigated. In the process of storage under long-term tests is not revealed significant changes in the monitored parameters of quality. The compliance value of quality requirements of the specification stability allows establishing the expired date - 24 months.
Keywords: *stability, conditions of storage, long-term / real time testing, storage period, the FS-1, tablets, quality parameters.*

Introduction. The FS-1 substance is a coordination compound of molecular iodine with organic ligands and metal salts [1]. According to the results of full-scale investigations including the non-clinical and clinical trials, standardized FS-1 substance was registered as domestic drug "FS-1 solution for oral use", the registration certificate № RK-LS-3№021305.
Based on the experimental study results of the physico-chemical and technological properties of FS-1, good pharmaceutical development, the rational formulation and optimal technology of coated FS-1 tablets are defined. A method for producing tablets - the method of direct compression, tablet coating carried out by modern coating AquaPolish® P Yellow, which is a combination of hypromellose, titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), macrogol 1500. This unique dry milled homogeneous mixture of film formers selected from cellulose ethers and plasticizing coloring additives ready to the use for applying a film coating to tablets using water as a solvent.
The finished product is a yellow film-coated tablets or almost yellow, round biconvex, containing 75 mg of active substance, and meet the requirements of the State Pharmacopoeia of the Republic of Kazakhstan, vol. 1, the general monograph for "Tablets".
The aim of this study - the study of the stability of the original drug in tablet form based on the FS-1 substance for 24 months during long storage under natural conditions (long-term / real time testing) [2-3]. The objectives of the tests are to establish long-term probation period of storage and use, as well as confirmation of the lack of impact of any changes in the composition of the drug and in the process on product stability [4-6].
Materials and methods. The dosage form is coated tablet, yellow or almost yellow color, round biconvex, diameter of 7 mm and a weight of 0.150 g. The investigated package for storage of tablets - plastic flask with screw cap with the control of the first opening. The number of tablets in the flask is 50.
To determine the stability and shelf life of the tablets FS-1 used a long-term tests in real time, which is sufficient research during their registration.
To determine the period of storage and storage conditions for the establishment were conducted long-term tests under natural conditions (long-term / real time testing) of three pilot sclae batches (table 1) which were obtained in experimental production of JSC "SCAID", Almaty.

Table 1 - General characteristics of the pilot scale batches of the drug

Batch №	Batch size, pcs.	Production date	Schedule testing, months
210413	2 000	21.04.2013 г.	0, 3, 6, 9, 12, 18, 24
060513	2 000	06.05.2013 г.	0, 3, 6, 9, 12, 18, 24
140513	2 000	14.05.2013 г.	0, 3, 6, 9, 12, 18, 24

Tests of the drug to meet quality specifications for the following parameters: description, identification, average weight and uniformity of weight, content uniformity, friability, dissolution, disintegration, loss on drying, microbiological purity, quantitative determination of: - iodine - potassium iodide; using validated methods [7-10], in primary packaging - polymer bank with a screw cap with the control of the first opening, identical to the proposed storage and sales. The storage temperature of the drug - (25±2) °C and relative humidity (RH) - (60±5) %. Description of the quality indicators are presented in table 2.

Table 2 – Specification of stability testing

Quality parameters	**Acceptability of criteria**	**Test methods**
Description	Tablets coated yellow or almost yellow color, biconvex round with weight 0.150 g.	Visually, SP RK, v. 1, the general monograph for "Tablets"
Identification	Staining chloroform layer into a violet-red color. IR spectrum must contain absorption band in the ranges:2959,2 ÷ 2888,5 $см^{-1}$, 1658,0 ÷ 1642,2 $см^{-1}$, 1336,9 ÷ 1323,9 $см^{-1}$, 1259,2 ÷ 1229,5 $см^{-1}$, 1156,0 ÷ 1147,8 $см^{-1}$, 1106,9 ÷ 1102,2 $см^{-1}$, 1070,1 ÷ 1081,4 $см^{1}$, 1023,7 ÷ 1015,5 $см^{-1}$, 529,1 ÷ 510,3 $см^{-1}$. UV spectrum should contain peaks in the ranges: 350 ÷ 353 нм, 286 ÷ 291 нм, 223 ÷ 226 нм	SP RK, v. 1, 2.3.1
The average weight and uniformity of weight	Deviation from the average weight of individual tablets is allowed in 18 of 20 tablets no more than ± 7,5 %, 2 of 20 tablets no more than ± 15 %.	SP RK, v. 1, *2.9.5*
Uniformity of content	From 85% to 115%	EPh, edition 6, v. 1, 2.2.34
Friability	Not more than 1 %	SP RK, v. 2, *2.9.7*
Dissolution	75% in 45 min in water P	SP RK, v. 2, *2.9.3*, Temporary AND project, EPh, edition 6, v. 1, 2.2.34
Disintegration	Not more than 30 minutes in water P	SP RK, v. 1, *2.9.1*
Loss on drying	Not more than 1 %	SP RK, v. 1, *2.2.32*
Microbiological purity	The product should meet the requirements SP RK, volume 1, category 3A. In 1 g of the drug, a maximum of 10^3 aerobic bacteria, 10^2 yeasts and fungi (in total). Not allowed in 1 g product availability E.coli. (category 3A).	SP RK, v. 1, *2.6.12* and v. 2, *2.6.13*

