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The Peculiarities of the Development of the Composition and Technology of the "Sedtab" Tablet

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ABSTRACT: Today, neurological diseases occupy one of the leading places in terms of prevalence among all diseases. According to the World Health Organization, over the past 65 years, the number of neurological diseases in the world has increased more than 20 times and amounts to approximately 40%. Despite the relatively wide availability of means for the prevention and treatment of neurological diseases, the development and implementation of new, more effective and safe means remains relevant. In this regard, preparations from medicinal plants deserve special attention, since they are closer to the human body than synthetic drugs, easily enter into metabolic processes, practically do not cause side effects and often reduce negative consequences.

The main goal of this work is to develop a new composition and technology for "Sedtab" tablets based on local plant materials, i.e. stinging nettle, lemon balm and motherwort, as well as the study of technological properties based on scientific criteria for the creation of medicinal products.

KEYWORDS: composition, technology, "Sedtab" tablet, dry extract, biologically active substance, excipient, flowability, bulk density, fractional composition, residual moisture.

RELEVANCE

The development of the pharmaceutical sector is of great social and economic importance at the present stage of development of sovereign Uzbekistan. The main goal of the State Drug Policy is to improve public health by ensuring access to safe, effective and high–quality medicines at affordable prices and their rational use [1,3,5,6,9,11,12,15].

The large–scale use of the republic's plant flora has led to the introduction of a number of medicinal plants into medicine and the enrichment of the arsenal of domestic drugs based on them. Over the years of independence of the Republic of Uzbekistan, a number of tasks have been identified to achieve improvement in the pharmaceutical industry [15,16,17,18].

In recent years, scientific directions in the pharmaceutical industry have been formed on the basis of innovative ideas that have found their place in the pharmaceutical market. Today, the range of drugs on the domestic pharmaceutical market is increasing every day [12,13,17,19,20].

EXPERIMENTAL PART

Previously, we developed an original method for obtaining the dry extract "Sedex" from the leaves of stinging nettle, lemon balm herb and motherwort leaves. The purpose of our work is research to develop technology for tablets with this dry extract. The task is urgent, since its solution will not only affect the strengthening of the position of domestic medicines in the pharmaceutical market of our country, but will also expand the circle of potential consumers, contributing to the improvement of the population's health. To create a dosage form in the form of tablets, first of all, it is necessary to develop a mixture for tableting that has the appropriate necessary technological characteristics. The technological characteristics of powders predetermine the possibility of using specific types of pressing and the need to introduce ingredients into the tablet mixture that are responsible both for the characteristics of the mixture, ensuring the stability of the tableting process (fluidity, uniform filling of the matrix, adhesion to the pressing tool, etc.), and for the quality of the resulting tablets (disintegration, solubility, hardness, etc.). Therefore, first of all, when developing "Sedtab" tablets, the technological characteristics of the substance were studied, including fractional composition, volumetric characteristics, flowability, compressibility, residual moisture, porosity. The results obtained showed unsatisfactory technological properties of the powders of the dry extract substance, and this in turn shows the need to introduce excipients into the composition of the tablets. It

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was noted that the high kinetics of moisture absorption of the dry extract has a direct impact on its technological properties. To improve the unsatisfactory technological properties of the dry extract, such as flowability, bulk density, porosity, angle of repose and extreme hygroscopicity of the dry extract, the introduction of auxiliary substances into the pressed mass is required. In order to improve the technological properties of the recommended dry extract, the following excipients used in pharmaceutical production were added to the composition: lactose, glucose, sucrose, potato starch, corn starch, microcrystalline cellulose, calcium carbonate, magnesium oxide, calcium stearate, magnesium stearate, stearic acid etc. More than 20 compositions have been studied when used separately and together in several compositions.

In initial studies of the proposed compositions, the possibility of tableting by direct compression was studied. Direct compression method, which has a number of advantages over other tableting technologies, namely: eliminating the effect of moisture on medicinal and excipients, reducing the number of technological operations, less microbial contamination, saving production space and costs for energy, equipment, etc. Table 1 presents compositions that showed similar research results.

Table 1. The compositions of a mixture of powders for producing "Sedtab" tablets by direct compression

Mixture components	The number of components						
	Compositions						
	CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7
Dry extract "Sedex"	0,25	0,25	0,25	0,25	0,25	0,25	0,25
Lactose		0,042	0,063			0,037	
Glucose	0,042	0,021			0,063		
Sucrose	0,021						0,063
Microcrystalline cellulose				0,063		0,026	
Calcium carbonate		0,011					
Potato starch	0,034		0,034	0,034		0,34	
Corn starch		0,023			0,034		0,034
Calcium stearate			0,003		0,003		0,003
Magnesium stearate	0,003					0,003	
Stearic acid		0,003		0,003			
Average weight	0,35	0,35	0,35	0,35	0,35	0,35	0,35

Research continued with a comparative study of the technological properties of pressed masses from the above compositions and dry extract. Among the technological properties, the following were studied: flowability, bulk density, fractional composition, residual moisture, compaction coefficient, compressibility, etc. The results obtained are presented in Table 2.

