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THE ASPECTS OF PHARMACEUTICAL DEVELOPMENT OF THE TABLETS BASED ON DRY EXTRACTS

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Determination of the critical parameters of the process is one of the important aspects of the pharmaceutical development of medicines of consistently high quality. The purpose of this work is to identify factors that can potentially affect the quality and stability of a tableted medicine containing althea dry extract – "Mukaltin, 50 mg tablets". To determine the parameters that are critical in the production of mukaltin tablets, the influence of a number of factors on the stability of this medicine during storage was studied: the humidity of the initial components; the residual moisture of the finished tablet; the physical and chemical properties of the auxiliary component (isomerization of tartaric acid); the material of the primary packaging. In the course of the study, it was found that among the factors studied, the critical parameters of the production process of mukaltin tablets include the humidity of the intermediates and the finished product and the packaging material.

Keywords: dry extract, tablets, Mucaltin, stability, storage

Herbal medicinal products, including tableted medicines based on plant extracts, are widely used in the pharmaceutical industry and have been used for a long time due to their high efficiency, availability, ease of use and low toxicity [1,8].

In addition to the obvious pharmacological advantages, this dosage form has certain technological features. Dry extracts for the most part have high hygroscopicity, as a result of which the pharmaceutical development of a tablet dosage form based on them requires a special approach [5,7,9].

One of the important aspects of the pharmaceutical development of consistently high quality medicines is the determination of critical parameters of the process [10].

The purpose of this work is to identify factors that can potentially affect the quality and stability of a tableted medicine containing althea dry extract – "Mukaltin, 50 mg tablets" (hereinafter referred to as mukaltin tablets) [2,6].

To determine the parameters that are critical in the production of mukaltin tablets, the influence of a number of the following factors on the stability of this medicine during storage was studied:

- moisture of the initial components;
- residual moisture of the finished tablet;
- the physical and chemical properties of the auxiliary component (isomerization of tartaric acid);
- packing material.

In order to determine as accurately as possible the factor or factors that have the most pronounced effect on the stability of the medicine "Mukaltin, 50 mg tablets", as well as in order to distinguish factors from each other (since a set of factors may participate in this process), the following assumptions were made:

1. Residual moisture of the tablet. If we assume that the packaging insulates the tablets as much as possible from the effects of external moisture, it is possible that the residual moisture of the tablets may be sufficient for the occurrence and course of a gas formation reaction [4,5].

2. Influence of the packaging material on the stability of the tablets. The permeability of the packaging material may well provoke a gas formation reaction in the tablet, taking into consideration that most of the components are hygroscopic substances [11].

3. Influence of physical and chemical properties of excipients (isomerization of tartaric acid). The tablets of mukaltin as an excipient include tartaric acid. It has isomers that have different properties [5,6].

MATERIALS AND METHODS

The following components were used for the production of mukaltin tablets [2,6]:

- althea dry extract ("Harms", Russia);
- tartaric acid – D-isomer (Rono Chem Co. Ltd, China);
- tartaric acid – D–L-isomer (KOHO, China);
- sodium hydrocarbonate (Bashkir Soda Company JSC, Russia);
- calcium stearate (Khimresurs LLC, Russia).

As a reference substance, mukaltin tablets were taken, produced by Obnovlenie JSC, Russia.

Packing material:

- polyvinylchlorid (PVC) with thickness of 200 μm;
- polyvinyldichloride (PVDC) with thickness of 200 μm.

The following methods were used to determine the quality parameters [3]:

- description of tablets in the package during storage:

a) the appearance of the tablets – the color was determined by the intensity of darkening in comparison with a tablet stored at constant humidity of 10±5% and temperature of 30°C (designation on a scale of 0), and a tablet stored at constant humidity of 75±5% and temperature of 30°C (designation on a scale of 3);

b) the appearance of the primary package is the presence or absence of cell swelling (where 0 is the absence of swelling, and 4 is the state in which a slight compression of the package cell causes it to break) [4].

The sum of values characterizes the overall assessment of two parameters in four storage conditions:

- weight loss during drying;
- change in tablet weight during storage;
- resistance to crushing of tablets.

Equipment:

- climatized chamber KBF 1020 (Binder) at operation conditions 30°C and humidity 75±5%;
- hot air oven TC-80M-2 at operation conditions 40°C;
- tablet strength tester TBH 125 (Erweka);
- scales BM-2202 (Vesta Experimental Design Bureau);
- Weight Humidity Analyzer АВГ-60 (Gosmetr).

RESULTS AND DISCUSSION

Immediately before the production of the tablets and during the process, the mass loss during drying was determined as components separately (Table 1), and the tablet mixture (Table 2) [10].

Further, for the experiment, 8 types of experimental samples of mukaltin tablets and 1 type of packaging with a reference substance repacked in a PVC blister were produced and packed (Table 3).

Table 1

WEIGHT LOSS DURING DRYING OF THE COMPONENTS OF MUCALTIN TABLETS

Climatic conditions in the laboratory room: t=22,7°C, humidity – 20,6%		
Component	**Drying temperature**	**Weight loss during drying, %**
Tartaric acid D, solid	100°C	0.77
Tartaric acid D, crushed		0.78
Tartaric acid (D,L)		0.56
Sodium hydrocarbonate		1.22
Althea dry extract		2.05
Calcium stearate		1.06

All tablets after packaging had the following parameters:

- Weight of a tablet: 0,300±0,005 g;
- Tablet fractural strength: 110±10 N;
- Height of a tablet: 3,82±0,1 mm;
- Weight loss when drying tablets that have not passed the drying stage: 1,75±0,1%;
- Weight loss during drying of tablets that have passed the drying stage: 0,94±0,1%.