Quality parameters	Acceptability of criteria	Test methods
Quantitative determination of: - iodine - Potassium iodide	 1,1-2,1 % 2,25-3,25 %	Temporary AND project, EPh, edition 6, v. 1, 2.2.34

Results and discussion. According to research prepared the report of stability studies in accordance with the requirements of "On approval of the rules of production and quality control and testing to establish stability and period of storage and re-monitoring of medicines, medical devices and medical equipment" from 05.12.2011. The results are presented in table 3-5.

During the storage period under standard conditions the drug "FS-1, tablets of 75 mg", placed in the primary package, are characterized by a constant composition over time, and its qualitative and quantitative characteristics are within regulated standards. Packaging provides protection from external influences of the drug because of its microbiological characteristics during storage does not change, and fully comply with the requirements of pharmacopoeia.

The stability study results also show the optimal composition of the developing product, in which excipients are chosen according to the physico-chemical and technological characteristics of the active substance. The above data indicate indifference excipients, as they do not affect adversely the structure of the active substances and thereby facilitate the proper therapeutic effect of the drug.

By the studies can be concluded that the optimal composition of the drug "FS-1, 75 mg" created in the form of tablets, stable for 2 years and provides good physical, mechanical and biopharmaceutical parameters.

According to the results long-term stability testing can conclude the following:

- for the control period (2 years) no significant changes in the quality of the drug "FS-1" was observed, which confirms its stability for 2 years;
- according the results of the experiment the storage period the drug "FS-1" is 2 years;
- the recommended storage conditions for the "FS-1" drug: "store in a dry dark place at a temperature no higher than 25 °C".

Thus, as a result of studies the stability of the drug “FS-1, 75 mg” in the form of tablets are investigated. During the storage under long-term testing did not reveal significant changes in the monitored parameters of quality. Compliance of quality values with specification stability requirements allows establishing storage period of 24 months.

Table 3 – The results of stability studies of the drug batches 210413

Storage requirements: t=25±2 °C, RH=60±5 %
Date of beginning and completion of testing: 21.04.2013 г. - 21.04.2015

Quality parameters	Month						
	1	3	6	9	12	18	24
Description	yes	yes	yes	yes	yes	yes	yes
Identification	yes	yes	yes	yes	yes	yes	yes
The average weight and uniformity of weight	0,199± 0,010	0,197± 0,020	0,198± 0,030	0,200± 0,010	0,201± 0,040	0,203± 0,044	0,201± 0,065
Uniformity of content	yes	yes	yes	yes	yes	yes	yes
Friability	yes	yes	yes	yes	yes	yes	yes
Dissolution	85	87	88	84	85	83	85
Disintegration	6,4±0,6	6,0±0,45	7,5±0,75	7,0±0,78	9,5±0,8	10,0±0,9	8,5±0,9
Loss on drying	yes	yes	yes	yes	yes	yes	yes
Microbiological purity	yes	yes	yes	yes	yes	yes	yes
Quantitative determination: - iodine - Potassium iodide	 1,66±0,45 2,74±0,6	 1,6±0,55 2,69±0,5	 1,56±0,6 2,7±0,6	 1,54±0,55 2,74±0,6	 1,55±0,65 2,74±0,6	 1,5±0,45 2,74±0,6	 1,48±0,5 2,74±0,6

Table 4 – The results of stability studies of the drug batches 060513

Storage requirements: t=25±2 °C, RH=60±5 %
Date of beginning and completion of testing: 06.05.2013 г. - 06.05.2015

