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

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Determination of critical process parameters is one of the important aspects of pharmaceutical development of the consistent high-quality medicines.

The purpose of this work is to identify factors that can potentially effect on the quality and stability of a tableted medicinal product containing althea dry extract such as "Mukaltin, 50 mg tablets".

To determine the parameters that are critical for the manufacturing process of Mukaltin tablets, the influence of a number of factors on the stability of the medicine during storage was studied. These factors include humidity of the starting materials; residual moisture of the finished tablet; physical and chemical properties of the excipients (tartaric acid isomerism); primary packaging material.

During the study, it was found that the critical parameters of the process of Mukaltin tablet manufacturing are the humidity of the intermediates and the finished product and the packaging material.

Keywords: Mukaltin, dry extract, tablets, 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, accessibility, ease of use and low toxicity [1,8].

In addition to the obvious pharmacological advantages, this dosage form has certain technological characteristics. 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 consistent high-quality medicines is the determination of critical parameters of the technological process. [10].

The purpose of this work is to identify the factors which are potentially capable of influencing on the quality and stability of a tableted medicinal product containing althea dry extract – "Mukaltin, 50 mg tablets" (hereinafter referred to as Mukaltin tablets) [2,6].

In order to determine as accurately as possible the factor or factors that are critical, that is, having the most pronounced effect on the stability of the medicine "Mukaltin, 50 mg tablets", and in order to distinguish them (since a combination of factors may participate in this process), the following assumptions were made:

1. The effect of the residual moisture of the tablet. Assuming 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. The influence of the packaging material. The permeability of the packaging material may well provoke a gas formation reaction in the tablet, taking into account that most of the components are hygroscopic substances [11].

3. Influence of physical and chemical properties of excipients (isomerization of tartaric acid). The composition of Mukaltin tablets includes tartaric acid as an excipient. Tartaric acid has isomers with different properties [5,6].

Based on the above assumptions, the influence of the following factors on the stability of Mukaltin tablets during storage was studied:

- humidity of the starting materials;
- residual moisture of the finished tablet;
- physical and chemical properties of excipient (isomerism of tartaric acid);
- packaging material.

MATERIALS AND METHODS

The following components were used for the manufacture of Mukaltin tablets [2,6]:

- althea dry extract produced by Harms, Russia;
- tartaric acid D- isomer produced by Rono Chem Co. Ltd, China;
- tartaric acid D–L-isomer produced by KONO, China;
- sodium bicarbonate produced by Bashkir Soda Company JSC, Russia;
- calcium stearate produced by Chemresource LLC, Russia.

As a reference product, Mukaltin tablets produced by Obnovlenie JSC, Russia were taken.

- Packaging material:
- polyvinyl chloride (PVC) 200 microns thick;
- polyvinylidene chloride (PVDC) 200 microns thick.

The following methods were used to determine the qualitative parameters [3].

Description of the appearance of tablets in a package during storage (scoring method):

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

b) *the appearance of the primary packaging* was assessed by the presence or absence of a blister bulge (where, according to a point scale, 0 is the absence of a bulge, and 4 is a condition in which a slight compression of the packaging blister causes it to rupture) [4].

The sum of the points characterizes the overall assessment of the appearance of the sample (assessment of the appearance of tablets and assessment of the appearance of the primary packaging) in various storage conditions;

- weight loss during drying;
- measurement of the weight of tablets during storage;
- tablet breaking force.

Equipment:

- climate chamber BINDER KBF1020 with operation temperature 30°C and humidity 75±5%;
- dry-air thermostat TC-80M-2 with operation temperature 40°C;
- tester for determining the strength of tablets Erweka THB 125;
- scales of OKB "Vesta" BM2202;

weight humidity analyzer "Gosmeter" AVG-60.

RESULTS AND DISCUSSION

Immediately before the manufacture of tablets and during the technological process, the weight loss of both components separately (Table. 1), and the tablet mixture during drying was determined (Table. 2) [10].

Table 1

WEIGHT LOSS OF MUKALTIN TABLET COMPONENTS DURING DRYING

Component	Drying temperature	Weight loss during drying, %
Tartaric acid D	100°C	0.77
Tartaric acid D crushed		0.78
Tartaric acid (D,L)		0.56
Sodium hydrocarbonate		1.22
Althea extract dry		2.05
Calcium stearate		1.06

Note: climatic conditions in the laboratory room: t=22,7°C, humidity =20,6%

Further, 8 types of experimental samples of Mukaltin tablets were manufactured and packaged for the experiment, differing in the physical and chemical properties of the excipient (tartaric acid), manufacturing process (with and without drying stage) and primary packaging material. The reference product was repackaged into a PVC blister. More detailed characteristics of the samples are presented in Table 3.

