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Development of composition and technology of granules with dry extracts of corn silk and roots of achyranthes bidentata

Nguyen Thi Ngan, M.G. Ozhigova, I.E. Kaukhova, V.A. Weinstein

St-Petersburg State Chemical and Pharmaceutical University;

14, Prof. Popov St., St. Petersburg, 197376, Russian Federation

INFORMATION ABOUT THE AUTHORS:

Nguyen Thi Ngan – post-graduate student of the Department of Industrial Technology of Drugs of the Saint-Petersburg State Chemical and Pharmaceutical University. Tel.: +7 (952) 274-20-58. E- mail: nganbn1504@gmail.com

Maria G. Ozhigova – Associate Professor of the Department of Industrial Technology of Drugs of the Saint-Petersburg State Chemical and Pharmaceutical University, candidate of pharmaceutical science, Associate Professor.

Irina E. Kaukhova – Head of the Department of Industrial Technology of Drugs of the Saint-Petersburg State Chemical and Pharmaceutical University, Doctor of Pharmaceutical Sciences, Professor. Tel.: +7 (911) 917-06-55. E-mail: Irina.Kaukhova @ pharminnotech.com

Victor A. Vainshtein – Professor of the Department of Industrial Technology of Drugs of the Saint-Petersburg State Chemical and Pharmaceutical University, Doctor of Pharmaceutical Sciences,Professor. Tel.: +7 (921) 8876-31-70. E-mail: Victor.Vainshtein @ pharminnotech.com

SUMMARY

Introduction. Researching new effective drugs and developing the dosage forms based on medicinal plants are the most important achievements of modern pharmacy. Drying extracts of corn silk (DECS), roots of Achyranthesbidentata (DEAB) and the substance of Rutin are the perspective sources to get phytopreparations.

Aim. To develop the composition and technology of granules with dry extracts and rutin. This research will be suitable for making solid gelatin capsule dosage form recommended to be used as potassium-sparing diuretics

Materials and methods. The research subjects are dry extracts of CS, AB andRutin.Excipients used in the granulation process are Lactose (anhydrous), magnesium carbonate, calcium carbonate, corn starch and microcrystalline cellulose (MCC 101). Technology properties and quality of granules were evaluated according to the methods described in the Russian State Pharmacopoeia (RSP).

Results and discussion. Analyzing the technology properties of the DECS and DEAB showed that all of them were unsatisfactory. Therefore, to combine them in a single dosage form, granulation needs to be used, and the excipients were selected. This selection allowed obtaining a flowability mass with homogeneous fractional composition. Many different compositions of DECS: DEAB: Rutin (1: 3: 1) and excipients were evaluated.The technology properties of the granules were studied to discover the optimal composition and technology which were selected for drug production. Choosing size of solid gelatin capsules for encapsulating. Based on the values of bulk density of granules and reasonable therapeutic dosage, capsules N0 00 were selected for packing.

Conclusion. The composition and technology of granules with dry extracts and rutin, satisfied technological characteristics. They can be used to produce a solid gelatin capsule dosage form. The selected size of solid gelatin capsules to meet production conditions is № 00.

Key words: corn stigmas, bicuspid straw roots, dry extract, granules, technological properties.

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РАЗРАБОТКА СОСТАВА И ТЕХНОЛОГИИ ГРАНУЛ С СУХИМИ ЭКСТРАКТАМИ СТОЛБИКОВ С РЫЛЬЦАМИ КУКУРУЗЫ И КОРНЕЙ СОЛОМОЦВЕТА ДВУЗУБОГО

Нгуен Тхи Нган, М.Г. Ожигова, И.Е. Каухова, В.А. Вайнштейн

Санкт-Петербургский химико-фармацевтический университет; Российская Федерация, 197376, Санкт-Петербург, ул. проф. Попова, д.14

СВЕДЕНИЯ ОБ АВТОРАХ

Нгуен Тхи Нган – аспирант кафедры промышленной технологии лекарственных препаратов Санкт-Петербургского государственного химико–фармацевтического университета (СПбХФУ). Тел.:+7 (952) 274-20-58. E- mail: nganbn1504@gmail.com

