WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 1, 267-276 Research Article ISSN 2278 – 4357

RESEARCH RESULTS IN THE DEVELOPMENT OF TECHNOLOGY OF "MELIFLOS" TABLETS

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Article Received on
08 Nov. 2018,

Revised on 28 Nov. 2018,
Accepted on 18 Dec. 2018

DOI: 10.20959/wjpps20191-12903

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ABSTRACT

This report presents the results of research in the field of development of technology tablets "Meliflos". The influence of the technological process of tableting on the quality of the recommended tablets has been studied. The technological properties of the obtained tablet masses and the finished product were studied.

KEYWORDS: Direct pressing, wet pressing, quality, technological properties.

INTRODUCTION

The medicinal plant contains one or more substances that are able to show certain medicinal properties in the human and animal body in the presence of known conditions. In comparison with synthetic drugs, the medicinal plant is known to be less toxic. Therefore, in modern pharmacy to create a drug based on medicinal plants is an urgent task. It is known that vegetable raw materials serve as a source of more than a third of all medicines.[1]

People with renal insufficiency are at risk for health reasons. Under these conditions, the search and development of new diuretics based on medicinal plants is of particular relevance. In recent years, the world has increased significantly medicinal plants. They are not perceived as foreign and, unlike synthetic drugs, are not rejected by the protective systems of the body. Among herbal drugs are widely used in medical practice are medicinal plants such as yarrow and Melilotus officinalis. Potassium-sparing diuretics have little effect on the level of sodium and fluid in the body, as well as on blood pressure as such. They do not have an independent value in the treatment of hypertension, but are often used in combination with other diuretics

to enhance their effect and avoid excessive loss of potassium by the patient's body. Currently, the development of new, easy-to-use, stable drugs from local medicinal plants is one of the main problems of modern pharmacy.[2,4]

Given the properties of drugs of plant origin, at the Department of pharmacognosy at the Tashkent pharmaceutical Institute was held scientific-research work on the creation of the collection “Meliflos”. This collection consists of equal parts of common yarrow - Achillea millefolium and Melilotus officinalis Desr. In connection with the above, the issue of creating an easy-to-use, standardized tablet dosage form “Meliflos”, characterized by sufficient biological availability and stability during storage, has become relevant.

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The aim of the research was to study the pharmacotechnological aspects of the development of technology of individual domestic diuretic drugs and drugs and the introduction of domestic production of developed dosage forms.

MATERIALS AND METHODS

The objects of study used dry extract “Meliflos” we have received the recommended technology. Dry extract “Meliflos” is a hygroscopic dry, fine powders from red to dark brown color with a specific smell. Analysis of the technological characteristics of the dry extract and auxiliary substances was carried out on the devices of the company “Erweka” (Germany); the particle size was estimated by microscopy using the program Video test. For the development of tablets, we have tested formulations with different compositions of excipients and their ratios. The main requirements for this group of auxiliary substances are the storage stability, good compressibility, the ability to quickly and completely release the active substance and form strong tablets. The analysis of tablets was carried out according to the current regulatory documentation.

RESULTS

Based on the technological properties of the dry extract “Meliflos” initially, we studied the possibility of obtaining tablets “Meliflos” by direct extrusion, which, as you know, has a number of advantages. Analysis of the obtained technological parameters of the dry extract

showed the need for the addition of auxiliary substances that improve flowability. Various auxiliary substances recommended by GF XI were used both individually and in combinations: glucose, lactose, potato starch, microcrystalline cellulose, calcium carbonate, magnesium oxide, calcium stearate, etc. Direct pressing allows to exclude 3-4 technological operations and thus has an advantage over tableting with pre-granulation of powders. However, despite the apparent advantages, direct pressing of this substance does not provide the required quality of the finished product. This is due to the fact that for the productive work of tablet machines, the pressed material must have optimal technological characteristics (flowability, compressibility, humidity, etc.).[3,5]

These characteristics has not received dry extract "Meliflos". The studied compositions are presented in table.1.

The essence of this method lies in the fact that the required amount of dry extract "Meliflos" mixed with auxiliary substances until a homogeneous mass. In this mass, calcium stearate is added last with constant stirring. The resulting tablet mass is pressed in a manual hydraulic press in a range of pressures from 100-180 MPa. Tablets obtained by direct pressing, did not meet the requirements of GF XI.

In subsequent research studied the technological properties of the obtained tablet mass of dry extract "Meliflos", prepared for direct compression. In table 2, the results of the study of technological properties of the above studies are presented.

From the data of the table it follows that the introduction of auxiliary substances leads to a change in the fractional composition and, accordingly, other technological indicators. The compressibility in the mixture decreased from 80 to 41.