All tablets after packaging had the following parameters:

- tablet weight – 0,300±0,005 g;
- tablet breaking strength – 110±10 N;
- tablet height – 3,82±0,1 mm;
- weight loss during drying of 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 4 different conditions [7]:

1) at 25°C and humidity 40±5% ("at room temperature");

2) at 40°C and humidity 40±5% ("in thermostat");

3) at 30°C and humidity 75±5% ("in a climate chamber simulating zone 4B");

4) in a double dense polyethylene bag at 25°C and humidity 40±5%.

Every week the appearance was visually evaluated, every month a part of the blisters were selected for testing.

The results of observations (after 3 months) are shown in Tables 4 and 5.

After 3 months of testing, all the samples in the climate chamber changed their appearance: the packaging blisters swelled, the tablets turned very dark. The average weight of the samples also decreased due to the gas formation

Table 2

WEIGHT LOSS OF TABLET MIXTURE DURING DRYING AT DIFFERENT STAGES OF MANUFACTURE

Tartaric acid isomer	Weight loss during drying, %				Note
	Tablet mixture	Tablet mixture after moistening	Tablets after tabletizing	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

CHARACTERISTICS OF THE STUDIED SAMPLES OF MUKALTIN TABLETS

Sample number	Tartaric acid isomer	Availability of the drying stage	Primary packaging material
1	Reference product		PVC
2	Racemic mixture	–	PVC
3	Racemic mixture	–	PVDC
4	D-isomer	–	PVDC
5	D-isomer	–	PVC
6	Racemic mixture	+	PVC
7	Racemic mixture	+	PVDC
8	D-isomer	+	PVDC
9	D-isomer	+	PVC

reaction (the weight 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 the climate chamber, but also had an unsatisfactory appearance (the packaging was swollen).

When stored at room temperature, the samples of tablets No. 7 and No. 8 showed the best stability. The appearance of these samples has not changed.

Tablets produced by Obnovlenie JSC, repackaged in a PVC blister, darkened and swollen in all storage conditions, while there was no change in appearance of the tablets in the original packaging.

The study allows us to make a number of conclusions.

The residual moisture content of the finished tablet plays an important role in ensuring the stability of Mukaltin tablets. Mukaltin tablets that have passed the drying stage demonstrate higher stability.

Table 4

EVALUATION OF THE APPEARANCE OF MUKALTIN TABLETS

Number of a sample	Appearance								Sum of indicators
	Discoloration				Bulging				
	cc*	therm*	room*	PE bag	cc	therm	room	PE bag	
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

Note: cc – climatic chamber; therm* – thermostat; room* – room temperature*

Table 5

SUMMARY OF TABLET CHARACTERISTICS AFTER 3 MONTHS OF TESTING

Number of a sample	Appearance of tablets, total score	Average tablet weight, g	Breaking strength, N	Weight loss during drying, %
1	21	0.254	33	3.93
2	23	0.236	28	3.80
3	22	0.242	30	3.11
4	23	0.217	26	7.01
5	22	0.254	31	3.93
6	20	0.233	28	7.15
7	12	0.280	35	2.27
8	12	0.291	38	2.04
9	20	0.262	33	3.74

The breaking strength of the tablets 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 it increased by 1.5 times.

According to experience, PVDC packaging has satisfactory barrier parameters. Only in this package the tablets were preserved for 3 months. The original packaging of the tablets produced by Obnovlenie JSC turned out to be thinner compared to the one used in this experiment (150 microns versus 200 microns). Probably, this thickness allows the package to remain permeable to the products of the gas formation reaction, 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.

CONCLUSIONS

Based on the studies conducted, 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-finished 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 finished tablets into the production process.

2. Packing material. Primary blister packaging made of PVDC provides better stability of the medicine.

3. Storage conditions. Mukaltin tablets are best stored at a temperature of up to 25 °C and a relative humidity of 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:

- humidity of the staring materials;
- isomerism of tartaric acid.

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 rejects of the entire batch. Therefore, when developing medicines of this group, it is necessary to carefully approach the definition of critical parameters and strictly control them throughout the entire process

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