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Development the composition and technology for obtaining a dietary supplement “Cachinol” with the antioxidant activity in the form of granules used in the polycystic ovary syndrome

Aim. To develop the composition and technology for obtaining a dietary supplement “Cachinol” with the antioxidant activity in the form of granules used in the polycystic ovary syndrome.

Materials and methods. To achieve the goal, physical, physicochemical, pharmacotechnological and statistical research methods, as well as generally accepted research methods of the State Pharmacopoeia of Ukraine (SPhU) 2.0 were used in the work.

Results and discussion. The rational dosage form is granules. The green tea leaf extract and myo-inositol were chosen as the active pharmaceutical ingredients of granules. For 3 batches of granules, the following parameters were determined: the fractional composition ranging from 13.2 to 17.9 % for 3-2 mm, from 45.3 to 56.2 % for 2-1 mm, from 20.1 to 26.1 % for 1-0.5 mm, from 8.1-12.4 for 0.5-0.25 mm, from 2.95-4.6 % for < 0.25 mm; the moisture content of granules ranging from 2.80-3.10 %; the bulk density – from 0.49 to 0.52 g/cm^3, the tapped density – from 0.54 to 0.58 g/cm^3; the flowability was in the range of 8.00-8.25 g/s; the angle of repose – from 30 to 33°; disintegration – from 41 to 45 s.

Conclusions. The flowchart for obtaining granules in industrial conditions has been developed. The technological process for obtaining granules consists of 8 technological stages. The studies of the technological parameters of granules have been performed in accordance with the requirements of the SPhU 2.0. It has been found that the granules developed meet the requirements of the SPhU 2.0 and can be recommended for further research.

***Key words**: development; composition; granule technology; green tea extract; dietary supplement*

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Розробка складу і технології одержання дієтичної добавки у вигляді гранул «Кахінол» з антиоксидантною активністю, що застосовують у разі синдрому полікістозу яєчників

Мета роботи – розробити склад і технологію одержання дієтичної добавки у вигляді гранул «Кахінол» з антиоксидантною активністю, що застосовують у разі синдрому полікістозу яєчників.

Матеріали та методи. Для досягнення визначеної мети в роботі було використано фізичні, фізико-хімічні, фармакотехнологічні та статистичні методи дослідження, а також загальноприйняті методики дослідження Державної фармакопеї України (ДФУ) 2.0.

Результати та їх обговорення. Раціональною лікарською формою є гранули. Як активний фармацевтичний інгредієнт гранул було обрано екстракт листя зеленого чаю та міо-інозит. Для 3 серій гранул було визначено: фракційний склад, що становить від 13,2 до 17,9 % для 3-2 мм, від 45,3 до 56,2 % для 2-1 мм, від 20,1 до 26,1 % для 1-0,5 мм, від 8,1 до 12,4 % для 0,5-0,25 мм, від 2,95 до 4,6 % для < 0,25 мм; вологість гранул – у межах від 2,80 до 3,10 %; щільність гранул до зсідання – від 0,49 до 0,52 г/см^3, щільність гранул після зсідання – від 0,54 до 0,58 г/см^3; плинність – в інтервалі 8,00-8,25 г/с; кут природного нахилу – від 30 до 33^o; розпадання – від 41 до 45 с.

Висновки. Розроблено технологічну схему одержання гранул у промислових умовах. Технологічний процес одержання гранул складається з 8 технологічних стадій. Проведено дослідження технологічних параметрів гранул відповідно до вимог ДФУ 2.0. Виявлено, що розроблені гранули відповідають вимогам ДФУ 2.0 та можуть бути рекомендовані для подальших досліджень.

***Ключові слова**: розробка; склад; технологія одержання гранул; екстракт зеленого чаю; дієтична добавка*

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Разработка состава и технологии получения диетической добавки в виде гранул «Кахинол» с антиоксидантной активностью, применяемой при синдроме поликистоза яичников

Цель работы – разработать состав и технологию получения диетической добавки в виде гранул «Кахинол» с антиоксидантной активностью, применяемой при синдроме поликистоза яичников.

Материалы и методы. Для достижения поставленной цели в работе были использованы физические, физико-химические, фармакотехнологические и статистические методы исследования, а также общепринятые методики исследования Государственной фармакопеи Украины (ГФУ) 2.0.

Результаты и их обсуждение. Рациональной лекарственной формой являются гранулы. В качестве активного фармацевтического ингредиента гранул был выбран экстракт листьев зеленого чая и мио-инозит. Для 3 серий гранул были определены: фракционный состав, который составляет от 13,2 до 17,9 % для 3-2 мм, от 45,3 до 56,2 % для 2-1 мм, от 20,1 до 26,1 % для 1-0,5 мм, от 8,1 до 12,4 % для 0,5-0,25 мм, от 2,95 до 4,6 % для < 0,25 мм; влажность гранул – в пределах от 2,80 до 3,10 %; плотность гранул до усадки – от 0,49 до 0,52 г/см^3; плотность гранул после усадки – от 0,54 до 0,58 г/см^3; сыпучесть – в интервале 8,00-8,25 г/с; угол естественного наклона – от 30 до 33º; распадаемость – от 41 до 45 с.

