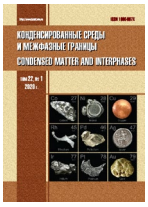

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Solid Dosage Forms of Nootropic Action Based on Pantogam and Succinic Acid

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Abstract

In recent years, research related to the search and study of the mode of action of new and used in medicine nootropic agents has been carried out at a high rate. The research related to the search for new combined drugs of nootropic action based on the substances of d-gamma-Pantothenate of calcium and succinic acid, which have neurometabolic, atigipoxic, and adaptogenic properties, is of interest. The purpose of this study was to develop and justify the optimal composition and manufacturing technologies of tablets with nootropic effect and standardise the proposed dosage forms containing Pantogam and succinic acid.

The method for preparing the tablet mixture is as follows: all components were weighed in the required amount, Pantogam was placed in the mortar, then succinic acid was added and ground to a consistent white powder. The tablets were pressed on a manual press at a pressure of 120 mn/m^2. The coating was applied on a laboratory fluidised bed unit with a single nozzle in a perforated drum with a volume of 1000 ml. The obtained tablets were evaluated according to the requirements for State Pharmacopoeia XIII and State Pharmacopoeia XIV. The comparison of the Pantogam tablets with succinic acid obtained by direct pressing and by wet granulation showed that the method of direct pressing allows obtaining tablets with good physical and mechanical properties and bioavailability. The methods based on acid-base titration and spectrophotometric determination were developed for the quantitative determination of Pantogam in tablets. The method of quantitative determination of succinic acid in dosage forms was validated.

Based on the study of physicochemical and technological properties of substances and excipients, the compositions and technology for obtaining tablets containing Pantogam and succinic acid were justified and developed. It was found that solid-phase interactions occur with the combined presence of Pantogam and succinic acid in the tablets. The methods of qualitative and quantitative analysis of dosage forms containing Pantogam and succinic acid based on complexometric titration and high-performance liquid chromatography were developed. The procedure of validation of the method for determining succinic acid by HPLC in the developed dosage forms confirmed the validity of the proposed method.

Keywords: Pantogam, succinic acid, tablets, complexometry, high-performance liquid chromatography, validation.

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1. Introduction

Cerebrovascular diseases remain an acute medical and social issue of modern society [1-3]. The pharmacological correction of cerebral circulation is a pressing problem of modern medicine as a significant number of cerebral diseases are based on the factors of vascular origin while the diseases themselves are accompanied by loss of capability to work, disablement, and death [4–7]. Today, pharmaceutical science and pharmaceutical technology, in particular, pay great attention to the search and creation of drugs that increase the resistance of the brain and the nervous system to disturbing factors, improve mental activity, activate memory and learning processes, protect the brain neurons from premature neurodegradation, and postpone senile dementia [8-11]. Nootropic drugs that are successfully used for the treatment of psychoneurological disorders in adults and children hold a valuable place among neuropsychotropics [12–15].

Pantogam, the calcium salt of D-homopantothenic acid, is one of the drugs used in psychoneurology. It is successfully used as a nootropic drug in paediatrics for the treatment of arrested development, complicated oligophrenia, hyperkinetic disorders, epilepsy, neurotic-like conditions, post traumatic stress disorder, etc. [16]. The neurometabolic action of Pantogam consists of the normalisation of energetic processes of metabolism of gamma-aminobutyric acid in the central nervous system and the improvement of cerebral circulation [17]. The neurotrophic activity is associated with the improved utilisation of glucose and the stimulation of synthesis of RNA, protein, and ATP in neurons. The neuroprotection is conditioned by the increase in the resistance of nerve cells to hypoxia and ischemia as well as the decrease in the blood cholesterol level [18].