The tablets were stored under four different conditions [7]:

1) at 25°C and humidity 40±5% ("at room temperature" is designated as "at r.t.", Table 4);

2) at 40°C and humidity 40±5% ("in thermostat" is designated as "therm", Table 5);

3) at 30°C and humidity 75±5% ("in a climatic chamber simulating a zone 4B", is designated as "cc", Table 4);

4) in a double dense PEG bag at 25°C and humidity of 40±5% ("to exclude external influences of moisture" is designated as "package", Table 4).

Each week, the appearance was inspected visually, and each month, some of the blisters were selected for testing.

The results of inspections (after 3 months) are shown in Table. 4 and 5.

After 3 months of testing, all the samples in the climatic chamber changed their appearance: the packaging blisters were swollen, the tablets were very dark. The average mass of the samples also decreased due to the gas formation reaction (the mass loss was about 20%). None of the studied samples showed stability in the conditions of the climatic chamber.

In a double plastic bag and a thermostat, the samples were preserved better than in

Table 2

WEIGHT LOSS DURING DRYING OF THE TABLET MIXTURE AT DIFFERENT STAGES OF PRODUCTION

Tartaric acid isomer	**Weight loss during drying, %**				**Note**
	Tablet mixture	**Tablet mixture after moistening**	**Tablets after tableting**	**Tablets after drying**	
Racemate (D,L)	1.60	2.08	1.75	0.94	Some of the tablets were selected before drying and packed separately
D-isomer	1.47	2.08	1.59	0.80	

Table 3

TYPES OF MUKALTIN TABLETS PROVIDED FOR STORAGE

Medicine	Physical and chemical properties of tartaric acid	Weight loss during drying of tartaric acid, %	Primary packing materials
Reference substance			PVC
Mukaltin, 50 mg tablets	Racemate	1.75	PVC
			PVDC
		0.94	PVC
			PVDC
	D-isomer	1.59	PVC
			PVDC
		0.80	PVC
			PVDC

the climatic chamber, but also had an unsatisfactory appearance (the packaging was swollen).

When stored at room temperature, the best stability was shown by samples of tablets 7 and 8. The appearance of these samples did not change. Tablets produced by Obnovlenie JSC, repackaged in a PVC blister, darkened and swollen in all storage conditions, while in the original packaging, there was no change in appearance.

The studies provided allow us to make a number of findings.

- The residual moisture content of the finished tablet plays an important role in ensuring the stability of the mucaltin tablets. Mukaltin tablets that have passed the drying stage show higher stability.
- The tablet fractural strength after storage in the climatic chamber decreased by 3 times, when stored at room temperature, the strength practically did not change, and at 40°C increased by 1.5 times.

Table 4

EVALUATION OF THE APPEARANCE OF MUKALTIN TABLETS

Sample number	Appearance								Sum of values
	Discoloration				Swelling				
	cc	therm	At r.t.	package	cc	therm	At r.t.	package	
1	3	1	2	2	4	4	3	2	**21**
2	3	2	2	3	4	4	2	3	**23**
3	3	2	2	2	4	4	2	3	**22**
4	3	1	2	2	4	4	3	4	**23**
5	3	1	2	3	4	3	3	3	**22**
6	3	0	1	3	4	2	3	4	**20**
7	3	0	0	1	4	2	0	2	**12**
8	3	0	0	1	4	2	0	2	**12**
9	3	0	1	2	4	3	3	4	**20**

Table 5

GENERAL CHARACTERISTICS OF TABLETS AFTER 3 MONTHS OF TESTING

Sample number	Tartaric acid isomer	The presence of the drying stage	Type of a film	Appearance of tablets, total score	Average tablet weight, g	Fractural strength, N	Weight loss during drying, %
1	reference substance		PVC	**21**	0,254	33	3.93
2	D–L	–	PVC	**23**	0,236	28	3.80
3	D–L	–	PVDC	**22**	0,242	30	3.11
4	D	–	PVDC	**23**	0,217	26	7.01
5	D	–	PVC	**22**	0,254	31	3.93
6	D–L	+	PVC	**20**	0,233	28	7.15
7	D–L	+	PVDC	**12**	0,280	35	2.27
8	D	+	PVDC	**12**	0,291	38	2.04
9	D	+	PVC	**20**	0,262	33	3.74

- According to experience, PVDC packaging has satisfactory barrier parameters. Only in this package, the tablets were preserved for 3 months. The tablet original packaging made by Obnovlenie JSC turned out to be thinner than the one used in this experiment (150 μm versus 200 μm). Probably, this thickness allows the package to remain permeable to the products of the gas formation reaction, and, therefore, the resulting carbon dioxide can escape through the pores of the material without damaging the blister, thereby preserving the marketable appearance of the medicine.

Based on the conducted studies, it can be concluded that from the studied factors, the critical parameters of the production process of mukaltin tablets include the following:

1. Humidity of semi-products and finished product. To achieve the best stability of the medicine under the stated conditions, it is recommended to include the drying stage of the finished tablets into the production process.

2. Packaging material. Primary blister pack made of PVDC provides better stability of the medicine.

3. Storage conditions. Mukaltin tablets are best stored at temperature of up to 25°C and relative humidity 40±5%.

Factors that do not have a pronounced effect on the quality and stability of mukaltin tablets and are not related to critical parameters:

- moisture of the initial components;
- tartaric acid isomerization.

This study shows that various production factors can have a pronounced effect on the stability of tablets containing dry extracts. Failure to comply with these requirements may result in the reject of the entire batch. Therefore, when developing medicines of this group, it is necessary to carefully determine the critical parameters and strictly control them throughout the entire process.

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