Ожигова Мария Георгиевна – доцент кафедры промышленной технологии лекарственных препаратов СПбХФУ, кандидат фармацевтических наук

Каухова Ирина Евгеньевна – заведующая кафедрой промышленной технологии лекарственных препаратов СПбХФУ, доктор фармацевтических наук, профессор. Тел.: +7 (911) 917-06-55. E- mail: Irina.Kaukhova @pharminnotech.com

Вайнштейн Виктор Абрамович – профессор кафедры промышленной технологии лекарственных препаратов СПбХФУ, доктор фармацевтических наук. Tel.: +7 (921) 8876-31-70. E- mail: Victor.Vainshtein@ pharminnotech.com

РЕЗЮМЕ

Введение. Поиск новых эффективных лекарственных средств (ЛС) и разработка лекарственных форм (ЛФ) на основе растительных субстанций – важнейшие задачи современной фармации. Перспективными источниками получения фитопрепаратов являются сухие экстракты столбиков с рыльцами кукурузы (СРК) и корней соломоцвета двузубого (КСД), а также субстанция флавоноида рутина.

Цель работы – разработка состава и технологии гранул композиции сухих экстрактов СРК и КСД с рутином, пригодных для получения лекарственной формы в виде твердых желатиновых капсул, предлагаемой в качестве диуретического калийсберегающего средства.

Материал и методы. Объекты исследования – разработанные авторами сухие экстракты СРК и КСД и субстанция рутина. Вспомогательные вещества, применяемые для процесса гранулирования: лактоза безводная, магния карбонат, кальция карбонат, крахмал кукурузный, микрокристаллическая целлюлоза МКЦ 101. Технологические свойства материалов и показатели качества гранулятов определяли по фармакопейным методикам (ГФ РФ XIV издания).

Результаты. Показано, что все сухие экстракты СРК и КСД обладают неудовлетворительными технологическими свойствами. Для получения сыпучей массы с однородным фракционным составом исследовали различные композиции, состоящие из смеси сухих экстрактов СРК, КСД и рутина в соотношении 1 : 3 : 1 и вспомогательных веществ. Изучены технологические свойства гранул, выбраны оптимальные состав и технология. Подобран размер твердых желатиновых капсул. Основываясь на значениях насыпной плотности гранул и терапевтически обоснованной дозы, для фасовки выбраны капсулы размером № 00.

Заключение. Разработан состав и технология получения гранулятов композиции сухих экстрактов столбиков с рыльцами кукурузы и корней соломоцвета двузубого с рутином, обладающих удовлетворительными технологическими характеристиками, позволяющими использовать их для получения лекарственной формы в виде твердых желатиновых капсул. Подобран размер твердых желатиновых капсул с целью апробирования технологии в производственных условиях.

Ключевые слова: сухой экстракт, кукурузные рыльца, Styli cum stigmatis Zeae maydis, корни соломоцвета двузубого, ***Radices Achyranthidis bidentatae***, гранулы, технологические свойства.

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Introduction

Not only synthetic drugs, but also medicinal substances derived from plants are used for the prevention and treatment of various diseases. These compounds are effective because of the presence of biologically active substances (BAC) that provide a wide range of pharmacological action. In this case, the purification of a herbal extract or individual medicinal substances of plant or synthetic origin are often used as active substances.

The phytocompositions selected for research include dry extracts of corn silk (CS), roots of *Achyranthes bidentata* (AB) and the substance of rutin. Corn silk has been used in traditional and official medicine in many different countries around the world. Besides cholagogue, diuretic, hemostatic effects, the modern pharmacological researchsproved it to possess anti-inflammatory, neuroprotective, hypoglycemic, anti-diabetic and many other pharmacological properties [1].

