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SUBSTANTIATION OF TECHNOLOGY FOR OBTAINING CAPSULES OF A MULTI-COMPONENT DRUG WITH NEUROTROPIC ACTION

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The aim of the work. *Theoretical and experimental substantiation of a rational technology for obtaining a preparation in the form of capsules based on uridine-5-monophosphate of disodium salt, cytidine-5-monophosphate of disodium salt, vitamin B_6, thioctic acid and magnesium lactate dihydrate, determination of process parameters that can affect critical quality characteristics active pharmaceutical ingredients in the product and establishing acceptance criteria for each critical process parameter to be used in batch production and process control.*

Materials and methods. *Objects of the research: masses for encapsulation, granulates and the finished product - capsules with the conventional name "Neuronucleos". To obtain capsules, active pharmaceutical ingredients (API) were used: uridine-5-monophosphate disodium salt and cytidine-5-monophosphate disodium salt (Shanghai Oripharm Co. Ltd., China), thioctic acid (Shanghai Modern Pharmaceutical Co., Ltd..", China), pyridoxine hydrochloride ("DSM Nutritional Products GmbH", Germany), magnesium lactate ("Moes Cantabra S.L.", Spain). The quality indicators were studied: description, average mass of content and uniformity of mass, uniformity of dosage units, dissolution, accompanying impurities, quantitative content of API. Methods of liquid chromatography and complexometric titration were used.*

Results. *It has been established that the use of the direct mixing method does not allow obtaining a mass for encapsulation corresponding to the indicator "Bulk density". The use of the wet granulation method in a fluidized bed has been substantiated. It has been shown that it is difficult to perform granulation in a fluidized bed of an API mixture containing thioctic acid. It has been established that it is rational to obtain a mass for encapsulation in two stages: obtaining a granulate from magnesium lactate dihydrate and pyridoxine hydrochloride with a moisturizer solution (sorbitol + uridine-5-monophosphate disodium salt + cytidine-5-monophosphate disodium salt) and then obtaining a mass for encapsulation from granulate, thioctic acid, anhydrous colloidal silicon dioxide and magnesium stearate by the direct mixing method.*

Conclusions. *On the basis of the performed technological research and analysis of the quality of the obtained capsules, a method for obtaining a capsule mass using the method of wet granulation in a fluidized bed was chosen. The granulation mode was substantiated and the optimal parameters for obtaining a high-quality product were selected, the acceptance criteria for each critical parameter of the technological process were established*

Keywords: *mass for encapsulation, granules, capsules, active pharmaceutical ingredients, technology, quality indicators*

1. Introduction

When developing an original drug, the developer faces a difficult task - the choice of a dosage form, since along with the high quality, efficacy and bioavailability of a drug for the consumer, convenience of use and storage is important. These requirements are most consistent with solid dosage forms - tablets, capsules, granules. About 75 % of all products on the pharmaceutical market are manufactured in this dosage form [1, 2].

In medicine, a dosage form for oral administration in the form of capsules and tablets, containing various combinations of APIs, has found wide application for the treatment of polyneuropathies: uridine-5-monophosphate (UMP) disodium salt, cytidine-5-monophosphate (CMP) disodium salt, vitamin B6, thioctic acid and magnesium lactate dihydrate ("Keltikan N" from "Trommsdorff-Gmbh", Germany; "Nucleo C.M.P. Forte", "Ferrer International, SA", Spain; "Magvit™", "GlaxoSmithKline", England; "Magne-B_6", " Sanofi", France; "Magnikum", "Kyiv Vitamin plant", Ukraine; "Alfa-Lipon", "Kyiv Vitamin plant", Ukraine; "Berlition", "Menarini Group/Berlin-Chemie", Italy/Germany; "Thioctacid", "MEDA Pharmaceuticals Switzerland", Sweden; "Espalipon", "Esparma", Germany) [3–5].

In the world nomenclature of drugs in the form of capsules, there is no drug containing the combination of API - uridine-5-monophosphate disodium salt (UMP), cytidine-5-monophosphate disodium salt (CMP), pyridoxine hydrochloride (PH), thioctic acid and magnesium lactate dihydrate [3–6]. We have developed a combined preparation "Neuronucleos", capsules, which contains (per dose) an original combination of API: UMP – 2.0 mg, CMP – 5.0 mg, PH – 50.0 mg, thioctic acid – 100.00 mg, magnesium lactate dihydrate – 393.00 mg, which corresponds to 40 mg of magnesium.