Выводы. Разработана технологическая схема получения гранул в промышленных условиях. Технологический процесс получения гранул состоит из 8 технологических стадий. Проведены исследования технологических параметров гранул в соответствии с требованиями ГФУ 2.0. Установлено, что разработанные гранулы соответствуют требованиям ГФУ 2.0 и могут быть рекомендованы для дальнейших исследований.

***Ключевые слова*:** *разработка; состав; технология получения гранул; экстракт зеленого чая; диетическая добавка*

Introduction. Nowadays, the polycystic ovary syndro me (PCOS) is one of the most common female endocri ne disorders with various metabolic and endocrine disorders and clinical symptoms. Polycystic ovary disease affects 6-10 % of women of the reproductive age. PCOS is a chronic disease that can lead to complications associated with reproductive failure and pregnancy, as well as long-term risks such as diabetes, cardiovascular disease, poor quality of life and overall mortality. Diagnostic signs of PCOS are hyperandrogenism, a change in the ratio of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) (2/3:1), chronic oligovulation or anovulation, and polycystic ovaries. The treatment of PCOS is aimed at restoring fertility, treating hirsutism or acne, and restoring ovulation [1].

Myo-inositol is a carbohydrate, the molecular formula of inositol is identical to that of glucose although it differs in its molecular structure. Myo-inositol is synthesized by the body directly from glucose-6-phosphate, and therefore, is often excreted as a pseudovitamin, a member of the B group called vitamin B_8. Myo-inositol plays a fundamental role as a secondary messenger in signaling cascades of protein receptors of gonadoliberin (gonadotropin-releasing hormone), FSH and LH [2].

The results of a comparative study [3, 4] of treating patients with PCOS and anovulation showed that 50 % of patients treated with metformin recovered spontaneous ovulation, 18 % became pregnant. In the group receiving myo-inositol in the dose of 4 g/day, spontaneous ovulation was restored in 65 % of patients, and 30 % of patients became pregnant, an increase in fertility, a decrease in the level of testosterone, triglycerides, insulin, and normalization of blood pressure were also revealed. In the group receiving myo-inositol there were no side effects of the therapy, and it increased adherence to it. In addition, the research results demonstrate a high level of safety of the myo-inositol molecule even when administered up to 12 g/day, causing only minor side effects from the gastrointestinal tract.

Green tea leaf is a rich source of phenolic compounds, which are represented by catechins, flavonols, flavones and phenolic compounds. Due to a wide variety of phenolic compounds, green tea has the antioxidant [5], anti-inflammatory [6], antiviral [7], antibacterial [8], antitumor [9], anxiolytic [10] activity. Many studies have shown that green tea catechins have a higher level of the antioxidant activity than other phenolic compounds [11, 12]. *In vivo* studies have shown that catechins contribute to the improvement of ovulation, maturation of follicles, and also prevent the formation of cysts in rats [13]. Shurie et al. [14] studied the effect of catechins on the treatment of dysmenoria in the model of inductive adenomyosis with tamoxifen in rats. As a result of the treatment with epigallocatechin-3-O-gallate in the dose of 5 and 50 mg/kg, a decrease in generalized hyperolysia and a decrease in plasma corticosterone levels were found. In addition, epigalocatechin-3-O-gallate reduced the uterine contractility and suppressed the myometrial infiltration.

To develop a dosage form, we took into account the pharmacological properties of the green tea extract. Based on them, we considered the following dosage forms: powders, granules and tablets. In our opinion, powders are quite inconvenient; in addition, during long-term storage they damp and stratify. At first glance, tablets are the most convenient dosage form for storage and administration. However, as a result of a strong mechanical stress during the pressing process, the disintegration of a tablet decreases, and the bioavailability decreases. Hence, in our opinion, granules are the optimal dosage form. It has, in turn, a number of advantages over a tablet. Above all, the disintegration rate of granules is very high; it increases the bioavailability of the active ingredients. Secondly, granules are convenient in that they allow preparing solutions extemporaneously.

The **aim** of the work was to develop the composition and technology for obtaining a dietary supplement "Cachinol" with the antioxidant activity in the form of granules used in the polycystic ovary syndrome.

Materials and methods. Physical, physicochemical, pharmacotechnological and statistical research methods, as well as generally accepted research methods of the State Pharmacopoeia of Ukraine (SPhU) 2.0 were used in the work.