Achyranthes bidentata Bl. is a tropical plant in the *Amaranthaceae* family. It has been used in traditional and official Chinese and Vietnamese medicine, as well as in other countries for the treatment of various diseases. The root of *A. bidentata* is an important herbal medicine, which contains significant amounts of biologically active compounds (BAC), such as triterpenoid saponins (oleanolic acid and its glycoside), phytosteroids (ecdysterone,in okosteronean drub rosterone), polysaccharides, amino acids, alkaloids and coumarins [2]. Achyranthes extract lowers high cholesterol, raises uterine tone, slows the heart rate and is used as a diuretic for the treatment of kidney diseases and hypertension. In addition, *Achyranthes bidentata* Bl. is applied in the treatment of rheumatic and in-flammatory diseases [3].

Rutin is one of the bioactive compounds which is contained in many plants and food derived from plant [4]. As a medicinal substance, rutin has a wide range of pharmacological activities, including antioxidant, cytoprotective, vasoprotective, anticar-cinogenic, neuroprotective and cardioprotective activities [5]. In Russia, rutin is registered in the State Register of Medicines (GRLS Russian Federation) and used as an angioprotector and microcirculation corrector.

The aim of this research is to develop the composition and technology of granulation made from dry extracts and rutin. It is suitable for preparing a solid gelatin capsule dosage form which is recommended to use as a potassium-sparing diuretic.

Materials and methods

The research objects were dry extracts of corn silk and *Achyranthes bidentata* [6,7]. Their main specifications are presented in table 1. Excipients used in the research are presented in table 2.

Technological characteristics of dry extracts and granules were determined according to generally accepted methods [8]. First, Fractional composition was determined by sieve analysis. Secondly, Bulk volume and bulk density were studied on a device Tapped Density Testers ERWEKA SVM 221. Besides, the Granulate flow tester ERWEKA GT was used to record Flowability. Finaly, Residual moisture was determined by the gravimetric method according to OFS «Weight Loss on Drying» State Pharmacopoeia RF.

Moisture absorption at relative air humidity of 98% was researched was studied with the help of a laboratory desiccator by the method: Put 2 dry extracts samples weighing about 200 mg (accurate to 0,1 mg) into 2 weighing bottles. Then each bottle was kept inside adesiccator bottle containing of 10% glycerol solution. The relative humidity was 98±1% and temperature was 25±2°C. This test last 72 hours,every 1 hour the mass change of powder was recorded.

The disintegration of granules was determined on Disintegration Tester ERWEKA ZT 221 according to OFS «Disintegration of tablets and capsules» State Pharmacopoeia RF.

Results and discussion

Technological and physicochemical characteristics of dry extract are the most important values in the development and production of dosage forms. Technological characteristics of dry extracts and granules were studied and the results are presented in table 3.

Analyzing the technology properties of the DECS and DEAB showed that all of them were unsatisfactory. Dry extract of CS is characterized by very bad flowability and low bulk density. The flowability of dry extract AD was a little higher, however it cannot

Table 1

Quality indicators of dry extractsof corn silk and Achyranthes bidentata

Name indicator	Characteristics of dry extract CS	Characteristics of dry extract AB
Description	Powder with a particle size of 0,1 to 0,5 mm, red-brown in color, with a specific smell.	Powder with a particle size of from 0,1 to 0,5 mm, from golden brown to yellow brown, with a slight specific smell and sweet taste
Qualitative analysis	TLC method in the system n-butanol acetic acid – water (4:1:5). Two spots (retention factor (Rf) 0,71±0,01 and 0,89±0,01) detected by spraying the plates with 2% ethanolic aluminum chloride. Rf value 0,89 indicated the presence of luteolin.	The TLC method in the system: n-butanol – ethanol – 25% ammonia solution (7:2:5). One spotwas detected by spraying the plates with 20% sulfuric acid. Rf value 0,9 indicated the presence of oleanolic acid.
Content BAC,%	The content of flavonoids (in terms of luteolin): 2,52 ± 0,07 %	The content of saponins (in terms of oleanolic acid): 5,75 ± 0,34%
Weightlosson drying, %	3,24 ± 0,31	2,76 ± 0,05