At the stage of pharmaceutical development (PD) of a medicinal product, in addition to formulation development, a manufacturing process should also be developed [7]. The results of the research are part of the registration dossier. When developing technology, it is neces-

sary to ensure uniformity, in particular, uniform distribution of active substances in the mass for encapsulation [8, 9]; it is necessary to quantify the excess of substances (in the case of solid dosage forms - a humidifier) in the composition per batch, necessary to compensate for the expected production losses, to establish the critical parameters of the process [10, 11]. To successfully implement these tasks, it is necessary to develop a rational technological process and technology transfer [12].

The aim of the work – theoretical and experimental substantiation of a rational technology for obtaining a preparation in the form of capsules based on uridine-5-monophosphate (UMP) disodium salt, cytidine-5-monophosphate (CMP) disodium salt, vitamin B_6, thioctic acid and magnesium lactate dihydrate, determination of process parameters that can influence the critical quality characteristics of active pharmaceutical ingredients in a product and establish acceptance criteria for each critical process parameter that is intended to be used in batch production and process control.

2. Planning (methodology) of research

PD is a complex experimental study on the development of a medicinal product, which convincingly shows that the selected dosage form, proposed composition, manufacturing technology, primary packaging and quality control meet the intended purpose. These studies accompany all stages of drug development, one of which is the choice of a scientifically grounded production process and its control.

A modern methodological approach to PD is presented in the manual (ICH Q8), the main concept of which is "Quality-by-Design" (QbD) [7]. This approach involves the establishment of a relationship between the characteristics of materials and process parameters (risk factors) and critical indicators of drug quality [10, 11]. Requirements for quality and research methods are presented in the SPhU, harmonized with the EP. The QbD approach was used by us when organizing the process of pharmaceutical drug development.

According to modern concepts, the planning of experimental trials in the framework of PD should be carried out taking into account the risk assessment for the quality of the final product. Effectively organized risk management allows obtaining information on the functional characteristics of medicinal products, depending on changes in the characteristics of the ingredients and materials used, the parameters of the technological process [7, 13, 14]. PD risk management activities consisted of the following stages:

– Determination of critical parameters of drug quality (CQAs).

– Identification of risk factors influencing the drug CQAs using the Ishikawa diagram;

– An initial qualitative assessment of the identified risk factors.

– Quantitative assessment of risk factors using FMEA method.

– Creation of a risk assessment map of the drug development process.

The results of these studies will be presented in our next works.

The stages of the research, starting from the choice of API and ending with obtaining the drug, were presented by us in the form of an algorithm, or a sequence of actions to achieve the set technological task:

– study of the physical and chemical properties of API;

– obtaining a mixture of APIs in therapeutic concentration;

– selection of auxiliary substances;

– selection of a humidifier with a justification of wet granulation technology;

– selection of the optimal composition of the capsule mass;

– substantiation of rational technology for obtaining capsules, highlighting critical production parameters.

3. Materials and methods

The objects of the research were laboratory samples of mass for encapsulation, granulates and finished product – capsules, samples of laboratory and industrial series of the drug "Neuronucleos", capsules. To obtain capsules, API was used: uridine-5-monophosphate disodium salt and cytidine-5-monophosphate disodium salt produced by "Shanghai Oripharm Co. Ltd.", China, corresponding to the requirements of the manufacturer's DMF, since these substances are not described in foreign pharmacopoeias, thioctic acid manufactured by "Shanghai Modern Pharmaceutical Co., Ltd.", China, pyridoxine hydrochloride manufactured by "DSM Nutritional Products GmbH", Germany, magnesium lactate produced by "Moes Cantabra S. L.", Spain [15]; excipients: sorbitol ("EVONIC Degussa GmbH", Germany) – a binder; sliding substance – magnesium stearate ("Calmags GmbH", Germany); disintegrant – anhydrous colloidal silicon dioxide ("EVONIC Degussa GmbH", Germany) [15], purified water (humidifier) [16]. Requirements for dosage forms containing a combination of selected APIs are not described in any of the pharmacopoeias (EP, BP, USP).