Quality parameters	Month						
	1	3	6	9	12	18	24
Description	yes	yes	yes	yes	yes	yes	yes
Identification	yes	yes	yes	yes	yes	yes	yes
The average weight and uniformity of weight	0,200± 0,030	0,205± 0,150	0,202± 0,065	0,212± 0,250	0,205± 0,080	0,213± 0,230	0,211± 0,165
Uniformity of content	yes	yes	yes	yes	yes	yes	yes
Friability	yes	yes	yes	yes	yes	yes	yes
Dissolution	90	88	87	85	88	86	89
Disintegration	7,5±0,8	7,0±0,55	7,9±0,80	8,0±0,89	7,5±0,67	9,0±0,8	7,5±0,9
Loss on drying	yes	yes	yes	yes	yes	yes	yes
Microbiological purity	yes	yes	yes	yes	yes	yes	yes

Storage requirements: t=25±2 °C, RH=60±5 % **Date of beginning and completion of testing:** 06.05.2013 г. - 06.05.2015							
Quality parameters	**Month**						
	1	**3**	**6**	**9**	**12**	**18**	**24**
Quantitative determination: - iodine - Potassium iodide	1,7±0,55 2,90±0,70	1,8±0,67 2,95±0,6	1,56±0,35 2,85±0,7	1,58±0,40 2,89±0,7	1,6±0,5 2,8±0,5	1,27±0,45 2,54±0,45	1,2±0,55 2,54±0,6

Table 5 – The results of stability studies of the drug batches 140513

Storage requirements: t=25±2 °C, RH=60±5 % **Date of beginning and completion of testing:** 14.05.2013 г. - 14.05.2015							
Quality parameters	**Month**						
	1	**3**	**6**	**9**	**12**	**18**	**24**
Description	yes	yes	yes	yes	yes	yes	yes
Identification	yes	yes	yes	yes	yes	yes	yes
The average weight and uniformity of weight	0,202± 0,035	0,200± 0,260	0,199± 0,055	0,205± 0,040	0,198± 0,030	0,204± 0,040	0,199± 0,065
Uniformity of content	yes	yes	yes	yes	yes	yes	yes
Friability	yes	yes	yes	yes	yes	yes	yes
Dissolution	90	88	87	85	88	86	89
Disintegration	8,2±0,040	8,4±0,030	8,8±0,070	8,6±0,080	9,0±0,056	9,0±0,86	7,9±0,08
Loss on drying	yes	yes	yes	yes	yes	yes	yes
Microbiological purity	yes	yes	yes	yes	yes	yes	yes
Quantitative determination: - iodine - Potassium iodide	1,54±0,45 2,83±0,60	1,5±0,60 2,87±0,6	1,47±0,55 2,85±0,65	1,53±0,40 2,89±0,7	1,58±0,65 2,88±0,7	1,45±0,30 2,75±0,40	1,34±0,75 2,54±0,65

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АНТИБАКТЕРИАЛДЫ ӘСЕРІ БАР ЖАҢА ТАБЛЕТКА ТҮРІНДЕГІ ДӘРІЛІК ҚАЛЫПТЫҚ ТУРАҚТЫЛЫҒЫН ЗЕРТТЕУ

Түйін: ФС-1 субстанция негізінде антибактериалды әсері бар жаңа таблетканы дәрілік қалыпты турақтылығын зерттеу. Узақ уақыт бойы сақтау мерзімі бойынша анықталды, тәжірбиенін нәтижесінде сапа көрсеткіштерін де ауытқу болмады. Осы зерттеулер нәтижесі қорытындылай келе және турақтылық спецификациясының көрсеткіштеріне сүйене отырып сақтау мерзімі 24 ай екендігі анықталды.

Түйінді сөздер: тұрақтылық, сақтау шарттары, ұзақ мерзімді сынау / нақты уақыт бойынша сынау, сақтау мерзімі, ФС-1, таблетка, сапалық параметрлері.

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ИССЛЕДОВАНИЕ СТАБИЛЬНОСТИ НОВОЙ ТАБЛЕТИРОВАННОЙ ЛЕКАРСТВЕННОЙ ФОРМЫ АНТИБАКТЕРИАЛЬНОГО ДЕЙСТВИЯ

Резюме: Исследована стабильность новой таблетированной лекарственной формы антибактериального действия на основе субстанции ФС-1. В процессе хранения в условиях долгосрочных испытаний не выявлено значительных изменений контролируемых параметров качества. Соответствие значений показателей качества требованиям спецификации стабильности позволяет установить срок хранения 24 месяца.
Ключевые слова: устойчивость, условия хранения, долгосрочные испытания / тестирование в реальном времени, срок хранения, ФС-1, таблетки, параметры качества.