Table 2

Characteristics of the excipients

№	Name of substances	Regulatory documents	Brand and country of manufacture
1	Lactose (anhydrous),	OST 49-63-85	DFE Pharma,Germany
2	Aerosil A-300	GOST 14922-77	SigmaAldrich, USA
3	Magnesium carbonate	GOST 6419-78	Sigma-Aldrich, Germany
4	Calcium carbonate	GOST 4530-76	Sigma-Aldrich, Germany
5	Cornstarch	GOST 32159-2013	Component-Reactive, LLC, Russia
6	Microcrystalline cellulose (MCC 101)	FS 42-08803-98	FelitsataHolding, LLC, Russia
7	Rutin	ND 42-11607-05	Merck ,Germany

be considered as a satisfaction. Therefore, to combine them in a single dosage form,wet granulation needs to be used. The composition of extract contains water-soluble adhesives, so binders are unnecessary, it is sufficient to moisten the mass with the selected solvent – alcohol solution.

Researching hygroscopic properties of DECS and DEAB is one of the most important properties that figures out their quality and stability.

Hygroscopicity was tested at relative humidity of air of 98% (fig.1).

Based on the results of the experiment, it was found that, at a relative air humidity of 98 % (fig.1), the moisture absorption kinetics were mostly similar between 2 extracts. After 6 hours of the experiment, the moisture content increased to 10 % (fig. 1a). Extracts turned into sticky, non-flowing powders. After 72 hours, the moisture content increased to 50% and the extracts became a dense, sticky mass (fig. 1b). The refore, in order to obtain granules with flowability mass and homogeneous fractional, it is necessary to determine the composition of excipients and granulation technology.

Previous research conducted in SPCPU showed that the composition including rutin and phytoextracts of corn silk and *Achyranthes bidentata* in the ratio 1:3:1 produced a comparable diuretic activity with standard Verospiron. On the basis of pharmacological researches, the composition and the magnitude of a dose of the active ingredients for the dosage form were recommended as following: DECS – 60 mg; DEAB – 180 mg; Rutin – 60 mg.

The next task was the choice of excipients and an appropriate granulation technology, which provided

Table 3

The technology properties of the DECS and DEAB

№	Name indicator	Dry extract CS	Dry extract AD	Reference Values
1	Flowability, g/sec	0,24±0,04	2,58±0,07	8,6–12 g/sec – very good 6,6–8,5 g/sec – good; 3–6,5 g/sec – fair; 2–3 g/sec – passable; 1–2 g/sec – bad; 0,3–1 g/sec – very bad
2	Angle of repose, Degrees	57,0±4,7	48,0±4,6	22–28° – very good; 28–32° – good; 32–40° – fair; 40–45° – passable; 45–50° – bad; 50–65° – verybad
3	Bulk volume after tapping, kg/m^3	465±9	925±28	> 2000 kg/m^3 – very heavy; from 1100 to 2000 kg/m^3 – heavy; from 600 to 1100 kg/m^3 – medium; < 600 kg/m^3 easy flowing powder
4	Residual moisture, %	3,42±0,32	3,67±0,41	Not more than 5%