Results and discussion. A liquid decaffeinated green tea extract was obtained. The total phenolic compounds, catechins, flavonoids and hydroxycinnamic acids content were quantified. Also, the antioxidant activity of the extract obtained was determined by the potentiometric method [16].

The dose of the green tea extract was calculated according to the daily antioxidant activity developed. Epigallocatechin-3-O-gallate (EGCG) was chosen as a "gold standard" of the antioxidant activity as there are various studies that consider EGCG as one of the most potent antioxidants among phenolic compounds [17]. According to the section "Dietary supplements" of the SPhU 2.3 [18],

the minimum content of each vitamin and/or mineral substance (nutrients) in the recommended daily amount of dietary supplements should be at least 15 % of the recommended daily intake. This rule was applied in formulating requirements for daily intake of drugs with the antioxidant activity. According to the "Regulation (EU) 2017/2470 of the European Parliament and of the Council of 20 November 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods" [19], the maximum recommended daily dose of EGCG is 300 mg, its antioxidant activity is 562 mmol-eq./g [20]. Thus, the maximum recommended dose of a drug with the antioxidant activity is 562 mmol-eq./g as minimum recommended dose is 84.30 mmol-eq./g.

In our study [21] it has been found that the antioxidant activity of one sachet (with the mass of 5.0 g) of "Cachinol" with the composition given below is equal to 268 mmol-eq./g. As the dietary supplement is applied twice a day, the daily intake of the drug with the antioxidant activity is 536 mmol-eq./g.

Myo-inositol was chosen as a filler for a number of reasons. Firstly, compared to other excipients, such as glucose, lactose, saccharose, myo-inositol increases the insulin