Physicochemical and pharmaco-technological properties of masses for encapsulation and finished dosage form (DF) were studied according to the methods of the State Pharmacopoeia of Ukraine (SPhU) [16].

The quality of the obtained capsules was evaluated according to the following pharmacological and technological parameters: description, average weight of content and uniformity of weight, uniformity of dosage units, fluidity, bulk density, fractional composition, dissolution, accompanying impurities (uridine-5-monophosphate, cytidine-5-monophosphate, pyridoxine hydrochloride), the quantitative content of UMP, CMP, pyridoxine hydrochloride, thioctic acid, and magnesium lactate. To assess the quality of the preparation, the following methods were used: visual, gravimetric, liquid chromatography, complexometric titration. The quantitative content of uridine-5-monophosphate disodium salt, cytidine-5-monophosphate disodium salt, pyridoxine hydrochloride and thioctic acid, accompanying impurities and identification in DF was carried out by liquid chromatography, according to SPhU, 2.2.29 [16]. The

quantitative content of magnesium lactate (in terms of magnesium) was determined by complexometric titration according to the SPhU method, 2.5.11 [16]. The dissolution test in the preparation was carried out in accordance with the requirements of SPhU, 2.9.3 [16], using a paddle apparatus, by liquid chromatography (SPhU, 2.2.29) [16].

4. Research results

In order to substantiate the technology of the combined preparation, the pharmacological and technological properties of the active substances were studied, the values of which showed that the substances of the active substances have different volumetric characteristics, some of them have insufficient flowability and electrification, and some are prone to the formation of agglomerates. Active substances have different particle sizes, which also affects the technological properties of their mixture [17]. Therefore, to ensure the necessary technological characteristics of the mass for encapsulation, auxiliary substances are introduced into the composition, which improve the mobility of the mass, the distribution of API in the mass for encapsulation, and prevent clumping.

At the first stage, to obtain capsules, we chose the direct mixing method, since it has a number of advantages: it is more economical, allows to significantly reduce the production process and, accordingly, energy costs, to improve the quality of the drug, and creates the most gentle technological regime for active substances. As a result of the studies carried out, it was found that the flowability of the mass for encapsulation has more acceptable values than the API mixture. However, the indicator "Bulk density" of the mass for encapsulation remains too high and does not correspond to the average capacity of capsules of size 00, which we have chosen for filling [18]. Therefore, further research was aimed at improving this indicator. For this purpose, the wet granulation method was used. To improve the pharmacological and technological properties of the mass for encapsulation, we chose an aqueous solution containing sorbitol 5 %, UMP and CMP as a moisturizer. The active substances – UMP and CMP are introduced into the composition of the humidifier in order to distribute them more evenly in the composition of the mass for encapsulation, since the amount of UMP and CMP is 0.36 % and 0.91 % of the total amount of API (550 mg). Pyridoxine hydrochloride, although its content is less than 10 %, it is advisable to add to the mass for encapsulation in dry form, since it is unstable in solutions with a pH above 4.8, and the solution of disodium salts of uridine-5-monophosphate and cytidine-5-monophosphate has an alkaline pH value.

A popular method is fluidized bed granulation, in which fine powder transforms into a so-called "boiling" state upon contact with air [19–21]. This method allows you to prolong the release of drugs from capsules, as well as reduce hygroscopicity.

The use of the method of granulation in a fluidized bed in the technology of obtaining a mass for encapsulation is due to the state of aggregation of the API, high bulk density (due to high dosage), low flow rate, and different sizes of API particles that are included in the dosage form.

When carrying out the granulation process in a fluidized bed, mixing of the components, moistening the mixture with a solution of an adhesive agent, granulation and drying of the granulate occur in one apparatus during one technological cycle. Therefore, the temperature factor of the impact on the API was taken into account. Since one of the APIs, namely thioctic acid, is thermolabile, exposure to elevated temperatures must be minimized. For this, two variants of the technology for obtaining mass for encapsulation were investigated. Technology 1: obtaining a mass for encapsulation in one technological cycle in fluidization. At the same time, magnesium lactate dihydrate, pyridoxine hydrochloride and thioctic acid were loaded into the granulation unit, granulation was carried out with a humidifier solution, observing the mode at which the product temperature was maintained no higher than 30–35 °C. Anhydrous colloidal silicon dioxide and magnesium stearate were added to the granulate and dusting was carried out. Technology 2: obtaining a mass for encapsulation in two stages:

– obtaining a granulate consisting of magnesium lactate dihydrate and pyridoxine hydrochloride using a humidifier solution by the fluidization method;

– obtaining a mass for encapsulation from the obtained granulate, thioctic acid and excipients (colloidal silicon dioxide and magnesium stearate) by the method of direct mixing.