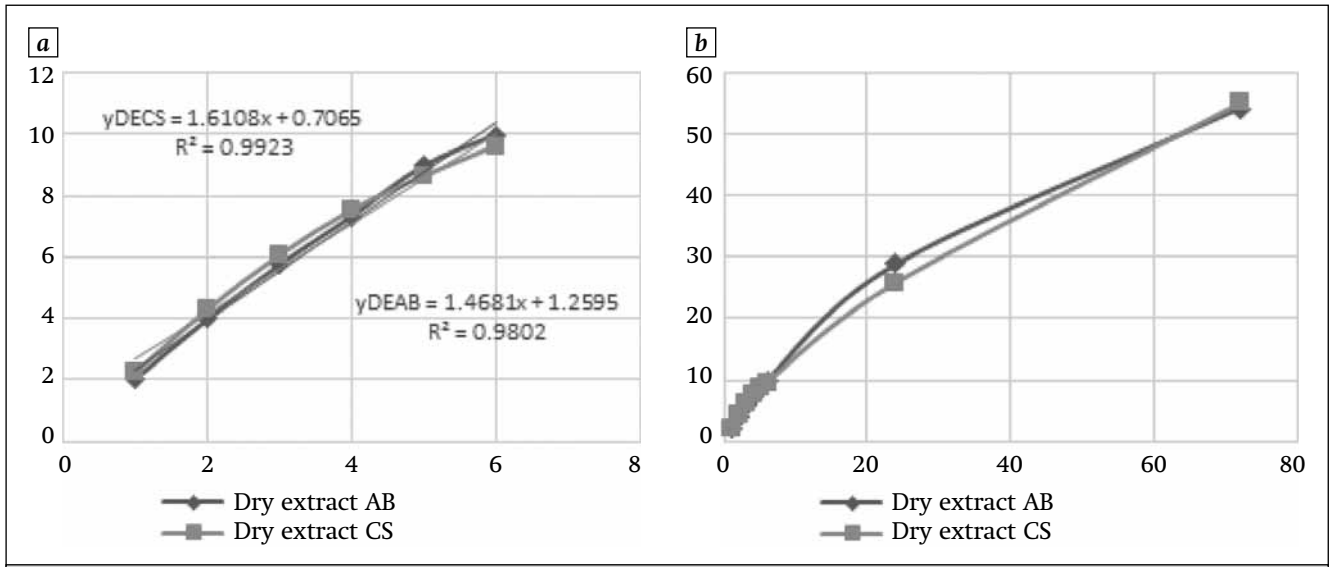

Fig.1. The hygroscopicity of dry extracts of corn silk (DECS) and Achyranthes bidentata (DEAB): *a* – 6 hours; *b* – 72 hours. X-axis : time, hours; Y-axis : moisture absorption, %.

the granule's technology properties: flowability, bulk density, angle of repose, fractional composition. Excipients were investigated: anhydrous lactose, magnesium carbonate, calcium carbonate, corn starch, and microcrystalline cellulose (MCC 101). Wet granulation technology was allowable to provide the greatest homogeneous fractional of the granules, however, aqueous solutions were unacceptable due to the high hygroscopicity of dry extracts. The studied binders included an alcoholic solution of 60% to 96% concentration and 5% PVP solution.

The composition of the mixture contained rutin, has low solubility in water. Therefore, to improve the uniformity of mixing, increases wettability and solubility, Tween-80 was added to the composition as a wetting agent (granules № 9 and № 10).

Granules were prepared as follows: BAC was introduced into the composition in the form of a mixture SESRK: SEKSD: rutin in the ratio 1: 3: 1. The filler wasadded and mixed thoroughly. The mixture was moistened with a moisturizing solution, thoroughly mixed until homogeneous, rubbed through a 2 mm sieve and dried in a drying cabinet at 70°C. Dry powder was rubbed through a 1 mm sieve and packaged in vials with stopperscap. Description and fractional composition of the obtained granules are presented in tables 4 and 5.

The collected experimental data demonstrated that the most significant factors for receiving optimal granules were the alcohol concentration of the binder and the type of filler. A higher alcohol content (96% and 90%, var. № 1 and № 3) did not provide enough binding strength of the powder, and a large amount of fraction less than 0,25 mm was formed in the particles. Using 70% alcohol for granulation was optimal because it achieved sufficient bonding, the granulation processstill capability occur, the mass did not stick to the sieve, was dried easily and kept grain. The best fillers were lactose anhydrous and the combination of lactose with starch, whereas magnesium and calcium carbonates (var. № 4 and № 6) led to the formation of fragile granules with a large amount of fine fraction. Thus, the obtained granules of compositions № 2,5,9 and 10 had satisfactory technological properties (fig. 2).