Succinic acid (SA) can be categorised as a nootropic drug. Antihypoxic action of SA is associated with its ability to intensify the utilisation of oxygen by tissues and the restoration of NAD-dependent cell respiration. SA's antistress and nootropic effect is conditioned by its influence on the transport of transmitter amino acids and the increased content of gamma-aminobutyric acid in the brain through the activation of Roberts shunt. The quick oxidation of SA by succinate dehydrogenase accelerates the resynthesis of ATP by cells, increases the concentration of restorable glutathione, and improves the resistance of mitochondria to peroxide degradation. SA can significantly intensify the diffusion of oxygen into different tissues and organs by stimulating cell respiration under stress and hypoxia [18]. This compound also shows cardiotropic, antioxidant, detoxicative, and adaptogenic actions [19].

Due to the unique pharmacological properties of Pantogam and succinic acid, the development of new effective dosage forms, which are more convenient for paediatrics, based on these substances is considered reasonable and prospective. Potentiation by the principal lines of Pantogam and SA's action on the organism should intensify the pharmacotherapeutic nootropic effect.

The purpose of this study was the experimental development and justification of the optimal compositions and manufacturing technologies of the tablets with nootropic effect as well as the standardisation of the proposed dosage forms containing Pantogam and succinic acid.

2. Experimental

To create tablets for the experiment, Pantogam substances (manufacturer FGUP "SKTB "Tekhnolog" of the Ministry of Education of the Russian Federation FSP 42-0348395903) and succinic acid substances (manufacturer OOO "Polisintez", Russia-FSP 42-0009-00) were used as well as the excipients that are registered in the Russian Federation and comply with the requirements of regulatory documents of Russian and foreign manufacturers in relation to the qualitative and quantitative content.

The method of preparation of the tablet mixture is as follows: all components were weighed in the required amount, Pantogam was placed in the mortar, then succinic acid was added and ground to a consistent white powder.

The coating was applied on a laboratory fluidised bed unit with a single nozzle in a perforated drum with a volume of 1000 ml. A commercial sonometer of ethyl acrylate with metacrylic acid, Kollicoat MAE 100, was used as a filming agent. After the conducted experiments, the following composition of the film coating was found optimal: copolymer Kollicoat MAE 100 –

5%, propylene glycol (plasticiser) – 0.9%, titanium dioxide (photoprotector) – 2.30%, and ethanol up to 100 %, viscosity η_{rel} = 1.98. Over the course of the experiment, the following parameters of the process and installation were determined: drum capacity – 30 %, drum rotation speed – 77 rpm, suspension feed rate – 20 ml/min, frequency of suspension solution spray – 2.0 ml after each 2.5 min, solution feed pressure – 2 kgf/cm^2, temperature of blast air – 75–80 °C.

IR spectroscopy was used to identify medicinal drugs [21, 22]. The spectra were collected on a Bruker Vertex 70. The quantitative determination of SA in tablets was conducted using high-performance liquid chromatography on an Agilent 1100 liquid chromatograph equipped with a multiwave detector with a diode matrix. A column with a reversed phase was used (Zerbax Extend-c18), size of the column – 2×150 mm, and a sorbent a particle size of 5 μm was used [23]. Detection was conducted with a wavelength range of 190–950 nm. The temperature of column thermostating was 35±0.3 °C, the volume of the induced sample was 20 mcl. The content of SA was calculated based on the peak areas on chromatograms of the working standard sample and the studied dosage forms.

Technological and biopharmaceutical studies of the substances and mixtures with the excipients were conducted at the Shared Research and Educational Centre of the People's Friendship University of Russia using testers to determine the density of the powders (Erweka "SVM 102"), a tester to determine the characteristics of the granulate (Erweka "GT"), an analytical sifting machine (Retsch "AS 200"), disintegration systems (Sotax "DT-2"), and a device for control of dissolution of solid dosage forms (Distek "Evolution 6100"). The microbiological research was conducted at the microbiological laboratory of the state unitary enterprise "Voronezhfarmatsia".

3. Results and discussion

3.1. Developing the composition of the tablets containing Pantogam and succinic acid

The tablet mixture of Pantogam with SA has a white colour and sourish taste. Experimentally determined technological properties of the mixture are presented in Table 1.

Six model mixtures using various combinations of the excipients were created in order to develop the production technology of the tablet cores of Pantogam with succinic acid (Table 2).