In parallel, technological parameters were studied that determine the course of the process (duration of operations, temperature of the fluidizing gas and product, liquid feed rate, etc.). The results of the analysis of the masses for filling capsules obtained by two variants of the technological solution are presented in Table 1.

From the above results (Table 1), it can be noted that the mass for encapsulation obtained by technology 1 has an inhomogeneous color, has low flowability, is prone to delamination, and sticks together when squeezed by hand. Microscopic examination showed an inhomogeneous granulometric composition, the presence of large granules and conglomerates of varying degrees of color. Determination of moisture in the mass is difficult. The bulk density of the granulate did not allow keeping the average weight of the capsule contents. Inhomogeneity and tendency to delamination led to nonuniformity and deviations in the quantitative content of components. As a result of unsatisfactory processing characteristics, filling the capsules is difficult. The granulation process, due to the correction of the temperature regime, turned out to be longer and did not lead to the desired results.

The mass for encapsulation, obtained by technology 2, has satisfactory appearance indicators, good flowability, does not delaminate when shaken. Microscopic examination revealed that the mass has a more rounded shape of particles, a more balanced fractional composition. The technological characteristics of the mass for encapsulation make it possible to carry out the process of filling the capsules as usual. The granulation process was quite efficient and did not require additional time, as in

technology 1, but additional refinement of the technological parameters, including the time and temperature regimes, the aerodynamic characteristics of the process, is required to determine the critical parameters and acceptance criteria. Therefore, further research was aimed at choosing the optimal granulation mode.

The formation and growth of granules in a fluidized bed occurs due to two physical processes: clumping during wetting and sticking with subsequent agglomeration. The quality of the granules and their fractional composition depend on many factors that determine the course of the process, the main of which are the speed of the fluidizing gas, the composition and feed rate of the granulating liquid, and the temperature in the bed.

To study the modes of granulation, we studied the masses for encapsulation at different values of the rate of supply of air and the humidifier solution to the granulation column, at several temperature conditions presented in Table 2.

The results of physicochemical and pharmaco-technological indicators of the obtained product are shown in Table 3.

Table 1

Influence of the order of introduction of active ingredients and excipients into the mass for filling capsules on quality indicators

Composition for 1 capsule		The name of the technological parameter and / or indicator	The values	
			Technology 1	Technology 2
Component name	%			
Technological properties of the mass for encapsulation				
Uridine-5-monophosphate disodium salt Cytidine-5-monophosphate disodium salt Pyridoxine hydrochloride Thioctic acid Magnesium lactate dihydrate Sorbitol Silicon dioxide colloidal anhydrous Magnesium stearate	0.35 0.87 8.65 17.30 67.99 2.68 1.30 0.86	Flowability (3.0–10.0), g/s	3.00±0.05	10.00±0.05
		Bulk weight (0.5–0.6), g/cm^3	0.575±0.01	0.605±0.01
		Bulk density (0.55–0.65), g/cm^3	0.619±0.01	0.668±0.01
		Weight loss on drying (2±1), %	Not determined	1.30±0.01
Pharmaco-technological indicators				
Description of the mass for encapsulation (fine heterogeneous granular powder of light yellow color with white and yellow blotches)			granular powder of light yellow color with white and yellow inclusions, with agglomerates and large granules, prone to delamination	fine heterogeneous granular powder of light yellow color with white and yellow blotches
Weight of capsule contents, 0.5780±10 % (0.5202–0.6358), g			Does not match	Matches
Related impurities:				
impurity of uridine, no more than 0.3 %			<0.3	<0.3
impurity of cytidine, no more than 0.3 %			<0.3	<0.3
impurity A pyridoxine, no more than 0.3 %			<0.3	<0.3
impurity B pyridoxine (deoxypyridoxine), no more than 0.3 %			<0.3	<0.3
Quantitative content per capsule:				
uridine-5-monophosphate, disodium salt (0.0019–0.0022), g			0.0019	0.0021
cytidine-5-monophosphate, disodium salt (0.0048–0.0055), g			0.0049	0.0051
pyridoxine hydrochloride (0.0480–0.0550), g			0.0452	0.0514
thioctic acid (0.0925–0.1075), g			0.0814	0.0986
magnesium lactate, (Mg), (0.0383–0.0417), g			0.0415	0.0409