In the first 5 hours, the weight gain of all particles is linear. The fastest increase in moisture was the granules № 5 (up to 5% in 5 hours). Granules № 2 and № 9 show the moisture absorption at the smallest speed (fig. 2a). Granules at the same time did notlose

Table 4

Composition and size of granules

№	Composition	Fractional composition (size of granules),%	
		less than 0,25 mm	from 0.25 to 1,0 mm
1	Mixture of BAC – 60 %; Lactose (anhydrous) – 39 %; Aerosil A-300 – 1 %; 95% ethanol solution – 35 ml per 100 g of mixture	14,16±0,03	85,84±0,92
2	Mixture of BAC – 60 %; Lactose (anhydrous) – 39 %; Aerosil A-300 – 1 %; 70% ethanol solution – 16 ml per 100 g of mixture	7,89±0,08	92,11±1,02
3	Mixture of BAC – 60 %; Lactose (anhydrous) – 39 %; Aerosil A-300 – 1 %; 5% PVP solution in 90% ethanol – 18 ml per 100 g of mixture	54,11±0,32	45,89±0,81
4	Mixture of BAC – 60 %; Magnesium carbonate – 30 %; Corn starch. – 10 %; 70% ethanol solution – 16 ml per 100 g of mixture	47,71±0,81	52,29±0,42
5	Mixture of BAC – 60 %; Lactose (anhydrous) – 34 %; Corn starch – 6 %; 70% ethanol solution – 16 ml per 100 g of mixture	5,46±0,05	94,54±1,05
6	Mixture of BAC – 60 %; Microcrystalline cellulose (MCC 101) – 10 %; Calcium carbonate – 30 %; 70% ethanol solution – 16 ml per 100 g of mixture	12,55±0,06	87,45±0,54
7	Mixture of BAC – 60 %; Microcrystalline cellulose (MCC 101) – 10 %; Lactose (anhydrous) – 30 %; 70% ethanol solution – 14 ml per 100 g of mixture	15,92±0,07	84,08±0,34
8	Mixture of BAC – 60 %; Microcrystalline cellulose (MCC 101) – 20 %; Lactose (anhydrous) – 20 %; 70% ethanol solution – 15 ml per 100 g of mixture	27,16±0,41	72,84±0,24
9	Mixture of BAC – 60 %; Tween-80 – 1%; Lactose (anhydrous) – 40 %; 70% ethanol solution – 14 ml per 100 g of mixture	3,74±0,02	96,26±0,60
10	Mixture of BAC – 60 %; Tween-80 – 1%; Lactose (anhydrous) – 34 %; Corn starch. – 6 %; 70% ethanol solution – 12 ml per 100 g of mixture	7,38±0,04	92,65±0,72

Table 5

Technological properties of granules

№ var. in table 4	Flow-ability g/sec*	Angle of repose, Degrees	Weight Losson Drying %	Disinte-gration time, min	Bulk volume before tapping, kg/m³	Bulk volume after tapping, kg/m³	Carr Compres-sibility Index $IC=100(V_0-V_t)/V_0$	Hausner ratio $HR=V_0/V_F$
1	4,6	35	2,81	0,86	470	540	13,0	1,15
2	7,0	27	3,36	0,56	560	660	15,1	1,18
3	2,6	37	2,53	4,49	370	410	9,75	1,11
4	4,5	35	3,26	0,56	450	500	10,0	1,11
5	7,3	25	3,35	1,11	570	610	6,55	1,07
6	5,3	35	2,63	1,84	690	760	9,21	1,1
7	5,6	30	2,59	1,01	480	550	12,7	1,145
8	4,7	37	1,96	0,74	500	540	7,4	1,08
9	**9,4**	**25**	**2,43**	**1,02**	**540**	**620**	**12,9**	**1,15**
10	7,9	27	2,23	1,02	520	610	14,7	1,17

the flowability. After 72 hours of the experiment, the moisture content increased to 30 % (granules № 5) and the granules turn into sticky, non-flowingmass (fig. 2b). Research showed that the № 9 component had the least moisture absorption.

Indicators of bulk density, flowability, hygroscopicity, Carr Index and Hausner ratio allowed to have an objective assessment of the technological properties and suitability of the granules for packaging in solid gelatin capsules. Based on the totality of properties, the composition and technology of granules № 9 should be selected for production. On the basis of the pharmacological researches, dosage of phytocomposition was selected. The preliminary composition of the mass for granulation is presented in table 6.