Table 2. The results of a comparative study of the technological properties of the dry extract "Sedex" and pressed masses

Studied technological indicators	Determination results							
	Dry extract "Sedex"	CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7
Factional composition (%): +2000 –2000 +1000 –1000 +500 –500 +250 –250	5,18 19,94 24,97 39,93 9,98	12,462 7,1635, 9829,4 53,60	11,462 5,1234, 9727,4 03,041	12,152 5,3927, 1128,0 57,30	14,12 27,11 29,53 30,14 3,60	12,46 25,16 33,08 29,45 4,60	14,54 25,55 26,45 28,30 5,16	15,43 23,56 25,21 30,23 5,57
Flowability, 10^{-3} kg/s	0,96	1,45	1,63	4,47	2,87	1,89	1,93	3,11

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The angle of repose, degree	27,43	36,76	43,98	38,85	44,36	39,98	44,69	42,18
Bulk density, kg/m3	395,37	654,34	712,43	698,43	711,43	675,99	698,23	701,56
Pressing ratio	0,96	6,12	6,67	5,99	7,11	6,98	7,25	6,97
Compaction factor	1,36	6,12	6,11	7,79	5,54	4,76	5,34	6,47
Residual humidity,%	4,11	4,95	4,84	3,25	3,99	4,05	5,22	4,67

The results of the study showed an improvement in the technological properties of the pressed masses compared to the dry extract. Judging by the results obtained, the excipients changed the fractional composition, and this, in turn, determined the positive values of the remaining technological properties. The tablet compressibility coefficient increased from 3.45 to 7.25, and the hygroscopicity index decreased from 6.74% to 3.95%. At the first stage of the study, tablets were obtained from the proposed compositions by direct compression. The process was carried out as follows: the dry extract and excipients were separately sifted through a sieve with a hole diameter of 0.16 mm, and calcium stearate was added by dusting. Compression of tablets was carried out in laboratory conditions on a single–punch tablet press HMTP–IA (HMP pharmachines wissgmbh, Switzerland). Table 3 presents the results of a study of the quality of Sedtab tablets obtained by direct compression.

Table 3. The results of quality indicators of "Sedtab" tablets obtained by direct compression method

Studied technological indicators	Determination results						
	CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7
Appearance	Tablets are cylindrical, brown in color, with uneven edges						
Ratio of tablet height to diameter, %	26	29	26	24	27	28	21
Average weight and deviation from weight, %	0,35 ± 2,87	0,35 ± 3,55	0,35 ± 4,22	0,35 ± 4,09	0,35 ± 2,99	0,35 ± 3,81	0,35 ± 2,86
Crushing strength, H	51,33	55,14	53,54	55,54	49,05	51,35	53,45
Abrasion strength, %	77,75	81,54	80,64	75,73	83,24	70,34	69,21
Disintegration, min.	17	18	16	18	22	18	19
Dissolution, %	96,98	96,98	96,98	96,98	96,98	96,98	96,98

The results of the study showed that Sedtab tablets obtained by direct compression do not meet the quality requirements for tablets. During pressing, the mass stuck to the pressing tools, and the resulting tablets did not meet the requirements for appearance. It was also noted that the ratio of height to diameter of the tablet, fracture strength and abrasion did not meet the requirements of the XIII Global Fund. Consequently, the substance of the dry extract "Sedex" cannot be used for direct pressing and requires the use of a wet granulation method; the introduction of special auxiliary substances is required to obtain a compressed mass with good fluidity, the required strength and a high bulk density.

To moisten the above tablet compositions, purified water, ethyl alcohol 40, 70, 96% concentrations, 2, 7, 10% starch paste solution were used. Granular masses and model tablets were obtained with each binder. When using purified water and ethyl alcohol of various concentrations as a binding component, the model tablets turned out to be very friable, fragile and easily crumbled. When 2% starch paste was added to the composition of the compressed mass, the tablets met the requirements for appearance, but they had low compressibility (26 N). To evaluate compressibility, a sample of powder weighing 0.5 g was pressed on a manual hydraulic press into a model tablet with a diameter of 11 mm at a pressure of 120 MPa (40 atm). The crushing load was determined using a spring dynamometer. When moistened with a 7–10% solution of starch paste, the resulting tablets met the requirements of the XIII Global Fund. From the point of view of economy, a 7% starch paste solution was chosen for further research.

The technological properties of model tablets obtained using 7% solution of starch paste are presented in Table 4.