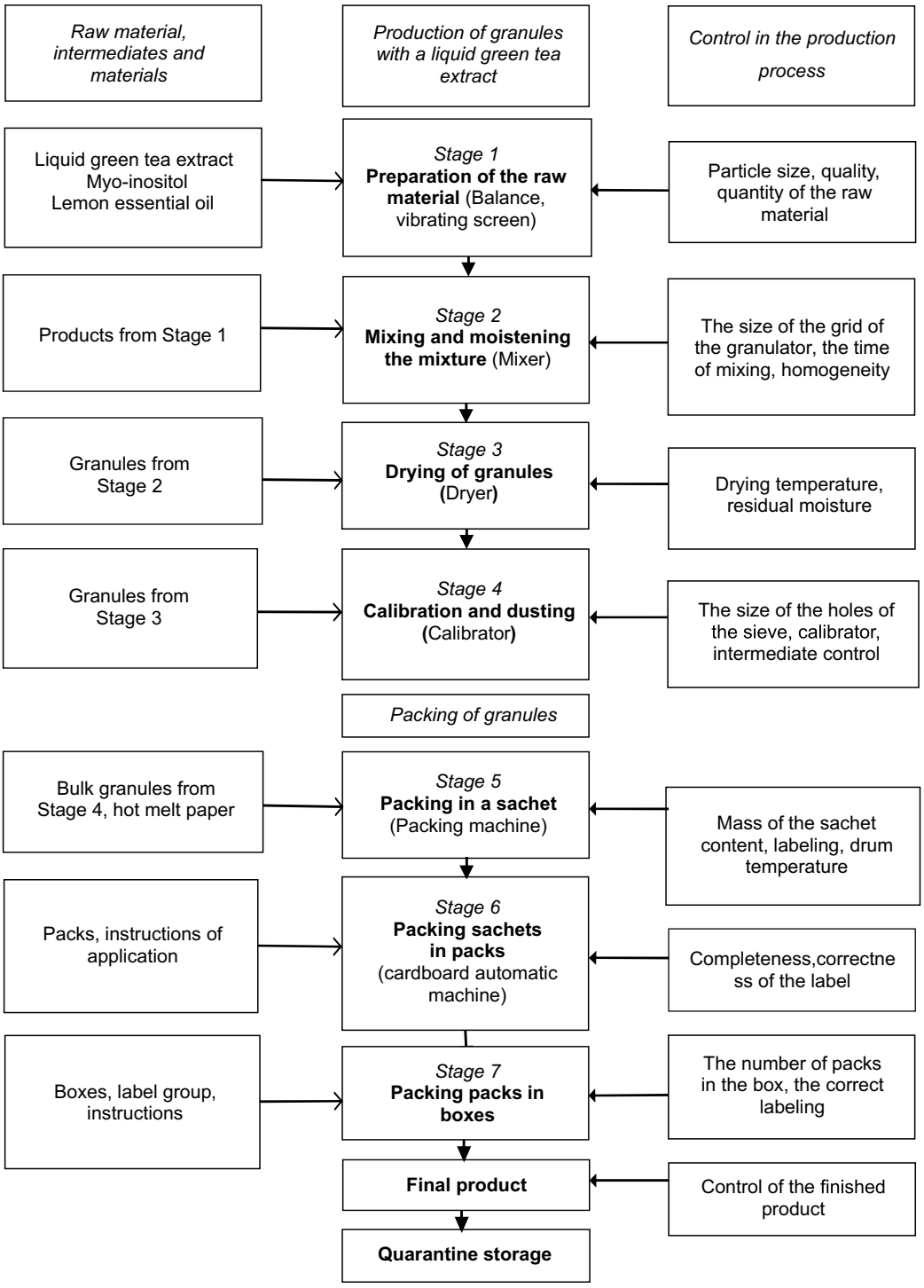

Fig. The flowchart for obtaining granules with a liquid green tea extract

Table

The technological parameters of granules with the green tea leaf extract

№ series	Fractional content, %					Moisture, %	Bulk density, g/cm³	Tapped density, g/cm³	Flowability, g/s	Angle of repose °	Disintegration, s
	3-2 mm	2-1 mm	1-0.5 mm	0,5-0.25 mm	< 0.25 mm						
11	21.5	48.7	14.1	11.1	4.6	2.80	0.49	0.54	8.10	31	42
22	17.9	44.3	23.2	12.4	3.5	3.10	0.51	0.56	8.00	30	45
33	23.2	44.2	20.1	8.1	4.4	2.95	0.52	0.58	8.25	33	41

sensitivity and the subsequent increase in the absorption of intracellular glucose. Thus, myo-inositol can be used by patients with type I and II diabetes mellitus. Secondly, myo-inositol does not have a laxative effect like sorbitol. Thirdly, myo-inositol is indifferent to the extract, there are no side effects.

The lemon essential oil was added to the composition of granules in order to improve a taste of the dietary supplement "Cachinol".

Thus, the following composition of the components of granules (%) based on the green tea leaf extract was proposed:

a liquid green tea extract	10.0
lemon essential oil	0.050
myo-inositol	up to 100.0.

The technology for obtaining "Cachinol" granules consists of the following stages: preparation of the raw material, mixing and wet granulation, drying of granules, calibration and dusting, packing granules in sachets, packing sachets flowchart for obtaining granules is given in Fig., which shows the critical parameters and critical stages, indicators that are controlled in the production process.

The technology for obtaining "Cachinol" granules is as follows: the calculated amount of myo-inositol (90.0 g) is weighed out, a liquid green tea leaf extract (10.0 g), 10 drops of lemon essential oil are added in small portions until a homogeneous wet mass is obtained, it should not stick to the fingers, and is crumpled into a "snow" lump (a sufficiently moist mass). The moistened mass is transferred to a perforated plate (called a granulator) with a hole diameter of 3 mm and wiped. The granulate is dried at t = 50 ± 5 °C in a thermostat for 1 hour. The dried granulate is rubbed again through a sieve with a hole diameter of 3 mm, sifted from dust through a sieve with a hole diameter of 1 mm. The residual moisture of granules is equal to 3.10 %.

The following technological parameters of granules with a liquid green tea leaf extract were determined: the fractional composition, moisture, bulk density, flowability, angle of repose, disintegration. The results are shown in Table.

The batches of granules obtained are grains of irregular shape, brown in color, with a lemon taste. It was found that the fractional composition was from 13.2 to 17.9 % for 3-2 mm, from 45.3 to 56.2 % for 2-1 mm, from 20.1 to 26.1 % for 1-0.5 mm, from 8.1-12.4 for 0.5-0.25 mm, from 2.95-4.6 % for < 0.25 mm. The moisture content of granules was determined in the range from 2.80-3.10 %; the bulk density was from 0.49 to 0.52 g/cm^3, the tapped density was from 0.54 to 0.58 g/cm^3; the flowability was in the range of 8.00-8.25 g/s; the angle of repose was from 30 to 33°; disintegration was from 41 to 45 s.

According to the research results, the granules developed meet the requirements of the SPhU 2.0 and can be recommended for further research with the aim of introducing them into production.

Conclusions and prospects for further research. Based on the theoretical and experimental studies, the composition and technology for obtaining a dietary supplement "Cachinol" with the antioxidant activity in the form of granules used in the polycystic ovarian syndrome have been developed. The main active pharmaceutical ingredient is the green tea leaf extract and myo-inositol. The flowchart for obtaining granules in industrial conditions has been developed. The technological process for obtaining granules consists of 8 technological stages.

The studies of the technological parameters of granules have been performed in accordance with the requirements of the SPhU 2.0. It has been found that the granules developed meet the requirements of the SPhU 2.0 and can be recommended for further research.

Conflict of interests: authors have no conflict of interests to declare.

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