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Research In The Field Of Development Of Technology Of Tablets "Sitmet"

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Abstract: The article presents the results of the development of the composition and technology of "Sitmet" tablets. In the course of the study, methods were used to evaluate the technological properties of powders and tablets in accordance with the XIII State Pharmacopoeia. It is shown that the nature and quantity of excipients affect the technological properties (compressive strength and abrasion, disintegration) of Sitmet tablets. Technological factors are determined: the mixing time of the tablet mixture, the time of powdering the granulate. It is shown that the developed technology with the use of wet granulation ensures the production of tablets that meet the requirements for 36 months of storage in natural conditions.

Key words: tablets, granulate, combined, expiration date.

Type 2 diabetes mellitus is a complex chronic disease caused by the inability of the human body to produce enough insulin or use it effectively. People living with type 2 diabetes need to receive treatment to control their insulin and blood sugar levels. People with type 2 diabetes, whose body gives an insufficient response to insulin or has resistance to it, may need treatment that will help their body process glucose better. Such therapy can prevent the development of serious complications [1,6,11,14].

Rational drug therapy is not sufficiently carried out in patients with an unsatisfactory glycemic profile. Low compliance of patients occurs due to violation of medical recommendations, namely, violations of the dosage regimen and the frequency of taking hypoglycemic drugs. Many patients, especially the elderly, negatively perceive the intake of several hypoglycemic drugs or a change in the frequency of their intake. The need for hypoglycemic therapy against the background of taking medications for the treatment of concomitant pathologies also leads to low adherence of patients to type 2 diabetes therapy. According to research data, glycemic control is one of the important methods of reducing the progression of the disease and its complications [2,4,8,10,12,13,15,17].

Therefore, a significant expansion of the range of antidiabetic medicines is a well-reasoned position. The emergence of new medicines, as a consequence, entailed the search and, of course, a detailed study of the original dosage forms, their development, technology, analysis [3,5,7,19,20].

Previously, we found that the technological properties of pharmaceutical substances and excipients do not ensure the production of tablets by direct pressing [9,18].

The purpose of this stage of the study was to develop the composition and technology for producing Sitmet tablets.

Methods. Pharmaceutical substances were used in the work: sitagliptin phosphate monohydrate and metformin, as well as auxiliary substances: microcrystalline cellulose, povidone, magnesium stearate and Twin 80.

22 tablet mixtures were obtained, differing in the nature and amount of excipients.

When developing tablet technology, special attention is paid to the selection of the type, concentration and quantity of binders. Purified water, sugar syrup, ethyl alcohol of various concentrations were used for humidification - 30, 40, 50, 70% 2-10% starch solutions and povidone. When moistened with ethyl alcohol of various strengths, sugar syrup, the powder did not respond to granulation (the formation of granules did not occur) and as a result, it was decided that the use of ethyl alcohol as a binder was not advisable. Further humidification was carried out with water, as it provided good granulation of the tablet mass. When wetting the substance with water, a lumpy, dough-like mass was formed. To reduce losses and the duration of the process, the mass, after moistening, was dried, and then dry granulation was performed. When moistening the mass with purified water, the granulate after drying turned out to be strong, the resulting tablets had a high-quality appearance, but the strength was unsatisfactory. In subsequent experiments, moistening was performed with starch paste of various concentrations. According to the results of the study, it was revealed that low starch concentrations lengthen the disintegration time of tablets, and also high concentrations of starch paste affect the decrease in strength. In order to optimize the technology of preparation of tablets, the introduction of starch was carried out in three ways. To do this , the masses were prepared in three ways:

1) adding starch to the mass before moistening;

2) the use of starch for powdering together with an antifriction agent;

3) dividing the amount of starch into 2 equal parts and using both for powdering and for introducing into the mass before moistening;

The technology of obtaining tablets was carried out as follows:

1. To obtain the granulate in the laboratory, the powdered mixture was added to the mass of povidone until moistened and wiped through a sieve with a hole diameter of 3 mm. Dried in a drying cabinet at a temperature no higher than 50 ° C to a residual humidity of 4-6%, then wiped through a sieve with a hole diameter of 1.5 mm. Powdered in a mortar with a plastic scoop. The granulates were pressed into tablets on a manual hydraulic press at a pressing pressure of 120 MPa. In industrial conditions, the tablet mass was prepared as follows: excipients and pharmaceutical substances were loaded into a high-speed granulator mixer, a binding agent solution was added and granulated for 15 minutes. The granulate was dried at a temperature of 30-45 °C for 90 minutes, wiped through a sieve with a hole diameter of 1.6 mm. The dusting was carried out on a two-cone mixer at a rotation speed of 20 revolutions per minute.

In the second technology, povidone was used for powdering together with an antifriction substance.

In the third technology, the amounts of povidone were divided into 2 equal parts and used both for powdering and for injection into the mass before moistening.