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Table 4. The results of quality indicators of "Sedtab" tablets obtained by wet granulation method

Studied technological indicators	Determination results						
	CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7
Appearance	The tablets have the correct shape, the edges are solid without chipped places, the surface is smooth, uniform, brown in color.						
The ratio of tablet height to diameter, %	23	21	37	20	24	26	18
Average weight and deviation from weight, %	0,33 ± 3,21	0,36 ± 2,89	0,32 ± 3,54	0,35 ± 1,35	0,34 ± 4,23	0,32 ± 4,76	0,33 ± 3,57
Crushing strength, H	57,54	58,53	65,99	59,25	59,67	58,76	57,97
Abrasion strength,%	81,32	85,98	98,21	77,98	86,78	74,67	73,57
Disintegration, min.	18	16	9	18	20	16	15
Dissolution, %.	98,11	98,43	98,95	97,89	98,43	98,21	98,46

The results of the qualitative indicators given in the table showed that Sedtab tablets obtained by the wet granulation method are better than tablets obtained by direct compression. In particular, the solubility of the tablets obtained in all compositions ranges from 98.71% to 98.95%, the fracture strength index is from 57.97 N to 65.99 N, the average weight and deviation from the weight of the tablets meets the requirements of the XIII Global Fund.

However, the unsatisfactory disintegration time of all compositions (15–20 minutes), with the exception of composition ST–3 (9 minutes), as well as the low ratio of tablet height to diameter (20–26%) showed the impossibility of obtaining high–quality tablets from these compositions. Based on this, composition ST–3 was chosen for further research. The technological process for producing "Sedtab" tablets was carried out in the following sequence: the weighed and sifted dry extract was thoroughly mixed with lactose until a homogeneous mass was formed and moistened with a 7% starch paste solution. The wet mass was dried in an oven at a temperature not exceeding 40–50°C, then rubbed through a stainless steel sieve with a hole diameter of 1.5 mm. The granules were dusted with a mixture of starch and calcium stearate, previously crushed and sifted through a nylon sieve with a hole diameter of 100 microns.

The technological process for producing "Sedtab" tablets obtained by wet granulation is schematically presented in Figure 1. The next stage of research continued with the study of the technological properties of the pressed mass obtained by wet granulation. The following technological indicators were studied: fractional composition, bulk density, flowability, angle of repose, porosity, compaction coefficient, compaction coefficient and residual moisture, as well as comparative results of the feedstock and mass obtained by two methods (Table 5).

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Figure 1. The technological diagram for the preparation of "Sedtab" tablets