The granulate was assessed using the optimal technological characteristics (Table 3). The table shows that the compositions using 5 % of starch paste provide granules that are not solid enough (screening 27–30 %, compressibility 42.1–50.0). The granulate of composition No. 6 provides the least amount of screening, has the best flowability (11.2 g/s), and rather high compressibility (84 %).

The tablets were pressed on a manual press at a pressure of 120 mn/m^2. The technological characteristics of the obtained granulates and tablets confirm that composition No. 6 will provide the most solid tablets with the optimal disintegration (10.5 min). The average weight of the tablets is 0.20 g.

The dynamics of the release of Pantogam and SA from the obtained tablets of the composition No. 6 was assessed using an Erweka "SVM 102". The data of the dissolution test are presented in Table 4.

The obtained tablets meet the requirements for State Pharmacopoeia XIII and State Pharmacopoeia XIV.

The studies of the development of tablets using direct mixture pressing were conducted in order to compare the qualitative characteristics of solid dosage forms of the new composition

Table 1. Technological characteristics of substances and their mixtures

Name of the measured indicator	Characteristics of the components		
	Succinic acid	Pantogam	Mixture of Pantogam and succinic acid
Flowability, g/cm	12.2	7.8	11.58
Bulk weight, g/cm^3	0.65	0.91	0.6
Compressibility, N	52	Does not compress	46
Angle of natural slope, °	32	50	39
Residual moisture, %	3.1	2.2	3.7

Table 2. Composition of model mixtures of Pantogam tablets with succinic acid

Name of the component	Number of components in the composition per tablet, g					
	1	2	3	4	5	6
Substances						
Pantogam	0.05	0.05	0.05	0.05	0.05	0.05
Succinic acid	0.05	0.07	0.04	0.05	0.05	0.05
Fillers						
Potato starch	0.088					0.044
Lactose		0.068				
Mannitol			0.099		0.086	0.04
Magnesium carbonate basic				0.088		
Binders						
*Starch (5 % paste)	0.002	0.002	0.001			
*Polyvinylpyrrolidone (10 % aqueous)				0.002	0.004	0.006
Lubricants						
Stearic acid	0.004	0.004	0.004	0,004	0,004	0.004
Aerosil	0.006	0.006	0.006	0.006	0.006	0.006
Tablet weight	0.2	0.2	0.2	0.2	0.2	0.2

Table 3. Technology characteristics of granulates and obtained tablets (x_1 n = 6)

Sub-item No.	Name of the indicator	No. of the mixture composition					
		1	2	3	4	5	6
Granulate							
1	Flowability, g/cm	8.7	8.0	9.1	10.2	10.8	11.2
2	Bulk weight, g/cm^3	0.67	0.62	0.70	0.60	0.58	0.60
3	Compressibility, N	58	62	53	63	78	84
4	Porosity	47.4	42.1	50.0	51.0	47.4	49.2
5	Angle of natural slope, °	34	31	35	36	33	32
Tablets							
6	Ejection pressure, MN/m^2	3.2	4.0	3.1	3.8	4.1	3.5
7	True density, g/cm^2	1.67	1.52	1.48	1.40	1.42	1.40
8	Disintegration, min	5.5	5.0	6.5	7.0	8.5	10.5
9	Abrasion resistance, %	93.2	94.3	97.0	96.8	96.8	98.9
10	Compression ratio	3.82	2.85	4.04	3.20	4.60	4.10

containing Pantogam and SA and to optimise the compositions and conditions of production of the tablet dosage form.

The study of the technological properties of the pharmaceutical mixtures shows that composition No. 5 has the best characteristics.