The results of the study of the qualitative indicators of "Sitmet" tablets prepared in three ways by wet granulation are shown in Table 1.

Table 1 The results of studying the qualitative indicators of "Sitmet" tablets prepared in three ways by wet granulation

№ methods	Disintegration, min.	Strength on		Deviation from the average weight g, %
		kink, H	abradability, %	

1	50-52 min	74	99,81	0,25±5,1
2	23-25 min	68	99,3	0,198±3,2
3	28-30 min	60	99,12	0,206±4,8

Studies have shown that all the studied compounds had the same data. From the data in the table it can be seen that the obtained tableted masses according to the first and third method ensured the production of tablets that meet the requirements of GF XIII for all defined indicators, with the exception of disintegration, which was 50-52 min and 28-39 min, respectively. Added to the tableted mass before granulation to improve disintegration, povidone lost its effectiveness. We tried adding povidone together with magnesium stearate antifriction agent as a dusting agent after wet granulation. The tablets obtained in this way disintegrated within 23-25 minutes. As can be seen from the table, the most significant influence on all the studied indicators (fracture strength, decay time) is exerted by the concentration of povidone, with a decrease in the amount of which the fracture strength and decay time increases.

Therefore, for further research, we chose the third method (dividing the amount of povidone into 2 equal parts and using both for powdering and for introducing it into the mass before moistening).

The influence of the nature and quantity of excipients on the quality indicators of "Sitmet" tablets are presented in Table 2.

Tablets obtained by the third technology were tested for quality. For this purpose, 15 series of "Sitmet" tablets were prepared in industrial conditions) and in laboratory conditions. The results of the study of tablets are presented in Table 2.

The results of studying the quality of tablets are shown in Table 2.

Table 2 The influence of the nature and quantity of excipients on the quality indicators of "Sitmet" tablets (laboratory samples)

Serial number	Disintegration, min. (n=6)	Abradability, %	Compressive strength, H (n=10)
1	31,0±0,55	0,17	66,4±3,80
2	34,0±0,64	0,12	74,2±4,21
3	23,7±0,87	0,25	74,6±3,62
4	22,1±0,65	0,31	63,4±3,33
5	24,4±0,54	0,24	68,6±3,43
6	33,7±0,88	0,18	65,9±4,44
Acceptable limits for the FS project	no more than 45	before 1	nevertheless 50

At the next stage of the study, the influence of the preparation technology on the quality indicators of Sitmet tablets (factory and laboratory samples) was studied(Table 3) .

Table 3 The influence of the preparation technology on the quality indicators of Sitmet tablets (factory and laboratory samples)

Series, №	Mixing time of	Mixing time of	Dusting time,	Tablet quality indicators			
				Disintegration,	Abradability,	Compressive	The number

	each serving, min.	the whole mass, min.	min	min. (n=6)	%	strength, H (n=10)	of tablets that do not meet the requirements for uniformity of content, pcs., (n=20)
Technology №2							
8	1	30	30	33,5±0,42	0,22	55,1±1,22	8
9		30		35,1±0,65	0,24	59,1±1,32	6
10		30		22,9±0,45	0,53	57,7±3,53	9
11		60		23,4±0,28	0,39	55,3±4,11	6
12		90		24,2±0,24	0,38	61,6±4,32	4
13	3	120		35,1±0,22	0,19	63,7±5,43	7
14		30	60	29,9±0,35	0,23	59,1±6,33	7
15		60		29,2±0,43	0,19	67,2±7,24	5
16		90		28,7±0,65	0,22	65,4±9,53	5
17		120		33,5±0,44	0,32	70,4±6,11	4
Technology №3							
18	-	30	60	24,5±0,41	0,35	54,7±4,19	5
19			120	33,1±0,58	0,43	58,1±1,21	2
20			180	31,7±0,45	0,19	59,1±1,26	2
Technology №4							
21	-	30	60	13,0±0,54	0,45	69,4±4,11	0
22				14,1±0,47	0,29	78,8±4,14	0
Acceptable limits for the FS project				no more 45	before 1	nevertheless 50	1

According to the results given in Table.3 it was found that an increase in the mixing time and the powdering time of tablets prepared according to technology No. 2 and No. 3 statistically significantly increases the compressive strength of tablets (rubbing, as well as the disintegration time. At the same time, according to these indicators, during the entire observation period, the tablets met the requirements (Table 3). The period of 2 years is set as the expiration date of "Sitmet" tablets.

Study of the kinetics of moisture absorption of "Sitmet" tablets. Rational modes of storage of medicines allow to maintain their quality for a long time, to reasonably approach the selection of packages for them. The process of long-term storage of goods is caused by the constant interaction of internal and external factors. Internal factors that make up the qualitative characteristics of the product - the properties and quality of the material, chemical composition, humidity, amount of active substances, etc. External factors include climate, time of year, type of storage and its condition, relative and absolute humidity and temperature of storage rooms, light, etc. The study of hygroscopic properties helps to create storage conditions corresponding to the physicochemical properties of substances, as well as to select packaging that ensures consistency of quality both during storage and during transportation.