Table 2

Granulation modes

Sample number (process step*)	Temperature, °C (min-max)			Humidifier solution consumption			Duration	
	incoming air	outgoing air	product	supply pressure, MPa	speed, g/min (min-max)	amount *, g	granulation, min	drying, s
1 (G)	65.0	28.8–35.1	24.4–44.2	1.6	3–17	450	45	–
1 (D)	65.0	35.1	44.2	–	–	–	–	48
2 (G)	60.0	28.6–32.7	23.4–40.8	1.5	3–15	450	51	–
2 (D)	60.0	33.3	40.8	–	–	–	–	52
3 (G)	60.0	28.5–33.6	23.4–42.7	1.4	3–12	450	48	–
3 (D)	60.0	34.7	42.7	–	–	–	–	50

*Note: * G – granulation, D – drying; ** – amount of humidifier for 1500 capsules*

Table 3

Pharmaco-technological properties of granulates and mass for encapsulation, depending on the granulation mode

Name of indicators (acceptance criterion), units	Results		
	Sample 1	Sample 2	Sample 3
Technological properties of granulate			
Flowability (3.0–10.0), g/s	10.0±0.05	10.0±0.05	12.0±0.05
Bulk weight (0.5–0.6), g/cm^3	0.597±0.01	0.600±0.01	0.611±0.01
Bulk density (0.55–0.65), g/cm^3	0.642±0.01	0.667±0.01	0.673±0.01
Weight loss on drying (2±1), %	1.3±0.01	1.3±0.01	1.4±0.01
Granulometric composition, % , > 710 μm, no more than 5 %	<5	<5	<5
<90 μm, no more than 10 %	<10	<10	<10
Technological properties of the mass for encapsulation			
Description of the mass for encapsulation (fine heterogeneous granular powder of light yellow color with white and yellow blotches)	corresponds	corresponds	corresponds
Flowability (3.0–10.0), g/s	10.0±0.05	10.0±0.05	12.0±0.05
Bulk weight (0.5–0.6), g/cm3	0.600±0.01	0.605±0.01	0.609±0.01
Bulk density (0.55–0.65), g/cm3	0.657±0.01	0.668±0.01	0.670±0.01
Weight loss on drying (2±1), %	1.3±0.01	1.3±0.01	1.4±0.01
Weight of capsule contents (average value of 10 capsules), g 0.5780±10 % (0.5202–0.6358)	0.550	0.578	0.580

The results are shown in Table 3, showed that all the obtained granulates (samples 1–3) have satisfactory flowability and bulk density, the moisture of the granulate is within the specified limits. The granulate is not hygroscopic, does not clump, does not raise dust. Microscopic examination revealed that the granules have a rounded shape, the fractional composition meets the requirements of regulatory documents. Differences are observed in the sizes of the main fraction of granulates: granules of samples 2 and 3 are almost identical and somewhat finer than granules of sample 1. This is due to a higher feed rate of the humidifier solution and a higher process temperature.

According to the indicators "Quantitative content" and "Associated impurities" the samples did not differ significantly and met the established acceptance criteria.

Pharmaco-technological characteristics of the mass for encapsulation make it possible to carry out the process of filling capsules without difficulty. The resulting capsules passed the average weight and weight uniformity tests. It should be noted that the average mass of the contents of the capsule of sample 1 turned out to be somewhat less than in samples 2 and 3, which is associated with the size of the granules. It was also noted that the granules of samples 2 and 3 in the size of the obtained granules more closely correspond to the size of the thioctic acid particles introduced into the mass for encapsulation at the second stage of preparation.

The resulting granules are more durable, less prone to abrasion and have better flowability. When mixing particles close to each other in shape, mixing practically occurs without separation, therefore, the granulation parameters of samples 2 and 3 are acceptable for this technology. Reducing the feed rate of the humidifier solution and the temperature of the incoming air is impractical, since it will increase the duration of the process and, possibly, lead to the production of a granulate with a non-optimal granulometric composition.