The obtained data indicate a decrease in the degree of hygroscopicity from 10.42 to 5.71 and the adhesive properties of powders. These are positive indicators. Some differences in the compaction coefficients and bulk density of the pressed masses of 95.32-100.12% are explained by the close bulk density of the used auxiliary substances.

In table 3, shows the results of qualitative research tablets "Meliflos", obtained by direct pressing.

As you can see. from presented in table.3, tablets “Meliflos” obtained in five series by direct pressing, meet the requirement in appearance, the ratio of the height of the tablets to the diameter, the quantitative content of the active substance, solubility. But, according to other indicators do not meet the requirement for tableted dosage forms.

Consequently, in further research we conducted research on the development of the technology of tablets “Meliflos” method of wet granulation.

The necessary amount of binders was determined empirically for each tableting mass. To do this, the powder is generally granulated, it must be moistened to a certain extent. The sufficiency of moisture was judged as follows: a small amount of mass (0.5 – 1G) was squeezed between the thumb and index finger; the resulting "cake" should not stick to the fingers (excessive moisture) and crumble when falling from a height of 15 – 20cm (insufficient moisture).

For the preparation of tablet mass was prepared 7 series of pressed masses «Meliflos» for the division is presented in table. 4. In studies selected excipients differ both in appearance and in the number of used excipients. Taking into account the physicochemical and technological properties of the dry extract, the possibility of using fillers such as lactose, sucrose, starch, cellulose derivatives MCC, HMPC, calcium carbonate was studied in the development of the composition and technology. Potato starch was used as baking powder and calcium stearate as antifriction agent. Pre-selection of fillers was also carried out on the basis of their ability to reduce the absorption of moisture by the substance.

Experimental samples of “Meliflos” tablets were prepared with the addition in various proportions and combinations of excipients. In table 4, shows the composition of seven formulations of tablets “Meliflos”, which differ in appearance, and the number of used auxiliary substances. The choice of these quantitative fillers was carried out on the basis of previous experiments.

The essence of wet granulation is as follows: the required amount of active substance and filler are mixed to obtain a homogeneous mass. The resulting homogeneous mass is moistened with an appropriate amount of moisturizing liquid, and the wet mass is dried in a heater drying cabinets at a temperature of 40-500C. The drying time is determined experimentally to the optimum residual moisture. Then the mass is granulated and powdered

with a mixture of starch and calcium stearate. For humidification used purified water, sugar syrup, and ethyl alcohol of different concentrations - 30, 40, 50, 70%, 90% and 2-10% starch solutions.

In subsequent experiments, moisture was produced by starch paste of different concentrations. The results of the study revealed that low concentrations of starch prolong the disintegration time of tablets, and also high concentrations of starch paste affect the reduction of strength.

When using water and sugar syrup formed lumps that deteriorated the quality of the finished product. Ethyl alcohol of different concentrations also did not give the desired effect. Therefore, after numerous experiments, moisture was performed 90% ethyl alcohol, as it provided a good granulation of the tablet mass. When moistening the mass with alcohol, the granulate after drying turned out to be strong, the resulting tablets had a quality appearance.

Studying the properties of the obtained tablets in seven prescriptions made sure that the prepared tablets in 7 composition met all the requirements presented by GF X1. Indicators of disintegration of tablets 1 and 5 composition did not meet the requirements of GF X1. Tablets obtained by 2 and 3 composition had a decay time of about 15 minutes. Therefore, these compounds were not selected for the next experiments. Best indicators for requirement of tablets received for 7 staff.

Further study was carried out with tablets obtained by 7 composition.

Thus, when selecting the composition of tablets, the effect of auxiliary substances on the quality of the finished product was studied.

The technological properties of the pressed mass by 7 composition are studied, and the results are given in table 5.

The fractional composition, bulk density, flowability, angle of repose, porosity, compactibility coefficient, compressibility coefficient and residual moisture were studied as technological indicators of the compressible mass. Determination of the above parameters was carried out according to the methods of the Global Fund XI and the relevant documentation. Used excipients improved some technological properties of the substance – flowability, bulk density.