Taking this into account, the moisture absorption properties of the pressed mass and ready-made "Sitmet" tablets were studied by the method of S.A.Nosovitskaya and co-authors at different values of relative humidity of the environment. The moisture absorption capacity was studied by gravimetric method [7,9].

To study the kinetics of moisture absorption, pre-weighed samples of granules (0.5g each) and tablets (0.1 g each) were placed in open buckets with a diameter of 2,0-2,6-3,3 then the buckets were placed in a desiccator containing a saturated solution of sodium bromide (relative humidity 58%) and purified water (relative humidity 100%). The increase in moisture content over time was determined by the gravimetric method. For 7 days, every 24 hours, the buckets were removed, covered with lids and weighed on analytical scales with an accuracy of +0.0001g.

The desiccators were thermostated at a temperature of 22 +10C.

The amount of moisture absorption (%) relative to the initial mass of the samples was calculated using the following formula:

$B = ((m - m_0) / m_0) \cdot 100$,

where:

m – the mass of the sample at certain intervals, g;

m_0 – initial mass of the sample, g.

The results of the research are presented in Fig. 1

From the research results shown in Table 4, it can be seen that the use of microcrystalline cellulose as fillers contributed to the least moisture absorption. Pressing granules into tablets reduced moisture absorption by an average of 1.5 - 2 times.

Table 4 Kinetics of moisture absorption of granules and model tablets "Sitmet" at different values of relative humidity of the environment

Compositions №	The amount of moisture absorbed, at relative humidity, %				
	Duration of the study, day	58%		100%	
		granules	pills	granules	pills
C-1	1	3,82	1,82	16,0	13,76
	2	2,45	1,63	19,57	16,69
	3	1,03	0,13	22,4	18,53
C-2	1	4,07	2,02	29,80	20,10
	2	3,65	1,88	38,80	27,58
	3	2,15	0,75	41,45	29,18
C-3	1	5,07	2,74	49,80	31,90
	2	4,65	2,24	98,80	85,18
	3	3,15	0,86	121,45	112,50
C-4	1	8,12	3,38	79,80	42,8
	2	6,14	3,45	138,83	65,0
	3	4,27	3,87	141,52	87,2
C-5	1	8,12	2,75	49,80	34,60
	2	4,13	1,98	88,80	44,84
	3	3,54	1,94	59,95	66,02

Another factor affecting the moisture-absorbing properties of powders is the size of the sample surface area. Studies were also conducted by the gravimetric method, in which the relative humidity of the environment is 58%, which was created due to a saturated solution of sodium bromide. A pre-weighed amount of the substance was placed in buckets of various diameters. Desiccators containing buckets were thermostated at a temperature of 22 ± 2 ° C.

The specific surface moisture absorption S (g/m2), which characterizes the amount of moisture sorbed through a surface unit, was calculated by the formula:

$y = (m – m_0) / S,$

Where,

m - the mass of the sample at certain intervals, g;

m_0 - initial mass of the sample, g;

S - specific surface moisture absorption, g/m^2

The results of the studies are shown in Fig.2. and 3.

Fig.2. Specific surface moisture absorption of the pressed mass at different sizes of the sample surface area

Thus, the studied samples contained in all three bucs did not lose their flowability properties until the end of the studies, while absorbing from 1.14% to 1.99% of moisture. From the data obtained, it is safe to say that an increase in the surface area of the sample causes a slight increase in the moisture absorption properties of the studied masses.

Fig.3. Specific surface moisture absorption of "Sitmet" tablets at different sizes of the sample surface area

As a result of the conducted studies, it was found that the tablets do not possess an increased moisture absorption capacity and to a lesser extent depends on the size of the surface area of the sample.

The results of studies of granules and tablets with various fillers in terms of moisture absorption ability allowed us to conclude that MCC can be used as promising fillers for Sitmet tablets.

Conclusion.

1. As a result of the conducted research, it was found that the introduction of microcrystalline cellulose into the composition of Sitmet tablets, a decrease in the amount of starch increased the compressive strength and disintegration time of the tablets, as well as reduced abrasion.

2. It was determined that the lengthening of the duration of mixing the ingredients of tablets at the stages of granulate production (from 30 to 120 minutes) and dusting (from 30 to 180 minutes) statistically significantly increased the time of their disintegration, compressive strength and reduced abrasion.

3. It is shown that the technology developed with the use of wet granulation ensures the production of tablets that meet the requirements of the III State Pharmacopoeia for 24 months of storage in natural conditions and in conditions of "Accelerated aging".

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