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STUDY OF STABILITY AND STORAGE CONDITIONS OF FITIROL TABLETS BASED ON IGPA OBTAINED FROM RICE FLOUR

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ANNOTATION

The results of experimental studies on stability studies and establishment of shelf life of "fitirol" tablets are presented. Tablets made according to the optimal composition and rational technology ensure the stability of their qualitative and quantitative indicators for 3 years and meet the requirements of GF XIV.

Keywords: Physical and mechanical parameters of phyrol tablets, quality and quantitative determination, stability, packaging, shelf life.

INTRODUCTION

Fitirol consists of a mixture of phytin and diphenhydramine. An industrial source of raw materials for the production of phytin is rice bran, from which phytin is extracted after being pre-fried by extraction. Phytin is a complex organic phosphorus preparation containing a mixture of calcium and magnesium salts of various inositol phosphoric acids, mainly inositol hexaphosphoric acid, and is widely used in medical practice [1]. The pharmacological study of Fytirol showed that the drug has a noticeable antihistamine effect, is low-toxic, does not significantly affect the behavior of animals. Purpose of the research: this work is devoted to studying the storage conditions of phytirol tablets and to establish the shelf life.

For the analysis, we used Fytirol tablets obtained under production conditions in the laboratory of Uzkhimfarm LLC named after V.I. K.S. Islambekov. The physicomechanical parameters of the tablets were determined according to the method described in the literature [2,3].

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MATERIALS

Experimental part: to assess the quality of the tablets, the following criteria were selected: appearance, tablet parameters, authenticity, fracture toughness, abrasion, disintegration, dissolution and quantitative determination of active ingredients.

Qualitative Analysis: (Authenticity Test)

a) 0.1 g of powder of crushed tablets is dissolved in 1.5 ml of nitric acid, 1 g of ammonium nitrate and 3 ml of ammonium molybdate solution are added; a white precipitate (phosphates) falls out.

b) 0.6 g of a powder of crushed tablets is shaken for 3 minutes with 15 ml of water and filtered through a paper filter (GOST 122026-76). The filtrate gives a characteristic reaction for chlorides [4].

c) 1.0 g of powder of crushed tablets is shaken with 15 ml of chloroform for 15 minutes, the chloroform extraction is filtered through a paper filter (GOST 12026-76) into a porcelain cup and evaporated to dryness in a water bath.

4 drops of concentrated sulfuric acid are applied to the watch glass and 0.02 g of dry residue is added; a bright yellow color appears, gradually turning into brick-red (oxonium salt of diphenhydramine). The color disappears from the addition of a few drops of water (decomposition of the oxonium salt of diphenhydramine). 0.1 g of crushed tablets is placed in a glass, added, 25 ml of 70% ethyl alcohol is shaken. The mixture is transferred into a separating funnel with a volume of 100 ml by adding 25 ml of n-hexane and stirred, after which the aqueous-alcoholic layer is transferred to a second separating funnel. The hexane fraction is mixed with 10 ml of alcohol, the alcohol layer is transferred into a funnel, discarding the hexane layer (2 times). The alcoholic layer is dried to dryness in a steam rotary vacuum. The dry residue is dissolved in 10 ml of methanol, transferred to a 25 ml flask and brought to the mark with the mobile phase (solution A).

Transfer 2 ml of solution A to a 25 ml flask and make up to the mark with methanol.

On the starting line of the Silufol UV-254 chromatographic plate, 0.01 ml of the obtained test solution and 0.01 ml of a working standard sample of witness substances (SBS) of diphenhydramine are applied. The plate is dried until the smell of methanol disappears completely, then it is placed in a chamber saturated with solvent vapors of ether - dimethylformamide-benzene (4: 1: 2) for 30 minutes and chromatographed. After the solvent front reaches the finish line, the plate is removed from the chamber, dried and viewed under UV light. On the

chromatogram of the test solution, brown spots should be found at the level of spots of the same color and intensity on the chromatogram of a solution of CBS of diphenhydramine, respectively.

Preparation of a solution of SOVS diphenhydramine. About 0.05 g (so-called) diphenhydramine is placed in a 25 ml volumetric flask, dissolved in 5 ml of methanol, then the volume is brought to the mark with the same solvent.