Good compressibility and flowability allow obtaining the tablets using the method of direct pressing. The quality of the obtained tablets was evaluated by their appearance, disintegration, and durability in accordance with the requirements of State Pharmacopoeia XIII and State Pharmacopoeia XIV (Table 5). The obtained tablets are of white colour and planocylindric shape with a bevel and a score line. Their weight is 0.50±0.05 g and their appearance complies with the requirements of State Pharmacopoeia XIV. As for disintegration and abrasion resistance (Table 6), composition No. 5 allows obtaining tablets with good parameters. The dynamics of the release of Pantogam and SA from the tablets with composition No. 5 was assessed using a

Table 4. Dynamics of release of Pantogam and SA from coated tablets

Time, min	Content of Pantogam, %	Content of succinic acid, %
15	30.8	28.9
22	42.8	46.2
30	60.5	65.3
37	79.0	75.4
45	99.0	98.7

Table 5. Technological characteristics of tablets based on Pantogam and succinic acid

Sub-item No.	Name of the indicator	Number of the composition					
		1	2	3	4	5	6
1	Abrasion resistance, %	97.8	98.0	98.3	97.9	98.5	97.7
2	Disintegration, min	6.5	7.5	9.0	10.0	11.0	8.0

PC-1 "rotating basket" device. The comparison of the obtained results (Table 7) with the data on the release of active ingredients from the coated tablets allows drawing the following conclusion: it is unreasonable to use a complicated and expensive production technology for Pantogam tablets with SA using the granulation method and further application of the protective polymer coating. The method of direct pressing allows obtaining the tablets with good physicochemical parameters and bioavailability, although not protected from the aggressive action of gastric juice.

The tablets with Pantogam and SA with a polymer coating were subject to testing in artificial gastric juice and artificial intestinal juice (Table 8). The results allow drawing a conclusion that these tablets correspond to the requirements of State Pharmacopoeia XIII and State Pharmacopoeia XIV.

Table 6. Dynamics of release of Pantogam and succinic acid from tablets

Time, min	Content of Pantogam, %	Content of succinic acid, %
15	31.4	27.6
22	45.2	48.3
30	59.6	63.3
37	78.0	82.7
45	98.7	98.9

Table 7. Test results of the tablets coated with an intestinal-soluble polymer shell

Name of the indicator		ND requirements	Test results
Resistance to artificial gastric juice		At least 1 hour	Corresponds to: 1.8 hours
Dissolution in artificial intestinal juice, %		At least 70	Corresponds to: 89±2
Quantitative content	Pantogam, g	0.047–0.053	0.049±0.002
	Succinic acid, g	0.047–0.053	0.0048±0.002
Disintegration in artificial intestinal juice, min		No more than 60	28±0.5

Table 8. Results of quantitative determination of succinic acid in tablets

Sample	Area S of the peak (S)	Content of SA	
		г	%
Sample No. 1	2996	0.197	98.6
Sample No. 2	1625	0.049	98.3

3.2. Development of standardisation methods for tablets

Analysis of IR spectra shows that in the region of 1700–400 cm^{-1} the characteristic maxima of the dosage form mainly coincide in the intensity and the position of wave numbers on the axis with those of Pantogam and SA, which can be indicative of possible solid phase interactions and allows using IR spectroscopy to identify medicinal drugs in the developed tablets. Quantitative determination of Pantogam of the new dosage forms required the development of several variations of the methods based on: 1) acid-base titration of the solution obtained after the release of the fatty base on ice. The titrant was a 0.05 M solution of Trilon B (EDTA). The obtained results comply with the requirements of regulatory documentation. 2) spectrophotometric determination based on the interaction of the solution obtained after the release of the fatty base on ice with hydroxylamine and further interaction of the obtained hydroxamate with $FeCl_3$.

The solution of the working standard sample of Pantogam and the buffer solution of hydroxylamine were prepared in accordance with FS 42-2480-00 (Pantogam tablets 0.25 and 0.5 g).

The identification of Pantogam in the tablets was conducted by a typical reaction to calcium ion (from the water extract of the powder of the ground tablet) during its interaction with ammonium oxalate.

The content of SA was calculated based on the peak areas on the working standard samples and the tested dosage forms (Fig. 1–3).