5. Discussion of research results

Every year, domestic and foreign researchers devote a significant number of scientific works to the creation and research of solid dosage forms. When creating drugs in the form of capsules, scientists are trying to solve the issues of optimal composition and technology in such a way that these studies lead to an effective and high-quality drug. Along with this, the practical implementation of the creation of new drugs is realized by scaling the process into production. Most of the reviewed works, which include [22–24], are devoted to general research. Scientific approaches to the development of the composition and technology of multicomponent preparations containing APIs with different physicochemical properties require careful theoretical and experimental substantiation. Development of the composition and rational technology for producing capsules, determining the technological parameters of obtaining, establishing acceptance criteria for each critical process parameter, determining the main quality indicators containing the proposed combination of uridine-5-monophosphate disodium salt, cytidine-5-monophosphate disodium salt, pyridoxine hydrochloride, thioctic acid and magnesium lactate dihydrate, was carried out for the first time.

Fluidized bed granulation of an API mixture including thioctic acid is difficult. The resulting product did not meet the established acceptance criteria.

The capsules obtained by technology 2 (Table 1) passed the tests for the average weight of the contents and uniformity by weight, according to the indicators "Quantitative content" and "Concomitant impurities" the samples also met the acceptance criteria of the regulatory documentation.

When choosing the optimal granulation mode, it was found that the investigated granulation modes shown in Tab. 2 make it possible to obtain a granulate and a mass for encapsulation based on it with good flowability (10 g/sec) and an optimal moisture content of 2.0±1 %.

Thus, the granulation mode was chosen, in which the maximum feed rate of the humidifier solution should

not exceed 15 g/min, the temperature of the incoming air should not exceed 60 °C. In this case, the duration of the process should not exceed 55 minutes and the product temperature, which is important for API data, should not exceed 41±1 °C.

The capsule production technology has been successfully tested on industrial equipment. The capsules obtained were in accordance with the quality indicators established by the MQC. The selected composition and technology ensure the compliance of the drug samples with the required standards for the release of thioctic acid under the conditions of the "Dissolution" test, which is confirmed by the results of studying the kinetics of capsule dissolution in three media (at pH 1.2; 4.5; 6.8).

Study limitations. The research carried out on the development of capsule technology in laboratory conditions and scaling up on pilot equipment does not fully reflect the possible risks of obtaining this dosage form in an industrial environment. Critical quality control parameters of the manufacturing process are described as predictable and require confirmation studies when performing prospective process validation.

Prospects for further research. The conducted research is a necessary part of the pharmaceutical development (PD) of a drug in the justification of its composition and technology. A promising direction for further research is the compilation of a PD report for a new original drug for the treatment of neuropathies, the development of technological regulatory documentation for the production of the drug, the validation of the technological process, which will ensure stable and guaranteed receipt of intermediate products and finished products that meet the quality parameters established by the regulatory document, as well as registration section 3.2.P.2.3 "Development of the production process" of the registration dossier of the CTD format - a set of documents that characterize the effectiveness, safety and quality of a medicinal product.

6. Conclusions

In the process of the research on the choice of a rational technology for producing combined capsules, the pharmaco-technological properties of the mass for encapsulation and granulates were studied and it was found that the use of the direct mixing method does not allow obtaining a mass for encapsulation corresponding to the "Bulk density" indicator.

Using the wet fluidized bed granulation method, it has been established:

– granulation of an API mixture containing thioctic acid is impossible due to the heterogeneity of the content and deviations in the quantitative content of the components.

– it is rational to obtain a mass for encapsulation in two stages: obtaining a granulate from magnesium lactate dihydrate and pyridoxine hydrochloride with a moisturizer solution containing sorbitol, uridine-5-monophosphate disodium salt and cytidine-5-monophosphate disodium salt, and then obtaining a mass for encapsulation from granulate, thioctic acid, anhydrous colloidal silicon dioxide and magnesium stearate by the direct mixing method to avoid decomposition of thioctic acid during the technological process and later during storage of the drug.

The granulation mode has been substantiated and the optimal parameters have been selected in order to obtain a high-quality mass for encapsulation. Acceptance criteria are established for each critical parameter of the capsule production process. The technology for obtaining the original combined preparation "Neuronucleos", capsules, has been tested in industrial conditions. The composition and technology are protected by the patent of Ukraine No. 140727.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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