1 ml of the resulting solution is transferred into a 25 ml volumetric flask and the volume is adjusted to the mark with methanol. The solution is used freshly prepared.

The results of the experimental data are presented in Table 1.

As can be seen from the data in Table 1, all series of experimental tablets meet the requirements of GF XI.

Qualitative characteristics of Fytirol tablets (n = 5)

Studied indicators and unit of measurement	**Analysis results**
Appearance	White with inconspicuous blotches, smooth edges
Authenticity	Compliant
Height to diameter ratio,%	32,70 ± 3,06
Average weight of tablets and deviation from average weight,%	0,35 ± 2,70
Dimensions: height / diameter, mm Disintegration, min Strength for: - abrasion,% -izlom,	3,3/10
Dissolution, not less than 75%	92,67±2,64

Quantification

The standard pharmacopoeial method for phytin analysis is the volumetric iodometric method. The determination is based on the replacement of calcium (magnesium) ions by copper (II) ions, the excess of which is oxidized by potassium iodide with the release of free iodine. The released iodine is titrated with sodium thiosulfate solution. This method is used in the analysis of phyrol tablets. Determination method. About 0.65 g (accurately weighed) of the powder of the crushed tablets is dissolved in 4 ml of 1 mol / l hydrochloric acid solution in a 200 ml volumetric flask, diluted with water to 120 ml, add exactly 25 ml of

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5% copper sulfate solution, 10 ml of sodium acetate solution, adjust water to the mark and mix well. After 5-10 minutes, the liquid is filtered through a dry filter (GOST 12026-76), discarding the first 25 ml of the filtrate. 100 ml of the filtrate is transferred into a flask with a ground stopper, 2 g of potassium iodide are added, mixed, left for 10 minutes and the released iodine is titrated with 0.1 mol / L sodium thiosulfate solution (indicator - starch).

In parallel, a control experiment is carried out - under the same conditions, 25 ml of a 5% solution of copper sulfate are titrated.

The content of phosphoric anhydride (phytin) in one tablet in grams (X) is calculated by the formula:

$$X = \frac{(V-V_0)\ T \cdot F \cdot 200 \cdot b}{a \cdot 100}$$

where: (V-V0) is the difference between the titration of the control and test solutions;

b is the average weight of the tablet, g;

a - sample of the preparation, g.

1 ml of 0.1 mol / l sodium thiosulfate solution corresponds to 0.00782 g of P2O5, which should be at least 0.0926 g, based on the average weight of one tablet. The technique was tested on the heels of a series of tablets, the results of the quantitative determination of phytin were statically processed and presented in Table 2.

Determination of diphenhydramine: About 0.35 g (accurately weighed) of the powder of crushed tablets of phytirol add 5 ml of chloroform and shake for 5 minutes. The chloroform layer is filtered through a paper filter, then this process is repeated. The filtrates are filtered through a filter with 5 g of alumina "for chromatography" degree of activity. The filter is washed with 5 ml of chloroform. Chloroform is distilled off in a water bath at a temperature of 50-600 C. 20 ml of purified water is added to the residue and filtered through a paper filter into a volumetric flask with a capacity of 100 ml, then the volume of the solution is brought to the mark with water and stirred. The optical density of the resulting solution is measured on a spectrophotometer at wavelength □ = 258 ± 2 nm in a cuvette with an optical layer thickness of 10 mm.

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METHODS

Purified water is used as a comparison solution. In parallel, the optical density of a standard solution of diphenhydramine is measured. 1 ml of a standard sample contains 0.0005 g of diphenhydramine.

The content of diphenhydramine in phytirol tablets should be from 0.0463 to 0.0537 g. The results of the quantitative determination of diphenhydramine were statically processed and presented in Table 2.

As can be seen from the data in Table 2, the relative error of the method for the quantitative determination of phytin and diphenhydramine at a confidence level of 0.95 and the number of experiments was 0.88% and 1.85%, respectively, and did not exceed the deviations permissible for this method of analysis.

Determination of dosage uniformity. To determine the uniformity of dosage, selection was made on 30 tablets.

One weighed tablet (accurately weighed) is placed in a 50 ml conical flask with a ground stopper, 10 ml of water is added and closed with a stopper, shaken vigorously for 15 minutes.