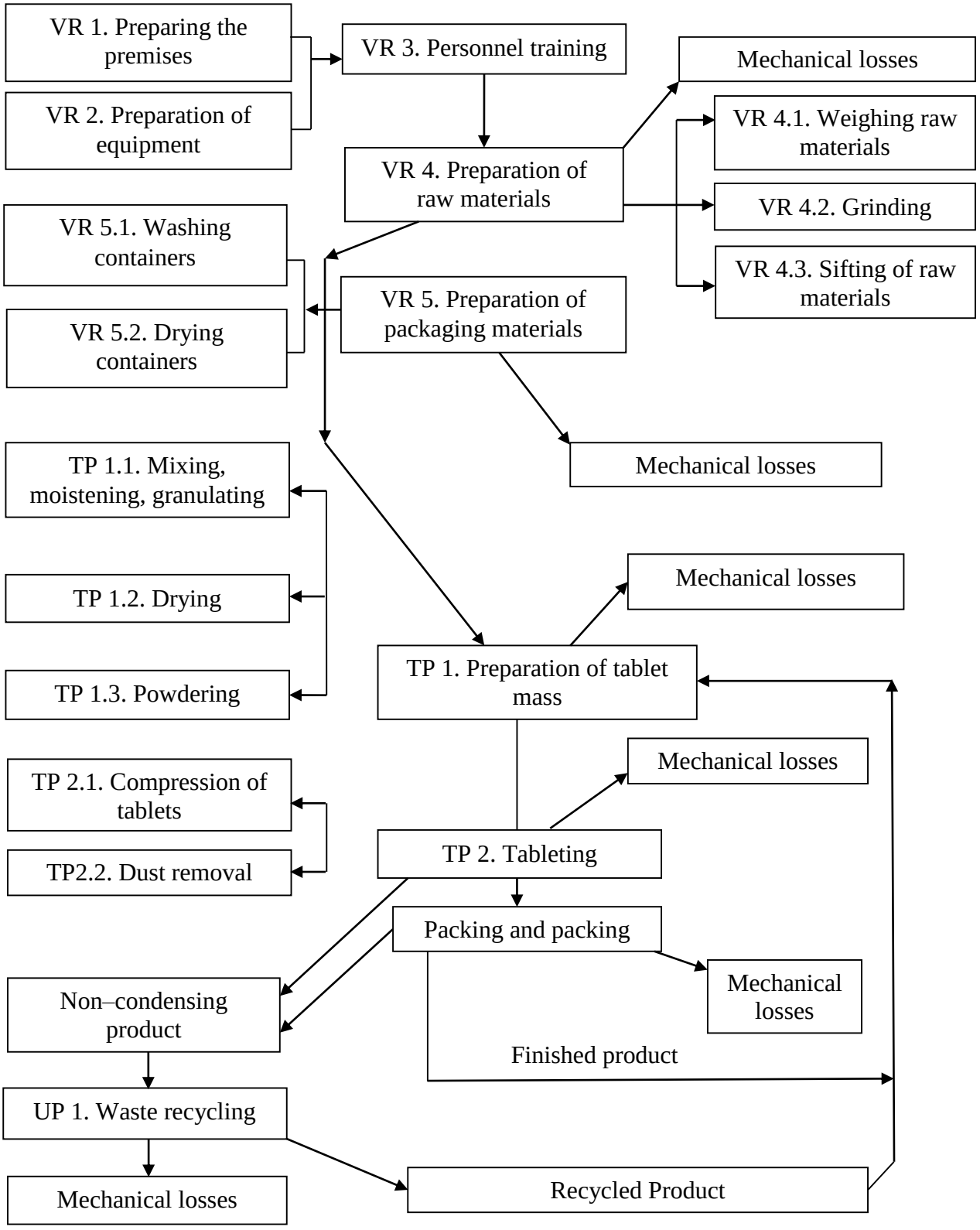

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Table 5. Results of a comparative study of the technological properties of the dry extract "Sedex" and pressed masses obtained by two methods

Studied technological indicators	Determination results														
	Dry extract "Sedex"	Tablet mass for direct compression							Tablet mass obtained by wet granulation method						
		CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7	CS–1	CS–2	CS–3	CS–4	CS–5	CS–6	CS–7
Factional composition (%): +2000	17,18	12,46	11,46	11,15	14,12	12,46	14,54	15,43	17,18	18,35	16,39	12,15	11,2825,	14,22	12,24
–2000 +1000	25,53	27,16	25,12	25,34	27,11	25,16	25,55	23,56	20,36	20,19	23,15	25,39	26	23,10	26,30
–1000 +500	28,97	35,98	34,97	28,14	29,53	33,08	26,45	25,21	28,21	26,16	28,16	27,11	29,26	27,31	27,11
–500 +250	18,82	29,45	27,40	26,06	30,14	29,45	28,30	30,23	28,00	28,10	26,10	28,05	28,08	29,11	30,17
–250	9,50	3,60	3,041	9,35	3,60	4,60	5,16	5,57	6,25	7,20	3,20	7,30	6,13	6,04	5,18
Flowability, 10^{-3} kg/s	0,96	1,45	1,63	3,43	2,87	1,89	1,93	3,11	3,47	4,47	6,47	4,32	3,67	4,01	5,11
Angle of repose, degree	27,43	36,76	43,98	48,98	44,36	39,98	44,69	42,18	43,78	48,78	45,25	39,32	42,54	43,93	48,15
Bulk density, kg/m^3	395,37	654,34	712,43	699,68	711,43	675,99	698,23	701,56	698,43	698,43	598,43	591,43	586,12	586,95	611,38
Pressing ratio	3,45	6,12	6,67	6,34	7,11	6,98	7,25	6,97	5,99	5,32	2,99	4,57	3,11	3,93	4,09
Compaction factor	1,36	6,12	6,11	7,83	5,54	4,76	5,34	6,47	5,22	5,86	4,22	5,97	6,10	5,22	5,18
Residual moisture, %	6,74	4,95	4,84	4,65	3,99	4,05	5,22	4,67	4,37	3,68	3,25	3,44	3,98	3,86	4,11

From Table 5 it can be seen that almost all the technological properties of the pressed mass prepared by the wet granulation method have changed in a positive direction. In particular, the bulk density, flowability, angle of repose, compressibility and compaction coefficients, as well as the fractional composition have changed.

These results, in turn, show the advantage of the wet granulation method, as well as the correct selection of excipients in these compositions.

Based on the above results, composition ST–3, obtained by the wet granulation method, was chosen for further research, and further research will be continued with these tablets, with this composition and technology.

CONCLUSIONS

More than 20 compositions recommended for obtaining Sedex dry extract tablets have been studied. The compositions are formulated using modern, readily available excipients and their combinations. The technological properties of the pressed masses were also studied and compared. Thus, based on the results of the research, composition ST–3 was selected from the studied compositions and the quality indicators of the tablets were determined.

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