In addition, according to table 5, it can be noted that the flowability of the dry extract in the granules increased, the bulk density doubled. The results of granulation indicate a significant enlargement of particle sizes, where the bulk of the mass corresponds to a fraction of -1000 + 500 microns. Such technological indicators as bulk density (625 kg/m3), flowability (6.5x10-3 kg/s), angle of repose (30 degrees), coefficients of compressibility[1,23], compactibility[2,5] and others had more positive values for the pressed mass than for the extract, which indicates the correct selection of auxiliary substances and the course of the technological process. The optimum is the residual moisture in the range of 3.22 - 3.5%. It should also be noted that the pressure of pressing tablets directly contributes to indicators such important properties as physico-mechanical properties, the strength of the tablets, raspadaemost, strength, resistance to abrasion etc. Therefore, a number of experimental research was devoted to studies of the influence of compacting pressure on quality tablets. At the same time, laboratory manual hydraulic presses were used. In the range from 50 to 350 MPa conducted research on the selection of the optimal compacting pressure tablets “Meliflos”. For rice.3.5. shows the results obtained, which shows that the pressure of the press depends on the quality of the finished product (i.e. the required performance change dependent on compacting pressure). Also, according to the results for pressing tablets “Meliflos” optimal are the pressing pressure 100-180 MPa.

In order to obtain tablets “Meliflos” used the method of wet granulation. The technological scheme for producing “Meliflos” tablets by wet granulation is as follows: crushed and sifted through a sieve (0.15 mm hole diameter) and the calculated amount of substance and MCC were then mixed with a solution of a binder with 90% ethyl alcohol. The wet mass was dried at a temperature of 30-40°C to a residual moisture content of 3.5%.

Further, the dried mass was wiped through a granulator with holes of 1 mm, powdered with a mixture of potato starch and calcium stearate, the mass was tableted on an impact type tablet machine of 0.5 g in diameter and 11 mm. The mass was pressed well, without sticking and easily pushed out of the mold, and the resulting tablets met the requirements of GF XI. Tablets of the above compositions were made on hand hydraulic presses. The specific pressing pressure was 100-180 MPa.

Subsequently, the qualitative parameters of the obtained tablets were studied in accordance with the requirements of GF XI, as well as other conventional methods. The quality assessment was carried out according to the following criteria: appearance, geometric shape,

height to diameter, average weight and quantitative content of the active substance, decay and dissolution, wear resistance and bending strength. Tablets all recipes for strength meet the requirements of GF XI. Tablets obtained by 1-3 recipes are characterized by a long decay time, which was more than 120 minutes. This indicates the absence of loosening ability of starch.

In the composition, where the MCC is mixed with an equal amount of starch, the decay time decreased, but the tablets did not meet the requirements of strength GF XI. At the same time, it was noted that the use of sucrose caused the granulate to stick to the surface of the press tool. The most positive indicators of the pressed mass were observed when using MCC, increasing the flowability of the mass and improving the appearance of tablets that meet the requirements of GF XI. For example, the fracture strength of tablets prepared with a filler-lactose was from 34.4 to 40.8 H, and tablets prepared with a filler-calcium carbonate – more than 2 times higher and is in the range from 83.7 to 88.2 H, the disintegration time of the tablets also varies depending on the fillers used.

The results obtained experimentally are given in the table 6.

According to these indicators tablets composition №7 meet the requirements of GF XI. Based on the above results, 7 members were selected for further research. The main indicators of the quality of tablets “Meliflos” prepared in the recommended formulations are shown in table 3. According to the results of the table, it can be determined that the composition 7, different from the previous compositions, fully meets all the requirements of tablets for GF XI.

According to Table 6, the tablets had a good appearance, the indicators of the tablets “Meliflos” deviation from the average weight of the intelligence community and the force meet the requirements of GF XI, vol. 2. The strength of the tablets ranges from 50 to 68 H. the tablets disintegrate in less than 15 minutes.

Thus, unsatisfactory results are investigated technological parameters of dry extract and diploid requires the use of auxiliary substances. The used auxiliary substances improve some technological properties of the substance-flowability, bulk density and compressibility.

Table 1: Compositions for making tablets "Meliflos" by direct extrusion.

Ingredients	The number of ingredients, g				
	Series				
	I	II	III	IV	V
Dry extract "Meliflos" Sucrose Lactose MCC Calcium carbonate Carbonate Potato starch Calcium Stearate	0,3 0,095 0,01 0,005	0,3 0,0975 0,0975 0,005	0,3 0,08 0,095 0,020 0,005	0,3 0,0975 0,0975 0,005	0,3 0,08 0,095 0,020 0,005
Mean weight	0,5	0,5	0,5	0,5	0,5

Table 2: Results of the study of the technological properties of the pressed mass prepared for direct pressing (n=5).