Results of the quantitative determination of Fytirol tablets

Hinge weight, g	Content of active ingredients in the preparation		Metrological characteristics	
	Г	%	Phytin	Diphenhydramine
	Phytin (P2O5)	Phytin (P2O5)		
0,6500	0,1027	41,09	$X_{cp.} = 0,1018$	$X_{cp.} = 0,0494$
0,6501	0,1015	40,60	$S^2 = 0,3 \cdot 10^5$	$S^2 = 0,3 \cdot 10^5$
0,6486	0,0990	39,60	S= 0,0016	S = 0,0016
0,6502	0,1030	41,20	$S_x = 0,72 \cdot 10^3$	$S_x = 0,72 \cdot 10^3$
0,6484	0,1026	41,04	$\Delta X = 0,002$	$\Delta X = 0,002$
			$\Delta X_{ўp.} = 0,89 \cdot 10^3$	$\Delta X_{ўp.} = 0,9 \cdot 10^3$
	Diphenhydramine	Diphenhydramine	$\varepsilon_x \% = 1,96$	$\varepsilon_x \% = 4,05$
0,3502	0,0478	95,60	$\varepsilon_{\bar{x}} \% = 0,88$	$\varepsilon_{\bar{x}} \% = 1,82$
0,3439	0,0479	96,00		
0,3412	0,0517	103,40		
0,3534	0,0503	100,60		
0,3609	0,0491	98,24		

Filter through a paper filter into a 100 ml volumetric flask, leaving a precipitate in the flask. The extraction, in the same way, is repeated 2 times, combining the filtrates in the same volumetric flask, bringing the volume of the solution to the mark with water and mixing.

Transfer 25 ml of the resulting solution into a 50 ml volumetric flask, bring the volume to the mark and mix. The optical density of the resulting solution is

measured on a spectrophotometer at wavelengths of 258 nm, in a cuvette with a layer thickness of 10 mm, using water as a reference solution.

In parallel, the optical density of a solution of a working standard sample of diphenhydramine is measured.

The content of diphenhydramine in one tablet, as a percentage, is calculated by the formula:

$$X = \frac{D_1 \cdot m_0 \cdot b \cdot W \cdot 1}{D_0 \cdot m_1},$$

Where:

D1 is the optical density of the test solution;

D0 is the optical density of the PCO solution of medicinal substances;

m1 is the mass of the sample of the preparation, in grams;

m0 is the weight of the sample of the RSO of medicinal substances in grams;

B - average weight of tablets, in grams

W is the content of medicinal substances in a standard sample, g

The results of the analysis are presented in table 3, from which it can be seen that all series of experimental tablets meet the requirements of the State Pharmacopoeia XI.

One of the objective indicators of the quality of drugs is their biopharmaceutical assessment. By the rate of dissolution of the active substance from the dosage form, one can preliminarily judge the intensity of absorption of medicinal substances in the gastrointestinal tract and, accordingly, their therapeutic effect. To assess the dissolution, a “rotating basket” device was used, the dissolution medium was 0.01 mol / l, hydrochloric acid solution, volume was 300 ml, the rotation speed of the basket was 100 rpm, and the dissolution time was 45 minutes. For testing, 2 tablets were placed in the basket. After 45 minutes, 25 ml of 55 copper sulfate solution and 10 ml of sodium acetate are added to the solution. The solution was left for 5 min and filtered through a paper filter (GOST 12026-76) under vacuum, discarding the first drops of the filtrate. Transfer 300 ml of the filtrate into a flask with a ground stopper with a capacity of 500 ml, add 2 g of potassium iodide, mix, leave for 10 minutes in a dark place. the released iodine is titrated with 0.1 mol / l sodium thiosulfate solution (indicator - starch).

RESULTS

In parallel, a control experiment is carried out - under the same conditions, 25 ml of a 5% solution of copper sulfate are titrated.

The content of phosphoric anhydride (phytin) passed into solution from tablets in percent (X) is calculated by the formula:

$$X = \frac{(V\text{-}V_0) \cdot K \cdot 0{,}00782 \cdot 100 \cdot 300}{n \cdot 0.0926 \cdot 300}$$

where: (V-V0) is the difference between the titration of the control and test solutions, ml;

b is the average weight of the tablet, g;

K-correction factor for molarity of 0.1 mol / l sodium thiosulfate solution;

0.00782 - the amount corresponding to 1 ml of 0.1 mol / l sodium thiosulfate solution, in grams;

n is the number of tablets taken to dissolve;

0.0926 - the content of phosphoric anhydride in one tablet in grams.