Quantitative determination of Pantogam in tablets was conducted using complexometric

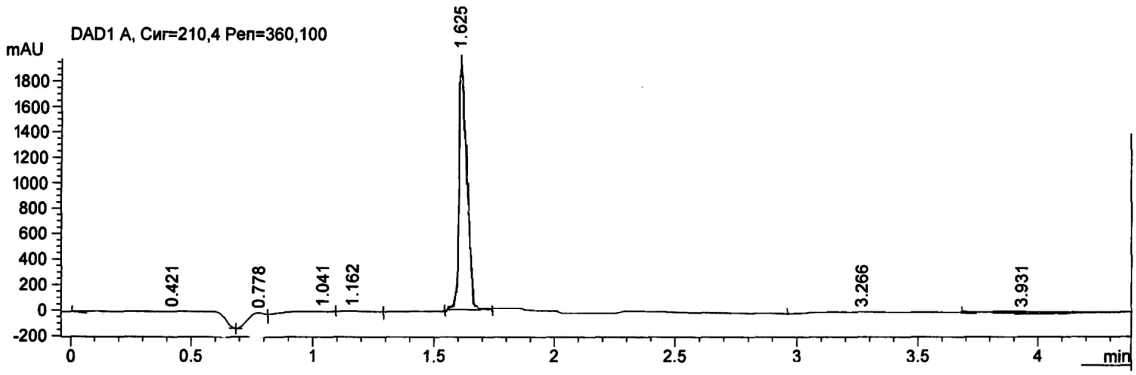

Fig. 1. Chromatogram of the working standard sample of succinic acid

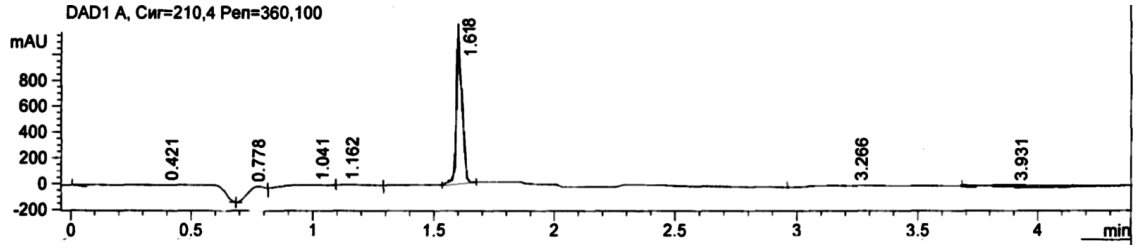

Fig. 2. Chromatogram of succinic acid in tablets of sample No. 1

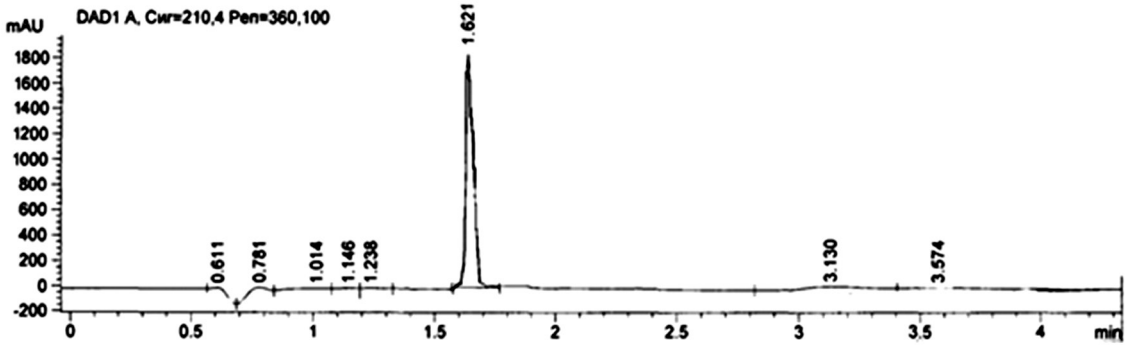

Fig. 3. Chromatogram of succinic acid in tablets of sample No. 2

titration of the solution of the powder made from the ground samples by Trilon B with the indicator mixture of Eriochrome Black T up to the bright blue colour. As a result of using this method, the content of Pantogam found in the tablets was 0.198 and 0.050 g, which complies with the requirements of State Pharmacopoeia XIV. This methodology provides clear reproducible results with the relative error of 1.14–1.20 %.