Indicators under study	Values of the indicator				
	I	II	III	IV	V
Fractional composition, micron, %:					
+2000	15,19	11,10	9,10	12,52	14,05
-2000+1000	22,50	24,05	23,06	21,43	31,34
-1000+500	37,19	39,23	36,85	36,45	27,67
-500+250	19,87	21,57	25,32	24,71	21,79
-250	5,25	3,60	5,67	4,89	5,20
Flowability, 10^{-3} kg/s	2,55	2,42	3,45	4,34	2,67
Angle of repose, degree	35,56	40,16	37,96	34,11	39,78
Bulk density, kg/m^3	721,34	754,32	767,04	744,34	765,81
Compressibility, H	32,56	37,45	41,23	39,11	40,77
Compaction factor	1,99	1,54	1,78	1,80	1,65
Residual moisture	4,98	5,71	4,81	5,07	4,89

Table 3: The results of qualitative research tablets "Meliflos" by direct extrusion.

Properties under study	Indicators				
	Series				
	I	II	III	IV	V
Appearance	Brown tablets, interspersed	-//-	-//-	-//-	-//-
The ratio of the height of the tablets to the diameter, %	40	37	35	40	39
Average weight and deviation from average weight, %	0,501±3,39	0,511±5,12	0,490±5,56	0,501±6,33	0,502±3,67
Fracture strength, H	25	26	35	30	25
Abrasion resistance, %	85,33	87,45	80,78	85,45	84,20
Disintegration, min	16	14	15	12	17
The quantitative content of the active substance,%	98,94	97,95	99,90	98,92	98,78
Solubility, %	97,5	90,4	97,8	96,1	97,7

Table 4: The studied compounds to obtain the pill "Meliflos", prepared by the method of wet granulation.

Indicators	Record number and number of ingredients, g						
	1	2	3	4	5	6	7
Dry extract "Meliflos"	0,3	0,3	0,3	0,3	0,3	0,3	***0,3***
Lactose	0,095				0,020		
Saccharose		0,0975					
Potato starch	0,100	0,0975	0,020	0,1000	0,080	0,090	***0,095***
MCC			0,080		0,095	0,150	***0,100***
Hydroxypropylmethyl cellulose (HPMC)				0,0975			
Calcium carbonate			0,095				
Calcium stearate	0,005	0,0050	0,005	0,0050	0,005	0,005	***0,005***
Average mass	0,5	0,5	0,5	0,5	0,5	0,5	***0,5***

Table 5: Results of the study of technological properties of the pressed mass.

Indicators under study	unit of measurement	Values of the indicator
Appearance		Homogeneous granules of cream color, sweet taste, odorless
Fractional composition: +2000 -2000+1000 -1000+500 -500+250 -250	mkm, %	 10,14 27,55 37,19 17,87 7,25
Flowability	10^{-3} kg/c	6,5
Angle of natural Repose	Gradus	30
Bulk density	kg/m^3	625
Compressibility	H	40
Compressibility factor		1,23
Compaction factor		2,5
Residual moisture	%	3,2
Porosity	%	52

Table 6: Results of the definition of quality indicators recommended tablets "Meliflos".

Indicators under study	Values of indicators
Appearance	Tablets of brown color with impregnations, flavourless, a round form, biconvex, with risk on one party
The ratio of the height of the tablets to the diameter, %	40
Average weight and deviation from average weight, %	0,501±3,45
Fracture strength, H	58,2
Abrasion resistance, %	99,71
Disintegration, min	11
The quantitative content of the active substance, %	98,9
Solubility, %	97,5

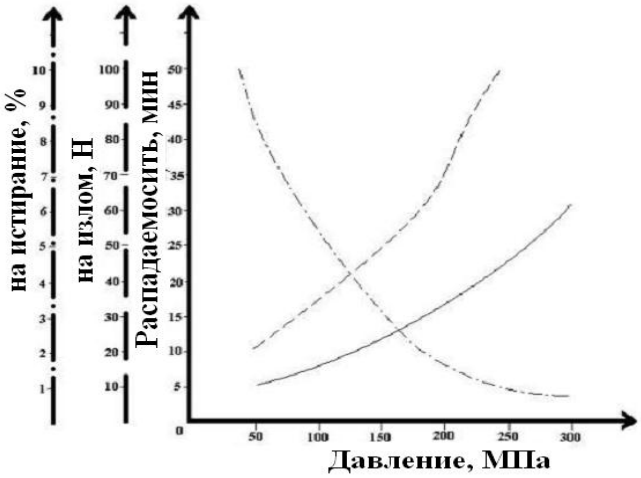

Fig. 1: The results of the study of the influence of compacting pressure on qualitative characteristics of tablets "Meliflos".

CONCLUSION

1. As a result of studies conducted taking into account the physico-chemical and technological characteristics of substances, the optimal composition and technology of a new diuretic drug based on the dry extract "Meliflos" was selected.
2. Developed and selected technology for producing high-quality finished product.
3. The quality indicators of tablets: disintegration, resistance to crushing and abrasion.

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