The bulk density of the granules was 620±21 kg/m³. Dosage of phytocomposition in one capsule should be 500–600 mg. The results of choosing solid gelatin capsule sizefor encapsulating werepresented in table 7. To obtain the final product, select the capsule № 00.

Conclusion

Analyzing the technology properties of the DECS and DEAB showed that all of themwere unsatisfactory.

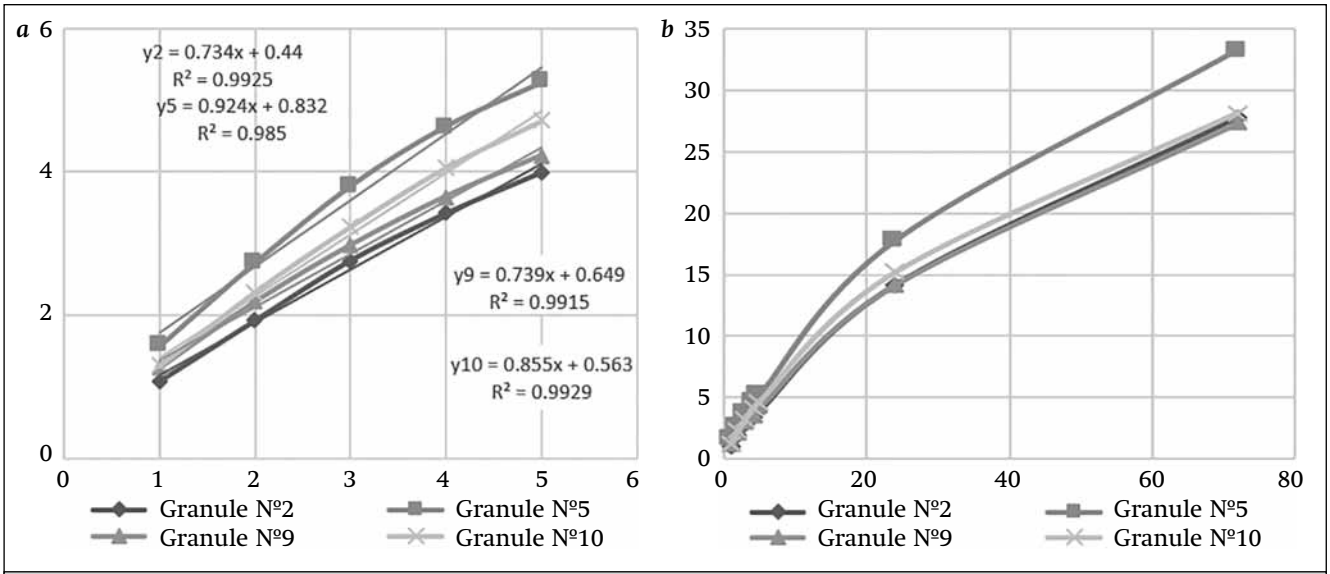

Fig.2. The granule's hygroscopicityof compositions № 2, 5, 9 and 10 (relative humidity of air of 98%): *a* – 5 hours; *b* – 72 hours. X-axis : time, hours; Y-axis : moisture absorption, %.)

Table 6

Composition of granules in one capsule

№	Name Component	Contents in one capsule, g
1	DECS	0,06
2	DEAB	0,18
3	Rutin	0,06
4	Lactose (anhydrous)	0,20
5	Tween-80	–
6	70% ethanol solution	–

The composition and technology of granules with dry extracts and rutin, satisfied technological characteristics. It is able to use them to produce a solid gelatin capsule dosage form. The selected size of solid gelatin capsules in order to apply production conditions is № 00.

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Table 7

Choosing the size of solid gelatin capsules

Size	000	00	0	1	2	3	4	5
Volume in ml	1,37	0,95	0,68	0,5	0,37	0,3	0,21	0,13
Weight of the selected composition, mg	–	547,9	387,3	269,1	–	144,3	–	–