The treated results are presented in Table 1. As the data in the table show, the rate of release of bioactive substances from tablets after 45 minutes is more than 75%.

The issues of studying the stability and establishing the shelf life of dosage forms are of great theoretical and practical importance. Fytirol tablets were laid:

No. 1. - cans or bottles made of molten glass with 1.1 lids. and level gaskets of type 2.1. according to OST 64-2-87- 81.

DISCUSSION

The study of the shelf life of the tablets was carried out at room temperature with an interval of temperature fluctuations of 18-350C and a relative humidity of 50-

No. 2. - plastic containers made of food polymeric materials according to TSt 64-0516543-03: 2003.

No. 3. - blister packaging made of PVC grade EP-73 and lacquered aluminum foil according to TU 48-21-270-94.

80% for 3 years. Samples for analysis were taken every 6 months. The physicomechanical parameters of the tablets were determined according to the method described in the

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Literature [2].

The analysis results are presented in Table 3, from which shows that all series of experimental tablets meet the requirements of ND.

Table 3 Qualitative characteristics of Fytirol tablets during storage at 200 C, n =5

Studied indicators and unit of measurement	Storage duration, month						
	0	6	12	18	24	36	42
No. 1							
Appearance	*	*	*	*	*	*	*
Authenticity	**	**	**	**	**	**	**
Strength for: - fracture, N	70,0	72,0	71,0	69,0	72,0	72,0	73,0
- abrasion,%	98,78	98,70	98,60	98,70	98,72	98,40	97,87
Disintegration, C	440	440	480	400	440	580	660
Dissolution: fitirol,%	93,70	93,35	93,88	92,65	91,76	92,58	91,84
Quantity: fitin, (P2O5) g	0,0943	0,0936	0,0939	0,0941	0,0931	0,0919	0,0909
- diphenhydramine	0,0498	0,0501	0,0495	0,0504	0,0484	0,0475	0,0485
Dosing uniformity, g	0,0487	0,0479	0,0481	0,0491	0,0476	0,0469	0,0446
No. 2.							
Appearance	*	*	*	*	*	*	*
Authenticity	**	**	**	**	**	**	**
Strength for: - fracture, N	70,0	71,5	72,0	72,0	71,0	74,0	74,0
- abrasion,%	98,78	98,72	98,64	98,70	98,69	98,40	98,40
Disintegration, C	440	432	460	480	500	680	720
Dissolution: fitirol,%	93,70	94,10	93,58	93,60	94,02	86,60	87,60
Quantity:fitin,(P2O5)g	0,0944	0,0944	0,0937	0,0942	0,0940	0,0932	0,0945
diphenhydramine	0,0498	0,0498	0,0487	0,0504	0,0478	0,0476	0,0456
Dosing uniformity, g	0,0487	0,0479	0,0481	0,0474	0,0475	0,0468	0,0448
Number 3.							
Appearance	*	*	*	*	*	*	*
Authenticity	**	**	**	**	**	**	**
Strength for: - fracture, N	70,0	71,5	72,0	72,0	71,0	74,0	74,0
- abrasion,%	98,78	98,65	98,70	98,48	98,89	98,60	98,80
Disintegration, C	445,0	440,0	450,0	470,0	480,0	650,0	660
Dissolution: fitirol,%	93,70	92,81	92,64	93,20	93,38	89,64	88,00
Quantity: fitin, (P2O5) g	0,0944	0,0942	0,0938	0,0938	0,0935	0,0928	0,0927
- diphenhydramine	0,0498	0,0497	0,0507	0,0493	0,0484	0,0482	0,0436
Dosing uniformity, g	0,0487	0,0501	0,0497	0,0476	0,0477	0,0459	0,0478

Note: * appearance - white tablets with inconspicuous inclusions, smooth edges meet the requirements of ND.

** authenticity - meet the requirements of ND.

CONCLUSION

A method for the qualitative and quantitative determination of phytirol has been developed for carrying out tests: "Authenticity", "Quantitative determination", "Dissolution" and "Uniformity of dosage". Studied the stability and established the shelf life of Fytirol tablets.

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