The obtained results of the quantitative determination of SA in tablets using HPLC (Table 8) showed that samples No. 1 and No. 2 of the studied tablets comply with the requirements of State Pharmacopoeia XIII and State Pharmacopoeia XIV.

To acknowledge HPLC, a method of determination of SA in dosage forms, and prove its viability, it was subject to validation assessment according to the requirements of GOST R ISO 5725 and recommendations of the International conference on harmonisation ICH Q2(RI) for such characteristics as linearity, analytical region, correctness, and precision.

The results of the validation assessment of the method are presented in Table 9.

The data presented in Table 9 allows drawing a conclusion that the method is reproducible and free from systematic errors.

Based on the results of the validation assessment of the SA determination method in dosage forms, it was established that the suggested method is characterised by correct accuracy and reproducibility, linear dependency (correlation coefficient for SA R = 0.999) in the analytical region in relation to the claimed content of SA in the medicinal product, which allows using it for the reliable assessment of the quality of medicinal products.

The stability of the developed dosage forms while in storage was determined for the studied samples on 5 series of each of them using standard measures in accordance with State Pharmacopoeia XIII and State Pharmacopoeia XIV.

The determination of shelf life of the developed tablet dosage forms based on Pantogam and SA conducted under standard conditions complying with the requirements of State Pharmacopoeia XIV (table 10) allows recommending the storage time of up to two years for these dosage forms at room temperature. The qualitative and quantitative

Table 9. Metrological characteristics of the method for determining succinic acid p = 99, t =2.4

x, %	S^2	S	Δx	E, %	$t_{calc.}$	F_{calc}
99.97	0.713	0.850	3.016	2.80	–0.85	1.6

Table 10. Quality indicators of the tablets with Pantogam and succinic acid during natural storage at 18-22 °C

Storage time, months	Requirements of ND to tablets (indicators of quality)						Category No. 3
	content, %		appea-rance	average weight of the tablet	abrasion resistance	disintegra-tion, min	Microbiological purity
	Pantogam	succinic acid					
tablets weighing 0.20 g							State Pharmacopoeia XIV
0	99.1	99.9	corresp.	204	98.6	10.8	corresp.
6	99.8	101.2	corresp.	201	98.0	10.2	corresp.
12	97.8	100.3	corresp.	198	97.2	10.5	corresp.
18	101.0	98.8	corresp.	199	97.8	9.8	corresp.
24	99.0	99.8	corresp.	202	97.9	10.0	corresp.
таблетки массой 0.50 г							State Pharmacopoeia XIV
0	99.2	99.7	corresp.	501	98.4	9.0	corresp.
6	98.7	99,8	corresp.	498	97.4	8.6	corresp.
12	99.0	100.0	corresp.	499	97.6	8.8	corresp.
18	98.0	100.9	corresp.	507	98	8.2	corresp.
24	100.5	99.4	corresp.	501	98.1	8.4	corresp.

content of the developed tablets remained unchanged over the course of 24 months.

4. Conclusions

1. Based on the study of physicochemical and technological properties of substances and excipients, the compositions and technology for obtaining tablets containing Pantogam and succinic acid were justified and developed. The composition of the tablets is as follows: Pantogam – 0.050 g; succinic acid – 0.050 g; mannitol – 0.086 g; aqueous polyvinylpyrrolidone 10 % – 0.004 g; stearic acid – 0.004 g; Aerosil – 0.006 g; total weight of the tablet – 0.200 g.

2. Methods of qualitative and quantitative analysis of medicinal forms containing Pantogam and succinic acid based on complexometric titration and high-performance liquid chromatography were developed. It was found that solid-phase interactions occur in case of the combined presence of Pantogam and succinic acid in tablets.

3. The method for the quantitative determination of succinic acid in the developed dosage forms was validated using HPLC for the following parameters: correctness, linearity, precision, and reproducibility.

4. The stability of the tablets in storage was studied in accordance with State Pharmacopoeia XIII and State Pharmacopoeia XIV. The study results allow recommending a storage time of two years for the developed tablets.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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